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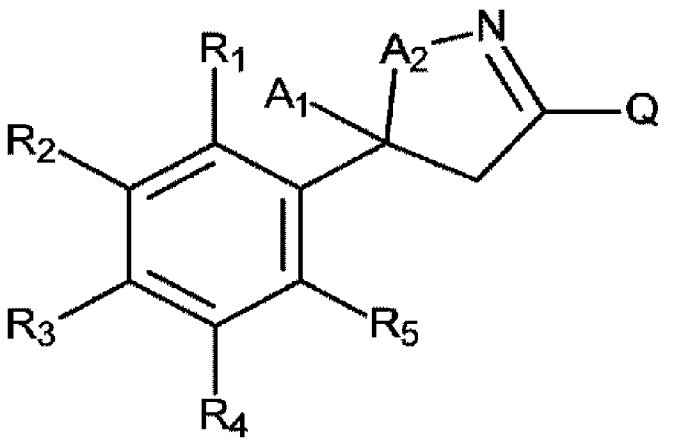
(54) Title: ISOXAZOLINE PESTICIDES



(I)

(57) Abrégé/Abstract:
The present invention provides compounds of formula (I) which are useful for long-lasting treatment and control of pests, for example fleas and ticks, in companion animals and livestock, and pharmaceutical compositions and methods of using the same.

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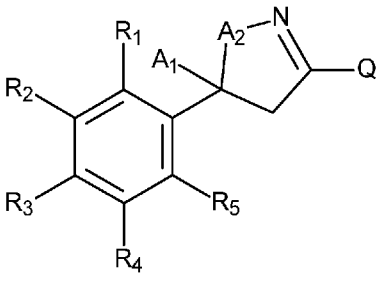

(I)

(57) Abstract: The present invention provides compounds of formula (I) which are useful for long-lasting treatment and control of pests, for example fleas and ticks, in companion animals and livestock, and pharmaceutical compositions and methods of using the same.

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ISOXAZOLINE PESTICIDES

FIELD

The present invention relates to medicinal chemistry, pharmacology, and veterinary and human medicine.

BACKGROUND

The aryl isoxazolines are used in agriculture, forestry, turf, household, wood products, nursery crops protection, and veterinary fields. The veterinary field includes companion animals and livestock, including fish. For example, such inhibitors are disclosed in WO 2005/085216, WO 2007/079162, US 2007/066617, US20130131017, WO 2009/002809, WO 2009/112275, WO 2010/003923, WO 2010/070068, WO 2012/120399, WO 2013/079407, and WO 2021/127188.

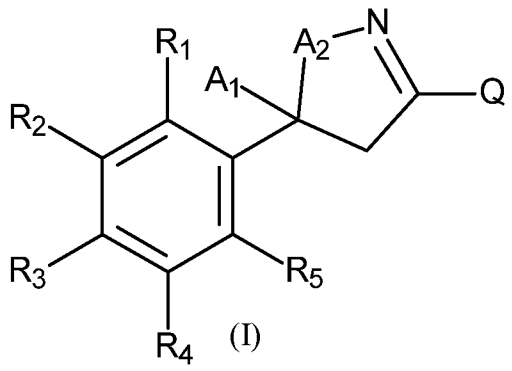
In many applications, long lasting effect against pests is desirable. Long lasting protection is particularly important with companion animals, such as dogs and cats and also mice, guinea pigs, ferrets, and rabbits; and with ranched animals such as cattle, sheep, pigs, and fish, in particular salmon and sea bass.

SUMMARY

The present invention relates to a compound of formula (I) having extended half-life in companion animals and livestock, in particular, warm-blooded animals, especially dogs, cats and cattle, and their use in the control of ectoparasites. In many cases the compound of formula (I) provides long duration of action for months after a single oral administration or an injection.

The present invention also provides compounds of formula (I) which effectively treat and/or control ectoparasites in companion animals and livestock.

In one embodiment, the present invention provides a compound of formula (I):



(I)

wherein

A_1 is selected from the group consisting of CF_3, CHF_2, CH_2F, and CF_2CF_3;

A_2 is O or S;

R_1 is selected from the group consisting of hydrogen and halogen;

R_2 is selected from the group consisting of hydrogen, halogen, difluoromethyl, and trifluoromethyl;

R_3 is selected from the group consisting of hydrogen, halogen, and trifluoromethyl;

R_4 is selected from the group consisting of hydrogen, halogen, difluoromethyl, and trifluoromethyl;

R_5 is selected from the group consisting of hydrogen and halogen;

provided that:

R_1 may be hydrogen only when R_2 is trifluoromethyl, difluoromethyl, or bromo;

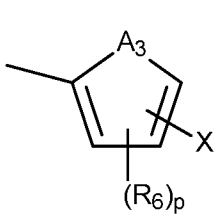
R_5 may be hydrogen only when R_4 is trifluoromethyl or bromo;

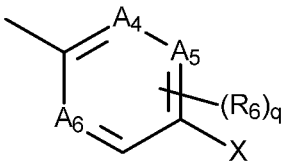
R_3 may be hydrogen only when one of R_2 or R_4 is either trifluoromethyl, difluoromethyl, or bromo;

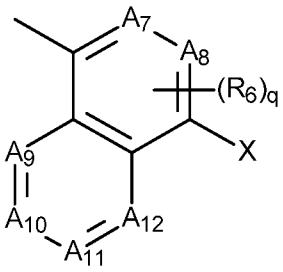
R_1, R_3, and R_5 cannot all be hydrogen when R_2 and R_4 are trifluoromethyl; and

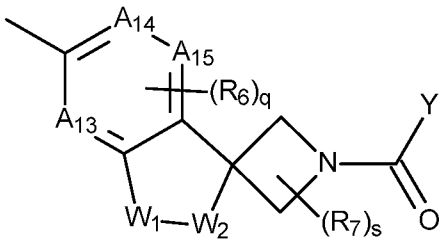
at most three of R_1, R_2, R_3, R_4, and R_5 are hydrogen;

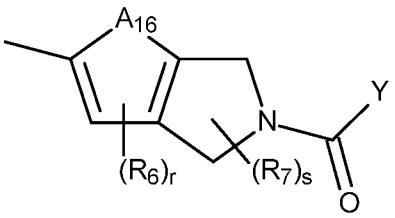
Q is selected from the group consisting of

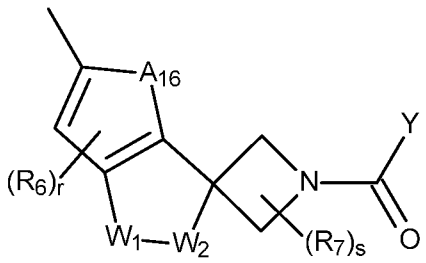




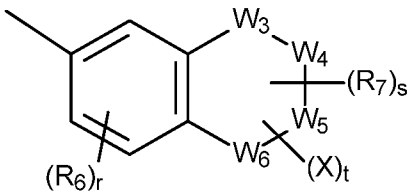








and



wherein

p is 0, 1, or 2;

q is 0, 1, 2, or 3;

r is 0 or 1;

s is 0, 1, or 2;

t is 0 or 1;

R_6, at each occurrence, is independently selected from the group consisting of halogen; cyano; nitro; hydroxyl; -NH_2; -NH(C_1-C_4 alkyl); -N(C_1-C_4 alkyl)$_2$; C_2-C_5-alkoxycarbonyl; C_1-C_6-alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, oxo, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, and -SO_2C_1-C_4 alkyl; C_1-C_6-alkoxy optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, oxo, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, -NH_2, C_1-C_7

aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, and -SO_2C_1-C_4 alkyl; -NR_8C(O)(C_1-C_4 alkyl) optionally substituted on the C_1-C_4 alkyl with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), and -N(C_1-C_4 alkyl)$_2$, wherein R_8 is independently selected from the group consisting of hydrogen and C_1-C_4 alkyl; -C(O)NR_8(C_1-C_4 alkyl) optionally substituted on the C_1-C_4 alkyl with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), and -N(C_1-C_4 alkyl)$_2$, wherein R_8 is independently selected from the group consisting of hydrogen and C_1-C_4 alkyl; -SC_1-C_6 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, oxo, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), and -N(C_1-C_4 alkyl)$_2$; and -S(O)C_1-C_6 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, oxo, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), and -N(C_1-C_4 alkyl)$_2$;

R_7, at each occurrence, is independently selected from the group consisting of oxo, C_1-C_4 alkyl, and C_3-C_6 cycloalkyl;

A_3 is O or S;

A_4 is CH or N;

A_5 is CH or N;

A_6 is CH or N;

A_7 is CH O, S, a bond, or N;

A_8 is CH O, S, a bond, or N;

A_9 is CH or N;

A_{10} is CH or N;

A_{11} is CH or N;

A_{12} is CH or N;

A_{13} is CH or N;

A_{14} is CH or N;

A_{15} is CH or N;

A_{16} is NR, O, or S, wherein R is selected from the group consisting of hydrogen, C_1-C_4 alkyl, and C_3-C_6 cycloalkyl;

W_1 is selected from the group consisting of -O-, -S-, -NR_9-, -$NC(O)R_{10}$-, -CH_2-, and -C(O)-;

W_2 is selected from the group consisting of -O-, -S-, -NR_9-, -$NC(O)R_{10}$-, -CH_2-, and -C(O)-;

provided that:

when W_1 is -O-, -S-, -NR_9-, or -$NC(O)R_{10}$- then W_2 is -CH_2- or -C(O)-; and

when W_2 is -O-, -S-, -NR_9-, or -$NC(O)R_{10}$- then W_1 is -CH_2- or -C(O)-;

W_3 is selected from the group consisting of nil, -O-, -S-, -S(O)-, -$S(O)_2$-, -NR_9-, -CH-, -N-, -CH_2-, and -C(O)-;

W_4 is selected from the group consisting of nil, -O-, -S-, -S(O)-, -$S(O)_2$-, -NR_9-, -CH-, -N-, -CH_2-, and -C(O)-;

W_5 is selected from the group consisting of nil, -O-, -S-, -S(O)-, -$S(O)_2$-, -NR_9-, -CH-, -N-, -CH_2-, and -C(O)-;

W_6 is selected from the group consisting of nil, -O-, -S-, -S(O)-, -$S(O)_2$-, -NR_9-, -CH-, -N-, -CH_2-, and -C(O)-;

wherein the bonds between W_1, W_2, W_3, and W_4 may be single or double bonds;

provided that:

(i) not more than two of W_1, W_2, W_3, and W_4 are nil;

(ii) not more than two of W_1, W_2, W_3, and W_4 are -O-, -S-, -S(O)-, -$S(O)_2$-, -NR_9-, or -C(O)-;

(iii) if two of W_1, W_2, W_3, and W_4 are -O- and/or -S- then at least one carbon atom is present between them; and

(iv) when W_1, W_2, W_3, or W_4 is -CH- and/or -NR_9- then a double bond is formed within the ring formed by W_1, W_2, W_3, and W_4;

R_9, at each occurrence, is independently selected from the group consisting of hydrogen and C_1-C_6-alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, oxo, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, and -SO_2C_1-C_4 alkyl;

R_{10}, at each occurrence, is independently selected from the group consisting of oxo, C_1-C_4 alkyl, and C_3-C_6 cycloalkyl;

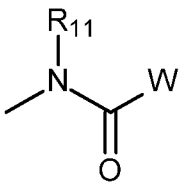
X is 5- to 10-membered heteroaryl having 1 or 2 heteroatoms selected from the group O, S, and N,

wherein the carbons of the 5- to 10-membered heteroaryl are optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, C_1-C_4 alkoxy, $-NH_2$, C_1-C_7 aminocarbonyl, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, $-SC_1$-C_4 alkyl, $-S(O)C_1$-C_4 alkyl, $-SO_2C_1$-C_4 alkyl, $-C(O)NH$-C_3-C_6 cycloalkyl, $-C(O)NH$-C_1-C_6 alkyl, and $-C(O)NH$-C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, $-C(O)NH$-C_3-C_6 cycloalkyl, $-C(O)NH$-C_1-C_6 alkyl, and $-C(O)NH$-C_1-C_6 haloalkyl,

wherein any N in the heteroaryl, valency permitting, is optionally substituted with a substituent selected from the group consisting of hydrogen, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, oxo, C_1-C_4 alkoxy, $-NH_2$, C_1-C_7 aminocarbonyl, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, $-SC_1$-C_4 alkyl, $-S(O)C_1$-C_4 alkyl, $-SO_2C_1$-C_4 alkyl, $-C(O)NH$-C_3-C_6 cycloalkyl, $-C(O)NH$-C_1-C_6 alkyl, and $-C(O)NH$-C_1-C_6 haloalkyl, and C_3-C_6 cycloalkyl;

or

X is selected from the group consisting of



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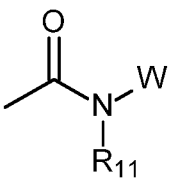


;

wherein

R_{11} is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_3-C_6 cycloalkyl, C_4-C_7 alkycycloalkyl, C_2-C_7 alkylcarbonyl, C_2-C_5 alkoxycarbonyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl;

W is selected from the group consisting of

(i) hydrogen;

(ii) C_1-C_6 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen; cyano; hydroxyl; oxo; C_1-C_4 alkoxy; C_3-C_6 cycloalkyl optionally substituted by 1 to 3 substituents independently selected from the group halogen and cyano; acetylenyl; -NH_2; C_1-C_7 aminocarbonyl; -NH(C_1-C_4 alkyl); -N(C_1-C_4 alkyl)$_2$; -SC_1-C_4 alkyl; -S(O)C_1-C_4 alkyl; -SO_2C_1-C_4 alkyl; -C(O)NH-C_3-C_6 cycloalkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, hydroxyl, cyano, and C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, and -NH_2; -C(O)NH-C_1-C_6 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, and -NH_2; -C(O)NH-C_1-C_6 cyanoalkyl optionally substituted with 1 to 3 halogen; -C(O)NH-C_1-C_6 haloalkyl; -C(O)-4- to 7-membered heterocycloalkyl attached by a nitrogen and optionally having 1 or 2 other heteroatoms selected from the group O, S, and N, wherein the carbons of the 4- to 7-membered heterocycloalkyl are optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, oxo, -NH_2, C_1-C_7 aminocarbonyl, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, oxo, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl, and C_3-C_6 cycloalkyl, wherein any other N in the 4- to 7-membered heterocycloalkyl, valency permitting, is substituted with a substituent selected from the group consisting of hydrogen, -NH_2, C_1-C_7 aminocarbonyl, -SO_2C_1-C_4 alkyl, -SO_2C_1-C_4 haloalkyl, and C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, C_1-C_4 alkoxy, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, -C(O)NH-C_1-C_6 alkyl, and -C(O)NH-C_1-C_6 haloalkyl; 5- to 10-membered heteroaryl having 1 or 2 heteroatoms selected from the group O, S, and N, wherein the carbons of the 5- to 10-membered heteroaryl are

optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, C_1-C_4 alkoxy, $-NH_2$, C_1-C_7 aminocarbonyl, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, $-SC_1$-C_4 alkyl, $-S(O)C_1$-C_4 alkyl, $-SO_2C_1$-C_4 alkyl, $-C(O)NH$-C_3-C_6 cycloalkyl, $-C(O)NH$-C_1-C_6 alkyl, and $-C(O)NH$-C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, $-NH_2$, C_1-C_7 aminocarbonyl, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, and $-C(O)NH$-C_3-C_6 cycloalkyl, wherein any N in the heteroaryl, valency permitting, is optionally substituted with a substituent selected from the group consisting of hydrogen, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, oxo, C_3-C_6 cycloalkyl,C_1-C_4 alkoxy, $-NH_2$, C_1-C_7 aminocarbonyl, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, $-SC_1$-C_4 alkyl, $-S(O)C_1$-C_4 alkyl, $-SO_2C_1$-C_4 alkyl, $-C(O)NH$-C_3-C_6 cycloalkyl, and $-C(O)NH$-C_1-C_6 alkyl, and C_3-C_6 cycloalkyl, wherein any S in the heteroaryl is optionally substituted with 1 or 2 oxygen atom(s); phenyl optionally substituted with 1 to 3 substituents selected from the group consisting of halogen, C_1-C_4 alkyl, cyano, and hydroxyl; C_3-C_6 cycloalkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, C_1-C_4 alkoxy, C_1-C_4 alkyl optionally substituted with 1 to 3 groups selected from the group consisting of halogen and cyano, C_1-C_4 haloalkyl,$-NH_2$, C_1-C_7 aminocarbonyl,$-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, $-SC_1$-C_4 alkyl, $-S(O)C_1$-C_4 alkyl, $-SO_2C_1$-C_4 alkyl, $-C(O)NH$-C_3-C_6 cycloalkyl, $-C(O)NH$-C_1-C_6 alkyl, $-C(O)NH$-C_1-C_6 haloalkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl; and 4- to 7-membered heterocycloalkyl having 1 or 2 heteroatoms selected from the group O, S, B, and N, wherein the heterocycloalkyl is optionally benzo-fused, wherein the carbons of the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl are optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, oxo, and C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, oxo, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, $-NH_2$, C_1-C_7 aminocarbonyl, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, $-SC_1$-C_4 alkyl, $-S(O)C_1$-C_4 alkyl, $-SO_2C_1$-C_4 alkyl, $-C(O)NH$-C_3-C_6 cycloalkyl, $-C(O)NH$-C_1-C_6 alkyl, and $-C(O)NH$-C_1-C_6 haloalkyl, wherein any B in the of the 4- to 7-membered

heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl, valency permitting, is substituted with hydroxyl, wherein any N in the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl, valency permitting, is substituted with a substituent selected from the group consisting of hydrogen, $-NH_2$, C_1-C_7 aminocarbonyl, $-SO_2C_1$-C_4 alkyl, $-SO_2C_1$-C_4 haloalkyl, $-C(O)-NH_2$, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, C_1-C_4 alkoxy, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, $-SC_1$-C_4 alkyl, $-S(O)C_1$-C_4 alkyl, $-SO_2C_1$-C_4 alkyl, $-C(O)NH$-C_3-C_6 cycloalkyl, and $-C(O)NH$-C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, 5- to 6-membered heteroaryl, and phenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_1-C_4 alkyl, cyano, and hydroxyl, wherein any S in the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl is optionally substituted with 1 or 2 oxygen atom(s);

(iii) C_3-C_6 cycloalkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, carboxyl, C_1-C_4 alkoxy, C_1-C_4 alkyl optionally substituted with 1 to 3 groups selected from the group consisting of halogen and cyano, C_1-C_4 haloalkyl,$-NH_2$, C_1-C_7 aminocarbonyl,$-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, $-SC_1$-C_4 alkyl, $-S(O)C_1$-C_4 alkyl, $-SO_2C_1$-C_4 alkyl, $-C(O)NH$-C_3-C_6 cycloalkyl, $-C(O)NH$-C_1-C_6 alkyl, $-C(O)NH$-C_1-C_6 haloalkyl, C_2-C_6 alkenyl optionally substituted with 1 to 3 halogens, and C_2-C_6 alkynyl;

(iv) 6-membered aryl or 5- to 10-membered heteroaryl having 1, 2 or 3 heteroatoms selected from the group O, S, and N, wherein the carbons of the 6-membered aryl and the 5- to 10-membered heteroaryl are optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, C_1-C_4 alkoxy, $-NH_2$, C_1-C_7 aminocarbonyl, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, $-SC_1$-C_4 alkyl, $-S(O)C_1$-C_4 alkyl, $-SO_2C_1$-C_4 alkyl, $-C(O)NH$-C_3-C_6 cycloalkyl, and $-C(O)NH$-C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, and $-C(O)NH$-C_3-C_6 cycloalkyl, wherein any N in the heteroaryl, valency permitting, is optionally substituted with a substituent selected from the group consisting of hydrogen,

and C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, oxo, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl;

(v) 4- to 7-membered heterocycloalkyl having 1 or 2 heteroatoms selected from the group O, S, and N, wherein the heterocycloalkyl is optionally benzo-fused, wherein the carbons of the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl are optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, oxo, C_1-C_4 alkoxy, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, oxo, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, -C(O)NH-C_1-C_6 alkyl, and-C(O)NH-C_1-C_6 haloalkyl, wherein any N in the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl, valency permitting, is substituted with a substituent selected from the group consisting of hydrogen, -NH_2, C_1-C_7 aminocarbonyl, -SO_2C_1-C_4 alkyl, -SO_2C_1-C_4 haloalkyl, -C(O)-NH_2, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, oxo, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_4 alkyl)$_2$, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, 5- to 6-membered heteroaryl, and phenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_1-C_4 alkyl, cyano, and hydroxyl, wherein any S in the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl is optionally substituted with 1 or 2 oxygen atom(s); and

(vi) -$NR_{12}R_{13}$

wherein

R_{12} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 alkylcycloalkyl, C_1-C_7 alkylcarbonyl, C_1-C_7 aminocarbonyl, and C_2-C_5 alkoxycarbonyl;

R_{13} is selected from the group consisting of hydrogen, C_1-C_6 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, nitro,hydroxyl, oxo, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, and -SO_2C_1-C_4 alkyl, C_3-C_6 cycloalkyl, -C(O)-C_1-C_6 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, nitro,hydroxyl, oxo, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, and -SO_2C_1-C_4 alkyl, 4- to 7-membered heterocycloalkyl having 1 or 2 heteroatoms selected from the group O, S, and N, wherein the heterocycloalkyl is optionally benzo-fused, wherein the carbons of the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl are optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, oxo, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, oxo, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, -C(O)NH-C_1-C_6 alkyl, and -C(O)NH-C_1-C_6 haloalkyl, and C_3-C_6 cycloalkyl, wherein any N in the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl, valency permitting, is substituted with a substituent selected from the group consisting of hydrogen, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 5- to 6-membered heteroaryl, and phenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_1-C_4 alkyl, cyano, and hydroxyl, wherein any S in the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl is optionally substituted with 1 or 2 oxygen atom(s); and 5- to 10-membered heteroaryl having 1 or 2 heteroatoms selected from the group O, S, and N, wherein the carbons of the 5- to 10-membered heteroaryl are optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, C_1-C_4 alkyl optionally

substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl,C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl, wherein any N in the heteroaryl, valency permitting, is optionally substituted with a substituent selected from the group consisting of hydrogen, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, oxo, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl, and C_3-C_6 cycloalkyl;

or

R_{11} and W are taken together with the nitrogen to which they are attached to form a 4- to 7-membered ring optionally containing 1 to 2 heteroatoms selected from the group consisting of N, S, and O, wherein the carbons of the ring are optionally substituted with 1 to 4 substituents independently selected of cyano, hydroxyl, oxo, halogen, C_1-C_2 alkoxy, N,N-di-C_1-C_4-alkylaminocarboxyl, N-C_1-C_4-alkylaminocarboxyl, C_1-C_7 aminocarboxyl, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, and -C(O)NH-C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl optionally substituted with 1 to 3 substituents selected from the group consisting of halogen, cyano, hydroxyl, and C_1-C_4 alkoxy, -C(O)NH-C_3-C_6 cycloalkyl, -C(O)NH-C_1-C_6 alkyl, -C(O)NH-C_1-C_6 haloalkyl, 5- to 6-membered heteroaryl, and phenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_1-C_4 alkyl, cyano, hydroxyl,C_1-C_2 alkoxy, N,N-di-C_1-C_4-alkylaminocarboxyl, N-C_1-C_4-alkylaminocarboxyl, and C_1-C_7 aminocarboxyl, wherein any N in the 4- to 7-membered ring is substituted with a substituent selected from the group consisting of hydrogen, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, and -C(O)NH-C_3-C_6 cycloalkyl, C_3-

C_6 cycloalkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, C_1-C_4 alkoxy, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl, 5- to 6-membered heteroaryl, and phenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_1-C_4 alkyl, cyano, and hydroxyl, wherein any S in the 4- to 7-membered ring is optionally substituted with 1 or 2 oxygen atom(s); and

Y is C_1-C_6 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, acetylenyl, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_4 alkyl)$_2$, -SO_2NH(C_1-C_4 haloalkyl), -C(O)NH-C_3-C_6 cycloalkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, hydroxyl, cyano, and C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, C_1-C_4 alkoxy, and -NH_2, -C(O)NH-C_1-C_6 alkyl, -C(O)NH-C_1-C_6 cyanoalkyl optionally substituted with 1 to 3 halogen, -C(O)NH-C_1-C_6 haloalkyl, phenyl optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, C_1-C_4 alkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, and -C(O)NH-C_3-C_6 cycloalkyl, and C_3-C_6 cycloalkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl,-NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, -C(O)NH-C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, 5- to 10-membered heteroaryl having 1 or 2 heteroatoms selected from the group O, S, and N, wherein the carbons of the 5- to 10-membered heteroaryl are optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, C_1-C_4 alkoxy, -NH_2,C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl, C_3-C_6

cycloalkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy,-NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl, wherein any N in the heteroaryl, valency permitting, is substituted with a substituent selected from the group consisting of hydrogen, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, oxo, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl, and C_3-C_6 cycloalkyl, and 4- to 7-membered heterocycloalkyl having 1 or 2 heteroatoms selected from the group O, S, and N, wherein the heterocycloalkyl is optionally benzo-fused, wherein the carbons of the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl are optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, oxo, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, oxo, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl, and C_3-C_6 cycloalkyl, wherein any N in the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl, valency permitting, is substituted with a substituent selected from the group consisting of hydrogen, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and 5- to 6-membered heteroaryl, wherein any S in the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl is optionally substituted with 1 or 2 oxygen atom(s);

or a salt thereof.

In one embodiment, the present invention also provides compositions, comprising: a compound of formula (I) or a salt thereof and at least one acceptable excipient, the composition optionally further comprising at least one additional active compound.

In one embodiment, the present invention also provides a method for treating pests, comprising: administering to a subject in need thereof an effective amount of a compound of formula (I) or a salt thereof, the method optionally further comprising an effective amount of at least one additional active compound.

In one embodiment, the present invention also provides a method for controlling pests, comprising: administering to a subject in need thereof an effective amount of a compound of formula (I) or a salt thereof, the method optionally further comprising an effective amount of at least one additional active compound.

In one embodiment, the present invention also provides a method for treating or controlling pests, comprising: contacting a subject's environment with an effective amount of a compound of formula (I) or a salt thereof, the method optionally further comprising an effective amount of at least one additional active compound.

Thus, the invention provides for the use of the compounds of the invention as a medicament, including for the manufacture of a medicament. In one embodiment, the invention provides the manufacture of a medicament comprising a compound of formula (I) or a salt thereof for treating parasites. In one embodiment, the invention provides the manufacture of a medicament comprising a compound of formula (I) or a salt thereof for controlling pests.

The present invention also provides processes from making compounds of the invention and intermediates thereof.

DETAILED DESCRIPTION

The term "C_1-C_2 alkyl" refers to a alkyl chain having from one to two carbon atoms and includes methyl and ethyl.

The term "C_1-C_4 alkyl" refers to a straight or branched alkyl chain having from one to four carbon atoms and includes methyl, ethyl, propyl, isopropyl, butyl, and the like.

Likewise, the term "C_1-C_6 alkyl" refers to a straight or branched alkyl chain having from one to six carbon atoms and includes methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl and the like.

The terms "C_1-C_4 haloalkyl" and "C_1-C_4 halogenoalkyl" refers to a straight or branched alkyl chain having from one to four carbon atoms and 1 to 5 halogen and includes fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 1,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, and the like.

The terms "C_1-C_6 haloalkyl" and "C_1-C_6 halogenoalkyl" refers to a straight or branched alkyl chain having from one to six carbon atoms and 1 to 5 halogen and includes fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 1,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, 4,4,4-trifluorobutyl, and the like.

The term "C_2-C_6 alkenyl" refers to a straight or branched alkenyl chain having from two to four carbon atoms and one carbon-carbon double bond, and includes ethylene, propylene, iso-propylene, butylene, iso-butylene, sec-butylene, and the like.

The term "C_2-C_6 alkynyl" refers to a straight or branched alkynyl chain having from two to four carbon atoms and one carbon-carbon triple bond, and includes acetylene, propargyl, and the like.

The term "C_1-C_2 alkoxy" refers to a C_1-C_2 alkyl attached through an oxygen atom and includes methoxy and ethoxy.

The term "C_1-C_4 alkoxy" refers to a C_1-C_4 alkyl attached through an oxygen atom and includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, and the like.

The term "C_1-C_6 alkoxy" refers to a C_1-C_6 alkyl attached through an oxygen atom and includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, and the like.

The term "C_3-C_6 cycloalkyl" refers to an alkyl ring(s) of three to six carbon atoms, and includes cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. It is understood that the cycloalkyl rings can be fused, bridged, or spiro-fused.

The term "C_4-C_7 alkylcycloalkyl" refers to a C_1-C_4 alkyl substituted with a C_3-C_6 cycloalkyl such that the total number of carbons is four to seven and includes cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclopropylethyl, and the like.

The terms "halo" "halogen" and "halo" refers to chloro, fluoro, bromo or iodo atom(s).

The terms "4- to 7-membered heterocycloalkyl having 1 or 2 heteroatoms selected from the group O, S, N, wherein the heterocycloalkyl is optionally benzo-fused" and "4- to 7-membered heterocycloalkyl having 1 or 2 heteroatoms selected from the group O, S, B, N, wherein the heterocycloalkyl is optionally benzo-fused" refers to a 4- to 7-membered saturated or partially (but not fully) unsaturated ring having one or two heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur or having one or two heteroatoms selected from the group consisting of nitrogen, oxygen, boron, and sulfur and the ring optionally includes a carbonyl to form a lactam or lactone. It is understood that where sulfur is included that the sulfur may be either -S-, -SO-, or -SO_2-. The heterocyclic ring can be monocyclic or bicyclic and any bicyclic rings can be fused, bridged, or spiro-fused. The defined 4 to 7 members are exclusive of any optional benzo fused ring. Also, as will be fully appreciated by the skilled person, the saturated or partially (but not fully) unsaturated 4- to 7-membered heterocycloalkyl ring applies to the heterocycloalkyl ring and does not apply to any benzo fused ring, which by its nature will be fully unsaturated. It is further understood that the group can be attached as a substituent by any of the ring heteroatoms, valency permitting, the carbon atoms of the heterocycloalkyl, or the carbon atoms of any benzo-fused ring. It is also understood that when an optionally benzo-fused 4- to 7-membered heterocycloalkyl is optionally substituted on carbon, the substituents can be on the carbon atoms of the heterocycle and/or the benzo fused ring. For example, but not limiting, the term includes azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, oxetanyl,

thioxetanyl, dioxolanyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrofuryl, hexahydropyrimidinyl, tetrahydropyrimidinyl, 2,6-diazaspiro[3.3]heptanyl, isoxazolidine, dihydroimidazolyl, indolyl, isoindolyl, and the like.

The term "5- or 6-membered heteroaryl" refers to a six membered, monocyclic, fully unsaturated ring with one to five carbon atoms and one or more, typically one to four, heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. For example, but not limiting, the term includes pyrrolyl, furyl, thienyl, imidazolyl, oxazoyl, isoxazoyl, thiazolyl, triazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidyl, and the like. It is understood that a 6-membered heteroaryl can be attached as a substituent through a ring carbon or a ring nitrogen atom where such an attachment mode is available.

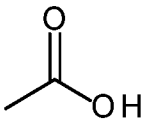
Where R_{11} and W are taken together with the nitrogen to which they are attached, the term "4- to 7-membered ring optionally containing 1 to 2 heteroatoms selected from the group consisting of N, S, and O" refers to a fully saturated or partially unsaturated (but not fully) ring having four to seven members inclusive of the nitrogen to which R_{11} and W are attached and includes azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, oxetanyl, dioxolanyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrofuryl, hexahydropyrimidinyl, tetrahydropyrimidinyl, dihydroimidazolyl, and the like.

The term "5- to 10-membered heteroaryl having 1 or 2 heteroatoms selected from the group O, S, and N" refers to a five to ten membered, monocyclic or polycyclic fully unsaturated, ring or ring system with one to nine carbon atoms and one or two heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. For example, but not limiting, the term includes furyl, thienyl, pyrrolyl, imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, thiazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidyl, azepinyl, diazepinyl, benzofuryl, benzothienyl, indolyl, isoindolyl, benzimidazolyl, benzisothiazolyl, benzisoxazolyl, benzoxazolyl, benzopyrazinyl, benzopyrazolyl, quinazolyl, thienopyridyl, quinolyl, isoquinolyl benzothiazolyl, and the like. It is understood that a 5- to 10-membered heteroaryl having

1 or 2 heteroatoms selected from the group O, S, and N can be attached as a substituent through a ring carbon or a ring nitrogen atom where such an attachment mode is available.

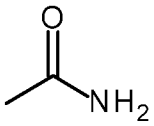
The term "oxo" refers to an oxygen atom doubly bonded to the carbon to which it is attached to form the carbonyl of an amide, ketone, or aldehyde. For example, a pryidone radical is contemplated as an oxo substituted 6-membered heteroaryl.

The term "carboxyl" refers to the group below:



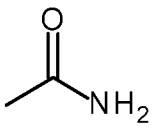
.

The term "N,N-di-C_1-C_4-alkylaminocarboxyl" refers to the group immediately below:



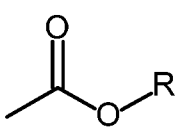
wherein the hydrogens on the nitrogen are substituted with two independently selected C_1-C_4 alkyl groups.

Likewise, term "N-C_1-C_4-alkylaminocarboxyl" refers to the group immediately below:



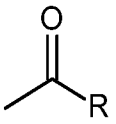
wherein one of the hydrogen on the nitrogen is substituted with a C_1-C_4 alkyl group.

The term "C_2-C_5 alkoxycarbonyl" refers the group below:



wherein R is a C_1-C_4 alkyl.

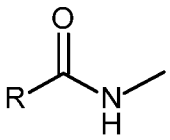
The term "C_2-C_7 alkylcarbonyl" refers the group below:



wherein R is a C_1-C_6 alkyl.

Likewise, the term "C_2-C_7 haloalkylcarbonyl" refers to the group immediately above wherein R is an C_1-C_6 haloalkyl.

The term "C_1-C_7 aminocarbonyl" refers to the group below:



wherein R is a hydrogen or C_1-C_4 alkyl.

The term "nil" as used herein with reference to a group, substituent, moiety, or the like, indicates that that group, substituent, or moiety is not present. Wherein a group, substituent, or moiety is ordinarily bonded to two or more other groups, substituents, or moieties, the others are bonded together in lieu of the group, substituent, or moiety which is nil. For example, with a compound having the structure A-B-C; wherein B is nil, then A is directly bonded to C and the compound is A-C. As another example, with a compound having the structure A-B-C; wherein C is nil, then the compound is A-B.

The terms "salt" and "salts" refers to salts of veterinary or pharmaceutically acceptable organic acids and bases or inorganic acids and bases. Such salts are well known in the art and include those described in Journal of Pharmaceutical Science, 66, 2-19 (1977). An example is the hydrochloride salt.

The term "substituted," including when used in "optionally substituted" refers to one or more hydrogen radicals of a group being replaced with non-hydrogen radicals (substituent(s)). It is understood that the substituents may be either the same or different at every substituted position. Combinations of groups and substituents envisioned by this invention are those that are stable or chemically feasible. For compounds described herein, groups and substituents thereof may be selected in accordance with permitted valence of the atoms and the substituents, such that the selections and substitutions result in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc.

The term "stable" refers to compounds that are not substantially altered when subjected to conditions to allow for their production. In a non-limiting example, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for about a week.

It is understood that, where the terms defined herein mention a number of carbon atoms, that the mentioned number refers to the mentioned group and does not include any carbons that may be present in any optional substituent(s) thereon or any carbons that may be present as part of a fused ring, including a benzo-fused ring.

The skilled artisan will appreciate that certain of the compounds of the present invention exist as isomers. All stereoisomers of the compounds of the invention, including geometric isomers, enantiomers, and diastereomers, in any ratio, are contemplated to be within the scope of the present invention.

As used herein, the term "(RS)" within chemical nomenclature refers to a racemic mixture at the indicated stereocenter.

As used herein, the term "(R or S)" or "(S or R)", within chemical nomenclature refers to one of two possible configurations at the indicated stereocenter.

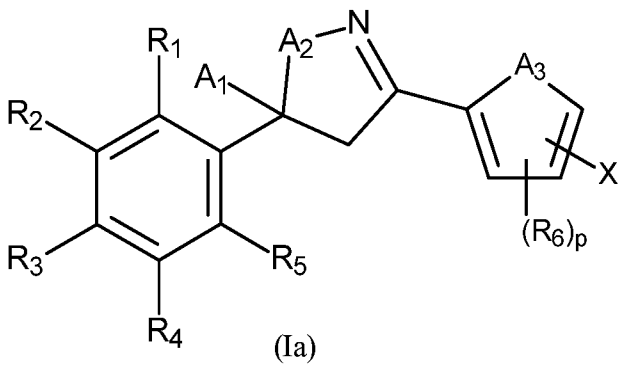
The skilled artisan will also appreciate that certain of the compounds of the present invention exist as tautomers. All tautomeric forms the compounds of the invention are contemplated to be within the scope of the present invention.

Compounds of the invention also include all isotopic variations, in which at least one atom of the predominant atom mass is replaced by an atom having the same atomic number, but an atomic mass different from the predominant atomic mass. Use of isotopic variations (*e.g.*, deuterium, ^{2}H) may afford greater metabolic stability. Additionally, certain isotopic variations of the compounds of the invention may incorporate a radioactive isotope (*e.g.*, tritium, ^{3}H, or ^{14}C), which may be useful in drug and/or substrate tissue distribution studies. Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, may be useful in Positron Emission Topography (PET) studies.

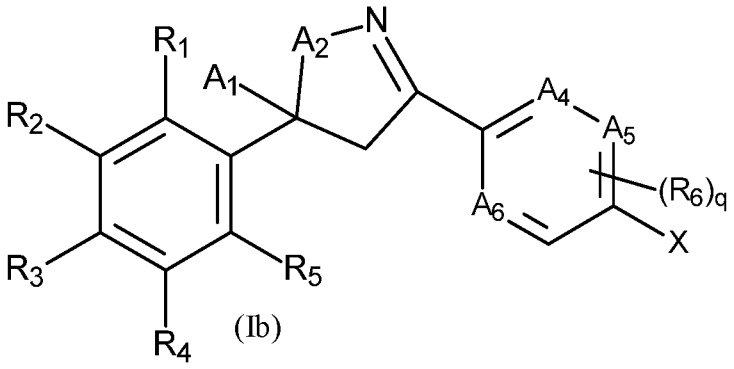
The terms “compounds of the invention” and “a compound of the invention” and “compounds of the present invention” and the like include the embodiment of formula (I) and the other more particular embodiments encompassed by formula (I) described herein and the exemplified compounds described herein and a salt of each of these embodiments.

The compound of formula (I) having various embodiments as follows:

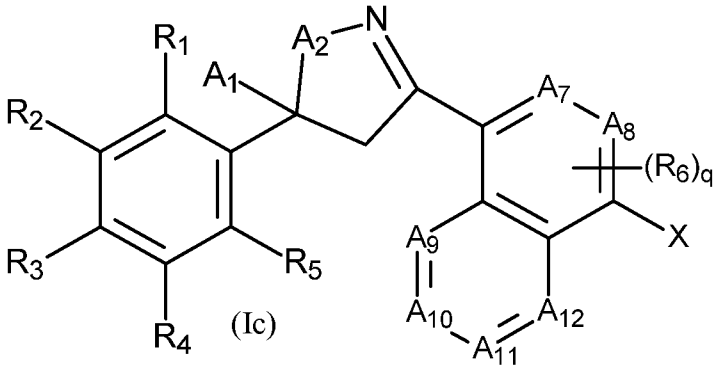
formula (I):



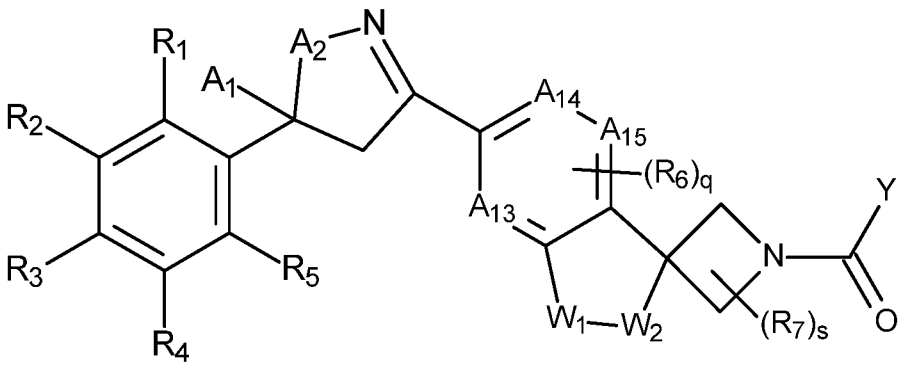
(Ia)



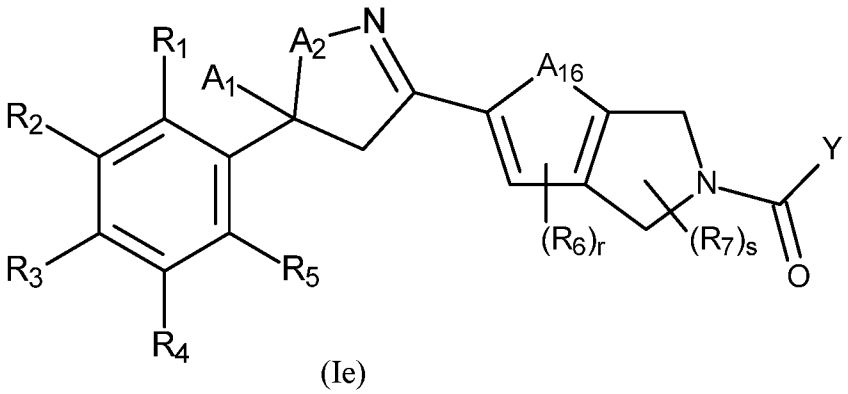
(Ib)



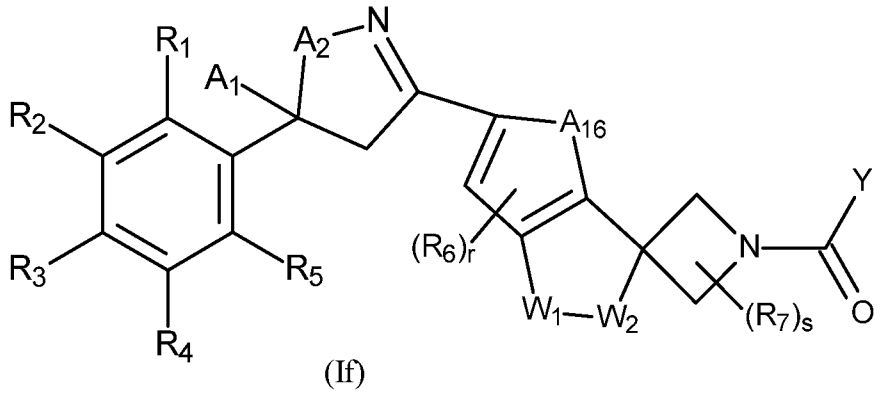
(Ic)



(Id)

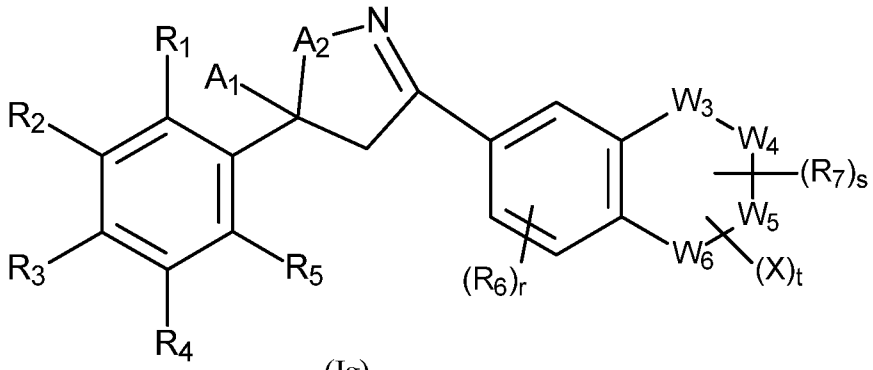


(Ie)



(If)

and



(Ig)

It is understood that for A_4, A_5, A_6, A_7, A_9, A_{10}, A_{11}, A_{12}, A_{14}, and/or A_{15} an R_6 substituent, when present, takes the place of the hydrogen of the CH.

It is further understood that for the compound of formula (Ig) the X group, when present, is attached at W_3, W_4, W_5, or W_6 by replacing a hydrogen of a -CH_2- or -CH- group or the R of an -NR- group.

Further embodiments of compounds of the invention are provided below:

(1) One embodiment relates to a compound of formula (I) or a salt thereof.

(a) One embodiment relates to compounds of formula (Ia) or a salt thereof.

(b) One embodiment relates to compounds of formula (Ib) or a salt thereof.

(c) One embodiment relates to compounds of formula (Ic) or a salt thereof.

(d) One embodiment relates to compounds of formula (Id) or a salt thereof.

(e) One embodiment relates to compounds of formula (Ie) or a salt thereof.

(f) One embodiment relates to compounds of formula (If) or a salt thereof.

(g) One embodiment relates to compounds of formula (Ig) or a salt thereof.

(h) One embodiment relates to embodiments (1), (a), (b), (c), (d), (e), (f), and (g) wherein R_1 is hydrogen, R_2 is trifluoromethyl, R_3 is hydrogen, R_4 is trifluoromethyl, and R_5 is halogen; or a salt thereof.

(i) One embodiment relates to embodiments (1), (a), (b), (c), (d), (e), (f), and (g) wherein R_1 is hydrogen, R_2 is trifluoromethyl, R_3 is hydrogen, R_4 is halogen, and R_5 is halogen; or a salt thereof.

(j) One embodiment relates to embodiments (1), (a), (b), (c), (d), (e), (f), and (g) wherein R_1 is hydrogen, R_2 is trifluoromethyl, R_3 is hydrogen, R_4 is chloro, and R_5 is halogen; or a salt thereof.

(k) One embodiment relates to embodiments (1), (a), (b), (c), (d), (e), (f), and (g) wherein R_1 is hydrogen, R_2 is trifluoromethyl, R_3 is hydrogen, R_4 is halogen, and R_5 is chloro; or a salt thereof.

(l) One embodiment relates to embodiments (1), (a), (b), (c), (d), (e), (f), and (g) wherein R_1 is hydrogen, R_2 is trifluoromethyl, R_3 is hydrogen, R_4 is halogen, and R_5 is fluoro; or a salt thereof.

(m) One embodiment relates to embodiments (1), (a), (b), (c), (d), (e), (f), and (g) wherein R_1 is hydrogen, R_2 is trifluoromethyl, R_3 is hydrogen, R_4 is chloro, and R_5 is fluoro; or a salt thereof.

(n) One embodiment relates to embodiments (1), (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), and (m) wherein A_2 is O; or a salt thereof.

(o) One embodiment relates to embodiments (1), (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), (m), and (n) wherein A_1 is CF_3; or a salt thereof.

(p) One embodiment relates to embodiments (1), (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), (m), and (n) wherein A_1 is CHF_2; or a salt thereof.

(q) One embodiment relates to embodiments (1), (a), (h), (i), (j), (k), (l), (m), (n), (o), and (p) wherein A_3 is S; or a salt thereof.

(r) One embodiment relates to embodiment (q) wherein p is 1 and R_5 is C_1-C_6 alkyl; or a salt thereof.

(s) One embodiment relates to embodiment (r) wherein R_6 is methyl; or a salt thereof.

(t) One embodiment relates to embodiments (1), (b), (h), (i), (j), (k), (l), (m), (n), (o), and (p) wherein A_4, A_5, and A_6 are CH; or a salt thereof.

(u) One embodiment relates to embodiment (t) wherein p is 1 and R_6 is C_1-C_6 alkyl; or a salt thereof.

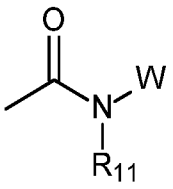
(v) One embodiment relates to embodiment (u) wherein R_6 is methyl; or a salt thereof.

(w) One embodiment relates to embodiments (1), (c), (h), (i), (j), (k), (l), (m), (n), (o), and (p) wherein A_7, A_8, A_9, A_{10}, A_{11}, and A_{12} are CH; or a salt thereof.

(x) One embodiment relates to embodiments (1), (d), (h), (i), (j), (k), (l), (m), (n), (o), and (p) wherein A_{13}, A_{14}, and A_{15} are CH; or a salt thereof.

(y) One embodiment relates to embodiment (x) wherein W_1 is -CH_2- and W_2 is O; or a salt thereof.

(z) One embodiment relates to embodiments (1), (a), (b), (c), (g), (h), (i), (j), (k), (l), (m), (n), (o), (p), (q), (r), (s), (t), (u), (v), (w), and (x) wherein X is



;

wherein R_{11} is hydrogen; or a salt thereof.

(aa) One embodiment relates to embodiment (z) wherein W is C_1-C_6 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of

halogen,

cyano,

hydroxyl,

oxo,

C_1-C_4 alkoxy,

C_3-C_6 cycloalkyl optionally substituted by 1 to 3 substituents independently selected from the group halogen and cyano,

acetylenyl,

-NH_2,

C_1-C_7 aminocarbonyl,

-NH(C_1-C_4 alkyl),

-N(C_1-C_4 alkyl)$_2$,
-SC_1-C_4 alkyl,
-S(O)C_1-C_4 alkyl,
-SO_2C_1-C_4 alkyl,
-C(O)NH-C_3-C_6 cycloalkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of
halogen,
hydroxyl,
cyano, and
C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of
halogen,
cyano,
hydroxyl,
C_1-C_4 alkoxy,
C_3-C_6 cycloalkyl, and
-NH_2,
-C(O)NH-C_1-C_6 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of
halogen,
cyano,
hydroxyl,
C_1-C_4 alkoxy,
C_3-C_6 cycloalkyl, and
-NH_2;
-C(O)NH-C_1-C_6 cyanoalkyl optionally substituted with 1 to 3 halogen,
-C(O)NH-C_1-C_6 haloalkyl,
-C(O)-4- to 7-membered heterocycloalkyl attached by a nitrogen and optionally having 1 or 2 other heteroatoms selected from the group O, S, N, wherein the carbons of the 4- to 7-membered heterocycloalkyl are optionally substituted with 1 to 4 substituents independently selected from the group consisting of
halogen,

cyano,
nitro,
hydroxyl,
oxo,
$-NH_2$,
C_1-C_7 aminocarbonyl,
C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of
halogen,
cyano,
hydroxyl,
acetylenyl,
oxo,
C_1-C_4 alkoxy,
$-NH_2$,
C_1-C_7 aminocarbonyl,
$-NH(C_1$-C_4 alkyl),
$-N(C_1$-C_4 alkyl)$_2$,
$-SC_1$-C_4 alkyl,
$-S(O)C_1$-C_4 alkyl,
$-SO_2C_1$-C_4 alkyl,
$-C(O)NH$-C_3-C_6 cycloalkyl, and
$-C(O)NH$-C_1-C_6 alkyl, and
C_3-C_6 cycloalkyl;
and any other N in the 4- to 7-membered heterocycloalkyl, valency permitting, is substituted with a substituent selected from the group consisting of
hydrogen,
$-NH_2$,
C_1-C_7 aminocarbonyl,
$-SO_2C_1$-C_4 alkyl,
$-SO_2C_1$-C_4 haloalkyl,

C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of
halogen,
cyano,
hydroxyl,
acetylenyl,
C_1-C_4 alkoxy,
-NH(C_1-C_4 alkyl),
-N(C_1-C_4 alkyl)$_2$,
-SC_1-C_4 alkyl,
-S(O)C_1-C_4 alkyl,
-SO_2C_1-C_4 alkyl,
-C(O)NH-C_3-C_6 cycloalkyl,
-C(O)NH-C_1-C_6 alkyl,
-C(O)NH-C_1-C_6 haloalkyl;

5- to 10-membered heteroaryl having 1 or 2 heteroatoms selected from the group O, S, and N and wherein the carbons of the 5- to 10-membered heteroaryl are optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of
halogen,
cyano,
nitro,
hydroxyl,
C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of
halogen,
cyano,
hydroxyl,
oxo,
C_1-C_4 alkoxy,
-NH_2,
C_1-C_7 aminocarbonyl,

-NH(C_1-C_4 alkyl),
-N(C_1-C_4 alkyl)$_2$,
-SC_1-C_4 alkyl,
-S(O)C_1-C_4 alkyl,
-SO_2C_1-C_4 alkyl,
-C(O)NH-C_3-C_6 cycloalkyl,
-C(O)NH-C_1-C_6 alkyl, and
-C(O)NH-C_1-C_6 haloalkyl;
C_3-C_6 cycloalkyl,
C_1-C_4 haloalkyl,
C_1-C_4 alkoxy,
-NH_2,
C_1-C_7 aminocarbonyl,
-NH(C_1-C_4 alkyl),
-N(C_1-C_4 alkyl)$_2$, and
-C(O)NH-C_3-C_6 cycloalkyl;

and any N in the heteroaryl, valency permitting, is optionally substituted with a substituent selected from the group consisting of

hydrogen,
C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of
halogen,
cyano,
hydroxyl,
acetylenyl,
oxo,
C_3-C_6 cycloalkyl,
C_1-C_4 alkoxy,
-NH_2,
C_1-C_7 aminocarbonyl,
-NH(C_1-C_4 alkyl),
-N(C_1-C_4 alkyl)$_2$,

-SC_1-C_4 alkyl,
-$S(O)C_1$-C_4 alkyl,
-SO_2C_1-C_4 alkyl,
-$C(O)NH$-C_3-C_6 cycloalkyl, and
-$C(O)NH$-C_1-C_6 alkyl; and

C_3-C_6 cycloalkyl;

and any S in the heteroaryl is substituted with 1 or 2 oxygen atom(s);

phenyl optionally substituted with 1 to 3 substituents selected from the group consisting of

halogen,
C_1-C_4 alkyl,
cyano, or
hydroxyl;

C_3-C_6 cycloalkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of

halogen,
cyano,
hydroxyl,
oxo,
C_1-C_4 alkoxy,
C_1-C_4 alkyl optionally substituted with 1 to 3 groups selected from the group consisting of halogen and cyano,
C_1-C_4 haloalkyl,
-NH_2,
C_1-C_7 aminocarbonyl,
-$NH(C_1$-C_4 alkyl),
-$N(C_1$-C_4 alkyl)$_2$,
-SC_1-C_4 alkyl,
-$S(O)C_1$-C_4 alkyl,
-SO_2C_1-C_4 alkyl,
-$C(O)NH$-C_3-C_6 cycloalkyl,
-$C(O)NH$-C_1-C_6 alkyl,

-C(O)NH-C_1-C_6 haloalkyl,
C_2-C_6 alkenyl, and
C_2-C_6 alkynyl; and

4- to 7-membered heterocycloalkyl having 1 or 2 heteroatoms selected from the group O, S, B, N, wherein the heterocycloalkyl is optionally benzo-fused, and wherein the carbons of the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl are optionally substituted with 1 to 4 substituents independently selected from the group consisting of

halogen,
cyano,
nitro,
hydroxyl,
oxo,
C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of

halogen,
cyano, hydroxyl,
acetylenyl,
oxo,
C_1-C_4 alkoxy,
C_3-C_6 cycloalkyl,
-NH_2,
C_1-C_7 aminocarbonyl,
-NH(C_1-C_4 alkyl),
-N(C_1-C_4 alkyl)$_2$,
-SC_1-C_4 alkyl,
-S(O)C_1-C_4 alkyl,
-SO_2C_1-C_4 alkyl,
-C(O)NH-C_3-C_6 cycloalkyl,
-C(O)NH-C_1-C_6 alkyl, and
and-C(O)NH-C_1-C_6 haloalkyl;

and any B in the of the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl, valency permitting, is substituted with hydroxyl,

and any N in the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl, valency permitting, is substituted with a substituent selected from the group consisting of

hydrogen,

$-NH_2$,

C_1-C_7 aminocarbonyl,

$-SO_2C_1$-C_4 alkyl,

$-SO_2C_1$-C_4 haloalkyl,

$-C(O)-NH_2$,

C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of

halogen,

cyano,

hydroxyl,

acetylenyl,

C_1-C_4 alkoxy,

$-NH(C_1$-C_4 alkyl),

$-N(C_1$-C_4 alkyl)$_2$,

$-SC_1$-C_4 alkyl,

$-S(O)C_1$-C_4 alkyl,

$-SO_2C_1$-C_4 alkyl,

$-C(O)NH-C_3$-C_6 cycloalkyl, and

$-C(O)NH-C_1$-C_6 haloalkyl;

C_3-C_6 cycloalkyl;

5- to 6-membered heteroaryl; and

phenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of

halogen,

C_1-C_4 alkyl,

cyano, and
hydroxyl; and
any S in the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl is substituted with 1 or 2 oxygen atom(s);
or a salt thereof.

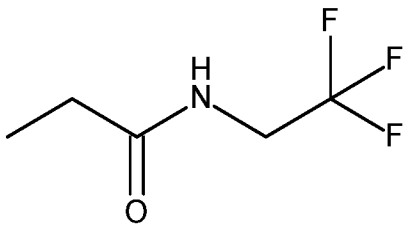
(ab) One embodiment related to embodiment (aa) wherein W is a C_1-C_6 alkyl substituted with a substituent selected from the group consisting of
-C(O)NH-C_1-C_6 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of
halogen,
cyano,
hydroxyl,
C_1-C_4 alkoxy,
C_3-C_6 cycloalkyl, and
-NH_2;
-C(O)NH-C_1-C_6 cyanoalkyl optionally substituted with 1 to 3 halogen,
-C(O)NH-C_1-C_6 haloalkyl, and
-C(O)-4- to 7-membered heterocycloalkyl attached by a nitrogen and optionally having 1 or 2 other heteroatoms selected from the group O, S, N, wherein the carbons of the 4- to 7-membered heterocycloalkyl are optionally substituted with 1 to 4 substituents independently selected from the group consisting of
halogen,
cyano,
nitro,
hydroxyl,
oxo,
-NH_2,
C_1-C_7 aminocarbonyl,
C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of
halogen,
cyano,

hydroxyl,
acetylenyl,
oxo,
C_1-C_4 alkoxy,
$-NH_2$,
C_1-C_7 aminocarbonyl,
$-NH(C_1$-C_4 alkyl),
$-N(C_1$-C_4 alkyl)$_2$,
$-SC_1$-C_4 alkyl,
$-S(O)C_1$-C_4 alkyl,
$-SO_2C_1$-C_4 alkyl,
$-C(O)NH$-C_3-C_6 cycloalkyl, and
$-C(O)NH$-C_1-C_6 alkyl, and
C_3-C_6 cycloalkyl;
and any other N in the 4- to 7-membered heterocycloalkyl, valency permitting, is substituted with a substituent selected from the group consisting of
hydrogen,
$-NH_2$,
C_1-C_7 aminocarbonyl,
$-SO_2C_1$-C_4 alkyl,
$-SO_2C_1$-C_4 haloalkyl,
C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of
halogen,
cyano,
hydroxyl,
acetylenyl,
C_1-C_4 alkoxy,
$-NH(C_1$-C_4 alkyl),
$-N(C_1$-C_4 alkyl)$_2$,
$-SC_1$-C_4 alkyl,

-S(O)C_1-C_4 alkyl,
-$SO_2$$C_1$-$C_4$ alkyl,
-C(O)NH-C_3-C_6 cycloalkyl,
-C(O)NH-C_1-C_6 alkyl,
-C(O)NH-C_1-C_6 haloalkyl;

or a salt thereof.

(ac) One embodiment relates to embodiment (ab) wherein W is



or a salt thereof.

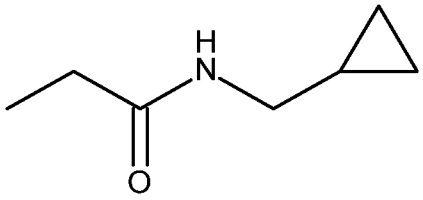
(ad) One embodiment relates to embodiment (z) wherein W is C_1-C_6 alkyl substituted with -C(O)NH-C_3-C_6 cycloalkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, hydroxyl, cyano, and C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, C_1-C_4 alkoxy, and -NH_2; or a salt thereof.

(ae) One embodiment relates to embodiment (z) wherein W is C_1-C_6 alkyl substituted with -C(O)NH-C_1-C_6 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of

halogen,
cyano,
hydroxyl,
C_1-C_4 alkoxy,
C_3-C_6 cycloalkyl, and
-NH_2;

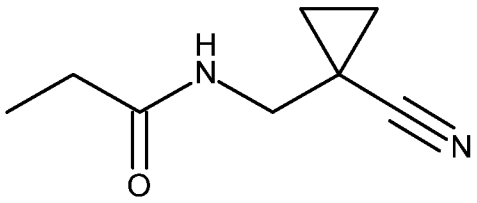
or a salt thereof.

(ae1) One embodiment relates to embodiment (ae) wherein W is



or a salt thereof.

(ae2) One embodiment relates to embodiment (ae) where in W is



or a salt thereof.

(af) One embodiment relates to embodiment (z) wherein W is C_1-C_6 alkyl substituted with a 5- to 10-membered heteroaryl having 1 or 2 heteroatoms selected from the group O, S, B, and N and wherein the carbons of the 5- to 10-membered heteroaryl are optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl; C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, and -C(O)NH-C_3-C_6 cycloalkyl; and any B in the heteroaryl is substituted with hydroxyl and any N in the heteroaryl, valency permitting, is optionally substituted with a substituent selected from the group consisting of hydrogen, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, oxo, C_3-C_6 cycloalkyl,C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl and any S in the heteroaryl is substituted with 1 or 2 oxygen atom(s); or a salt thereof.

(af1) One embodiment relates to embodiment (z) wherein W is C_1-C_6 alkyl substituted with a pyridine optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, C_1-C_4 alkoxy, $-NH_2$, C_1-C_7 aminocarbonyl, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, $-SC_1$-C_4 alkyl, $-S(O)C_1$-C_4 alkyl, $-SO_2C_1$-C_4 alkyl, $-C(O)NH$-C_3-C_6 cycloalkyl, and $-C(O)NH$-C_1-C_6 alkyl; C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, and $-C(O)NH$-C_3-C_6 cycloalkyl; or a salt thereof.

(af2) One embodiment relates to embodiment (z) wherein W is C_1-C_6 alkyl substituted with a thiazole optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, C_1-C_4 alkoxy, $-NH_2$, C_1-C_7 aminocarbonyl, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, $-SC_1$-C_4 alkyl, $-S(O)C_1$-C_4 alkyl, $-SO_2C_1$-C_4 alkyl, $-C(O)NH$-C_3-C_6 cycloalkyl, and $-C(O)NH$-C_1-C_6 alkyl; C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, and $-C(O)NH$-C_3-C_6 cycloalkyl; or a salt thereof.

(ag) One embodiment relates to embodiment (z) wherein W is a 4- to 7-membered heterocycloalkyl having 1 or 2 heteroatoms selected from the group O, S, N, wherein the heterocycloalkyl is optionally benzo-fused, and wherein the carbons of the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl are optionally substituted with 1 to 4 substituents independently selected from the group consisting of

- halogen,
- cyano,
- nitro,
- hydroxyl,
- oxo,
- C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of
  - halogen,

cyano, hydroxyl,
acetylenyl,
oxo,
C_1-C_4 alkoxy,
C_3-C_6 cycloalkyl,
-NH_2,
C_1-C_7 aminocarbonyl,
-NH(C_1-C_4 alkyl),
-N(C_1-C_4 alkyl)$_2$,
-SC_1-C_4 alkyl,
-S(O)C_1-C_4 alkyl,
-SO_2C_1-C_4 alkyl,
-C(O)NH-C_3-C_6 cycloalkyl,
-C(O)NH-C_1-C_6 alkyl,
and
-C(O)NH-C_1-C_6 haloalkyl; and

and any N in the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl, valency permitting, is substituted with a substituent selected from the group consisting of

hydrogen,
-NH_2,
C_1-C_7 aminocarbonyl,
-SO_2C_1-C_4 alkyl,
-SO_2C_1-C_4 haloalkyl,
-C(O)-NH_2,
C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of

halogen,
cyano,
hydroxyl,
acetylenyl,
C_1-C_4 alkoxy,

C_3-C_6 cycloalkyl,
-NH(C_1-C_4 alkyl),
-N(C_1-C_4 alkyl)$_2$,
-SC_1-C_4 alkyl,
-S(O)C_1-C_4 alkyl,
-SO_2C_1-C_4 alkyl,
-C(O)NH-C_3-C_6 cycloalkyl, and
-C(O)NH-C_1-C_6 haloalkyl;
C_3-C_6 cycloalkyl;
5- to 6-membered heteroaryl; and
phenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of
halogen,
C_1-C_4 alkyl,
cyano, and
hydroxyl; and
any S in the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl is substituted with 1 or 2 oxygen atom(s);
or a salt thereof.

(ag1) One embodiment relates to embodiment (ag) wherein W is a 4- to 7-membered heterocycloalkyl having 1 or 2 heteroatoms selected from the group O, S, N is selected from the group consisting or pyrrolyl, azetidinyl, 2-oxoazetidinyl, isoxazolidinyl, 2,6-diazaspiro[3.3]heptanyl, and 1,6-diazaspiro[3.3]heptanyl wherein the carbons of the 4- to 7-membered heterocycloalkyl are optionally substituted with 1 to 4 substituents independently selected from the group consisting of
halogen,
cyano,
nitro,
hydroxyl,
oxo,
C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of

halogen,
cyano, hydroxyl,
acetylenyl,
oxo,
C_1-C_4 alkoxy,
C_3-C_6 cycloalkyl,
-NH_2,
C_1-C_7 aminocarbonyl,
-NH(C_1-C_4 alkyl),
-N(C_1-C_4 alkyl)$_2$,
-SC_1-C_4 alkyl,
-S(O)C_1-C_4 alkyl,
-SO_2C_1-C_4 alkyl,
-C(O)NH-C_3-C_6 cycloalkyl,
-C(O)NH-C_1-C_6 alkyl,
and
-C(O)NH-C_1-C_6 haloalkyl;

and any N in the 4- to 7-membered heterocycloalkyl 4- to 7-membered heterocycloalkyl, valency permitting, is substituted with a substituent selected from the group consisting of

hydrogen,
-SO_2C_1-C_4 alkyl,
-SO_2C_1-C_4 haloalkyl,
-C(O)-NH_2,
C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of

halogen,
cyano,
hydroxyl,
acetylenyl,
C_1-C_4 alkoxy,
C_3-C_6 cycloalkyl,
-NH(C_1-C_4 alkyl),

-N(C_1-C_4 alkyl)$_2$,
-SC_1-C_4 alkyl,
-S(O)C_1-C_4 alkyl,
-SO_2C_1-C_4 alkyl,
-C(O)NH-C_3-C_6 cycloalkyl, and
-C(O)NH-C_1-C_6 haloalkyl; and

C_3-C_6 cycloalkyl;

or a salt thereof.

(ah) One embodiment relates to embodiments (ag) and (ag1) wherein the carbons of the 4- to 7-membered heterocycloalkyl is optionally substituted with 1 to 2 substituents independently selected from the group consisting of oxo and C_1-C_4 alkyl and any N in the 4- to 7-membered heterocycloalkyl, valency permitting, is substituted by hydrogen and C_1-C_4 alkyl optionally substituted with 1 to 3 halogen, cyano, acetylenyl, or C_3-C_6 cycloalkyl; or a salt thereof.

(ai) One embodiment relates to embodiments (ag), (ag1), and (ah) wherein the carbons of the 4- to 7-membered heterocycloalkyl are substituted with 1 oxo and any N in the 4- to 7-membered heterocycloalkyl, valency permitting, is substituted by C_1-C_4 alkyl substituted by 1 cyano; or a salt thereof.

(aj) One embodiment relates to embodiments (ag), (ag1), and (ah) wherein the carbons of the 4- to 7-membered heterocycloalkyl are substituted with 1 oxo and any N in the 4- to 7-membered heterocycloalkyl, valency permitting, is substituted by C_1-C_4 alkyl substituted with 1 to 3 halogens; or a salt thereof.

(ak) One embodiment relates to embodiments (ag), (ag1), and (ah) wherein the carbons of the 4- to 7-membered heterocycloalkyl are substituted with 1 oxo and any N in the 4- to 7-membered heterocycloalkyl, valency permitting, is substituted by C_1-C_4 alkyl substituted with 1 C_3-C_6 cycloalkyl; or a salt thereof.

(al) One embodiment relates to embodiments (ag), (ag1), and (ah) wherein any N in the 4- to 7-membered heterocycloalkyl, valency permitting, is substituted by C_1-C_4 alkyl substituted with 1 cyano; or a salt thereof.

(am) One embodiment relates to embodiments (ag), (ag1), and (ah) wherein any N in the 4- to 7-membered heterocycloalkyl, valency permitting, is substituted by C_1-C_4 alkyl substituted with 1 to 3 halogens; or a salt thereof.

(an) One embodiment relates to embodiments (ag), (ag1), and (ah) wherein any N in the 4- to 7-membered heterocycloalkyl, valency permitting, is substituted by C_1-C_4 alkyl substituted with 1 C_3-C_6 cycloalkyl; or a salt thereof.

(an1) One embodiment relates to embodiment (z) wherein W is a C_3-C_6 cycloalkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of

halogen,
cyano,
hydroxyl,
oxo,
C_1-C_4 alkoxy,
C_1-C_4 alkyl optionally substituted with 1 to 3 groups selected from the group consisting of halogen and cyano,
C_1-C_4 haloalkyl,
$-NH_2$,
C_1-C_7 aminocarbonyl,
$-NH(C_1$-C_4 alkyl),
$-N(C_1$-C_4 alkyl$)_2$,
$-SC_1$-C_4 alkyl,
$-S(O)C_1$-C_4 alkyl,
$-SO_2C_1$-C_4 alkyl,
$-C(O)NH$-C_3-C_6 cycloalkyl,
$-C(O)NH$-C_1-C_6 alkyl,
$-C(O)NH$-C_1-C_6 haloalkyl,
C_2-C_6 alkenyl optionally substituted with 1 to 3 halogens; and
C_2-C_6 alkynyl;

or a salt thereof.

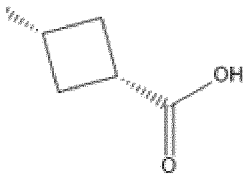
(ao) One embodiment relates to embodiments (1), (d), (e), (f), (h), (i), (j), (k), (l), (m), (n), (o), (p), (t), (x), and (y) wherein Y is C_1-C_6 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of

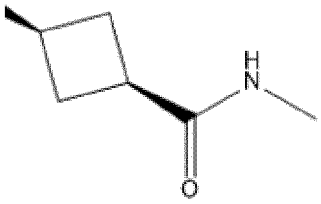
halogen,
cyano,

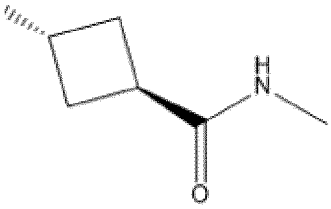
hydroxyl,
oxo,
C_3-C_6 cycloalkyl,
C_1-C_4 alkoxy,
acetylenyl,
-NH_2,
C_1-C_7 aminocarbonyl,
-NH(C_1-C_4 alkyl),
-N(C_1-C_4 alkyl)$_2$,
-SC_1-C_4 alkyl,
-S(O)C_1-C_4 alkyl,
-SO_2C_1-C_4 alkyl,
-C(O)NH-C_3-C_6 cycloalkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of
halogen,
hydroxyl,
cyano, and
C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of
halogen,
cyano,
hydroxyl,
C_1-C_4 alkoxy, and
-NH_2,
-C(O)NH-C_1-C_6 alkyl,
-C(O)NH-C_1-C_6 cyanoalkyl optionally substituted with 1 to 3 halogen,
-C(O)NH-C_1-C_6 haloalkyl;
or a salt thereof.

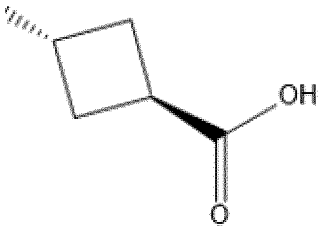
(ap) One embodiment relates to embodiment (ao) wherein Y is C_1-C_6 alkyl substituted with 1 -SO_2C_1-C_4 alkyl; or a salt thereof.

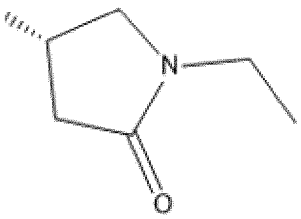
(aq) One embodiment relates to embodiment (ao) or (ap) wherein Y is C_1-C_6 alkyl substituted with 1 -SO_2CH_3; or a salt thereof.

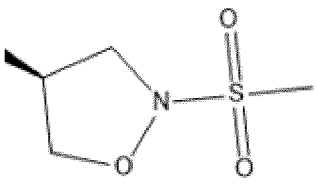
(ar) One embodiment relates to embodiment (z) wherein W is  .

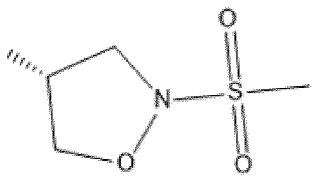
(as) One embodiment relates to embodiment (z) wherein W is  .

(at) One embodiment relates to embodiment (z) wherein W is  .

(au) One embodiment relates to embodiment (z) wherein W is  .

(as) One embodiment relates to embodiment (z) wherein W is  .

(at) One embodiment relates to embodiment (z) wherein W is  .

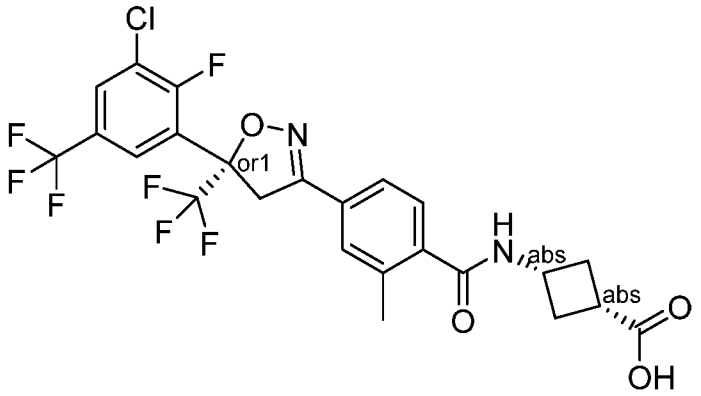
(au) One embodiment relates to embodiment (z) wherein W is  .

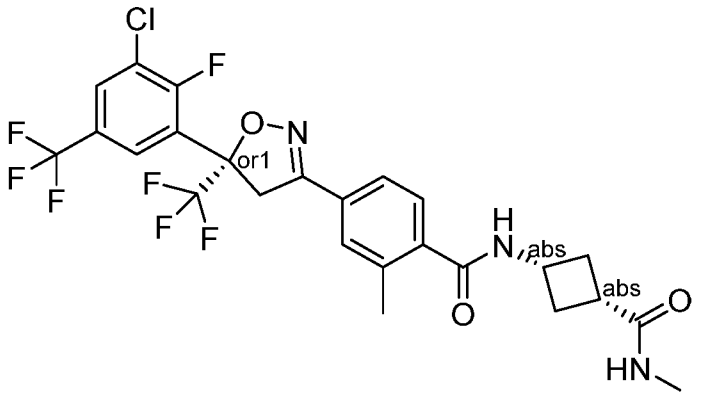
(xa) Another embodiment relates to each of the exemplified compounds or a salt thereof.
(xb) Another embodiement relates to each stereoisomer of each exemplified, depicted, or named compound; or a salt thereof.
(xc) Another embodiment relates to a salt of each of the exemplified compounds.

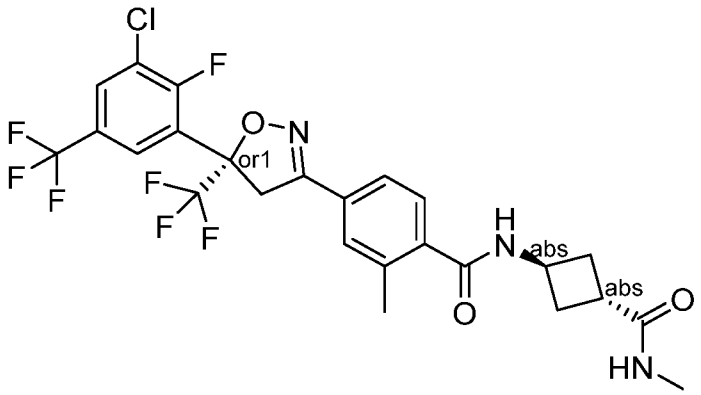
The compounds of the invention can be prepared by a variety of procedures many of which are already described in the art. For example, see WO 2005/085216, WO 2007/079162, US 2007/066617, US20130131017, WO 2009/002809, WO 2009/112275, WO 2010/003923, WO 2010/070068, WO 2012/120399, and WO 2013/079407.

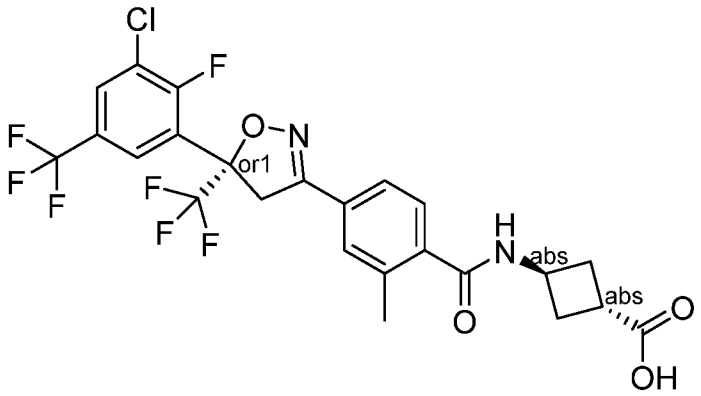
This present disclosure relates to compounds of formula (I) having extended half-lives. The compounds of formula (I) have either a trifluoromethyl group in the meta position or a halogen in the para and/or ortho position(s). Thus, the compounds of formula (I) include the following features: a trifluoromethyl group at one or both meta position(s); a halogen at ortho position; a halogen at each of the ortho and the para positions; or a halogen at each of the ortho positions and a trifluoromethyl at the para position. It is understood that the compounds of formula (I) may have other substituents, but the groups mentioned above are included. Without being bound to any particular theory the applicant believes that inhibition of metabolism at both of the ortho and the para position provide enhanced duration after oral administration or an injection.

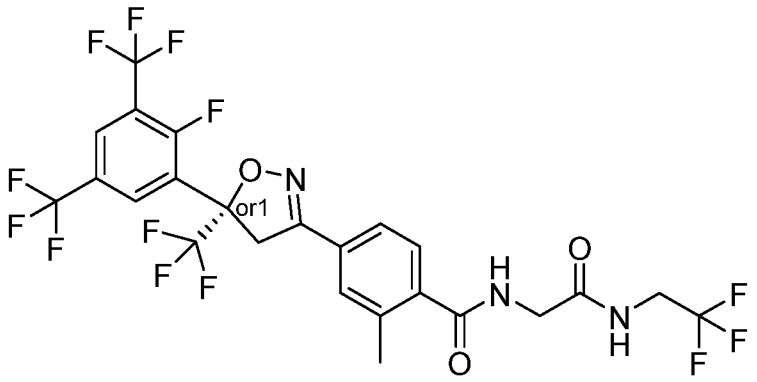
The following examples are intended to be illustrative and non-limiting, and represent specific embodiments of the present invention.

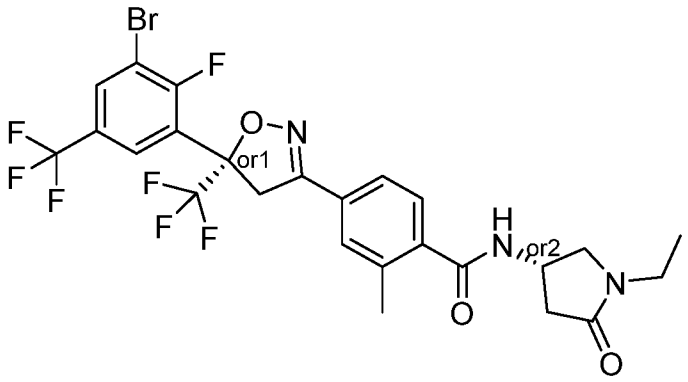


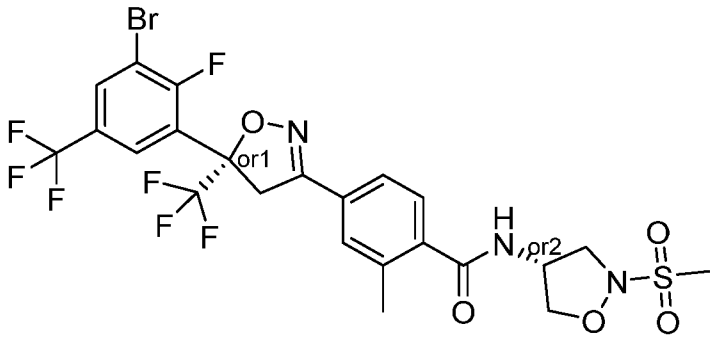








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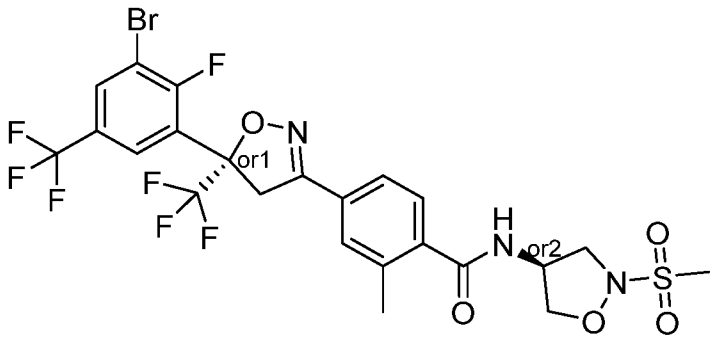
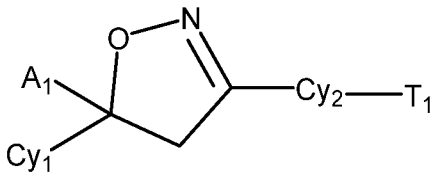


and each stereoisomer of the compounds above.

In another aspect, disclosed are compounds of formula (II), or a salt thereof,

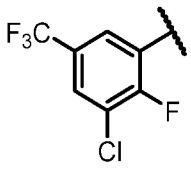
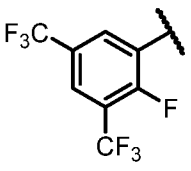
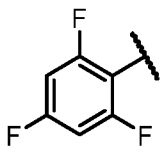
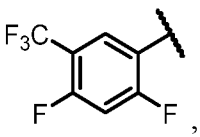
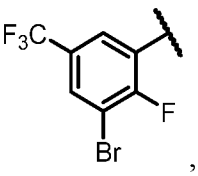


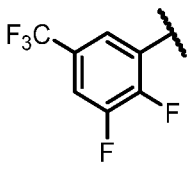
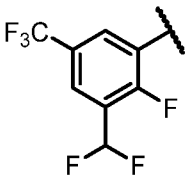
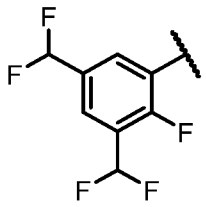
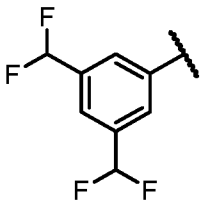
(II)

wherein,

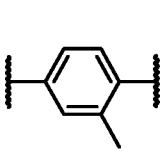
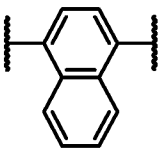
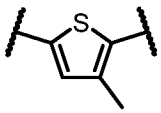
A_1 is $-CF_3$ or $-CHF_2$;

Cy_1 is selected from:

 ,  ,  ,  ,  ,

 ,  ,  , and  ;

Cy_2 is selected from:

 ,  , and  ; and

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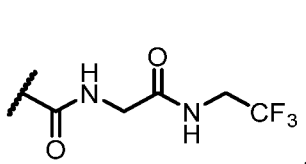
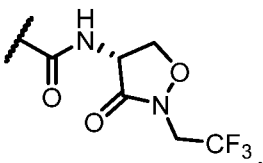
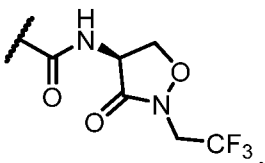
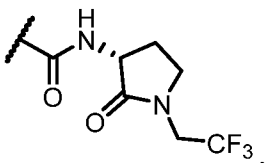
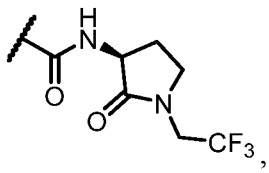
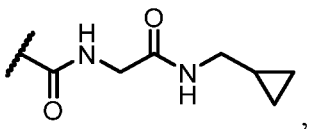
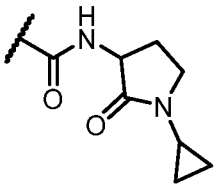
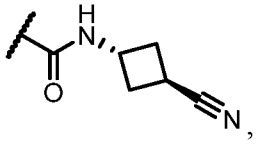
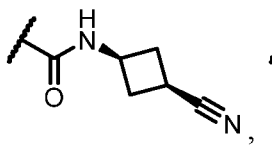
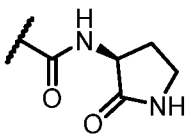
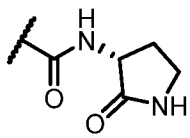
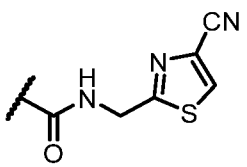
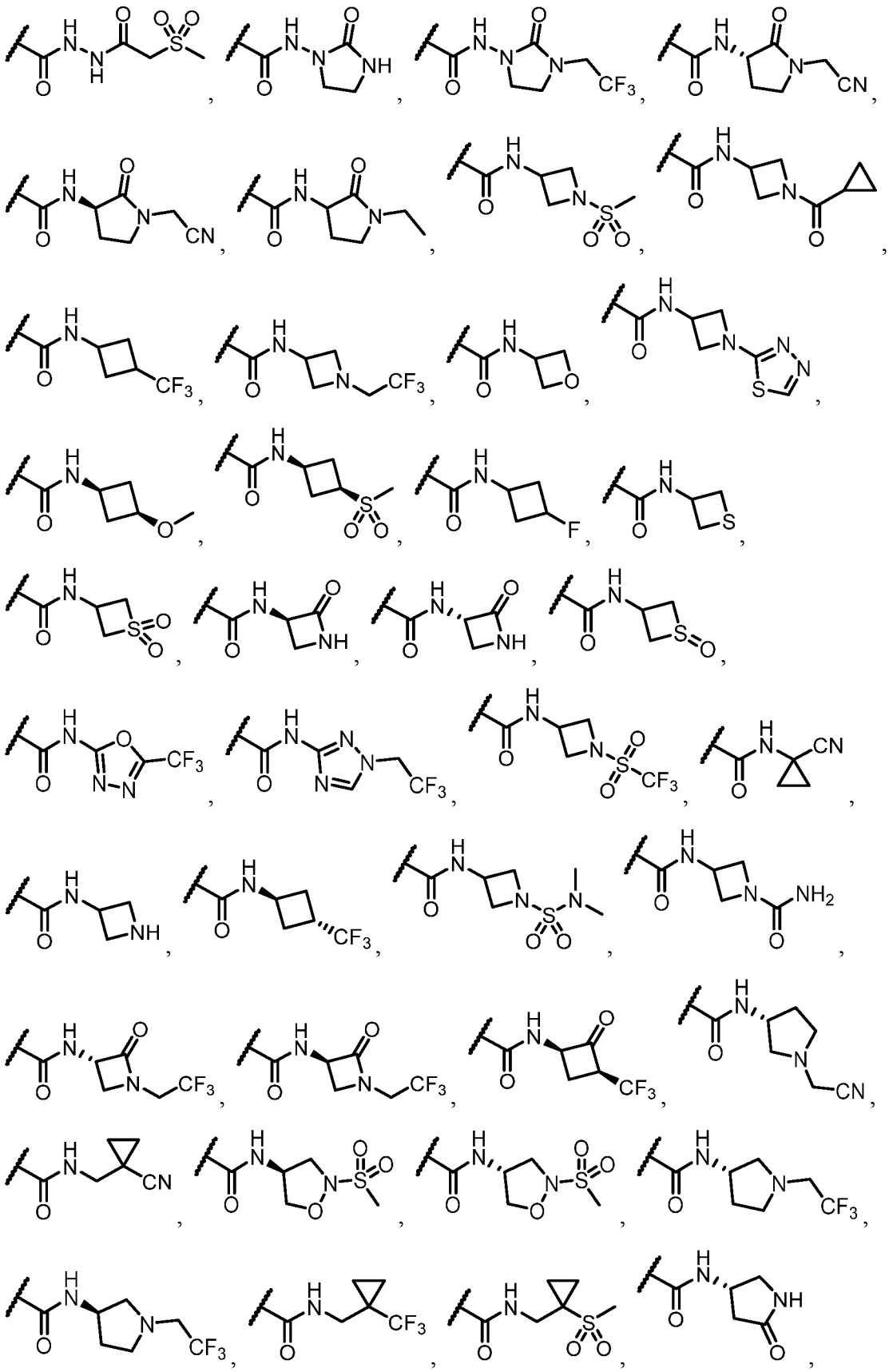
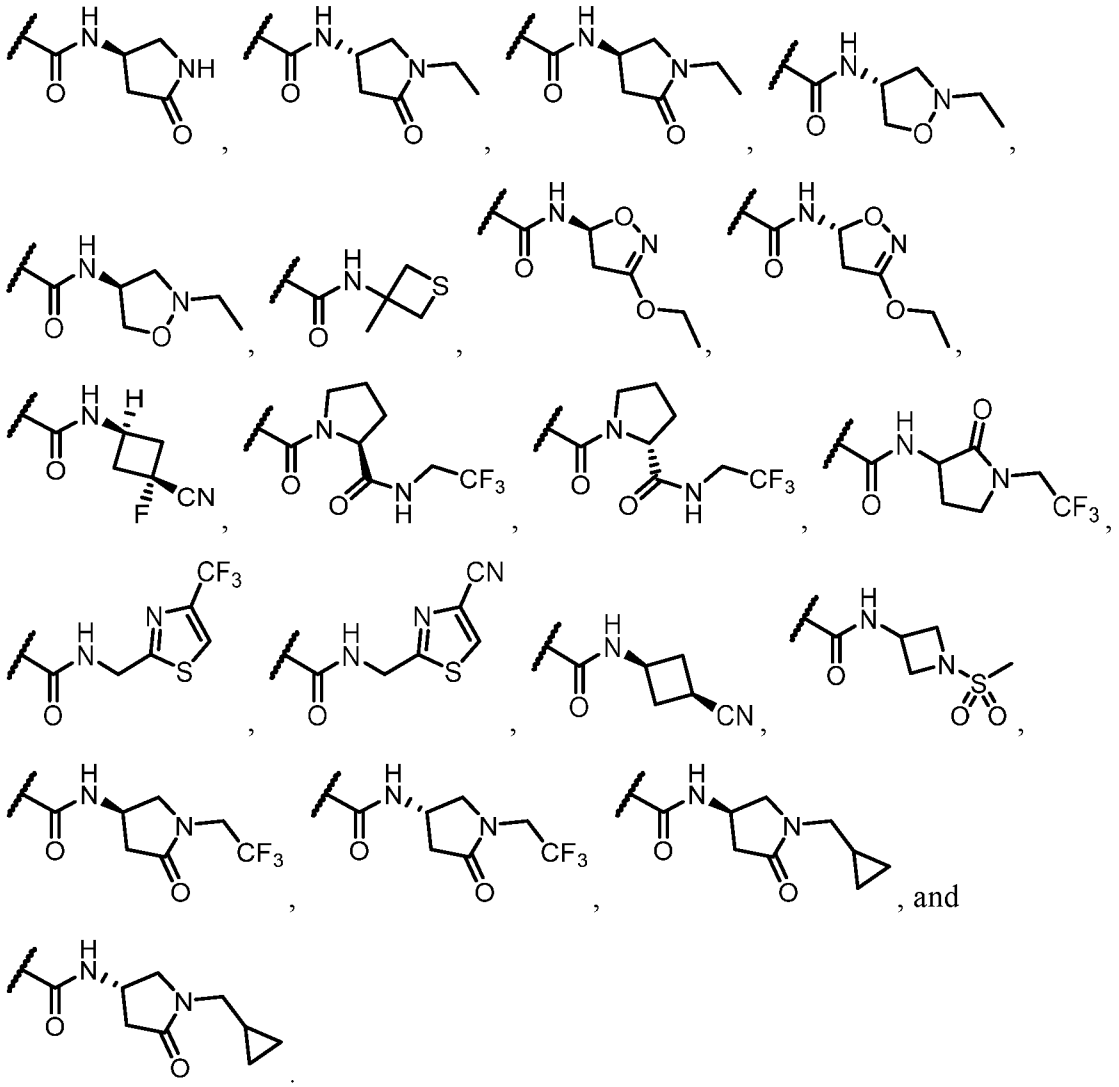
 ,  ,  ,  ,

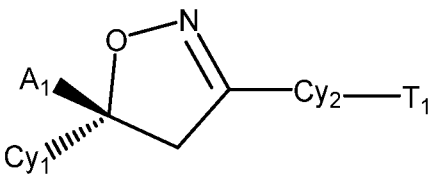
 ,  ,  ,  ,

 ,  ,  ,  ,





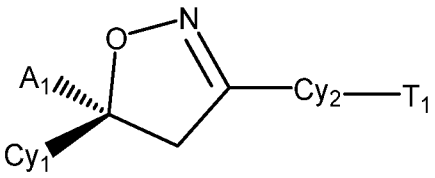
In an embodiment, disclosed are compounds of formula (IIa), or a salt thereof,



(IIa)

wherein A_1, Cy_1, Cy_2, and T_1 are as defined above.

In another embodiment, disclosed are compounds of formula (IIb), or a salt thereof,

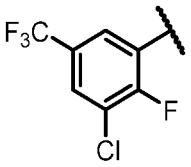


(IIb)

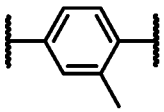
wherein A_1, Cy_1, Cy_2, and T_1 are as defined above.

In certain embodiments, A_1 in formulae (II), (IIa), or (IIb) is $-CF_3$.

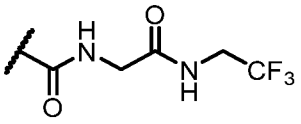
In certain embodiments, Cy_1 in formulae (II), (IIa), or (IIb) is



In certain embodiments, Cy_2 in formulae (II), (IIa), or (IIb) is



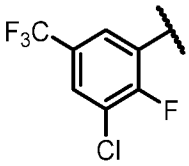
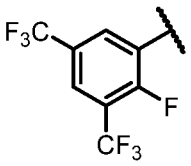
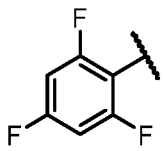
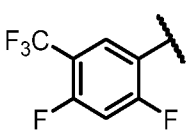
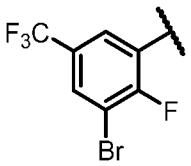
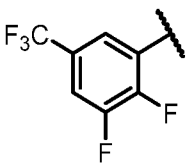
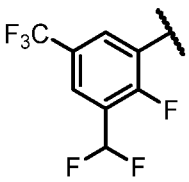
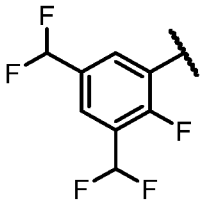
In certain embodiments, T_1 in formulae (II), (IIa), or (IIb) is



In certain embodiments, disclosed are compounds of formulae (II), (IIa), and (IIb), or a salt thereof, wherein

A_1 is $-CF_3$;

Cy_1 is selected from: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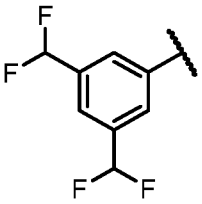
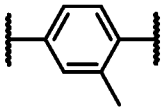
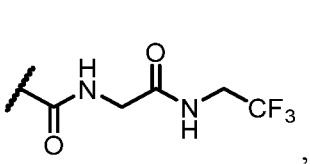
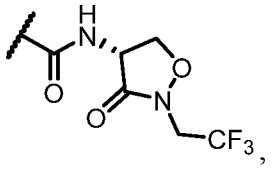
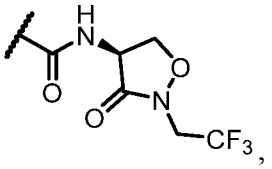
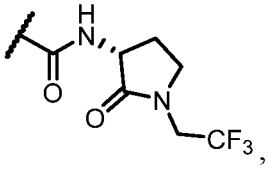
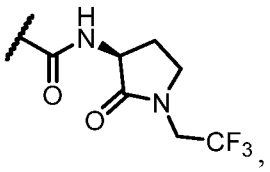
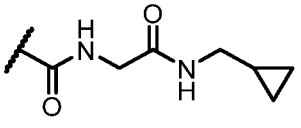
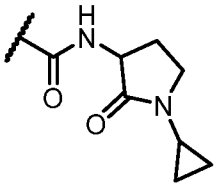
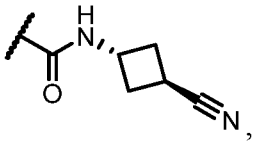
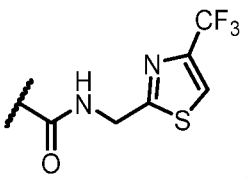
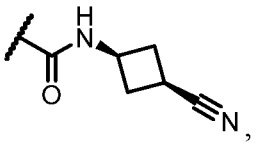
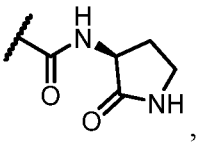
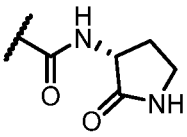
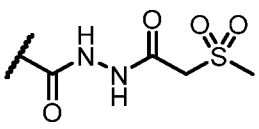
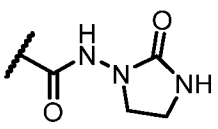
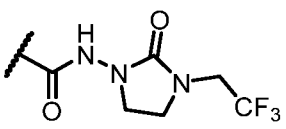
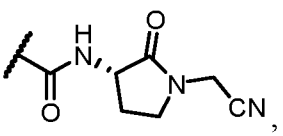
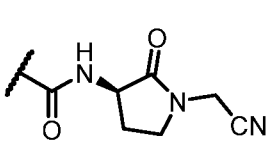
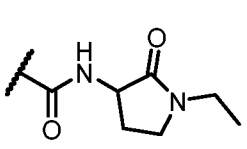
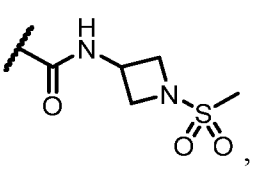
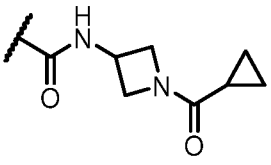

;

Cy_2 is


; and

T_1 is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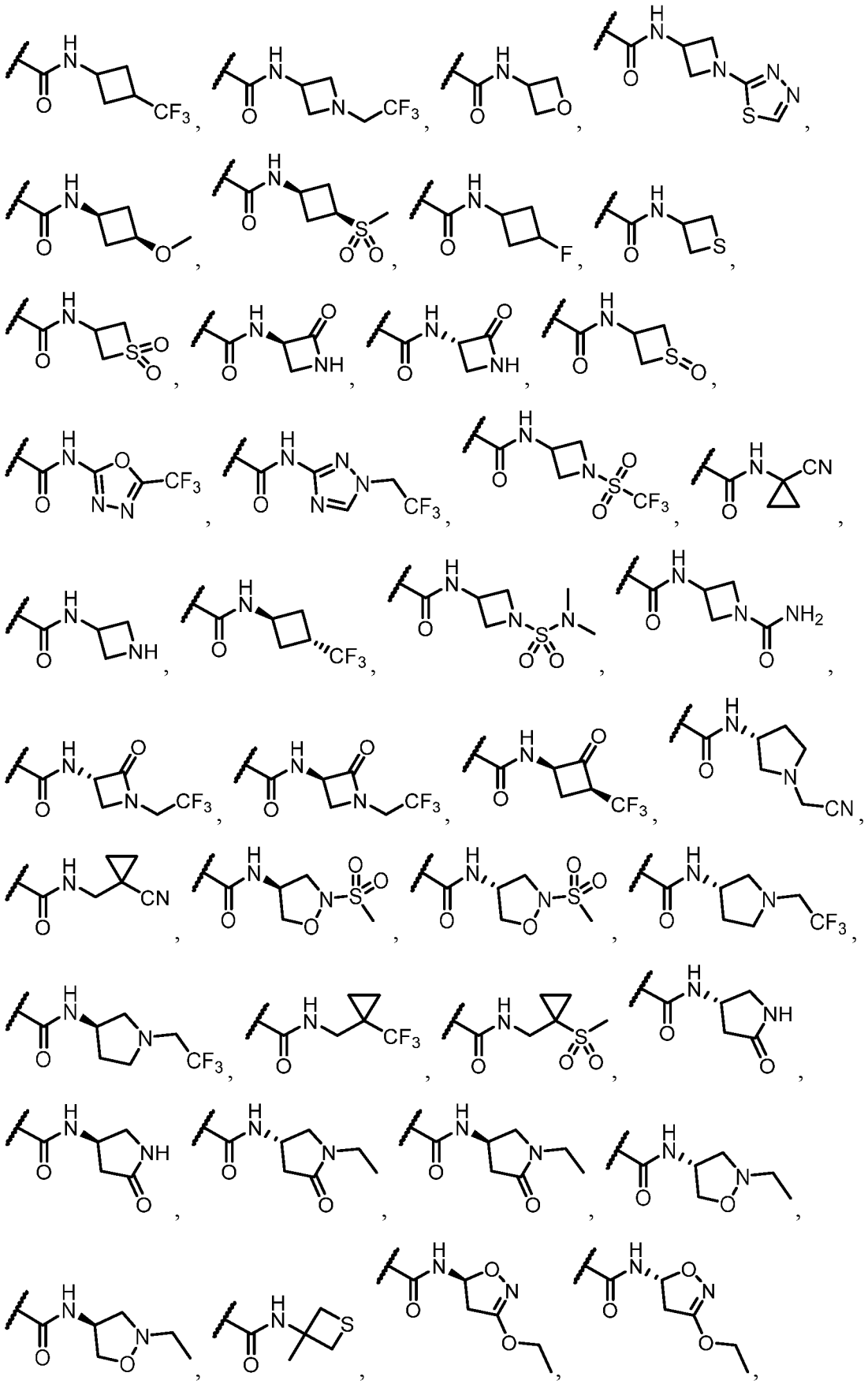
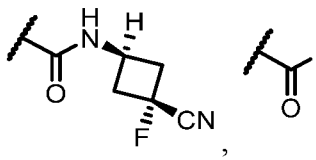
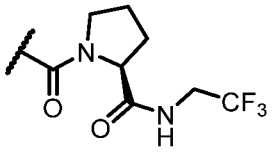
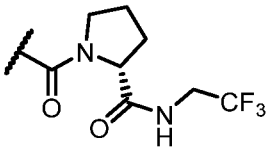
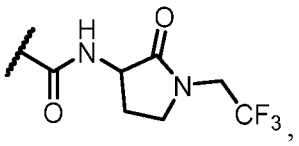
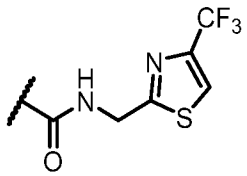
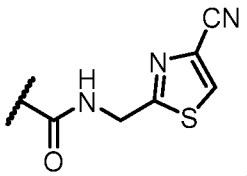
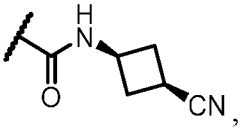
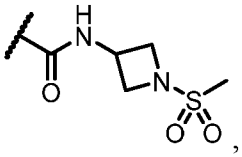
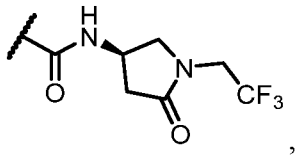
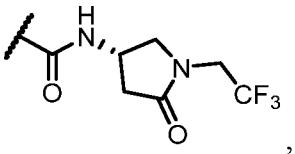
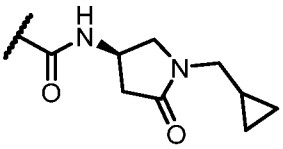
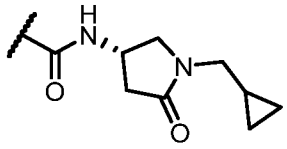
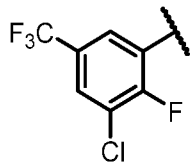


 ,  ,  ,  ,
 ,  ,  ,  ,
 ,  ,  , and
 .

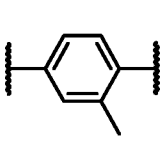
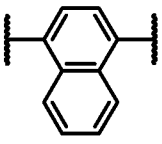
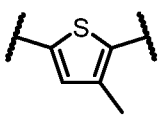
In certain embodiments, disclosed are compounds of formulae (II), (IIa), and (IIb), or a salt thereof, wherein

A_1 is $-CF_3$;

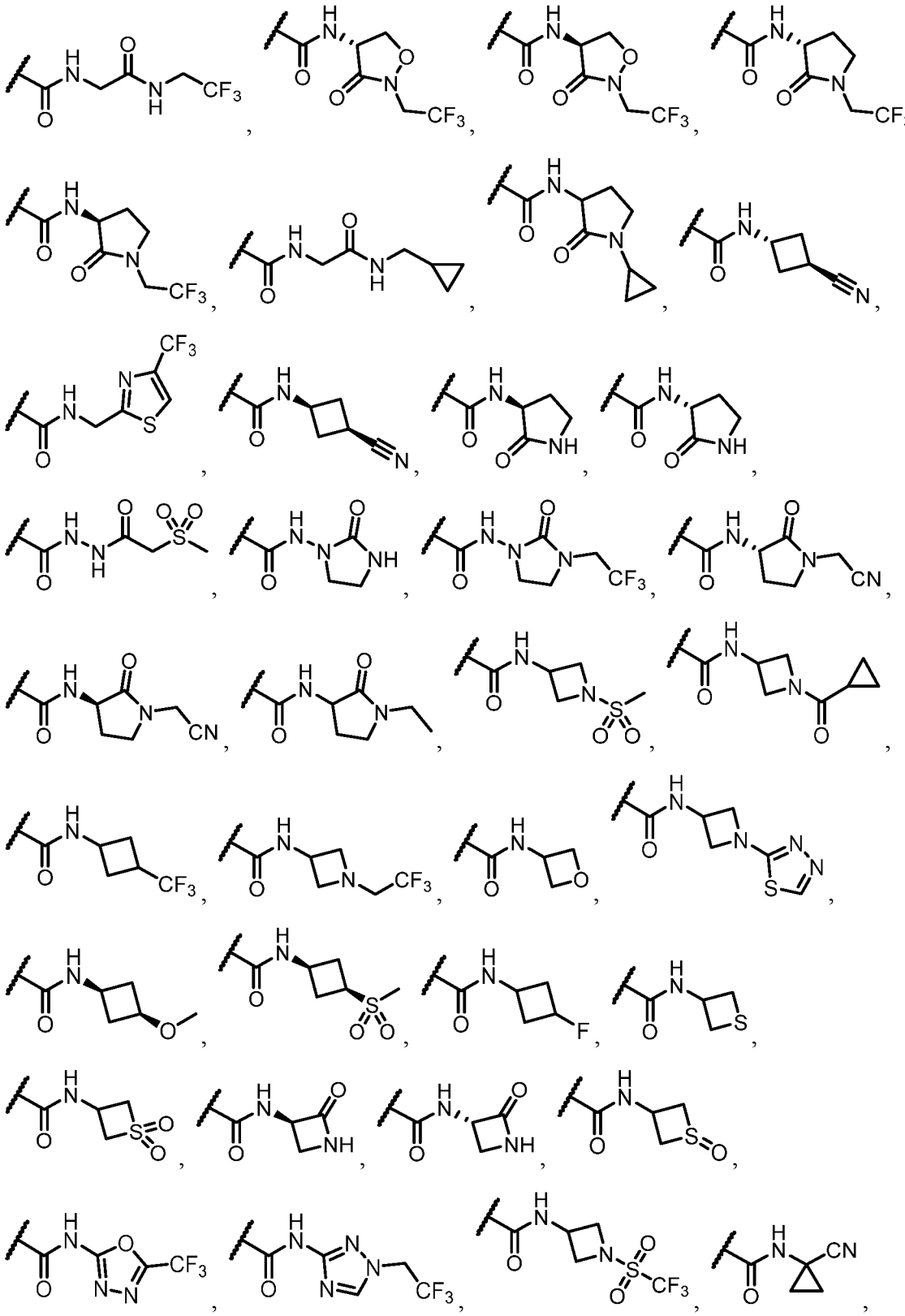
Cy_1 is

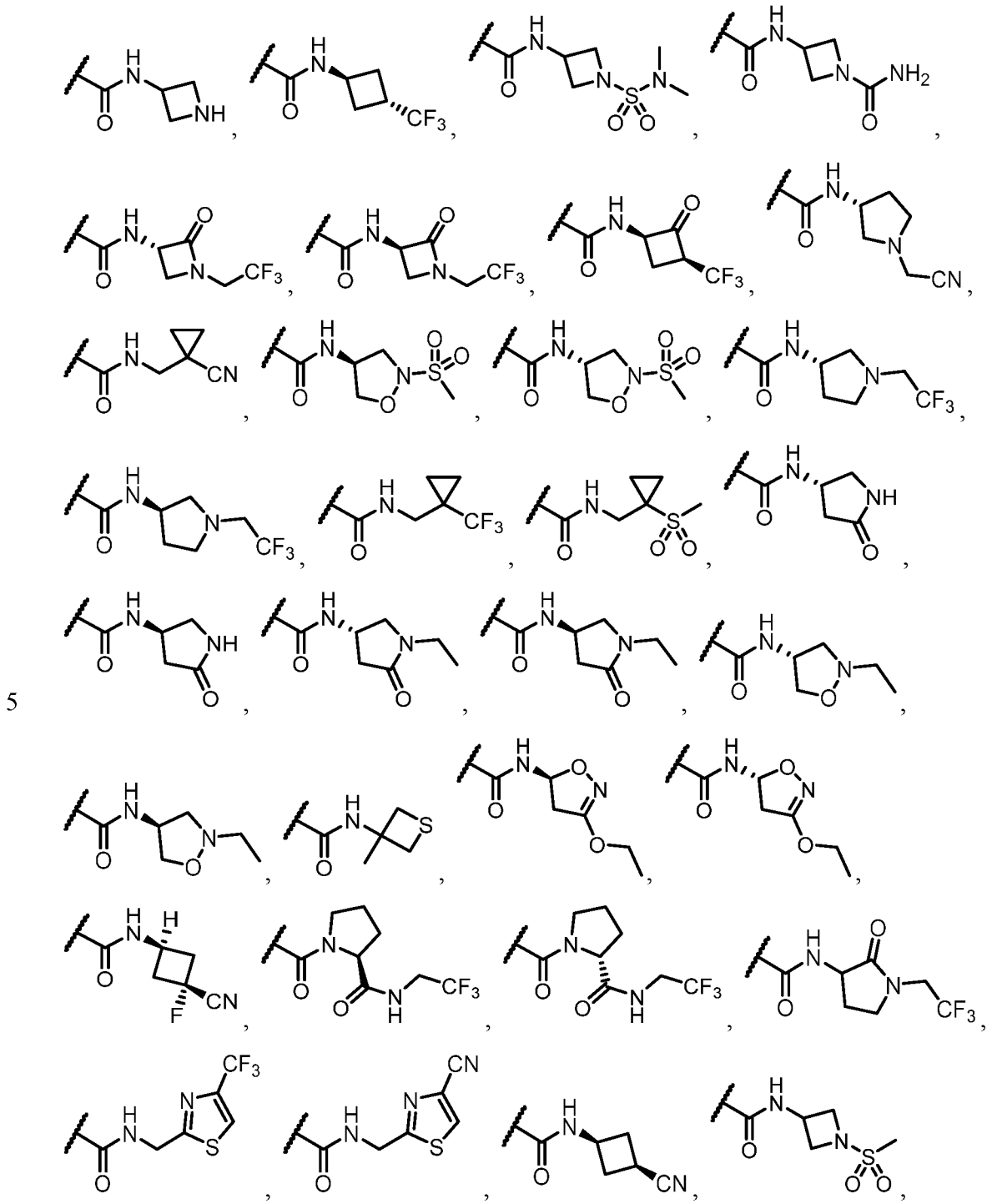
 ;

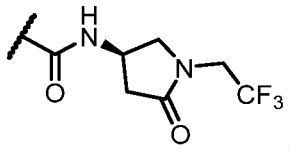
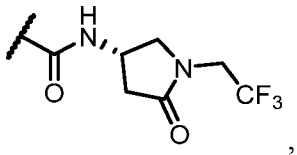
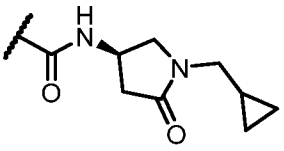
Cy_2 is selected from:

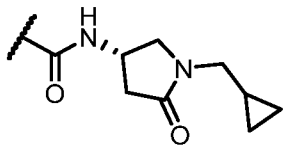
 ,  , and  ; and

T_1 is





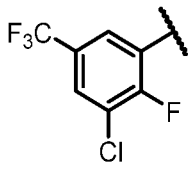
 ,  ,  , and

 .

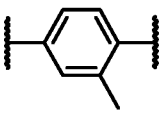
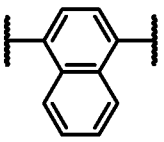
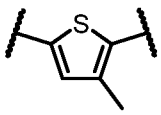
In certain embodiments, disclosed are compounds of formulae (II), (IIa), and (IIb), or a salt thereof, wherein

A_1 is $-CF_3$;

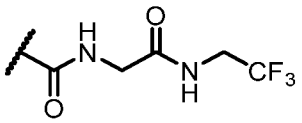
Cy_1 is

 ;

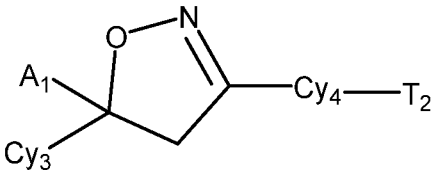
Cy_2 is selected from:

 ,  , and  ; and

T_1 is

 .

In another aspect, disclosed are compounds of formula (III), or a salt thereof,

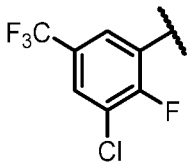
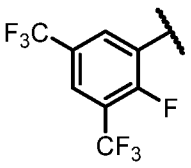
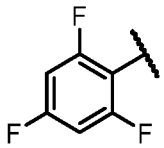
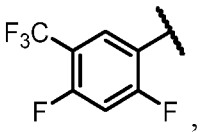
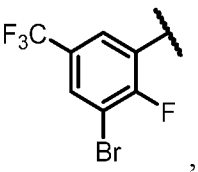


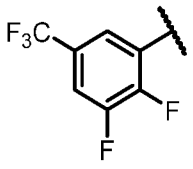
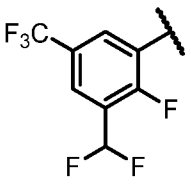
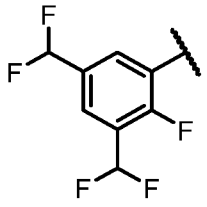
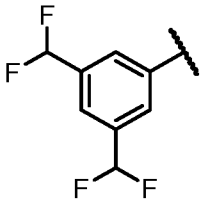
(III)

wherein,

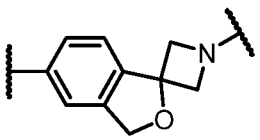
A_1 is $-CF_3$ or $-CHF_2$;

Cy_3 is selected from:

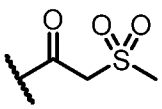
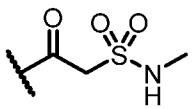
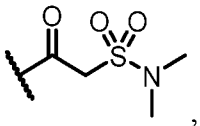
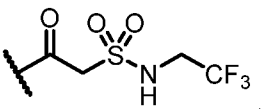
 ,  ,  ,  ,  ,

 ,  ,  , and  ;

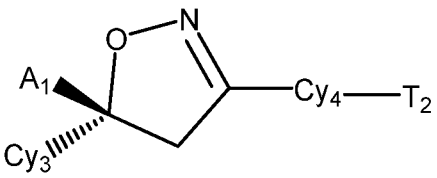
Cy_4 is:

 ; and

T_2 is selected from:

 ,  ,  , and  .

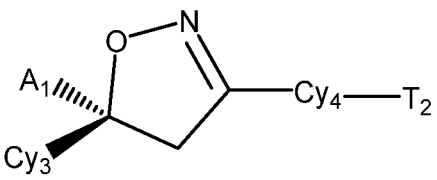
In an embodiment, disclosed are compounds of formula (IIIa), or a salt thereof,



(IIIa)

wherein A_1, Cy_3, Cy_4, and T_2 are as defined above.

In another embodiment, disclosed are compounds of formula (IIIb), or a salt thereof,

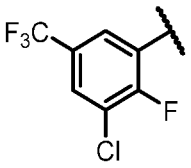


(IIIb)

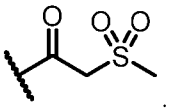
wherein A_1, Cy_3, Cy_4, and T_2 are as defined above.

In certain embodiments, A_1 in formulae (III), (IIIa), or (IIIb) is $-CF_3$.

In certain embodiments, Cy_3 in formulae (III), (IIIa), or (IIIb) is



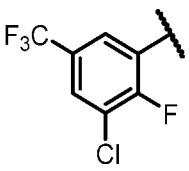
In certain embodiments, T_2 in formulae (III), (IIIa), or (IIIb) is



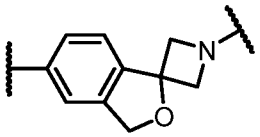
In certain embodiments, disclosed are compounds of formulae (III), (IIIa), and (IIIb), or a salt thereof, wherein

A_1 is $-CF_3$;

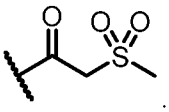
Cy_3 is


;

Cy_4 is selected from:


; and

T_3 is



The following examples are intended to be illustrative and non-limiting, and represent specific embodiments of the present invention.

Analyses were performed using a Waters Acquity UPLC Liquid Chromatography (LC) system, coupled to a Waters SQ Detector 2 single quadrupole mass spectrometry (MS) detector. The UV (DAD) acquisition was performed with a scan range of 200-400 nm (by 1.2nm resolution). The MS was operated with an electro-spray ionization source (ESI) in both positive and negative ion mode. Capillary Voltage 3.50 (kV), Cone Voltage 35 (V), and Desolvation Temperature of 550 °C. Desolvation gas flow 1000 (L/Hr), Cone gas flow 50 (L/Hr). The MS acquisition range was set to 100-1500 *m/z* . MS scan cycle time was 0.5 s. Data acquisition was performed with Waters Masslynx software.

Method A: Analyses were carried out on an Acquity UPLC BEH C18 column of 50 mm length, 2.1 mm internal diameter and 1.7 µm particle size. The mobile phase used was: A= water with 0.1% formic acid / B= CH_3CN with 0.1% formic acid.

Method B: Analyses were carried out on an Acquity UPLC BEH C18 column of 50 mm length, 2.1 mm internal diameter and 1.7 µm particle size. The mobile phase used was: A= water with 0.1% formic acid / B= CH_3CN.

Method C: Analyses were carried out on an Acquity UPLC BEH C18 column of 50 mm length, 2.1 mm internal diameter and 1.7 µm particle size. The mobile phase used was: A= water with 10 mM ammonium acetate / B= CH_3CN.

Analysis were performed using an Ultra High Performance Liquid Chromatography (UHPLC) system (Make- Thermo Scientific), coupled with an Ion trap mass analyzer. The UV acquisition was performed with a scan range of 200-400 nm (by 1nm resolution). The MS was operated with an electro-spray ionization source (ESI) in both positive & negative ion mode, with sheath gas flow rate(arb): 40, Aux gas flow rate (arb): 20, sweep gas flow rate(arb): 1, spray voltage (kv): 5, capillary temp (◦C): 350 ,capillary voltage (V):30 ,tube lens (V): positive mode 30 and negative mode -30. The MS acquisition range was set to 100-2000 *m/z*. MS scan cycle time was 3 micro scans. Data acquisition was performed with Xcalibur software.

Method D: Analyses were carried out on Ascentis Express C18 of 5cm length, 2.1 mm internal diameter and 2.7µm particle size. The mobile phase used was: A= water with 0.1% formic acid / B= 100% CH_3CN.

Analyses were performed using a Liquid Chromatography (LC) system, coupled to a quadrupole mass spectrometry (MS) detector. The UV (DAD) acquisition was performed with a scan range of 200-400 nm.

LC-MS, Analytical Method E:

Instrument: SHIMADZU LCMS - UFLC 20-AD - LCMS 2020 MS detector; Column: Ascentis Express C18 2.7 µm, 50 x 3.0 mm; eluent A: water + 0.05 vol % trifluoroacetic acid, eluent B: CH_3CN + 0.05 vol % trifluoroacetic acid.

LC-MS, Analytical Method F:

Instrument: SHIMADZU LCMS - UFLC 20-AD - LCMS 2020 MS detector; Column: Kinetex EVO C18 2.6 µm, 50 x 3.0 mm; eluent A: water + 0.05 vol % ammonium hydrogencarbonate, eluent B: CH_3CN.

As used herein: aq. refers to aqueous, br refers to broad, CH_3CN refers to acetonitrile, d refers to doublet, dd refers to doublet of doublet, DCM refers to dichloromethane, DCE refers to dichloroethane, DIPEA refers to N-diisopropylethylamine, DMF refers to N,N-dimethylformamide, DMSO refers to dimethylsulfoxide, ee: refers to enantiomeric excess, ES refers to electrospray ionization, EtOAc refers to ethyl acetate, h refers to hour(s), HATU refers to 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate, HPLC refers to high performance liquid chromatography, iPrOH refers to isopropanol, J refers to coupling constant, LCMS refers to liquid chromatography – mass spectrometry, *m/z*: refers to mass-to-charge ratio, M refers to molarity, m refers to multiplet, MeOH refers to methanol, min refers to minutes, $NaHCO_3$ refers to sodium bicarbonate, Na_2CO_3 refers to sodium carbonate, NEt_3 refers to triethylamine, NMR refers to nuclear magnetic resonance, q refers to quartet, quint refers to quintet, rt refers to room temperature, R_t refers to retention time, s refers to singlet, sat.

refers to saturated, T refers to temperature, t refers to triplet, td refers to triplet of doublets, THF refers to tetrahydrofuran, wt refers to weight, and δ refers to chemical shift.

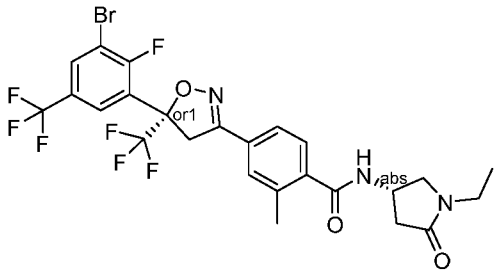
4-((*R**)-5-(3-bromo-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-((*S*)-1-ethyl-5-oxopyrrolidin-3-yl)-2-methylbenzamide

(Example 1.1)

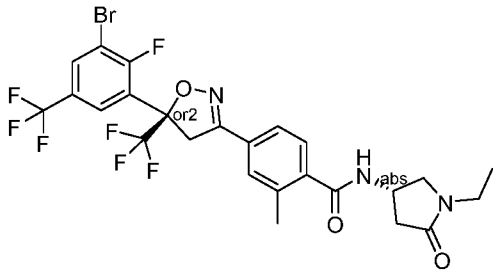
and

4-((*S**)-5-(3-bromo-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-((*S*)-1-ethyl-5-oxopyrrolidin-3-yl)-2-methylbenzamide

(Example 1.2)



and



To a stirred solution of 2-[3-bromo-2-fluoro-5-(trifluoromethyl)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.3 g, 3.5 mmol) in THF (15 mL) and water (7.5 mL) was added dipotassium carbonate (1.02 g, 7.38 mmol) and the mixture was degassed with N_2-gas for 10 min. 2-Bromo-3,3,3-trifluoro-prop-1-ene (0.76 g, 4.3 mmol) and bis(triphenylphosphine)palladium(II) dichloride (0.25 g, 0.36 mmol) were added and the reaction mixture was heated at 80°C for 3 h. Then, the mixture was allowed to cool to rt and was extracted with diethyl ether (2x10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford 1-bromo-2-fluoro-5-(trifluoromethyl)-3-[1-(trifluoromethyl)vinyl]benzene as brown liquid, which was immediately used in the next step without further purification.

To a stirred solution of methyl 4-(hydroxyiminomethyl)-2-methyl-benzoate (500 mg, 2.59 mmol) in DMF (5 mL) was added N-chlorosuccinimide (0.45 g, 3.4 mmol) at rt and the mixture was heated at 40°C for 10 min. Then, the mixture was cooled to 0°C and 1-bromo-2-fluoro-5-(trifluoromethyl)-3-[1-(trifluoromethyl)vinyl]benzene (1.05 g, 3.12 mmol) was added followed by NEt_3 (0.40 mL, 2.85 mmol) and the reaction was stirred at rt for 3 h. The reaction mixture was quenched by adding water (10 mL) and extracted with EtOAc (30 mL) The organic layer was washed with brine (3x 15 mL), dried over

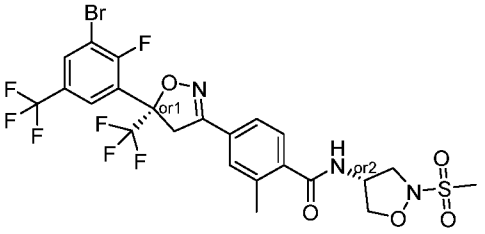
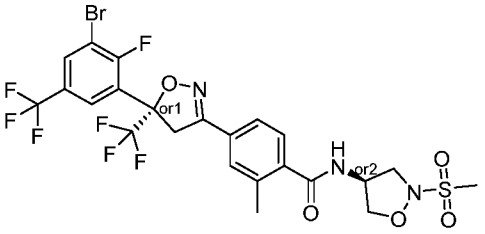
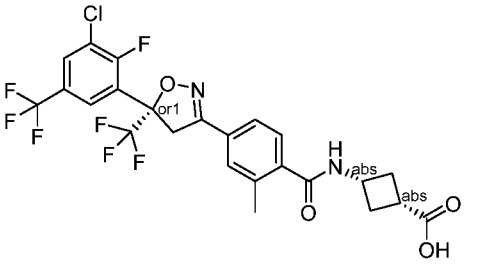
anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (0-20% EtOAc in petroleum ether) to afford methyl 4-[5-[3-bromo-2-fluoro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4H-isoxazol-3-yl]-2-methyl-benzoate as beige semisolid. LC-MS (method A) R_t= 2.78 min, *m/z*= 528.1 $[M+H]^+$.

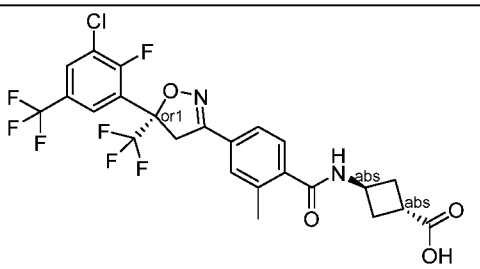
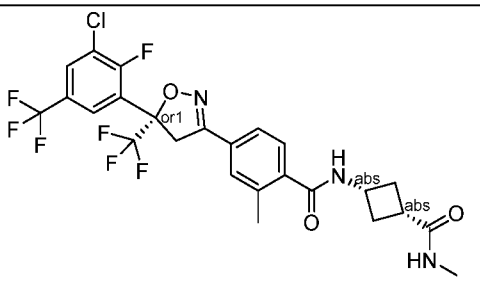
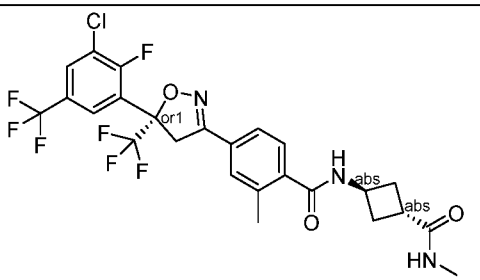
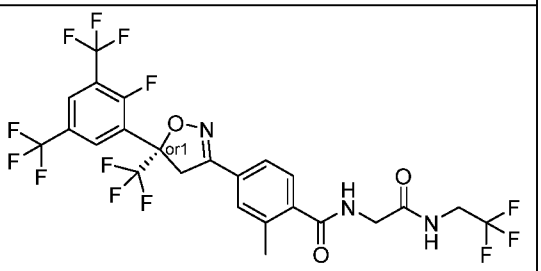
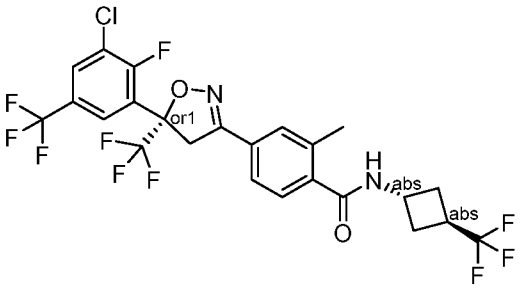
To a stirred solution of methyl 4-[5-[3-bromo-2-fluoro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4H-isoxazol-3-yl]-2-methyl-benzoate (500 mg, 0.9 mmol) in THF (5 mL) and water (5 mL) was added lithiumhydroxide monohydrate (0.12 g, 2.9 mmol) at rt and the mixture was heated at 60°C for 16 h. Then, the mixture was allowed to cool to rt and the solvent was evaporated under reduced pressure. The residue was dissolved in water (5 mL), acidified to pH ~2-3 with an HCl solution (1M) and extracted with EtOAc (2x 25 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford 4-[5-[3-bromo-2-fluoro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4H-isoxazol-3-yl]-2-methyl-benzoic acid as a beige solid. LC-MS (method D) R_t= 2.74 min, *m/z*= 514.3 $[M+H]^+$.

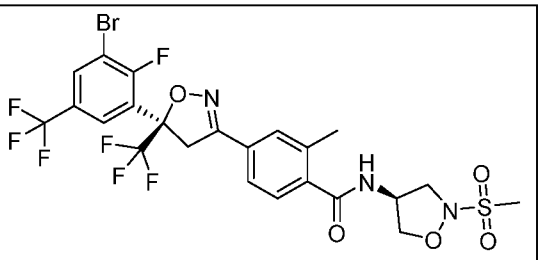
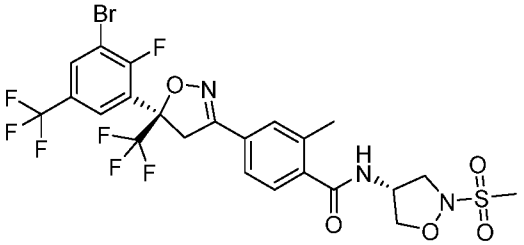
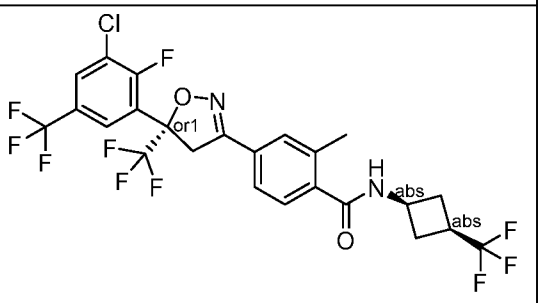
To a stirred solution of 4-[5-[3-bromo-2-fluoro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4H-isoxazol-3-yl]-2-methyl-benzoic acid (0.31 g, 0.60 mmol) and (*S*)-4-amino-1-ethylpyrrolidin-2-one·HCl (121 mg, 0.73 mmol) in DMF (5 mL) was added HATU (0.28 g, 0.74 mmol) followed by DIPEA (0.32 mL, 1.8 mmol) at rt and the mixture was stirred for 2 h. The reaction mixture was quenched by adding water (5 mL) and was extracted with EtOAc (3x 15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford the title compound. LC-MS (method B) R_t= 2.26 min, *m/z*= 624.1 $[M+H]^+$. ^1H NMR (DMSO-d6, 400 MHz) δ 8.77 (d, J = 6.8 Hz, 1 H), 8.45-8.40 (m, 1 H), 7.96-7.91 (m, 1 H), 7.68-7.61 (m, 2 H), 7.42 (d, J = 8.0 Hz, 1 H), 4.55 (d, J = 18 Hz, 1 H), 4.53-4.47 (m, 1 H), 4.38 (d, J = 18 Hz, 1 H), 3.72 (dd, J = 10, 7.2 Hz, 1 H), 3.29-3.17 (m, 3 H), 2.68-2.61 (m, 1 H), 2.37 (s, 3 H), 2.34-2.25 (m, 1 H), 1.03 (t, J = 7.2 Hz, 3 H).

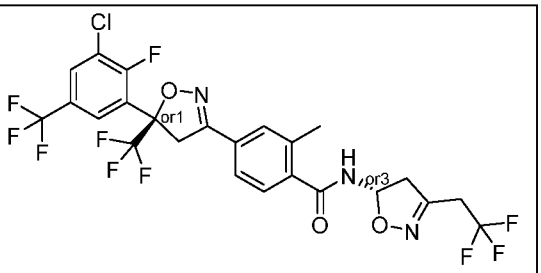
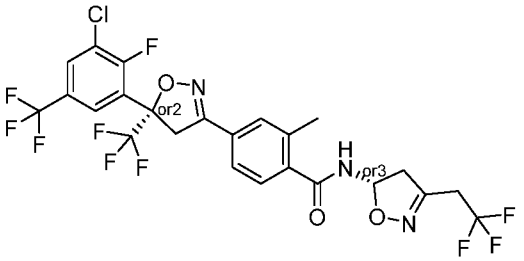
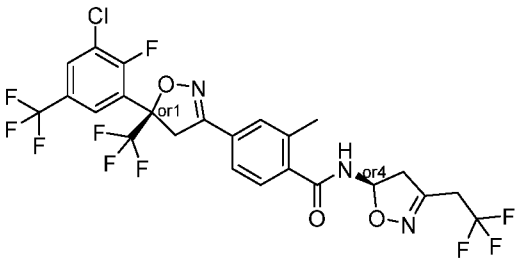
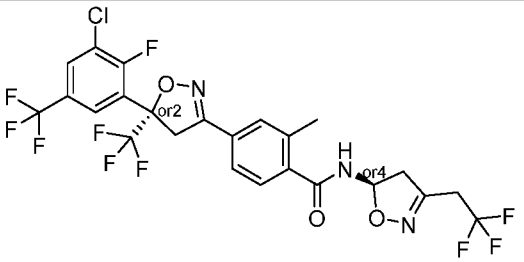
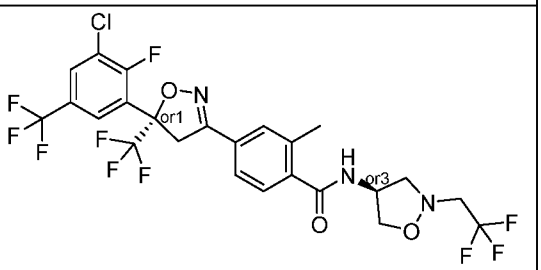
The two enantiomers were separated by SFC. The separation was performed on Chiralcel-OJ-H with column dimensions of 250 mm × 30 mm (5 µm), a flow rate of 95.0 g/min, and a CO_2-based mobile phase with 10% *i*PrOH containing 0.2% N,N-isopropylamine as additive to give Example 1.1: 4-((*R**)-5-(3-bromo-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-((*S*)-1-ethyl-5-oxopyrrolidin-3-yl)-2-methylbenzamide and Example 1.2: 4-((*S**)-5-(3-bromo-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-((*S*)-1-ethyl-5-oxopyrrolidin-3-yl)-2-methylbenzamide

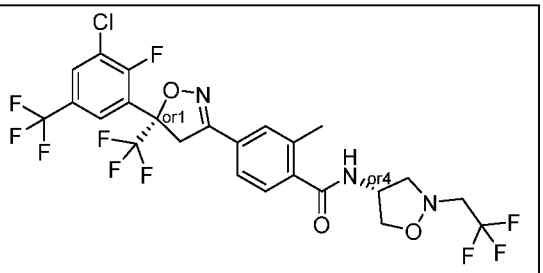
The following compounds were prepared analogously by the methodology of Examples 1.1 and 1.2:

Ex.	Name	Structure
1.3	4-(rel-(*S*)-5-(3-bromo-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methyl-N-(rel-(*S*)-2-(methylsulfonyl)isoxazolidin-4-yl)benzamide	
1.4	4-(rel-(*S*)-5-(3-bromo-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methyl-N-(rel-(*R*)-2-(methylsulfonyl)isoxazolidin-4-yl)benzamide	
2.1	*cis*-3-(4-((S*)-5-(3-chloro-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methylbenzamido)cyclobutane-1-carboxylic acid	

2.2	*trans*-3-(4-((S*)-5-(3-chloro-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methylbenzamido)cyclobutane-1-carboxylic acid	
2.3	4-((S*)-5-(3-chloro-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methyl-N-(*cis*-3-(methylcarbamoyl)cyclobutyl)benzamide	
2.4	4-((S*)-5-(3-chloro-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methyl-N-(*trans*-3-(methylcarbamoyl)cyclobutyl)benzamide	
3.1	rel-(S)-4-(5-(2-fluoro-3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methyl-N-(2-oxo-2-((2,2,2-trifluoroethyl)amino)ethyl)benzamide	
1.5	4-((S*)-5-(3-chloro-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methyl-N-((trans)-3-(trifluoromethyl)cyclobutyl)benzamide	

1.6	4-(rel-(R)-5-(3-bromo-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methyl-N-(rel-(S)-2-(methylsulfonyl)isoxazolidin-4-yl)benzamide	
1.7	4-(rel-(R)-5-(3-bromo-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methyl-N-(rel-(R)-2-(methylsulfonyl)isoxazolidin-4-yl)benzamide	
1.8	4-((S*)-5-(3-chloro-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methyl-N-((cis)-3-(trifluoromethyl)cyclobutyl)benzamide	

1.9	rel-4-((R)-5-(3-chloro-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methyl-N-((S*)-3-(2,2,2-trifluoroethyl)-4,5-dihydroisoxazol-5-yl)benzamide	
1.10	rel-4-((S)-5-(3-chloro-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methyl-N-((S*)-3-(2,2,2-trifluoroethyl)-4,5-dihydroisoxazol-5-yl)benzamide	
1.11	rel-4-((R)-5-(3-chloro-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methyl-N-((R*)-3-(2,2,2-trifluoroethyl)-4,5-dihydroisoxazol-5-yl)benzamide	
1.12	rel-4-((S)-5-(3-chloro-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methyl-N-((R*)-3-(2,2,2-trifluoroethyl)-4,5-dihydroisoxazol-5-yl)benzamide	
1.13	rel-4-((S)-5-(3-chloro-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methyl-N-((R*)-2-(2,2,2-trifluoroethyl)isoxazolidin-4-yl)benzamide	

1.14	rel-4-((S)-5-(3-chloro-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methyl-N-((S3)-2-(2,2,2-trifluoroethyl)isoxazolidin-4-yl)benzamide	

Experimental details for compounds in the tables:

Ex.	LC-MS	^{1}H NMR
1.3	LC-MS (method B) R_t= 2.37 min, *m/z*= 662.3 $[M+H]^+$	^{1}H NMR (DMSO-d6, 400 MHz) δ 8.90 (d, J = 6.0 Hz, 1 H), 8.45-8.41 (m, 1 H), 7.96-7.91 (m, 1 H), 7.69-7.62 (m, 2 H), 7.46 (d, J = 8.0 Hz, 1 H), 4.95-4.86 (m, 1 H), 4.56 (d, J = 18 Hz, 1 H), 4.42-4.30 (m, 2 H), 4.08-4.00 (m, 2 H), 3.46 (dd, J = 12, 4.8 Hz, 1 H), 3.20 (s, 3 H), 2.38 (s, 3 H).
1.4	LC-MS (method B) R_t= 2.37 min, *m/z*= 662.3 $[M+H]^+$	^{1}H NMR (DMSO-d6, 400 MHz) δ 8.90 (d, J = 6.0 Hz, 1 H), 8.45-8.41 (m, 1 H), 7.95-7.91 (m, 1 H), 7.69-7.62 (m, 2 H), 7.46 (d, J = 8.0 Hz, 1 H), 4.94-4.86 (m, 1 H), 4.56 (d, J = 18 Hz, 1 H), 4.42-4.30 (m, 2 H), 4.08-4.00 (m, 2 H), 3.46 (dd, J = 12, 4.8 Hz, 1 H), 3.20 (s, 3 H), 2.38 (s, 3 H).
1.5	LC-MS (method C) R_t= 2.63 min, *m/z*= 591.1 $[M+H]^+$	1H NMR (400 MHz, DMSO-d6): δ 8.78 (d, J = 7.2 Hz, 1 H), 8.37-8.33 (d, 1 H), 7.92-7.88 (d, 1 H), 7.67-7.63 (m, 2 H), 7.44 (d, J = 7.6 Hz, 1 H), 4.61-4.35 (m, 3 H), 3.16-3.06 (m, 1 H), 2.47-2.35 (m, 7 H).
1.6	LC-MS (method B) R_t= 2.37 min, *m/z*= 662 $[M+H]^+$	1H NMR (DMSO-d6, 400 MHz) δ 8.90 (d, J = 6.0 Hz, 1 H), 8.45-8.41 (m, 1 H), 7.96-7.91 (m, 1 H), 7.69-7.62 (m, 2 H), 7.46 (d, J = 8.0 Hz, 1 H), 4.95-4.86 (m, 1 H), 4.56 (d, J = 18 Hz, 1 H), 4.42-4.30 (m, 2 H), 4.08-4.00 (m, 2 H), 3.46 (dd, J = 12, 4.8 Hz, 1 H), 3.20 (s, 3 H), 2.38 (s, 3 H).

1.7	LC-MS (method B) R_t= 2.37 min, *m/z*= 662 $[M+H]^+$	1H NMR (DMSO-d6, 400 MHz) δ 8.90 (d, J = 6.0 Hz, 1 H), 8.45-8.41 (m, 1 H), 7.95-7.91 (m, 1 H), 7.69-7.62 (m, 2 H), 7.46 (d, J = 8.0 Hz, 1 H), 4.94-4.86 (m, 1 H), 4.56 (d, J = 18 Hz, 1 H), 4.42-4.30 (m, 2 H), 4.08-4.00 (m, 2 H), 3.46 (dd, J = 12, 4.8 Hz, 1 H), 3.20 (s, 3 H), 2.38 (s, 3 H).
1.8	LC-MS (method C) R_t= 2.57 min, *m/z*= 591.0 $[M+H]^+$	1H NMR (400 MHz, DMSO-d6): δ 8.74 (d, J = 7.2 Hz, 1 H), 8.37-8.34 (d, 1 H), 7.92-7.88 (d, 1 H), 7.67-7.62 (m, 2 H), 7.43 (d, J = 7.6 Hz, 1 H), 4.56 (d, J = 18 Hz, 1 H), 4.43-4.34 (m, 2 H), 3.01-2.87 (m, 1 H), 2.47-2.42 (m, 2 H), 2.36 (s, 3 H), 2.17-2.10 (m, 2 H).
1.9	LC-MS (method F) R_t = 1.35 min; *m/z*= 620 $(M+H)^+$	1H NMR (300 MHz, DMSO-d6) δ 9.45-9.42 (d, 1H), 8.38-8.36 (m, 1H), 7.91-7.90 (m, 1H), 7.69-7.66 (m, 2H), 7.46-7.43 (d, 1H), 6.34-6.27 (m, 1H), 4.61-4.60 (m, 1H), 4.43-4.37 (d, 1H), 3.64-3.48 (m, 2H), 3.41-3.38 (m, 1H), 2.97-4.90 (dd, 1H), 2.38 (s, 3H).
1.10	LC-MS (method F) R_t= 1.34 min; *m/z*= 620 $(M+H)^+$	1H NMR (300 MHz, DMSO-d6) δ 9.45-9.42 (d, 1H), 8.38-8.36 (m, 1H), 7.91-7.89 (m, 1H), 7.69-7.66 (m, 2H), 7.46-7.43 (d, 1H), 6.34-6.27 (m, 1H), 4.61-4.60 (m, 1H), 4.43-4.37 (d, 1H), 3.64-3.48 (m, 2H), 3.41-3.38 (m, 1H), 2.98-2.90 (m, 1H), 2.38 (s, 3H).
1.11	LC-MS (method F) R_t= 1.35 min; *m/z*= 620 $(M+H)^+$	1H NMR (300 MHz, DMSO-d6) δ 9.45-9.42 (d, 1H), 8.38-8.36 (m, 1H), 7.91-7.90 (m, 1H), 7.69-7.66 (m, 2H), 7.46-7.43 (d, 1H), 6.34-6.27 (m, 1H), 4.61-4.60 (m, 1H), 4.43-4.37 (d, 1H), 3.64-3.48 (m, 2H), 3.41-3.38 (m, 1H), 2.98-2.90 (m, 1H), 2.38 (s, 3H).
1.12	LC-MS (method F) R_t= 1.35 min; *m/z*= 620 $(M+H)^+$	1H NMR (300 MHz, DMSO-d6) δ 9.45-9.42 (d, 1H), 8.38-8.36 (m, 1H), 7.91-7.90 (m, 1H), 7.69-7.66 (m, 2H), 7.46-7.43 (d, 1H), 6.34-6.27 (m, 1H), 4.61-4.60 (d, 1H), 4.43-4.37 (d, 1H), 3.64-3.47 (m, 2H), 3.41-3.38 (m, 1H), 2.97-2.90 (m, 1H), 2.38 (s, 3H).

1.13	LC-MS (method E) R_t= 1.21 min; *m/z*= 622 $(M+H)^+$	1H-NMR (400 MHz, DMSO-d6) δ 8.67-8.65 (d, 1H), 8.38-8.37 (d, 1H), 7.91-7.90 (d, 1H), 7.70-7.68 (d, 2H), 7.49-7.46 (d, 1H), 4.85-4.77 (m, 1H), 4.61-4.60 (d, 1H), 4.54-4.37 (d, 1H), 4.22-4.12 (m, 1H), 4.10-4.00 (m, 1H), 3.73-3.72 (d, 1H), 3.28-3.23 (m, 2H), 3.19-3.04 (d, 1H), 2.49 (s, 3H).
1.14	LC-MS (method E) R_t= 1.21 min; *m/z*= 622 $(M+H)^+$	1H-NMR (400 MHz, DMSO-d6) δ 8.37-8.36 (d, 1H), 8.29-8.26 (d, 1H), 7.91-7.90 (d, 1H), 7.66-7.63 (d, 2H), 7.41-7.39 (d, 1H), 4.70-4.59 (m, 2H),4.53-4.36 (d, 1H), 4.16-4.11 (m, 1H), 4.07-3.98 (m, 1H), 3.54-3.47 (m, 1H), 3.41-3.37 (m, 1H),3.20-3.16 (d, 1H), 2.76-2.65 (m, 1H), 2.29-2.27 (s, 3H).
2.1	LC-MS (method C) R_t= 2.51 min, *m/z*= 567.1 $[M+H]^+$	^{1}H NMR (DMSO-d6, 400 MHz) δ 8.64 (d, J = 7.2 Hz, 1 H), 8.48 (br s, 1 H), 8.37-8.34 (m, 1 H), 7.92-7.89 (m, 1 H), 7.65-7.60 (m, 2 H), 7.40 (d, J = 8.0 Hz, 1 H), 4.56 (d, J = 18 Hz, 1 H), 4.39 (d, J = 18 Hz, 1 H), 4.30-4.20 (m, 1 H), 2.69-2.61 (m, 1 H), 2.48-2.30 (m, 5 H), 2.19-2.08 (m, 2 H).
2.2	LC-MS (method B) R_t= 2.24 min, *m/z*= 567.2 $[M+H]^+$	^{1}H NMR (DMSO-d6, 400 MHz) δ 12.2 (br s, 1 H), 8.68 (d, J = 7.6 Hz, 1 H), 8.38-8.34 (m, 1 H), 7.93-7.88 (m, 1 H), 7.68-7.61 (m, 2 H), 7.42 (d, J = 8.0 Hz, 1 H), 4.56 (d, J = 19 Hz, 1 H), 4.53-4.45 (m, 1 H), 4.40 (d, J = 18 Hz, 1 H), 3.00-2.90 (m, 1 H), 2.50-2.41 (m, 2 H), 2.36 (s, 3 H), 2.34-2.19 (m, 2 H).
2.3	LC-MS (method B) R_t= 2.20 min, *m/z*= 580.2 $[M+H]^+$	^{1}H NMR (DMSO-d6, 400 MHz) δ 8.63 (d, J = 7.6 Hz, 1 H), 8.38-8.34 (m, 1 H), 7.93-7.89 (m, 1 H), 7.72-7.67 (m, 1 H), 7.66-7.59 (m, 2 H), 7.39 (d, J = 8.0 Hz, 1 H), 4.56 (d, J = 18 Hz, 1 H), 4.39 (d, J = 18 Hz, 1 H), 4.31-4.21 (m, 1 H), 2.69-2.61 (m, 1 H), 2,56 (d, J = 4.8 Hz, 3 H), 2.39-2.29 (m, 5 H), 2.19-2.08 (m, 2 H).
2.4	LC-MS (method B) R_t= 2.49 min, *m/z*= 580.1 $[M+H]^+$	^{1}H NMR (DMSO-d6, 400 MHz) δ 8.62 (d, J = 7.2 Hz, 1 H), 8.38-8.33 (m, 1 H), 7.93-7.88 (m, 1 H), 7.74-7.61 (m, 3 H), 7.41 (d, J = 8.0 Hz, 1 H), 5.00-4.45 (m, 2 H), 4.40 (d, J = 18 Hz, 1 H), 2.92-2.84 (m, 1 H), 2.59 (d, J = 4,4 Hz, 3 H), 2.43-2.30 (m, 5 H), 2.24-2.14 (m, 2 H).

3.1	LC-MS (method B) R_t= 2.22 min, *m/z*= 642.4 $[M+H]^+$	^{1}H NMR (DMSO-d6, 400 MHz) δ 8.65-8.57 (m, 2 H), 8.43-8.39 (m, 1 H), 8.29-8.24 (m, 1 H), 7.69-7.64 (m, 2 H), 7.49 (d, J = 8.0 Hz, 1 H), 4.61 (d, J = 18 Hz, 1 H), 4.45 (d, J = 18 Hz, 1 H), 4.02-3.89 (m, 4 H), 2.40 (s, 3 H).

The compounds of the invention are valuable active ingredients for use in pest control. The term "pests" includes ectoparasites and endoparasites on and in animals and in the hygiene field. Particular pests are fleas, ticks, mites, flies, worms, and lice. Even more particular pests are fleas and ticks.

Animals in the context of the invention are understood to include vertebrates. The term vertebrate in this context is understood to comprise, for example fishes, amphibians, reptiles, birds, and mammals including humans. One preferred group of vertebrates according to the invention comprises warm-blooded animals including farm animals, such as cattle, horses, pigs, sheep and goats, poultry such as chickens, turkeys, guinea fowls and geese, fur-bearing animals such as mink, foxes, chinchillas, rabbits and the like, as well as companion animals such as ferrets, guinea pigs, rats, hamster, cats and dogs, and also humans. A further group of preferred vertebrates according to the invention comprises fishes including salmons.

In the context of the present invention, ectoparasites are understood to be in particular insects, acari (mites and ticks), and crustaceans (sea lice). These include insects of the following orders: *Lepidoptera*, *Coleoptera*, *Homoptera*, *Hemiptera*, *Heteroptera*, *Diptera*, *Dictyoptera*, *Thysanoptera*, *Orthoptera*, *Anoplura*, *Siphonaptera*, *Mallophaga*, *Thysanura*, *Isoptera*, *Psocoptera* and *Hymenoptera*. However, the ectoparasites which may be mentioned in particular are those which trouble humans or animals and carry pathogens, for example flies such as *Musca domestica*, *Musca vetustissima*, *Musca autumnalis*, *Fannia canicularis*, *Sarcophaga carnaria*, *Lucilia cuprina*, *Lucilia sericata*, *Hypoderma bovis*, *Hypoderma lineatum*, *Chrysomyia chloropyga*, *Dermatobia hominis*, *Cochliomyia hominivorax*, *Gasterophilus intestinalis*, *Oestrus ovis*, biting flies such as *Haematobia irritans irritans*, *Haematobia irritans exigua*, *Stomoxys calcitrans*, horse-

flies (*Tabanids*) with the subfamilies of *Tabanidae* such as *Haematopota* spp. (e.g. *Haematopota pluvialis*) and *Tabanus* spp, (e.g.*Tabanus nigrovittatus*) and *Chrysopsinae* such as *Chrysops* spp. (e.g. *Chrysops caecutiens*); *Hippoboscids* such as *Melophagus ovinus* (sheep ked); tsetse flies, such as *Glossinia* spp,; other biting insects like midges, such as *Ceratopogonidae* (biting midges), *Simuliidae* (Blackflies), *Psychodidae* (Sandflies); but also blood-sucking insects, for example mosquitoes, such as *Anopheles* spp, Aedes spp and *Culex* spp, fleas, such as *Ctenocephalides felis* and *Ctenocephalides canis* (cat and dog fleas), *Xenopsylla cheopis*, *Pulex irritans*, *Ceratophyllus gallinae*, *Dermatophilus penetrans*, blood-sucking lice (*Anoplura*) such *as Linognathus* spp, *Haematopinus* spp, *Solenopotes* spp, *Pediculus humanis*; but also chewing lice (*Mallophaga*) such as *Bovicola* (*Damalinia*) *ovis*, *Bovicola (Damalinia) bovis* and other *Bovicola* spp. . Ectoparasites also include members of the order *Acarina*, such as mites (e.g. *Chorioptes bovis, Cheyletiella* spp., *Dermanyssus gallinae*, *Ortnithonyssus* spp., *Demodex canis*, *Sarcoptes scabiei*, *Psoroptes ovis* and *Psorergates* spp. and ticks. Representatives ticks are, for example, *Boophilus*, *Amblyomma*, *Anocentor*, *Dermacentor*, *Haemaphysalis*, *Hyalomma*, *Ixodes*, *Rhipicentor*, *Margaropus*, *Rhipicephalus*, *Argas*, *Otobius* and *Ornithodoros* and the like, which preferably infest vertebrates, for example warm-blooded animals including farm animals, such as cattle, horses, pigs, sheep and goats, poultry such as chickens, turkeys, guinea fowls, and geese, fur-bearing animals such as mink, foxes, chinchillas, rabbits and the like, as well as companion animals such as ferrets, guinea pigs, rats, hamster, cats and dogs, but also humans and fishes.

The compounds of the invention according to the invention are also active against all or individual development stages of animal pests showing normal sensitivity, as well as those showing resistance to widely used parasiticides. This is especially true for resistant insects and members of the order *Acarina*. The insecticidal, ovicidal and/or acaricidal effect of the active substances of the invention can manifest itself directly, i.e. killing the pests either immediately or after some time has elapsed, for example when moulting occurs, or by destroying their eggs, or indirectly, e.g. reducing the number of eggs laid and/or the hatching rate, good efficacy corresponding to a pesticidal rate (mortality) of at least 50 to 60%.

Compounds of the invention can also be used against hygiene pests, especially of the order *Diptera* of the families *Muscidae*, *Sarcophagidae*, *Anophilidae* and *Culicidae*; the orders *Orthoptera*, *Dictyoptera* (e.g. the family *Blattidae* (cockroaches), such as *Blatella germanica*, *Blatta orientalis*, *Periplaneta americana*) and *Hymenoptera* (e.g. the families *Formicidae* (ants) and *Vespidae* (wasps).

The compounds of formula (I) are also effective against ectoparasites of fishes, especially the sub-class of *Copepoda* (e.g. order of *Siphonostomatoida* (sea lice), whilst being well tolerated by fish.

The compounds of formula (I) can also be used against worms of the class *Cestoda*, including the subclasses *Eucestoda* and *Cestodaria*.

Compounds of the invention also have sustainable efficacy on parasitic mites and insects of plants. In the case of spider mites of the order *Acarina*, they are effective against eggs, nymphs and adults of *Tetranychidae* (*Tetranychus spp.* and *Panonychus spp.*).

They have high activity against sucking insects of the order *Homoptera*, especially against pests of the families *Aphididae, Delphacidae, Cicadellidae, Psyllidae, Loccidae, Diaspididae* and *Eriophydidae* (e.g. rust mite on citrus fruits); the orders *Hemiptera, Heteroptera* and *Thysanoptera*, and on the plant-eating insects of the orders *Lepidoptera, Coleoptera, Diptera* and *Orthoptera*

They are similarly suitable as a soil insecticide against pests in the soil.

The compounds of formula (I) are therefore effective against all stages of development of sucking insects and eating insects on crops such as cereals, cotton, rice, maize, soya, potatoes, vegetables, fruit, tobacco, hops, citrus, avocados and other crops.

The compounds of formula I are also effective against plant nematodes of the species *Meloidogyne, Heterodera, Pratylenchus, Ditylenchus, Radopholus, Rizoglyphus* etc.

The compounds of the invention are effective against helminths. Helminths are commercially important because they cause serious diseases in mammals and poultry, e.g. in sheep, pigs, goats, cattle, horses, donkeys, camels, dogs, cats, rabbits, guinea-pigs,

hamsters, chicken, turkeys, guinea fowls and other farmed birds, as well as exotic birds. Typical nematodes are: Haemonchus, Trichostrongylus, Ostertagia, Nematodirus, Cooperia, Ascaris, Bunostonum, Oesophagostonum, Charbertia, Trichuris, Strongylus, Trichonema, Dictyocaulus, Capillaria, Heterakis, Toxocara, Ascaridia, Oxyuris, Ancylostoma, Uncinaria, Toxascaris and Parascaris. The trematodes include, in particular, the family of Fasciolideae, especially Fasciola hepatica.

The pesticidal activity of the compounds of formula (I) according to the invention corresponds to a mortality rate of about 50-60% of the pests mentioned, more preferably to a mortality rate over 90%, most preferably to 95-100%. The compounds of formula (I) are preferably employed internally and externally in unmodified form or preferably together with the adjuvants conventionally used in the art of formulation and may therefore be processed in a known manner to give, for example, liquid formulations (e.g. spot-on, pour-on, spray-on, emulsions, suspensions, solutions, emulsifiable concentrates, solution concentrates), semi-solid formulations (e.g. creams, ointments, pastes, gels, liposomal preparations) and solid preparations (e.g. food additives tablets including e. g. capsules, powders including soluble powders, granules, or embeddings of the active ingredient in polymeric substances, like implants and microparticles). As with the compositions, the methods of application are selected in accordance with the intended objectives and the prevailing circumstances.

The compounds of the invention can be administered alone or in the form of a composition. In practice, the compounds of the invention are usually administered in the form of compositions, that is, in admixture with at least one acceptable excipient. The proportion and nature of any acceptable excipient(s) are determined by the properties of the selected compound of the invention, the chosen route of administration, and standard practice as in the veterinary and pharmaceutical fields.

In one embodiment, the present invention provides compositions comprising: a compound of invention and at least one acceptable excipient.

In effecting such treatment and/or control, a compound of the invention can be administered in any form and route which makes the compound bioavailable. The compounds of the invention can be administered by a variety of routes, including orally, in particularly by tablets and capsules. The compounds of the invention can be administered parenteral routes, more particularly by inhalation, subcutaneously, intramuscularly, intravenously, intraarterially, transdermally, intranasally, rectally, vaginally, occularly, topically, sublingually, and buccally, intraperitoneally, intraadiposally, intrathecally and via local delivery for example by catheter or stent. One skilled in the art can readily select the proper form and route of administration depending upon the particular characteristics of the compound selected, the disorder or condition to be treated, the stage of the disorder or condition, and other relevant circumstances. The pharmaceutical compositions of the invention may be administered to the subject, for example, in the form of tablets, including chewable tablets, capsules, cachets, papers, lozenges, wafers, elixirs, boli, ointments, transdermal patches, aerosols, inhalants, suppositories, drenches, solutions, injections, and suspensions.

The term “acceptable excipient” refers to those excipients typically used in preparing veterinary and pharmaceutical compositions and should be pure and non-toxic in the amounts used. They generally are a solid, semi-solid, or liquid material which in the aggregate can serve as a vehicle or medium for the active ingredient. Some examples of acceptable excipients are found in Remington’s Pharmaceutical Sciences and the Handbook of Pharmaceutical Excipients and include diluents, vehicles, carriers, ointment bases, binders, disintegrates, lubricants, glidants, sweetening agents, flavoring agents, gel bases, sustained release matrices, stabilizing agents, preservatives, solvents, suspending agents, buffers, emulsifiers, dyes, propellants, coating agents, and others.

In one embodiment, the composition is adapted for oral administration, such as a tablet or a capsule or a liquid formulation, for example, a solution or suspension, adapted for oral administration. In one embodiment, the composition is adapted for oral administration, such as chewable formulation, adapted for oral administration. In still another embodiment, the composition is a liquid or semi-solid formulation, for example, a solution or suspension or a paste, adapted for parenteral administration.

In one embodiment, the composition is adapted for injection administration, such as a solution or suspension, adapted for injection administration.

Particular compositions for usage on subjects in the treatment and/or control of nematodes/ helminths comprise solutions; injectables; emulsions including classical emulsions, microemulsions and self-emulsifying compositions, that are waterless organic, preferably oily, compositions which form emulsions, together with body fluids, upon addition to the subject's body; suspensions (drenches); pour-on formulations; food additives; powders; tablets including effervescent tablets; boli; capsules including micro-capsules; and chewable treats. Particularly composition forms are tablets, capsules, food additives or chewable treats.

The compositions of the present invention are prepared in a manner well known in the veterinary and pharmaceutical art and include at least one of the compounds of the invention as the active ingredient. The amount of a compound of the present invention may be varied depending upon its particular form and may conveniently be between 1% to about 50% of the weight of the unit dose form. The present pharmaceutical compositions are preferably formulated in a unit dose form, each dose typically containing from about 0.5 mg to about 100 mg of a compounds of the invention. One or more unit dose form(s) may be taken to affect the treatment dosage.

In one embodiment, the present invention also provides a method for treating pests, comprising: administering to a subject in need thereof an effective amount of a compound of formula (I) or a salt thereof, the method optionally further comprising an effective amount of at least one additional active compound.

In one embodiment, the present invention also provides a method for controlling pests, comprising: administering to a subject in need thereof an effective amount of a compound of formula (I) or a salt thereof, the method optionally further comprising an effective amount of at least one additional active compound.

In one embodiment, the present invention also provides a method for treating or controlling pests, comprising: contacting a subject's environment with an effective amount of a compound of formula (I) or a salt thereof, the method optionally further comprising an effective amount of at least one additional active compound.

Thus, the invention provides for the use of the compounds of the invention as a medicament, including for the manufacture of a medicament. In one embodiment, the invention provides the manufacture of a medicament comprising a compound of formula (I) or a salt thereof for treating pests. In one embodiment, the invention provides the manufacture of a medicament comprising a compound of the invention or a salt thereof for controlling pests.

The terms "treating", "to treat", "treated", or "treatment", include without limitation restraining, slowing, stopping, reducing, ameliorating, reversing the progression or severity of an existing symptom, or preventing a disorder, condition, or disease. For example, an adult heartworm infection would be treated by administering a compound of the invention. A treatment may be applied or administered therapeutically.

The terms "control", "controlling" or "controlled" refers to include without limitation decreasing, reducing, or ameliorating the risk of a symptom, disorder, condition, or disease, and protecting an animal from a symptom, disorder, condition, or disease. Controlling may refer to therapeutic, prophylactic, or preventative administration. For example, a larvae or immature pest may be asymptomatic but would be controlled by acting on the larvae or immature pest preventing the infection from progressing to a symptomatic or debilitating infection by mature pest.

Thus, the use of the compounds of the invention in the treatment and/or control of pests, in particular helminths, in which the endoparasitic nematodes and trematodes refers to the use of the compounds of the invention to act on the various forms of the pest throughout its life cycle, independent of whether a subject is manifesting a symptom, including morbidity or mortality, and independently of the phase(s) of the challenge.

As used herein, “administering to a subject” includes but is not limited to cutaneous, subcutaneous, intramuscular, mucosal, submucosal, transdermal, oral or intranasal administration. Administration could include injection or topical administration, for example, pour-on or spot-on administration. The pour-on or spot-on method is especially advantageous for use on herd animals such as cattle, horses, sheep or pigs, in which it is difficult or time-consuming to treat all the animals orally or by injection. Because of its simplicity, this method can of course also be used for all other animals, including individual domestic animals or pets, and is greatly favoured by the keepers of the animals, as it can often be carried out without the specialist presence of the veterinarian.

The terms “subject” and “patient” refers includes humans and non-human mammalian animals and fish, the vertebrates described herein, such as dogs, cats, mice, rats, guinea pigs, rabbits, ferrets, cows, horses, sheep, goats, and pigs. Particular subjects are mammalian pets or companion animals, such as dogs and cats and also mice, guinea pigs, ferrets, and rabbits.

The term “effective amount” refers to an amount which gives the desired benefit to the subject and includes administration for both treatment and control. The amount will vary from one individual subject to another and will depend upon a number of factors, including the overall physical condition of the subject and the severity of the underlying cause of the condition to be treated, concomitant treatments, and the amount of compound of the invention used to maintain desired response at a beneficial level.

An 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, the dose, a number of factors are considered by the attending diagnostician, including, but not limited to: the species of patient; its size, age, and general health; the specific condition, disorder, infection, or disease involved; the degree of or involvement or the severity of the condition, disorder, or disease, the response of the individual patient; 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. An effective amount of the present invention, the treatment dosage, is expected to range from 0.5 mg to 100 mg. Specific amounts can be determined by the skilled person. Although these dosages are based on a subject having a mass of about 1 kg to about 20 kg, the diagnostician will be able to determine the appropriate dose for a subject whose mass falls outside of this weight range. An effective amount of the present invention, the treatment dosage, is expected to range from 0.1 mg to 10 mg/kg of the subject. The dosing regimen is expected to be monthly, quarterly, semi-annual, or annual administration.

The compounds of the invention may be combined with one or more other active compounds or therapies for the treatment of one or more disorders, diseases or conditions, including the treatment of pests, for which it is indicated. The compounds of the invention may be administered simultaneously, sequentially or separately in combination with one or more compounds or therapies for treating pests and other disorders.

Thus, it is understood that the compositions and methods of the present invention optionally include comprising an effective amount of at least one additional active compound. Additional active compounds useful in the present invention include those used to treat fleas, ticks, flies, and mosquitos and include macrocyclic lactones, like milbemycin oxime, imidacloprid, spinosad, pyriproxyfen, premethrin, S-methoprene, praziquantel and moxidectin. Further exemplary addition active compounds include, but are not limited to, afoxolaner, broflanilide, fluralaner, fluxametamide, isocycloseram, lotilaner, modoflaner, nicofluprole, sarolaner,tigolaner, albendazole, cambendazole, fenbendazole, flubendazole, mebendazole, oxfendazole, parabendazole, tiabendazole, triclabendazole, amitraz, demiditraz, clorsulon, closantel, oxyclonazide, rafoxanide, cyphenothrin, deltamethrin, flumethrin, permethrin, cyromazine, derquantel, diamphenetide, dicyclanil, dinotefuran, imidacloprid, nitenpyram, thiamethoxam, abamectin, doramectin, emamectin, eprinomectin, ivermectin, moxidectin, selamectin, milbemycin oxime, emodepside, epsiprantel, fipronil, fluazuron, fluhexafon, indoxacarb, levamisol, lufenuron, metaflumizone, methoprene, monepantel, morantel, niclosamide, nitroscanate, nitroxynil, novaluron, oxantel, praziquantel, pyrantel, pyriprole,

pyriproxyfen, sisapronil, spinosad, spinetoram and triflumezopyrim, or a salt of any of the foregoing.

The activity of the compounds of the invention may be determined by a variety of methods, including in vitro and in vivo methods.

Example A

In vitro evaluation of ingestion activity against adult cat fleas

To prepare the test blood mixture for feeding fleas, the test substance is dissolved in dimethyl sulphoxide and diluted with citrated cattle blood to the desired concentration. To assemble the test set-up, about 20 unfed adult male and female cat fleas (Ctenocephalides felis) are placed into a chamber which is closed at the top and bottom with gauze. A metal cylinder is sealed at one end with parafilm membrane, placed with the sealed base onto the chamber, and filled with the test blood mixture, which can be imbibed by the fleas through the parafilm membrane. The blood cylinder part of the assembled test set-up is contained at about 37 °C in an isolated air heated container above the isolating carrier plate holding the flea chambers. The flea chamber part is kept at room temperature. After 48 hours, the insecticidal activity against fleas is determined. 100% means that all of the fleas have been killed or rendered moribund; 0% means that none of the fleas have been affected at the dose administered. From a dose response curve the respective EC50 was calculated (4-parameter logistic curve fitting). A substance shows good insecticidal activity against *Ctenocephalides felis* if the EC50 is below an application rate of 20 ppm.

In this test for example, the following compounds from the preparation examples showed EC_{50} < 1 ppm: Examples 1.5, 1.8, 1.9, 1.11, 1.13, 1.14, 2.3, and 3.1.

In this test for example, the following compounds from the preparation examples showed EC_{50} < 5 ppm: Examples 1.1, 1.5, 1.8, 1.9, 1.11, 1.13, 1.14, 2.3, 2.4, and 3.1.

In this test for example, the following compounds from the preparation examples showed EC_{50} < 20 ppm: Examples 1.1, 1.3, 1.4, 1.5, 1.8, 1.9, 1.11, 1.13, 1.14, 2.3, 2.4, and 3.1.

For the data above, where single isomers were tested, without knowing the absolute configuration of the isomer, the data indicates that the test article is one isomer or another, for example, Example 1.1 or its enantiomer.

Example B

In vitro evaluation of contact activity against adult Brown Dog ticks

In vitro contact tests with ticks are conducted with adult males and females of *Rhipicephalus sanguineus*. For the coating of the test vials, the test substance is dissolved and diluted in acetone p.a. to the desired concentration. The solution is then homogeneously applied to the inner walls and base of a glass vial by turning and rocking on an orbital shaker until complete evaporation of the solvent. For example, with 900 ppm solution of test substance an area-based dose of 5 µg/cm² is achieved. After the solvent is completely evaporated, 5 -10 adult ticks are applied to each coated test vial, which is then sealed with a perforated plastic lid and incubated in a horizontal position in the dark at room temperature and ambient humidity. Acaricidal activity is determined after 48 h. For this, ticks are moved to the base of the test vial by gentle knocking, and test vials are then incubated on a hotplate at 45-50°C for no longer than 5 min. Ticks which remain motionless on the base of the test vial or move uncoordinated without deliberately climbing up to avoid the heat are considered dead or moribund, respectively. An acaricidal activity of 100% means all ticks were dead or moribund. An acaricidal activity of 0% means none of the ticks was found dead or moribund. From a dose response curve the respective EC50 was calculated (4-parameter logistic curve fitting). A substance shows good acaricidal activity against *Rhipicephalus sanguineus* if the EC50 is below an application rate of 5 µg/cm².

In this test for example, the following compounds from the preparation examples showed $EC_{50} < 0.04$ $\mu g/cm^2$: Examples 1.3, 1.5, 1.8. and 3.1.

In this test for example, the following compounds from the preparation examples showed $EC_{50} < 0.25$ $\mu g/cm^2$: Examples 1.1, 1.3, 1.4, 1.5, 1.8 and 3.1.

In this test for example, the following compounds from the preparation examples showed $EC_{50} < 1$ $\mu g/cm^2$: Examples 1.1, 1.3, 1.4, 1.5, 1.8, 2.3 and 3.1.

For the data above, where single isomers were tested, without knowing the absolute configuration of the isomer, the data indicates that the test article is one isomer or another, for example, Example 1.1 or its enantiomer.

Example C

In vitro evaluation of contact activity against adult Cat fleas

In vitro contact tests with ticks are conducted with adult males and females of *Ctenocephalides felis*. For the coating of the test vials, the test substance is dissolved and diluted in acetone p.a. to the desired concentration. The solution is then homogeneously applied to the inner walls and base of a glass vial by turning and rocking on an orbital shaker until complete evaporation of the solvent. For example, with 900 ppm solution of test substance an area-based dose of 5 µg/cm² is achieved.

After the solvent is completely evaporated, approximately 10 adult fleas are applied to each coated test vial, which is then sealed with a perforated plastic lid and incubated in a horizontal position in the dark at room temperature and ambient humidity. Insecticidal activity is determined after 48 h. Fleas which remain motionless on the base of the test vial or move uncoordinated without occasionally jumping or walking straight are considered dead or moribund, respectively. An insecticidal activity of 100% means all fleas were dead or moribund. An insecticidal activity of 0% means none of the fleas was affected. From a dose response curve the respective EC50 was calculated (4-parameter logistic curve fitting).

A substance shows good insecticidal activity against *Ctenocephalides felis* if the EC50 is below an application rate of 5 µg/cm².

In this test for example, the following compounds from the preparation examples showed $EC_{50} < 0.05$ $\mu g/cm^2$: Examples 3.1.

In this test for example, the following compounds from the preparation examples showed $EC_{50} < 0.1$ $\mu g/cm^2$: Examples 1.1, 1.3, 1.4, 1.8 and 3.1.

For the data above, where single isomers were tested, without knowing the absolute configuration of the isomer, the data indicates that the test article is one isomer or another, for example, Example 1.1 or its enantiomer.

Example D

In vitro evaluation of systemic activity against female engorged Cattle ticks

To prepare the test compound mixture for injecting ticks, the test substance is dissolved in dimethyl sulphoxide and diluted with the same solvent to the desired concentration. 1 µl of the test mixture is injected into each abdomen of 5 engorged adult female cattle ticks (*Rhipicephalus (Boophilus) microplus*). The ticks are indidusally transferred into the single

compartments of 5x5 replica plates and kept in a climate-controlled chamber (28°C, 85% rel. hum.). Acaricidal activity against cattle ticks is assessed after 7 days by assessment of laid fertile eggs. Eggs which do not appear normal may be stored in a climate-controlled cabinet [28°C, 85% rel h.] until larval hatch after 42 days. An acaricidal activity of 100% means that none of the ticks has laid eggs or laid eggs were infertile; 0% means that all the eggs are fertile. From a dose response curve the respective EC50 was calculated (4-parameter logistic curve fitting). A substance shows good systemic acaricidal activity against *Rhipicephalus microplus* if the EC50 is below an application rate of 10 µg/tick.

In this test for example, the following compounds from the preparation examples showed EC_{50} < 1 µg/tick: Examples 1.5, 1.8, 2.3, and 3.1.

In this test for example, the following compounds from the preparation examples showed EC_{50} < 2 µg/tick: Examples 1.1, 1.3, 1.5, 1.8, 2.3, 2.4, and 3.1.

In this test for example, the following compounds from the preparation examples showed EC_{50} < 10 µg/tick: Examples 1.1, 1.3, 1.5, 1.8, 2.1, 2.2, 2.3, 2.4, and 3.1.

For the data above, where single isomers were tested, without knowing the absolute configuration of the isomer, the data indicates that the test article is one isomer or another, for example, Example 1.1 or its enantiomer.

Example E

In vitro evaluation of contact activity against larval cattle ticks

This *In vitro* contact tests are conducted with with larvae of *Rhipicephalus microplus*. For the coating of the test vials, the test substance is dissolved and diluted in acetone p.a. to the desired concentration. The solution is then homogeneously applied to the inner walls and base of a glass vial by turning and rocking on an orbital shaker until complete evaporation of the solvent. For example, with 900 ppm solution of test substance an area-based dose of 5 µg/cm² is achieved. After the solvent is completely evaporated, 10-20 larval ticks are applied to each coated test vial, which is then sealed with a perforated plastic lid and incubated in a horizontal position in trays that are kept in a climate-controlled chamber (28°C, 85% rel. hum.). Acaricidal activity is determined after 48 h. For this, vials are placed vertically and the natural negative egeotactic behavior of cattel tick larvaer is used to evaluate the effects.. Tick larvae which remain motionless on the base of the test vial or move uncoordinated without deliberately climbing up are considered dead or moribund,

respectively. An acaricidal activity of 100% means all tick larvae were dead or moribund. An acaricidal activity of 0% means none of the tick larvae was affected. From a dose response curve the respective EC50 was calculated (4-parameter logistic curve fitting). A substance shows good acaricidal activity against *Rhipicephalus sanguineus* if the EC50 is below an application rate of 5 µg/cm².

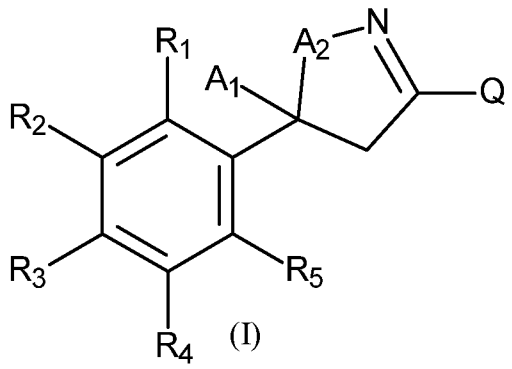
In this test for example, the following compounds from the preparation examples showed $EC_{50} < 0.01$ $\mu g/cm^2$: Examples 1.3, 1.5, and 3.1.

In this test for example, the following compounds from the preparation examples showed $EC_{50} < 0.1$ $\mu g/cm^2$: Examples 1.1, 1.3, 1.4, 1.5, 2.3, and 3.1.

For the data above, where single isomers were tested, without knowing the absolute configuration of the isomer, the data indicates that the test article is one isomer or another, for example, Example 1.1 or its enantiomer.

WE CLAIM:

1. A compound of formula (I):



(I)

wherein

A_1 is selected from the group consisting of CF_3, CHF_2, CH_2F, and CF_2CF_3;

A_2 is O or S;

R_1 is selected from the group consisting of hydrogen and halogen;

R_2 is selected from the group consisting of hydrogen, halogen, difluoromethyl, and trifluoromethyl;

R_3 is selected from the group consisting of hydrogen, halogen, and trifluoromethyl;

R_4 is selected from the group consisting of hydrogen, halogen, difluoromethyl, and trifluoromethyl;

R_5 is selected from the group consisting of hydrogen and halogen;

provided that:

R_1 may be hydrogen only when R_2 is trifluoromethyl, difluoromethyl, or bromo;

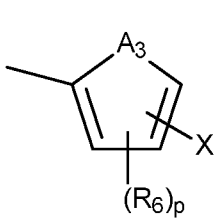
R_5 may be hydrogen only when R_4 is trifluoromethyl or bromo;

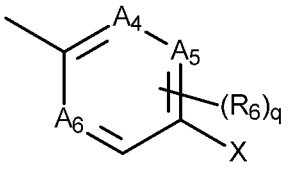
R_3 may be hydrogen only when one of R_2 or R_4 is either trifluoromethyl, difluoromethyl, or bromo;

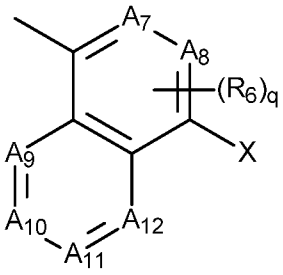
R_1, R_3, and R_5 cannot all be hydrogen when R_2 and R_4 are trifluoromethyl; and

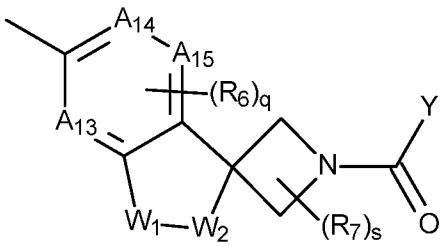
at most three of R_1, R_2, R_3, R_4, and R_5 are hydrogen;

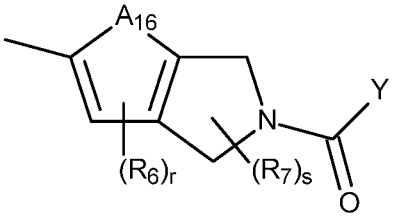
Q is selected from the group consisting of

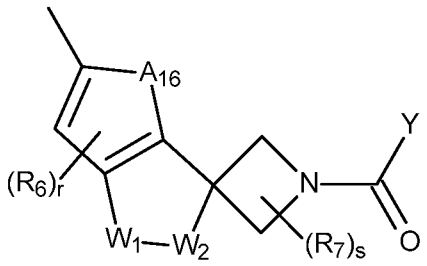




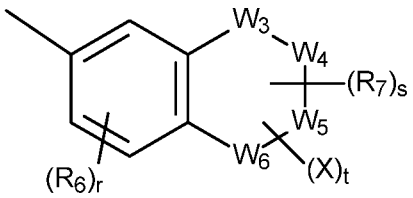








and



wherein

p is 0, 1, or 2;

q is 0, 1, 2, or 3;

r is 0 or 1;

s is 0, 1, or 2;

t is 0 or 1;

R_6, at each occurrence, is independently selected from the group consisting of halogen; cyano; nitro; hydroxyl; $-NH_2$; $-NH(C_1\text{-}C_4$ alkyl); $-N(C_1\text{-}C_4$ alkyl$)_2$; $C_2\text{-}C_5$-alkoxycarbonyl; $C_1\text{-}C_6$-alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, oxo, $C_3\text{-}C_6$ cycloalkyl, $C_1\text{-}C_4$ alkoxy, $-NH_2$, $C_1\text{-}C_7$ aminocarbonyl, $-NH(C_1\text{-}C_4$ alkyl), $-N(C_1\text{-}C_4$ alkyl$)_2$, $-SC_1\text{-}C_4$ alkyl, $-S(O)C_1\text{-}C_4$ alkyl, and $-SO_2C_1\text{-}C_4$ alkyl; $C_1\text{-}C_6$-alkoxy optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, oxo, $C_3\text{-}C_6$ cycloalkyl, $C_1\text{-}C_4$ alkoxy, $-NH_2$, $C_1\text{-}C_7$

aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, and -SO_2C_1-C_4 alkyl; -NR_8C(O)(C_1-C_4 alkyl) optionally substituted on the C_1-C_4 alkyl with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), and -N(C_1-C_4 alkyl)$_2$, wherein R_8 is independently selected from the group consisting of hydrogen and C_1-C_4 alkyl; -C(O)NR_8(C_1-C_4 alkyl) optionally substituted on the C_1-C_4 alkyl with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), and -N(C_1-C_4 alkyl)$_2$, wherein R_8 is independently selected from the group consisting of hydrogen and C_1-C_4 alkyl; -SC_1-C_6 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, oxo, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), and -N(C_1-C_4 alkyl)$_2$; and -S(O)C_1-C_6 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, oxo, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), and -N(C_1-C_4 alkyl)$_2$;

R_7, at each occurrence, is independently selected from the group consisting of oxo, C_1-C_4 alkyl, and C_3-C_6 cycloalkyl;

A_3 is O or S;

A_4 is CH or N;

A_5 is CH or N;

A_6 is CH or N;

A_7 is CH O, S, a bond, or N;

A_8 is CH O, S, a bond, or N;

A_9 is CH or N;

A_{10} is CH or N;

A_{11} is CH or N;

A_{12} is CH or N;

A_{13} is CH or N;

A_{14} is CH or N;

A_{15} is CH or N;

A_{16} is NR, O, or S, wherein R is selected from the group consisting of hydrogen, C_1-C_4 alkyl, and C_3-C_6 cycloalkyl;

W_1 is selected from the group consisting of -O-, -S-, -NR_9-, -$NC(O)R_{10}$-, -CH_2-, and -C(O)-;

W_2 is selected from the group consisting of -O-, -S-, -NR_9-, -$NC(O)R_{10}$-, -CH_2-, and -C(O)-;

provided that:

when W_1 is -O-, -S-, -NR_9-, or -$NC(O)R_{10}$- then W_2 is -CH_2- or -C(O)-; and

when W_2 is -O-, -S-, -NR_9-, or -$NC(O)R_{10}$- then W_1 is -CH_2- or -C(O)-;

W_3 is selected from the group consisting of nil, -O-, -S-, -S(O)-, -$S(O)_2$-, -NR_9-, -CH-, -N-, -CH_2-, and -C(O)-;

W_4 is selected from the group consisting of nil, -O-, -S-, -S(O)-, -$S(O)_2$-, -NR_9-, -CH-, -N-, -CH_2-, and -C(O)-;

W_5 is selected from the group consisting of nil, -O-, -S-, -S(O)-, -$S(O)_2$-, -NR_9-, -CH-, -N-, -CH_2-, and -C(O)-;

W_6 is selected from the group consisting of nil, -O-, -S-, -S(O)-, -$S(O)_2$-, -NR_9-, -CH-, -N-, -CH_2-, and -C(O)-;

wherein the bonds between W_1, W_2, W_3, and W_4 may be single or double bonds;

provided that:

(i) not more than two of W_1, W_2, W_3, and W_4 are nil;

(ii) not more than two of W_1, W_2, W_3, and W_4 are -O-, -S-, -S(O)-, -$S(O)_2$-, -NR_9-, or -C(O)-;

(iii) if two of W_1, W_2, W_3, and W_4 are -O- and/or -S- then at least one carbon atom is present between them; and

(iv) when W_1, W_2, W_3, or W_4 is -CH- and/or -NR_9- then a double bond is formed within the ring formed by W_1, W_2, W_3, and W_4;

R_9, at each occurrence, is independently selected from the group consisting of hydrogen and C_1-C_6-alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, oxo, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, and -SO_2C_1-C_4 alkyl;

R_{10}, at each occurrence, is independently selected from the group consisting of oxo, C_1-C_4 alkyl, and C_3-C_6 cycloalkyl;

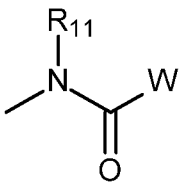
X is 5- to 10-membered heteroaryl having 1 or 2 heteroatoms selected from the group O, S, and N,

wherein the carbons of the 5- to 10-membered heteroaryl are optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, C_1-C_4 alkoxy, $-NH_2$, C_1-C_7 aminocarbonyl, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, $-SC_1$-C_4 alkyl, $-S(O)C_1$-C_4 alkyl, $-SO_2C_1$-C_4 alkyl, $-C(O)NH$-C_3-C_6 cycloalkyl, $-C(O)NH$-C_1-C_6 alkyl, and $-C(O)NH$-C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, $-C(O)NH$-C_3-C_6 cycloalkyl, $-C(O)NH$-C_1-C_6 alkyl, and $-C(O)NH$-C_1-C_6 haloalkyl,

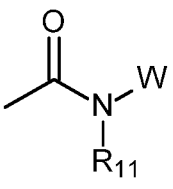
wherein any N in the heteroaryl, valency permitting, is optionally substituted with a substituent selected from the group consisting of hydrogen, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, oxo, C_1-C_4 alkoxy, $-NH_2$, C_1-C_7 aminocarbonyl, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, $-SC_1$-C_4 alkyl, $-S(O)C_1$-C_4 alkyl, $-SO_2C_1$-C_4 alkyl, $-C(O)NH$-C_3-C_6 cycloalkyl, $-C(O)NH$-C_1-C_6 alkyl, and $-C(O)NH$-C_1-C_6 haloalkyl, and C_3-C_6 cycloalkyl;

or

X is selected from the group consisting of



and



;

wherein

R_{11} is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_3-C_6 cycloalkyl, C_4-C_7 alkycycloalkyl, C_2-C_7 alkylcarbonyl, C_2-C_5 alkoxycarbonyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl;

W is selected from the group consisting of

(i) hydrogen;

(ii) C_1-C_6 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen; cyano; hydroxyl; oxo; C_1-C_4 alkoxy; C_3-C_6 cycloalkyl optionally substituted by 1 to 3 substituents independently selected from the group halogen and cyano; acetylenyl; $-NH_2$; C_1-C_7 aminocarbonyl; $-NH(C_1$-C_4 alkyl); $-N(C_1$-C_4 alkyl$)_2$; $-SC_1$-C_4 alkyl; $-S(O)C_1$-C_4 alkyl; $-SO_2C_1$-C_4 alkyl; $-C(O)NH$-C_3-C_6 cycloalkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, hydroxyl, cyano, and C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, and $-NH_2$; $-C(O)NH$-C_1-C_6 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, and $-NH_2$; $-C(O)NH$-C_1-C_6 cyanoalkyl optionally substituted with 1 to 3 halogen; $-C(O)NH$-C_1-C_6 haloalkyl; -C(O)-4- to 7-membered heterocycloalkyl attached by a nitrogen and optionally having 1 or 2 other heteroatoms selected from the group O, S, and N, wherein the carbons of the 4- to 7-membered heterocycloalkyl are optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, oxo, $-NH_2$, C_1-C_7 aminocarbonyl, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, oxo, C_1-C_4 alkoxy, $-NH_2$, C_1-C_7 aminocarbonyl, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl$)_2$, $-SC_1$-C_4 alkyl, $-S(O)C_1$-C_4 alkyl, $-SO_2C_1$-C_4 alkyl, $-C(O)NH$-C_3-C_6 cycloalkyl, and $-C(O)NH$-C_1-C_6 alkyl, and C_3-C_6 cycloalkyl, wherein any other N in the 4- to 7-membered heterocycloalkyl, valency permitting, is substituted with a substituent selected from the group consisting of hydrogen, $-NH_2$, C_1-C_7 aminocarbonyl, $-SO_2C_1$-C_4 alkyl, $-SO_2C_1$-C_4 haloalkyl, and C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, C_1-C_4 alkoxy, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl$)_2$, $-SC_1$-C_4 alkyl, $-S(O)C_1$-C_4 alkyl, $-SO_2C_1$-C_4 alkyl, $-C(O)NH$-C_3-C_6 cycloalkyl, $-C(O)NH$-C_1-C_6 alkyl, and $-C(O)NH$-C_1-C_6 haloalkyl; 5- to 10-membered heteroaryl having 1 or 2 heteroatoms selected from the group O, S, and N, wherein the carbons of the 5- to 10-membered heteroaryl are

optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, C_1-C_4 alkoxy, $-NH_2$, C_1-C_7 aminocarbonyl, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, $-SC_1$-C_4 alkyl, $-S(O)C_1$-C_4 alkyl, $-SO_2C_1$-C_4 alkyl, $-C(O)NH$-C_3-C_6 cycloalkyl, $-C(O)NH$-C_1-C_6 alkyl, and $-C(O)NH$-C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, $-NH_2$, C_1-C_7 aminocarbonyl, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, and $-C(O)NH$-C_3-C_6 cycloalkyl, wherein any N in the heteroaryl, valency permitting, is optionally substituted with a substituent selected from the group consisting of hydrogen, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, oxo, C_3-C_6 cycloalkyl,C_1-C_4 alkoxy, $-NH_2$, C_1-C_7 aminocarbonyl, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, $-SC_1$-C_4 alkyl, $-S(O)C_1$-C_4 alkyl, $-SO_2C_1$-C_4 alkyl, $-C(O)NH$-C_3-C_6 cycloalkyl, and $-C(O)NH$-C_1-C_6 alkyl, and C_3-C_6 cycloalkyl, wherein any S in the heteroaryl is optionally substituted with 1 or 2 oxygen atom(s); phenyl optionally substituted with 1 to 3 substituents selected from the group consisting of halogen, C_1-C_4 alkyl, cyano, and hydroxyl; C_3-C_6 cycloalkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, C_1-C_4 alkoxy, C_1-C_4 alkyl optionally substituted with 1 to 3 groups selected from the group consisting of halogen and cyano, C_1-C_4 haloalkyl,$-NH_2$, C_1-C_7 aminocarbonyl,$-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, $-SC_1$-C_4 alkyl, $-S(O)C_1$-C_4 alkyl, $-SO_2C_1$-C_4 alkyl, $-C(O)NH$-C_3-C_6 cycloalkyl, $-C(O)NH$-C_1-C_6 alkyl, $-C(O)NH$-C_1-C_6 haloalkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl; and 4- to 7-membered heterocycloalkyl having 1 or 2 heteroatoms selected from the group O, S, B, and N, wherein the heterocycloalkyl is optionally benzo-fused, wherein the carbons of the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl are optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, oxo, and C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, oxo, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, $-NH_2$, C_1-C_7 aminocarbonyl, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, $-SC_1$-C_4 alkyl, $-S(O)C_1$-C_4 alkyl, $-SO_2C_1$-C_4 alkyl, $-C(O)NH$-C_3-C_6 cycloalkyl, $-C(O)NH$-C_1-C_6 alkyl, and $-C(O)NH$-C_1-C_6 haloalkyl, wherein any B in the of the 4- to 7-membered

heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl, valency permitting, is substituted with hydroxyl, wherein any N in the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl, valency permitting, is substituted with a substituent selected from the group consisting of hydrogen, $-NH_2$, C_1-C_7 aminocarbonyl, $-SO_2C_1$-C_4 alkyl, $-SO_2C_1$-C_4 haloalkyl, -C(O)-NH_2, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, C_1-C_4 alkoxy, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, $-SC_1$-C_4 alkyl, $-S(O)C_1$-C_4 alkyl, $-SO_2C_1$-C_4 alkyl, $-C(O)NH$-C_3-C_6 cycloalkyl, and $-C(O)NH$-C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, 5- to 6-membered heteroaryl, and phenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_1-C_4 alkyl, cyano, and hydroxyl, wherein any S in the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl is optionally substituted with 1 or 2 oxygen atom(s);

(iii) C_3-C_6 cycloalkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, carboxyl, C_1-C_4 alkoxy, C_1-C_4 alkyl optionally substituted with 1 to 3 groups selected from the group consisting of halogen and cyano, C_1-C_4 haloalkyl,$-NH_2$, C_1-C_7 aminocarbonyl,$-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, $-SC_1$-C_4 alkyl, $-S(O)C_1$-C_4 alkyl, $-SO_2C_1$-C_4 alkyl, $-C(O)NH$-C_3-C_6 cycloalkyl, $-C(O)NH$-C_1-C_6 alkyl, $-C(O)NH$-C_1-C_6 haloalkyl, C_2-C_6 alkenyl optionally substituted with 1 to 3 halogens, and C_2-C_6 alkynyl;

(iv) 6-membered aryl or 5- to 10-membered heteroaryl having 1, 2 or 3 heteroatoms selected from the group O, S, and N, wherein the carbons of the 6-membered aryl and the 5- to 10-membered heteroaryl are optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, C_1-C_4 alkoxy, $-NH_2$, C_1-C_7 aminocarbonyl, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, $-SC_1$-C_4 alkyl, $-S(O)C_1$-C_4 alkyl, $-SO_2C_1$-C_4 alkyl, $-C(O)NH$-C_3-C_6 cycloalkyl, and $-C(O)NH$-C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, and $-C(O)NH$-C_3-C_6 cycloalkyl, wherein any N in the heteroaryl, valency permitting, is optionally substituted with a substituent selected from the group consisting of hydrogen,

and C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, oxo, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl;

(v) 4- to 7-membered heterocycloalkyl having 1 or 2 heteroatoms selected from the group O, S, and N, wherein the heterocycloalkyl is optionally benzo-fused, wherein the carbons of the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl are optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, oxo, C_1-C_4 alkoxy, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, oxo, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, -C(O)NH-C_1-C_6 alkyl, and-C(O)NH-C_1-C_6 haloalkyl, wherein any N in the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl, valency permitting, is substituted with a substituent selected from the group consisting of hydrogen, -NH_2, C_1-C_7 aminocarbonyl, -SO_2C_1-C_4 alkyl, -SO_2C_1-C_4 haloalkyl, -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_4 alkyl)$_2$, -C(O)-NH_2, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, oxo, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, 5- to 6-membered heteroaryl, and phenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_1-C_4 alkyl, cyano, and hydroxyl, wherein any S in the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl is optionally substituted with 1 or 2 oxygen atom(s); and

(vi) -$NR_{12}R_{13}$

wherein

R_{12} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 alkylcycloalkyl, C_1-C_7 alkylcarbonyl, C_1-C_7 aminocarbonyl, and C_2-C_5 alkoxycarbonyl;

R_{13} is selected from the group consisting of hydrogen, C_1-C_6 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, nitro,hydroxyl, oxo, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, $-NH_2$, C_1-C_7 aminocarbonyl, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, $-SC_1$-C_4 alkyl, $-S(O)C_1$-C_4 alkyl, and $-SO_2C_1$-C_4 alkyl, C_3-C_6 cycloalkyl, $-C(O)$-C_1-C_6 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, nitro,hydroxyl, oxo, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, $-NH_2$, C_1-C_7 aminocarbonyl, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, $-SC_1$-C_4 alkyl, $-S(O)C_1$-C_4 alkyl, and $-SO_2C_1$-C_4 alkyl, 4- to 7-membered heterocycloalkyl having 1 or 2 heteroatoms selected from the group O, S, and N, wherein the heterocycloalkyl is optionally benzo-fused, wherein the carbons of the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl are optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, oxo, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, oxo, C_1-C_4 alkoxy, $-NH_2$, C_1-C_7 aminocarbonyl, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, $-SC_1$-C_4 alkyl, $-S(O)C_1$-C_4 alkyl, $-SO_2C_1$-C_4 alkyl, $-C(O)NH$-C_3-C_6 cycloalkyl, $-C(O)NH$-C_1-C_6 alkyl, and $-C(O)NH$-C_1-C_6 haloalkyl, and C_3-C_6 cycloalkyl, wherein any N in the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl, valency permitting, is substituted with a substituent selected from the group consisting of hydrogen, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, C_1-C_4 alkoxy, $-NH_2$, C_1-C_7 aminocarbonyl, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, $-SC_1$-C_4 alkyl, $-S(O)C_1$-C_4 alkyl, $-SO_2C_1$-C_4 alkyl, $-C(O)NH$-C_3-C_6 cycloalkyl, and $-C(O)NH$-C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 5- to 6-membered heteroaryl, and phenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_1-C_4 alkyl, cyano, and hydroxyl, wherein any S in the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl is optionally substituted with 1 or 2 oxygen atom(s); and 5- to 10-membered heteroaryl having 1 or 2 heteroatoms selected from the group O, S, and N, wherein the carbons of the 5- to 10-membered heteroaryl are optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, C_1-C_4 alkyl optionally

substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl,C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl, wherein any N in the heteroaryl, valency permitting, is optionally substituted with a substituent selected from the group consisting of hydrogen, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, oxo, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl, and C_3-C_6 cycloalkyl;

or

R_{11} and W are taken together with the nitrogen to which they are attached to form a 4- to 7-membered ring optionally containing 1 to 2 heteroatoms selected from the group consisting of N, S, and O, wherein the carbons of the ring are optionally substituted with 1 to 4 substituents independently selected of cyano, hydroxyl, oxo, halogen, C_1-C_2 alkoxy, N,N-di-C_1-C_4-alkylaminocarboxyl, N-C_1-C_4-alkylaminocarboxyl, C_1-C_7 aminocarboxyl, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, and -C(O)NH-C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl optionally substituted with 1 to 3 substituents selected from the group consisting of halogen, cyano, hydroxyl, and C_1-C_4 alkoxy, -C(O)NH-C_3-C_6 cycloalkyl, -C(O)NH-C_1-C_6 alkyl, -C(O)NH-C_1-C_6 haloalkyl, 5- to 6-membered heteroaryl, and phenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_1-C_4 alkyl, cyano, hydroxyl,C_1-C_2 alkoxy, N,N-di-C_1-C_4-alkylaminocarboxyl, N-C_1-C_4-alkylaminocarboxyl, and C_1-C_7 aminocarboxyl, wherein any N in the 4- to 7-membered ring is substituted with a substituent selected from the group consisting of hydrogen, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, and -C(O)NH-C_3-C_6 cycloalkyl, C_3-

C_6 cycloalkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, C_1-C_4 alkoxy, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl, 5- to 6-membered heteroaryl, and phenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_1-C_4 alkyl, cyano, and hydroxyl, wherein any S in the 4- to 7-membered ring is optionally substituted with 1 or 2 oxygen atom(s); and

Y is C_1-C_6 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, acetylenyl, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_4 alkyl)$_2$, -SO_2NH(C_1-C_4 haloalkyl), -C(O)NH-C_3-C_6 cycloalkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, hydroxyl, cyano, and C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, C_1-C_4 alkoxy, and -NH_2, -C(O)NH-C_1-C_6 alkyl, -C(O)NH-C_1-C_6 cyanoalkyl optionally substituted with 1 to 3 halogen, -C(O)NH-C_1-C_6 haloalkyl, phenyl optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, C_1-C_4 alkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, and -C(O)NH-C_3-C_6 cycloalkyl, and C_3-C_6 cycloalkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl,-NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, -C(O)NH-C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, 5- to 10-membered heteroaryl having 1 or 2 heteroatoms selected from the group O, S, and N, wherein the carbons of the 5- to 10-membered heteroaryl are optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, C_1-C_4 alkoxy, -NH_2,C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl, C_3-C_6

cycloalkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy,-NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl, wherein any N in the heteroaryl, valency permitting, is substituted with a substituent selected from the group consisting of hydrogen, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, oxo, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl, and C_3-C_6 cycloalkyl, and 4- to 7-membered heterocycloalkyl having 1 or 2 heteroatoms selected from the group O, S, and N, wherein the heterocycloalkyl is optionally benzo-fused, wherein the carbons of the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl are optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, oxo, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, oxo, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl, and C_3-C_6 cycloalkyl, wherein any N in the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl, valency permitting, is substituted with a substituent selected from the group consisting of hydrogen, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and 5- to 6-membered heteroaryl, wherein any S in the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl is optionally substituted with 1 or 2 oxygen atom(s);

or a salt thereof.

2. A compound according to claim 1, wherein

W is selected from the group consisting of

(i) hydrogen;

(ii) C_1-C_6 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen; cyano; hydroxyl; oxo; C_1-C_4 alkoxy; C_3-C_6 cycloalkyl optionally substituted by 1 to 3 substituents independently selected from the group halogen and cyano; acetylenyl; -NH_2; C_1-C_7 aminocarbonyl; -NH(C_1-C_4 alkyl); -N(C_1-C_4 alkyl)$_2$; -SC_1-C_4 alkyl; -S(O)C_1-C_4 alkyl; -SO_2C_1-C_4 alkyl; -C(O)NH-C_3-C_6 cycloalkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, hydroxyl, cyano, and C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, and -NH_2; -C(O)NH-C_1-C_6 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, and -NH_2; -C(O)NH-C_1-C_6 cyanoalkyl optionally substituted with 1 to 3 halogen; -C(O)NH-C_1-C_6 haloalkyl; -C(O)-4- to 7-membered heterocycloalkyl attached by a nitrogen and optionally having 1 or 2 other heteroatoms selected from the group O, S, and N, wherein the carbons of the 4- to 7-membered heterocycloalkyl are optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, oxo, -NH_2, C_1-C_7 aminocarbonyl, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, oxo, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl, and C_3-C_6 cycloalkyl, wherein any other N in the 4- to 7-membered heterocycloalkyl, valency permitting, is substituted with a substituent selected from the group consisting of hydrogen, -NH_2, C_1-C_7 aminocarbonyl, -SO_2C_1-C_4 alkyl, -SO_2C_1-C_4 haloalkyl, and C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, C_1-C_4 alkoxy, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, -C(O)NH-C_1-C_6 alkyl, and -C(O)NH-C_1-C_6 haloalkyl; 5- to 10-membered heteroaryl having 1 or 2 heteroatoms selected from the group O, S, and N, wherein the carbons of the 5- to 10-membered heteroaryl are optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano,

hydroxyl, oxo, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, -C(O)NH-C_1-C_6 alkyl, and -C(O)NH-C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, and -C(O)NH-C_3-C_6 cycloalkyl, wherein any N in the heteroaryl, valency permitting, is optionally substituted with a substituent selected from the group consisting of hydrogen, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, oxo, C_3-C_6 cycloalkyl,C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl, and C_3-C_6 cycloalkyl, wherein any S in the heteroaryl is optionally substituted with 1 or 2 oxygen atom(s); phenyl optionally substituted with 1 to 3 substituents selected from the group consisting of halogen, C_1-C_4 alkyl, cyano, and hydroxyl; C_3-C_6 cycloalkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, C_1-C_4 alkoxy, C_1-C_4 alkyl optionally substituted with 1 to 3 groups selected from the group consisting of halogen and cyano, C_1-C_4 haloalkyl,-NH_2, C_1-C_7 aminocarbonyl,-NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, -C(O)NH-C_1-C_6 alkyl, -C(O)NH-C_1-C_6 haloalkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl; and 4- to 7-membered heterocycloalkyl having 1 or 2 heteroatoms selected from the group O, S, B, and N, wherein the heterocycloalkyl is optionally benzo-fused, wherein the carbons of the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl are optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, oxo, and C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, oxo, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, -C(O)NH-C_1-C_6 alkyl, and -C(O)NH-C_1-C_6 haloalkyl, wherein any B in the of the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl, valency permitting, is substituted with hydroxyl, wherein any N in the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl, valency

permitting, is substituted with a substituent selected from the group consisting of hydrogen, -NH_2, C_1-C_7 aminocarbonyl, -SO_2C_1-C_4 alkyl, -SO_2C_1-C_4 haloalkyl, -C(O)-NH_2, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, C_1-C_4 alkoxy, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, 5- to 6-membered heteroaryl, and phenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_1-C_4 alkyl, cyano, and hydroxyl, wherein any S in the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl is optionally substituted with 1 or 2 oxygen atom(s);

(iii) C_3-C_6 cycloalkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, carboxyl, C_1-C_4 alkoxy, C_1-C_4 alkyl optionally substituted with 1 to 3 groups selected from the group consisting of halogen and cyano, C_1-C_4 haloalkyl,-NH_2, C_1-C_7 aminocarbonyl,-NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, -C(O)NH-C_1-C_6 alkyl, -C(O)NH-C_1-C_6 haloalkyl, C_2-C_6 alkenyl optionally substituted with 1 to 3 halogens, and C_2-C_6 alkynyl;

(iv) 5- to 10-membered heteroaryl having 1 or 2 heteroatoms selected from the group O, S, and N, wherein the carbons of the 5- to 10-membered heteroaryl are optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, and -C(O)NH-C_3-C_6 cycloalkyl, wherein any N in the heteroaryl, valency permitting, is optionally substituted with a substituent selected from the group consisting of hydrogen, and C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, oxo, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4

alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl;

(v) 4- to 7-membered heterocycloalkyl having 1 or 2 heteroatoms selected from the group O, S, and N, wherein the heterocycloalkyl is optionally benzo-fused, wherein the carbons of the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl are optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, oxo, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, oxo, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, -C(O)NH-C_1-C_6 alkyl, and-C(O)NH-C_1-C_6 haloalkyl, wherein any N in the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl, valency permitting, is substituted with a substituent selected from the group consisting of hydrogen, -NH_2, C_1-C_7 aminocarbonyl, -SO_2C_1-C_4 alkyl, -SO_2C_1-C_4 haloalkyl, -C(O)-NH_2, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, 5- to 6-membered heteroaryl, and phenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_1-C_4 alkyl, cyano, and hydroxyl, wherein any S in the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl is optionally substituted with 1 or 2 oxygen atom(s); and

(vi) -$NR_{12}R_{13}$

wherein

R_{12} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 alkylcycloalkyl, C_1-C_7 alkylcarbonyl, C_1-C_7 aminocarbonyl, and C_2-C_5 alkoxycarbonyl;

R_{13} is selected from the group consisting of hydrogen, C_1-C_6 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, nitro,hydroxyl, oxo, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, -NH_2, C_1-C_7

aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, and -SO_2C_1-C_4 alkyl, C_3-C_6 cycloalkyl, -C(O)-C_1-C_6 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, nitro,hydroxyl, oxo, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, and -SO_2C_1-C_4 alkyl, 4- to 7-membered heterocycloalkyl having 1 or 2 heteroatoms selected from the group O, S, and N, wherein the heterocycloalkyl is optionally benzo-fused, wherein the carbons of the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl are optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, oxo, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, oxo, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, -C(O)NH-C_1-C_6 alkyl, and -C(O)NH-C_1-C_6 haloalkyl, and C_3-C_6 cycloalkyl, wherein any N in the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl, valency permitting, is substituted with a substituent selected from the group consisting of hydrogen, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 5- to 6-membered heteroaryl, and phenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_1-C_4 alkyl, cyano, and hydroxyl, wherein any S in the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl is optionally substituted with 1 or 2 oxygen atom(s); and 5- to 10-membered heteroaryl having 1 or 2 heteroatoms selected from the group O, S, and N, wherein the carbons of the 5- to 10-membered heteroaryl are optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-

C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl,C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl, wherein any N in the heteroaryl, valency permitting, is optionally substituted with a substituent selected from the group consisting of hydrogen, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, oxo, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl, and C_3-C_6 cycloalkyl;

or

R_{11} and W are taken together with the nitrogen to which they are attached to form a 4- to 7-membered ring optionally containing 1 to 2 heteroatoms selected from the group consisting of N, S, and O, wherein the carbons of the ring are optionally substituted with 1 to 4 substituents independently selected of cyano, hydroxyl, oxo, halogen, C_1-C_2 alkoxy, N,N-di-C_1-C_4-alkylaminocarboxyl, N-C_1-C_4-alkylaminocarboxyl, C_1-C_7 aminocarboxyl, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, and -C(O)NH-C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl optionally substituted with 1 to 3 substituents selected from the group consisting of halogen, cyano, hydroxyl, and C_1-C_4 alkoxy, -C(O)NH-C_3-C_6 cycloalkyl, -C(O)NH-C_1-C_6 alkyl, -C(O)NH-C_1-C_6 haloalkyl, 5- to 6-membered heteroaryl, and phenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_1-C_4 alkyl, cyano, hydroxyl,C_1-C_2 alkoxy, N,N-di-C_1-C_4-alkylaminocarboxyl, N-C_1-C_4-alkylaminocarboxyl, and C_1-C_7 aminocarboxyl, wherein any N in the 4- to 7-membered ring is substituted with a substituent selected from the group consisting of hydrogen, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, and -C(O)NH-C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, C_1-C_4 alkoxy, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl, 5- to 6-membered heteroaryl, and phenyl

optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_1-C_4 alkyl, cyano, and hydroxyl, wherein any S in the 4- to 7-membered ring is optionally substituted with 1 or 2 oxygen atom(s); and

Y is C_1-C_6 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, acetylenyl, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, hydroxyl, cyano, and C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, C_1-C_4 alkoxy, and -NH_2, -C(O)NH-C_1-C_6 alkyl, -C(O)NH-C_1-C_6 cyanoalkyl optionally substituted with 1 to 3 halogen, -C(O)NH-C_1-C_6 haloalkyl, phenyl optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, C_1-C_4 alkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, and -C(O)NH-C_3-C_6 cycloalkyl, and C_3-C_6 cycloalkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl,-NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, -C(O)NH-C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, 5- to 10-membered heteroaryl having 1 or 2 heteroatoms selected from the group O, S, and N, wherein the carbons of the 5- to 10-membered heteroaryl are optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, C_1-C_4 alkoxy, -NH_2,C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy,-NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl, wherein any N in the heteroaryl, valency permitting, is substituted with a substituent selected from the group consisting of hydrogen, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents

independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, oxo, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl, and C_3-C_6 cycloalkyl, and 4- to 7-membered heterocycloalkyl having 1 or 2 heteroatoms selected from the group O, S, and N, wherein the heterocycloalkyl is optionally benzo-fused, wherein the carbons of the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl are optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, oxo, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, oxo, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl, and C_3-C_6 cycloalkyl, wherein any N in the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl, valency permitting, is substituted with a substituent selected from the group consisting of hydrogen, C_1-C_4 alkyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, cyano, hydroxyl, acetylenyl, C_1-C_4 alkoxy, -NH_2, C_1-C_7 aminocarbonyl, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -SC_1-C_4 alkyl, -S(O)C_1-C_4 alkyl, -SO_2C_1-C_4 alkyl, -C(O)NH-C_3-C_6 cycloalkyl, and -C(O)NH-C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and 5- to 6-membered heteroaryl, wherein any S in the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl is optionally substituted with 1 or 2 oxygen atom(s);

or a salt thereof.

3. A compound according to claim 1 wherein A_1 is trifluoromethyl, A_2 is O, R_1 is hydrogen, R_2 is trifluoromethyl, R_3 is hydrogen, R_4 is trifluoromethyl or halogen, and R_5 is halogen; or a salt thereof.

4. A compound according to claim 3 wherein R_4 is halogen; or a salt thereof.

5. A compound according to claim 3 wherein R_4 is trifluoromethyl; or a salt thereof.

6. A compound according to claim 4 wherein R_4 is chloro or bromo; or a salt thereof.

7. A compound according to claim 4 wherein R_4 is bromo; or a salt thereof.

8. A compound according to claim 4 wherein R_4 is chloro; or a salt thereof.

9. A compound according to any of claims 1–8 wherein R_5 is fluoro; or a salt thereof.

10. A compound according to claim 1, selected from the group consisting of:

4-(rel-(*S*)-5-(3-bromo-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-((*S*)-1-ethyl-5-oxopyrrolidin-3-yl)-2-methylbenzamide
4-(rel-(*S*)-5-(3-bromo-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methyl-N-(rel-(*S*)-2-(methylsulfonyl)isoxazolidin-4-yl)benzamide
4-(rel-(*S*)-5-(3-bromo-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methyl-N-(rel-(*R*)-2-(methylsulfonyl)isoxazolidin-4-yl)benzamide
cis-3-(4-((S*)-5-(3-chloro-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methylbenzamido)cyclobutane-1-carboxylic acid

trans-3-(4-((S*)-5-(3-chloro-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methylbenzamido)cyclobutane-1-carboxylic acid
4-((S*)-5-(3-chloro-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methyl-N-(*cis*-3-(methylcarbamoyl)cyclobutyl)benzamide
4-((S*)-5-(3-chloro-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methyl-N-(*trans*-3-(methylcarbamoyl)cyclobutyl)benzamide
rel-(S)-4-(5-(2-fluoro-3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methyl-N-(2-oxo-2-((2,2,2-trifluoroethyl)amino)ethyl)benzamide
4-((S*)-5-(3-chloro-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methyl-N-((trans)-3-(trifluoromethyl)cyclobutyl)benzamide
4-(rel-(R)-5-(3-bromo-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methyl-N-(rel-(S)-2-(methylsulfonyl)isoxazolidin-4-yl)benzamide

4-(rel-(R)-5-(3-bromo-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methyl-N-(rel-(R)-2-(methylsulfonyl)isoxazolidin-4-yl)benzamide
4-((S*)-5-(3-chloro-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methyl-N-((cis)-3-(trifluoromethyl)cyclobutyl)benzamide
rel-4-((R)-5-(3-chloro-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methyl-N-((S*)-3-(2,2,2-trifluoroethyl)-4,5-dihydroisoxazol-5-yl)benzamide
rel-4-((S)-5-(3-chloro-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methyl-N-((S*)-3-(2,2,2-trifluoroethyl)-4,5-dihydroisoxazol-5-yl)benzamide
rel-4-((R)-5-(3-chloro-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methyl-N-((R*)-3-(2,2,2-trifluoroethyl)-4,5-dihydroisoxazol-5-yl)benzamide
rel-4-((S)-5-(3-chloro-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methyl-N-((R*)-3-(2,2,2-trifluoroethyl)-4,5-dihydroisoxazol-5-yl)benzamide

rel-4-((S)-5-(3-chloro-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methyl-N-((R*)-2-(2,2,2-trifluoroethyl)isoxazolidin-4-yl)benzamide
rel-4-((S)-5-(3-chloro-2-fluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methyl-N-((S3)-2-(2,2,2-trifluoroethyl)isoxazolidin-4-yl)benzamide

or a salt of any of the foregoing.

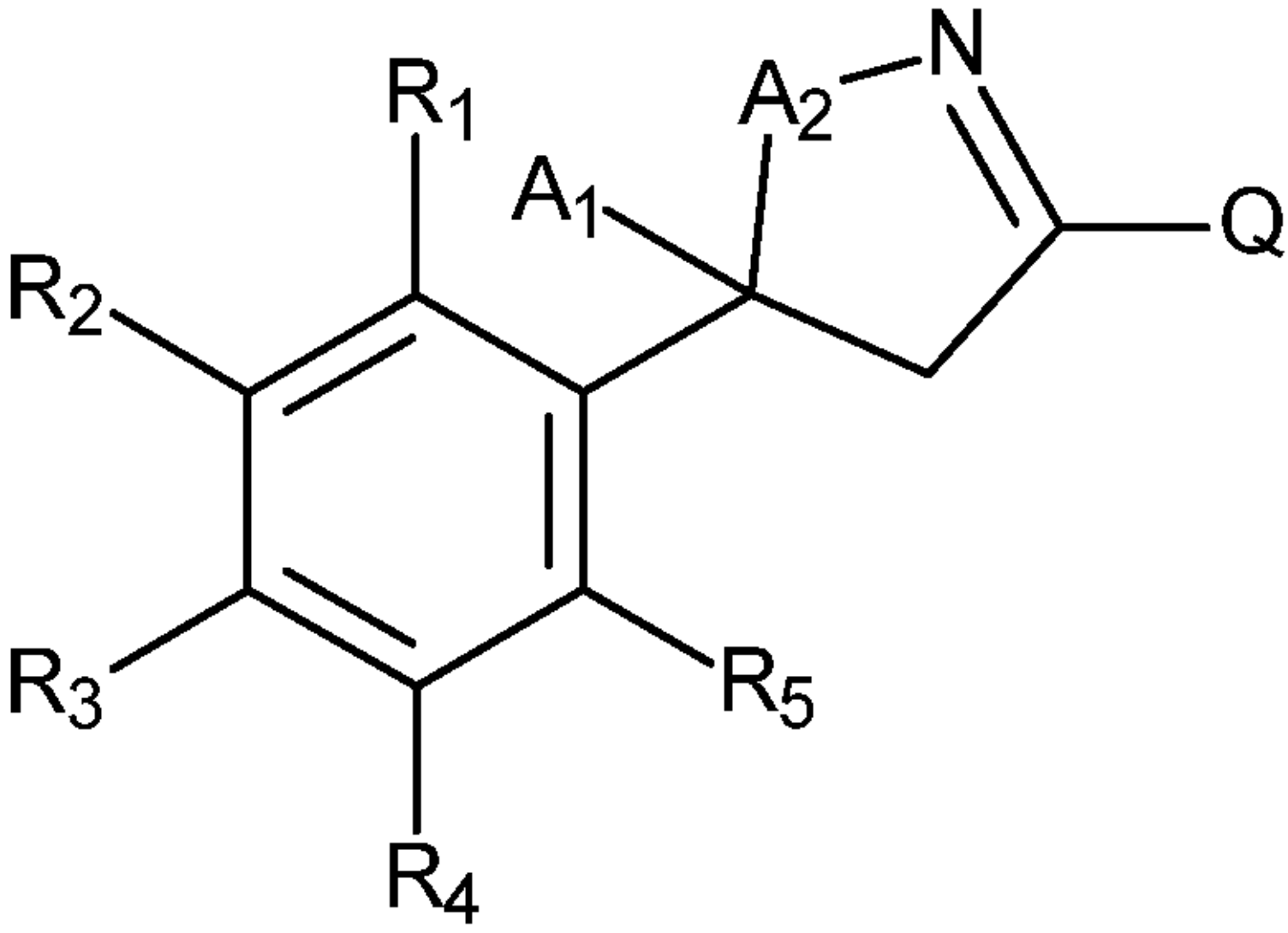
11. A composition comprising a compound of any one of claims 1 to 10, or a salt thereof, and at least one acceptable carrier.

12. The use of a compound of any one of claims 1 to 10, or a salt thereof, as a medicament.

13. The use of a compound of any one of claims 1 to 10, or a salt thereof, in the manufacture of a medicament for treating pests.

14. The use of a compound of any one of claims 1 to 10, or a salt thereof, in the manufacture of a medicament for treating fleas.

15. The use of a compound of any one of claims 1 to 10, or a salt thereof, in the manufacture of a medicament for controlling ticks.



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