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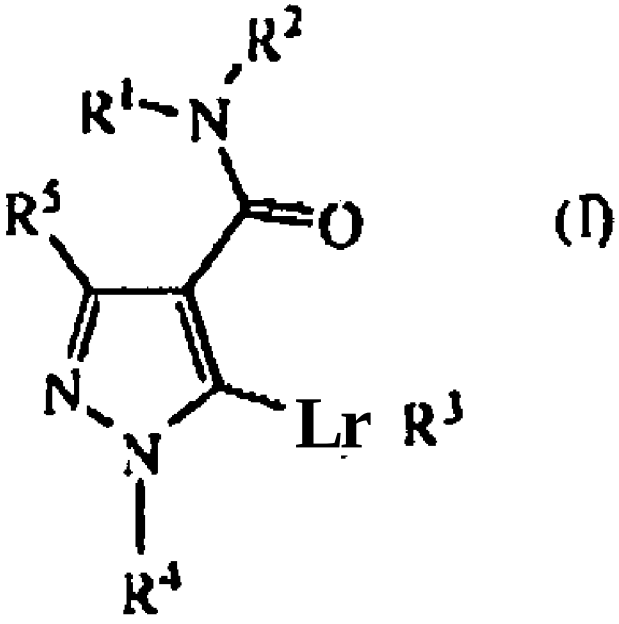
(54) Title: COMPOUNDS AND COMPOSITIONS AS TGR5 AGONISTS



(I)

(57) Abstract: The invention provides compounds of formula (I), pharmaceutical compositions comprising such compounds and methods of using such compounds to treat or prevent diseases or disorders associated with TGR5.

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COMPOUNDS AND COMPOSITIONS AS TGR5 AGONISTS

FIELD OF THE INVENTION

[0001] The invention relates to compounds, compositions and methods for modulating TGR5.

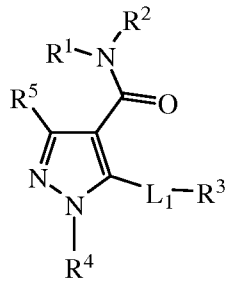
BACKGROUND OF THE INVENTION

[0002] Bile acids (BAs) are released from the gallbladder after each meal and subsequently facilitate the digestion of nutrients. A multitude of endocrine, neural, and metabolic signaling pathways are activated upon food intake to coordinate the effective use of the available energy. Bile acids are known to be involved in lipid absorption and cholesterol homeostasis. However, bile acids are also regarded as signaling hormones endowed with paracrine and endocrine functions related to the homeostasis of cholesterol levels, control of lipid and carbohydrate metabolism, and regulation of the immune system. TGR5 (also known as GPBARl or M-BAR) has been identified as the endogenously specific metabotropic receptor of bile acids.

SUMMARY OF THE INVENTION

[0003] Provided herein are compounds and pharmaceutical compositions thereof, which are useful agonists of TGR5.

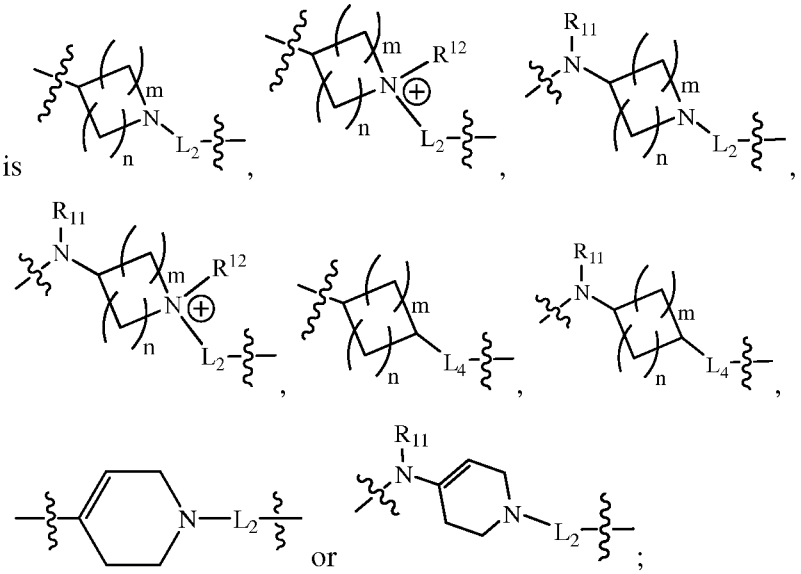
[0004] In one aspect provided herein such compounds, and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, enantiomers, racemic mixtures, individual stereoisomers and mixture of stereoisomers thereof, have a structure according to Formula (I):



(I)

wherein,

R^1 and R^2 are each independently selected from Ci-Cealkyl, and C_2-C_6alkene, and taken together with the N atom to which they are attached form a 4 to 6 membered heterocycloalkyl ring containing a N heteroatom, a 9 to 14 membered fused bicyclic heterocycloalkyl ring containing a N heteroatom, or a 9 to 14 membered fused bicyclic heteroaryl containing an N heteroatom, wherein such heterocycloalkyl and fused bicyclic heteroaryl are each optionally substituted with 1 to 5 substituents independently selected from halogen, deuterium, C_1-C_6alkyl, Ci-Cehaloalkyl, -CN, R^9, -OR^9, phenyl, phenoxy, Cioaryl and C_{14}aryl, wherein such phenyl, phenoxy, Cioaryl and C_{14}aryl are each optionally substituted with 1 to 5 substituents independently selected from halogen, deuterium and -OR^9;

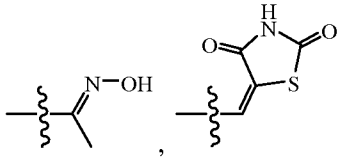
L_1 is 

L_2 is selected from -C(O)-, -C(0)0-, -$(CH_2)_q$C(0)0-, -S(0) $_2$-, C_1-C_6alkylene, phenylene, Cioarylene, C^arylene, a 5, 6, 9, 10 or 14 membered heteroarylene containing 1 to 2 heteroatoms independently selected from N, O and S, or a bond, wherein the Ci-Cealkylene ,arylene and heteroarylene of L_2 are optionally substituted with 1 to 3 substituents independently selected from deuterium, R^9 and -C(0)OR ^{9};

L_3 is Ci-C_6alkylene optionally substituted with 1 to 3 substituents independently selected deuterium, R^9 and -C(0)OR ^{9}, or Ci-Cealkenylene optionally substituted with 1 to 3 substituents independently selected from deuterium, R^9 and -C(0)OR ^{9};

L_4 is selected from a -NR^9-, -$NR^9C(0)0$-, -$NR^9(CH_2)_q$ -, -$C(0)NR^9$-, -$S(0)_2$-, -0-, C_1-Cealkylene, phenylene, Cioarylene, C_{14}arylene, a 5, 6, 9, 10 or 14 membered heteroarylene containing 1 to 2 heteroatoms independently selected from N, O and S, wherein the Ci-Cealkylene, arylene and heteroarylene of L_4 are optionally substituted with 1 to 3 substituents independently selected from deuterium, R^9 and -$C(0)OR^9$;

R^3 is selected from Ci-Cealkyl, Ci-Cehaloalkyl, C_3-C_8cycloalkyl, -L_3R^6, phenyl, Cioaryl, C_{14}aryl, a 5, 6, 9, 10 or 14 membered heteroaryl containing 1 to 3 N heteroatoms and optionally one heteroatom selected from O and S, and a 4 to 7 membered heterocycloalkyl ring containing 1 to 2 heteroatoms independently selected from N, O and S, wherein the Ci-Cealkyl, aryl, heterocycloalkyl, C_3-Cscycloalkyl and heteroaryl groups of R^3 are each optionally substituted with 1 to 3 substituents independently selected from halogen, R^9, R^6, -OR^9, -$N(R^9)_2$, -$C(0)N(R^9)_2$, -$C(0)NR^9OH$, -$C(0)OR^9$, -$C(0)OL_3R^6$, -$L_3C(0)OR^9$, -$C(0)R^9$, -CN, -$S(0)_2R^9$, -$S(0)_2N(R^9)_2$, -$S(0)_2NR^9C(0)R^9$, -$S(0)_2L_3C(0)OR^9$, -$OS(0)_2N(R^9)_2$, -$S(0)_2NR^9OH$, -$OL_3C(0)OR^9$, -$C(0)NR^9L_3C(0)OR^9$, -L_3R^6



and a 5 membered heteroaryl containing 1 to 4 N heteroatoms and optionally one heteroatom selected from O and S;

R^4 is selected from H, Ci-Cealkyl, phenyl, Cioaryl, C_{14}aryl, C_3-Cscycloalkyl, 5-6 membered heteroaryl containing one or more N heteroatoms, wherein the Cr C_6alkyl, aryl, heteroaryl and C_3-Cscycloalkyl groups of R^4 are each optionally substituted with 1 to 3 substituents independently selected from halogen, -CN, R^9, and -OR^9;

R^5 is H, Ci-C_6alkyl or C_1-C_6haloalkyl.

R^6 is C_3-C_8cycloalkyl, phenyl, Cioaryl, C_{14}aryl, a 5, 6, 9, 10 or 14 membered heteroaryl containing 1 to 2 heteroatoms independently selected from N, O and S, a 4 to 7 membered heterocycloalkyl ring containing 1 to 2 heteroatoms independently selected from N, O and S, and a 9 to 14 membered fused bicyclic heterocycloalkyl ring containing containing 1 to 2 heteroatoms independently selected from N, O and S, each of which is optionally substituted with 1 to 5

substituents independently selected from halogen, deuterium, R^9, -OR^9, -CN and -C(0)OR^9;

R^9 is H, Ci-C_6alkyl optionally substituted with 1 to 4 -OH groups or Ci-Cehaloalkyl;

R^{11} is H or Ci-C_6alkyl;

R^{12} is Ci-C_4alkyl, -CH_2C(0)OH or -(CHR^{13})C(0)OH;

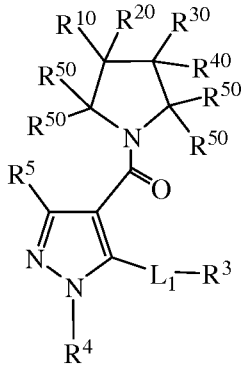
R^{13} is H or Ci-C_4alkyl;

each m is independently 1, 2 or 3;

each n is independently 1, 2 or 3, and

each q is independently 1, 2, 3, 4, 5, or 6.

[0005] In certain embodiments, such the compounds of Formula (I) are compounds having the structure of Formula (II):



(II)

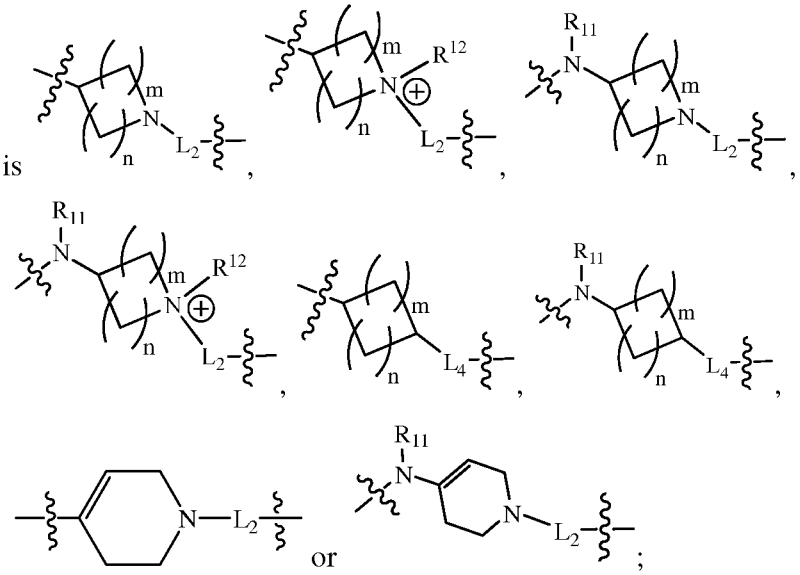
wherein,

R^{10} and R^{20} are each independently selected from H, -OR^9, deuterium or halogen;

R^{30} is selected from phenyl, phenoxy, Cioaryl and C_{14}aryl, each of which is optionally substituted with 1 to 5 substituents independently selected from halogen, deuterium and -OR^9;

R^{40} is selected from H, deuterium, Ci-Cealkyl and Ci-Cehaloalkyl;

each R^{50} is independently selected from H or deuterium;

L_1 is 

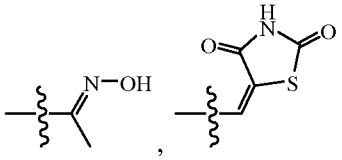
L_2 is selected from -C(0)-, -C(0)0-, $-(CH_2)_qC(0)0-$, $-S(0)_2-$, C_1-C_6alkylene, phenylene, Cioarylene, C^arylene, a 5, 6, 9, 10 or 14 membered heteroarylene containing 1 to 2 heteroatoms independently selected from N, O and S, or a bond, wherein the Ci-Cealkylene ,arylene and heteroarylene of L_2 are optionally substituted with 1 to 3 substituents independently selected from deuterium, R^9 and $-C(0)OR^9$;

L_3 is C_1-C_6alkylene optionally substituted with 1 to 3 substituents independently selected deuterium, R^9 and $-C(0)OR^9$, or Ci-Cealkenylene optionally substituted with 1 to 3 substituents independently selected from deuterium, R^9 and $-C(0)OR^9$;

L_4 is selected from a $-NR^9-$, $-NR^9C(0)0-$, $-NR^9(CH_2)_q-$, $-C(0)NR^9-$, $-S(0)_2-$, -0-, C_1-C_6alkylene, phenylene, Cioarylene, C^arylene, a 5, 6, 9, 10 or 14 membered heteroarylene containing 1 to 2 heteroatoms independently selected from N, O and S, wherein the Ci-Cealkylene, arylene and heteroarylene of L_4 are optionally substituted with 1 to 3 substituents independently selected from deuterium, R^9 and $-C(0)OR^9$;

R^3 is selected from Ci-Cealkyl, Ci-Cehaloalkyl, C_3-Cscycloalkyl, $-L_3R^6$, phenyl, Cioaryl, C_{14}aryl, a 5, 6, 9, 10 or 14 membered heteroaryl containing 1 to 3 N heteroatoms and optionally one heteroatom selected from O and S, and a 4 to 7 membered heterocycloalkyl ring containing 1 to 2 heteroatoms independently selected from N, O and S, wherein the Ci-Cealkyl, aryl, heterocycloalkyl, C_3-Cscycloalkyl and heteroaryl groups of R^3 are each optionally substituted with 1 to

3 substituents independently selected from halogen, R^9, R^6, $-OR^9$, $-N(R^9)_2$, $-C(0)N(R^9)_2$, $-C(0)NR^9OH$, $-C(0)OR^9$, $-C(0)OL_3R^6$, $-L_3C(0)OR^9$, $-C(0)R^9$, $-CN$, $-S(0)_2R^9$, $-S(0)_2N(R^9)_2$, $-S(0)_2NR^9C(0)R^9$, $-S(0)_2L_3C(0)OR^9$, $-OS(O)_2N(R^9)_2$, $-S(0)_2NR^9OH$, $-OL_3C(0)OR^9$, $-C(0)NR^9L_3C(0)OR^9$, $-L_3R^6$



and a 5 membered heteroaryl containing 1 to 4 N heteroatoms and optionally one heteroatom selected from O and S;

R^4 is selected from H, Ci-Cealkyl, phenyl, Cioaryl, C_{14}aryl, C_3-Cscycloalkyl, 5-6 membered heteroaryl containing one or more N heteroatoms, wherein the Cr C_6alkyl, aryl, heteroaryl and C_3-Cscycloalkyl groups of R^4 are each optionally substituted with 1 to 3 substituents independently selected from halogen, -CN, R^9, and $-OR^9$;

R^5 is H, Ci-C_6alkyl or C_1-C_6haloalkyl.

R^6 is C_3-C_8cycloalkyl, phenyl, Cioaryl, C_{14}aryl, a 5, 6, 9, 10 or 14 membered heteroaryl containing 1 to 2 heteroatoms independently selected from N, O and S, a 4 to 7 membered heterocycloalkyl ring containing 1 to 2 heteroatoms independently selected from N, O and S, and a 9 to 14 membered fused bicyclic heterocycloalkyl ring containing containing 1 to 2 heteroatoms independently selected from N, O and S, each of which is optionally substituted with 1 to 5 substituents independently selected from halogen, deuterium, R^9, $-OR^9$, -CN and $-C(0)OR^9$;

R^9 is H, Ci-C_6alkyl optionally substituted with 1 to 4 -OH groups or Ci-Cehaloalkyl;

R^{11} is H or Ci-C_6alkyl;

R^{12} is Ci-C_4alkyl, $-CH_2C(0)OH$ or $-(CHR^{13})C(0)OH$;

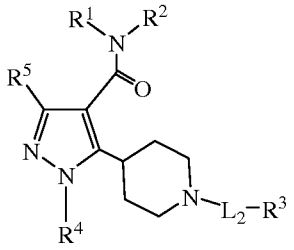
R^{13} is H or C_1-C_4alkyl;

each m is independently 1, 2 or 3;

each n is independently 1, 2 or 3, and

each q is independently 1, 2, 3, 4, 5, or 6.

[0006] In certain embodiments, compounds of Formula (I) are compounds having the structure of Formula (III), Formula (IV) or Formula (V):



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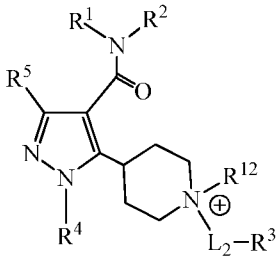

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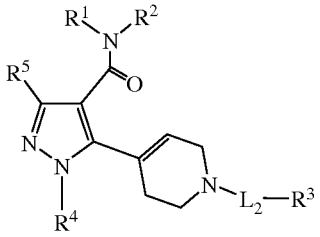
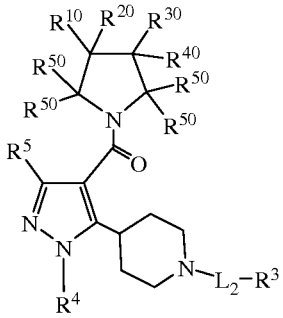


(V).

[0007] In certain embodiments of compounds of Formula (I), Formula (III), Formula (IV) or Formula (V), R^1 and R^2 are each independently selected from Ci-Cealkyl and C_2-C_6alkene, and taken together with the N atom to which they are attached form a 1,2,3,4-tetrahydroisoquinoline or an azetidine, each of which is optionally substituted with 1 to 3 substituents independently selected from halogen, deuterium, -CN, R^9, -OR^9, phenyl and phenoxy, wherein such phenyl and phenoxy are each optionally substituted with 1 to 5 substituents independently selected from halogen, deuterium and -OR^9.

[0008] In certain embodiments, compounds of Formula (I) or Formula (II) are compounds having the structure of Formula (VI), Formula (VII) or Formula (VIII):



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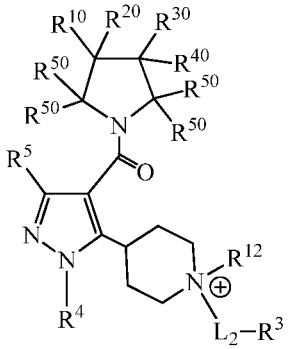
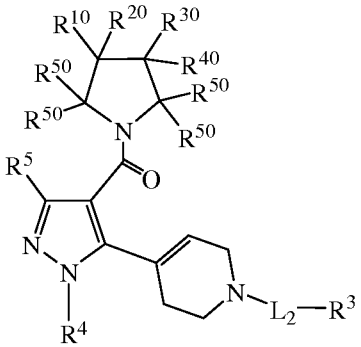


(VII)



(VIII).

[0009] In certain embodiments of the compounds of Formula (I), Formula (II) and Formula (VI), Formula (VII) or Formula (VIII), R^{10} and R^{20} are each independently selected from H, deuterium or F.

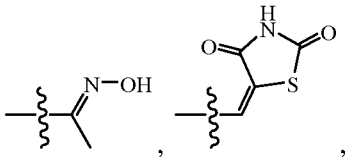
[00010] In certain embodiments of the compounds of Formula (I), Formula (II) and Formula (VI), Formula (VII) or Formula (VIII), R^{40} is selected from H, deuterium, -CH_3 -CF_3 and -CF_2CH_3.

[00011] In certain embodiments of the compounds of Formula (I), Formula (II) and Formula (VI), Formula (VII) or Formula (VIII), R^{30} is selected from phenyl, phenoxy, Cioaryl and C_{14}aryl, each of which is optionally substituted with 1 to 5 substituents

independently selected from F, deuterium and methoxy.

[00012] In certain embodiments of the compounds of Formulas (I)-(VIII), R^4 is selected from H, methyl, ethyl, propyl, butyl, phenyl, pyridinyl, pyrimidinyl, and cyclohexyl, each of which is optionally substituted with 1 to 3 substituents independently selected from -F, -Br, -CI, -CN, R^9, and $-OR^9$.

[00013] In certain embodiments of the compounds of Formulas (I)-(VIII), R^3 is selected from $-CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2C(CH_3)_3$, $-CH_2CH_2C(CH_3)_3$, $-CF_3$, cyclopropyl, cyclohexyl, phenyl, tetrahydro-2H-pyranyl, oxazolyl, oxadiazolyl, pyrazolyl, isoxazolyl, 1H-benzo[d][l,2,3]triazolyl, piperidinyl, pyridinyl, pyrimidinyl, benzthiazolyl and tetrazolyl, each of which is each optionally substituted with 1 to 3 substituents independently selected from -F, -Br, -CI, R^9, $-OR^9$, $-N(R^9)_2$, $-C(0)N(R^9)_2$, $-C(0)NR^9OH$, $-C(0)OR^9$, $-C(0)OL_3R^6$, $-L_3C(0)OR^9$, $-C(0)R^9$, -CN, $-S(0)_2R^9$, $-S(0)_2N(R^9)_2$, $-S(0)_2NR^9C(0)R^9$, $-S(0)_2L_3C(0)OR^9$, $-OS(0)_2N(R^9)_2$, $-S(0)_2NR^9OH$, $-OL_3C(0)OR^9$, $-C(0)NR^9L_3C(0)OR^9$,



, tetrazolyl, pyrazolyl and $-L_3R^6$.

[00014] In certain embodiments of the compounds of Formulas (I)-(VIII), R^9 is H, methyl, ethyl, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CF_3$, propyl substituted with 1 to 2 -OH groups.

[00015] In certain embodiments of the compounds of Formulas (I)-(VIII), R^5 is H or methyl.

[00016] In certain embodiments of the compounds of Formulas (I)-(VIII), R^{12} is methyl, ethyl or n-propyl.

[00017] In certain embodiments of the compounds of Formulas (I)-(VIII), R^{13} is H or methyl.

[00018] In certain embodiments of the compounds of Formula (I), Formula (II) or Formula (III), are selected from: tert-butyl 4-[l-(4-fluorophenyl)-4-[(3-phenylpyrrolidin-l-yl)carbonyl]-lH-pyrazol-5-yl]piperidine-l-carboxylate, tert-butyl 4-[l-(4-bromophenyl)-4-[(3-phenylpyrrolidin-l-yl)carbonyl]-lH-pyrazol-5-yl]piperidine-l-carboxylate, tert-butyl 4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5-yl]piperidine-1-carboxylate, tert-butyl 4-[l-(4-chlorophenyl)-4-{ [3-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine-l-carboxylate, tert-butyl 4-[l-(4-chlorophenyl)-4-{[(3R)-3-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine-l-

carboxylate, tert-butyl 4-[l-(2,4-difluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine-l-carboxylate, tert-butyl 4-[l-(4-chloro-2-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- l-yl]carbonyl }- 1H-pyrazol-5 -yl]piperidine- 1-carboxylate, tert-butyl 4-[l-(4-fluorophenyl)-4-{ [3-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine-l-carboxylate, tert-butyl 4-[l-(4-methoxyphenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine-l-carboxylate, tert-butyl 4-[1-(4-cyanophenyl)-4- {[(3R)-3 -phenylpyrrolidin- 1-yljcarbonyl }- 1H-pyrazol-5 -yljpiperidine- 1-carboxylate, tert-butyl 4-(4- {[(3R)-3-phenylpyrrolidin- l-yl]carbonyl }- 1-(pyrimidin-2-yl)-lH-pyrazol-5-yl)piperidine-l -carboxylate, tert-butyl 4-[l-(2-chloro-4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- l-yl]carbonyl }- 1H-pyrazol-5 -yljpiperidine- 1-carboxylate, tert-butyl 4-[l-(4-fluorophenyl)-4-{ [3-(2-fluorophenyl)pyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine-l-carboxylate, tert-butyl 4-[l-(4-methylphenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine-l-carboxylate, tert-butyl 4-[1-(4-chlorophenyl)-4- [(3-methyl-3 -phenylpyrrolidin- 1-yl)carbonyl] - 1H-pyrazol-5 -yljpiperidine- 1-carboxylate, tert-butyl 4-(l-phenyl-4-{ [(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl)piperidine-l-carboxylate, tert-butyl (3S)-3-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]pyrrolidine-l-carboxylate, tert-butyl (3R)-3-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine-l-carboxylate, tert-butyl (3R)-3-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]pyrrolidine-l-carboxylate, tert-butyl 3-[1-(4-chlorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }- lH-pyrazol-5-yl]pyrrolidine-l -carboxylate, tert-butyl 3-[l-(4-fluorophenyl)-4-{ [(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }- 1H-pyrazol-5 -yl] azetidine- 1-carboxylate, tert-butyl 3-[1-(4-fluorophenyl)-4-[(3-phenylpyrrolidin-l-yl)carbonyl]-lH-pyrazol-5-yl]piperidine-l-carboxylate, 1-methylcyclopropyl 4-[l-(4-chlorophenyl)-4-{ [(3R)-3-phenylpyrrolidin-l-yljcarbonyl }-lH-pyrazol-5 -yljpiperidine- 1-carboxylate, 1-{4-[1-(4-chlorophenyl)-4-[(3-phenylpyrrolidin- 1-yl)carbonyl]-1H-pyrazol-5-yljpiperidin- 1-yl }-3,3-dimethylbutan- 1-one, propan-2-yl 4-[l-(4-chlorophenyl)-4-[(3-phenylpyrrolidin-l-yl)carbonyl]-lH-pyrazol-5-yljpiperidine- 1-carboxylate, benzyl 4-[1-(4-chlorophenyl)-4-[(3-phenylpyrrolidin- 1-yl)carbonyl]-lH-pyrazol-5-yl]piperidine-l-carboxylate, propan-2-yl 4-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine-l-carboxylate, tert-butyl 4-[1-(4-chlorophenyl)-4- {[(3R)-3 -phenylpyrrolidin- 1-yljcarbonyl }- 1H-pyrazol-5 -yl]- 1,2,3,6-tetrahydropyridine-l -carboxylate, benzyl 4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-

phenylpyrrolidin- 1-yljcarbonyl }- 1H-pyrazol-5 -yljpiperidin- 1-yl }methyl)piperidine- 1-carboxylate, l-benzoyl-4-[l-(4-chlorophenyl)-4-[(3-phenylpyrrolidin-l-yl)carbonyl]-lH-pyrazol-5-yl]piperidine, 4-[l-(4-chlorophenyl)-4-[(3-phenylpyrrolidin-l-yl)carbonyl]-lH-pyrazol-5 -yl] - 1-cyclohexanecarbonylpiperidine, 1-{4-[1-(4-chlorophenyl)-4- {[(3R)-3 -phenylpyrrolidin- 1-yl]carbonyl }- 1H-pyrazol-5 -yl]piperidin- 1-yl }-3,3-dimethylbutan- 1-one, l-benzoyl-4-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine, 4-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]-l-cyclohexanecarbonylpiperidine, 4-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin- 1-yl]carbonyl }- 1H-pyrazol-5 -yl] - 1-[(2-fluorophenyl)carbonyl]piperidine, 4-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]-l-[(3-fluorophenyl)carbonyl]piperidine, 4-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]-l-[(4-fluorophenyl)carbonyl]piperidine, 4-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]-l-[(4-chlorophenyl)carbonyl]piperidine, 4-[1-(4-chlorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yl]carbonyl}-lH-pyrazol-5-yl]-l-[(oxan-4-yl)carbonyl]piperidine, 4-[l-(4-chlorophenyl)-4-{[(3R)-3 -phenylpyrrolidin- 1-yl]carbonyl }- 1H-pyrazol-5 -yl] - 1-[(2,5-dimethyl- 1,3 -oxazol-4-yl)carbonyl]piperidine, 4-[1-(4-chlorophenyl)-4- {[(3R)-3 -phenylpyrrolidin- 1-yl]carbonyl }-lH-pyrazol-5-yl]-l-[(3-methoxyphenyl)carbonyl]piperidine, 4-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin- l-yl]carbonyl} -lH-pyrazol-5-yl]- 1-[(4-methoxyphenyl)carbonyl]piperidine, 4-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl }-lH-pyrazol-5 -yl] - 1-[(5 -methyl- 1,3 ,4-oxadiazol-2-yl)carbonyl]piperidine, 4-[1-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]-l-{[l-methyl-5-(trifluoromethyl)-lH-pyrazol-3-yl]carbonyl}piperidine, 4-[l-(4-chlorophenyl)-4-{[(3R)-3 -phenylpyrrolidin- 1-yl]carbonyl }- 1H-pyrazol-5 -yl] - 1-[(1,5-dimethyl- 1H-pyrazol-3 -yl)carbonyl]piperidine, 5-({4-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl }-lH-pyrazol-5 -yl]piperidin- 1-yl }carbonyl)-2-methylpyridine, (2R)-2-amino- 1-{4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin- 1-yl }-4,4-dimethylpentan- 1-one, 4-(methoxycarbonyl)phenyl 4-[l-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- l-yl]carbonyl }- 1H-pyrazol-5 -yl]piperidine- 1-carboxylate, 4-fluorophenyl 4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine-l-carboxylate, phenyl 4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine-l-carboxylate, methyl 4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-

yl]piperidine-l-carboxylate, l-(3,5-dimethyl-l,2-oxazole-4-sulfonyl)-4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine, 4-[l-(4-chlorophenyl)-4-[(3-phenylpyrrolidin-1-yl)carbonyl]-1H-pyrazol-5-yl]-1-methanesulfonylpiperidine, l-(benzenesulfonyl)-4-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yljcarbonyl}-1H-pyrazol-5-yljpiperidine, tert-butyl 4-[1-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine-l-carboxylate, l-benzyl-4-[l-(4-chlorophenyl)-4-[(3-phenylpyrrolidin-l-yl)carbonyl]-lH-pyrazol-5-yl]piperidine, 4-((4-(4-(3,3-difluoro-4-phenylpyrrolidine-l-carbonyl)-l-(4-fluorophenyl)-1H-pyrazol-5-yl)piperidin-1-yl)methyl)benzenesulfonamide, 4-[1-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]-l-[(4-fluorophenyl)methyl]piperidine, 4-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yljcarbonyl}-lH-pyrazol-5-yl]-1-[(2-fluorophenyl)methyl]piperidine, 4-({4-[1-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-l-yl}methyl)benzoic acid, 4-[1-(4-chlorophenyl)-4-[(3-phenylpyrrolidin-1-yl)carbonyl]-1H-pyrazol-5-yl]-l-cyclohexylpiperidine, 4-({4-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yl]carbonyl}-1H-pyrazol-5-yl]piperidin-1-yl}methyl)benzonitrile, 4-[1-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]-l-(oxan-4-ylmethyl)piperidine, 3-({4-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-l-yl}methyl)benzoic acid, l-benzyl-4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yl]carbonyl}-1H-pyrazol-5-yl]piperidine, 4-{[4-(1-cyclohexyl-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl)piperidin-l-yl]methyl}benzonitrile, l-benzyl-4-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine, 4-({4-[l-(4-chlorophenyl)-4-[(l, 2,3,4-tetrahydroisoquinolin-2-yl)carbonyl]-lH-pyrazol-5-yl]piperidin-l-yl}methyl)benzonitrile, 4-({4-[l-(4-chloro-2-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-1-yl}methyl)benzonitrile, 4-({4-[l-(2,4-difluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yl]carbonyl}-1H-pyrazol-5-yl]piperidin-1-yl}methyl)benzonitrile, methyl 2-{4-[l-(2,4-difluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-1-yl}-2-phenylacetate, 4-({4-[1-(4-fluorophenyl)-4-{[3-(4-fluorophenyl)pyrrolidin-1-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-1-yl}methyl)benzonitrile, 5-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-1-yl}methyl)-1-methyl-1H-1,2,3-benzotriazole, 4-[1-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]-1-[(4-

methanesulfonylphenyl)methyl]piperidine, 4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-(4-fluorophenyl)pyrrolidin- 1-yljcarbonyl }-lH-pyrazol-5 -yljpiperidin- 1-yl }methyl)benzonitrile, 4-({4-[l-(4-fluorophenyl)-4-{[(3S)-3-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin- 1-yl }methyl)benzonitrile, 1-[(4-methanesulfonylphenyl)methyl] -4- [1-(4-methoxyphenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine, 4-(5-{1-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl }-4- {[(3R)-3-phenylpyrrolidin- 1-yl]carbonyl}-lH-pyrazol-l-yl)benzonitrile, 2-(5-{ l-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl}-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-l-yl)pyrimidine, 5-chloro-2-(5-{l-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl }-4- {[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol- 1-yl)pyridine, 1-[(4-methanesulfonylphenyl)methyl]-4-(4- {[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-lH-pyrazol-5-yl)piperidine, 4-(4-{[(3S,4S)-3-fluoro-4-phenylpyrrolidin-l-yl]carbonyl}-l-(4-fluorophenyl)-lH-pyrazol-5-yl)-l-[(4-methanesulfonylphenyl)methyl]piperidine, 4-(4-{[(4R)-2,2-dihydrogenio-4-(2,3,4,5,6-pentahydrogeniophenyl)pyrrolidin-l-yl]carbonyl}-l-(4-fluorophenyl)- lH-pyrazol-5-yl)- 1-[(4-methanesulfonylphenyl)methyl]piperidine, 4-[1-(4-fluorophenyl)-4-{ [(3R)-3-(2,3,4,5,6-pentahydrogeniophenyl)pyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]-1-[(4-methanesulfonylphenyl)methyl]piperidine, 4-({4-[1-(4-fluorophenyl)-4-{[(3R)-3-(3-fluorophenyl)pyrrolidin- l-yl]carbonyl} -lH-pyrazol-5-yl]piperidin- 1-yl}methyl)benzonitrile, 4-[l-(4-fluorophenyl)-4-{[(3S)-3-phenyl-3-(trifluoromethyl)pyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5-yl]-1-[(4-methanesulfonylphenyl)methyl]piperidine, 4-[1-(4-fluorophenyl)-4- {[3-phenyl-3-(trifluoromethyl)pyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5-yl]-1-[(4-methanesulfonylphenyl)methyl]piperidine, 4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenyl-3-(trifluoromethyl)pyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5-yl]-1-[(4-methanesulfonylphenyl)methyl]piperidine, 4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-(2-methoxyphenyl)pyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5-yl]piperidin-1-yl }methyl)benzonitrile, 4-[1-(4-fluorophenyl)-4-[(3-phenoxypyrrolidin- 1-yl)carbonyl]-1H-pyrazol-5-yl]-1-[(4-methanesulfonylphenyl)methyl]piperidine, 4-{[4-(1-phenyl-4-{[(3R)-3-phenylpyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5-yl)piperidin- 1-yl]methyl }benzonitrile, 4-[1-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]-l-(l-phenylethyl)piperidine, 4-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]-l-[(3,4-difluorophenyl)methyl]piperidine, 4-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin- l-yl]carbonyl} -lH-pyrazol-5-yl]- 1-{[4-

(trifluoromethyl)phenyl] methyl }piperidine, 4-({ 4-[1-(4-fluorophenyl)-4- {[(3R)-3-(4-methoxyphenyl)pyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5 -yljpiperidin- 1-yl }methyl)benzonitrile, 4-[l-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- l-yl]carbonyl }-lH-pyrazol-5-yl]-l-(2,2,2-trifluoroethyl)piperidine, 2-[4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5 -yljpiperidin- 1-yl }methyl)phenoxy] acetic acid, (3S,4R)-l-{ [l-(4-fluorophenyl)-5-{ l-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl }-lH-pyrazol-4-yl]carbonyl }-4-phenylpyrrolidin-3-ol, 2-chloro-5-({4-[1-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-l-yl }methyl)pyridine, 4-({ 4-[l-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- l-yl]carbonyl }-lH-pyrazol-5-yl]piperidin-l-yl}methyl)benzonitrile, 5-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5 -yljpiperidin- 1-yl }methyl)pyridine-2-carbonitrile, 5-fluoro-2-(5-{ l-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl}-4-{ [(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol- 1-yl)pyridine, 3-({4-[1-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5 -yljpiperidin- 1-yl }methyl)pyridine, 3-fluoro-4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin- 1-yl }methyl)benzonitrile, 4-[l-(4-fluorophenyl)-3-methyl-4- {[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5 -yl] -1-[(4-methanesulfonylphenyl)methyl]piperidine, 3-bromo-4-({4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5 -yljpiperidin- 1-yl }methyl)benzonitrile, 5-({4-[1-(4-fluorophenyl)-4- {[(3R)-3 -phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5 -yljpiperidin-l-yl}methyl)-2-methanesulfonylpyridine, 4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5 -yljpiperidin- 1-yl }methyl)benzene- 1-sulfonamide, 4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]-l-[(4-fluorophenyl)methyl]piperidine, 2-fluoro-4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5 -yljpiperidin- 1-yl }methyl)benzonitrile, 4-({4-[1-(4-fluorophenyl)-4- {[(3R)-3 -phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5 -yljpiperidin- 1-yl }methyl)pyridine, [4-({4-[1-(4-fluorophenyl)-4- {[(3R)-3 -phenylpyrrolidin- 1-yljcarbonyl }-lH-pyrazol-5 -yljpiperidin- 1-yl }methyl)phenyl] sulfamate, 4-({4-[1-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-l-yl}methyl)-N-methylbenzene-l-sulfonamide, 4-(l-{4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5 -yljpiperidin- 1-yl }ethyl)benzonitrile, [5-({4-[1-(4-fluorophenyl)-4- {[(3R)-3 -phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5 -yljpiperidin- 1-yl }methyl)pyridin-2-yl]methanol, 1-[(3 ,4-difluorophenyl)methyl] -4-[1-(4-fluorophenyl)-4-

{[(3R)-3-phenylpyrrolidin-1-yljcarbonyl}-1H-pyrazol-5-yljpiperidine, methyl 5-({4-[1-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-l-yl}methyl)pyridine-2-carboxylate, l-[(2,4-difluorophenyl)methyl]-4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yljcarbonyl}-1H-pyrazol-5-yljpiperidine, 4-({4-[1-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-l-yl}methyl)-N-hydroxybenzene-l-sulfonamide, 2-fluoro-4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yljcarbonyl}-lH-pyrazol-5-yljpiperidin-1-yl}methyl)benzamide, 1-[(2-chloro-4-fluorophenyl)methyl]-4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine, S-[4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yljcarbonyl}-1H-pyrazol-5-yljpiperidin-1-yl}methyl)phenyl]-2-hydroxypropane-1-sulfonamido, 4-({4-[1-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yljcarbonyl}-lH-pyrazol-5-yljpiperidin-1-yl}methyl)benzamide, 1-[(4-fluoro-2-methoxyphenyl)methyl]-4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine, 2-fluoro-5-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yljcarbonyl}-1H-pyrazol-5-yljpiperidin-1-yl}methyl)benzonitrile, 4-[1-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yljcarbonyl}-1H-pyrazol-5-yl]-1-[(3-fluorophenyl)methyl]piperidine, l-[(4-fluoro-3-methoxyphenyl)methyl]-4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine, (E)-N-{l-[4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yljpiperidin-1-yl}methyl)phenyl]ethylidene}hydroxylamine, 4-[1-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]-l-[(2,3,4-trifluorophenyl)methyl]piperidine, 2-chloro-4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-1H-pyrazol-5-yljpiperidin-1-yl}methyl)pyridine, (5E)-5-{[4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yljpiperidin-1-yl}methyl)phenyl]methylidene}-1,3-thiazolidine-2,4-dione, 2-({4-[1-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-l-yl}methyl)pyridine, tert-butyl 2-{4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-l-yl} acetate, l-{[3-fluoro-4-(2H-l,2,3,4-tetrazol-5-yl)phenyl]methyl}-4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine, N-(2,3-dihydroxypropyl)-4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yljcarbonyl}-1H-pyrazol-5-yljpiperidin-1-yl}methyl)benzamide, 2-chloro-4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yljpiperidin-1-yl}methyl)pyrimidine, 1-[4-({4-[1-(4-fluorophenyl)-4-{[(3R)-3-

phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5 -yl]piperidin- 1-yl }methyl)phenyl]ethan- 1-one, 2-{[1-(4-fluorophenyl)-5 -{1-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl }-1H-pyrazol-4-yl]carbonyl}-l,2,3,4-tetrahydroisoquinoline, 4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5 -yl]-1-[(4-methanesulfonylphenyl)methyl] -1,2,3,6-tetrahydropyridine, 4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]-l-[(4-methylphenyl)methyl]piperidine, tert-butyl 3-{ [4-({4-[1-(4-fluorophenyl)-4- {[(3R)-3 -phenylpyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5 -yl]piperidin-1-yl }methyl)phenyl]formamido }propanoate, 4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5 -yl]-1-[2-(4-methanesulfonylphenyl)ethyl]piperidine, 4-[1-(4-fluorophenyl)-4- [(3 -phenylazetidin- 1-yl)carbonyl] -lH-pyrazol-5 -yl]-1-[(4-methanesulfonylphenyl)methyl]piperidine, 5-({4-[1-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-l-yl}methyl)pyridine-2-carboxylic acid, 3-{[4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5 -yl]piperidin- 1-yl }methyl)phenyl]formamido }propanoic acid, 1-[(3-chloro-4-fluorophenyl)methyl] -4-[1-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine, 4-[l-(4-fluorophenyl)-3-methyl-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]-l-[(4-methanesulfonylphenyl)methyl]- 1,2,3,6-tetrahydropyridine, 4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]-l-{[4-(2H-l,2,3,4-tetrazol-5-yl)phenyl]methyl}piperidine, l-(4-fluorophenyl)-5-{ l-[(4-methanesulfonylphenyl)methyl] azetidin-3 -yl }-4-[(3 -methyl-3-phenylpyrrolidin- 1-yl)carbonyl]- lH-pyrazole, 5-({4-[l-(4-fluorophenyl)-4- [(3-methyl-3-phenylpyrrolidin- 1-yl)carbonyl]-lH-pyrazol-5-yl]piperidin-l-yl}methyl)pyridine-2-carboxylic acid, 2-fluoro-5-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin- 1-yl }methyl)benzamide, N-{[4-({4-[l-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5 -yl]piperidin- 1-yl }methyl)benzene] sulfonyl }acetamide, 1-[2-(2-benzyl-2H- 1,2,3 ,4-tetrazol-5-yl)ethyl] -4-[1-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine, 4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]-1,2,3,6-tetrahydropyridin-l-yl}methyl)pyridine, 4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5 -yl]-1-[(3 -methylphenyl)methyl]piperidine, 4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin- 1-yl }methyl)-N-hydroxybenzamide, 4-[l-(4-fluorophenyl)-4- {[(3R)-3-

phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5-yl]-1-[2-(4-fluorophenyl)ethyl]piperidine, 2-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin- 1-yl }methyl)- 1,3-benzothiazole, 1-(cyclopropylmethyl)-4-[1-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5-yl]piperidine, 4-[1-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]-l-(2-methanesulfonylethyl)piperidine, l-(4-fluorophenyl)-5-{ l-[2-(4-methanesulfonylphenyl)ethyl]azetidin-3-yl}-4-[(3-methyl-3-phenylpyrrolidin-l-yl)carbonyl]-lH-pyrazole, 4-(2-{4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin- 1-yl }ethyl)benzoic acid, 4-({4-[1-(4-chlorophenyl)-4- {[(3R)-3-methyl-3-phenylpyrrolidin- l-yl]carbonyl }-lH-pyrazol-5-yl]piperidin- 1-yl }methyl)benzonitrile, 4-({ 4-[1-(4-fluorophenyl)-4-[(3-methyl-3-phenylpyrrolidin- 1-yl)carbonyl]-lH-pyrazol-5-yl]piperidin-l-yl}methyl)benzonitrile, 3-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-l-yl }methyl)benzonitrile, 4-({ 4-[l-(4-fluorophenyl)-4- {[(3R)-3-methyl-3-phenylpyrrolidin- 1-yl]carbonyl }-lH-pyrazol-5-yl]piperidin- 1-yl }methyl)benzonitrile, 4-({4-[1-(4-fluorophenyl)-4-{[(3S)-3-methyl-3-phenylpyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5-yl]piperidin- 1-yl }methyl)benzonitrile, 4-[l-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- l-yl]carbonyl }-lH-pyrazol-5-yl]-l-(3,3,3-trifluoropropyl)piperidine, tert-butyl 3-{4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5-yl]piperidin- 1-yl }pyrrolidine- 1-carboxylate, l-(l-benzylpyrrolidin-3-yl)-4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yl]carbonyl }-1H-pyrazol-5-yl]piperidine, 1-[(1,3-dimethyl- 1H-pyrazol-5-yl)methyl]-4-[1-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine, 1-[(3,5-dimethyl-l,2-oxazol-4-yl)methyl]-4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine, 4-({4-[l-(4-chlorophenyl)-4-{[(3S)-3-(2-fluorophenyl)pyrrolidin- 1-yl]carbonyl }-lH-pyrazol-5 -yl]piperidin- 1-yl }methyl)benzonitrile, 4-({4-[l-(4-chlorophenyl)-4-{[(3R)-3-(2-fluorophenyl)pyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin- 1-yl }methyl)benzonitrile, 4-({4-[1-(2,4-difluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5-yl]piperidin- 1-yl }methyl)benzoic acid, 4-[1-(2,4-difluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5-yl]-1-{[4-(lH-l,2,3,4-tetrazol-5-yl)phenyl]methyl}piperidine, 4-[l-(4-chloro-2-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]-l-{[4-(lH-l,2,3,4-tetrazol-5-yl)phenyl]methyl}piperidine, 4-[l-(4-fluorophenyl)-4-[(3-methyl-3-phenylpyrrolidin-l-yl)carbonyl]-lH-pyrazol-5-yl]-l-{[4-(lH-l,2,3,4-tetrazol-5-yl)phenyl]methyl}piperidine, 2-

[4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-l-yl}methyl)phenyl]propanoic acid, 2-[4-({4-[l-(4-fluorophenyl)-4-{ [(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5-yl]piperidin- 1-yl }methyl)phenyl] acetic acid, 4-({4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5-yljpiperidin- 1-yl }methyl)benzoic acid, 1-[(1,5-dimethyl- lH-pyrazol-3-yl)methyl]-4- [1-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine, 4-({4-[1-(4-fluorophenyl)-4- [(3-methyl-3-phenylpyrrolidin- 1-yl)carbonyl]- lH-pyrazol-5-yljpiperidin- 1-yl }methyl)benzoic acid, 4-[1-(4-fluorophenyl)-4- [(3-methyl-3-phenylpyrrolidin- 1-yl)carbonyl]-1H-pyrazol-5-yl]-1-[(4-methanesulfonylphenyl)methyl]piperidine, 5-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5-yljpiperidin- 1-yl }methyl)- 1,2-oxazole-3-carboxylic acid, 5-({4-[l-(4-fluorophenyl)-4-{ [(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-l-yl}methyl)-l-methyl-lH-pyrazole-3-carboxylic acid, 2-{ [4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-l-yl}methyl)benzene]sulfonyl} acetic acid, (2E)-3-[4-({4-[l-(4-fluorophenyl)-4-{ [(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5-yljpiperidin- 1-yl }methyl)phenyl]prop-2-enoic acid, 4-[1-(4-fluorophenyl)-4- {[3-(2-fluorophenyl)pyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5-yl]-1-[(4-methanesulfonylphenyl)methyl]piperidine, 1-{[4-(ethanesulfonyl)phenyl]methyl}-4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine, 4-[l-(4-fluorophenyl)-4-[(2,2,5,5-tetrahydrogenio-3-methyl-3-phenylpyrrolidin- 1-yl)carbonyl]-1H-pyrazol-5-yl]-1-[(4-methanesulfonylphenyl)methyl]piperidine, 4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin- l-yl]carbonyl}- 1H-pyrazol-5-yl]-1-{[4-(propane-2-sulfonyl)phenyl]methyl }piperidine, 4-{4-[(3,3-difluoro-4-phenylpyrrolidin- 1-yl)carbonyl]-1-(4-fluorophenyl)-lH-pyrazol-5-yl}-l-[(4-methanesulfonylphenyl)methyl]piperidine, 4-(4-{[(4R)-3,3-difluoro-4-phenylpyrrolidin- 1-yl]carbonyl }-1-(4-fluorophenyl)- lH-pyrazol-5-yl)-l-[(4-methanesulfonylphenyl)methyl]piperidine, 4-(4-{[(4S)-3,3-difluoro-4-phenylpyrrolidin- l-yl]carbonyl }-1-(4-fluorophenyl)- lH-pyrazol-5-yl)- 1-[(4-methanesulfonylphenyl)methyl]piperidine, tert-butyl N-{4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5-yl]cyclohexyl }carbamate, N-{4-[1-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]cyclohexyl}-4-methanesulfonylaniline, 5-fluoro-2-(5-{1-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl}-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-l-yl)pyrimidine, 5-fluoro-2-(5-

{l-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl} -4-{ [(3S)-3-phenyl-3-(trifluoromethyl)pyrrolidin- 1-yljcarbonyl }-1H-pyrazol- 1-yl)pyrimidine, 2-{4-[(3,3-difluoro-4-phenylpyrrolidin-l-yl)carbonyl]-5-{l-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl}-lH-pyrazol-l-yl}-5-fluoropyrimidine, 2-(4-{[(4R)-3,3-difluoro-4-phenylpyrrolidin-l-yljcarbonyl }-5- {1-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl }-lH-pyrazol- 1-yl)-5-fluoropyrimidine, 2-(4-{ [(4S)-3,3-difluoro-4-phenylpyrrolidin-l-yl]carbonyl}-5-{ l-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl}-lH-pyrazol-l-yl)-5-fluoropyrimidine, 5-fluoro-2-(4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-5-[l-(pyrimidin-5-ylmethyl)piperidin-4-yl]-lH-pyrazol-l-yl)pyrimidine, 4-({4-[l-(5-fluoropyrimidin-2-yl)-4-{[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5-yljpiperidin- 1-yl }methyl)benzene- 1-sulfonamide, 5-chloro-2-(5-{l-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl}-4-{[(3R)-3-phenylpyrrolidin- l-yl]carbonyl }-lH-pyrazol- 1-yl)pyrimidine, 4-({4-[l-(5-bromopyrimidin-2-yl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yljpiperidin- 1-yl }methyl)benzene- 1-sulfonamide, 4-({4-[1-(5-fluoropyrimidin-2-yl)-4-{[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5-yljpiperidin- 1-yl}methyl)benzonitrile, 3-fluoro-4-({4-[l-(5-fluoropyrimidin-2-yl)-4-{[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5-yljpiperidin- 1-yl }methyl)benzonitrile, 2-(5-{l-[(6-chloropyridin-3-yl)methyl]piperidin-4-yl}-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-l-yl)-5-fluoropyrimidine, 5-fluoro-2-(4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-5-(l-{[6-(lH-pyrazol-l-yl)pyridin-3-yl]methyl}piperidin-4-yl)-lH-pyrazol-l-yl)pyrimidine, 5-({4-[l-(5-fluoropyrimidin-2-yl)-4-{[(3R)-3-phenylpyrrolidin-l-yljcarbonyl }-lH-pyrazol-5 -yljpiperidin- 1-yl }methyl)pyridin-2-amine, 5-({4-[1-(5-fluoropyrimidin-2-yl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-l-yl}methyl)pyrimidin-2-amine, 5-fluoro-2-(4-{[(3R)-3-phenylpyrrolidin-l-yljcarbonyl }-5-[1-(pyridin-4-ylmethyl)piperidin-4-yl] -1H-pyrazol- 1-yl)pyrimidine, 4-[(4- {4-[(3,3-difluoro-4-phenylpyrrolidin-l-yl)carbonyl]-l-(5-fluoropyrimidin-2-yl)-lH-pyrazol-5-yl }piperidin- 1-yl)methyl]benzonitrile, 2-(5-{1-[(6-chloropyridin-3-yl)methyl]piperidin-4-yl }-4-[(3,3-difluoro-4-phenylpyrrolidin- 1-yl)carbonyl] -lH-pyrazol- 1-yl)-5-fluoropyrimidine, 4-[(4- {4-[(3,3-difluoro-4-phenylpyrrolidin- 1-yl)carbonyl] -1-(5-fluoropyrimidin-2-yl)- 1H-pyrazol-5-yl }piperidin- 1-yl)methyl]benzene- 1-sulfonamide, 2-{4-[(3,3-difluoro-4-phenylpyrrolidin- 1-yl)carbonyl]-5-[1-(pyridin-4-ylmethyl)piperidin-4-yl] -1H-pyrazol- 1-yl }-5-fluoropyrimidine, 4-{[4-(4-{[(4R)-3,3-difluoro-4-phenylpyrrolidin-l-yl]carbonyl}-l-(4-fluorophenyl)-lH-pyrazol-5-yl)piperidin-l-yl]methyl}benzene-l-sulfonamide, 4-{[4-(4-

{[(4S)-3,3-difluoro-4-phenylpyrrolidin-l-yl]carbonyl}-l-(4-fluorophenyl)-lH-pyrazol-5-yl)piperidin- 1-yljmethyl }benzene- 1-sulfonamide, 4-{4-[(3,3-difluoro-4-phenylpyrrolidin- 1-yl)carbonyl]-1-(4-fluorophenyl)-3-methyl- 1H-pyrazol-5-yl }-1-[(4-methanesulfonylphenyl)methyl]piperidine, 2-{4-[(3,3-difluoro-4-phenylpyrrolidin- 1-yl)carbonyl]-5-(l-{[6-(trifluoromethyl)pyridin-3-yl]methyl}piperidin-4-yl)-lH-pyrazol-l-yl }-5-fluoropyrimidine, 2-{4-[(3,3-difluoro-4-phenylpyrrolidin- 1-yl)carbonyl]-5-{1-[(6-methoxypyridin-3-yl)methyl]piperidin-4-yl}-lH-pyrazol-l-yl}-5-fluoropyrimidine, 2-(4-{[(4R)-3,3-difluoro-4-phenylpyrrolidin-l-yl]carbonyl}-5-(l-{[6-(trifluoromethyl)pyridin-3-yl]methyl}piperidin-4-yl)-lH-pyrazol-l-yl)-5-fluoropyrimidine, 2-(4-{[(4R)-3,3-difluoro-4-phenylpyrrolidin- 1-yljcarbonyl }-5-{1-[(6-methoxypyridin-3-yl)methyl]piperidin-4-yl }-1H-pyrazol- 1-yl)-5-fluoropyrimidine, 2-(4- {[(4R)-3,3-difluoro-4-phenylpyrrolidin- 1-yl]carbonyl}-5-(l-{[4-(trifluoromethane)sulfonylphenyl]methyl}piperidin-4-yl)-lH-pyrazol-l-yl)-5-fluoropyrimidine, 2-(4-{[(4S)-3,3-difluoro-4-phenylpyrrolidin-l-yl]carbonyl}-5-(l-{[4-(trifluoromethane)sulfonylphenyl]methyl}piperidin-4-yl)-lH-pyrazol-l-yl)-5-fluoropyrimidine, 4-({4-[1-(4-fluorophenyl)-4- {[3-(4-fluorophenyl)pyrrolidin- 1-yljcarbonyl }-lH-pyrazol-5 -yljpiperidin- 1-yl }methyl)benzene- 1-sulfonamide, 4-[1-(4-fluorophenyl)-4- {[3-(4-fluorophenyl)pyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5-yl]-1-[(4-methanesulfonylphenyl)methyl]piperidine, 4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-(4-fluorophenyl)pyrrolidin- 1-yljcarbonyl }-lH-pyrazol-5 -yljpiperidin- 1-yl }methyl)benzene- 1-sulfonamide, 4-({4-[l-(4-fluorophenyl)-4-{[(3S)-3-(4-fluorophenyl)pyrrolidin-l-yljcarbonyl }-lH-pyrazol-5 -yljpiperidin- 1-yl }methyl)benzene- 1-sulfonamide, 4-[1-(4-fluorophenyl)-4-{[(3R)-3-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]-l-[(4-methanesulfonylphenyl)methyl]piperidine, 4-[l-(4-fluorophenyl)-4-{[(3S)-3-(4-fluorophenyl)pyrrolidin- 1-yljcarbonyl }-lH-pyrazol-5 -yl]-1-[(4-methanesulfonylphenyl)methyl]piperidine, 4-{ [4-(4-{ [3,3-difluoro-4-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-l-(4-fluorophenyl)-lH-pyrazol-5-yl)piperidin-l-yl]methyl }benzene- 1-sulfonamide, 4-(4- {[3,3-difluoro-4-(4-fluorophenyl)pyrrolidin- 1-yl]carbonyl }-l-(4-fluorophenyl)- lH-pyrazol-5-yl)- 1-[(4-methanesulfonylphenyl)methyl]piperidine, methyl 2-(4-{4-[(3,3-difluoro-4-phenylpyrrolidin-l-yl)carbonyl]-l-(4-fluorophenyl)-lH-pyrazol-5-yl}piperidin-l-yl)-2-(4-methanesulfonylphenyl)acetate, 4-{ [4-(4-{ [(4R)-3,3-difluoro-4-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-l-(4-fluorophenyl)-lH-pyrazol-5-yl)piperidin-l-yl]methyl}benzene-l-sulfonamide, 4-{[4-(4-{[(4S)-3,3-difluoro-4-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-l-(4-

fluorophenyl)-lH-pyrazol-5-yl)piperidin-l-yl]methyl}benzene-l-sulfonamide, 4-(4-{[(4R)-3,3-difluoro-4-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-l-(4-fluorophenyl)-lH-pyrazol-5-yl)-l-[(4-methanesulfonylphenyl)methyl]piperidine, 4-(4-{[(4S)-3,3-difluoro-4-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-l-(4-fluorophenyl)-lH-pyrazol-5-yl)-l-[(4-methanesulfonylphenyl)methyl]piperidine, 4-{[4-(4-{[3-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-l-(5-fluoropyrimidin-2-yl)-lH-pyrazol-5-yl)piperidin-l-yl]methyl}benzene-l-sulfonamide, 4-{[4-(4-{[3,3-difluoro-4-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-l-(5-fluoropyrimidin-2-yl)-lH-pyrazol-5-yl)piperidin-l-yl]methyl}benzene-l-sulfonamide, 2-(4-{[3,3-difluoro-4-(4-fluorophenyl)pyrrolidin-1-yljcarbonyl}-5-{1-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl}-1H-pyrazol-1-yl)-5-fluoropyrimidine, 4-{4-[(3,3-difluoro-4-phenylpyrrolidin-l-yl)carbonyl]-l-(4-fluorophenyl)-lH-pyrazol-5-yl}-l-[(3-fluoro-4-methanesulfonylphenyl)methyl]piperidine, 5-fluoro-2-(4-{[3-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-5-{l-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl}-1H-pyrazol-1-yl)pyrimidine, 4-{[4-(4-{[(3R)-3-(4-fluorophenyl)pyrrolidin-1-yl]carbonyl}-l-(5-fluoropyrimidin-2-yl)-lH-pyrazol-5-yl)piperidin-l-yl]methyl}benzene-l-sulfonamide, 4-{[4-(4-{[(3S)-3-(4-fluorophenyl)pyrrolidin-1-yljcarbonyl}-1-(5-fluoropyrimidin-2-yl)-1H-pyrazol-5-yl)piperidin-1-yl]methyl}benzene-1-sulfonamide, 5-fluoro-2-(4-{[(3R)-3-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-5-{l-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl}-1H-pyrazol-1-yl)pyrimidine, 5-fluoro-2-(4-{[(3S)-3-(4-fluorophenyl)pyrrolidin-1-yljcarbonyl}-5-{1-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl}-lH-pyrazol-l-yl)pyrimidine, 4-{[4-(4-{[(4R)-3,3-difluoro-4-(4-fluorophenyl)pyrrolidin-1-yljcarbonyl}-1-(5-fluoropyrimidin-2-yl)-lH-pyrazol-5-yl)piperidin-l-yl]methyl}benzene-l-sulfonamide, 2-(4-{[(4R)-3,3-difluoro-4-(4-fluorophenyl)pyrrolidin-1-yljcarbonyl}-5-{1-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl}-lH-pyrazol-l-yl)-5-fluoropyrimidine, 2-(4-{[3,3-difluoro-4-(4-fluorophenyl)pyrrolidin-1-yljcarbonyl}-5-{1-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl}-1H-pyrazol-1-yl)-5-fluoropyridine, 4-{4-[(3,3-difluoro-4-phenylpyrrolidin-1-yl)carbonyl]-1-(4-fluorophenyl)-1H-pyrazol-5-yl}-1-{[4-methanesulfonyl-2-(trifluoromethyl)phenyl]methyl}piperidine, 5-[(4-{4-[(3,3-difluoro-4-phenylpyrrolidin-1-yl)carbonyl]-1-(4-fluorophenyl)-1H-pyrazol-5-yl}piperidin-1-yl)methyl]-2-methanesulfonylbenzonitrile, 2-(4-{[(4R)-3,3-difluoro-4-(4-fluorophenyl)pyrrolidin-l-yljcarbonyl}-5-{1-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl}-lH-pyrazol-1-yl)-5-fluoropyridine, 4-{4-[(3,3-difluoro-4-phenylpyrrolidin-1-yl)carbonyl]-1-(4-fluorophenyl)-

lH-pyrazol-5-yl }-1-[(2-fluoro-4-methanesulfonylphenyl)methyl]piperidine, 4-{4-[(3,3-difluoro-4-phenylpyrrolidin- 1-yl)carbonyl]- 1-(4-fluorophenyl)- lH-pyrazol-5-yl }-1-[(4-methanesulfonylphenyl)-l,l-(dideuterium) methyljpiperidine, 4-{[4-(4-{[(4R)-3,3-difluoro-4-phenylpyrrolidin- l-yl]carbonyl} -l-(2,4-difluorophenyl)- lH-pyrazol-5-yl)piperidin- 1-yl]methyl }benzene- 1-sulfonamide, 4-(4- {[3,3-difluoro-4-(4-fluorophenyl)pyrrolidin- 1-yljcarbonyl }-l-(4-fluorophenyl)- lH-pyrazol-5-yl)- 1-[(4-methanesulfonylphenyl)- 1,1-(dideuterium) methyljpiperidine, l-[(4-methanesulfonylphenyl)methyl]-4-(l-methyl-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl)piperidine, 4-(4-{[3,3-difluoro-4-(4-fluorophenyl)pyrrolidin- 1-yljcarbonyl }-1-propyl- lH-pyrazol-5-yl)- 1-[(4-methanesulfonylphenyl)methyl]piperidine, 1-[(4-methanesulfonylphenyl)methyl] -4-(4-{[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1-propyl- lH-pyrazol-5-yl)piperidine, 4-(l -butyl-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl)-l-[(4-methanesulfonylphenyl)methyl]piperidine, 4-{4-[(3,3-difluoro-4-phenylpyrrolidin- 1-yl)carbonyl] -1-propyl- 1H-pyrazol-5-yl }-1-[(4-methanesulfonylphenyl)methyl]piperidine, 4-[(4-{4-[(3,3-difluoro-4-phenylpyrrolidin-l-yl)carbonyl]-l-propyl-lH-pyrazol-5-yl}piperidin-1-yl)methyl]benzene- 1-sulfonamide, 4-[(4- {4-[(3,3-difluoro-4-phenylpyrrolidin- 1-yl)carbonyl] -1-propyl- 1H-pyrazol-5-yl }piperidin- 1-yl)methyl]benzene- 1-sulfonamide, 4-{1-butyl-4-[(3,3-difluoro-4-phenylpyrrolidin- 1-yl)carbonyl] -lH-pyrazol-5 -yl }-1-[(4-methanesulfonylphenyl)methyl]piperidine, 4-(4-{[(4R)-3,3-difluoro-4-phenylpyrrolidin-l-yl]carbonyl}-l-ethyl-lH-pyrazol-5-yl)-l-[(4-methanesulfonylphenyl)methyl]piperidine, 4-{[4-(4-{[(4R)-3,3-difluoro-4-phenylpyrrolidin-l-yl]carbonyl}-l-ethyl-lH-pyrazol-5-yl)piperidin- 1-yljmethyl }benzene- 1-sulfonamide, 4-[(4- {1-butyl-4-[(3,3-difluoro-4-phenylpyrrolidin- 1-yl)carbonyl] -1H-pyrazol-5 -yl }piperidin- 1-yl)methyl]benzene- 1-sulfonamide, 4-{[4-(4-{[(4R)-3,3-difluoro-4-phenylpyrrolidin-l-yl]carbonyl}-l-propyl-lH-pyrazol-5-yl)piperidin-l-yl]methyl}benzene-l-sulfonamide, 4-{[4-(4-{[(4S)-3,3-difluoro-4-phenylpyrrolidin- l-yl]carbonyl }-1-propyl- lH-pyrazol-5-yl)piperidin- l-yl]methyl }benzene-1-sulfonamide, 4-(l-ethyl-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl)-l-[(4-methanesulfonylphenyl)methyl]piperidine, 4-{[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5-yljmethyl }-1-(4-methanesulfonylphenyl)piperidine, 4-{4-[(3,3-difluoro-4-phenylpyrrolidin- 1-yl)carbonyl]- 1-(4-fluorophenyl)- lH-pyrazol-5-yl }-1-[l-(4-methanesulfonylphenyl)ethyl]piperidine, 3-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]-l-(4-methanesulfonylphenyl)piperidine, N-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-

yl]carbonyl}-lH-pyrazol-5-yl]-l-(4-methanesulfonylphenyl)piperidin-4-amine, 3-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]-l-[(4-methanesulfonylphenyl)methyl]piperidine, 4-[1-(4-{4-[(3,3-difluoro-4-phenylpyrrolidin-1-yl)carbonyl]-l-(4-fluorophenyl)-lH-pyrazol-5-yl}piperidin-l-yl)-2,2,2-trifluoroethyl]benzonitrile, 4-[1-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yljcarbonyl}-lH-pyrazol-5-yl]-N-[(4-methanesulfonylphenyl)methyl]cyclohexan-1-amine, 4-[1-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yljcarbonyl}-1H-pyrazol-5-yl]-1-[(4-methanesulfonylphenyl)methyl]-l-methylpiperidin-l-ium, 4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yljcarbonyl}-1H-pyrazol-5-yl]-1-[(4-methanesulfonylphenyl)methyl]-1-methylpiperidin-l-ium, and l-ethyl-4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]-1-[(4-methanesulfonylphenyl)methyl]piperidin-1-ium.

[00019] Another aspect provided herein are pharmaceutical compositions comprising a therapeutically effective amount of a compound of any of the aforementioned compounds of Formulas (I)-(VIII), and a pharmaceutically acceptable excipient.

[00020] Another aspect provided herein are medicaments for treating a TGR5 mediated disease or disorder, wherein the medicament comprises a therapeutically effective amount of any of the aforementioned compounds of Formulas (I)-(VIII). In certain embodiments of such medicaments, the TGR5 mediated disease or disorder is selected from diabetes, an inflammatory disorders and an autoimmune disease. In certain embodiments of such medicaments, the TGR5 mediated disease or disorder is type II diabetes or psoriasis.

[00021] Another aspect provided herein is the use of a compound of Formulas (I)-(VIII) in the manufacture of a medicament for treating a TGR5 mediated disease or disorder, wherein the disease or disorder is selected from diabetes, an inflammatory disorders and an autoimmune disease. In certain embodiments of such uses the TGR5 mediated disease or disorder is type II diabetes or psoriasis.

[00022] Another aspect provided herein is methods for treating a TGR5 mediated disease or disorder comprising administering to a subject in need thereof, a therapeutically effective amount of any of the aforementioned compounds of Formulas (I)-(VIII). In certain embodiments of such methods, the TGR5 mediated disease or disorder is selected from diabetes, an inflammatory disorders and an autoimmune disease. In certain embodiments of such methods, the TGR5 mediated disease or disorder is type II diabetes or psoriasis. In certain embodiments of such methods, the compound is an agonist of TGR5.

[00023] Another aspect provided herein is a compound for use in a method of medical

treatment, wherein the method of medical treatment is for treating a TGR5 mediated disease or disorder, wherein the disease is selected from diabetes, an inflammatory disorders and an autoimmune disease, and wherein the compound is any of the aforementioned compounds of Formulas (I)-(VIII), or pharmaceutically acceptable salt thereof. In certain embodiments of this aspect, the TGR5 mediated disease or disorder is type II diabetes or psoriasis.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[00024] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by those of ordinary skill in the art to which this invention pertains. The following references provide one of skill with a general definition of many of the terms used in this invention: *Oxford Dictionary of Biochemistry and Molecular Biology*, Smith et al. (eds.), Oxford University Press (revised ed., 2000); *Dictionary of Microbiology and Molecular Biology,* Singleton et al. (Eds.), John Wiley & Sons (3rd ed., 2002); and *A Dictionary of Biology (Oxford Paperback Reference)*, Martin and Hine (Eds.), Oxford University Press (4th ed., 2000). In addition, the following definitions are provided to assist the reader in the practice of the invention.

[00025] The term "alkene" or "alkenyl", as used herein, refers to a partially unsaturated branched or straight chain hydrocarbon having at least one carbon-carbon double bond. Atoms oriented about the double bond are in either the cis (Z) or trans (E) conformation. As used herein, the terms "C_2-C_4alkenyl", "C_2-C_5alkenyl", "C_2-C_6alkenyl", "C_2-C_7alkenyl", and "C_2-C_8alkenyl" refer to an alkenyl group containing at least 2, and at most 4, 5, 6, 7 or 8 carbon atoms, respectively. Non-limiting examples of alkenyl groups, as used herein, include ethenyl, propenyl, allyl (2-propenyl), butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl and the like. In certain embodiments an alkene or alkenyl group is optionally substituted.

[00026] The term "alkenylene," as used herein, refers to a saturated branched or straight chain divalent hydrocarbon radical derived from an alkenyl group. In certain embodiments an alkenylene group is optionally substituted. As used herein, the terms "C_{2-C3} alkenylene", "C_2-C_4alkenylene", "C_2-C_5alkenylene", "C_2-C_6alkenylene", "C_2-C_7alkenylene" and "C_2-Csalkenylene" refer to an alkenylene group containing at least 2, and at most 3, 4, 5, 6, 7 or 8 carbon atoms respectively. Non-limiting examples of alkenylene groups as used herein

include, ethenlene, n-propenylene, isopropenylene, n-butenylene, isobutenylene, sec-butenylene, t-butenylene, n-pentenylene, isopentenylene, hexenylene and the like.

[00027] The term "alkyl," as used herein, refers to a saturated branched or straight chain hydrocarbon. An alkyl group can be optionally substituted. As used herein, the terms "C_1-C_3alkyl", "Ci-C_4alkyl", "Ci-C_5alkyl", "Ci-C_6alkyl", "Ci-C_7alkyl" and "Ci-C_8alkyl" refer to an alkyl group containing at least 1, and at most 3, 4, 5, 6, 7 or 8 carbon atoms, respectively. Non-limiting examples of alkyl groups as used herein include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, hexyl, heptyl, octyl, nonyl, decyl and the like. In certain embodiments an alkyl group is optionally substituted.

[00028] The term "alkylene," as used herein, refers to a saturated branched or straight chain divalent hydrocarbon radical derived from an alkyl group. In certain embodiments the alkylene group is optionally substituted. As used herein, the terms "Ci-C_3alkylene", "Cr C_4alkylene", "C_1-C_5alkylene", "C_1-C_6alkylene", "C_1-C_7alkylene" and "C_1-C_8alkylene" refer to an alkylene group containing at least 1, and at most 3, 4, 5, 6, 7 or 8 carbon atoms respectively. Non-limiting examples of alkylene groups as used herein include, methylene, ethylene, n-propylene, isopropylene, n-butylene, isobutylene, sec-butylene, t-butylene, n-pentylene, isopentylene, hexylene and the like.

[00029] The term "alkyne" or "alkynyl", as used herein, refers to a partially unsaturated branched or straight chain hydrocarbon radical having at least one carbon-carbon triple bond. As used herein, the terms "C_2-C_4alkynyl", "C_2-C_5alkynyl", "C_2-C_6alkynyl", "C_2-C_7alkynyl", and "C_2-C_8alkynyl" refer to an alkynyl group containing at least 2, and at most 4, 5, 6, 7 or 8 carbon atoms, respectively. Non-limiting examples of alkynyl groups, as used herein, include ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl and the like. In certain embodiments the alkyne or alkynyl group is optionally substituted.

[00030] The term "alkynylene," as used herein, refers to a saturated branched or straight chain divalent hydrocarbon radical derived from an alkynyl group. In certain embodiments the alkynylene group is optionally substituted. As used herein, the terms "C_2-C_3alkynylene", "C_2-C_4alkynylene", "C_2-C_5alkynylene", "C_2-C_6alkynylene", "C_2-C_7alkynylene" and "C_2-Csalkynylene" refer to an alkynylene group containing at least 2, and at most 3, 4, 5, 6, 7 or 8 carbon atoms respectively. Non-limiting examples of alkenylene groups as used herein include, ethynlene, propynylene, butynylene, pentynylene, hexynylene and the like.

[00031] The term "alkoxy," as used herein, refers to the group -OR_a, where R_a is an alkyl group as defined herein. In certain embodiments the alkoxy group is optionally substituted.

As used herein, the terms "C_1-C_3alkoxy", "C_1-C_4alkoxy", "C_1-C_5alkoxy", "C_1-C_6alkoxy", "Ci-C_7alkoxy" and "Ci-Csalkoxy" refer to an alkoxy group wherein the alkyl moiety contains at least 1, and at most 3, 4, 5, 6, 7 or 8, carbon atoms. Non-limiting examples of alkoxy groups, as used herein, include methoxy, ethoxy, n-propoxy, isopropoxy, n-butyloxy, t-butyloxy, pentyloxy, hexyloxy, heptyloxy, octyloxy, nonyloxy, decyloxy and the like.

[00032] The term "Cioaryl," as used herein, refers to naphthenyl or azulenyl, each of which is optionally substituted.

[00033] The term "C_{14}aryl," as used herein, refers to anthracenyl or phenanthrenyl, each of which is optionally substituted.

[00034] The term "arylene," as used means a divalent radical derived from a phenyl, Cioaryl or a C_{14}aryl group. In certain embodiments the arylene group is optionally substituted.

[00035] The term "cyano," as used herein, refers to a -CN group.

[00036] The term "cycloalkyl," as used herein, refers to a saturated, monocyclic, fused bicyclic, fused tricyclic or bridged polycyclic ring assembly. As used herein, the terms "C_3-C_5cycloalkyl", "C_3-C_6cycloalkyl", "C_3-C_7cycloalkyl", "C_3-C_8cycloalkyl, "C_3-C_9cycloalkyl and "C_3-Ciocycloalkyl refer to a cycloalkyl group wherein the saturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly contain at least 3, and at most 5, 6, 7, 8, 9 or 10, carbon atoms. In certain embodiments the cycloalkyl group is optionally substituted. Non-limiting examples of cycloalkyl groups, as used herein, include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, decahydronaphthalenyl and the like.

[00037] The term "cycloalkylene," as used means a divalent radical derived from a cycloalkyl group. In certain embodiments the cycloalkylene group is optionally substituted.

[00038] The term "halogen," as used herein, refers to fluorine (F), chlorine (CI), bromine (Br), or iodine (I).

[00039] The term "halo," as used herein, refers to the halogen radicals: fluoro (-F), chloro (-C1), bromo (-Br), and iodo (-1).

[00040] The terms "haloalkyl" or "halo-substituted alkyl," as used herein, refers to an alkyl group as defined herein, substituted with one or more halogen groups, wherein the halogen groups are the same or different. In certain embodiments the haloalkyl group is optionally substituted. Non-limiting examples of such branched or straight chained haloalkyl groups, as used herein, include methyl, ethyl, propyl, isopropyl, isobutyl and n-butyl

substituted with one or more halogen groups, wherein the halogen groups are the same or different, including, but not limited to, trifluoromethyl, pentafluoroethyl, and the like.

[00041] The terms "haloalkenyl" or "halo-substituted alkenyl," as used herein, refers to an alkenyl group as defined herein, substituted with one or more halogen groups, wherein the halogen groups are the same or different. In certain embodiments the haloalkenyl group is optionally substituted. Non-limiting examples of such branched or straight chained haloalkenyl groups, as used herein, include ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl and the like substituted with one or more halogen groups, wherein the halogen groups are the same or different.

[00042] The terms "haloalkynyl" or "halo-substituted alkynyl," as used herein, refers to an alkynyl group as defined above, substituted with one or more halogen groups, wherein the halogen groups are the same or different. In certain embodiments the haloalkynyl group is optionally substituted. Non-limiting examples of such branched or straight chained haloalkynyl groups, as used herein, include ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, and the like substituted with one or more halogen groups, wherein the halogen groups are the same or different.

[00043] The term "haloalkoxy" or "halo-substituted-alkoxy," as used herein, refers to an alkoxy group as defined herein, substituted with one or more halogen groups, wherein the halogen groups are the same or different. In certain embodiments the haloalkoxy group is optionally substituted. Non-limiting examples of such branched or straight chained haloalkynyl groups, as used herein, include methoxy, ethoxy, n-propoxy, isopropoxy, n-butyloxy, t-butyloxy, pentyloxy, hexyloxy, heptyloxy, octyloxy, nonyloxy, decyloxy and the like, substituted with one or more halogen groups, wherein the halogen groups are the same or different.

[00044] The term "heteroalkyl," as used herein, refers to an alkyl group as defined herein wherein one or more carbon atoms are independently replaced by one or more of oxygen, sulfur, nitrogen, or combinations thereof.

[00045] The term "heteroaryl," as used herein, refers to monocyclic, fused bicyclic, and fused tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic, at least one ring in the system contains one or more heteroatoms selected from nitrogen, oxygen and sulfur, and wherein each ring in the system contains 3 to 7 ring members. A heteroaryl group may contain one or more substituents. In certain embodiments the heteroaryl group is optionally substituted. Non-limiting examples of

heteroaryl groups, as used herein, include benzofuranyl, benzofurazanyl, benzoxazolyl, benzopyranyl, benzthiazolyl, benzothienyl, benzazepinyl, benzimidazolyl, benzothiopyranyl, benzo[l,3]dioxole, benzo[b]furyl, benzo[b]thienyl, cinnolinyl, furazanyl, furyl, furopyridinyl, imidazolyl, indolyl, indolizinyl, indolin-2-one, indazolyl, isoindolyl, isoquinolinyl, isoxazolyl, isothiazolyl, 1,8-naphthyridinyl, oxazolyl, oxaindolyl, oxadiazolyl, pyrazolyl, pyrrolyl, phthalazinyl, pteridinyl, purinyl, pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, quinoxalinyl, quinolinyl, quinazolinyl, 4H-quinolizinyl, thiazolyl, thiadiazolyl, thienyl, triazinyl,triazolyl and tetrazolyl.

[00046] The term "heteroarylene," as used means a divalent radical derived from a heteroaryl group. In certain embodiments the heteroarylene group is optionally substituted.

[00047] The term "heterocycloalkyl," as used herein, refers to a cycloalkyl, as defined herein, wherein one or more of the ring carbons are replaced by a moiety selected from -0-, -N=, -NR-, -C(O)-, -S-, -S(O) - or -S(0) $_2$-, wherein R is hydrogen, C_1-C_4alkyl or a nitrogen protecting group, with the proviso that the ring of said group does not contain two adjacent O or S atoms. In certain embodiments the heterocycloalkyl group is optionally substituted. Non-limiting examples of heterocycloalkyl groups, as used herein, include azetidinyl, morpholino, pyrrolidinyl, pyrrolidinyl-2-one, piperazinyl, piperidinyl, piperidinyl-2-one, piperidinyl-3-one, piperidinyl-4-one, l,4-dioxa-8-aza-spiro[4.5]dec-8-yl, 2H-pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl, 1,3-dioxolanyl, 2-imidazolinyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, 1,4-dioxanyl, 1,4-dithianyl, thiomorpholinyl, azepanyl, hexahydro-1,4-diazepinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, thioxanyl, azetidinyl, oxetanyl, thietanyl, oxepanyl, thiepanyl, 1,2,3,6-tetrahydropyridinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, and 3-azabicyclo[4.1.0]heptanyl.

[00048] The term "heterocycloalkylene," as used means a divalent radical derived from a heterocycloalkyl group. In certain embodiments the heterocycloalkylene group is optionally substituted.

[00049] The term "heteroatom," as used herein, refers to one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon.

[00050] The term "hydroxyl," as used herein, refers to the group -OH.

[00051] The term "hydroxyalkyl" or hydroxyl-substituted-alkyl," as used herein, refers to an alkyl group as defined herein substituted with one or more hydroxyl group. Non-limiting

examples of branched or straight chained "C1-C6 hydroxyalkyl groups as used herein include methyl, ethyl, propyl, isopropyl, isobutyl and n-butyl groups substituted with one or more hydroxyl groups.

[00052] The term "optionally substituted," as used herein, means that the referenced group may or may not be substituted with one or more additional group(s) individually and independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, hydroxyl, alkoxy, mercaptyl, cyano, halo, carbonyl, thiocarbonyl, isocyanato, thiocyanato, isothiocyanato, nitro, perhaloalkyl, perfluoroalkyl, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. Non-limiting examples of optional substituents include, halo, -CN, =0, -OR, -C(0)R, -C(0)OR, -OC(0)R, -OC(0)OR, -C(0)NHR, -C(0)NR $_2$, -OC(0)NHR, -OC(0)NR $_2$, -SR-, -S(0)R, -S(0) $_2$R, -NHR, -N(R)$_2$, -NHC(0)R, -NRC(0)R, -NHC(0)OR, -NRC(0)OR, S(0) $_2$NHR, -S(0) $_2$N(R)$_2$, -NHS(0) $_2$, -NRS(0) $_2$, -NHS(0) $_2$R, -NRS(0) $_2$R, C_1-C_8alkyl, C_1-C_8alkoxy, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, halo-substituted Ci-Csalkyl, halo-substituted Cr Csalkoxy, where each R is independently selected from H, halo, Ci-Csalkyl, Ci-Csalkoxy, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, halo-substituted Ci-Csalkyl, and halo-substituted Ci-Csalkoxy. The placement and number of such substituent groups is done in accordance with the well-understood valence limitations of each group, for example =0 is a suitable substituent for an alkyl group but not for an aryl group.

[00053] The term "solvate," as used herein, refers to a complex of variable stoichiometry formed by a solute (by way of example, a compound of Formula (I), or a salt thereof, as described herein) and a solvent. Non-limiting examples of a solvent are water, acetone, methanol, ethanol and acetic acid.

[00054] The term "acceptable" with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

[00055] The term "administration" or "administering" of the subject compound means providing a compound of Formula (I), a pharmaceutically acceptable salt, a pharmaceutically acceptable solvate, or prodrug thereof to a subject in need of treatment.

[00056] The term "agent" or "test agent," as used herein, includes any substance, molecule, element, compound, entity, or a combination thereof. It includes, but is not limited to a protein, a polypeptide, a small organic molecule, a polysaccharide, a polynucleotide, and the like. It can be a natural product, a synthetic compound, or a chemical compound, or a

combination of two or more substances. Unless otherwise specified, the terms "agent", "substance", and "compound" can be used interchangeably.

[00057] The term "cardiovascular disease," as used herein refers to diseases affecting the heart or blood vessels or both, including but not limited to: arrhythmia; atherosclerosis and its sequelae; angina; myocardial ischemia; myocardial infarction; cardiac or vascular aneurysm; vasculitis, stroke; peripheral obstructive arteriopathy of a limb, an organ, or a tissue; reperfusion injury following ischemia of the brain, heart or other organ or tissue; endotoxic, surgical, or traumatic shock; hypertension, valvular heart disease, heart failure, abnormal blood pressure; shock; vasoconstriction (including that associated with migraines); vascular abnormality, inflammation, insufficiency limited to a single organ or tissue.

[00058] The term "carrier," as used herein, refers to chemical compounds or agents that facilitate the incorporation of a compound described herein into cells or tissues.

[00059] The terms "co-administration" or "combined administration" or the like as used herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

[00060] The term "contacting," as used herein, has its normal meaning and refers to combining two or more molecules (by way of example only, a small molecule organic compound and a polypeptide) or combining molecules and cells (by way of example only, a compound and a cell). Contacting can occur *in-vitro,* by way of example only, combining two or more agents or combining a compound and a cell or a cell lysate in a test tube or other container. Contacting can also occur in a cell or *in-situ,* by way of example only, contacting two polypeptides in a cell by coexpression in the cell of recombinant polynucleotides encoding the two polypeptides, or in a cell lysate. Contacting can occur *in-vivo.*

[00061] The term "diluent," as used herein, refers to chemical compounds that are used to dilute a compound described herein prior to delivery. Diluents can also be used to stabilize compounds described herein.

[00062] The terms "effective amount" or "therapeutically effective amount," as used herein, refer to a sufficient amount of a compound described herein being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic uses is the amount of the composition comprising a

compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate "effective" amount in any individual case may be determined using techniques, such as a dose escalation study.

[00063] The terms "enhance" or "enhancing," as used herein, means to increase or prolong either in potency or duration a desired effect. Thus, in regard to enhancing the effect of therapeutic agents, the term "enhancing" refers to the ability to increase or prolong, either in potency or duration, the effect of other therapeutic agents on a system. An "enhancing-effective amount," as used herein, refers to an amount adequate to enhance the effect of another therapeutic agent in a desired system.

[00064] The term "iatrogenic," as used herein, means a condition, disorder, or disease created or worsened by medical or surgical therapy.

[00065] The term "inflammatory disorders", as used herein, refers to those diseases or conditions that are characterized by one or more of the signs of pain (dolor, from the generation of noxious substances and the stimulation of nerves), heat (calor, from vasodilatation), redness (rubor, from vasodilatation and increased blood flow), swelling (tumor, from excessive inflow or restricted outflow of fluid), and loss of function (functio laesa, which may be partial or complete, temporary or permanent). Inflammation takes many forms and includes, but is not limited to, inflammation that is one or more of the following: acute, adhesive, atrophic, catarrhal, chronic, cirrhotic, diffuse, disseminated, exudative, fibrinous, fibrosing, focal, granulomatous, hyperplastic, hypertrophic, interstitial, metastatic, necrotic, obliterative, parenchymatous, plastic, productive, proliferous, pseudomembranous, purulent, sclerosing, seroplastic, serous, simple, specific, subacute, suppurative, toxic, traumatic, and/or ulcerative. Inflammatory disorders further include, without being limited to those affecting the blood vessels (polyarteritis, temporarl arteritis); joints (arthritis: crystalline, osteo-, psoriatic, reactive, rheumatoid, Reiter's); gastrointestinal tract (Disease,); skin (dermatitis); or multiple organs and tissues (systemic lupus erythematosus).

[00066] The term "pharmaceutically acceptable," as used herein, refers a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compounds described herein. Such materials are administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

[00067] The term "pharmaceutically acceptable salt," as used herein, refers to a formulation of a compound that does not cause significant irritation to an organism to which

it is administered and does not abrogate the biological activity and properties of the compounds described herein.

[00068] The term "prevent" or "prevention," as used herein, refers to a complete inhibition of development of primary or secondary tumors or any secondary effects of disease.

[00069] The terms "combination" or "pharmaceutical combination," as used herein mean a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, by way of example, a compound of Formula (I) and an additional therapeutic agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, by way of example, a compound of Formula (I) and an additional therapeutic agent, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the 2 compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of 3 or more active ingredients.

[00070] The terms "composition" or "pharmaceutical composition," as used herein, refers to a mixture of at least one compound of Formula (I) described herein with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients.

[00071] The term "prodrug," as used herein, refers to an agent that is converted into the parent drug *in vivo.* A non-limiting example of a prodrug of the compounds described herein is a compound described herein administered as an ester which is then metabolically hydrolyzed to a carboxylic acid, the active entity, once inside the cell. A further example of a prodrug is a short peptide bonded to an acid group where the peptide is metabolized to reveal the active moiety.

[00072] The term "subject" includes mammals, especially humans. It also encompasses other non-human animals such as cows, horses, sheep, pigs, cats, dogs, mice, rats, rabbits, guinea pigs, monkeys.

[00073] The term "therapeutically effective amount," as used herein, refers to any amount of a compound which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The

term also includes within its scope amounts effective to enhance normal physiological function.

[00074] The terms "treat," "treating" or "treatment," as used herein, refers to methods of alleviating, abating or ameliorating a disease or condition symptoms, preventing additional symptoms, ameliorating or preventing or delaying the underlying metabolic causes of symptoms, inhibiting the disease or condition, arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically (prevent or delay the onset of the disease, or to prevent the manifestation of clinical or subclinical symptoms thereof) and/or therapeutically.

[00075] The compound names provided herein were obtained using ChemDraw Ultra 10.0 (CambridgeSoft®) or JChem version 5.3.1 (ChemAxon).

[00076] Other objects, features and advantages of the methods, compositions and combinations described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only.

Description of Preferred Embodiments

[00077] Provided herein are compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof that are agonists of TGR5.

[00078] Further provided herein are compounds, pharmaceutically acceptable salts, solvates, N-oxides, prodrugs, enantiomers and isomers thereof, and pharmaceutical compositions containing such pharmaceutically acceptable salts, solvates, N-oxides, prodrugs, enantiomers and isomers thereof, for the treatment and/or prevention of TGR5 mediated diseases and/or disorders.

[00079] Also provided herein are compounds, pharmaceutically acceptable salts, solvates, N-oxides, prodrugs, enantiomers and isomers thereof, and pharmaceutical compositions containing such pharmaceutically acceptable salts, solvates, N-oxides, prodrugs, enantiomers and isomers thereof, in combination with one or more additional therapeutic agents for the treatment and/or prevention of TGR5 mediated diseases and/or disorders.

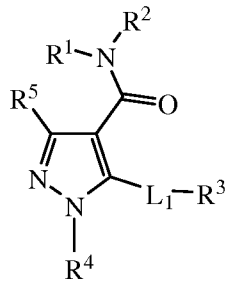
[00080] Such TGR5 mediated diseases or disorders include, but are not limited to, gallstones, cholestasis, diabetes, an inflammatory disorders and an autoimmune disease, such as, by way of example only, type II diabetes or psoriasis.

[00081] Such autoimmune diseases and/or disorders and autoimmune -mediated diseases and/or disorders include, but are not limited to, destructive arthritis, rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, multiple sclerosis, dermatomyositis, progressive systemic sclerosis, diseases affecting the nose including allergic rhinitis, and inflammatory disease in which autoimmune reactions are implicated or having an autoimmune component or aetiology, including autoimmune haematological disorders (e.g. haemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), primary binary cirrhosis (PBC), lupus, systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (e.g. ulcerative colitis and Crohn's disease), endocrine opthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary billiary cirrhosis, uveitis (anterior and posterior), kerato-conjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy).

[00082] Such inflammatory diseases and/or disorders include, but are not limited to, uveitis, atherosclerosis, atherogenesis, glomerulonephritis, Kawasaki disease, inflammatory responses, polymyositis, arthritis, neurological inflammation, chronic arthritis inflammation and osteoarthritis.

Compounds and compositions

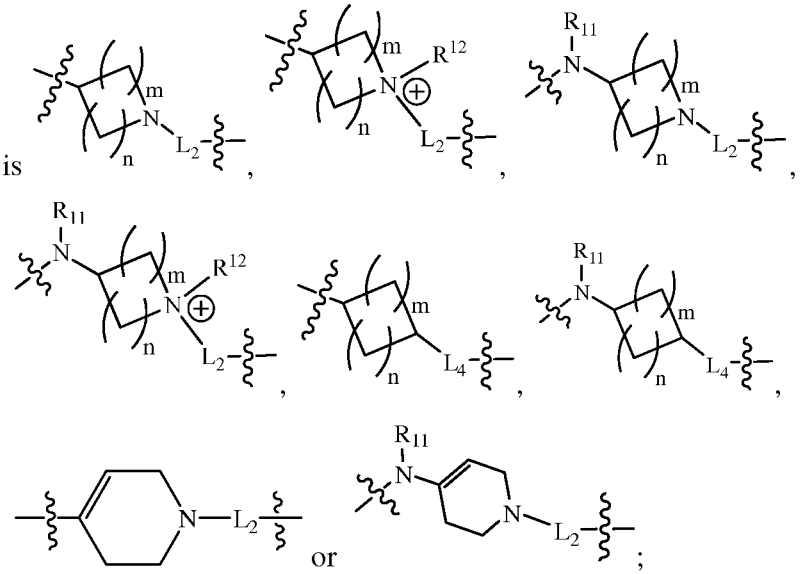
[00083] The aforementioned compounds and pharmaceutically acceptable salts, solvates, N-oxides, prodrugs, enantiomers and isomers thereof, that are agonists of TGR5 are compounds having structures according to Formula (I) or Formula (II):



(I)

wherein,

R^1 and R^2 are each independently selected from Ci-Cealkyl, and C_2-C_6alkene, and taken together with the N atom to which they are attached form a 4 to 6 membered heterocycloalkyl ring containing a N heteroatom, a 9 to 14 membered fused bicyclic heterocycloalkyl ring containing a N heteroatom, or a 9 to 14 membered fused bicyclic heteroaryl containing an N heteroatom, wherein such heterocycloalkyl and fused bicyclic heteroaryl are each optionally substituted with 1 to 5 substituents independently selected from halogen, deuterium, C_1-C_6alkyl, Ci-Cehaloalkyl, -CN, R^9, -OR^9, phenyl, phenoxy, Cioaryl and C_{14}aryl, wherein such phenyl, phenoxy, Cioaryl and C_{14}aryl are each optionally substituted with 1 to 5 substituents independently selected from halogen, deuterium and -OR^9;

L_1 is 

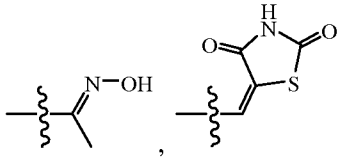
;

L_2 is selected from -C(O)-, -C(0)0-, -$(CH_2)_q$C(0)0-, -S(0) $_2$-, C_1-C_6alkylene, phenylene, Cioarylene, C^arylene, a 5, 6, 9, 10 or 14 membered heteroarylene containing 1 to 2 heteroatoms independently selected from N, O and S, or a bond, wherein the Ci-Cealkylene ,arylene and heteroarylene of L_2 are optionally substituted with 1 to 3 substituents independently selected from deuterium, R^9 and -C(0)OR ^{9};

L_3 is Ci-C_6alkylene optionally substituted with 1 to 3 substituents independently selected deuterium, R^9 and -C(0)OR ^{9}, or Ci-Cealkenylene optionally substituted with 1 to 3 substituents independently selected from deuterium, R^9 and -C(0)OR ^{9};

L_4 is selected from a -NR^9-, -$NR^9C(0)0$-, -$NR^9(CH_2)_q$ -, -C(0)NR^9-, -S(0) $_2$-, -0-, C_1-Cealkylene, phenylene, Cioarylene, C_{14}arylene, a 5, 6, 9, 10 or 14 membered heteroarylene containing 1 to 2 heteroatoms independently selected from N, O and S, wherein the Ci-Cealkylene, arylene and heteroarylene of L_4 are optionally substituted with 1 to 3 substituents independently selected from deuterium, R^9 and -C(0)OR^9;

R^3 is selected from Ci-Cealkyl, Ci-Cehaloalkyl, C_3-C_8cycloalkyl, -L_3R^6, phenyl, Cioaryl, C_{14}aryl, a 5, 6, 9, 10 or 14 membered heteroaryl containing 1 to 3 N heteroatoms and optionally one heteroatom selected from O and S, and a 4 to 7 membered heterocycloalkyl ring containing 1 to 2 heteroatoms independently selected from N, O and S, wherein the Ci-Cealkyl, aryl, heterocycloalkyl, C_3-Cscycloalkyl and heteroaryl groups of R^3 are each optionally substituted with 1 to 3 substituents independently selected from halogen, R^9, R^6, -OR^9, -$N(R^9)_2$, -C(0)$N(R^9)_2$, -C(0)NR^9OH, -C(0)OR^9, -C(0)OL_3R^6, -L_3C(0)OR^9, -C(0)R^9, -CN, -S(0) $_2R^9$, -S(0) $_2N(R^9)_2$, -S(0) $_2NR^9C(0)R^9$, -$S(0)_2L_3C(0)OR^9$, -$OS(0)_2N(R^9)_2$, -S(0) $_2NR^9$OH, -$OL_3C(0)OR^9$, -C(0)$NR^9L_3C(0)OR^9$, -L_3R^6



and a 5 membered heteroaryl containing 1 to 4 N heteroatoms and optionally one heteroatom selected from O and S;

R^4 is selected from H, Ci-Cealkyl, phenyl, Cioaryl, C_{14}aryl, C_3-Cscycloalkyl, 5-6 membered heteroaryl containing one or more N heteroatoms, wherein the Cr C_6alkyl, aryl, heteroaryl and C_3-Cscycloalkyl groups of R^4 are each optionally substituted with 1 to 3 substituents independently selected from halogen, -CN, R^9, and -OR^9;

R^5 is H, Ci-C_6alkyl or C_1-C_6haloalkyl.

R^6 is C_3-C_8cycloalkyl, phenyl, Cioaryl, C_{14}aryl, a 5, 6, 9, 10 or 14 membered heteroaryl containing 1 to 2 heteroatoms independently selected from N, O and S, a 4 to 7 membered heterocycloalkyl ring containing 1 to 2 heteroatoms independently selected from N, O and S, and a 9 to 14 membered fused bicyclic heterocycloalkyl ring containing containing 1 to 2 heteroatoms independently selected from N, O and S, each of which is optionally substituted with 1 to 5

substituents independently selected from halogen, deuterium, R^9, -OR^9, -CN and -C(0)OR^9;

R^9 is H, Ci-C_6alkyl optionally substituted with 1 to 4 -OH groups or Ci-Cehaloalkyl;

R^{11} is H or Ci-C_6alkyl;

R^{12} is Ci-C_4alkyl, -CH_2C(0)OH or -(CHR^{13})C(0)OH;

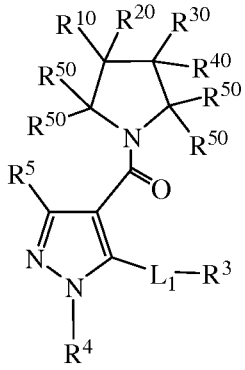
R^{13} is H or Ci-C_4alkyl;

each m is independently 1, 2 or 3;

each n is independently 1, 2 or 3, and

each q is independently 1, 2, 3, 4, 5, or 6.

[00084] In certain embodiments, such the compounds of Formula (I) are compounds having the structure of Formula (II):



(II)

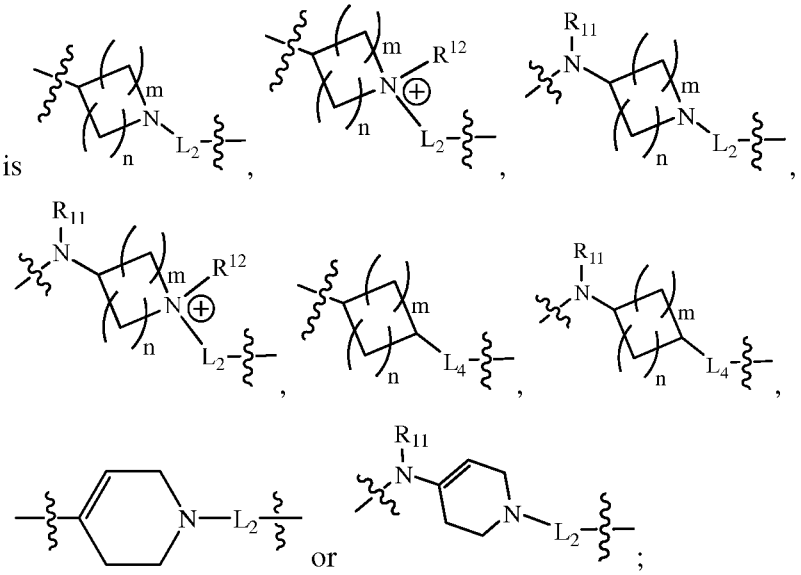
wherein,

R^{10} and R^{20} are each independently selected from H, -OR^9, deuterium or halogen;

R^{30} is selected from phenyl, phenoxy, Cioaryl and C_{14}aryl, each of which is optionally substituted with 1 to 5 substituents independently selected from halogen, deuterium and -OR^9;

R^{40} is selected from H, deuterium, Ci-Cealkyl and Ci-Cehaloalkyl;

each R^{50} is independently selected from H or deuterium;

L_1 is 

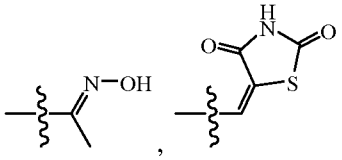
L_2 is selected from -C(0)-, -C(0)0-, $-(CH_2)_qC(0)0-$, $-S(0)_2-$, C_1-C_6alkylene, phenylene, Cioarylene, C^arylene, a 5, 6, 9, 10 or 14 membered heteroarylene containing 1 to 2 heteroatoms independently selected from N, O and S, or a bond, wherein the Ci-Cealkylene ,arylene and heteroarylene of L_2 are optionally substituted with 1 to 3 substituents independently selected from deuterium, R^9 and $-C(0)OR^9$;

L_3 is C_1-C_6alkylene optionally substituted with 1 to 3 substituents independently selected deuterium, R^9 and $-C(0)OR^9$, or Ci-Cealkenylene optionally substituted with 1 to 3 substituents independently selected from deuterium, R^9 and $-C(0)OR^9$;

L_4 is selected from a $-NR^9-$, $-NR^9C(0)0-$, $-NR^9(CH_2)_q-$, $-C(0)NR^9-$, $-S(0)_2-$, -0-, C_1-C_6alkylene, phenylene, Cioarylene, C^arylene, a 5, 6, 9, 10 or 14 membered heteroarylene containing 1 to 2 heteroatoms independently selected from N, O and S, wherein the Ci-Cealkylene, arylene and heteroarylene of L_4 are optionally substituted with 1 to 3 substituents independently selected from deuterium, R^9 and $-C(0)OR^9$;

R^3 is selected from Ci-Cealkyl, Ci-Cehaloalkyl, C_3-Cscycloalkyl, $-L_3R^6$, phenyl, Cioaryl, C_{14}aryl, a 5, 6, 9, 10 or 14 membered heteroaryl containing 1 to 3 N heteroatoms and optionally one heteroatom selected from O and S, and a 4 to 7 membered heterocycloalkyl ring containing 1 to 2 heteroatoms independently selected from N, O and S, wherein the Ci-Cealkyl, aryl, heterocycloalkyl, C_3-Cscycloalkyl and heteroaryl groups of R^3 are each optionally substituted with 1 to

3 substituents independently selected from halogen, R^9, R^6, $-OR^9$, $-N(R^9)_2$, $-C(0)N(R^9)_2$, $-C(0)NR^9OH$, $-C(0)OR^9$, $-C(0)OL_3R^6$, $-L_3C(0)OR^9$, $-C(0)R^9$, $-CN$, $-S(0)_2R^9$, $-S(0)_2N(R^9)_2$, $-S(0)_2NR^9C(0)R^9$, $-S(0)_2L_3C(0)OR^9$, $-OS(O)_2N(R^9)_2$, $-S(0)_2NR^9OH$, $-OL_3C(0)OR^9$, $-C(0)NR^9L_3C(0)OR^9$, $-L_3R^6$



and a 5 membered heteroaryl containing 1 to 4 N heteroatoms and optionally one heteroatom selected from O and S;

R^4 is selected from H, Ci-Cealkyl, phenyl, Cioaryl, C_{14}aryl, C_3-Cscycloalkyl, 5-6 membered heteroaryl containing one or more N heteroatoms, wherein the Cr C_6alkyl, aryl, heteroaryl and C_3-Cscycloalkyl groups of R^4 are each optionally substituted with 1 to 3 substituents independently selected from halogen, -CN, R^9, and $-OR^9$;

R^5 is H, Ci-C_6alkyl or C_1-C_6haloalkyl.

R^6 is C_3-C_8cycloalkyl, phenyl, Cioaryl, C_{14}aryl, a 5, 6, 9, 10 or 14 membered heteroaryl containing 1 to 2 heteroatoms independently selected from N, O and S, a 4 to 7 membered heterocycloalkyl ring containing 1 to 2 heteroatoms independently selected from N, O and S, and a 9 to 14 membered fused bicyclic heterocycloalkyl ring containing containing 1 to 2 heteroatoms independently selected from N, O and S, each of which is optionally substituted with 1 to 5 substituents independently selected from halogen, deuterium, R^9, $-OR^9$, -CN and $-C(0)OR^9$;

R^9 is H, Ci-C_6alkyl optionally substituted with 1 to 4 -OH groups or Ci-Cehaloalkyl;

R^{11} is H or Ci-C_6alkyl;

R^{12} is Ci-C_4alkyl, $-CH_2C(0)OH$ or $-(CHR^{13})C(0)OH$;

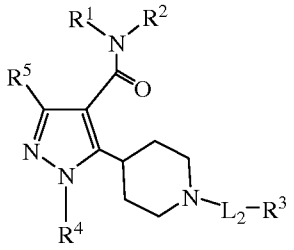
R^{13} is H or C_1-C_4alkyl;

each m is independently 1, 2 or 3;

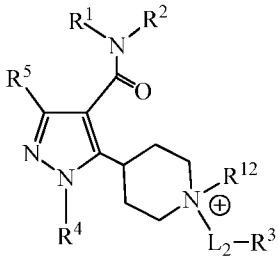
each n is independently 1, 2 or 3, and

each q is independently 1, 2, 3, 4, 5, or 6.

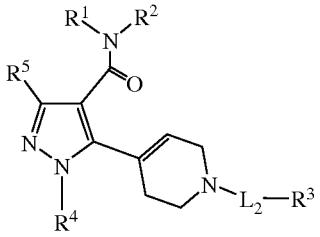
[00085] In certain embodiments, compounds of Formula (I) are compounds having the structure of Formula (III), Formula (IV) or Formula (V):



(III)

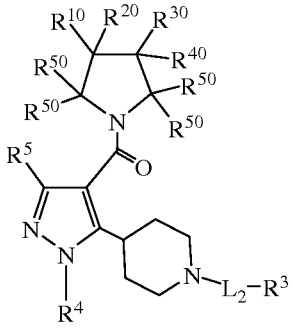


(IV)

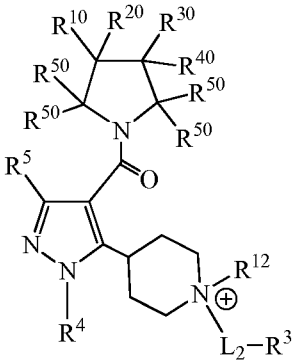


(V).

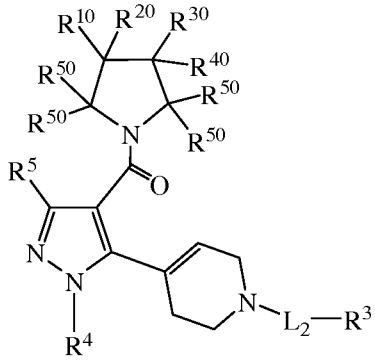
[00086] In certain embodiments, compounds of Formula (I) or Formula (II) are compounds having the structure of Formula (VI), Formula (VII) or Formula (VIII):



(VI)



(VII)



(VIII).

[00087] Non-limiting examples of such compounds of Formulas (I)-(VIII) are presented in the examples and tables provided herein.

[00088] The compounds of Formulas (I)-(VIII), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions provided herein also includes all suitable isotopic variations of such compounds, and pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions. An isotopic variation of a compound of the invention or a pharmaceutically acceptable salt thereof is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Examples of isotopes that may be incorporated into the compounds of the invention and pharmaceutically acceptable salts thereof include but are not limited to isotopes of hydrogen, carbon, nitrogen and oxygen such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, $^{17}0$, ^{18}O, ^{35}S, ^{18}F, ^{36}CI and ^{123}I. Certain isotopic variations of the compounds of the invention and pharmaceutically acceptable salts thereof, for example, those in which a radioactive isotope such as ^{3}H or ^{14}C is incorporated, are useful in drug and/or substrate tissue distribution studies. In particular examples, ^{3}H and ^{14}C isotopes may be used for their ease of preparation

and detectability. In other examples, substitution with isotopes such as ^{2}H may afford certain therapeutic advantages resulting from greater metabolic stability, such as increased *in-vivo* half-life or reduced dosage requirements. Isotopic variations of the compounds, and pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions provided herein are prepared by conventional procedures using appropriate isotopic variations of suitable reagents.

Processes for Making Compounds of Formula (I) and Formula (II)

[00089] General procedures for preparing compounds of Formula (I) and Formula (II) are described in the Examples, *infra.* In the reactions described, reactive functional groups, for example hydroxyl, amino, imino, thio or carboxy groups, where these are desired in the final product, may be protected to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice (see e.g., T.W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry," John Wiley and Sons, 1991).

[00090] In certain embodiments, the compounds of Formula (I)-(VIII) described herein are prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound of Formula (I)-(VIII) with a pharmaceutically acceptable organic acid or inorganic acid. In other embodiments, a pharmaceutically acceptable base addition salt of compounds of Formula (I)-(VIII) described herein is prepared by reacting the free acid form of the compound of Formula (I)-(VIII) with a pharmaceutically acceptable organic base or inorganic base. Alternatively, the salt forms of the compounds of Formula (I)-(VIII) described herein are prepared using salts of the starting materials or intermediates. In certain embodiments, the compounds of Formula (I)-(VIII) described herein are in the form of other salts including, but not limited to, oxalates and trifluoroacetates. In certain embodiments, hemisalts of acids and bases are formed, for example, hemisulphate and hemicalcium salts.

[00091] Such pharmaceutically acceptable acid addition salts of compounds of Formula (I)-(VIII) include, but are not limited to, a hydrobromide, hydrochloride, hydroiodide, sulfate, bisulphate, nitrate, phosphate, succinate, maleate, formate, acetate, adipate, besylatye, bicarbonate/carbonate, propionate, fumarate, citrate, tartrate, lactate, benzoate, salicylate, glutamate, aspartate, p-toluenesulfonate, benzenesulfonate, methanesulfonate, ethanesulfonate, naphthalenesulfonate (e.g. 2-naphthalenesulfonate), hexanoate salt, bisulphate/sulphate, borate, camsylate, cyclamate, edisylate, esylate, gluceptate, gluconate, glucuronate, pyruvate, hexafluorophosphate, hibenzate, hydrochloride/chloride,

hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, orotate, oxalate, oxaloacetate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, saccharate, stearate, tannate, tosylate, trifluoroacetate and xinofoate salts.

[00092] The organic acid or inorganic acids used to form certain pharmaceutically acceptable acid addition salts of compounds of Formula (I)-(VIII) include, but are not limited to, hydrobromic, hydrochloric, sulfuric, nitric, phosphoric, succinic, maleic, formic, acetic, propionic, fumaric, citric, tartaric, lactic, benzoic, salicylic, glutamic, aspartic, p-toluenesulfonic, benzenesulfonic, methanesulfonic, ethanesulfonic, naphthalenesulfonic such as 2-naphthalenesulfonic, or hexanoic acid.

[00093] Such pharmaceutically acceptable base addition salt of a compound of Formula (I)-(VIII) include, but are not limited to, aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

[00094] In certain embodiments, the free acid or free base forms of the compounds of Formula (I)-(VIII) described herein are prepared from the corresponding base addition salt or acid addition salt from, respectively. For example a compound Formula (I)-(VIII) in an acid addition salt form is converted to the corresponding free base by treating with a suitable base (by way of example only, an ammonium hydroxide solution, a sodium hydroxide, and the like). For example, a compound of Formula (I)-(VIII) in a base addition salt form is converted to the corresponding free acid by treating with a suitable acid (by way of example only, hydrochloric acid).

[00095] In certain embodiments, the compounds of Formula (I)-(VIII) described herein in unoxidized form are prepared from N-oxides of compounds Formula (I)-(VIII) by treating with a reducing agent (by way of example only, sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like) in a suitable inert organic solvent (by way of example only, acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80°C.

[00096] In certain embodiments, prodrug derivatives of compounds Formula (I)-(VIII) described herein are prepared using methods known to those of ordinary skill in the art (e.g., for further details see Saulnier et al., (1994), Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985). For example, appropriate prodrugs are prepared by reacting a non-

derivatized compound of Formula (I)-(VIII) with a suitable carbamylating agent (by way of example only, 1,1-acyloxyalkylcarbanochloridate, para-nitrophenyl carbonate, or the like).

[00097] In certain embodiments, the compounds of Formula (I)-(VIII) described herein are prepared as protected derivatives using methods known to those of ordinary skill in the art. A detailed description of the techniques applicable to the creation of protecting groups and their removal can be found in T. W. Greene, "Protecting Groups in Organic Chemistry," 3rd edition, John Wiley and Sons, Inc., 1999.

[00098] In certain embodiments, the compounds of Formula (I)-(VIII) described herein are prepared or formed, as solvates (e.g., hydrates). In certain embodiments, hydrates of compounds of Formula (I)-(VIII) are prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

[00099] In certain embodiments, the compounds of Formula (I)-(VIII) described herein are prepared as their individual stereoisomers. In other embodiments, the compounds of Formula (I)-(VIII) described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. In certain embodiments, resolution of enantiomers is carried out using covalent diastereomeric derivatives of the compounds of Formula (I)-(VIII), or by using dissociable complexes (e.g., crystalline diastereomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubility, reactivity, etc.) and are readily separated by taking advantage of these dissimilarities. In certain embodiments, the diastereomers are separated by chromatography, or by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions," John Wiley And Sons, Inc., 1981.

[000100] Compounds of Formula (I)-(VIII) are made by processes described herein and as illustrated in the Examples. In certain embodiments, compounds of Formula (I)-(VIII) are made by:

(a) optionally converting a compound of the invention into a pharmaceutically acceptable salt;

(b) optionally converting a salt form of a compound of the invention to a non-salt form;

(c) optionally converting an unoxidized form of a compound of the invention into a pharmaceutically acceptable N-oxide;

(d) optionally converting an N-oxide form of a compound of the invention to its unoxidized form;

(e) optionally resolving an individual isomer of a compound of the invention from a mixture of isomers;

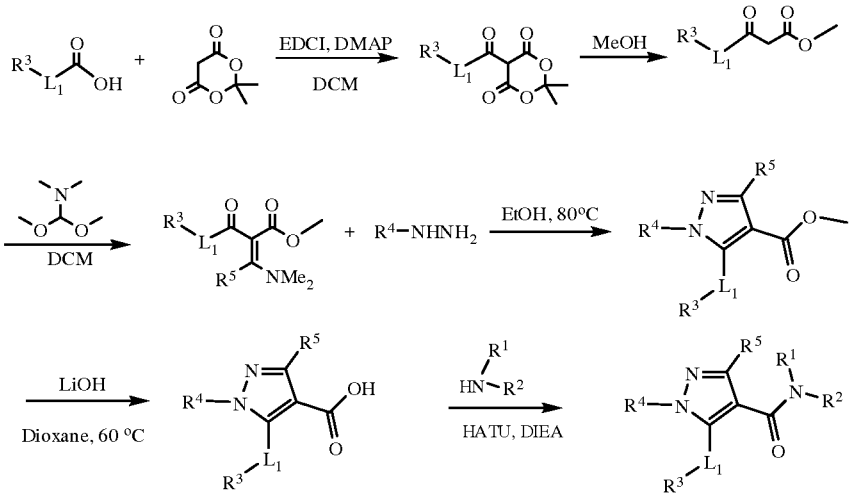
(f) optionally converting a non-derivatized compound of the invention into a pharmaceutically acceptable prodrug derivative; and

(g) optionally converting a prodrug derivative of a compound of the invention to its non-derivatized form.

[000101] Non-limiting examples of synthetic schemes used to make compounds of Formula (I)-(VIII) described herein are illustrated in reaction schemes (I)-(IX), wherein m, n, q, L^1, L^2, L^3, L^4, R^1, R^2, R^3, R^4, R^5, R^6, R^9, R^{10}, R^{20}, R^{30}, R^{40} and R^{50} are as defined herein.

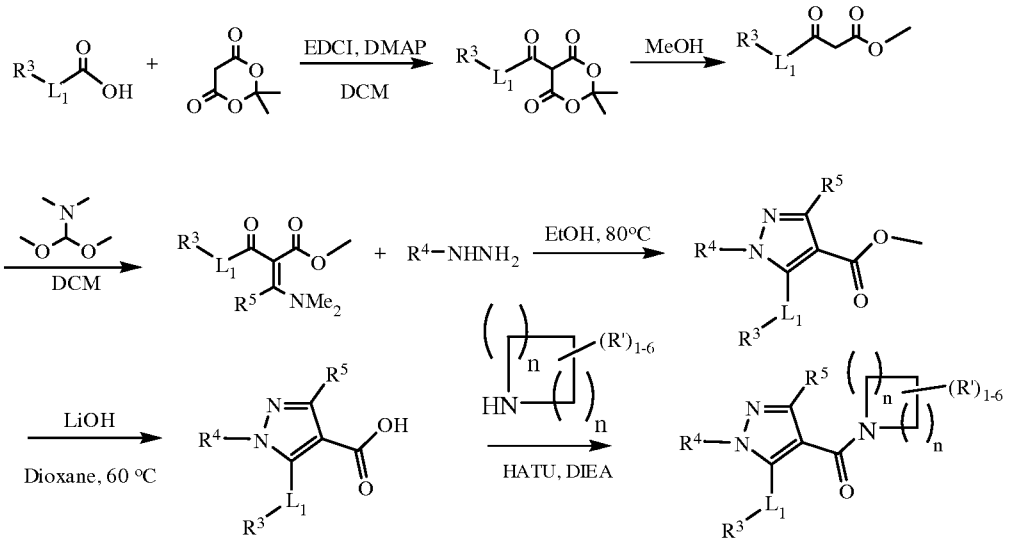
[000102] Reaction scheme (I) illustrates the synthesis of certain embodiments of compounds of Formula (I).

Reaction Scheme (I)



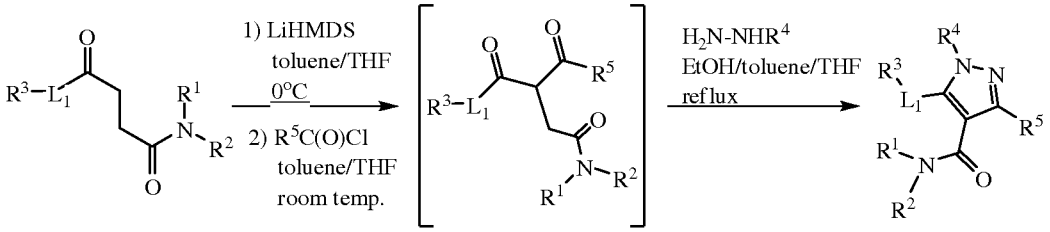
[000103] Reaction scheme (II) illustrates the synthesis of certain embodiments of compounds of Formula (I).

Reaction Scheme (II)



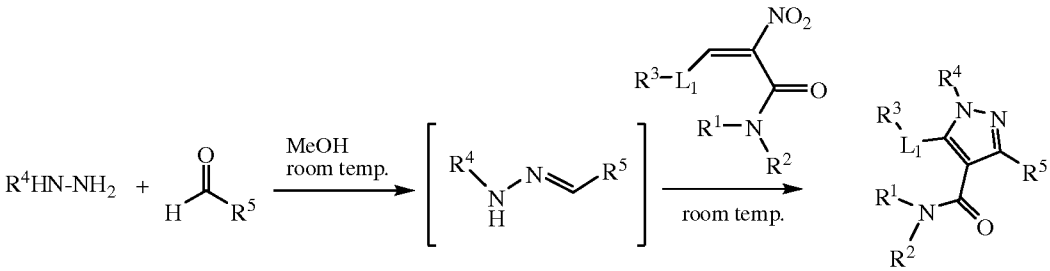
[000104] Reaction scheme (III) illustrates the synthesis of certain embodiments of compounds of Formula (I).

Reaction Scheme (III)



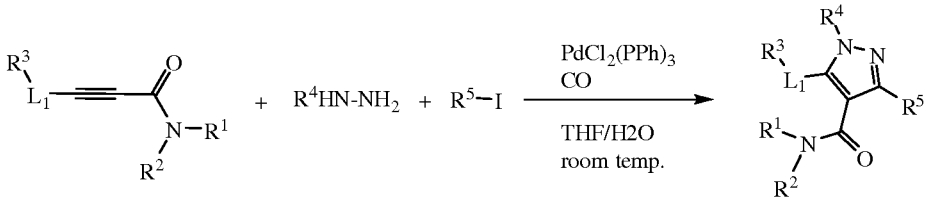
[000105] Reaction scheme (IV) illustrates the synthesis of certain embodiments of compounds of Formula (I).

Reaction Scheme (IV)



[000106] Reaction scheme (V) illustrates the synthesis of certain embodiments of compounds of Formula (I).

Reaction Scheme (V)



[000107] Insofar as the production of the starting materials is not particularly described, the compounds are known or can be prepared analogously to methods known in the art or as disclosed in the Examples hereinafter.

[000108] Detailed examples of the synthesis of compounds of Formula (I) can be found in the Examples, *infra.*

Pharmacology and Utility

[000109] A multitude of endocrine, neural, and metabolic signaling pathways are activated upon food intake to coordinate the effective use of the available energy. Bile acids (BAs) are released from the gallbladder after each meal and subsequently facilitate the digestion of nutrients. Since concentrations of BAs increase postprandially in the serum, they are also signals of food availability that bridge nutrition with metabolism.

[000110] Bile acids are known to be involved in lipid absorption and cholesterol homeostasis. However, bile acids are also regarded as signaling hormones endowed with paracrine and endocrine functions related to the homeostasis of cholesterol levels, control of lipid and carbohydrate metabolism, and regulation of the immune system. TGR5 (also known as GPBAR1 or M-BAR) has been identified as the endogenously specific metabotropic receptor of bile acids, and the activation of the membrane TGR5 receptor is thought to be the pathway to non-genomic functions of bile acids.

[000111] TGR5 is a member of the Rhodopsin-like subfamily of G-protein-coupled receptors (GPCR's) that mediates some of the endocrine functions of its bile acid ligands. TGR5 is highly expressed in the adipose tissue and in macrophages. In addition, TGR5 expression levels are high in the gall bladder, the gastrointestinal tract and in immune cells such as dendritic cells and monocytes, and show enrichment in organs like the spleen and lung, intestine (Werner et al. 2004; Kawatama et al. 2003) and in certain areas of the central nervous system. Both primary and secondary bile acids, such as lithocholic acid (LCA) and taurolithocholic acid (TLCA), have been shown to be the natural ligands of this receptor (Maruyama et al. 2002) and to inhibit LPS-induced TNFa and IL-12 production in monocytes/macrophages (Kawamata et al. 2003).

[000112] TGR5 agonists inhibit production of the pro-inflammatory cytokine TNFa and the Thl-driving cytokine IL-12 (but not IL-10) in human DC and monocytes, and in LPS-stimulated whole blood and PBMC. In addition, TLCA inhibits IFNy (but not IL-4) production in activated DC/T cell co-cultures and in LPS stimulated human whole blood (Werner et al 2004). These inflammatory cytokines have been shown to play key roles in the pathogenesis of autoimmune diseases, such as psoriasis. A recent report described TGR5 expression in Kupffer cells in the liver and activation of this receptor leads to down regulation of expression of TNFa, IL-la, IL-1β, and IL-6 in LPS stimulated cell model (Keitel et al 2008).

[000113] The natural TGR5 ligand TLCA, which is produced by intestinal Clostridia, is found in higher levels in children that do not have autoimmune disease (J. Allergy Clin Immunol 2001, 107:29-39). In addition, oral bile acid (dehydrocholic acid) treatment was efficacious in more than 80% of psoriasis patients in one study (Pathophysiology 2003, 10:57), and bile acids have been used by traditional Chinese medicine in chronic inflammatory diseases (Biochem. Pharmacol. 2002, 63:533). Together, this gives further support for pursuing low molecular weight agonists of TGR5 for autoimmune diseases.

[000114] Thus, agonists of TGR5 are expected to be useful in the treatment of autoimmune diseases characterized by Thl pathology helping to redirect the response towards a Th2 phenotype. Such autoimmune diseases include, but are not limited to, psoriasis. Psoriasis is an autoimmune disease with a prevalence of between 1.5 and 4% in the population, occurring most commonly in Caucasians. Many patients also develop psoriatic arthritis which impacts quality of life even more. With few safe and cost effective treatments available, psoriasis remains an unmet medical need.

[000115] TGR5 is associated with the intracellular accumulation of cyclic adenosine monophosphate (cAMP), which is widely expressed in diverse cell types. Although the activation of TGR5 in macrophages decreases proinflammatory cytokine production, the stimulation of TGR5 by bile acids in adipocytes and myocytes enhances energy expenditure. This control of energy metabolism by TGR5 involves the c-AMP-dependent induction of type 2 iodothyronine deiodinase (D2) enzyme. The up-regulation of D2 depends on the activation the membrane bound TGR5 by bile acids, which then mobilizes cAMP. D2 then locally converts the prohormone thyroxine (T_4) to the active hormone 3,5,3'-triiodothyronine (T_3), which gives rise to increases thyroid hormone activity and increased energy expenditure.

[000116] Bile acid stimulation of TGR5 has been shown to regulate multiple metabolic processes including glucose-dependent gut incretin glucose-like peptide 1 (GLP-1) secretion and mitochondrial energy homeostasis. TGR5 expression levels are high in the small and large intestine. Mice lacking the TGR5 receptor showed increased weight and body fat when on a high fat diet (WO2006070718). Specific receptor agonists cause an increase in the secretion of GLP-1 both *in-vitro* and *in-vivo* (EP1591120), and lead to prevention of hyperglycemia and improved glucose tolerance in the GK rat model (WO2007127505). The beneficial action of TGR5 agonists on TNFa levels may also be beneficial in Type II diabetes, where elevated levels contribute to insulin resistance and other pathologies.

[000117] In addition, TGR5 appears to be important in the regulation of nitric oxide production via c-AMP-dependent activation of endothelial nitric oxide synthase (eNOS). This may scavange bile acid induced reactive oxygen species and protect the liver against lipid peroxidation and bile acid-induced injury.

[000118] The number of people in the world with diabetes is estimated to increase 46% between 2000 and 2010 and to double by the year 2025 to approximately 300 million people. The majority of these increases will be type II (non-insulin dependent) diabetes resulting largely from physical inactivity, poor diet, stress and obesity. Type II insulin-resistant diabetes mellitus afflicts an estimated 6% of adults in Western nations. The heterogeneity of the disorder is highlighted by the lack of long-term efficacy of existing therapies in a significant proportion of patients. The high economic and social cost of diabetes emphasizes the need for effective strategies for the prevention and treatment of the disease. Inducing GLP-1 secretion and glucose-stimulated insulin secretion can normalize glucose levels without causing hypoglycemia. Therefore, because TGR5 agonists increase glucose dependent GLP-1 secretion, they are useful in the treatment of Type II Diabetes. Furthermore, TGR5 agonists have the potential for additive/synergistic effects with DPP-4 inhibitors for Type II insulin-resistant diabetes mellitus treatment. In addition, the ability of TGR5 agonists to decrease TNFa has a positive impact on the inflammatory component of Type II Diabetes.

[000119] TGR5, with its ability to enhance incretin levels, is involved in metabolic diseases and energy homeostasis, plus TGR5, with its ability to decrease pro-inflammatory cytokines, is involved in autoimmune diseases and inflammatory disorders. This suggests a role for TGR5 agonists in the treatment of Type II Diabetes, inflammatory disorders and Th-l mediated autoimmune diseases.

[000120] Thus, provided herein are compounds and compositions which are agonists of TGR5. Also provided herein are methods utilizing such compounds and composition to enhance TGR5 activity to treat diseases and/or disorders associated with TGR5 activity. Such diseases and/or disorders include, but are not limited to, diabetes, inflammatory disorders and autoimmune diseases. By way of example only, the compounds, compositions and methods provided herein are used to treat gallstones, cholestasis, Type II Diabetes, psoriasis and Th-1 mediated autoimmune diseases.

[000121] This methods provided herein are either prophylactic or therapeutic treatment of TGR5-related disorders and/or TGR5-related diseases. Such methods involve administering to a subject in need of treatment a compound of Formula (I)-(VIII), or a pharmaceutical composition that contains a therapeutically effective amount of one or more compounds of Formula (I)-(VIII), wherein such compounds are an agonists of TGR5. In certain embodiments, such prophylactic or therapeutic treatment methods are used to treat diabetes, gallstones, cholestasis, inflammatory disorders and autoimmune diseases, including but not limited to, Type II Diabetes, psoriasis and Th-1 mediated autoimmune diseases.

[000122] The methods of treatment provide herein are effective for both human and animal subjects. Animal subjects include both domestic animals and livestock, raised either as pets or for commercial purposes. Examples include, but are not limited to, dogs, cats, cattle, horses, sheep, hogs, and goats.

[000123] In certain embodiments of compounds of Formula (I), Formula (II), Formula (IV) and Formula (VII), such compounds have minimal systemic exposure and are primarily gastrointestinally exposed.

[000124] In accordance with the foregoing, the present invention further provides a method for preventing or treating any of the diseases or disorders described herein in a subject in need of such treatment, which method comprises administering to a subject a therapeutically effective amount (See, "Administration and Pharmaceutical Compositions", infra) of a compound of Formula (I)-(VIII) or a pharmaceutically acceptable salt, solvate, N-oxide, prodrug or isomers thereof.

[000125] Also provided herein are methods for preventing or treating any of the diseases or disorders described herein in a subject in need of such treatment, which method comprises administering to a subject a pharmaceutical compositions containing therapeutically effective amount of a compound of Formula (I)-(VIII) or a pharmaceutically acceptable salt, solvate, N-oxide, prodrug, enantiomer or isomers thereof. For any of the above uses, the required

dosage will vary depending on the mode of administration, the particular condition to be treated and the effect desired.

Administration and Pharmaceutical Compositions

[000126] For the therapeutic uses of compounds of Formula (I)-(VIII), or pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, described herein, such compounds are administered in therapeutically effective amounts either alone or as part of a pharmaceutical composition. Accordingly, provided herein are pharmaceutical compositions, which comprise at least one compound of Formulas (I)-(VIII) described herein, pharmaceutically acceptable salts and/or solvates thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. In addition, such compounds and compositions are administered singly or in combination with one or more additional therapeutic agents. The method of administration of such compounds and compositions include, but are not limited to, oral administration, rectal administration, parenteral, intravenous administration, intravitreal administration, intramuscular administration, inhalation, intranasal administration, topical administration, ophthalmic administration or otic administration.

[000127] In certain embodiments, such compounds of Formula (I)-(VIII) are agonists of TGR5, formulated in an amount sufficient to inhibit production of the pro-inflammatory cytokine TNFa and the Thl-driving cytokine IL-12 both *in-vitro* and *in-vivo.* In other embodiments, such compounds of Formula (I)-(VIII) are agonists of TGR5, formulated in an amount sufficient to increases thyroid hormone activity and increased energy expenditure both *in-vitro* and *in-vivo.* In other embodiments, such compounds of Formula (I)-(VIII) are agonists of TGR5, formulated in an amount sufficient to increase the secretion of GLP-1 both *in-vitro* and *in-vivo.*

[000128] The therapeutically effective amount will vary depending on, among others, the disease indicated, the severity of the disease, the age and relative health of the subject, the potency of the compound administered, the mode of administration and the treatment desired. In certain embodiments, the daily dosage of a compound of Formula (I)-(VIII), satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.03 to 2.5mg/kg per body weight. In certain embodiments, the daily dosage of a compound of Formula (I)-(VIII), administered by inhalation, is in the range from 0.05 micrograms per kilogram body weight ^g/kg) to 100 micrograms per kilogram body weight ^g/kg). In other embodiments, the daily dosage of a compound of Formula (I)-(VIII), administered orally, is

in the range from 0.01 micrograms per kilogram body weight ^g/kg) to 100 milligrams per kilogram body weight (mg/kg). An indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5mg to about lOOmg of a compound of Formula (I)-(VIII), conveniently administered, e.g. in divided doses up to four times a day or in controlled release form. In certain embodiment, unit dosage forms for oral administration comprise from about 1 to 50 mg of a compound of Formula (I)-(VIII).

[000129] Other aspects provided herein are processes for the preparation of pharmaceutical composition which comprise at least one compound of Formulas (I)-(VIII) described herein, or pharmaceutically acceptable salts and/or solvates thereof. In certain embodiments, such processes include admixing a compound of the Formula (I)-(VIII) described herein, and pharmaceutically acceptable salts and solvates thereof, with one or more pharmaceutically acceptable carriers, diluents or excipients. In certain embodiments, the pharmaceutical compositions comprising a compound of Formula (I)-(VIII) in free form or in a pharmaceutically acceptable salt or solvate form, in association with at least one pharmaceutically acceptable carrier, diluent or excipient are manufactured by mixing, granulating and/or coating methods. In other embodiments, such compositions are optionally contain excipients, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In other embodiments, such compositions are sterilized.

Oral Dosage Forms

[000130] In certain embodiments, the pharmaceutical compositions containing at least one compound of Formula (I)-(VIII) are administered orally as discrete dosage forms, wherein such dosage forms include, but are not limited to, capsules, gelatin capsules, caplets, tablets, chewable tablets, powders, granules, syrups, flavored syrups, solutions or suspensions in aqueous or non-aqueous liquids, edible foams or whips, and oil-in-water liquid emulsions or water-in-oil liquid emulsions.

[000131] The capsules, gelatin capsules, caplets, tablets, chewable tablets, powders or granules, used for the oral administration of at least one compound of Formula (I)-(VIII) are prepared by admixing at least one compound of Formula (I)-(VIII) (active ingredient) together with at least one excipient using conventional pharmaceutical compounding techniques. Non-limiting examples of excipients used in oral dosage forms described herein include, but are not limited to, binders, fillers, disintegrants, lubricants, absorbents, colorants, flavors, preservatives and sweeteners.

[000132] Non-limiting examples of such binders include, but are not limited to, corn starch, potato starch, starch paste, pre-gelatinized starch, or other starches, sugars, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, tragacanth, guar gum, cellulose and its derivatives (by way of example only, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethylcellulose, methyl cellulose, hydroxypropyl methylcellulose and microcrystalline cellulose), magnesium aluminum silicate, polyvinyl pyrrolidone and combinations thereof.

[000133] Non-limiting examples of such fillers include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. In certain embodiments, the binder or filler in pharmaceutical compositions provided herein are present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

[000134] Non-limiting examples of such disintegrants include, but are not limited to, agar-agar, alginic acid, sodium alginate, calcium carbonate, sodium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums, and combinations thereof. In certain embodiments, the amount of disintegrant used in the pharmaceutical compositions provided herein is from about 0.5 to about 15 weight percent of disintegrant, while in other embodiments the amount is from about 1 to about 5 weight percent of disintegrant.

[000135] Non-limiting examples of such lubricants include, but are not limited to, sodium stearate, calcium stearate, magnesium stearate, stearic acid, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, sodium lauryl sulfate, talc, hydrogenated vegetable oil (by way of example only, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, sodium oleate, ethyl oleate, ethyl laureate, agar, silica, a syloid silica gel (AEROSIL 200, manufactured by W.R. Grace Co. of Baltimore, Md.), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Piano, Tex.), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, Mass.) and combinations thereof. In certain embodiments, the amount of lubricants used in the pharmaceutical compositions provided herein is in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms.

[000136] Non-limiting examples of such diluents include, but are not limited to, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, glycine or combinations thereof.

[000137] In certain embodiments, tablets and capsules are prepared by uniformly admixing at least one compound of Formula (I)-(VIII) (active ingredients) with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary. In certain embodiments, tablets are prepared by compression. In other embodiments, tablets are prepared by molding.

[000138] In certain embodiments, at least one compound of Formula (I)-(VIII) is orally administered as a controlled release dosage form. Such dosage forms are used to provide slow or controlled-release of one or more compounds of Formula (I)-(VIII). Controlled release is obtained using, for example, hydroxypropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof. In certain embodiments, controlled-release dosage forms are used to extend activity of the compound of Formula (I)-(VIII), reduce dosage frequency, and increase patient compliance.

[000139] Administration of compounds of Formula (I)-(VIII) as oral fluids such as solution, syrups and elixirs are prepared in unit dosage forms such that a given quantity of solution, syrups or elixirs contains a predetermined amount of a compound of Formula (I)-(VIII). Syrups are prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions are formulated by dispersing the compound in a non-toxic vehicle. Non-limiting examples of excipients used in as oral fluids for oral administration include, but are not limited to, solubilizers, emulsifiers, flavoring agents, preservatives, and coloring agents. Non-limiting examples of solubilizers and emulsifiers include, but are not limited to, water, glycols, oils, alcohols, ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers. Non-limiting examples of preservatives include, but are not limited to, sodium benzoate. Non-limiting examples of flavoring agents include, but are not limited to, peppermint oil or natural sweeteners or saccharin or other artificial sweeteners.

Parenteral Dosage Forms

[000140] In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I)-(VIII) are administered parenterally by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intraarterial.

[000141] Such parenteral dosage forms are administered in the form of sterile or sterilizable injectable solutions, suspensions, dry and/or lyophylized products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection (reconstitutable powders) and emulsions. Vehicles used in such dosage forms include, but are not limited to, Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

Transdermal Dosage Forms

[000142] In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I)-(VIII) are administered transdemally. Such transdermal dosage forms include "reservoir type" or "matrix type" patches, which are applied to the skin and worn for a specific period of time to permit the penetration of a desired amount of a compound of Formula (I)-(VIII). By way of example only, such transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin. In other embodiments, matrix transdermal formulations are used.

[000143] Formulations for transdermal delivery of a compound of Formula (I)-(VIII) include an effective amount of a compound of Formula (I)-(VIII), a carrier and an optional diluent. A carrier includes, but is not limited to, absorbable pharmacologically acceptable solvents to assist passage through the skin of the host, such as water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and combinations thereof.

[000144] In certain embodiments, such transdermal delivery systems include penetration enhancers to assist in delivering one or more compounds of Formula (I)-(VIII) to the tissue. Such penetration enhancers include, but are not limited to, acetone; various alcohols such as ethanol, oleyl, and tetrahydrofuryl; alkyl sulfoxides such as dimethyl sulfoxide; dimethyl acetamide; dimethyl formamide; polyethylene glycol; pyrrolidones such as polyvinylpyrrolidone; Kollidon grades (Povidone, Polyvidone); urea; and various water-

soluble or insoluble sugar esters such as Tween 80 (polysorbate 80) and Span 60 (sorbitan monostearate).

[000145] In other embodiments, the pH of such a transdermal pharmaceutical composition or dosage form, or of the tissue to which the pharmaceutical composition or dosage form is applied, is adjusted to improve delivery of one or more compounds of Formula (I)-(VIII). In other embodiments, the polarity of a solvent carrier, its ionic strength, or tonicity are adjusted to improve delivery. In other embodiments, compounds such as stearates are added to advantageously alter the hydrophilicity or lipophilicity of one or more compounds of Formula (I)-(VIII) so as to improve delivery. In certain embodiments, such stearates serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-enhancing or penetration-enhancing agent. In other embodiments, different salts, hydrates or solvates of the compounds of Formula (I)-(VIII) are used to further adjust the properties of the resulting composition.

Topical Dosage Forms

[000146] In certain embodiments at least one compound of Formula (I)-(VIII) is administered by topical application of pharmaceutical composition containing at least one compound of Formula (I)-(VIII) in the form of lotions, gels, ointments solutions, emulsions, suspensions or creams. Suitable formulations for topical application to the skin are aqueous solutions, ointments, creams or gels, while formulations for ophthalmic administration are aqueous solutions. Such formulations optionally contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[000147] Such topical formulations include at least one carrier, and optionally at least one diluent. Such carriers and diluents include, but are not limited to, water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and combinations thereof.

[000148] In certain embodiments, such topical formulations include penetration enhancers to assist in delivering one or more compounds of Formula (I)-(VIII) to the tissue. Such penetration enhancers include, but are not limited to, acetone; various alcohols such as ethanol, oleyl, and tetrahydrofuryl; alkyl sulfoxides such as dimethyl sulfoxide; dimethyl acetamide; dimethyl formamide; polyethylene glycol; pyrrolidones such as polyvinylpyrrolidone; Kollidon grades (Povidone, Polyvidone); urea; and various water-soluble or insoluble sugar esters such as Tween 80 (polysorbate 80) and Span 60 (sorbitan monostearate).

[000149] In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I)-(VIII) are administered by inhalation. Dosage forms for inhaled administration are formulated as aerosols or dry powders. Aerosol formulations for inhalation administration comprise a solution or fine suspension of at least one compound of Formula (I)-(VIII) in a pharmaceutically acceptable aqueous or non-aqueous solvent. In addition, such pharmaceutical compositions optionally comprise a powder base such as lactose, glucose, trehalose, mannitol or starch, and optionally a performance modifier such as L-leucine or another amino acid, and/or metals salts of stearic acid such as magnesium or calcium stearate.

[000150] In certain embodiments, compounds of Formula (I)-(VIII) are be administered directly to the lung by inhalation using a Metered Dose Inhaler ("MDI"), which utilizes canisters that contain a suitable low boiling propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas, or a Dry Powder Inhaler (DPI) device which uses a burst of gas to create a cloud of dry powder inside a container, which is then be inhaled by the patient. In certain embodiments, capsules and cartridges of gelatin for use in an inhaler or insufflator are formulated containing a powder mixture of a compound of Formula (I)-(VIII) and a powder base such as lactose or starch. In certain embodiments, compounds of Formula (I)-(VIII) are delivered to the lung using a liquid spray device, wherein such devices use extremely small nozzle holes to aerosolize liquid drug formulations that can then be directly inhaled into the lung. In other embodiments, compounds of Formula (I)-(VIII) are delivered to the lung using a nebulizer device, wherein a nebulizers creates an aerosols of liquid drug formulations by using ultrasonic energy to form fine particles that can be readily inhaled. In other embodiments, compounds of Formula (I)-(VIII) are delivered to the lung using an electrohydrodynamic ("EHD") aerosol device wherein such EHD aerosol devices use electrical energy to aerosolize liquid drug solutions or suspensions.

[000151] In certain embodiments, the pharmaceutical composition containing at least one compound of Formula (I)-(VIII), or pharmaceutically acceptable salts and solvates thereof, described herein, also contain one or more absorption enhancers. In certain embodiments, such absorption enhancers include, but are not limited to, sodium glycocholate, sodium caprate, N-lauryl-β-D-maltopyranoside, EDTA, and mixed micelles.

[000152] In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I)-(VIII) are administered nasally. The dosage forms for nasal administration are formulated as aerosols, solutions, drops, gels or dry powders.

[000153] In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I)-(VIII) are administered rectally in the form of suppositories, enemas, ointment, creams rectal foams or rectal gels. In certain embodiments such suppositories are prepared from fatty emulsions or suspensions, cocoa butter or other glycerides.

[000154] In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I)-(VIII) are administered opthamically as eye drops. Such formulations are aqueous solutions that optionally contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[000155] In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I)-(VIII) are administered otically as ear drops. Such formulations are aqueous solutions that optionally contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[000156] In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I)-(VIII) are formulated as a depot preparation. Such long acting formulations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. In certain embodiments, such formulations include polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

Combination Treatment

[000157] In certain embodiments, a compound of Formulas (I)-(VIII) provided herein, or a pharmaceutically acceptable salt, N-oxide, isomer or solvate thereof, or a pharmaceutical composition containing at least one compound of Formula (I)-(VIII) provided herein, is administered alone (without an additional therapeutic agent) for the treatment of one or more of the TGR5-related diseases and/or disorders described herein.

[000158] In other embodiments, a compound of Formulas (I)-(VIII) provided herein, or a pharmaceutically acceptable salt, N-oxide, isomer or solvate thereof, or a pharmaceutical composition containing at least one compound of Formulas (I)-(VIII) provided herein, is

administered in combination with one or more additional therapeutic agents, for the treatment of one or more of the TGR5-related diseases and/or disorders described herein.

[000159] In other embodiments, a compound of Formulas (I)-(VIII) provided herein, or a pharmaceutically acceptable salt, N-oxide, isomer or solvate thereof, or a pharmaceutical composition containing at least one compound of Formula (I)-(VIII) provided herein, is formulated in combination with one or more additional therapeutic agents and administered for the treatment of one or more of the TGR5-related diseases and/or disorders described herein.

[000160] In other embodiments, a compound of Formulas (I)-(VIII) provided herein, or a pharmaceutically acceptable salt, N-oxide, isomer or solvate thereof, or a pharmaceutical composition containing at least one compound of Formula (I)-(VIII) provided herein, is administered sequentially with one or more additional therapeutic agents, for the treatment of one or more of the TGR5-related diseases and/or disorders described herein.

[000161] In other embodiments, the combination treatments provided herein include administration of a compound of Formulas (I)-(VIII) provided herein, or a pharmaceutically acceptable salt, N-oxide, isomer or solvate thereof, or a pharmaceutical composition containing at least one compound of Formula (I)-(VIII) provided herein, prior to administration of one or more additional therapeutic agents, for the treatment of one or more of the TGR5-related diseases and/or disorders described herein.

[000162] In other embodiments, the combination treatments provided herein include administration of a compound of Formulas (I)-(VIII) provided herein, or a pharmaceutically acceptable salt, N-oxide, isomer or solvate thereof, or a pharmaceutical composition containing at least one compound of Formula (I)-(VIII) provided herein, subsequent to administration of one or more additional therapeutic agents, for the treatment of one or more of the TGR5-related diseases and/or disorders described herein.

[000163] In certain embodiments, the combination treatments provided herein include administration of a compound of Formulas (I)-(VIII) provided herein, or a pharmaceutically acceptable salt, N-oxide, isomer or solvate thereof, or a pharmaceutical composition containing at least one compound of Formula (I)-(VIII) provided herein, concurrently with one or more additional therapeutic agents, for the treatment of one or more of the TGR5-related diseases and/or disorders described herein.

[000164] In certain embodiments, the combination treatments provided herein include administration of a compound of Formulas (I)-(VIII) provided herein, or a pharmaceutically

acceptable salt, N-oxide, isomer or solvate thereof, or a pharmaceutical composition containing at least one compound of Formula (I)-(VIII) provided herein, formulated with one or more additional therapeutic agents, for the treatment of one or more of the TGR5-related diseases and/or disorders described herein.

[000165] In certain embodiments of the combination therapies described herein, the compounds of Formula (I)-(VIII) provided herein, or a pharmaceutically acceptable salts, N-oxides, isomers or solvates thereof, and the additional therapeutics agent(s) act additively. In other embodiments of the combination therapies described herein, the compounds of Formula (I)-(VIII) provided herein, or a pharmaceutically acceptable salts, N-oxides, isomers or solvates thereof, and the additional therapeutics agent(s) act synergistically.

[000166] The additional therapeutic agents used in combination with at least one compound of Formula (I)-(VIII) described herein, or a pharmaceutically acceptable salt, N-oxide, isomer or solvate thereof, include, but are not limited to immunomodulatory, anti-inflammatory substances and other anti-diabetes therapeutic agents.

[000167] The other anti-diabetes therapeutic agents used in combination with at least one compound of Formula (I)-(VIII) described herein or a pharmaceutically acceptable salt, N-oxide, isomer or solvate thereof include, but are not limited, sulfonylureas (by way of example, chloropropamide, acetohexamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide), meglitinides (by way of example, repaglinide, nateglinide) biguanides (by way of example, metformin), thiazolidinediones (by way of example, rosiglitazone, pioglitazone),and alpha-glucosidase inhibitors (by way of example, acarbose, miglitol).

[000168] The anti-inflammatory agents used in combination with at least one compound of Formula (I)-(VIII) described herein or a pharmaceutically acceptable salt, N-oxide, isomer or solvate thereof include, but are not limited to, non-steroidal anti-inflammatory drugs such as salicylic acid, acetylsalicylic acid, methyl salicylate, diflunisal, salsalate, olsalazine, sulfasalazine, acetaminophen, indomethacin, sulindac, etodolac, mefenamic acid, meclofenamate sodium, tolmetin, ketorolac, dichlofenac, ibuprofen, naproxen, naproxen sodium, fenoprofen, ketoprofen, flurbinprofen, oxaprozin, piroxicam, meloxicam, ampiroxicam, droxicam, pivoxicam, tenoxicam, nabumetome, phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine, apazone and nimesulide, leukotriene antagonists including, but not limited to, zileuton, aurothioglucose, gold sodium thiomalate and auranofin, steroids including, but not limited to, alclometasone diproprionate, amcinonide, beclomethasone dipropionate, betametasone, betamethasone benzoate, betamethasone

diproprionate, betamethasone sodium phosphate, betamethasone valerate, clobetasol proprionate, clocortolone pivalate, hydrocortisone, hydrocortisone derivatives, desonide, desoximatasone, dexamethasone, flunisolide, flucoxinolide, flurandrenolide, halcinocide, medrysone, methylprednisolone, methprednisolone acetate, methylprednisolone sodium succinate, mometasone furoate, paramethasone acetate, prednisolone, prednisolone acetate, prednisolone sodium phosphate, prednisolone tebuatate, prednisone, triamcinolone, triamcinolone acetonide, triamcinolone diacetate, and triamcinolone hexacetonide and other anti-inflammatory agents including, but not limited to, methotrexate, colchicine, allopurinol, probenecid, thalidomide or a derivative thereof, 5-aminosalicylic acid, retinoid, dithranol or calcipotriol, sulfinpyrazone and benzbromarone.

[000169] The immunomodulatory agents used in combination with at least one compound of Formula (I)-(VIII) described herein, or a pharmaceutically acceptable salt or solvate thereof, include, but are not limited to, azathioprine, tacrolimus, cyclosporin methothrexate, leflunomide, corticosteroids, cyclophosphamide, cyclosporine A, cyclosporin G, mycophenolate mofetil, ascomycin, rapamycin (sirolimus), FK-506, mizoribine, deoxyspergualin, brequinar, mycophenolic acid, malononitriloamindes (such as, by way of example only, leflunamide), T cell receptor modulators, and cytokine receptor modulators, peptide mimetics, and antibodies (such as, by way of example only, human, humanized, chimeric, monoclonal, polyclonal, Fvs, ScFvs, Fab or F(ab)2 fragments or epitope binding fragments), nucleic acid molecules (such as, by way of example only, antisense nucleic acid molecules and triple helices), small molecules, organic compounds, and inorganic compounds. Examples of T cell receptor modulators include, but are not limited to, anti-T cell receptor antibodies (such as, by way of example only, anti-CD4 antibodies (such as, by way of example only, cM-T412 (Boehringer), IDEC-CE9.1™ (IDEC and SKB), mAB 4162W94, Orthoclone and OKTcdr4a (Janssen-Cilag)), anti-CD3 antibodies (such as, by way of example only, Nuvion (Product Design Labs), OKT3 (Johnson & Johnson), or Rituxan (IDEC)), anti-CD5 antibodies (such as, by way of example only, an anti-CD5 ricin-linked immunoconjugate), anti-CD7 antibodies (such as, by way of example only, CHH-380 (Novartis)), anti-CD8 antibodies, anti-CD40 ligand monoclonal antibodies (such as, by way of example only, IDEC-131 (IDEC)), anti-CD52 antibodies (such as, by way of example only, CAMPATH 1H (Ilex)), anti-CD2 antibodies, anti-CDlla antibodies (such as, by way of example only, Xanelim (Genentech)), anti-B7 antibodies (such as, by way of example only, IDEC-114 (IDEC)), CTLA4-immunoglobulin, and other toll receptor-like (TLR)

modulators. Examples of cytokine receptor modulators include, but are not limited to, soluble cytokine receptors (such as, by way of example only, the extracellular domain of a TNF-oc receptor or a fragment thereof, the extracellular domain of an IL-Iβ receptor or a fragment thereof, and the extracellular domain of an IL-6 receptor or a fragment thereof), cytokines or fragments thereof (such as, by way of example only, interleukin (IL)-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-15, TNF-.alpha., interferon (IFN)-cc, IFN-β, IFN-γ, and GM-CSF), anti-cytokine receptor antibodies (such as, by way of example only, anti-IFN receptor antibodies, anti-IL-2 receptor antibodies (such as, by way of example only, Zenapax (Protein Design Labs)), anti-IL-4 receptor antibodies, anti-IL-6 receptor antibodies, anti-IL-10 receptor antibodies, and anti-IL-12 receptor antibodies), anti-cytokine antibodies (such as, by way of example only, anti-IFN antibodies, anti-TNF-oc antibodies, anti-IL-Iβ antibodies, anti-IL-6 antibodies, anti-IL-8 antibodies (such as, by way of example only, ABX-IL-8 (Abgenix)), and anti-IL-12 antibodies).

[000170] The cytokines or modulator of cytokine function used in combination with at least one compound of Formula (I)-(VIII) described herein, or a pharmaceutically acceptable salt or solvate thereof, include, but are not limited to, interleukin-2 (IL-2), interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-6 (IL-6), interleukin-7 (IL-7), interleukin-9 (IL-9), interleukin- 10 (IL-10), interleukin- 12 (IL-12), interleukin 15 (IL-15), interleukin 18 (IL-18), platelet derived growth factor (PDGF), erythropoietin (Epo), epidermal growth factor (EGF), fibroblast growth factor (FGF), granulocyte macrophage stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), macrophage colony stimulating factor (M-CSF), prolactin, alpha-, beta-, and gamma-interferon, interferon β-la, interferon β-lb, interferon oc-1, interferon oc-2a (roferon), interferon a -2b, pegylated interferons (by way of example only, peginterferon oc-2a and peginterferon oc-2b), intron, Peg-Intron, Pegasys, consensus interferon (infergen), albumin-interferon a and albuferon.

[000171] In other embodiments, a compound of Formula (I)-(VIII) described herein, or a pharmaceutically acceptable salt, N-oxide, isomer or solvate thereof, or a pharmaceutical composition containing such compounds of Formula (I)-(VIII), is administered to a patient who has not previously undergone or is not currently undergoing treatment with another therapeutic agent.

[000172] Where the compounds of Formula (I)-(VIII) are administered in conjunction with other therapies, dosages of the co-administered compounds will of course vary depending on

the type of co-drug employed, on the specific drug employed, on the condition being treated and so forth.

Kits

[000173] Also provided herein are pharmaceutical packs or kits that include one or more containers containing a compound of Formula (I)-(VIII) useful for the treatment or prevention of a TGR5-related disease or disorder. In other embodiments, such pharmaceutical packs or kits include one or more containers containing a compound of Formula (I)-(VIII) useful for the treatment or prevention of a TGR5-related disease or disorder and one or more containers containing an additional therapeutic agent. In certain embodiments, such pharmaceutical packs or kits optionally include instructions for its administration of a compound of Formula (I)-(VIII). In certain embodiments of such kits, the compound of Formula (I)-(VIII) is in free form or in pharmaceutically acceptable salt or N-oxide form.

[000174] One of skill in the art will appreciate that the above transformations are only representative of methods for preparation of the compounds of the present invention, and that other well known methods can similarly be used.

Examples

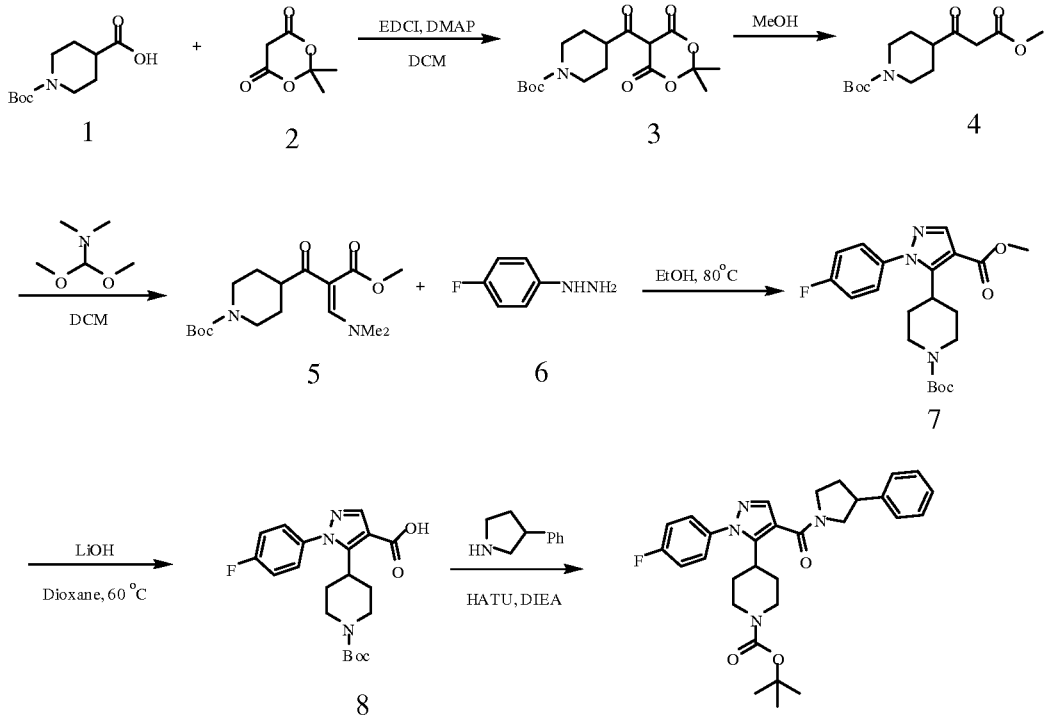
[000175] The compounds provided herein are further exemplified, but not limited, by the following example that illustrates the preparation of compounds of Formula (I) and Formula (II).

Example 1

Preparation of tert-butyl 4-(l-(4-fluorophenyl)-4-(3-phenylpyrrolidine-l-carbonyl)-lH-pyrazol-5-yl)piperidine-l-carboxylate (Ex. No. 1)

[000176] The preparation of (tert-butyl 4-(l-(4-fluorophenyl)-4-(3-phenylpyrrolidine-l-carbonyl)-lH-pyrazol-5-yl)piperidine-l-carboxylate is illustrated in scheme 1.

Scheme 1:



Ex. No. 1

[000177] To a solution of the l-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (1) (6.9 g, 30 mmol) in dichlormethane (DCM) (75 mL) was added Meldrum's acid (2) (4.76 g, 33 mmol, 1.1 eq) followed by 4-dimethylaminopyridine (DMAP) (5.13g, 45 mmol , 1.5 eq). The solution was cooled to 0 °C, then l-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDCI) (8.63 g, 42 mmol, 1.4 eq) was added in small portions over approximately 5 minutes. The reaction was stirred for 17 hours and allowed to warm to room temperature. The reaction was quenched with water (50 mL), and the layers were allowed to separate. The organic layer was washed with 0.1 M HC1 3 times. The combined organics were dried over sodium sulfate, filtered, and concentrated to give tert-butyl 4-(2,2-dimethyl-4,6-dioxo-l,3-dioxane-5-carbonyl)piperidine-l-carboxylate (3) as a syrup which solidified on standing.

[000178] Tert-butyl 4-(2,2-dimethyl-4,6-dioxo- 1,3-dioxane-5-carbonyl)piperidine- 1-carboxylate (3) was heated to 50 °C in methanol until the reaction was complete (2-4 hours) by LC-MS. The methanol was evaporated to dryness and the crude product was purified by silica gel chromatography (80 g of silica) using a gradient of 10-100 % ethyl acetate/hexanes to give tert-butyl 4-(3-methoxy-3-oxopropanoyl)piperidine-l-carboxylate (4).

[000179] Tert-butyl 4-(3-methoxy-3-oxopropanoyl)piperidine-l-carboxylate (4) (7.55 g, 26.5 mmol) was dissolved in DCM (50 mL) and treated with dimethylformamide dimethylacetal (DMFDMA) (17 mL, 127 mmol, 4.8 eq) at reflux for 4 hours (complete by LC-MS). The solvent was evaporated to give (Z)-tert-butyl 4-(3-(dimethylamino)-2-(methoxycarbonyl)acryloyl)piperidine-l-carboxylate (5) as a crude product that was carried forward without any further purification.

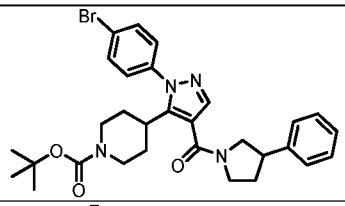
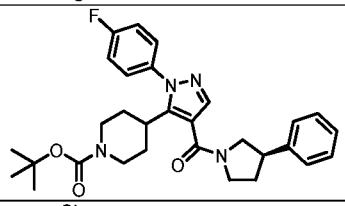
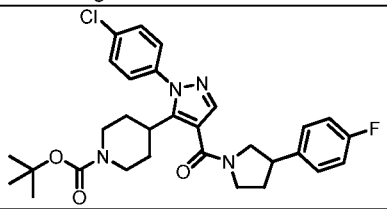
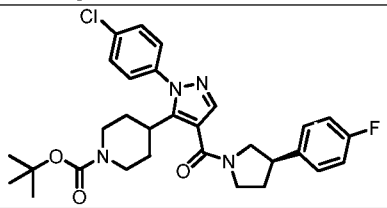
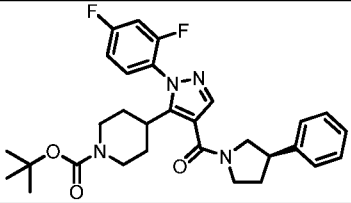
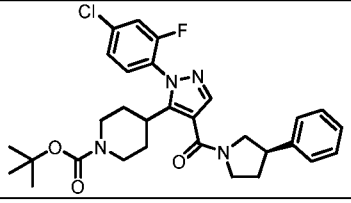
[000180] (Z)-tert-butyl 4-(3-(dimethylamino)-2-(methoxycarbonyl)acryloyl)piperidine-l-carboxylate (5) (2 g, 5.9 mmol) was treated with 4-fluorophenylhydrazine hydrochloride (6) (1.15 g, 7.1 mmol, 1.2 eq) in ethanol (2 mL) at 80 °C overnight. The reaction was concentrated to dryness and purified by silica gel chromatography (40 g, 5-50 % ethyl acetate/hexanes) to give tert-butyl 4-(l-(4-fluorophenyl)-4-(methoxycarbonyl)-lH-pyrazol-5-yl)piperidine-l-carboxylate (7) as an oil.

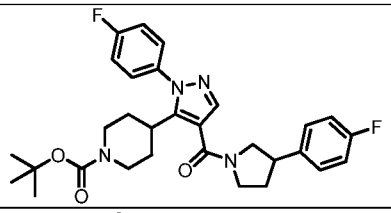
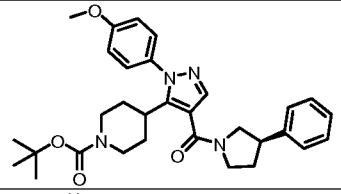
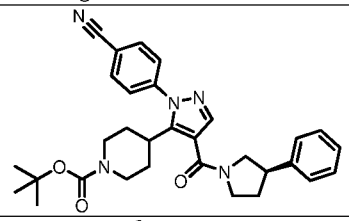
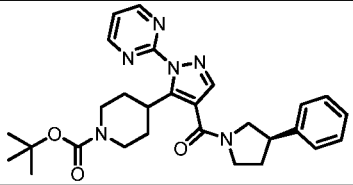
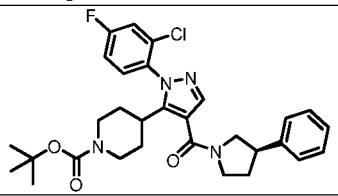
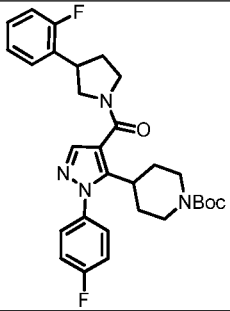
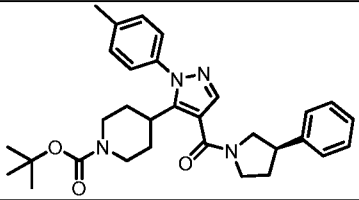
[000181] Tert-butyl 4-(l-(4-fluorophenyl)-4-(methoxycarbonyl)-lH-pyrazol-5-yl)piperidine-l-carboxylate (7) was dissolved in dioxane (20 mL) and treated with 3 M LiOH (2.6 mL) at 80 °C until complete by LC-MS (4-6 hours). The reaction was cooled to room temperature, quenched with 10% citric acid solution (3-5 mL), diluted with water (~3 mL) and extracted with ethyl acetate. The extracts were combined and dried over magnesium sulfate, filtered, and concentrated to dryness to give 5-(l-(tert-butoxycarbonyl)piperidin-4-yl)-l-(4-fluorophenyl)-lH-pyrazole-4-carboxylic acid (8) which was used in the next step without further purification.

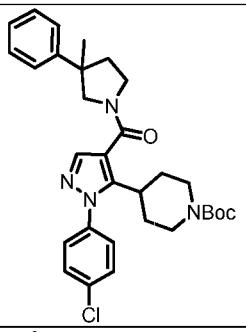
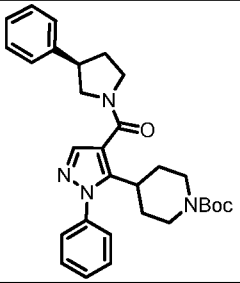
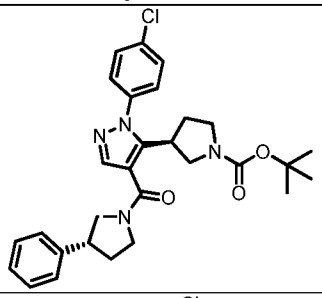
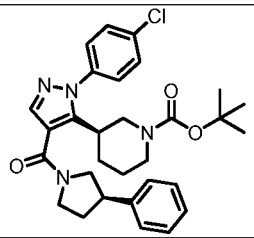
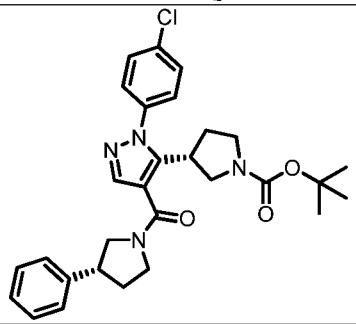
[000182] 5-(l-(tert-butoxycarbonyl)piperidin-4-yl)-l-(4-fluorophenyl)-lH-pyrazole-4-carboxylic acid (8) (50 mg, 0.13 mmol) was dissolved in acetonitrile (1 mL) and treated with diisopropylethylamine (48 μL, 0.28 mmol, 2 eq.) and HATU (53 mg, 0.14 mmol, 1.1 eq.). After 5 minutes, 3-phenylpyrroldine hydrochloride (26 mg, 0.14 mmol) was added. After 60 minutes, the reaction was complete by HPLC. The reaction solution was diluted with 0.5 mL water, filtered through 0.45 μM Whatman filter and then purified by reversed phase HPLC (C-18, 100 mL/min, 10-90%, water (0.05 % TFA)/ACN) to yield tert-butyl 4-(l-(4-fluorophenyl)-4-(3-phenylpyrrolidine- 1-carbonyl)- lH-pyrazol-5-yl)piperidine- 1-carboxylate (Ex. No. 1) as a white solid. ^{1}H NMR ($CDC1_3$) δ 7.64 (1H), 7.36-7.32 (5H), 7.24-7.18 (4H), 4.15-3.92 (3H), 3.75-3.42 (3H), 2.96-2.82 (1H), 2.58-2.35 (3H), 2.18-1.92 (3H), 1.69-1.60 (3H), 1.44 (9H); HPLC-MS calculated for $C_{30}H_35FN4O_3$ ($M+H^+$) 519.3, found 519.3; R_T 2.6 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).

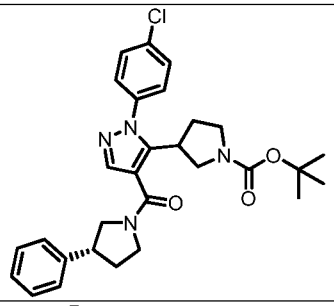
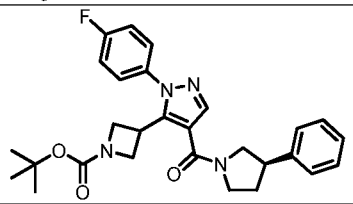
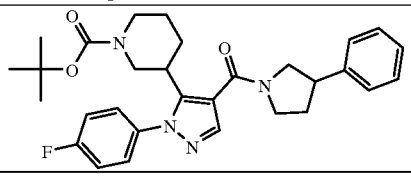
[000183] By repeating the procedures described in Example 1, using appropriate starting materials, the following compounds of Formula **(I)** or Formula **(II)**, as identified in Table 1, were obtained.

Table 1

Example No.	Structure	Physical Data 1H NMR 400 MHz (CDCl3 or acetone-d6) and/or MS (m/z)
2		HPLC-MS calculated for C30H35BrN4O3 (M+H+) 579.2, found 579.2; RT 2.8 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA/ACN)
3		HPLC-MS calculated for C30H35FN4O3 (M+H+) 519.3, found 519.3; RT 2.9 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN)
4		HPLC-MS calculated for C30H34ClFN4O3 (M+H+) 553.2, found 553.3; RT 3.1 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN)
5		HPLC-MS calculated for C30H34ClFN4O3 (M+H+) 553.2, found 553.3; Separate procedure for sepn conditions
6		HPLC-MS calculated for C30H34F2N4O3 (M+H+) 537.3, found 537.3; RT 3.0 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN)
7		HPLC-MS calculated for C30H34ClFN4O3 (M+H+) 553.2, found 553.2; RT 3.2 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN)

Example No.	Structure	Physical Data 1H NMR 400 MHz (CDCl3 or acetone-d6) and/or MS (m/z)
8		HPLC-MS calculated for C30H34F2N4O3 (M+H+) 537.3, found 537.3; RT 3.5 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN)
9		HPLC-MS calculated for C31H38N4O4 (M+H+) 531.3, found 531.2; RT 3.4 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN)
10		HPLC-MS calculated for C31H35N5O3 (M+H+) 526.3, found 526.3; RT 3.4 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN)
11		HPLC-MS calculated for C28H34N6O3 (M+H+) 503.3, found 503.3; RT 2.4 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN)
12		HPLC-MS calculated for C30H34ClFN4O3 (M+H+) 553.2, found 553.2; RT 3.6 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN)
13		HPLC-MS calculated for C30H34F2N4O3 (M+H+) 537.61, found 537.20; RT 3.5 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
14		HPLC-MS calculated for C31H38N4O3 (M+H+) 515.3, found 515.3; RT 3.0 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN)

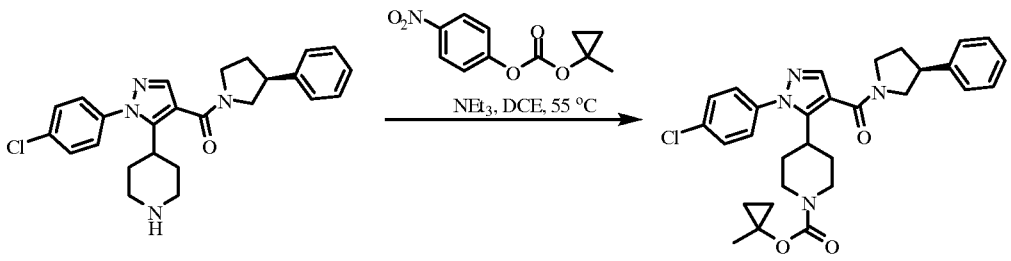
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDCl3 or acetone-d6) and/or MS (m/z)
15		HPLC-MS calculated for C31H37ClN4O3 (M+H+) 550.10, found 550.30; RT 3.1 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
16		HPLC-MS calculated for C30H36N4O3 (M+H+) 501.63, found 501.29; RT 2.8 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
17		HPLC-MS calculated for C29H33ClN4O3 (M+H+) 521.2, found 521.1; RT 1.8 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
18		HPLC-MS calculated for C30H35ClN4O3 (M+H+) 535.2, found 535.2; RT 1.9 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
19		HPLC-MS calculated for C29H33ClN4O3 (M+H+) 521.2, found 521.3; RT 2.7 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN

Example No.	Structure	Physical Data 1H NMR 400 MHz (CDCl3 or acetone-d6) and/or MS (m/z)
20		HPLC-MS calculated for C29H33ClN4O3 (M+H+) 521.2, found 521.2; RT 2.4 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
21		HPLC-MS calculated for C28H31FN4O3 (M+H+) 491.2, found 491.5; RT 2.2 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
22		HPLC-MS calculated for C30H35FN4O3 (M+H+) 519.3, found 519.0; RT 3.8min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN

Example 23
Preparation of (S)-l-methylcyclopropyl 4-(l-(4-chlorophenyl)-4-(3-phenylpyrrolidine-l-carbonyl)-lH-pyrazol-5-yl)piperidine-l-carboxylate (Ex. No. 23)

[000184] The preparation of (S)-l-methylcyclopropyl 4-(l-(4-chlorophenyl)-4-(3-phenylpyrrolidine-l-carbonyl)-lH-pyrazol-5-yl)piperidine-l-carboxylate (Ex. No. 23) is illustrated in scheme 2.

Scheme 2:



Ex. No. 23

[000185] 1-methylcyclopropyl 4-nitrophenyl carbonate (196 mg, 0.83 mmol, 1.04 eq) was added to a solution of (S)-(l-(4-chlorophenyl)-5-(piperidin-4-yl)-lH-pyrazol-4-yl)(3-phenylpyrrolidin-l-yl)methanone (deprotected compound 5) (350 mg, 0.8 mmol, 1. eq) and

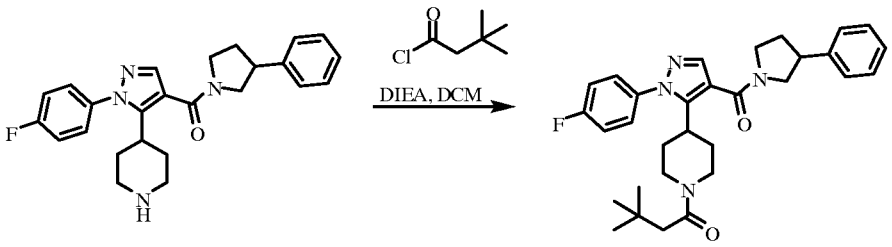
NEt_3 (167 μL, 1.2 mmol, 1.5 eq) in DCE (6 mL). After stirring overnight at 55 °C, the reaction was concentrated and purified by silica gel chromatography using a gradient of 0-5 % methanol/DCM to give (S)-l-methylcyclopropyl 4-(l-(4-chlorophenyl)-4-(3-phenylpyrrolidine-l-carbonyl)-lH-pyrazol-5-yl)piperidine-l-carboxylate (Ex. No. 23) as a colorless foam. ^{1}H NMR (CD_3OD) δ 7.83 (d, ***J*** = 12.6 Hz, IH), 7.59 (t, ***J*** = 8.6 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.36-7.21 (m, 5H), 4.12 (br. s, IH), 4.05-3.84 (m, 2H), 3.73-3.44 (m, 4H), 2.96-2.86 (m, IH), 2.66 (br. s, 2H), 2.45-2.34 (m, IH), 2.24-1.86 (m, 3H), 1.73-1.64 (m, 2H), 1.52-1.50 (m, 3H), 0.86-0.84 (m, 2H), 0.63-0.62 (m, 2H). HPLC-MS calculated for $C_{30}H_{33}CIN4O_3$ ($M+H^+$) 534.06, found 534.23.

Example 24

Preparation of l-(4-(l-(4-fluorophenyl)-4-(3-phenylpyrrolidine-l-carbonyl)-lH-pyrazol-5-yl)piperidin-l-yl)-3,3-dimethylbutan-l-one (Ex. No. 24)

[000186] The preparation of l-(4-(l-(4-fluorophenyl)-4-(3-phenylpyrrolidine-l-carbonyl)-lH-pyrazol-5-yl)piperidin-l-yl)-3,3-dimethylbutan-l-one (Ex. No. 24) is illustrated in scheme 3.

Scheme 3:



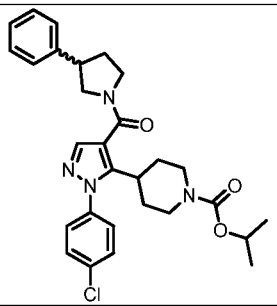
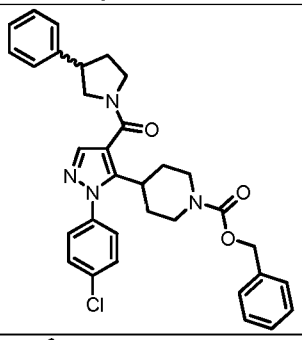
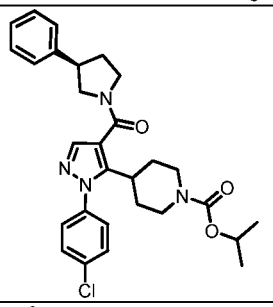
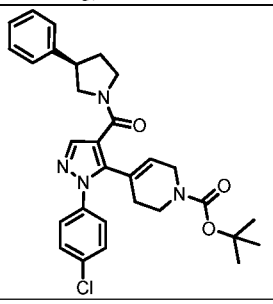
Ex. No. 24

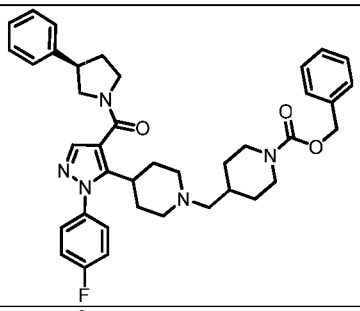
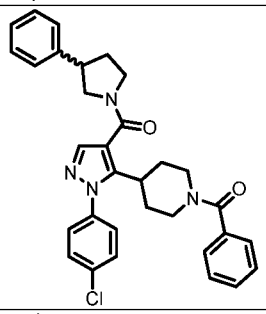
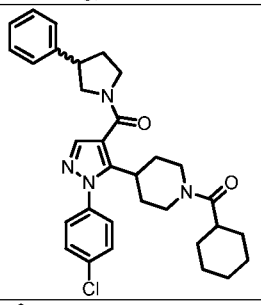
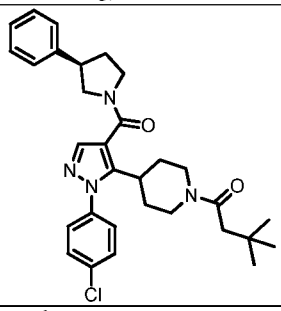
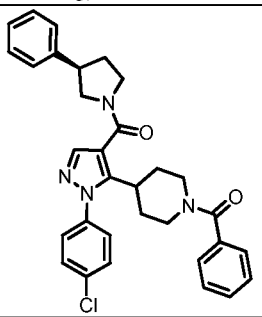
[000187] 3,3-dimethylbutanoyl chloride (20 μE, 0.14 mmol, 1.4 eq) was added to a solution of (l-(4-fluorophenyl)-5-(piperidin-4-yl)-lH-pyrazol-4-yl)(3-phenylpyrrolidin-l-yl)methanone (deprotected compound 6) (43 mg, 0.1 mmol, 1 eq) and DIEA (35 μE, 0.2 mmol, 2 eq) in DCM (1 mL). The reaction was stirred at room temperature for 2 hours, loaded directly onto a silica gel column, and purified using a gradient of 0-5 % methanol/DCM to give l-(4-(l-(4-fluorophenyl)-4-(3-phenylpyrrolidine-l-carbonyl)-lH-pyrazol-5-yl)piperidin-l-yl)-3,3-dimethylbutan-l-one (Ex. No. 24) as a colorless solid. ^{1}H NMR ($CDCI_3$) δ 7.71-7.65 (IH), 7.50-7.46 (2H), 7.38-7.28 (6H), 7.25-7.21 (IH), 4.79-4.76 (IH), 3.99-3.87 (2H), 3.77-3.61 (2H), 3.57-3.40 (2H), 3.10-3.00 (IH), 2.97-2.88 (IH), 2.42-2.34 (2H), 2.24 (2H), 1.91-1.66 (4H), 1.03-1.02 (9H). HPLC-MS calculated for

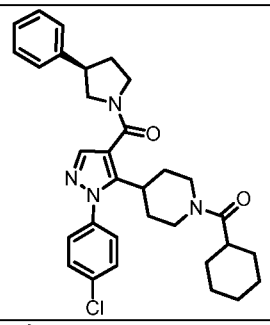
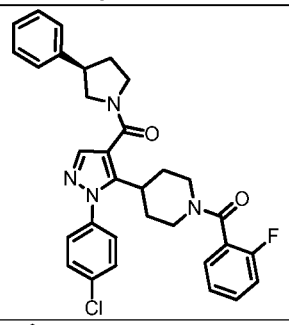
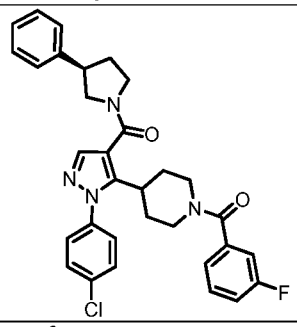
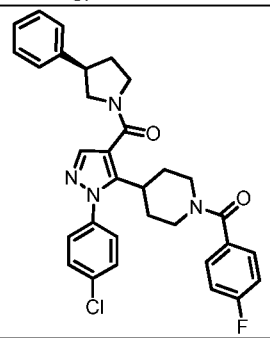
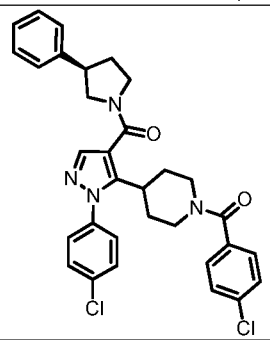
$C_{31}H_{37}ClN_4O_2$ ($M+H^+$) 534.10, found, 534.20; R_T 2.7 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).

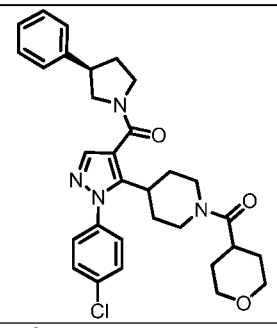
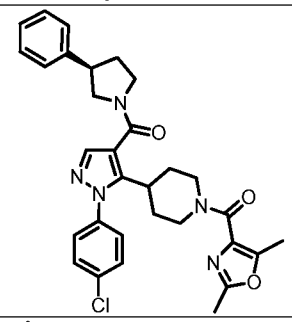
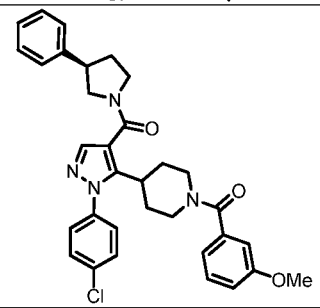
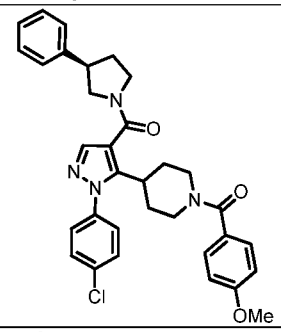
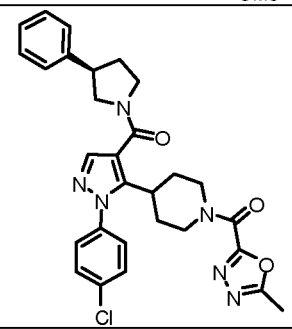
[000188] By repeating the procedures described in example 23 and 24, using appropriate starting materials, the following compounds of Formula **(I)** or Formula **(II)**, as identified in Table 2, were obtained.

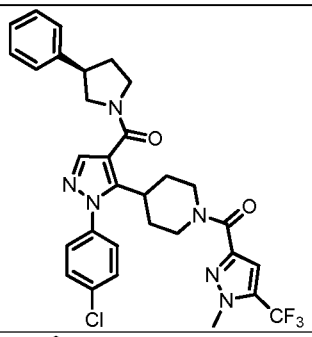
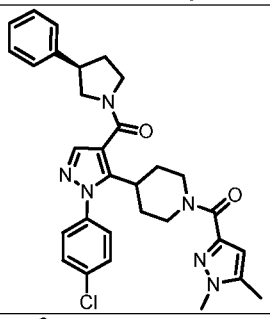
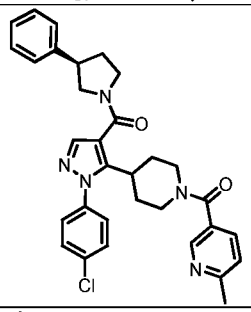
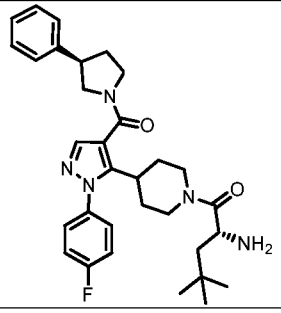
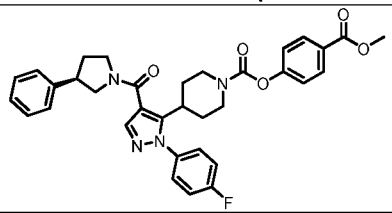
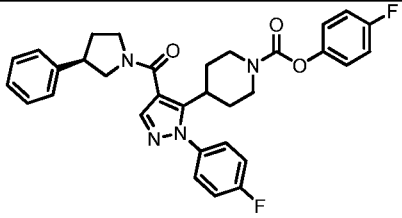
Table 2

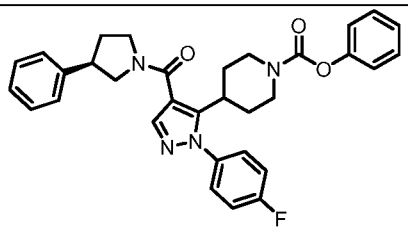
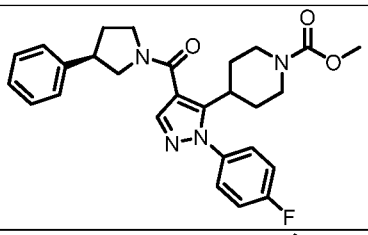
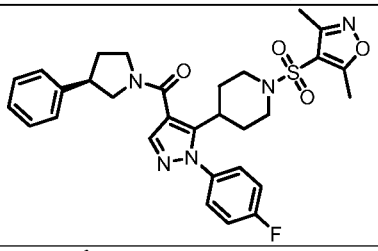
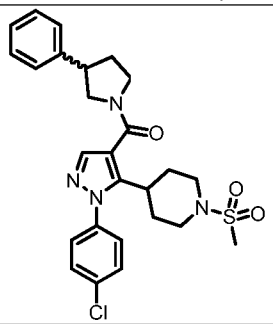
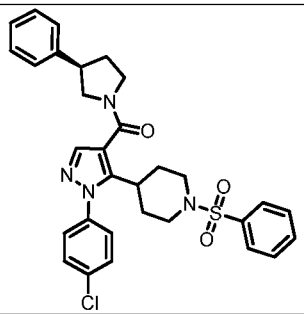
Example No.	**Structure**	**Physical Data 1H NMR 400 MHz (CDCl3 or acetone-d6) and/or MS (m/z)**
25		HPLC-MS calculated for C29H33ClN4O3 (M+H+) 522.05, found, 522.20; RT 2.5 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
26		HPLC-MS calculated for C33H33ClN4O3 (M+H+) 570.09, found 570.20; RT 2.7 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
27		HPLC-MS calculated for C29H33ClN4O3 (M+H+) 522.05, found 521.90; RT 2.5 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
28		HPLC-MS calculated for C30H33ClN4O3 (M+H+) 534.06, found 534.23; RT 3.0 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).

29		HPLC-MS calculated for C39H44FN5O3 (M+H+) 650.80, found 650.40; RT 3.0 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
30		HPLC-MS calculated for C32H31ClN4O2 (M+H+) 540.07, found 540.10; RT 2.8 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
31		HPLC-MS calculated for C32H37ClN4O2 (M+H+) 546.11, found 546.20; RT 2.3 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
32		HPLC-MS calculated for C31H37ClN4O2 (M+H+) 534.10, found 534.20; RT 2.7 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
33		HPLC-MS calculated for C32H31ClN4O2 (M+H+) 540.07, found 540.22; RT 2.8 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).

34		HPLC-MS calculated for C32H37ClN4O2 (M+H+) 546.11, found 546.27; RT 2.3 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
35		HPLC-MS calculated for C32H30ClFN4O2 (M+H+) 558.06, found 558.21; RT 2.7 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
36		HPLC-MS calculated for C32H30ClFN4O2 (M+H+) 558.06, found 558.21; RT 2.7 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
37		HPLC-MS calculated for C32H30ClFN4O2 (M+H+) 558.06, found 558.21; RT 2.8 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
38		HPLC-MS calculated for C32H30Cl2N4O2 (M+H+) 574.51, found 574.18; RT 2.6 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).

39		HPLC-MS calculated for C31H35ClN4O3 (M+H+) 548.09, found 548.25; RT 2.1 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
40		HPLC-MS calculated for C31H32ClN5O3 (M+H+) 559.07, found 559.23; RT 2.3 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
41		HPLC-MS calculated for C33H33ClN4O3 (M+H+) 570.09, found 570.23; RT 2.8 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
42		HPLC-MS calculated for C33H33ClN4O3 (M+H+) 570.09, found 570.20; RT 2.7 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
43		HPLC-MS calculated for C29H29ClN6O3 (M+H+) 546.03, found 546.20; RT 2.5 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).

44		HPLC-MS calculated for C31H30ClF3N6O2 (M+H+) 612.06, found 612.20; RT 2.9 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
45		HPLC-MS calculated for C31H33ClN6O2 (M+H+) 558.09, found 558.20; RT 2.5 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
46		HPLC-MS calculated for C32H32ClN5O2 (M+H+) 555.08, found 555.20; RT 2.1 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
47		HPLC-MS calculated for C32H40FN5O2 (M+H+) 546.69, found 546.40; RT 2.2 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
48		HPLC-MS calculated for C34H33FN4O5 (M+H+) 597.2, found 597.3; RT 2.9 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
49		HPLC-MS calculated for C32H30F2N4O3 (M+H+) 557.2, found 557.0; RT 2.3 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN

50		HPLC-MS calculated for C32H31FN4O3 (M+H+) 539.2, found 539.0; RT 2.3min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
51		HPLC-MS calculated for C27H29FN4O3 (M+H+) 477.2, found 477.1; RT 1.9 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
52		HPLC-MS calculated for C30H32FN5O4S (M+H+) 578.2, found 578.2; RT 3.0 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/CAN
53		HPLC-MS calculated for C26H29ClN4O3S (M+H+) 514.05, found 514.10 RT 2.3 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
54		HPLC-MS calculated for C31H31ClN4O3S (M+H+) 576.12, found 576.40; RT 3.0 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).

Example 56

Preparation of (R)-(5-(l-benzylpiperidin-4-yl)-l-(4-chlorophenyl)-lH-pyrazol-4-yl)(3-phenylpyrrolidin-l-yl)methanone (Ex. No. 56)

[000189] The preparation of (R)-(5-(l-benzylpiperidin-4-yl)-l-(4-chlorophenyl)-lH-pyrazol-4-yl)(3-phenylpyrrolidin-l-yl)methanone (Ex. No. 55) is illustrated in scheme 4.

Scheme 4:

Ex. No. 55 Ex. No. 56

[000190] To a solution of (R)-tert-butyl 4-(l-(4-chlorophenyl)-4-(3-phenylpyrrolidine-l-carbonyl)-lH-pyrazol-5-yl)piperidine-l-carboxylate (Ex. No. 55) (100 mg, 0.19 mmol) in DCM (1 mL) was added 0.5 mL of TFA and the solution was stirred for 1 hour at room temperature. Upon completion of the reaction, the solvent was concentrated en vacuo and then the residue was dissolved in DCM and washed with saturated bicarbonate solution. The organic layer was dried over sodium sulfate, filtered, and concentrated to dryness and used in the subsequent step without any further purification.

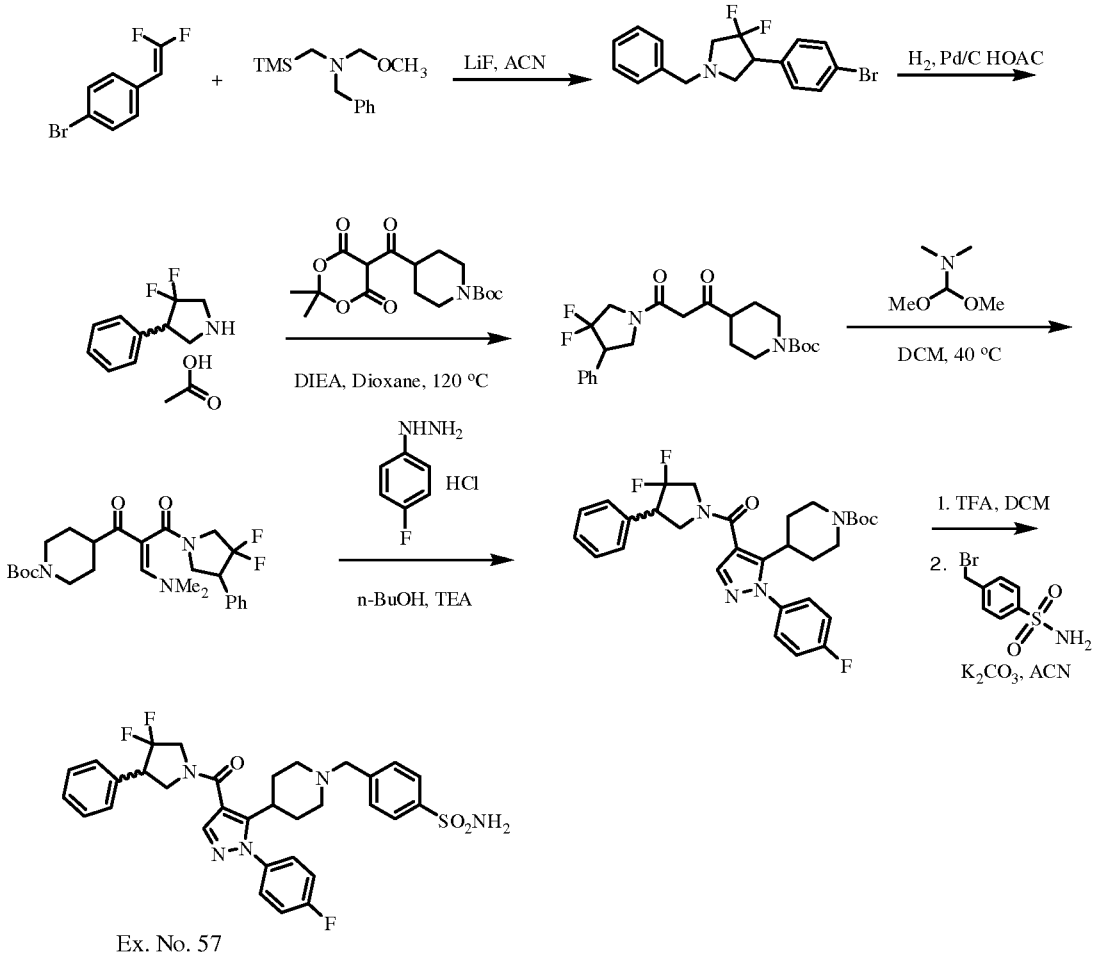
[000191] To a solution of the product from the above step in acetonitrile (2 mL) was added benzaldehyde (25 mg, 0.24 mmol, 1.25 eq), sodium triacetoxyborohydride (80 mg, 0.38 mmol, 2 eq) and catalytic acetic acid (~1 drop). The mixture was heated to 50 °C for 1 hour. The mixture was then diluted with 0.5 mL water, filtered through a 0.45 μM Whatman filter and purified by reversed phase HPLC (C-18, 100 mL/min, 10-90%, water (0.05 % TFA)/ACN) to yield (R)-(5-(l-benzylpiperidin-4-yl)-l-(4-chlorophenyl)-lH-pyrazol-4-yl)(3-phenylpyrrolidin-l-yl)methanone (Ex. No. 56) as a white solid. ^{1}H NMR ($CDC1_3$) δ 7.64 (1H), 7.48 (2H), 7.34-7.20 (12H), 4.17-3.89 (2H), 3.80-3.30 (6H), 2.90 (2H), 2.73 (1H), 2.44-2.04 (5H), 1.86 (2H); HPLC-MS calculated for $C_{32}H_{33}ClN_4O$ ($M+H^+$) 525.2, found 525.0; R_T 2.8 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).

Example 57

Preparation of 4-((4-(4-(3,3-difluoro-4-phenylpyrrolidine-l-carbonyl)-l-(4-fluorophenyl)-lH-pyrazol-5-yl)piperidin-l-yl)methyl)benzenesulfonamide (Ex. No. 57)

[000192] The preparation of 4-((4-(4-(3,3-difluoro-4-phenylpyrrolidine-l-carbonyl)-l-(4-fluorophenyl)-lH-pyrazol-5-yl)piperidin-l-yl)methyl)benzenesulfonamide (Ex. No. 57) is illustrated in scheme 5.

Scheme 5



Ex. No. 57

[000193] To a a solution of l-bromo-4-(2,2-difluorovinyl)benzene (1.14 g, 5.2 mmol) in acetonitrile (10 mL) was added N-benzyl-l-methoxy-N-((trimethylsilyl)methyl)methanamine (2.0 mL, 7.8 mmol) and lithium fluoride (263 mg, 10.1 mmol). The reaction vessel was purged with argon, sealed, and sonicated at room temperature for 17 hours. The crude reaction mixture was filtered to remove the inorganic salts and concentrated to dryness then purified by silica gel chromatography (0-40 % ethyl acetate/hexanes) to give l-benzyl-4-(4-bromophenyl)-3,3-difluoropyrrolidine as a colorless, semi-viscous liquid.

[000194] To a solution of l-benzyl-4-(4-bromophenyl)-3,3-difluoropyrrolidine (5.5 g, 16 mmol) in acetic acid (80 mL) was added 10 % palladium on carbon (1.7 g, 1.6 mmol, Degussa type wet). The vessel was sealed and fitted with a hydrogen- filled balloon and stirred vigourously overnight. Upon completion, the catalyst was removed by filtration on pad of celite and concentrated to dryness to give the product (3,3-difluoro-4-phenylpyrrolidine acetate) as a white to off-white solid.

[000195] To a 40 mL microwave reaction vessel was added 3,3-difluoro-4-phenylpyrrolidine acetate (1.0 g, 4.1 mmol), and tert-butyl 4-(2,2-dimethyl-4,6-dioxo-l,3-dioxane-5-carbonyl)piperidine-l-carboxylate (1.8 g, 4.9 mmol), dioxane (15 mL) and diisopropylethylamine (1.8 mL, 10.3 mmol). The vessel was sealed and heated to 120 °C for 20 minutes. Upon completion, the reaction was diluted with 10 % citric acid and extracted with ethyl acetate. The combined organics were washed with brine, dried over magnesium sulfate, filtered concentrated en vacuo and purified by silica gel chromatography (50-100% Ethyl acetate/Hexanes) to give tert-butyl 4-(3-(3,3-difluoro-4-phenylpyrrolidin-l-yl)-3-oxopropanoyl)piperidine-l-carboxylate as syrup.

[000196] Tert-butyl 4-(3-(3,3-difluoro-4-phenylpyrrolidin-l-yl)-3-oxopropanoyl)piperidine-l-carboxylate (7.55 g, 17.3 mmol) was dissolved in DCM (50 mL) and treated with dimethylformamide dimethylacetal (DMFDMA) (11 mL, 83 mmol, 4.8 eq) at reflux for 4 hours (complete by LC-MS). The solvent was evaporated to give ((Z)-tert-butyl 4-(2-(3,3-difluoro-4-phenylpyrrolidine-l-carbonyl)-3-(dimethylamino)acryloyl)piperidine-l-carboxylate) as a crude product that was carried forward without any further purification.

[000197] To a solution of (Z)-tert-butyl 4-(2-(3,3-difluoro-4-phenylpyrrolidine-l-carbonyl)-3-(dimethylamino)acryloyl)piperidine-l-carboxylate (250 mg, 0.5 mmol) in n-butanol (3 mL) was added 4-fluorophenylhydrazine hydrochloride (248 mg, 1.5 mmol) and diisopropylethylamine (0.7 mL, 5 mmol). The mixture was heated to 90 °C for 2 hours and was then filtered on celite, washed with ethyl acetate and concentrated to dryness. Tert-butyl 4-(4-(3,3-difluoro-4-phenylpyrrolidine-l-carbonyl)-l-(4-fluorophenyl)-lH-pyrazol-5-yl)piperidine-l-carboxylate was obtained as an oil upon purification by silica gel chromatography (20-100 % ethyl acetate/hexanes).

[000198] To a solution of tert-butyl 4-(4-(3,3-difluoro-4-phenylpyrrolidine-l-carbonyl)-l-(4-fluorophenyl)-lH-pyrazol-5-yl)piperidine-l-carboxylate (100 mg, 0.18 mmol) in DCM (1 mL) was added 0.5 mL of TFA and the solution was stirred for 1 hour at room temperature. Upon completion of the reaction, the solvent was concentrated en vacuo and then the residue was dissolved in DCM and washed with saturated bicarbonate solution. The organic layer was dried over sodium sulfate, filtered, and concentrated to dryness and used in the subsequent step without any further purification.

[000199] To a solution of the product from the above step in acetonitrile (2 mL) was added 4-(bromomethyl)benzenesulfonamide (56.3 mg, 0.24 mmol, 1.25 eq) and K_2C0_3. The mixture was

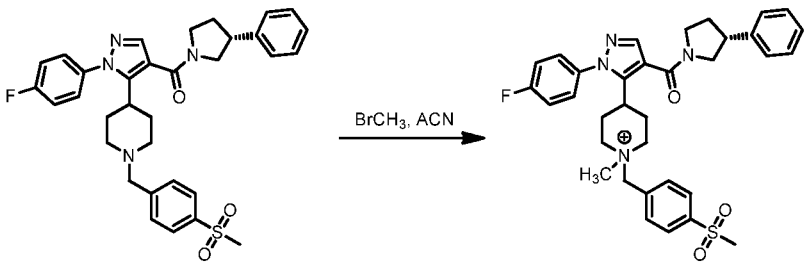
heated to 50 °C for 1 hour. The mixture was then diluted with 0.5 mL water, filtered through a 0.45 μM Whatman filter and purified by reversed phase HPLC (C-18, 100 mL/min, 10-90%, water (0.05 % TFA)/ACN) to yield (4-((4-(4-(3,3-difluoro-4-phenylpyrrolidine-l-carbonyl)-l-(4-fluorophenyl)-lH-pyrazol-5-yl)piperidin-l-yl)methyl)benzenesulfonamide) (Ex. No. 57). The material was then resolved by chiral HPLC (stationary phase: 20X250 mm ChiralPaklA, mobile phase: 70/25/5 Hexane/chloroform/ethanol, flow rate: 18 mL/min) to yield Examples 218 and 219, respectively.

[000200] By repeating the procedures described in example 56 and 57, using appropriate starting materials, compounds of Formula **(I)** or Formula **(II),** as identified in Table 3, were obtained.

Example 280

Preparation of (R)-4-(l-(4-fluorophenyl)-4-(3-phenylpyrrolidine-l-carbonyl)-lH-pyrazol-5-yl)-l-methyl-l-(4-(methylsulfonyl)benzyl)piperidin-l-ium (Ex. No. 280)

Example 280

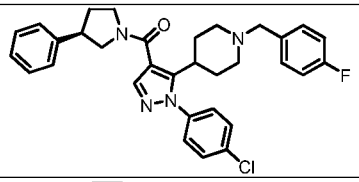
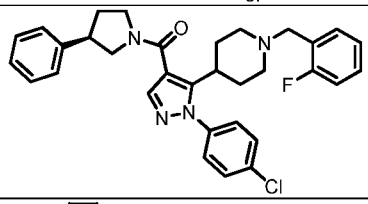
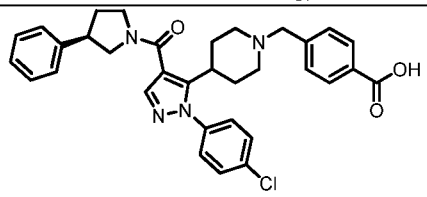
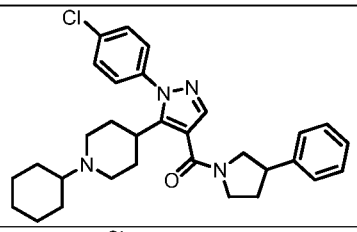
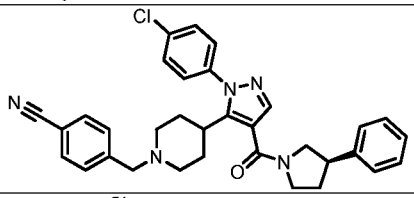
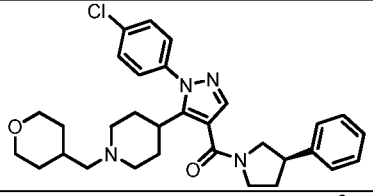
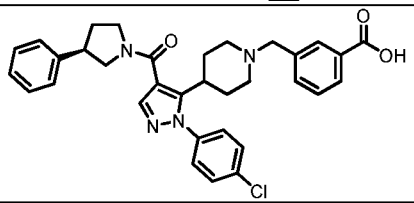
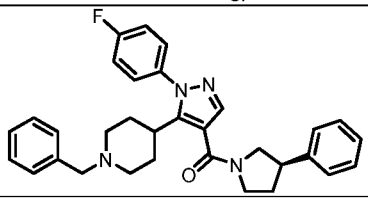


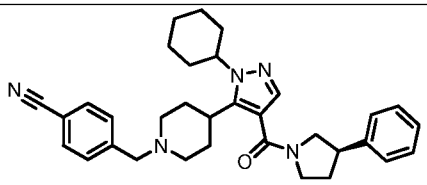
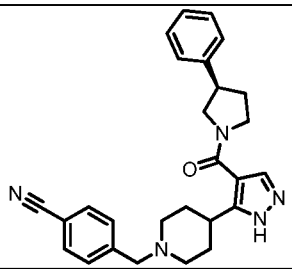
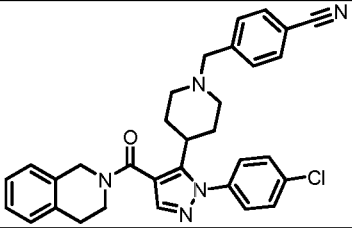
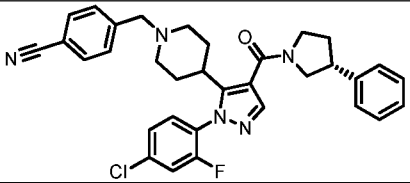
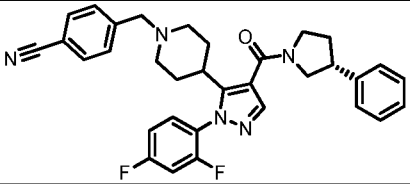
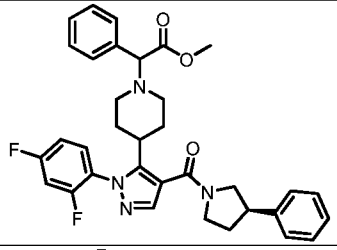
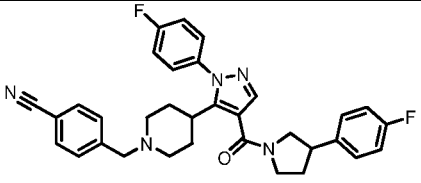
[000201] A solution of (R)-(l-(4-fluorophenyl)-5-(l-(4-(methylsulfonyl)benzyl)piperidin-4-yl)-lH-pyrazol-4-yl)(3-phenylpyrrolidin-l-yl)methanone (100 mg, 0.17 mmol) in acetonitrile (2 mL) was treated with excess bromomethane (0.5 mL) and heated to 80 °C until complete conversion was observed by HPLC-MS. The solvent and excess reagents were removed by evaporation to give the quaternary ammonium salt, (R)-4-(l-(4-fluorophenyl)-4-(3-phenylpyrrolidine- 1-carbonyl) -1H-pyrazol- 5-yl) -1-methyl- 1-(4-(methylsulfonyl)benzyl)piperidin-l-ium. HPLC-MS calculated for C34H38FN403S+ (M+) 601.3, found 601.3; RT 2.09 min. (4.5 min) (C18, 10-100%, water (0.05 % TFA)/ACN.

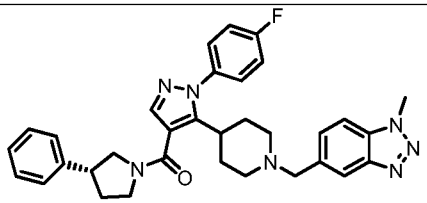
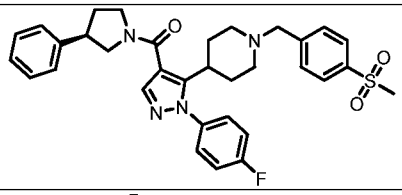
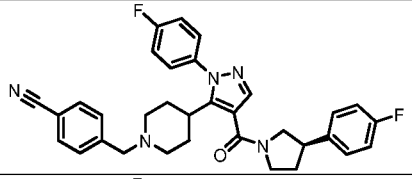
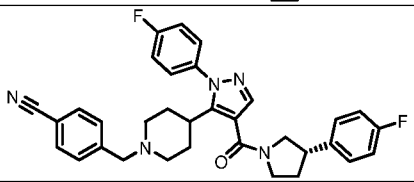
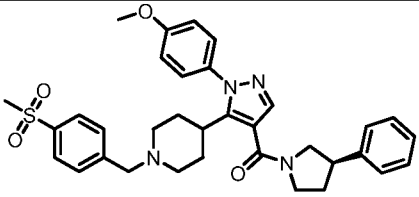
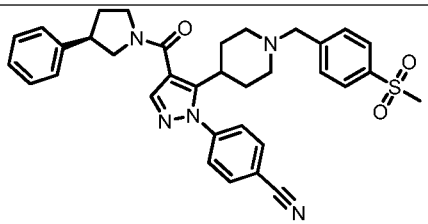
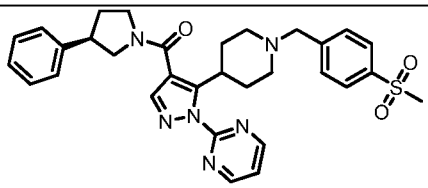
[000202] By repeating the procedures described in example 280, using appropriate starting materials, compounds of Formula **(I)** or Formula **(II),** as identified in Table 3, were obtained.

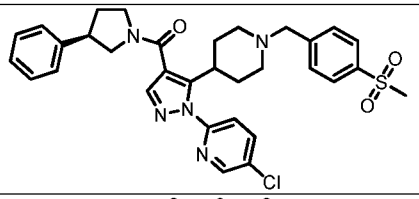
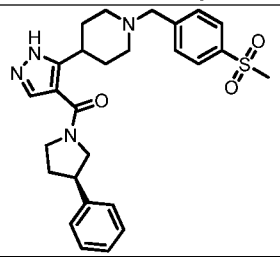
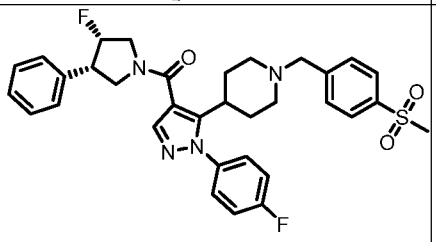
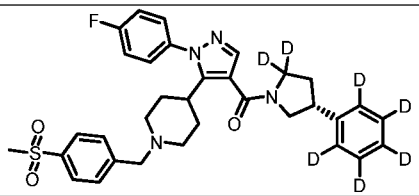
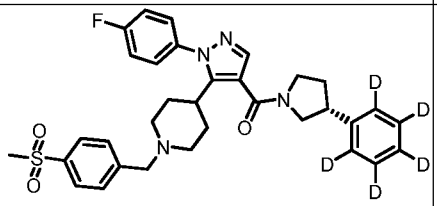
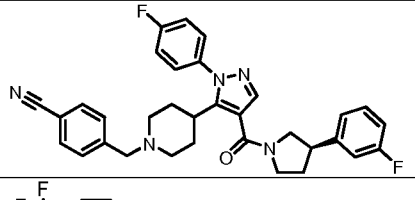
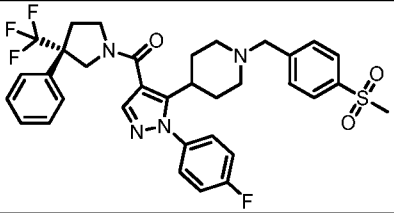
Table 3

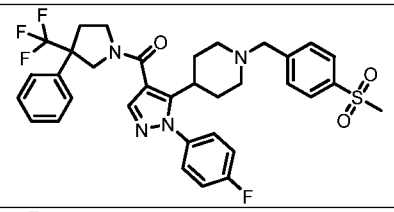
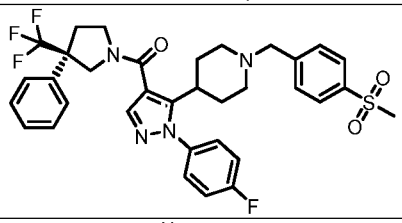
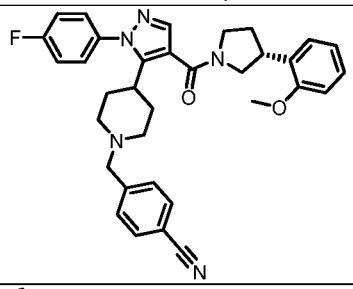
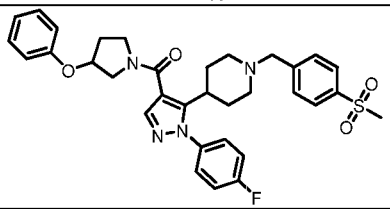
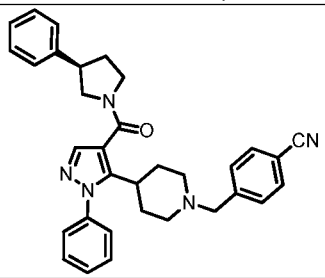
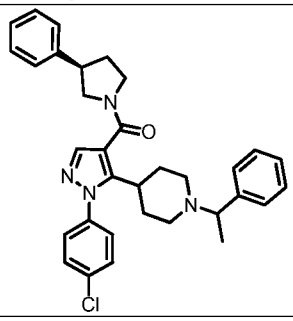
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDC13 or acetone-d6) and/or MS (m/z)

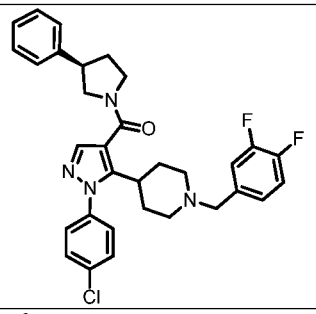
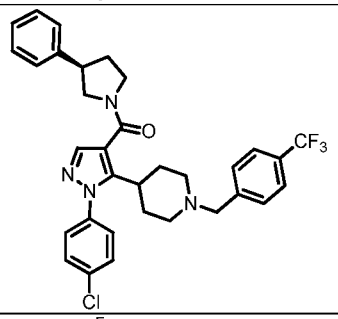
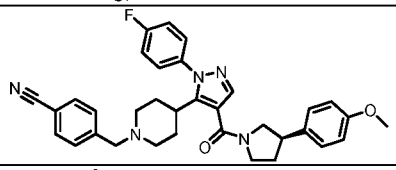
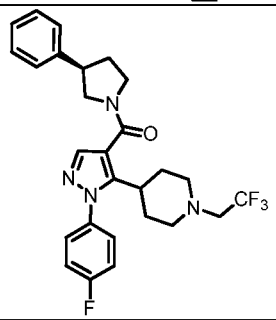
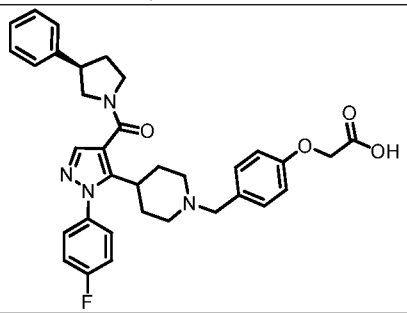
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDCl3 or acetone-d6) and/or MS (m/z)
58		HPLC-MS calculated for C32H32ClFN4O (M+H+) 543.2, found 543.2; RT 2.8 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
59		HPLC-MS calculated for C32H32ClFN4O (M+H+) 543.2, found 543.2; RT 2.8 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN Add RT
60		HPLC-MS calculated for C33H33ClN4O3 (M+H+) 569.2, found 569.2; RT 2.4 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
61		HPLC-MS calculated for C31H37ClN4O (M+H+) 517.3, found 517.3; RT 2.1 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
62		HPLC-MS calculated for C33H32ClN5O (M+H+) 550.2, found 550.2; RT 2.7 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
63		HPLC-MS calculated for C31H37ClN4O2 (M+H+) 533.3, found 533.3: RT 0.3 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
64		HPLC-MS calculated for C33H33ClN4O3 (M+H+) 569.2, found 569.2; RT 2.6 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
65		HPLC-MS calculated for C32H33FN4O (M+H+) 509.3, found 509.2; RT 2.7 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN

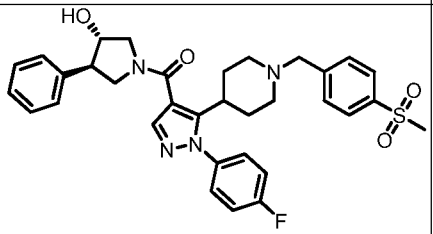
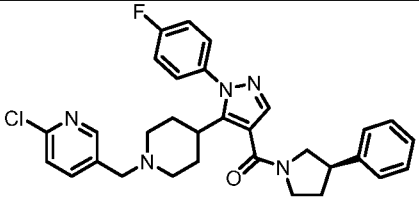
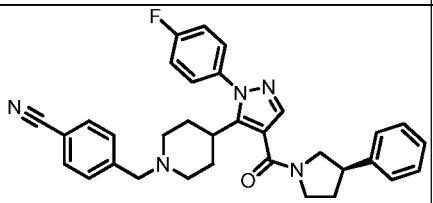
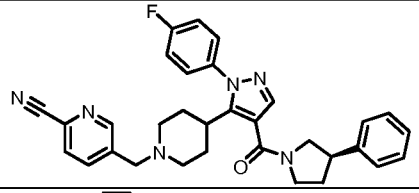
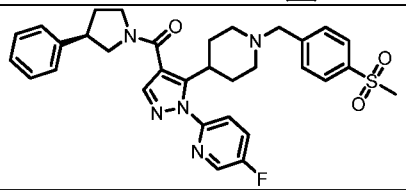
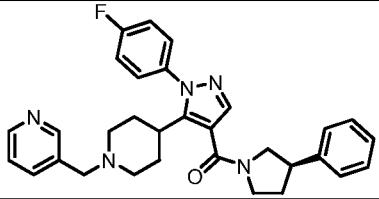
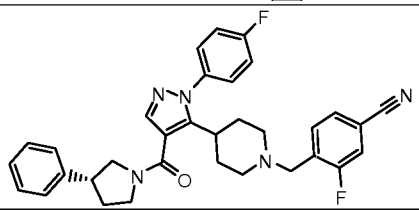
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDCl3 or acetone-d6) and/or MS (m/z)
66		HPLC-MS calculated for C33H39N5O (M+H+) 522.3, found 522.3; RT 2.3 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
67		HPLC-MS calculated for C27H29N5O (M+H+) 440.2, found 440.2; RT 1.8 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
68		HPLC-MS calculated for C32H30ClN5O (M+H+) 536.2, found 536.2; RT2.2 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
69		HPLC-MS calculated for C33H31ClFN5O (M+H+) 568.2, found 568.2; RT 2.7 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
70		HPLC-MS calculated for C33H31F2N5O (M+H+) 552.2, found 552.2; RT 2.6 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
71		HPLC-MS calculated for C34H34F2N4O3 (M+H+) 585.3, found 585.2; RT 2.8 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
72		HPLC-MS calculated for C33H31F2N5O (M+H+) 552.2, found 552.3; RT 2.3 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN

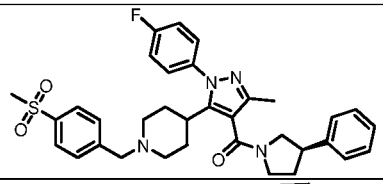
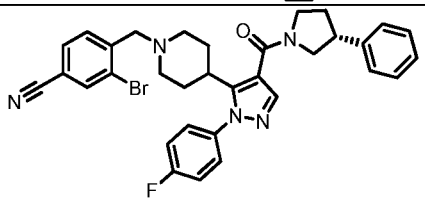
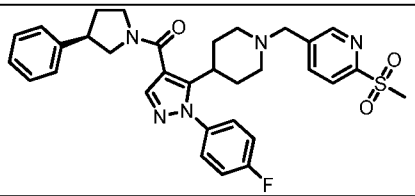
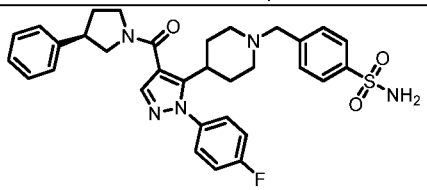
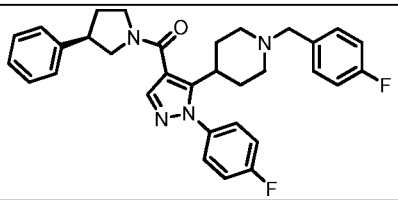
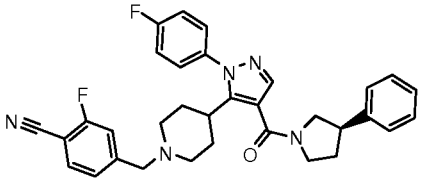
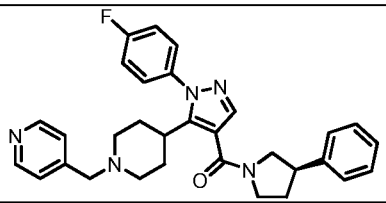
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDC13 or acetone-d6) and/or MS (m/z)
73		HPLC-MS calculated for C33H34FN70 (M+H+) 564.3, found 564.4; RT 2.5 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
74		HPLC-MS calculated for C33H35FN403S (M+H+) 587.2, found 587.4; RT 2.5 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
75		HPLC-MS calculated for C33H31F2N50 (M+H+) 552.2, found 552.3; RT 2.5 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
76		HPLC-MS calculated for C33H31F2N50 (M+H+) 552.2, found 552.3; RT 2.5 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
77		HPLC-MS calculated for C34H38N404S (M+H+) 599.3, found 599.2; RT 2.3 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
78		HPLC-MS calculated for C34H35N503S (M+H+) 594.2, found 594.3; RT 2.4 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
79		HPLC-MS calculated for C31H34N603S (M+H+) 571.2, found 571.3; RT 2.8 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN

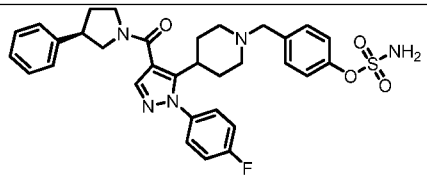
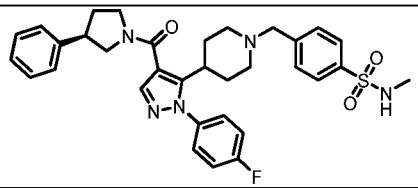
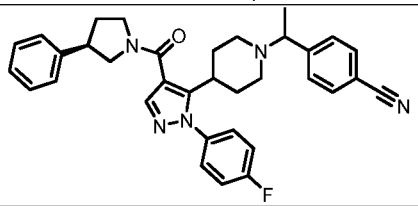
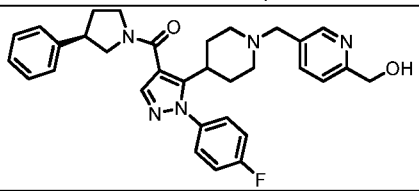
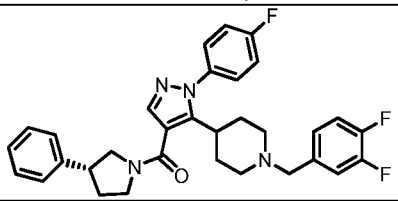
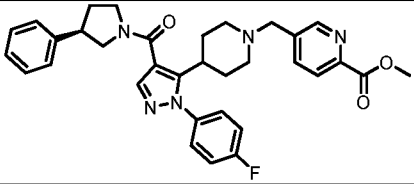
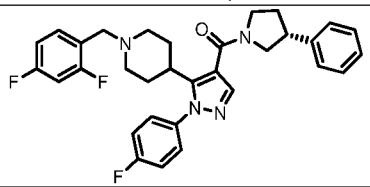
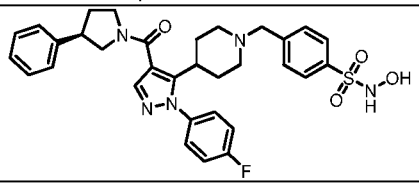
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDCl3 or acetone-d6) and/or MS (m/z)
80		HPLC-MS calculated for C32H34ClN5O3S (M+H+) 604.2, found 604.3; RT 2.5 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
81		HPLC-MS calculated for C27H32N4O3S (M+H+) 493.2, found 493.2; RT 2.0 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
82		HPLC-MS calculated for C33H34F2N4O3S (M+H+) 605.2, found 605.1; RT 1.37 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
83		HPLC-MS calculated for C33H28D7FN4O3S (M+H+) 594.3, found 594.4; RT 0.89 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
84		HPLC-MS calculated for C33H30D5FN4O3S (M+H+) 592.3, found 592.4; RT 0.89 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
85		HPLC-MS calculated for C33H31F2N5O (M+H+) 552.3, found 552.1; RT 1.3 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
86		HPLC-MS calculated for C34H34F4N4O3S (M+H+) 655.2, found 655.1; RT 1.45 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN

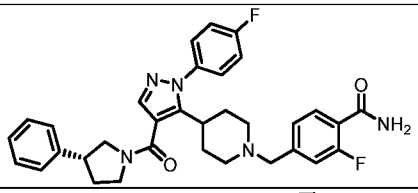
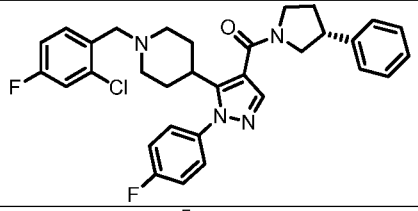
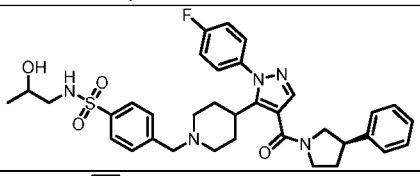
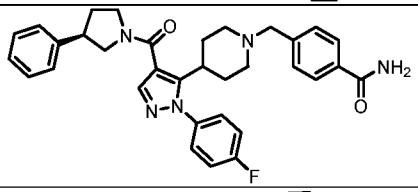
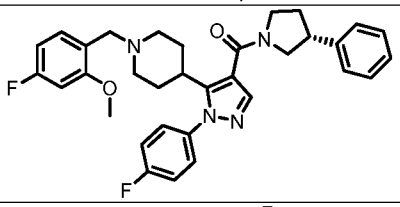
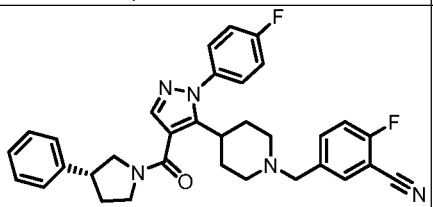
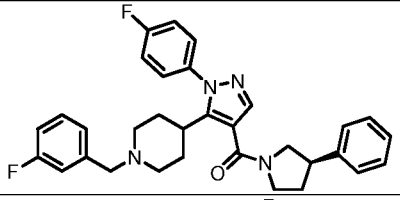
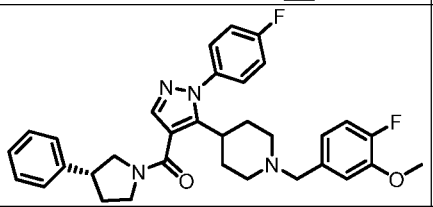
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDCl3 or acetone-d6) and/or MS (m/z)
87		HPLC-MS calculated for C34H34F4N4O3S (M+H+) 655.2, found 655.2; RT 1.48 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
88		HPLC-MS calculated for C34H34F4N4O3S (M+H+) 655.2, found 655.2; RT 1.45 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
89		HPLC-MS calculated for C34H34FN5O2 (M+H+) 564.3, found 564.3; RT 1.44 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
90		HPLC-MS calculated for C33H35FN4O4S (M+H+) 603.2, found 603.2; RT 0.89 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
91		HPLC-MS calculated for C33H33N5O (M+H+) 516.65, found 516.28; RT 2.9 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
92		HPLC-MS calculated for C33H35ClN4O (M+H+) 540.11, found 540.20; RT 2.8 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).

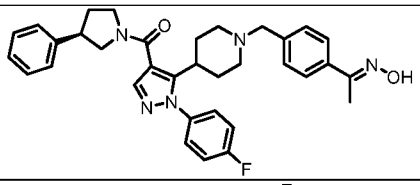
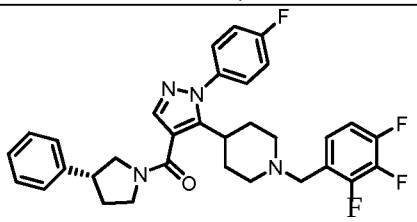
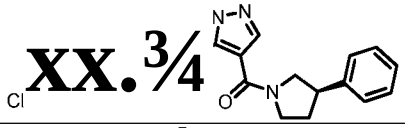
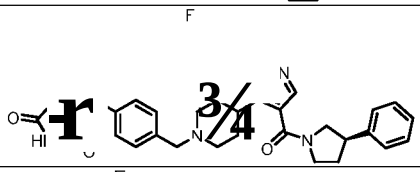
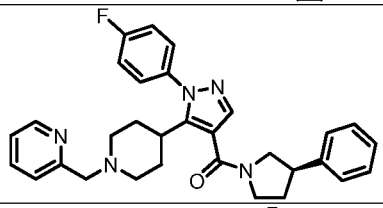
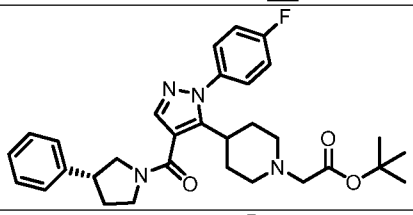
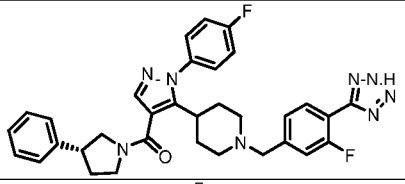
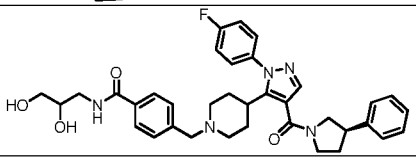
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDCl3 or acetone-d6) and/or MS (m/z)
93		HPLC-MS calculated for C32H31ClF2N4O (M+H+) 562.06, found 562.22; RT 2.4 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
94		HPLC-MS calculated for C33H32ClF3N4O (M+H+) 594.08, found 594.23; RT 2.5 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
95		HPLC-MS calculated for C34H34FN5O2 (M+H+) 564.3, found 564.3; RT 1.42 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
96		HPLC-MS calculated for C27H28F4N4O (M+H+) 501.53, found 501.20; RT 2.2 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
97		HPLC-MS calculated for C34H35FN4O4 (M+H+) 583.66, found 583.20; RT 2.4 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).

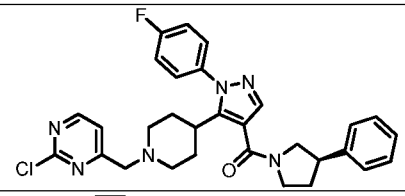
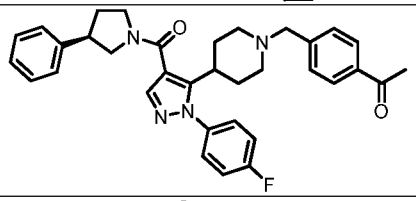
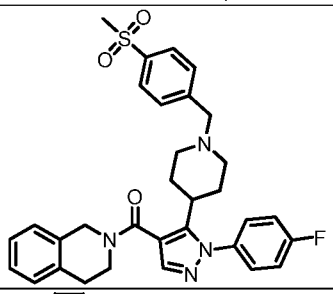
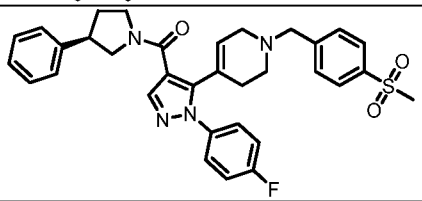
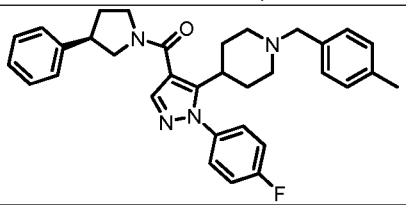
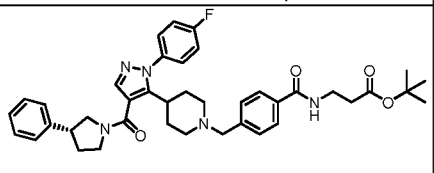
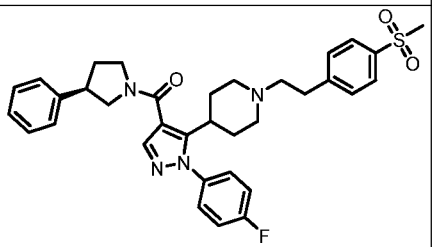
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDCl3 or acetone-d6) and/or MS (m/z)
98		HPLC-MS calculated for C33H35FN4O4S (M+H+) 603.2, found 603.4; RT 1.12 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
99		HPLC-MS calculated for C31H31ClFN5O (M+H+) 544.2, found 544.3; RT 2.1 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
100		HPLC-MS calculated for C33H32FN5O (M+H+) 534.3, found 534.3; RT 2.1 min. (1.8 min) (C18, 10-90%, water (0.05 % TFA)/ACN
101		HPLC-MS calculated for C32H31FN6O (M+H+) 535.3, found 535.3; RT 2.1 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
102		HPLC-MS calculated for C32H34FN5O3S (M+H+) 588.2, found 588.4; RT 1.2 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
103		HPLC-MS calculated for C31H32FN5O (M+H+) 510.3, found 510.3; RT 1.2 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
104		HPLC-MS calculated for C32H34FN5O3S (M+H+) 588.2, found 588.4; RT 1.2 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN

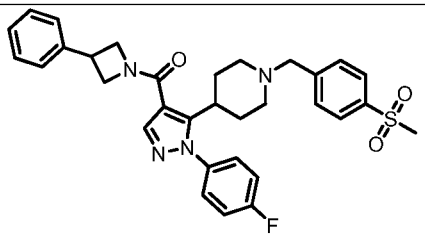
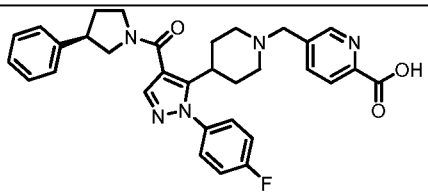
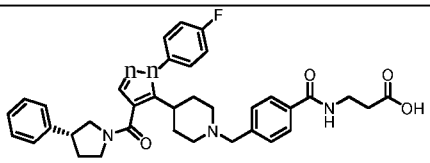
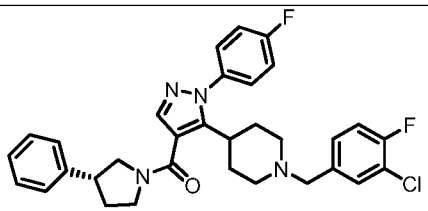
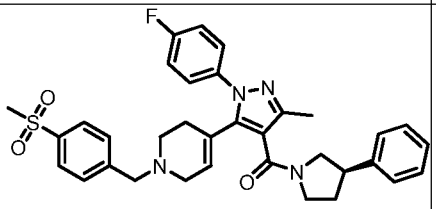
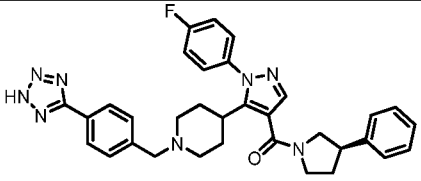
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDC13 or acetone-d6) and/or MS (m/z)
105		HPLC-MS calculated for C34H37FN403S (M+H+) 601.3, found 601.3; RT 0.9 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
106		HPLC-MS calculated for C33H31BrFN50 (M+H+) 612.2, found 612.2; RT 2.3 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
107		HPLC-MS calculated for C32H34FN503S (M+H+) 588.2, found 588.2; RT 1.3 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
108		HPLC-MS calculated for C32H34FN503S (M+Na+) 610.4, found 610.4; RT 1.5 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
109		HPLC-MS calculated for C32H32F2N40 (M+H+) 527.3, found 527.2; RT 1.5 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
110		HPLC-MS calculated for C33H31F2N50 (M+H+) 552.3, found 552.3; RT 2.2 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
111		HPLC-MS calculated for C31H32FN50 (M+H+) 510.3, found 510.2; RT 1.2 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN

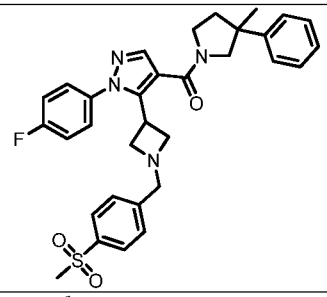
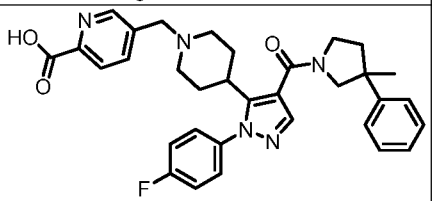
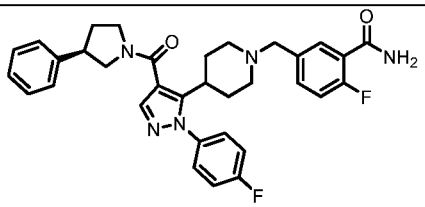
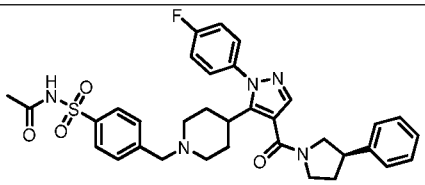
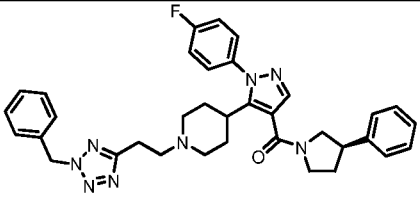
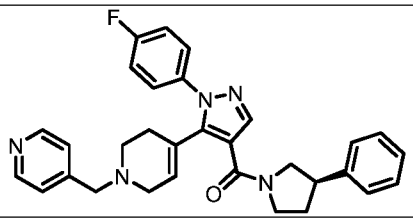
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDC13 or acetone-d6) and/or MS (m/z)
112		HPLC-MS calculated for C32H34FN504S (M+H+) 604.2, found 604.2; RT 0.9 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
113		HPLC-MS calculated for C33H36FN503S (M+H+) 602.2, found 602.0; RT 1.3 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
114		HPLC-MS calculated for C34H34FN50 (M+H+) 548.3, found 548.3; RT 1.5 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
115		HPLC-MS calculated for C32H34FN502 (M+H+) 540.3, found 540.3; RT 1.2 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
116		HPLC-MS calculated for C32H31F3N40 (M+H+) 545.2, found 545.3; RT 2.0 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
117		HPLC-MS calculated for C33H34FN503 (M+H+) 568.3, found 568.3; RT 1.7 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
118		HPLC-MS calculated for C32H31F3N40 (M+H+) 545.2, found 545.2; RT 1.5min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
119		HPLC-MS calculated for C32H34FN504S (M+H+) 604.3, found 604.3; RT 0.9min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN

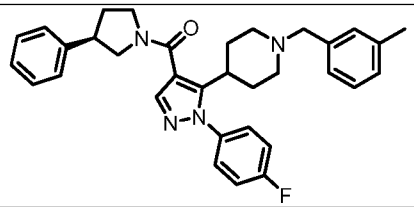
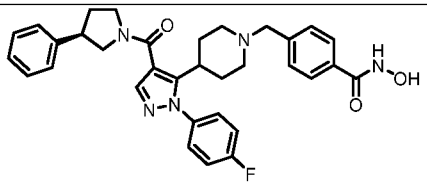
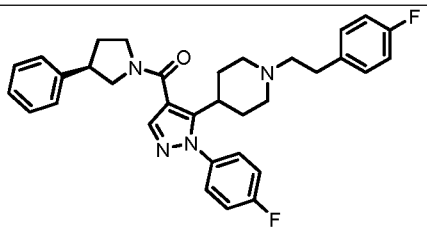
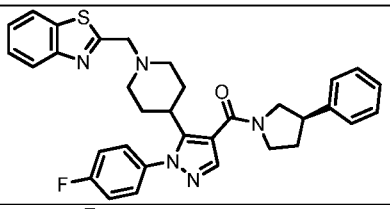
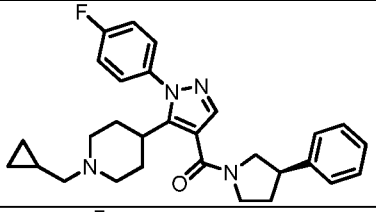
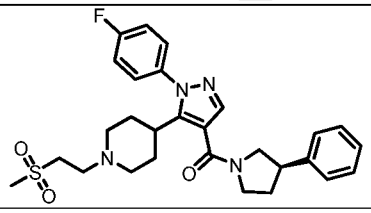
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDCl3 or acetone-d6) and/or MS (m/z)
120		HPLC-MS calculated for C33H33F2N5O2 (M+H+) 570.3, found 570.3; RT 2.0 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
121		HPLC-MS calculated for C33H31ClF2N4O (M+H+) 560.2, found 561.2; RT 2.0min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
122		HPLC-MS calculated for C34H40FN5O4S (M+H+) 646.2, found 646.0; RT 1.2min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
123		HPLC-MS calculated for C33H34FN5O2 (M+H+) 552.3, found 552.2; RT 1.3min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
124		HPLC-MS calculated for C33H34F2N4O2 (M+H+) 557.3, found 557.2; RT 1.6min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
125		HPLC-MS calculated for C33H31F2N5O (M+H+) 552.3, found 552.3; RT 2.3 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
126		HPLC-MS calculated for C32H32F2N4O (M+H+) 527.3, found 527.2; RT 1.5 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
127		HPLC-MS calculated for C33H34F2N4O2 (M+H+) 557.3, found 557.2; RT 1.5 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN

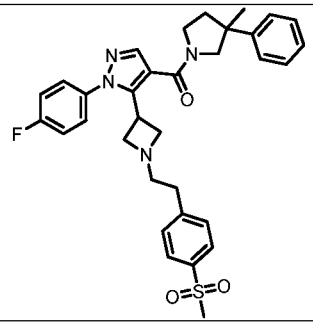
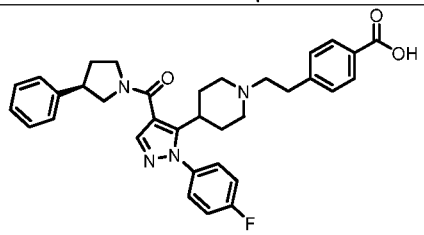
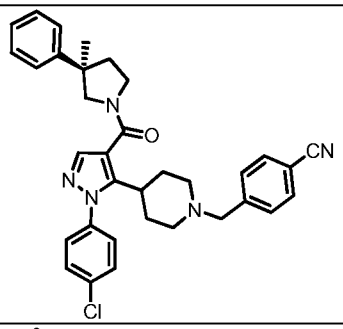
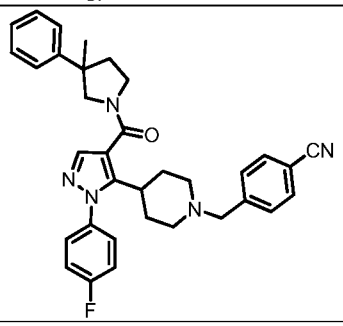
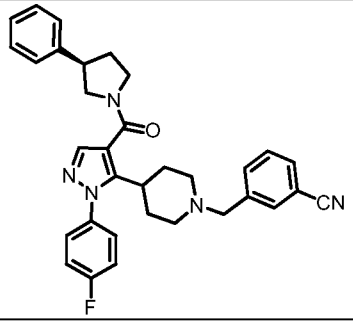
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDC13 or acetone-d6) and/or MS (m/z)
128		HPLC-MS calculated for C34H36FN502 (M+H+) 566.3, found 566.3; RT 1.4 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
129		HPLC-MS calculated for C32H30F4N4O (M+H+) 563.2, found 563.3; RT 2.0 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
130		HPLC-MS calculated for C31H31C1FN50 (M+H+) 544.2, found 544.0; RT 1.3 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
131		HPLC-MS calculated for C36H34FN503S (M+H+) 636.2, found 636.3; RT 2.3 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
132		HPLC-MS calculated for C31H32FN50 (M+H+) 510.3, found 510.3; RT 1.3 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
133		HPLC-MS calculated for C31H37FN403 (M+H+) 533.3, found 533.3; RT 1.6 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
134		HPLC-MS calculated for C33H32F2N60 (M+H+) 595.3, found 595.3; RT 1.8 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
135		HPLC-MS calculated for C36H40FN5O4 (M+H+) 626.3, found 626.1; RT 1.1 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN

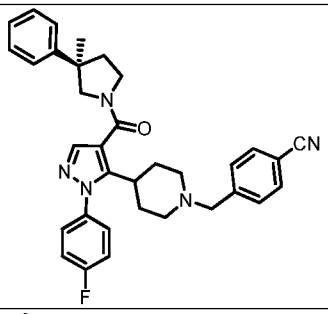
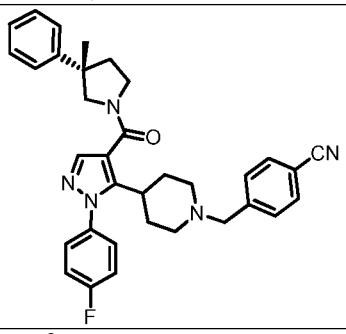
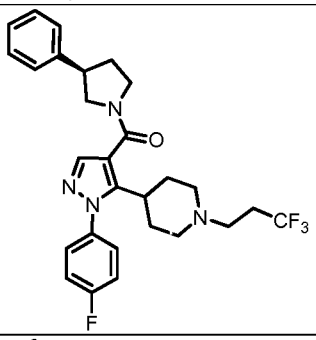
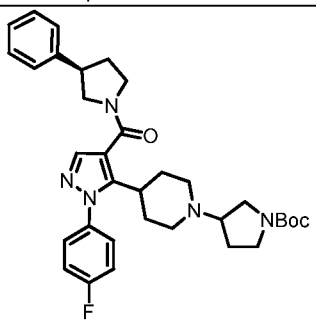
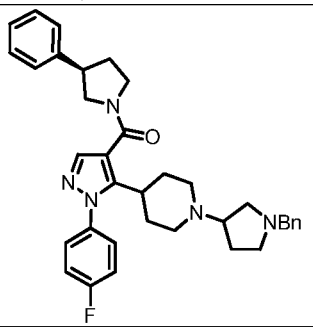
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDC13 or acetone-d6) and/or MS (m/z)
136		HPLC-MS calculated for C30H30C1FN6O (M+H+) 545.2, found 545.0; RT 1.3 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
137		HPLC-MS calculated for C34H35FN402 (M+H+) 551.3, found 551.3; RT 2.1 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
138		HPLC-MS calculated for C32H33FN403S (M+H+) 573.2, found 573.4; RT 1.4 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
139		HPLC-MS calculated for C33H33FN403S (M+H+) 585.2, found 585.1; RT 1.2 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
140		HPLC-MS calculated for C33H35FN40 (M+H+) 523.3, found 523.4; RT 2.1 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
141		HPLC-MS calculated for C40H46FN5O4 (M+H+) 680.4, found 680.3; RT 1.6 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
142		HPLC-MS calculated for C34H37FN403S (M+H+) 601.3, found 601.3; RT 1.0 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN

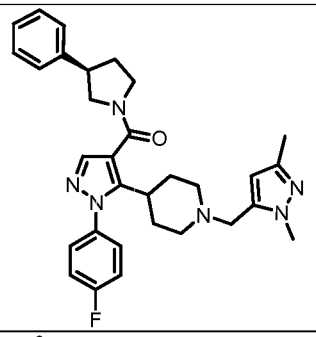
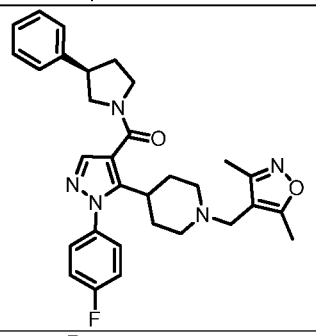
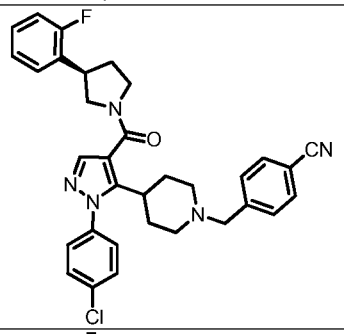
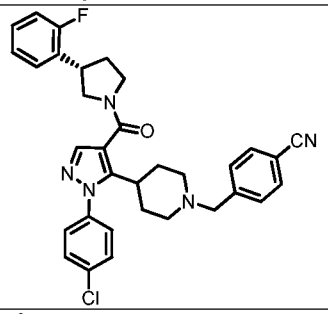
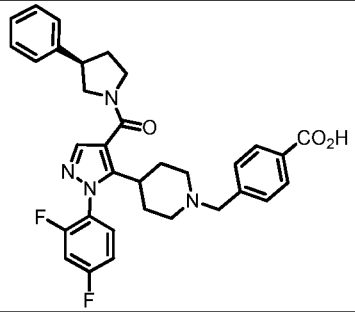
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDC13 or acetone-d6) and/or MS (m/z)
143		HPLC-MS calculated for C32H33FN403S (M+H+) 573.2, found 573.3; RT 1.6 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
144		HPLC-MS calculated for C32H32FN503 (M+H+) 554.2, found 554.2; RT 1.3 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
145		HPLC-MS calculated for C36H38FN504 (M+H+) 624.3, found 624.1; RT 1.2 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
146		HPLC-MS calculated for C32H31C1F2N40 (M+H+) 561.2, found 561.3; RT 2.1 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
147		HPLC-MS calculated for C34H35FN403S (M+H+) 599.2, found 599.2; RT 1.3 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
148		HPLC-MS calculated for C33H33FN80 (M+H+) 577.3, found 577.2; RT 1.4 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN

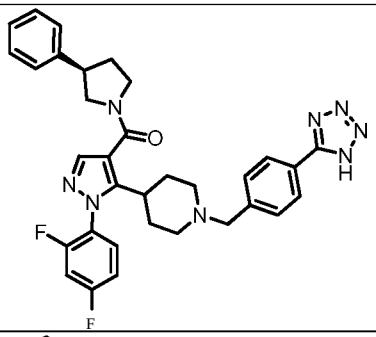
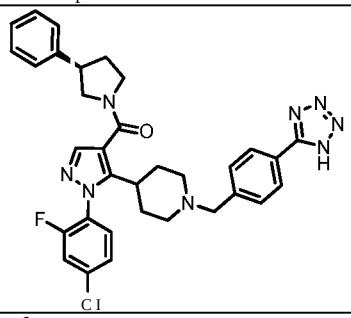
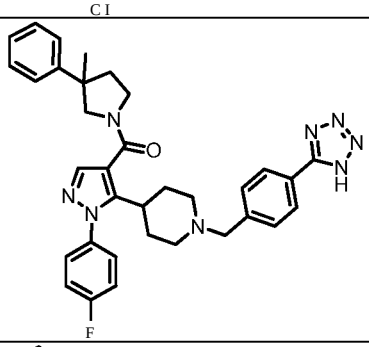
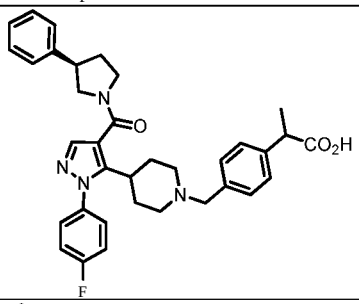
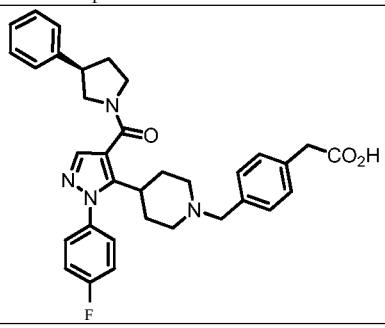
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDCl3 or acetone-d6) and/or MS (m/z)
149		HPLC-MS calculated for C32H33FN4O3S (M+H+) 573.2, found 573.0; RT 1.3 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
150		HPLC-MS calculated for C33H34FN5O3 (M+H+) 568.3, found 568.1; RT 1.2 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
151		HPLC-MS calculated for C33H33F2N5O2 (M+H+) 570.3, found 570.3; RT 2.0 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
152		HPLC-MS calculated for C34H36FN5O4S (M+H+) 630.3, found 630.7; RT 1.4 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
153		HPLC-MS calculated for C35H37FN8O (M+H+) 605.3, found 605.4; RT 2.3 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
154		HPLC-MS calculated for C31H30FN5O (M+H+) 508.2, found 508.1; RT 1.2 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN

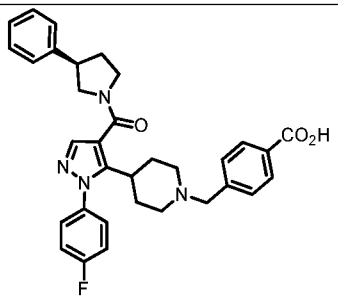
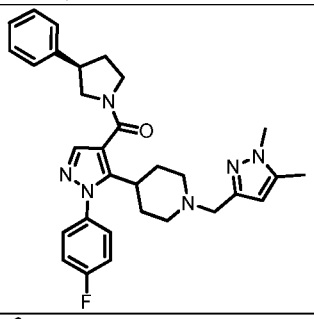
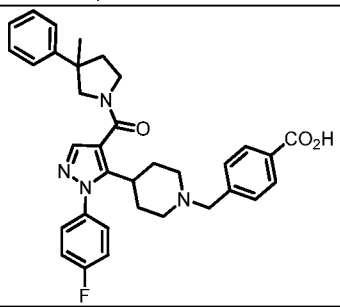
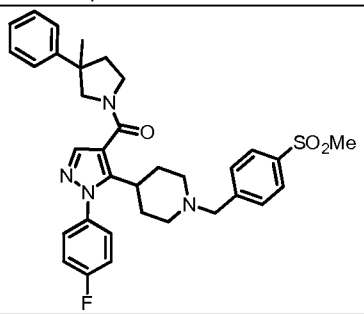
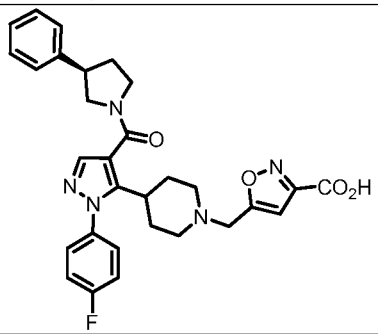
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDC13 or acetone-d6) and/or MS (m/z)
155		HPLC-MS calculated for C33H35FN40 (M+H+) 523.3, found 523.4; RT 2.1 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
156		HPLC-MS calculated for C33H34FN503 (M+H+) 568.3, found 568.3; RT 0.9 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
157		HPLC-MS calculated for C33H34F2N40 (M+H+) 541.3, found 541.3; RT 2.0 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
158		HPLC-MS calculated for C33H32FN50S (M+H+) 566.2, found 566.3; RT 2.3 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
159		HPLC-MS calculated for C29H33FN40 (M+H+) 473.3, found 473.3; RT 2.2 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
160		HPLC-MS calculated for C28H33FN403S (M+H+) 525.2, found 525.2; RT 1.9 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN

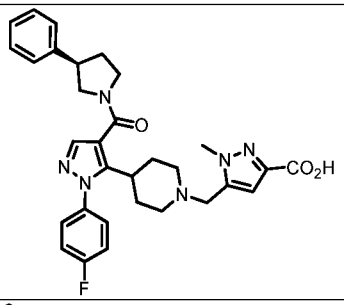
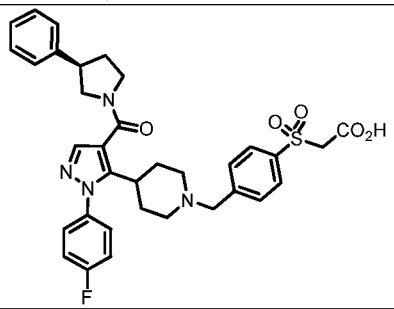
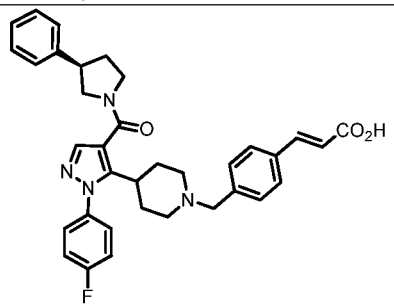
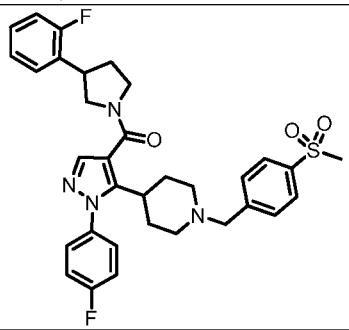
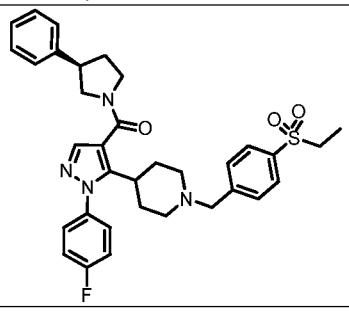
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDCl3 or acetone-d6) and/or MS (m/z)
161		HPLC-MS calculated for C33H35FN4O3S (M+H+) 587.2, found 587.3; RT 0.9min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
162		HPLC-MS calculated for C34H35FN4O3 (M+H+) 567.3, found 567.4; RT 1.6 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
163		HPLC-MS calculated for C34H34ClN5O (M+H+) 565.12, found 565.25; RT 2.8 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
164		HPLC-MS calculated for C34H34FN5O (M+H+) 548.67, found 548.20; RT 2.6 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
165		HPLC-MS calculated for C33H32FN5O (M+H+) 534.64, found 534.30; RT 2.6 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).

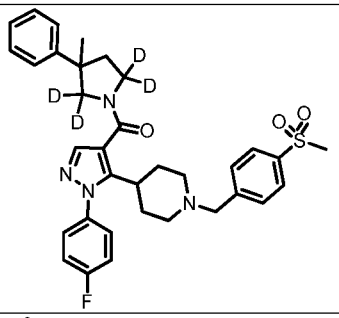
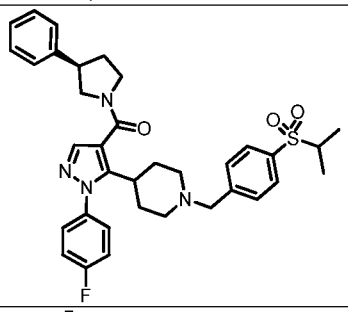
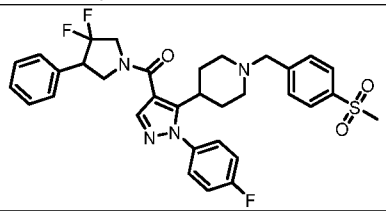
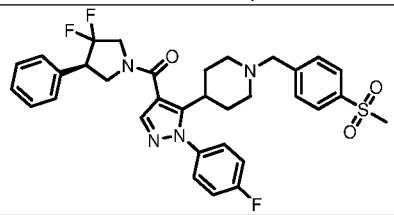
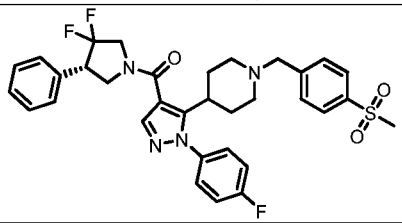
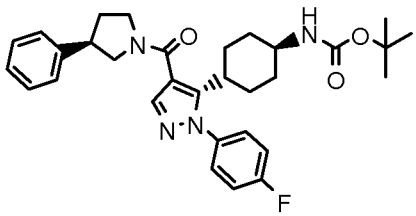
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDCl3 or acetone-d6) and/or MS (m/z)
166		HPLC-MS calculated for C34H34FN5O (M+H+) 548.67, found 548.20; RT 2.6 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
167		HPLC-MS calculated for C34H34FN5O (M+H+) 548.67, found 548.20; RT 2.6 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
168		HPLC-MS calculated for C28H30F4N4O (M+H+) 515.56, found 515.30; RT 2.6 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
169		HPLC-MS calculated for C34H42FN5O3 (M+H+) 588.73, found 588.40; RT 2.7 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
170		HPLC-MS calculated for C36H40FN5O (M+H+) 578.73, found 578.40; RT 2.3 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).

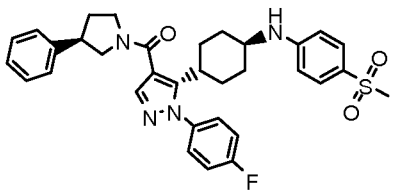
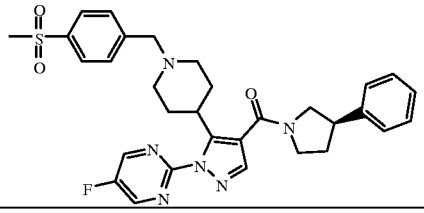
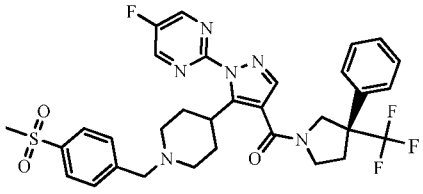
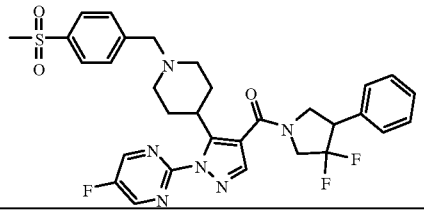
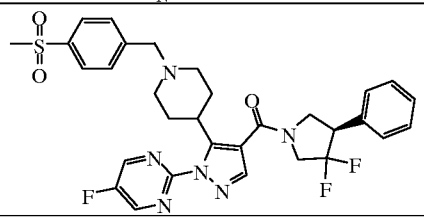
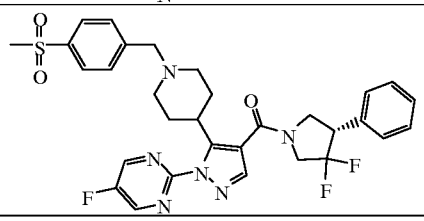
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDCl3 or acetone-d6) and/or MS (m/z)
171		HPLC-MS calculated for C31H35FN6O (M+H+) 527.65, found 527.40; RT 2.4 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
172		HPLC-MS calculated for C31H34FN5O2 (M+H+) 528.63, found 528.40; RT 2.5 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
173		HPLC-MS calculated for C33H31ClFN5O (M+H+) 569.08, found 569.23; RT 2.6 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
174		HPLC-MS calculated for C33H31ClFN5O (M+H+) 569.08, found 569.23; RT 2.6 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
175		HPLC-MS calculated for C33H32F2N4O3 (M+H+) 571.63, found 571.30; RT 2.1 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).

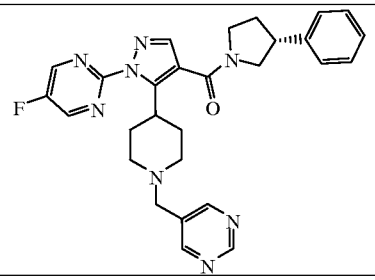
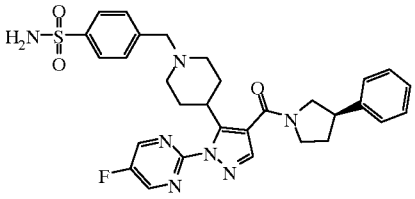
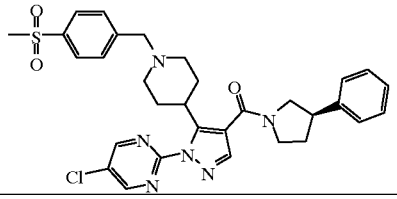
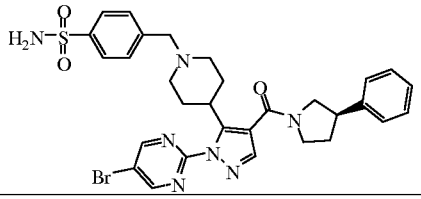
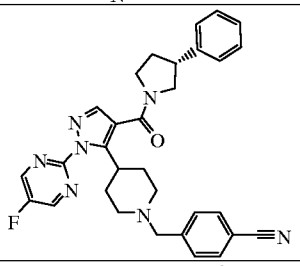
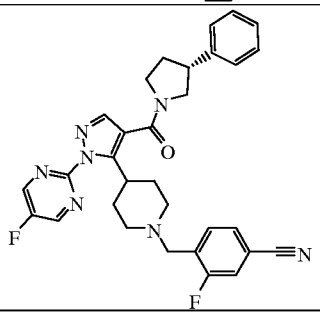
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDC13 or acetone-d6) and/or MS (m/z)
176		HPLC-MS calculated for C33H32F2N80 (M+H+) 595.66, found 595.30; RT 2.1 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
177		HPLC-MS calculated for C33H32C1FN80 (M+H+) 612.11, found 612.25; RT 2.7 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
178		HPLC-MS calculated for C34H35FN80 (M+H+) 591.69, found 591.40; RT 2.4 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
179		HPLC-MS calculated for C35H37FN403 (M+H+) 581.69, found 581.30; RT 2.5 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
180		HPLC-MS calculated for C34H35FN403 (M+H+) 567.67, found 567.30; RT 2.3 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).

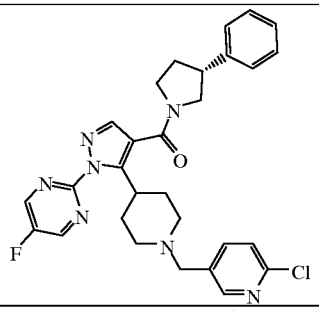
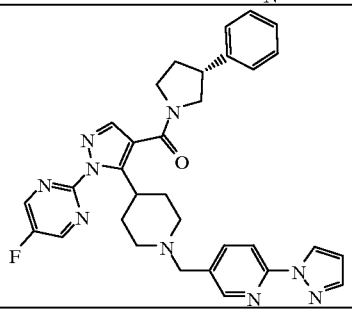
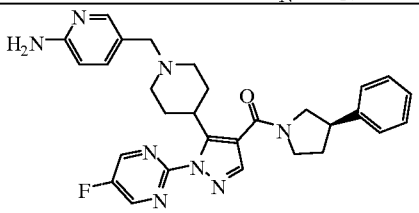
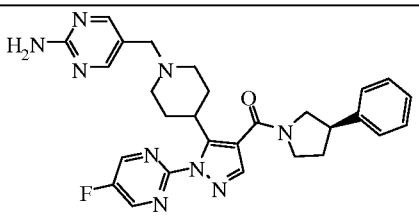
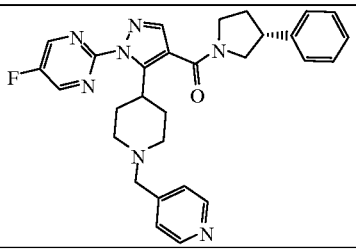
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDCl3 or acetone-d6) and/or MS (m/z)
181		HPLC-MS calculated for C33H33FN4O3 (M+H+) 553.64, found 553.30; RT 2.4 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
182		HPLC-MS calculated for C31H35FN6O (M+H+) 527.65, found 527.30; RT 2.4 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
183		HPLC-MS calculated for C34H35FN4O3 (M+H+) 567.67, found 567.30; RT 2.5 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
184		HPLC-MS calculated for C34H37FN4O3S (M+H+) 601.75, found 601.20; RT 2.4 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
185		HPLC-MS calculated for C30H30FN5O4 (M+H+) 544.59, found 544.30; RT 2.2 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).

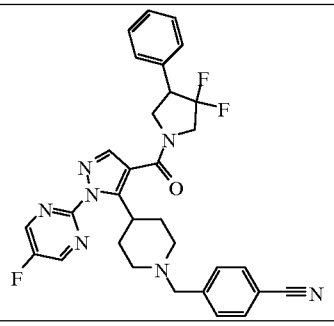
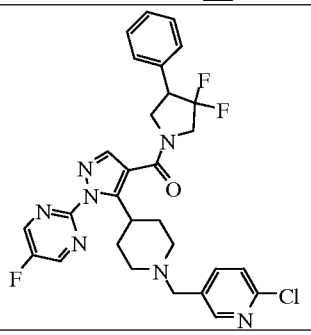
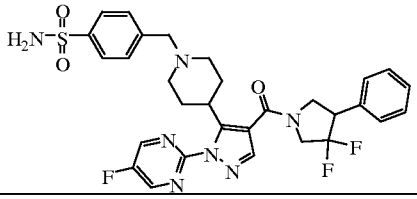
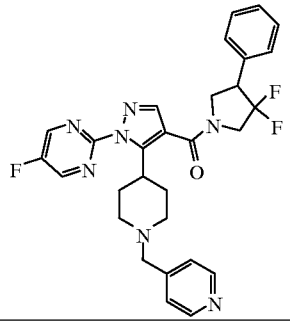
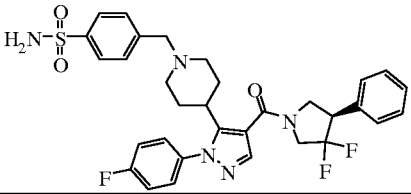
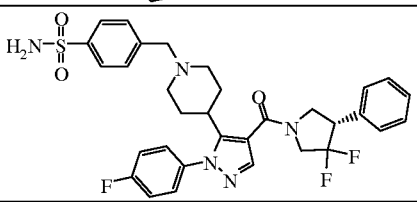
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDCl3 or acetone-d6) and/or MS (m/z)
186		HPLC-MS calculated for C31H33FN6O3 (M+H+) 557.63, found 557.30; RT 2.2 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
187		HPLC-MS calculated for C34H35FN4O5S (M+H+) 631.73, found 631.30; RT 2.4 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
188		HPLC-MS calculated for C35H35FN4O3 (M+H+) 579.68, found 579.30; RT 2.5 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
189		HPLC-MS calculated for C33H34F2N4O3S (M+H+) 605.71, found 605.30; RT 2.5 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
190		HPLC-MS calculated for C34H37FN4O3S (M+H+) 601.75, found 601.30; RT 0.3 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).

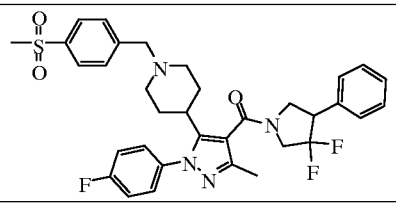
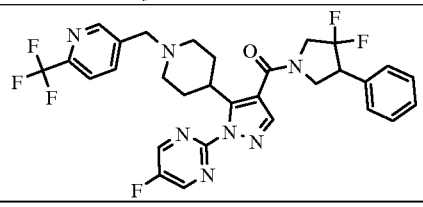
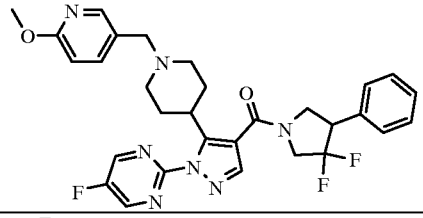
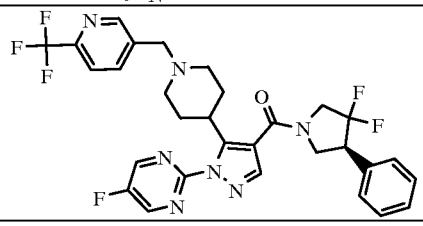
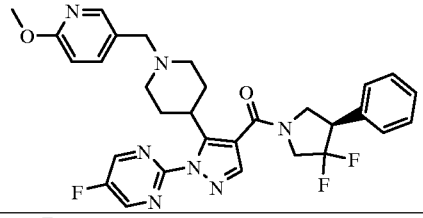
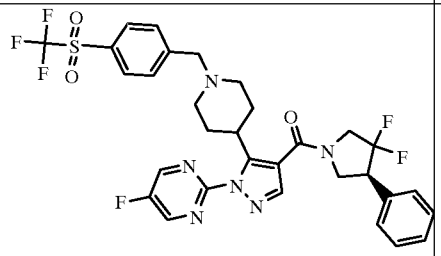
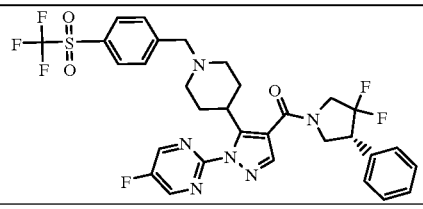
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDCl3 or acetone-d6) and/or MS (m/z)
191		HPLC-MS calculated for C34H33D4FN4O3S (M+H+) 605.77, found 605.40; RT 2.4 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
192		HPLC-MS calculated for C35H39FN4O3S (M+H+) 615.77, found 615.20; RT 2.5 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN).
193		HPLC-MS calculated for C33H33F3N4O3S (M+H+) 623.2, found 623.1; RT 1.44 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
194		HPLC-MS calculated for C33H33F3N4O3S (M+H+) 623.2, found 623.0; RT 1.45 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
195		HPLC-MS calculated for C33H33F3N4O3S (M+H+) 623.2, found 623.0; RT 1.45 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
196		1H NMR (d6-DMSO) δ 7.98 (1H), 7.80 (1H), 7.48 (2H), 7.35-7.22 (6H), 4.00-3.80 (2H), 3.71-3.46 (4H), 2.48-2.10 (3H), 2.00-1.71 (6H), 1.41 (9H), 1.10 (2H); HPLC-MS calculated for C31H37FN4O3 (M+H+) 533.3, found 533.3; RT 2.8 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN)

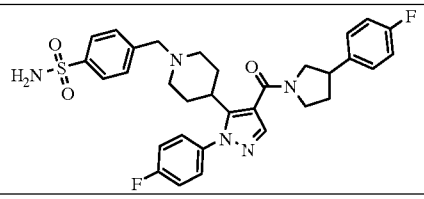
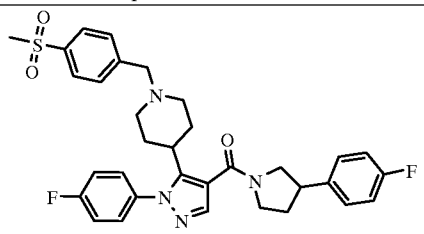
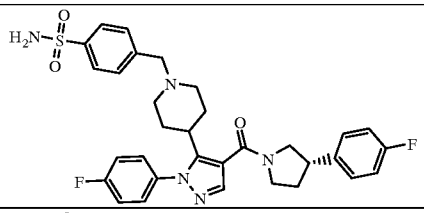
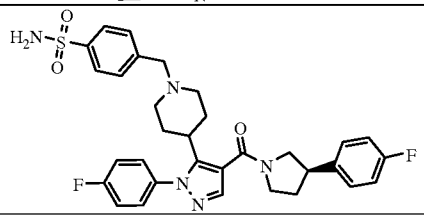
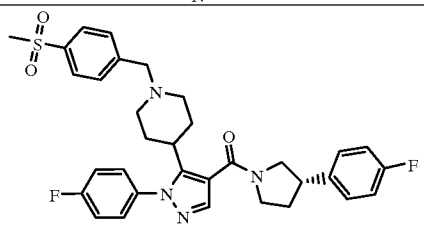
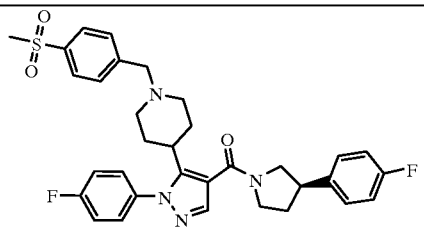
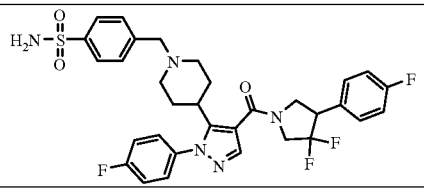
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDCl3 or acetone-d6) and/or MS (m/z)
197		1H NMR (d6-DMSO) δ 7.70 (1H), 7.48 (2H), 7.40 (2H), 7.26-7.11 (7H), 6.56 (2H), 4.01-3.78 (2H), 3.66-3.37 (5H), 2.60 (1H), 2.40-1.69 (8H), 1.03 (2H); HPLC-MS calculated for C33H35FN4O3S (M+H+) 587.2, found 587.3; RT 3.1 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN)
198		HPLC-MS calculated for C31H33FN6O3S (M+H+) 589.2, found 589.2; RT 2.09 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
199		HPLC-MS calculated for C32H32F4N6O3S (M+H+) 657.2, found 657.3; RT; 2.53 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
200		HPLC-MS calculated for C31H31F3N6O3S (M+H+) 625.2, found 625.1; RT; 2.24 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
201		HPLC-MS calculated for C31H31F3N6O3S (M+H+) 625.2, found 625.1; RT; 2.21 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
202		HPLC-MS calculated for C31H31F3N6O3S (M+H+) 625.2, found 625.1; RT; 2.21 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN

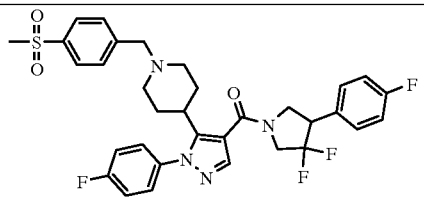
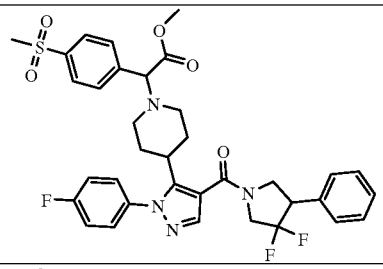
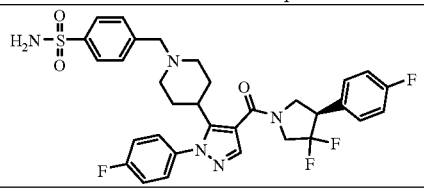
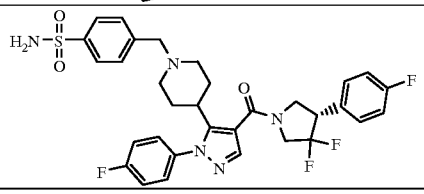
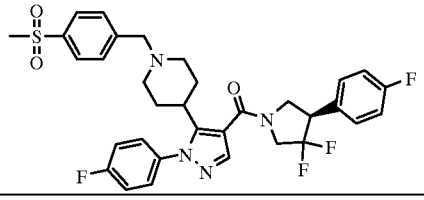
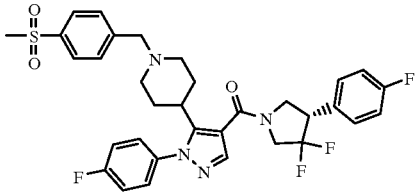
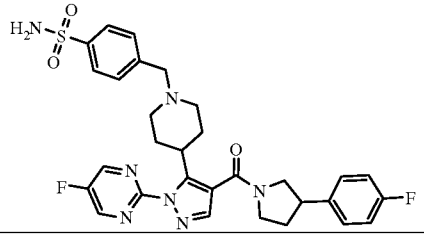
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDCl3 or acetone-d6) and/or MS (m/z)
203		HPLC-MS calculated for C28H29FN8O (M+H+) 513.2, found 513.3; RT 2.43 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
204		HPLC-MS calculated for C30H32FN7O3S (M+H+) 590.2, found 590.1; RT 2.00 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
205		HPLC-MS calculated for C31H33ClN6O3S (M+H+) 605.3, found 605.2; RT 2.49 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
206		HPLC-MS calculated forC30H32BrN7O3S (M^+) 650.59, found 650.1; RT 1.48 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN)
207		HPLC-MS calculated for C31H30FN7O (M+H+) 536.3, found 536.2; RT 2.17 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
208		HPLC-MS calculated for C31H29F2N7O (M+H+) 554.2, found 554.2; RT 2.19 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN

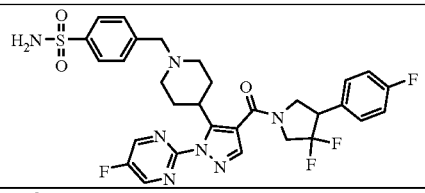
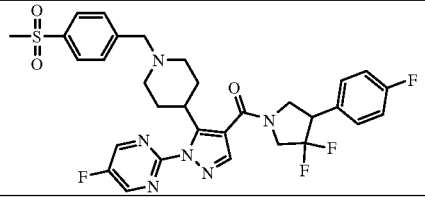
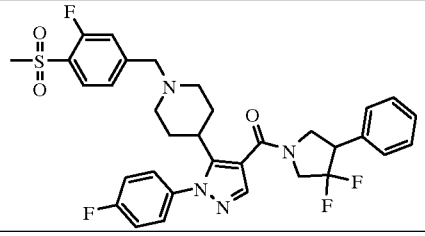
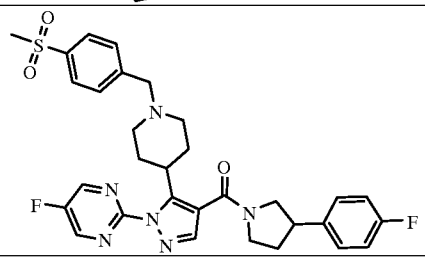
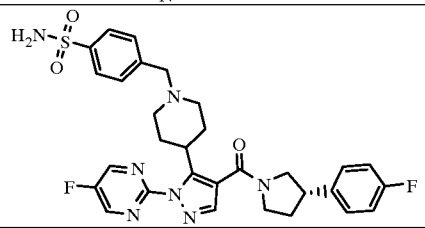
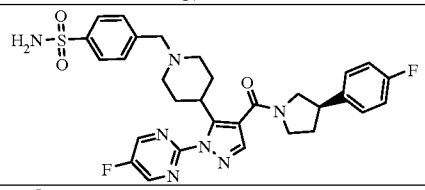
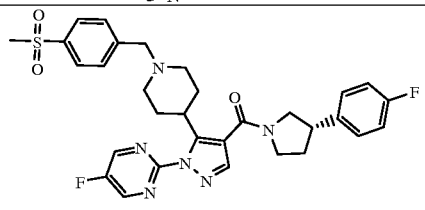
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDCl3 or acetone-d6) and/or MS (m/z)
209		HPLC-MS calculated for C29H29ClFN7O (M+H+) 546.2, found 546.2; RT 2.61 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
210		HPLC-MS calculated for C32H32FN9O (M+H+) 578.3, found 578.2; RT 2.23 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
211		HPLC-MS calculated for C29H31FN8O (M+H+) 527.3, found 527.3; RT 1.52 min. (4.5 min) (C18, 10-100%, water (0.05 % TFA)/ACN
212		HPLC-MS calculated for C28H30FN9O (M+H+) 528.3, found 528.3; RT 1.64 min. (4.5 min) (C18, 10-100%, water (0.05 % TFA)/ACN
213		HPLC-MS calculated for C29H30FN7O (M+H+) 512.3, found 512.3; RT 1.55 min. (4.5 min) (C18, 10-100%, water (0.05 % TFA)/ACN

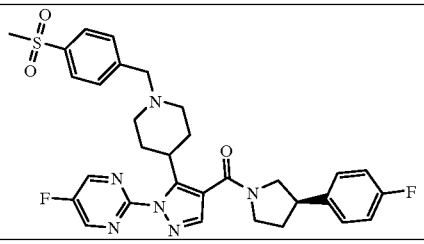
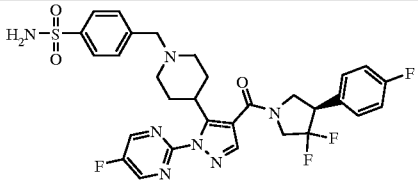
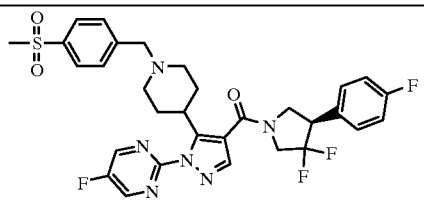
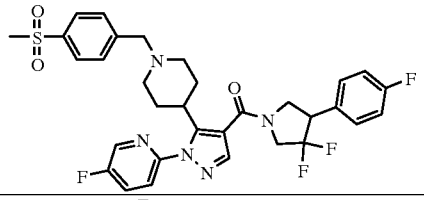
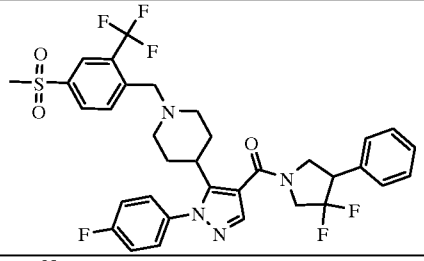
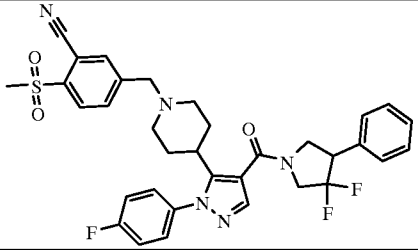
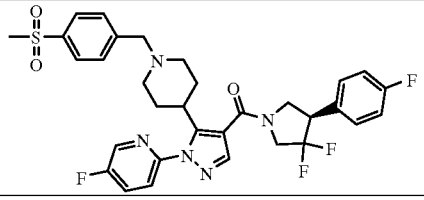
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDCl3 or acetone-d6) and/or MS (m/z)
214		HPLC-MS calculated for C31H28F3N7O (M+H+) 572.2, found 572.2; RT 2.36 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
215		HPLC-MS calculated for C29H27ClF2N7O (M+H+) 582.2, found 582.2; RT 2.24 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
216		HPLC-MS calculated for C30H30F3N7O3S (M+H+) 626.2, found 626.2; RT 2.13 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
217		HPLC-MS calculated for C29H28F3N7O (M+H+) 548.2, found 548.2; RT 1.82 min. (4.5 min) (C18, 10-100%, water (0.05 % TFA)/ACN
218		HPLC-MS calculated for C32H32F3N5O3S (M+H+) 624.2, found 624.2; RT 2.32 min. (4.5 min) (C18, 10-100%, water (0.05 % TFA)/ACN
219		HPLC-MS calculated for C32H32F3N5O3S (M+H+) 624.2, found 624.2; RT 2.32 min. (4.5 min) (C18, 10-100%, water (0.05 % TFA)/ACN

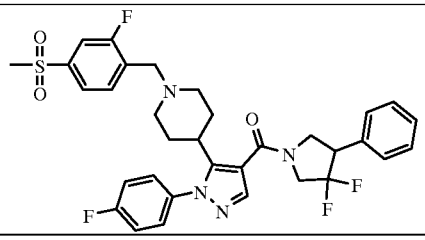
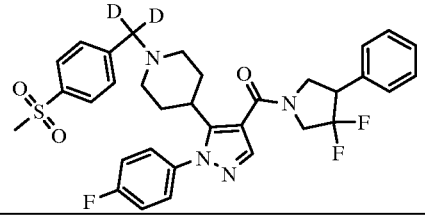
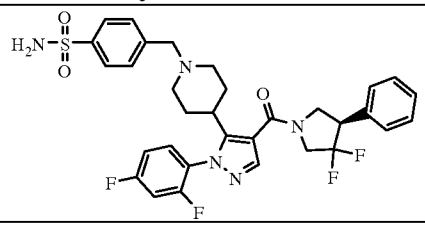
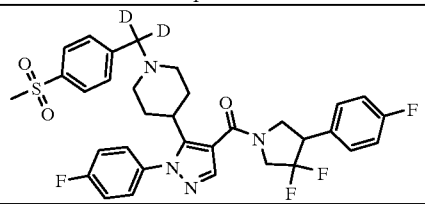
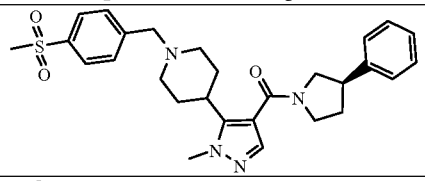
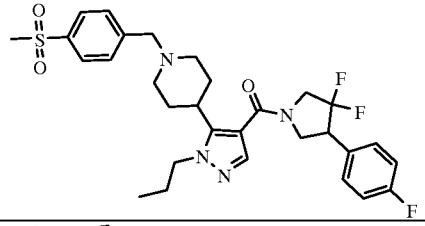
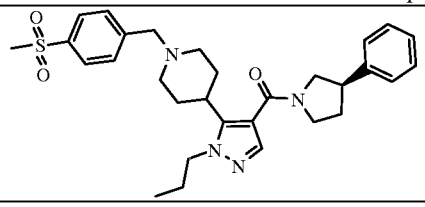
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDCl3 or acetone-d6) and/or MS (m/z)
220		HPLC-MS calculated for C34H35F3N4O3S (M+H+) 637.2, found 637.3; RT 2.30 min. (4.5 min) (C18, 10-100%, water (0.05 % TFA)/ACN
221		HPLC-MS calculated for C30H27F6N7O (M+H+) 616.2, found 616.2; RT 2.28 min. (4.5 min) (C18, 10-100%, water (0.05 % TFA)/ACN
222		HPLC-MS calculated for C30H30F3N7O2 (M+H+) 578.2, found 578.3; RT 2.10 min. (4.5 min) (C18, 10-100%, water (0.05 % TFA)/ACN
223		HPLC-MS calculated for C30H27F6N7O (M+H+) 616.2, found 616.3; RT 2.26 min. (4.5 min) (C18, 10-100%, water (0.05 % TFA)/ACN
224		HPLC-MS calculated for C30H30F3N7O2 (M+H+) 578.2, found 578.2; RT 2.10 min. (4.5 min) (C18, 10-100%, water (0.05 % TFA)/ACN
225		HPLC-MS calculated for C31H28F6N6O3S (M+H+) 679.2, found 679.2; RT 2.48 min. (4.5 min) (C18, 10-100%, water (0.05 % TFA)/ACN
226		HPLC-MS calculated for C31H28F6N6O3S (M+H+) 679.2, found 679.2; RT 2.48 min. (4.5 min) (C18, 10-100%, water (0.05 % TFA)/ACN

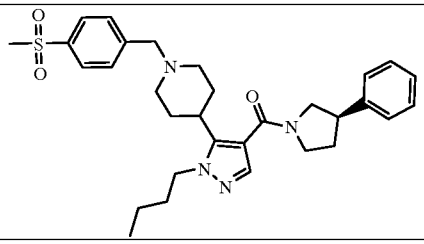
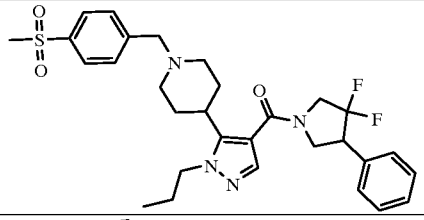
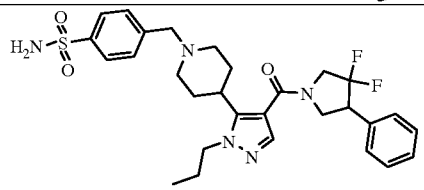
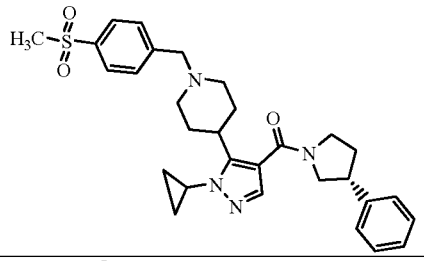
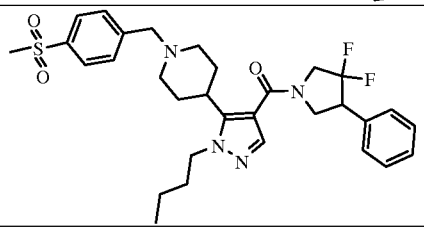
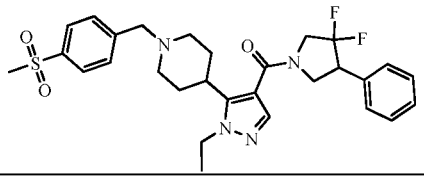
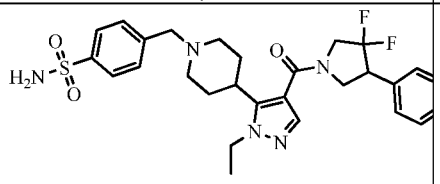
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDCl3 or acetone-d6) and/or MS (m/z)
227		HPLC-MS calculated for C32H33F2N5O3S (M+H+) 606.2, found 606.7; RT 1.08 min. (2 min) (C18, 10-100%, water (0.05 % TFA)/ACN
228		HPLC-MS calculated for C33H34F2N4O3S (M+H+) 605.2, found 604.7; RT 1.12 min. (2 min) (C18, 10-100%, water (0.05 % TFA)/ACN
229		HPLC-MS calculated for C32H33F2N5O3S (M+H+) 606.2, found 606.7; RT 0.73 min. (2 min) (C18, 30-100%, water (0.05 % TFA)/ACN
230		HPLC-MS calculated for C32H33F2N5O3S (M+H+) 606.2, found 606.7; RT 0.73 min. (2 min) (C18, 30-100%, water (0.05 % TFA)/ACN
231		HPLC-MS calculated for C33H34F2N4O3S (M+H+) 605.2, found 604.7; RT 0.72 min. (2 min) (C18, 30-100%, water (0.05 % TFA)/ACN
232		HPLC-MS calculated for C33H34F2N4O3S (M+H+) 605.2, found 604.7; RT 0.72 min. (2 min) (C18, 30-100%, water (0.05 % TFA)/ACN
233		HPLC-MS calculated for C32H31F4N5O3S (M+H+) 642.2, found 641.6; RT 0.84 min. (2 min) (C18, 30-100%, water (0.05 % TFA)/ACN

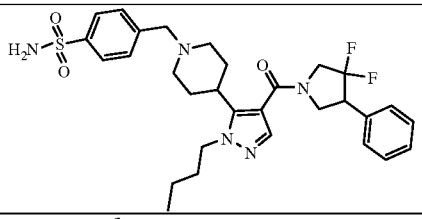
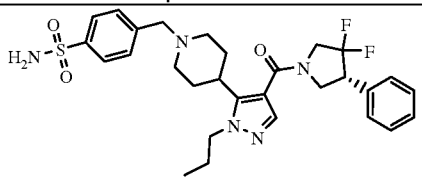
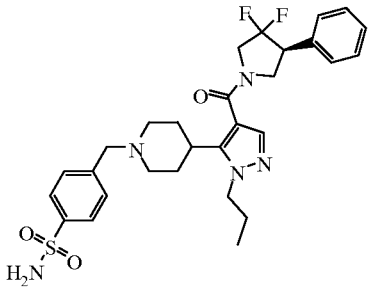
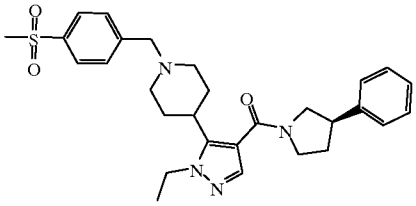
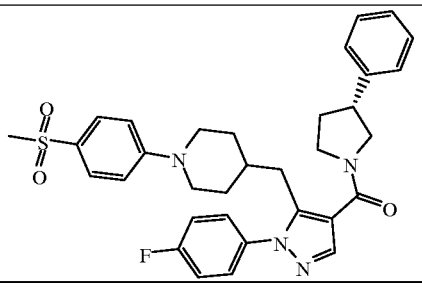
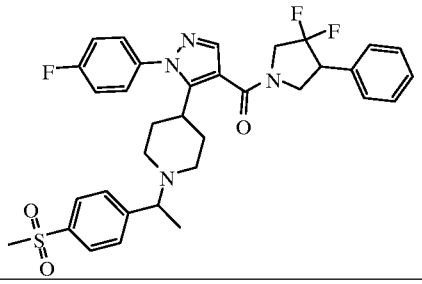
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDCl3 or acetone-d6) and/or MS (m/z)
234		HPLC-MS calculated for C33H32F4N4O3S (M+H+) 641.2, found 640.6; RT 0.76 min. (2 min) (C18, 30-100%, water (0.05 % TFA)/ACN
235		HPLC-MS calculated for C35H36F3N4O5S(M+H+) 681.24, found 681.23; RT 1.94 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
236		HPLC-MS calculated for C32H31F4N5O3S (M+H+) 642.2, found 642.2; RT 0.72 min. (2 min) (C18, 30-100%, water (0.05 % TFA)/ACN
237		HPLC-MS calculated for C32H31F4N5O3S (M+H+) 642.2, found 642.2; RT 0.72 min. (2 min) (C18, 30-100%, water (0.05 % TFA)/ACN
238		HPLC-MS calculated for C33H32F4N4O3S (M+H+) 641.2, found 641.2; RT 0.76 min. (2 min) (C18, 30-100%, water (0.05 % TFA)/ACN
239		HPLC-MS calculated for C33H32F4N4O3S (M+H+) 641.2, found 641.2; RT 0.76 min. (2 min) (C18, 30-100%, water (0.05 % TFA)/ACN
240		HPLC-MS calculated for C30H31F2N7O3S (M+H+) 608.2, found 607.7; RT 0.99 min. (2 min) (C18, 10-100%, water (0.05 % TFA)/ACN

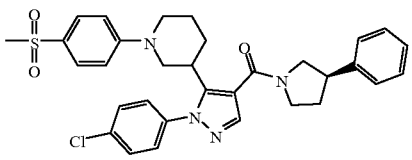
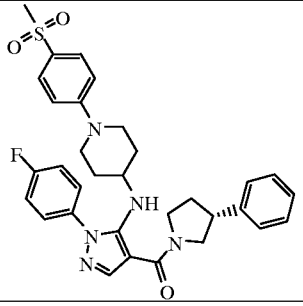
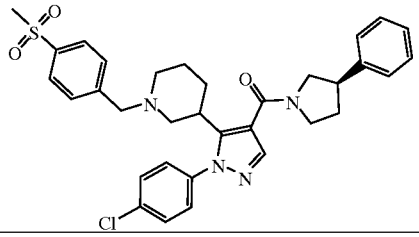
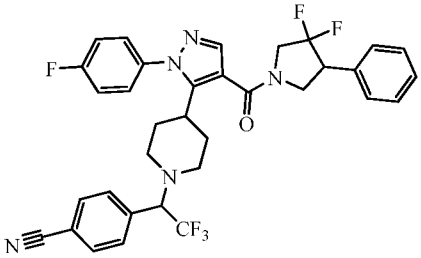
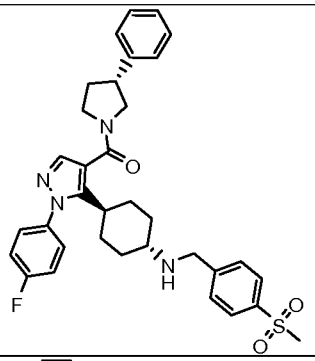
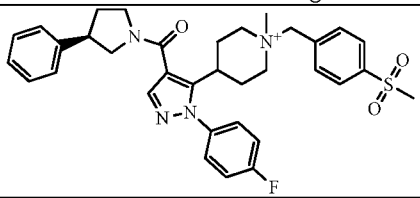
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDCl3 or acetone-d6) and/or MS (m/z)
241		HPLC-MS calculated for C30H29F4N7O3S (M+H+) 644.2, found 644.2; RT 0.76 min. (2 min) (C18, 20-100%, water (0.05 % TFA)/ACN
242		HPLC-MS calculated for C31H30F4N6O3S (M+H+) 643.2, found 643.2; RT 0.77 min. (2 min) (C18, 20-100%, water (0.05 % TFA)/ACN
243		HPLC-MS calculated for C33H33F4N4O3S (M+H+) 641.22, found 641.22; RT 1.69 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
244		HPLC-MS calculated for C31H32F2N6O3S (M+H+) 607.2, found 606.7; RT 1.04 min. (2 min) (C18, 10-100%, water (0.05 % TFA)/ACN
245		HPLC-MS calculated for C30H31F2N7O3S (M+H+) 608.2, found 608.2; RT 0.88 min. (2 min) (C18, 10-100%, water (0.05 % TFA)/ACN
246		HPLC-MS calculated for C30H31F2N7O3S (M+H+) 608.2, found 608.2; RT 0.88 min. (2 min) (C18, 10-100%, water (0.05 % TFA)/ACN
247		HPLC-MS calculated for C31H32F2N6O3S (M+H+) 607.2, found 607.2; RT 0.91 min. (2 min) (C18, 10-100%, water (0.05 % TFA)/ACN

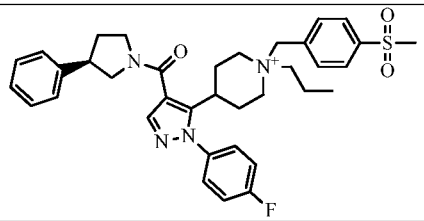
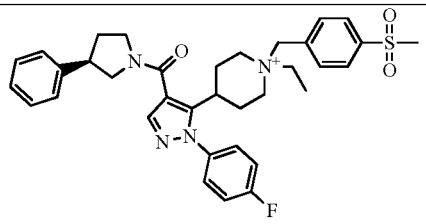
Example No.	Structure	Physical Data 1H NMR 400 MHz (CDCl3 or acetone-d6) and/or MS (m/z)
248		HPLC-MS calculated for C31H32F2N6O3S (M+H+) 607.2, found 607.2; RT 0.91 min. (2 min) (C18, 10-100%, water (0.05 % TFA)/ACN
249		HPLC-MS calculated for C30H29F4N7O3S (M+H+) 644.2, found 644.2; RT 0.93 min. (2 min) (C18, 10-100%, water (0.05 % TFA)/ACN
250		HPLC-MS calculated for C31H30F4N6O3S (M+H+) 643.2, found 643.2; RT 0.77 min. (2 min) (C18, 10-100%, water (0.05 % TFA)/ACN
251		HPLC-MS calculated for C32H31F4N5O3S (M+H+) 643.2, found 643.2; RT 0.77 min. (2 min) (C18, 20-100%, water (0.05 % TFA)/ACN
252		HPLC-MS calculated for C34H33F6N4O3S (M+H+) 691.22, found 691.21; RT 1.91 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
253		HPLC-MS calculated for C34H33F3N5O3S (M+H+) 648.23, found 648.22; RT 1.64 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
254		HPLC-MS calculated for C32H31F4N5O3S (M+H+) 643.2, found 643.2; RT 0.98 min. (2 min) (C18, 10-100%, water (0.05 % TFA)/ACN

Example No.	Structure	Physical Data 1H NMR 400 MHz (CDCl3 or acetone-d6) and/or MS (m/z)
255		HPLC-MS calculated for C33H33F4N4O3S (M+H+) 641.22, found 641.22; RT 1.71 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
256		HPLC-MS calculated for C33H31D2F3N4O3S (M+H+) 624.2, found 625.3; RT 2.37 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
257		HPLC-MS calculated for C32H31F4N5O3S (M+H+) 641.7, found 641.7; RT 1.6 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
258		HPLC-MS calculated for C33H30D2F4N4O3S (M+H+) 642.2, found 643.3; RT 2.17min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
259		HPLC-MS calculated for C28H34N4O3S (M+H+) 507.2, found 507.3; RT 2.209 min. (4.5 min) (C18, 10-100%, water (0.05 % TFA)/ACN
260		HPLC-MS calculated for C30H36F3N4O3S (M+H+) 589.25, found 589.24; RT 1.52 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
261		HPLC-MS calculated for C30H39N4O3S (M+H+) 535.27, found 535.27; RT 1.48 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN

Example No.	Structure	Physical Data 1H NMR 400 MHz (CDCl3 or acetone-d6) and/or MS (m/z)
262		HPLC-MS calculated for C31H41N4O3S (M+H+) 549.29, found 549.29; RT 1.66 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
263		HPLC-MS calculated for C30H37F2N4O3S (M+H+) 571.26, found 571.25; RT 1.58 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
264		HPLC-MS calculated for C29H36F2N5O3S (M+H+) 572.25, found 572.25; RT 1.51 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
265		HPLC-MS calculated for C30H37N4O3S (M+H+) 533.26, found 533.25; RT 1.48 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
266		HPLC-MS calculated for C31H39F2N4O3S (M+H+) 585.27, found 585.27; RT 1.67 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
267		HPLC-MS calculated for C29H35F2N4O3S (M+H+) 557.24, found 585.24; RT 1.49 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
268		HPLC-MS calculated for C29H36F2N5O3S (M+H+) 572.25, found 572.25; RT 1.54 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN

Example No.	Structure	Physical Data 1H NMR 400 MHz (CDCl3 or acetone-d6) and/or MS (m/z)
269		HPLC-MS calculated for C30H38F2N5O3S (M+H+) 586.27, found 586.26; RT 1.61 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
270		HPLC-MS calculated for C29H36F2N5O3S (M+H+) 572.25, found 572.25; RT 1.55 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
271		HPLC-MS calculated for C29H36F2N5O3S (M+H+) 572.25, found 572.25; RT 1.57 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
272		HPLC-MS calculated forC29H37N4O3S (M+H+) 521.26, found 521.25; RT 1.43 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
273		HPLC-MS calculated for C33H35FN4O3S (M+H+) 586.2, found 587.3; RT 2.55 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
274		HPLC-MS calculated for C34H36F3N4O3S (M+H+) 637.25, found 637.24; RT 1.65 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN

Example No.	Structure	Physical Data 1H NMR 400 MHz (CDCl3 or acetone-d6) and/or MS (m/z)
275		HPLC-MS calculated for C32H33ClN4O3S (M+H+) 588.2, found 589.2; RT 2.71min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
276		HPLC-MS calculated for C32H34FN5O3S (M+H+) 587.2, found 588.2; RT 2.72 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
277		HPLC-MS calculated for C33H35ClN4O3S (M+H+) 602.2, found 603.2; RT 2.12 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
278		HPLC-MS calculated for C34H30F6N5O (M+H+) 638.24, found 638.23; RT 2.22 min. (3.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
279		HPLC-MS calculated for C34H38FN4O3S (M+H+) 601.3, found 601.3; RT 2.36 min. (4.5 min) (C18, 10-90%, water (0.05 % TFA)/ACN
280		HPLC-MS calculated for C34H38FN4O3S+ (M+) 601.3, found 601.3; RT 2.09 min. (4.5 min) (C18, 10-100%, water (0.05 % TFA)/ACN

Example No.	Structure	Physical Data 1H NMR 400 MHz (CDC13 or acetone-d6) and/or MS (m/z)
281		HPLC-MS calculated for C36H42FN403S+ (M+) 629.3, found 629.3; RT 2.29 min. (4.5 min) (C18, 10-100%, water (0.05 % TFA)/ACN
282		HPLC-MS calculated for C35H40FN4O3S+ (M+) 615.3, found 615.3; RT 2.12 min. (4.5 min) (C18, 10-100%, water (0.05 % TFA)/ACN

Assays

[000203] Compounds were assessed for their ability to activate human TGR5 in cAMP HTRF assays (Cisbio). Briefly, Jurkat cells stably expressing either human TGR5 were seeded into 384-well plates (Greiner) in AIM V media supplemented with IBMX (ImM) followed by transfer of agonist compounds in DMSO by Pintool (GNF Systems). After a 30-60 minute incubation at 37 °C, cAMP HiRange HTRF reagents were added (Cisbio) and incubated for 1 hour followed by reading the emission at both 620nM and 665nM on the Envision (Perkin Elmer). Data is expressed as the emission ratio 665/620 and normalized to the DMSO alone control. Percent efficacy is calculated relative to a known TGR5 full agonist.

Certain Assay Results

[000204] Various compounds of Formula (I) and (II) in free form or in pharmaceutically acceptable salt form, exhibit pharmacological properties, for example, as indicated by the *in vitro* tests described in this application. The EC_{50} value in those experiments is given as that concentration of the test compound in question that provoke a response halfway between the baseline and maximum responses. In certain examples compounds of Formula (I) and Formula (II) have EC_{50} values from 1 nM to 5 μM. In other examples, compounds of Formula (I) and Formula (II) have EC_{50} values from 1 nM to 4 μM. In other examples, compounds of Formula (I) and Formula (II) have EC_{50} values from 1 nM to 3 μM. In other examples, compounds of Formula (I) and Formula (II) have EC_{50} values from 1 nM to 2 μM.

In other examples, compounds of Formula (I) and Formula (II) have $EC5_0$ values from 1 nM to 1 μM. In other examples, compounds of Formula (I) and Formula (II) have $EC5_0$ values from 1 nM to 500nM. In other examples, compounds of Formula (I) and Formula (II) have $EC5_0$ values from 1 nM to 400nM. In other examples, compounds of Formula (I) and Formula (II) have $EC5_0$ values from 1 nM to 300nM. In other examples, compounds of Formula (I) and Formula (II) have $EC5_0$ values from 1 nM to 200nM. In other examples, compounds of Formula (I) and Formula (II) have $EC5_0$ values from 1 nM to IOOηM. In other examples, compounds of Formula (I) and Formula (II) have $EC5_0$ values from 1 nM to 80nM. In other examples, compounds of Formula (I) and Formula (II) have $EC5_0$ values from 1 nM to 60nM. In other examples, compounds of Formula (I) and Formula (II) have $EC5_0$ values from 1 nM to 40nM. In other examples, compounds of Formula (I) and Formula (II) have $EC5_0$ values from 1 nM to 20nM. In other examples, compounds of Formula (I) and Formula (II) have $EC5_0$ values from 1 nM to IOηM. In other examples, compounds of Formula (I) and Formula (II) have $EC5_0$ values from 1 nM to 5nM.

[000205] By way of example only, the $EC5_0$ for TGR5 activation by certain compounds of Formula (I) and Formula (II) are listed in Table 4 below. The identifying number for each is the Ex. No. given for the compound in the Example above.

Table 4

Example	human TGR5 cAMP (μM)	Example	human TGR5 cAMP (μM)
1	0.167	142	0.261
2	0.645	143	0.256
3	0.124	144	0.264
4	1.813	145	0.313
5	1.270	146	0.321
6	0.072	147	0.329
7	0.187	148	0.353
8	3.230	149	0.401
9	3.092	150	0.477
10	1.545	151	0.460
11	1.329	152	0.574
12	3.800	153	0.678
13	0.079	154	0.806
14	2.669	155	0.848
15	0.181	156	1.430
16	0.28	157	1.986
17	1.586	158	2.132
18	1.600	159	3.700
19	1.656	160	3.920
20	3.820	161	4.690
21	5.847	162	4.825

22	1.359	163	0.047
23	0.166	164	0.028
24	1.71	165	0.151
25	0.192	166	0.006
26	0.975	167	0.013
27	0.293	168	0.171
28	0.438	169	0.042
29	0.085	170	0.868
30	0.413	171	0.041
31	0.315	172	0.188
32	1.328	173	0.009
33	0.518	174	0.647
34	0.315	175	1.279
35	0.354	176	0.599
36	0.983	177	0.215
37	0.677	178	0.346
38	0.810	179	0.683
39	2.144	180	0.119
40	4.342	181	0.965
41	0.677	182	1.914
42	0.37	183	0.858
43	1.960	184	0.010
44	1.311	185	1.362
45	0.861	186	3.390
46	0.260	187	0.025
47	1.499	188	0.213
48	0.087	189	0.008
49	0.164	190	0.01
50	0.165	191	0.014
51	1.600	192	0.036
52	0.128	193	0.015
53	1.313	194	0.017
54	0.357	195	0.34
55	0.113	196	0.865
56	0.084	197	0.141
57		198	0.04
58	0.033	199	0.383
59	0.045	200	0.08
60	1.502	201	0.039
61	0.39	202	0.657
62	0.013	203	0.605
63	0.481	204	0.108
64	2.28	205	0.129
65	0.011	206	0.493
66	2.968	207	0.034
67	0.445	208	0.034
68	0.316	209	0.024
69	0.023	210	0.267
70	0.013	211	1.006
71	0.085	212	0.891
72	0.083	213	0.261

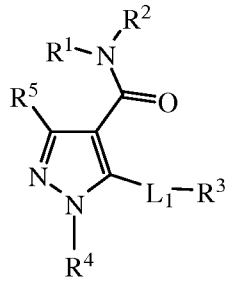
73	0.198	214	0.132
74	0.003	215	0.114
75	0.041	216	0.165
76	0.296	217	0.734
77	0.191	218	0.009
78	0.031	219	0.252
79	0.266	220	0.039
80	0.091	221	0.153
81	1.358	222	0.567
82	0.005	223	0.17
83	0.01	224	0.246
84	0.01	225	0.225
85	0.030	226	0.77
86	0.075	227	0.014
87	0.361	228	0.011
88	0.443	229	0.009
89	0.460	230	0.093
90	0.533	231	0.007
91	0.013	232	0.055
92	0.081	233	0.04
93	0.023	234	0.026
94	0.063	235	0.329
95	1.390	236	0.02
96	0.188	237	0.534
97	2.358	238	0.011
98	1.589	239	0.437
99	0.004	240	0.244
100	0.007	241	0.477
101	0.009	242	0.199
102	0.01	243	0.02
103	0.012	244	0.113
104	0.011	245	0.131
105	0.013	246	0.934
106	0.011	247	0.091
107	0.013	248	0.514
108	0.014	249	0.152
109	0.014	250	0.092
110	0.017	251	0.125
111	0.018	252	0.319
112	0.018	253	0.298
113	0.023	254	0.051
114	0.023	255	0.01
115	0.033	256	0.014
116	0.033	257	0.174
117	0.036	258	0.011
118	0.036	259	0.465
119	0.042	260	0.083
120	0.044	261	0.041
121	0.046	262	0.03
122	0.057	263	0.071
123	0.069	264	0.289

124	0.069	265	0.127
125	0.069	266	0.11
126	0.078	267	0.307
127	0.069	268	0.304
128	0.098	269	0.092
129	0.101	270	0.091
130	0.111	271	4.35
131	0.121	272	0.064
132	0.140	273	0.017
133	0.153	274	0.025
134	0.159	275	0.134
135	0.165	276	0.174
136	0.167	277	0.231
137	0.177	278	0.149
138	0.184	279	1.883
139	0.186	280	0.138
140	0.208	281	0.135
141	0.261	282	0.035

[000206] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference for all purposes.

WE CLAIM:

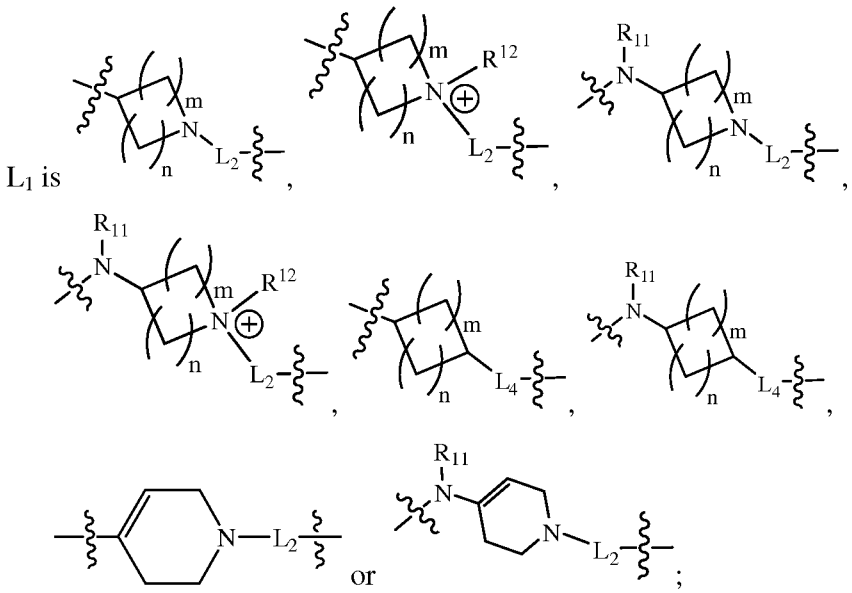
1. A compound having the structure of Formula **(I):**



(I)

wherein,

R^1 and R^2 are each independently selected from Ci-Cealkyl, and $_{C\ 2}$-C_6alkene, and taken together with the N atom to which they are attached form a 4 to 6 membered heterocycloalkyl ring containing a N heteroatom, a 9 to 14 membered fused bicyclic heterocycloalkyl ring containing a N heteroatom, or a 9 to 14 membered fused bicyclic heteroaryl containing an N heteroatom, wherein such heterocycloalkyl and fused bicyclic heteroaryl are each optionally substituted with 1 to 5 substituents independently selected from halogen, deuterium, Ci-Cealkyl, Ci-Cehaloalkyl, -CN, R^9, -OR^9, phenyl, phenoxy, Cioaryl and C_{14}aryl, wherein such phenyl, phenoxy, Cioaryl and C_{14}aryl are each optionally substituted with 1 to 5 substituents independently selected from halogen, deuterium and -OR^9;

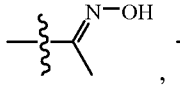
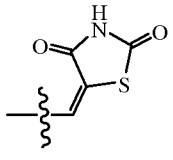
L_1 is 

;

L_2 is selected from -C(O)-, -C(0)0-, $-(CH_2)_qC(0)0-$, $-S(0)_2-$, C_1-C_6alkylene, phenylene, Cioarylene, C_{14}arylene, a 5, 6, 9, 10 or 14 membered heteroarylene containing 1 to 2 heteroatoms independently selected from N, O and S, or a bond, wherein the Ci-Cealkylene ,arylene and heteroarylene of L_2 are optionally substituted with 1 to 3 substituents independently selected from deuterium, R^9 and $-C(0)OR^9$;

L_3 is C_1-C_6alkylene optionally substituted with 1 to 3 substituents independently selected deuterium, R^9 and $-C(0)OR^9$, or Ci-Cealkenylene optionally substituted with 1 to 3 substituents independently selected from deuterium, R^9 and $-C(0)OR^9$;

L_4 is selected from a $-NR^9-$, $-NR^9C(0)0-$, $-NR^9(CH_2)_q-$, $-C(0)NR^9-$, $-S(0)_2-$, -0-, Ci-C_6alkylene, phenylene, Cioarylene, C_{14}arylene, a 5, 6, 9, 10 or 14 membered heteroarylene containing 1 to 2 heteroatoms independently selected from N, O and S, wherein the Ci-Cealkylene, arylene and heteroarylene of L_4 are optionally substituted with 1 to 3 substituents independently selected from deuterium, R^9 and $-C(0)OR^9$;

R^3 is selected from Ci-Cealkyl, Ci-Cehaloalkyl, C_3-Cscycloalkyl, $-L_3R^6$, phenyl, Cioaryl, C_{14}aryl, a 5, 6, 9, 10 or 14 membered heteroaryl containing 1 to 3 N heteroatoms and optionally one heteroatom selected from O and S, and a 4 to 7 membered heterocycloalkyl ring containing 1 to 2 heteroatoms independently selected from N, O and S, wherein the Ci-Cealkyl, aryl, heterocycloalkyl, C_3-Cscycloalkyl and heteroaryl groups of R^3 are each optionally substituted with 1 to 3 substituents independently selected from halogen, R^9, R^6, $-OR^9$, $-N(R^9)_2$, $-C(0)N(R^9)_2$, $-C(0)NR^9OH$, $-C(0)OR^9$, $-C(0)OL_3R^6$, $-L_3C(0)OR^9$, $-C(0)R^9$, -CN, $-S(0)_2R^9$, $-S(0)_2N(R^9)_2$, $-S(0)_2NR^9C(0)R^9$, $-S(0)_2L_3C(0)OR^9$, $-OS(0)_2N(R^9)_2$, $-S(0)_2NR^9OH$, $-OL_3C(0)OR^9$, $-C(0)NR^9L_3C(0)OR^9$, $-L_3R^6$  ,  and a 5 membered heteroaryl containing 1 to 4 N heteroatoms and optionally one heteroatom selected from O and S;

R^4 is selected from H, Ci-Cealkyl, phenyl, Cioaryl, C_{14}aryl, $_{C\ 3}$-Cscycloalkyl, 5-6 membered heteroaryl containing one or more N heteroatoms, wherein the C_1-C_6alkyl, aryl, heteroaryl and $_{C\ 3}$-Cscycloalkyl groups of R^4 are each optionally substituted with 1 to 3 substituents independently selected from halogen, -CN, R^9, and -OR^9;

R^5 is H, C_1-C_6alkyl or C_1-C_6haloalkyl.

R^6 is $_{C\ 3}$-Cscycloalkyl, phenyl, Cioaryl, C_{14}aryl, a 5, 6, 9, 10 or 14 membered heteroaryl containing 1 to 2 heteroatoms independently selected from N, O and S, a 4 to 7 membered heterocycloalkyl ring containing 1 to 2 heteroatoms independently selected from N, O and S, and a 9 to 14 membered fused bicyclic heterocycloalkyl ring containing containing 1 to 2 heteroatoms independently selected from N, O and S, each of which is optionally substituted with 1 to 5 substituents independently selected from halogen, deuterium, R^9, -OR^9, -CN and -C(0)OR^{9};

R^9 is H, Ci-C_6alkyl optionally substituted with 1 to 4 -OH groups or Cr Cehaloalkyl;

R^{11} is H or C_1-C_6alkyl;

R^{12} is Ci-C_4alkyl, -CH_2C(0)OH or -(CHR^{13})C(0)OH;

R^{13} is H or Ci-C_4alkyl;

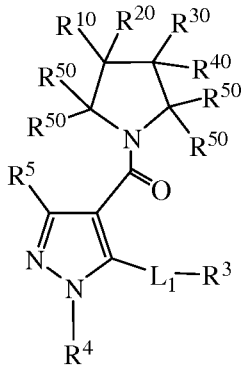
each m is independently 1, 2 or 3;

each n is independently 1, 2 or 3, and

each q is independently 1, 2, 3, 4, 5, or 6,

and pharmaceutically acceptable salts and enantiomers thereof.

2. The compound of claim 1, wherein the compound of Formula **(I)** is a compound having the structure of Formula **(II):**



(II)

wherein,

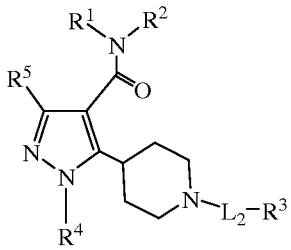
R^{10} and R^{20} are each independently selected from **H, -OR^9,** deuterium or halogen;

R^{30} is selected from phenyl, phenoxy, Cioaryl and C_{14}aryl, each of which is optionally substituted with 1 to 5 substituents independently selected from halogen, deuterium and **-OR^9;**

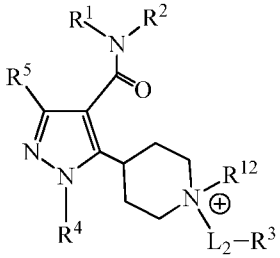
R^{40} is selected from **H,** deuterium, Ci-Cealkyl and Ci-Cehaloalkyl, and

each R^{50} is independently selected from **H** or deuterium.

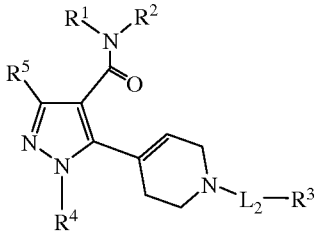
3. The compound of claim 1, wherein the compound of Formula **(I)** is a compound having the structure of Formula (III), Formula (IV) or Formula (V):



(HI)



(IV)

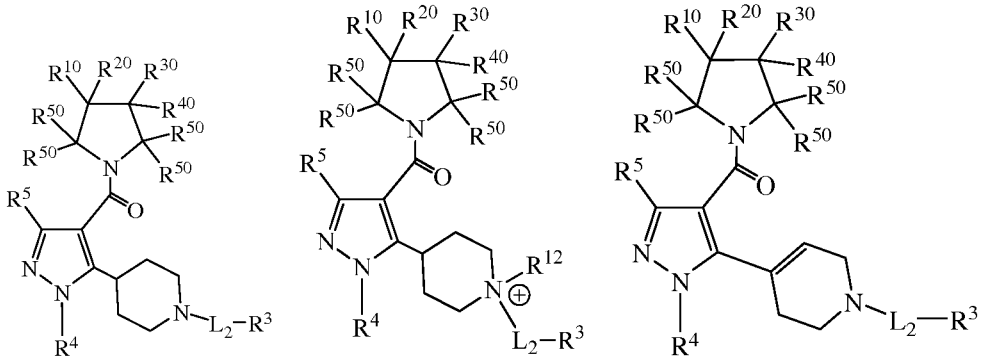


(V).

4. The compound of claim 1 or claim 3, wherein,

R^1 and **R^2** are each independently selected from Ci-Cealkyl, and C_{2}-C_6alkene, and taken together with the N atom to which they are attached form a 1,2,3,4-tetrahydroisoquinoline or an azetidine, each of which is optionally substituted with 1 to 3 substituents independently selected from halogen, deuterium,-CN, **R^9, -OR^9,** phenyl and phenoxy, wherein such phenyl and phenoxy are each optionally substituted with 1 to 5 substituents independently selected from halogen, deuterium and **-OR^9.**

5. The compound of claim 1 or claim 2, wherein the compound of Formula **(I)** or Formula **(II)** is a compound having the structure of Formula **(VI),** Formula **(VII)** or Formula **(VIII):**



(VI) (VII) (VIII).

6. The compound of claim 2 or claim 5, wherein R^{10} and R^{20} are each independently selected from H, deuterium or F.

7. The compound of any one of claims 2 or claim 5-6, wherein R^{40} is selected from H, deuterium, $-CH_3$ $-CF_3$ and $-CF_2CH_3$.

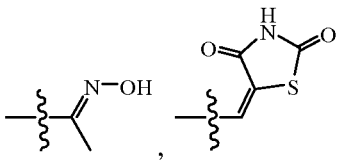
8. The compound of any one of claims 2 or claim 5-7, wherein R^{30} is selected from phenyl, phenoxy, Cioaryl and C_{14}aryl, each of which is optionally substituted with 1 to 5 substituents independently selected from F, deuterium and methoxy.

9. The compound of any one of claims 1 to 8, wherein,

R^4 is selected from H, methyl, ethyl, propyl, butyl, phenyl, pyridinyl, pyrimidinyl, and cyclohexyl, each of which is optionally substituted with 1 to 3 substituents independently selected from -F, -Br, -CI, -CN, R^9, and $-OR^9$.

10. The compound of any one of claims 1 to 9, wherein,

R^3 is selected from $-CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2C(CH_3)_3$, $-CH_2CH_2C(CH_3)_3$, $-CF_3$, cyclopropyl, cyclohexyl, phenyl, tetrahydro-2H-pyranyl, oxazolyl, oxadiazolyl, pyrazolyl, isoxazolyl, lH-benzo[d][l,2,3]triazolyl, piperidinyl, pyridinyl, pyrimidinyl, benzthiazolyl and tetrazolyl, each of which is each optionally substituted with 1 to 3 substituents independently selected from -F, -Br, -CI, R^9, $-OR^9$, $-N(R^9)_2$, $-C(0)N(R^9)_2$, $-C(0)NR^9OH$, $-C(0)OR^9$, $-C(0)OL_3R^6$, $-L_3C(0)OR^9$, $-C(0)R^9$, -CN, $-S(0)_2R^9$, $-S(0)_2N(R^9)_2$, $-S(0)_2NR^9C(0)R^9$, $-S(0)_2L_3C(0)OR^9$, $-OS(0)_2N(R^9)_2$, $-S(0)_2NR^9OH$, $-OL_3C(0)OR^9$, $-C(0)NR^9L_3C(0)OR^9$,



, tetrazolyl, pyrazolyl and $-L_3R^6$.

11. The compound of any one of claims 1 to 10, wherein,

R^9 is H, methyl, ethyl, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CF_3$, propyl substituted with 1 to 2 -OH groups.

12. The compound of any one of claims 1 to 11, wherein R^5 is H or methyl.

13. The compound of any one of claims 1 to 12, wherein R^{12} is methyl, ethyl or n-propyl.

14. The compound of any one of claims 1 to 12, wherein R^{13} is H or methyl.

15. The compound of claim 1 or claim 2, selected from

tert-butyl 4-[l-(4-fluorophenyl)-4-[(3-phenylpyrrolidin-l-yl)carbonyl]-lH-pyrazol-5-yljpiperidine-1-carboxylate;

tert-butyl 4-[l-(4-bromophenyl)-4-[(3-phenylpyrrolidin-l-yl)carbonyl]-lH-pyrazol-5-yljpiperidine-1-carboxylate;

tert-butyl 4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yljcarbonyl}-1H-pyrazol-5-yl]piperidine-l-carboxylate;

tert-butyl 4-[l-(4-chlorophenyl)-4-{[3-(4-fluorophenyl)pyrrolidin-1-yljcarbonyl}-lH-pyrazol-5-yl]piperidine-l-carboxylate;

tert-butyl 4-[l-(4-chlorophenyl)-4-{[(3R)-3-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine-l-carboxylate;

tert-butyl 4-[l-(2,4-difluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yljcarbonyl}-1H-pyrazol-5-yl]piperidine-l-carboxylate;

tert-butyl 4-[l-(4-chloro-2-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine-l-carboxylate;

tert-butyl 4-[l-(4-fluorophenyl)-4-{[3-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine-l-carboxylate;

tert-butyl 4-[l-(4-methoxyphenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine-l-carboxylate;

tert-butyl 4-[l-(4-cyanophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yljcarbonyl}-1H-pyrazol-5-yl]piperidine-l-carboxylate;

tert-butyl 4-(4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-l-(pyrimidin-2-yl)-lH-pyrazol-5-yl)piperidine-l-carboxylate;

tert-butyl 4-[l-(2-chloro-4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine-l-carboxylate;

tert-butyl 4-[l-(4-fluorophenyl)-4-{[3-(2-fluorophenyl)pyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine-l-carboxylate;

tert-butyl 4-[l-(4-methylphenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine-l-carboxylate;

tert-butyl 4-[l-(4-chlorophenyl)-4-[(3-methyl-3-phenylpyrrolidin-l-yl)carbonyl]-lH-pyrazol-5-yl]piperidine-l-carboxylate;

tert-butyl 4-(l-phenyl-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl)piperidine- 1-carboxylate;

tert-butyl (3S)-3-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]pyrrolidine- 1-carboxylate;

tert-butyl (3R)-3-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine- 1-carboxylate;

tert-butyl (3R)-3-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]pyrrolidine- 1-carboxylate;

tert-butyl 3-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]pyrrolidine- 1-carboxylate;

tert-butyl 3-[l-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5-yl]azetidine- 1-carboxylate;

tert-butyl 3-[l-(4-fluorophenyl)-4-[(3-phenylpyrrolidin-l-yl)carbonyl]-lH-pyrazol-5-yl]piperidine- 1-carboxylate;

1-methylcyclopropyl 4-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine- 1-carboxylate;

1-{4-[1-(4-chlorophenyl)-4- [(3-phenylpyrrolidin- 1-yl)carbonyl]-lH-pyrazol-5 -yljpiperidin- 1-yl }-3,3-dimethylbutan- 1-one;

propan-2-yl 4-[l-(4-chlorophenyl)-4-[(3-phenylpyrrolidin-l-yl)carbonyl]-lH-pyrazol-5-yl]piperidine-l-carboxylate;

benzyl 4-[1-(4-chlorophenyl)-4- [(3-phenylpyrrolidin- 1-yl)carbonyl]- lH-pyrazol-5-yljpiperidine- 1-carboxylate;

propan-2-yl 4-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine-l-carboxylate;

tert-butyl 4-[l-(4-chlorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5-yl]- 1,2,3,6-tetrahydropyridine- 1-carboxylate;

benzyl 4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yljpiperidin- 1-yl }methyl)piperidine- 1-carboxylate;

1-benzoyl-4-[1-(4-chlorophenyl)-4-[(3-phenylpyrrolidin-1-yl)carbonyl]-1H-pyrazol-5-yl]piperidine;

4-[1-(4-chlorophenyl)-4-[(3-phenylpyrrolidin-1-yl)carbonyl]-1H-pyrazol-5-yl]-1-cyclohexanecarbonylpiperidine;

1-{4-[1-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yl]carbonyl}-1H-pyrazol-5-yl]piperidin-1-yl}-3,3-dimethylbutan-1-one;

1-benzoyl-4-[1-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yl]carbonyl}-1H-pyrazol-5-yl]piperidine;

4-[1-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yl]carbonyl}-1H-pyrazol-5-yl]-1-cyclohexanecarbonylpiperidine;

4-[1-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yl]carbonyl}-1H-pyrazol-5-yl]-1-[(2-fluorophenyl)carbonyl]piperidine;

4-[1-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yl]carbonyl}-1H-pyrazol-5-yl]-1-[(3-fluorophenyl)carbonyl]piperidine;

4-[1-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yl]carbonyl}-1H-pyrazol-5-yl]-1-[(4-fluorophenyl)carbonyl]piperidine;

4-[1-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yl]carbonyl}-1H-pyrazol-5-yl]-1-[(4-chlorophenyl)carbonyl]piperidine;

4-[1-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yl]carbonyl}-1H-pyrazol-5-yl]-1-[(oxan-4-yl)carbonyl]piperidine;

4-[1-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yl]carbonyl}-1H-pyrazol-5-yl]-1-[(2,5-dimethyl-1,3-oxazol-4-yl)carbonyl]piperidine;

4-[1-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yl]carbonyl}-1H-pyrazol-5-yl]-1-[(3-methoxyphenyl)carbonyl]piperidine;

4-[1-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yl]carbonyl}-1H-pyrazol-5-yl]-1-[(4-methoxyphenyl)carbonyl]piperidine;

4-[1-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yl]carbonyl}-1H-pyrazol-5-yl]-1-[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]piperidine;

4-[1-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yl]carbonyl}-1H-pyrazol-5-yl]-1-{[1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl]carbonyl}piperidine;

4-[1-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yl]carbonyl}-1H-pyrazol-5-yl]-1-[(1,5-dimethyl-1H-pyrazol-3-yl)carbonyl]piperidine;

5-({4-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-l-yl}carbonyl)-2-methylpyridine;

(2R)-2-amino-l-{4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-l-yl}-4,4-dimethylpentan-l-one;

4-(methoxycarbonyl)phenyl 4-[l-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin-1-yl]carbonyl}-lH-pyrazol-5-yl]piperidine-l-carboxylate;

4-fluorophenyl 4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine-l-carboxylate;

phenyl 4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine-l-carboxylate;

methyl 4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine-l-carboxylate;

l-(3,5-dimethyl-l,2-oxazole-4-sulfonyl)-4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine;

4-[1-(4-chlorophenyl)-4-[(3-phenylpyrrolidin-1-yl)carbonyl]-1H-pyrazol-5-yl]-1-methanesulfonylpiperidine;

l-(benzenesulfonyl)-4-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine;

tert-butyl 4-[l-(4-chlorophenyl)-4- {[(3R)-3-phenylpyrrolidin-1-yljcarbonyl }-1H-pyrazol-5-yl]piperidine-l-carboxylate;

1-benzyl-4-[1-(4-chlorophenyl)-4-[(3-phenylpyrrolidin-1-yl)carbonyl]-1H-pyrazol-5-yl]piperidine;

4-((4-(4-(3,3-difluoro-4-phenylpyrrolidine-1-carbonyl)-1-(4-fluorophenyl)-1H-pyrazol-5-yl)piperidin-l-yl)methyl)benzenesulfonamide;

4-[1-(4-chlorophenyl)-4- {[(3R)-3-phenylpyrrolidin-1-yljcarbonyl }-lH-pyrazol-5-yl]-1-[(4-fluorophenyl)methyl]piperidine;

4-[1-(4-chlorophenyl)-4- {[(3R)-3-phenylpyrrolidin-1-yljcarbonyl }-lH-pyrazol-5-yl]-1-[(2-fluorophenyl)methyl]piperidine;

4-({4-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-1-yl }methyl)benzoic acid;

4-[1-(4-chlorophenyl)-4-[(3-phenylpyrrolidin-1-yl)carbonyl]-1H-pyrazol-5-yl]-1-cyclohexylpiperidine;

4-({4-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-1-yl}methyl)benzonitrile;

4-[1-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yljcarbonyl}-lH-pyrazol-5-yl]-1-(oxan-4-ylmethyl)piperidine;

3-({4-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-1-yl}methyl)benzoic acid;

l-benzyl-4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yljpiperidine;

4-{[4-(l-cyclohexyl-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl)piperidin-1-yl]methyl}benzonitrile;

l-benzyl-4-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yljpiperidine;

4-({4-[l-(4-chlorophenyl)-4-[(l,2,3,4-tetrahydroisoquinolin-2-yl)carbonyl]-lH-pyrazol-5-yljpiperidin-1-yl}methyl)benzonitrile;

4-({4-[1-(4-chloro-2-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yljcarbonyl}-1H-pyrazol-5-yljpiperidin-1-yl}methyl)benzonitrile;

4-({4-[l-(2,4-difluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yljpiperidin-1-yl}methyl)benzonitrile;

methyl 2-{4-[1-(2,4-difluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yljcarbonyl}-lH-pyrazol-5-yl]piperidin-l-yl}-2-phenylacetate;

4-({4-[l-(4-fluorophenyl)-4-{[3-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yljpiperidin-1-yl}methyl)benzonitrile;

5-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-1-yl}methyl)-1-methyl-1H-1,2,3-benzotriazole;

4-[1-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yljcarbonyl}-1H-pyrazol-5-yl]-l-[(4-methanesulfonylphenyl)methyl]piperidine;

4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-1-yl}methyl)benzonitrile;

4-({4-[1-(4-fluorophenyl)-4-{[(3S)-3-(4-fluorophenyl)pyrrolidin-1-yl]carbonyl}-1H-pyrazol-5-yl]piperidin-1-yl}methyl)benzonitrile;

l-[(4-methanesulfonylphenyl)methyl]-4-[l-(4-methoxyphenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine;

4-(5-{l-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl}-4-{[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol- 1-yl)benzonitrile;

2-(5-{l-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl}-4-{[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol- 1-yl)pyrimidine;

5-chloro-2-(5-{l-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl}-4-{[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol- 1-yl)pyridine;

l-[(4-methanesulfonylphenyl)methyl]-4-(4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl)piperidine;

4-(4-{[(3S,4S)-3-fluoro-4-phenylpyrrolidin-l-yl]carbonyl}-l-(4-fluorophenyl)-lH-pyrazol-5-yl)-l-[(4-methanesulfonylphenyl)methyl]piperidine;

4-(4-{[(4R)-2,2-dihydrogenio-4-(2, 3,4,5,6-pentahydrogeniophenyl)pyrrolidin-l-yljcarbonyl }-1-(4-fluorophenyl)- lH-pyrazol-5 -yl)- 1-[(4-methanesulfonylphenyl)methyl]piperidine;

4-[l-(4-fluorophenyl)-4-{[(3R)-3-(2,3,4,5,6-pentahydrogeniophenyl)pyrrolidin-l-yljcarbonyl }-1H-pyrazol-5-yl]-1-[(4-methanesulfonylphenyl)methyl]piperidine;

4-({4-[1-(4-fluorophenyl)-4- {[(3R)-3-(3-fluorophenyl)pyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5-yl]piperidin- 1-yl }methyl)benzonitrile;

4-[l-(4-fluorophenyl)-4-{[(3S)-3-phenyl-3-(trifluoromethyl)pyrrolidin-l-yl]carbonyl }-1H-pyrazol-5-yl]-1-[(4-methanesulfonylphenyl)methyl]piperidine;

4-[1-(4-fluorophenyl)-4- {[3-phenyl-3-(trifluoromethyl)pyrrolidin- 1-yl]carbonyl }-lH-pyrazol-5-yl]-l-[(4-methanesulfonylphenyl)methyl]piperidine;

4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenyl-3-(trifluoromethyl)pyrrolidin-l-yl]carbonyl }-1H-pyrazol-5-yl]-1-[(4-methanesulfonylphenyl)methyl]piperidine;

4-({4-[1-(4-fluorophenyl)-4- {[(3R)-3-(2-methoxyphenyl)pyrrolidin- 1-yl]carbonyl }-1H-pyrazol- 5-yl]piperidin- 1-yl }methyl)benzonitrile ;

4-[1-(4-fluorophenyl)-4-[(3-phenoxypyrrolidin- 1-yl)carbonyl]-1H-pyrazol-5-yl]-1-[(4-methanesulfonylphenyl)methyl]piperidine;

4-{[4-(l-phenyl-4- {[(3R)-3-phenylpyrrolidin- l-yl]carbonyl} -lH-pyrazol-5-yl)piperidin- 1-yl]methyl }benzonitrile ;

4-[1-(4-chlorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yl]carbonyl }-lH-pyrazol-5-yl]-1-(1-phenylethyl)piperidine ;

4-[1-(4-chlorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yl]carbonyl }-lH-pyrazol-5-yl]-1-[(3,4-difluorophenyl)methyl]piperidine;

4-[1-(4-chlorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-lH-pyrazol-5-yl]-l-{ [4-(trifluoromethyl)phenyl]methyl }piperidine;

4-({4-[1-(4-fluorophenyl)-4- {[(3R)-3-(4-methoxyphenyl)pyrrolidin- 1-yljcarbonyl }-1H-pyrazol- 5-yljpiperidin- 1-yl }methyl)benzonitrile ;

4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5-yl]-1-(2,2,2-trifluoroethyl)piperidine;

2-[4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yljpiperidin- 1-yl }methyl)phenoxy] acetic acid;

(3S,4R)- 1-{[1-(4-fluorophenyl)-5-{1-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl }-lH-pyrazol-4-yl]carbonyl }-4-phenylpyrrolidin-3-ol;

2-chloro-5-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yljpiperidin- 1-yl }methyl)pyridine ;

4-({4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5-yl]piperidin- 1-yl }methyl)benzonitrile;

5-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-l-yl}methyl)pyridine-2-carbonitrile;

5-fluoro-2-(5-{l-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl}-4-{[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol- 1-yl)pyridine;

3-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin- 1-yl }methyl)pyridine;

3-fluoro-4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yljpiperidin- 1-yl }methyl)benzonitrile;

4-[l-(4-fluorophenyl)-3-methyl-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]-1-[(4-methanesulfonylphenyl)methyl]piperidine;

3-bromo-4-({4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5-yl]piperidin- 1-yl }methyl)benzonitrile;

5-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-l-yl}methyl)-2-methanesulfonylpyridine;

4-({4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5-yl]piperidin- 1-yl }methyl)benzene- 1-sulfonamide;

4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5-yl]-l-[(4-fluorophenyl)methyl]piperidine;

2-fluoro-4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yljpiperidin- 1-yl }methyl)benzonitrile;

4-({4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5-yl]piperidin- 1-yl }methyl)pyridine;

[4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-l-yl}methyl)phenyl] sulfamate;

4-({4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5-yl]piperidin- 1-yl }methyl)-N-methylbenzene- 1-sulfonamide;

4-(l-{4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yljpiperidin- 1-yl }ethyl)benzonitrile;

[5-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-l-yl}methyl)pyridin-2-yl]methanol;

1-[(3,4-difluorophenyl)methyl] -4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin-1-yljcarbonyl }-1H-pyrazol-5-yljpiperidine;

methyl 5-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yljpiperidin- 1-yl }methyl)pyridine-2-carboxylate ;

1-[(2,4-difluorophenyl)methyl] -4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin-1-yljcarbonyl }-1H-pyrazol-5-yljpiperidine;

4-({4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5-yl]piperidin- 1-yl }methyl)-N-hydroxybenzene- 1-sulfonamide;

2-fluoro-4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yljpiperidin- 1-yl }methyl)benzamide;

l-[(2-chloro-4-fluorophenyl)methyl]-4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine;

S-[4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yljpiperidin- 1-yl }methyl)phenyl]-2-hydroxypropane- 1-sulfonamido;

4-({4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5-yl]piperidin- 1-yl }methyl)benzamide;

1-[(4-fluoro-2-methoxyphenyl)methyl]-4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine;

2-fluoro-5-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yljpiperidin- 1-yl }methyl)benzonitrile;

4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5-yl]-l-[(3-fluorophenyl)methyl]piperidine;

l-[(4-fluoro-3-methoxyphenyl)methyl]-4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine;

(E)-N-{l-[4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-1H-pyrazol- 5-yljpiperidin- 1-yl }methyl)phenyl] ethylidene }hydroxylamine ;

4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5-yl]-1-[(2,3,4-trifluorophenyl)methyl]piperidine;

2-chloro-4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin- 1-yl }methyl)pyridine ;

(5E)-5-{[4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin- 1-yl }methyl)phenyl]methylidene }-1,3-thiazolidine-2,4-dione ;

2-({4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5-yl]piperidin- 1-yl }methyl)pyridine;

tert-butyl 2-{4-[l-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5-yl]piperidin- 1-yl }acetate;

1-{[3-fluoro-4-(2H-l,2,3,4-tetrazol-5-yl)phenyl]methyl}-4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine;

N-(2,3-dihydroxypropyl)-4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl }-1H-pyrazol-5-yl]piperidin- 1-yl }methyl)benzamide;

2-chloro-4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin- 1-yl }methyl)pyrimidine ;

1-[4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin- 1-yl }methyl)phenyl]ethan- 1-one;

2-{[1-(4-fluorophenyl)-5 -{1-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl }-1H-pyrazol-4-yl]carbonyl }-1,2,3,4-tetrahydroisoquinoline;

4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5-yl]-l-[(4-methanesulfonylphenyl)methyl]- 1,2,3,6-tetrahydropyridine;

4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5-yl]-l-[(4-methylphenyl)methyl]piperidine;

tert-butyl 3-{[4-({4-[l-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5-yl]piperidin- 1-yl }methyl)phenyl]formamido }propanoate;

4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5-yl]-l-[2-(4-methanesulfonylphenyl)ethyl]piperidine;

4-[1-(4-fluorophenyl)-4- [(3-phenylazetidin- 1-yl)carbonyl]-1H-pyrazol-5-yl]-1-[(4-methanesulfonylphenyl)methyl]piperidine;

5-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-l-yl}methyl)pyridine-2-carboxylic acid;

3-{[4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yljpiperidin- 1-yl }methyl)phenyl]formamido }propanoic acid;

l-[(3-chloro-4-fluorophenyl)methyl]-4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine;

4-[l-(4-fluorophenyl)-3-methyl-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]-1-[(4-methanesulfonylphenyl)methyl] -1,2,3,6-tetrahydropyridine ;

4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5-yl]-l-{[4-(2H-l,2,3,4-tetrazol-5-yl)phenyl]methyl}piperidine;

1-(4-fluorophenyl)-5-{l-[(4-methanesulfonylphenyl)methyl]azetidin-3-yl}-4-[(3-methyl-3-phenylpyrrolidin- l-yl)carbonyl]- lH-pyrazole;

5-({4-[l-(4-fluorophenyl)-4-[(3-methyl-3-phenylpyrrolidin-l-yl)carbonyl]-lH-pyrazol-5-yl]piperidin- 1-yl }methyl)pyridine-2-carboxylic acid;

2-fluoro-5-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin- 1-yl }methyl)benzamide;

N-{[4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin- 1-yl }methyl)benzene] sulfonyl }acetamide;

l-[2-(2-benzyl-2H-l,2,3,4-tetrazol-5-yl)ethyl]-4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine;

4-({4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5-yl]- 1,2,3,6-tetrahydropyridin-l-yl}methyl)pyridine;

4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5-yl]-l-[(3-methylphenyl)methyl]piperidine;

4-({4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5-yl]piperidin-l-yl}methyl)-N-hydroxybenzamide;

4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5-yl]-l-[2-(4-fluorophenyl)ethyl]piperidine;

2-({4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5-yl]piperidin- 1-yl }methyl)- 1,3-benzothiazole;

l-(cyclopropylmethyl)-4- [1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yl]carbonyl}-lH-pyrazol-5-yl]piperidine;

4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5-yl]-1-(2-methanesulfonylethyl)piperidine ;

l-(4-fluorophenyl)-5-{l-[2-(4-methanesulfonylphenyl)ethyl]azetidin-3-yl}-4-[(3-methyl-3-phenylpyrrolidin- l-yl)carbonyl]- lH-pyrazole;

4-(2-{4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yljpiperidin- 1-yl }ethyl)benzoic acid;

4-({4-[l-(4-chlorophenyl)-4-{[(3R)-3-methyl-3-phenylpyrrolidin-l-yl]carbonyl}-1H-pyrazol- 5-yljpiperidin- 1-yl }methyl)benzonitrile ;

4-({4-[l-(4-fluorophenyl)-4-[(3-methyl-3-phenylpyrrolidin-l-yl)carbonyl]-lH-pyrazol-5-yljpiperidin- 1-yl }methyl)benzonitrile;

3-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin- 1-yl }methyl)benzonitrile;

4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-methyl-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yljpiperidin- 1-yl }methyl)benzonitrile;

4-({4-[l-(4-fluorophenyl)-4-{[(3S)-3-methyl-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yljpiperidin- 1-yl }methyl)benzonitrile;

4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5-yl]-1-(3,3,3-trifluoropropyl)piperidine ;

tert-butyl 3-{4-[l-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5-yl]piperidin-l-yl}pyrrolidine-l-carboxylate;

l-(l-benzylpyrrolidin-3-yl)-4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine;

l-[(l,3-dimethyl-lH-pyrazol-5-yl)methyl]-4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine;

l-[(3,5-dimethyl-l,2-oxazol-4-yl)methyl]-4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine;

4-({4-[1-(4-chlorophenyl)-4- {[(3S)-3-(2-fluorophenyl)pyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5-yl]piperidin- 1-yl }methyl)benzonitrile;

4-({4-[l-(4-chlorophenyl)-4-{[(3R)-3-(2-fluorophenyl)pyrrolidin-l-yl]carbonyl}-1H-pyrazol-5-yljpiperidin-1-yl}methyl)benzonitrile ;

4-({4-[l-(2,4-difluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yljpiperidin-1-yl}methyl)benzoic acid;

4-[1-(2,4-difluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yljcarbonyl}-lH-pyrazol-5-yl]-l-{[4-(lH-l,2,3,4-tetrazol-5-yl)phenyl]methyl}piperidine;

4-[l-(4-chloro-2-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]-l-{[4-(lH-l,2,3,4-tetrazol-5-yl)phenyl]methyl}piperidine;

4-[1-(4-fluorophenyl)-4-[(3-methyl-3-phenylpyrrolidin-1-yl)carbonyl]-1H-pyrazol-5-yl]-l-{[4-(lH-l,2,3,4-tetrazol-5-yl)phenyl]methyl}piperidine;

2-[4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yljpiperidin-1-yl}methyl)phenyl]propanoic acid;

2-[4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yljpiperidin-1-yl}methyl)phenyl]acetic acid;

4-({4-[1-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-1-yljcarbonyl}-1H-pyrazol-5-yl]piperidin-1-yl}methyl)benzoic acid;

1-[(l,5-dimethyl-lH-pyrazol-3-yl)methyl]-4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine;

4-({4-[l-(4-fluorophenyl)-4-[(3-methyl-3-phenylpyrrolidin-l-yl)carbonyl]-lH-pyrazol-5-yljpiperidin-1-yl}methyl)benzoic acid;

4-[1-(4-fluorophenyl)-4-[(3-methyl-3-phenylpyrrolidin-1-yl)carbonyl]-1H-pyrazol-5-yl]-1-[(4-methanesulfonylphenyl)methyl]piperidine ;

5-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-l-yl}methyl)-l,2-oxazole-3-carboxylic acid;

5-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-l-yl}methyl)-l-methyl-lH-pyrazole-3-carboxylic acid;

2-{[4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yljpiperidin-1-yl}methyl)benzene]sulfonyl}acetic acid;

(2E)-3-[4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yljpiperidin-1-yl}methyl)phenyl]prop-2-enoic acid;

4-[1-(4-fluorophenyl)-4-{[3-(2-fluorophenyl)pyrrolidin-1-yljcarbonyl}-lH-pyrazol-5-yl]-1-[(4-methanesulfonylphenyl)methyl]piperidine ;

1-{[4-(ethanesulfonyl)phenyl]methyl}-4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidine;

4-[l-(4-fluorophenyl)-4-[(2,2,5,5-tetrahydrogenio-3-methyl-3-phenylpyrrolidin-l-yl)carbonyl]-lH-pyrazol-5-yl]-l-[(4-methanesulfonylphenyl)methyl]piperidine;

4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin-1-yljcarbonyl }-1H-pyrazol-5-yl]-1-{[4-(propane-2-sulfonyl)phenyl]methyl }piperidine;

4-{4-[(3,3-difluoro-4-phenylpyrrolidin-1-yl)carbonyl]-1-(4-fluorophenyl)-1H-pyrazol-5-yl }-1-[(4-methanesulfonylphenyl)methyl]piperidine;

4-(4- {[(4R)-3,3-difluoro-4-phenylpyrrolidin-1-yljcarbonyl }-1-(4-fluorophenyl)-1H-pyrazol-5-yl)-l-[(4-methanesulfonylphenyl)methyl]piperidine;

4-(4-{[(4S)-3,3-difluoro-4-phenylpyrrolidin-l-yl]carbonyl}-l-(4-fluorophenyl)-lH-pyrazol-5-yl)-l-[(4-methanesulfonylphenyl)methyl]piperidine;

tert-butyl N-{4-[l-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin-1-yljcarbonyl }-1H-pyrazol-5-yl]cyclohexy1}carbamate;

N-{4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin-1-yljcarbonyl }-lH-pyrazol-5-yl]cyclohexyl}-4-methanesulfonylaniline;

5-fluoro-2-(5-{l-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl}-4-{[(3R)-3-phenylpyrrolidin-1-yljcarbonyl }-1H-pyrazol-1-yl)pyrimidine;

5-fluoro-2-(5-{l-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl}-4-{[(3S)-3-phenyl-3-(trifluoromethyl)pyrrolidin-l-yl]carbonyl }-IH-pyrazol-1-yl)pyrimidine;

2-{4-[(3,3-difluoro-4-phenylpyrrolidin-1-yl)carbonyl]-5-{1-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl }-1H-pyrazol-1-yl }-5-fluoropyrimidine;

2-(4-{[(4R)-3,3-difluoro-4-phenylpyrrolidin-l-yl]carbonyl}-5-{l-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl}-lH-pyrazol-l-yl)-5-fluoropyrimidine;

2-(4-{[(4S)-3,3-difluoro-4-phenylpyrrolidin-l-yl]carbonyl}-5-{l-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl}-lH-pyrazol-l-yl)-5-fluoropyrimidine;

5-fluoro-2-(4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-5-[l-(pyrimidin-5-ylmethyl)piperidin-4-yl]- IH-pyrazol- l-yl)pyrimidine;

4-({4-[l-(5-fluoropyrimidin-2-yl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-l-yl}methyl)benzene-l-sulfonamide;

5-chloro-2-(5-{l-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl}-4-{[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol- 1-yl)pyrimidine;

4-({4-[l-(5-bromopyrimidin-2-yl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-l-yl}methyl)benzene-l-sulfonamide;

4-({4-[l-(5-fluoropyrimidin-2-yl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yljpiperidin- 1-yl }methyl)benzonitrile;

3-fluoro-4-({4-[l-(5-fluoropyrimidin-2-yl)-4-{[(3R)-3-phenylpyrrolidin-l-yljcarbonyl }-1H-pyrazol-5-yl]piperidin- 1-yl }methyl)benzonitrile ;

2-(5-{l-[(6-chloropyridin-3-yl)methyl]piperidin-4-yl}-4-{[(3R)-3-phenylpyrrolidin-1-yljcarbonyl }-1H-pyrazol- 1-yl)-5-fluoropyrimidine;

5-fluoro-2-(4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-5-(l-{[6-(lH-pyrazol-l-yl)pyridin-3-yljmethyl }piperidin-4-yl)- 1H-pyrazol- 1-yl)pyrimidine;

5-({4-[l-(5-fluoropyrimidin-2-yl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yljpiperidin- 1-yl }methyl)pyridin-2-amine;

5-({4-[l-(5-fluoropyrimidin-2-yl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin- 1-yl }methyl)pyrimidin-2-amine;

5-fluoro-2-(4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-5-[l-(pyridin-4-ylmethyl)piperidin-4-yl]- lH-pyrazol- l-yl)pyrimidine;

4-[(4- {4-[(3,3-difluoro-4-phenylpyrrolidin- 1-yl)carbonyl] -1-(5-fluoropyrimidin-2-yl)-l H-pyrazol-5-yl }piperidin- 1-yl)methyl]benzonitrile;

2-(5-{l-[(6-chloropyridin-3-yl)methyl]piperidin-4-yl}-4-[(3,3-difluoro-4-phenylpyrrolidin-l-yl)carbonyl]-lH-pyrazol-l-yl)-5-fluoropyrimidine;

4-[(4- {4-[(3,3-difluoro-4-phenylpyrrolidin- 1-yl)carbonyl] -1-(5-fluoropyrimidin-2-yl)-l H-pyrazol-5-yl }piperidin- 1-yl)methyl]benzene- 1-sulfonamide;

2-{4-[(3,3-difluoro-4-phenylpyrrolidin- 1-yl)carbonyl] -5-[1-(pyridin-4-ylmethyl)piperidin-4-yl]- lH-pyrazol- 1-yl) -5-fluoropyrimidine;

4-{[4-(4- {[(4R)-3,3-difluoro-4-phenylpyrrolidin- 1-yljcarbonyl }-1-(4-fluorophenyl)-1H-pyrazol- 5-yl)piperidin- 1-yl]methyl }benzene- 1-sulfonamide ;

4-{[4-(4-{[(4S)-3,3-difluoro-4-phenylpyrrolidin-l-yl]carbonyl}-l-(4-fluorophenyl)-1H-pyrazol- 5-yl)piperidin- 1-yl]methyl }benzene- 1-sulfonamide ;

4-{4-[(3,3-difluoro-4-phenylpyrrolidin- 1-yl)carbonyl]- 1-(4-fluorophenyl)-3-methyl-lH-pyrazol-5-yl }-1-[(4-methanesulfonylphenyl)methyl]piperidine;

2-{4-[(3,3-difluoro-4-phenylpyrrolidin- 1-yl)carbonyl]-5-(1-{[6-(trifluoromethyl)pyridin-3-yl]methyl }piperidin-4-yl)- IH-pyrazol- 1-yl }-5-fluoropyrimidine ;

2-{4-[(3,3-difluoro-4-phenylpyrrolidin- 1-yl)carbonyl]-5-{1-[(6-methoxypyridin-3-yl)methyl]piperidin-4-yl }-IH-pyrazol- 1-yl }-5-fluoropyrimidine;

2-(4-{[(4R)-3,3-difluoro-4-phenylpyrrolidin-l-yl]carbonyl}-5-(l-{[6-(trifluoromethyl)pyridin-3-yl]methyl}piperidin-4-yl)-lH-pyrazol-l-yl)-5-fluoropyrimidine ;

2-(4-{[(4R)-3,3-difluoro-4-phenylpyrrolidin-l-yl]carbonyl}-5-{l-[(6-methoxypyridin-3-yl)methyl]piperidin-4-yl}-lH-pyrazol-l-yl)-5-fluoropyrimidine;

2-(4-{[(4R)-3,3-difluoro-4-phenylpyrrolidin-l-yl]carbonyl}-5-(l-{[4-(trifluoromethane)sulfonylphenyl]methyl}piperidin-4-yl)-lH-pyrazol-l-yl)-5-fluoropyrimidine ;

2-(4-{[(4S)-3,3-difluoro-4-phenylpyrrolidin-l-yl]carbonyl}-5-(l-{[4-(trifluoromethane)sulfonylphenyl]methyl}piperidin-4-yl)-lH-pyrazol-l-yl)-5-fluoropyrimidine ;

4-({4-[l-(4-fluorophenyl)-4-{[3-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-l-yl}methyl)benzene-l-sulfonamide;

4-[1-(4-fluorophenyl)-4- {[3-(4-fluorophenyl)pyrrolidin- 1-yljcarbonyl }-lH-pyrazol-5-yl]-1-[(4-methanesulfonylphenyl)methyl]piperidine ;

4-({4-[l-(4-fluorophenyl)-4-{[(3R)-3-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]piperidin-l-yl}methyl)benzene-l-sulfonamide;

4-({4-[1-(4-fluorophenyl)-4- {[(3S)-3-(4-fluorophenyl)pyrcolidin- 1-yljcarbonyl }-1H-pyrazol-5-yl]piperidin-l-yl}methyl)benzene-l-sulfonamide;

4-[1-(4-fluorophenyl)-4- {[(3R)-3-(4-fluorophenyl)pyrrolidin- l-yl]carbonyl }-1H-pyrazol-5-yl]-1-[(4-methanesulfonylphenyl)methyl]piperidine;

4-[1-(4-fluorophenyl)-4- {[(3S)-3-(4-fluorophenyl)pyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5-yl]-1-[(4-methanesulfonylphenyl)methyl]piperidine;

4-{[4-(4-{[3,3-difluoro-4-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-l-(4-fluorophenyl)-1H-pyrazol-5-yl)piperidin- 1-yl]methyl }benzene- 1-sulfonamide ;

4-(4- {[3,3-difluoro-4-(4-fluorophenyl)pyrrolidin- 1-yl]carbonyl }-1-(4-fluorophenyl)-lH-pyrazol-5-yl)-l-[(4-methanesulfonylphenyl)methyl]piperidine;

methyl 2-(4-{4-[(3,3-difluoro-4-phenylpyrrolidin-1-yl)carbonyl]-1-(4-fluorophenyl)-lH-pyrazol-5-yl}piperidin-l-yl)-2-(4-methanesulfonylphenyl)acetate;

4-{[4-(4-{[(4R)-3,3-difluoro-4-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-l-(4-fluorophenyl)-1H-pyrazol-5-yl)piperidin-1-yl]methyl }benzene-1-sulfonamide;

4-{[4-(4-{[(4S)-3,3-difluoro-4-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-l-(4-fluorophenyl)-1H-pyrazol-5-yl)piperidin-1-yl]methyl }benzene-1-sulfonamide;

4-(4-{[(4R)-3,3-difluoro-4-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-l-(4-fluorophenyl)-lH-pyrazol-5-yl)-l-[(4-methanesulfonylphenyl)methyl]piperidine;

4-(4-{[(4S)-3,3-difluoro-4-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-l-(4-fluorophenyl)-lH-pyrazol-5-yl)-l-[(4-methanesulfonylphenyl)methyl]piperidine;

4-{[4-(4-{[3-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-l-(5-fluoropyrimidin-2-yl)-1H-pyrazol-5-yl)piperidin-1-yl]methyl }benzene-1-sulfonamide;

4-{[4-(4-{[3,3-difluoro-4-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-l-(5-fluoropyrimidin-2-yl)-1H-pyrazol-5-yl)piperidin-1-yl]methyl }benzene-1-sulfonamide;

2-(4-{[3,3-difluoro-4-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-5-{l-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl}-lH-pyrazol-l-yl)-5-fluoropyrimidine;

4-{4-[(3,3-difluoro-4-phenylpyrrolidin-1-yl)carbonyl]-1-(4-fluorophenyl)-1H-pyrazol-5-yl}-l-[(3-fluoro-4-methanesulfonylphenyl)methyl]piperidine;

5-fluoro-2-(4-{[3-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-5-{l-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl }-1H-pyrazol-1-yl)pyrimidine;

4-{[4-(4-{[(3R)-3-(4-fluorophenyl)pyrrolidin-1-yl]carbonyl }-l-(5-fluoropyrimidin-2-yl)-lH-pyrazol-5-yl)piperidin-l-yl]methyl}benzene-1-sulfonamide;

4-{[4-(4-{[(3S)-3-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl }-l-(5-fluoropyrimidin-2-yl)-lH-pyrazol-5-yl)piperidin-l-yl]methyl}benzene-1-sulfonamide;

5-fluoro-2-(4-{[(3R)-3-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-5-{l-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl }-1H-pyrazol-1-yl)pyrimidine;

5-fluoro-2-(4-{[(3S)-3-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-5-{l-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl }-1H-pyrazol-1-yl)pyrimidine;

4-{[4-(4-{[(4R)-3,3-difluoro-4-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-l-(5-fluoropyrimidin-2-yl)-1H-pyrazol-5-yl)piperidin-1-yl]methyl }benzene-1-sulfonamide;

2-(4-{[(4R)-3,3-difluoro-4-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-5-{l-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl}-lH-pyrazol-l-yl)-5-fluoropyrimidine;

2-(4-{[3,3-difluoro-4-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-5-{l-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl}-lH-pyrazol-l-yl)-5-fluoropyridine;

4-{4-[(3,3-difluoro-4-phenylpyrrolidin-1-yl)carbonyl]-1-(4-fluorophenyl)-1H-pyrazol-5-yl}-1-{[4-methanesulfonyl-2-(trifluoromethyl)phenyl]methyl}piperidine;

5-[(4-{4-[(3,3-difluoro-4-phenylpyrrolidin-1-yl)carbonyl]-1-(4-fluorophenyl)-1H-pyrazol-5-yl}piperidin-1-yl)methyl]-2-methanesulfonylbenzonitrile;

2-(4-{[(4R)-3,3-difluoro-4-(4-fluorophenyl)pyrrolidin-l-yl]carbonyl}-5-{l-[(4-methanesulfonylphenyl)methyl]piperidin-4-yl}-lH-pyrazol-l-yl)-5-fluoropyridine;

4-{4-[(3,3-difluoro-4-phenylpyrrolidin-1-yl)carbonyl]-1-(4-fluorophenyl)-1H-pyrazol-5-yl}-l-[(2-fluoro-4-methanesulfonylphenyl)methyl]piperidine;

4-{4-[(3,3-difluoro-4-phenylpyrrolidin-1-yl)carbonyl]-1-(4-fluorophenyl)-1H-pyrazol-5-yl}-1-[(4-methanesulfonylphenyl)-1,1-(dideuterium) methyljpiperidine;

4-{[4-(4-{[(4R)-3,3-difluoro-4-phenylpyrrolidin-l-yl]carbonyl}-l-(2,4-difluorophenyl)-1H-pyrazol-5-yl)piperidin-1-yl]methyl}benzene-1-sulfonamide;

4-(4-{[3,3-difluoro-4-(4-fluorophenyl)pyrrolidin-1-yl]carbonyl}-1-(4-fluorophenyl)-1H-pyrazol-5-yl)-1-[(4-methanesulfonylphenyl)-1,1-(dideuterium) methyl]piperidine;

1-[(4-methanesulfonylphenyl)methyl]-4-(1-methyl-4-{[(3R)-3-phenylpyrrolidin-1-yl]carbonyl}-lH-pyrazol-5-yl)piperidine;

4-(4-{[3,3-difluoro-4-(4-fluorophenyl)pyrrolidin-1-yl]carbonyl}-1-propyl-1H-pyrazol-5-yl)-l-[(4-methanesulfonylphenyl)methyl]piperidine;

l-[(4-methanesulfonylphenyl)methyl]-4-(4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-1-propyl-1H-pyrazol-5-yl)piperidine;

4-(l-butyl-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl)-l-[(4-methanesulfonylphenyl)methyl]piperidine;

4-{4-[(3,3-difluoro-4-phenylpyrrolidin-1-yl)carbonyl]-1-propyl-lH-pyrazol-5-yl}-1-[(4-methanesulfonylphenyl)methyl]piperidine;

4-[(4-{4-[(3,3-difluoro-4-phenylpyrrolidin-1-yl)carbonyl]-1-propyl-1H-pyrazol-5-yl}piperidin-1-yl)methyl]benzene-1-sulfonamide;

4-[(4- {4-[(3,3-difluoro-4-phenylpyrrolidin- 1-yl)carbonyl]-1-propyl- 1H-pyrazol-5-yl }piperidin- 1-yl)methyl]benzene- 1-sulfonamide;

4-{1-butyl-4-[(3,3-difluoro-4-phenylpyrrolidin- 1-yl)carbonyl]-1H-pyrazol-5-yl }-1-[(4-methanesulfonylphenyl)methyl]piperidine;

4-(4-{[(4R)-3,3-difluoro-4-phenylpyrrolidin-l-yl]carbonyl}-l-ethyl-lH-pyrazol-5-yl)-l- [(4-methanesulfonylphenyl)methyl]piperidine ;

4-{[4-(4- {[(4R)-3,3-difluoro-4-phenylpyrrolidin- 1-yfjcarbonyl }-1-ethyl- lH-pyrazol-5-yl)piperidin-l-yl]methyl}benzene-l-sulfonamide;

4-[(4-{l-butyl-4-[(3,3-difluoro-4-phenylpyrrolidin-l-yl)carbonyl]-lH-pyrazol-5-yl }piperidin- 1-yl)methyl]benzene- 1-sulfonamide;

4-{[4-(4- {[(4R)-3,3-difluoro-4-phenylpyrrolidin- 1-yfjcarbonyl }-1-propyl- 1H-pyrazol-5-yl)piperidin- 1-yl]methyl }benzene- 1-sulfonamide;

4-{[4-(4-{[(4S)-3,3-difluoro-4-phenylpyrrolidin-l-yl]carbonyl}-l-propyl-lH-pyrazol-5-yl)piperidin- 1-yl]methyl }benzene- 1-sulfonamide;

4-(l-ethyl-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl)-l-[(4-methanesulfonylphenyl)methyl]piperidine;

4-{[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]methyl }-1-(4-methanesulfonylphenyl)piperidine;

4-{4-[(3,3-difluoro-4-phenylpyrrolidin- 1-yl)carbonyl]- 1-(4-fluorophenyl)- 1H-pyrazol-5-yl }-1-[1-(4-methanesulfonylphenyl)ethyl]piperidine;

3-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]-1-(4-methanesulfonylphenyl)piperidine ;

N-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]-l-(4-methanesulfonylphenyl)piperidin-4-amine;

3-[l-(4-chlorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]-1-[(4-methanesulfonylphenyl)methyl]piperidine ;

4-[l-(4-{4-[(3,3-difluoro-4-phenylpyrrolidin-l-yl)carbonyl]-l-(4-fluorophenyl)-lH-pyrazol-5-yl}piperidin-l-yl)-2,2,2-trifluoroethyl]benzonitrile; 4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]-N-[(4-methanesulfonylphenyl)methyl]cyclohexan-l-amine;

4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yl]carbonyl }-1H-pyrazol-5-yl]-1-[(4-methanesulfonylphenyl)methyl] -1-methylpiperidin- 1-ium;

4-[1-(4-fluorophenyl)-4- {[(3R)-3-phenylpyrrolidin- 1-yljcarbonyl }-1H-pyrazol-5-yl]-1-[(4-methanesulfonylphenyl)methyl] -1-methylpiperidin- 1-ium, and l-ethyl-4-[l-(4-fluorophenyl)-4-{[(3R)-3-phenylpyrrolidin-l-yl]carbonyl}-lH-pyrazol-5-yl]-1-[(4-methanesulfonylphenyl)methyl]piperidin- 1-ium.

16. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of claims 1-15 and a pharmaceutically acceptable excipient.
17. A medicament for treating a TGR5 mediated disease or disorder, wherein the medicament comprises a therapeutically effective amount of a compound of any one of claims 1-15.
18. The medicament of claim 17, wherein the TGR5 mediated disease or disorder is selected from diabetes, an inflammatory disorders and an autoimmune disease.
19. The medicament of claim 18, wherein the TGR5 mediated disease or disorder is type II diabetes or psoriasis.
20. The use of a compound of any one of claims 1-15 in the manufacture of a medicament for treating a TGR5 mediated disease or disorder, wherein the disease or disorder is selected from diabetes, an inflammatory disorders and an autoimmune disease.
21. The use of claim 20, wherein the TGR5 mediated disease or disorder is type II diabetes or psoriasis.
22. A method for treating a TGR5 mediated disease or disorder comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of any one of claims 1-15.
23. The method of claim 22, wherein the TGR5 mediated disease or disorder is selected from diabetes, an inflammatory disorders and an autoimmune disease.
24. The method of claim 23, wherein the TGR5 mediated disease or disorder is type II diabetes or psoriasis.
25. A compound for use in a method of medical treatment, wherein the method of medical treatment is for treating a TGR5 mediated disease or disorder selected from diabetes, an inflammatory disorders and an autoimmune disease, and wherein the compound is a compound of any one of claims 1-15, or pharmaceutically acceptable salt thereof.
26. The compound of claim 25, wherein the TGR5 mediated disease or disorder is type II diabetes or psoriasis.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/064983

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 C07D403/14 C07D413/14 C07D417/14 A61K31/506
A61K31/4155 A61K31/4439 A61P3/10 A61P29/0Q
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal , WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 22 May 2008 (2008-05-22), XP002671297, retrieved from STN Database accession no. 1021960-12-2 CAS Registry Numbers: 1021960-12-2, 1021959-99-8, 1021959-96-5, 1021959-79-4, 1021959-77-2, 1021959-61-4, 1021959-57-8, 1021959-53-4, 1021959-38-5, 1021959-35-2, 1021959-22-7, 1021959-03-4, 1021959-02-3, 1021959-00-1, 1021958-88-2, 1021958-82-6, 1021958-76-8, 1021958-57-5, 1021958-40-6 and 1021958-26-8 ----- -/-	1-3,5-15

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 March 2012	21/03/2012

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/064983

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 14 May 2008 (2008-05-14), XP002671298, retrieved from STN Database accession no. 1020714-10-6 CAS Registry Number: 1020714-10-6 -----	1-3,5-15
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 9 May 2008 (2008-05-09), XP002671299, retrieved from STN Database accession no. 1020185-12-9 CAS Registry Numbers: 1020185-12-9 and 1020181-71-8 -----	1-3,5-15
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 8 May 2008 (2008-05-08), XP002671300, retrieved from STN Database accession no. 1020060-91-6 CAS Registry Numbers: 1020060-91-6, 1020060-74-5, 1020060-69-8, 1020060-52-9, 1020060-47-2, 1020060-43-8, 1020060-34-7, 1020060-18-7, 1020060-04-1, 1020059-91-9, 1020059-85-1, 1020059-66-8 and 1020059-64-6 -----	1-3,5-15
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 20 July 2006 (2006-07-20) , XP002671301, retrieved from STN Database accession no. 894886-79-4 CAS Registry Numbers: 894886-79-4, 894883-67-1, 894883-35-3, 894883-11-5, 894880-13-8, 894877-88-4, 894877-59-9, 894877-47-5, 894874-56-7, 894871-59-1, 894869-54-6, 894867-26-6 and 894865-41-9 ----- -/--	1-14

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International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 19 July 2006 (2006-07-19), XP002671302, retrieved from STN Database accession no. 894687-28-6 CAS Registry Numbers: 894687-28-6, 894685-72-4, 894682-45-2, 894681-97-1, 894678-32-1, 894677-97-5 , 894674-99-8, 894674-50-1, 894672-05-0 , 894671-64-8, 894669-30-8, 894666-09-2 , 894665-81-7, 894665-60-2, 894661-51-9 and 894657-17-1 -----	1-14
X	W0 2010/093845 Al (EXELIXIS INC [US]; BOLLU VENKATAIAH [US] ; BOREN BRANT CLAYTON [US]; DA) 19 August 2010 (2010-08-19) abstract; claim 21 -----	1-26

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2011/064983

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010093845 A1	19-08-2010	AR 075255 A1	16-03-2011
		EP 2396304 A1	21-12-2011
		KR 20110119790 A	02-11-2011
		TW 201040168 A	16-11-2010
		US 2012040985 A1	16-02-2012
		WO 2010093845 A1	19-08-2010