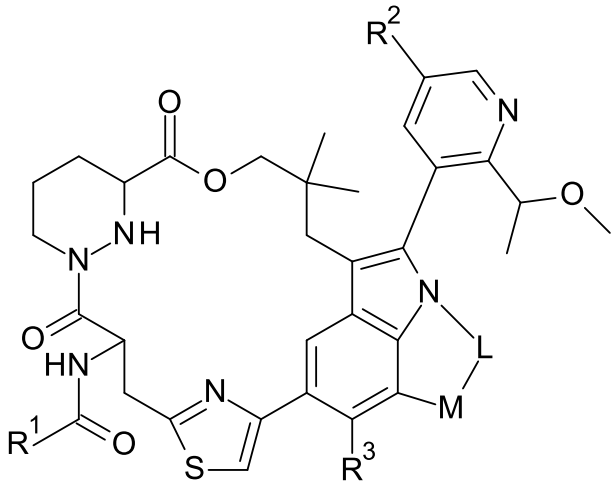
(MEK) and extracellular signal-regulated kinase (ERK), and propagates the growth signal. Of the RAF family of protein kinases (three known isoforms ARAF, BRAF, CRAF/RAF1), BRAF is most frequently mutated and remains the most potent activator of MEK. Despite that individual RAS and RAF family members revealed distinct binding preferences, all RAFs possess the conserved RBD for forward transmission of MAPK singnaling, frequently used for characterize KRAS inhibition (e.g. KRAS-BRAF^{RBD} herein). For KRAS, mutations at positions 12, 13, 61, and 146 lead to a shift toward the active KRAS form through impairing nucleotide hydrolysis or activating nucleotide exchange, leading to hyper-activation of the MAPK pathway that results in tumorigenesis.

Despite its well-recognized importance in cancer malignancy, continuous efforts in the past failed to develop approved therapies for KRAS mutant cancer until recently, the first selective drug AMG510 has fast approval as second line treatment in KRAS G12C driven non-small cell lung cancer (NSCLC). Nevertheless, the clinical acquired resistance to KRAS G12C inhibitors emerge rigorously with disease progresses after around 6 month of treatment. All of the mutations converge to reactivate RAS–MAPK signaling, with secondary RAS mutants at oncogenic hotspots (e.g. G12/G13/Q61) and within the switch II pocket (e.g. H95, R68, and Y96) have been observed; moreover, over 85% of all KRAS-mutated or wild-type amplified driven cancers still lack novel agents. Altogether, both the myriad of escape mechanism and various oncogenic alleles, highlight the urgent medical need for additional RAS therapies. As such, we invented oral compounds that target and inhibit RAS alleles for the treatment of RAS mutant driven cancers.

SUMMARY

The present disclosure relates to novel compounds of formula (Ib),



(Ib),

wherein

R^1 is 2-oxabicyclo[2.1.1]hexanyl,

3-oxabicyclo[3.1.0]hexanyl,

6-bicyclo[3.1.0]hexanyl substituted twice by halogen,

6-tricyclo[3.1.1.$0^{3,6}$]heptanyl,

C_{3-7}cycloalkyl substituted once, twice or three times by the substituents independently selected from C_{1-6}alkyl, C_{1-6}alkylpyridinyl, C_{1-6}alkylpyrimidinyl, C_{1-6}alkyltetrazolyl, C_{3-7}cycloalkyl, haloC_{1-6}alkyl, halogen, halophenyl, hydroxy, phenyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl and thiazolyl, or tetrahydropyranyl;

R^2 is 1,3,4,6,7,8,9,9a-octahydropyrido[1,2-a]pyrazinyl,

3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazinyl,

morpholinyl, or

piperazinyl unsubstituted or substituted by substituents independently selected from C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, morpholinylC_{1-6}alkyl, oxetanyl, oxopyrrolidinylC_{1-6}alkyl and tetrahydrofuranyloxyC_{1-6}alkyl;

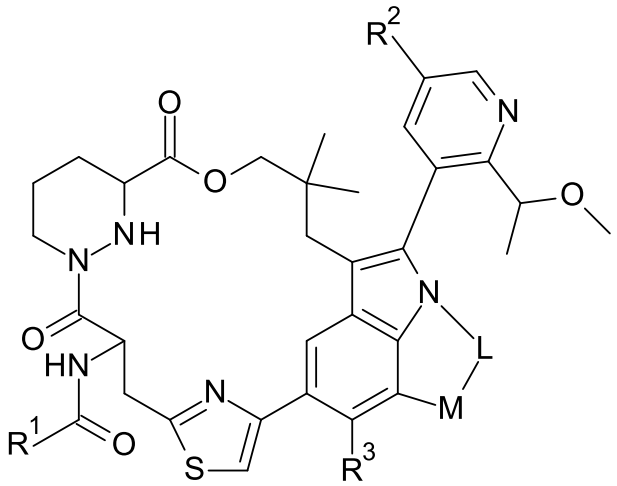
R^3 is H or halogen;

M is C_{1-6}alkylene or O;

L is C_{1-6}alkylene, hydroxyC_{1-6}alkylene or haloC_{1-6}alkylene;

or a pharmaceutically acceptable salt, enantiomers and diastereomers thereof.

In one aspect, the present disclosure relates to a compound of formula (Ib),



(Ib),

wherein

R^1 is 2-oxabicyclo[2.1.1]hexanyl,

3-oxabicyclo[3.1.0]hexanyl,

6-bicyclo[3.1.0]hexanyl substituted twice by halogen,

6-tricyclo[3.1.1.$0^{3,6}$]heptanyl,

C_{3-7}cycloalkyl substituted once, twice or three times by the substituents independently selected from C_{1-6}alkyl, C_{1-6}alkylpyridinyl, C_{1-6}alkylpyrimidinyl, C_{1-6}alkyltetrazolyl, C_{3-7}cycloalkyl, haloC_{1-6}alkyl, halogen, halophenyl, hydroxy, phenyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl and thiazolyl, or

tetrahydropyranyl;

R^2 is 1,3,4,6,7,8,9,9a-octahydropyrido[1,2-a]pyrazinyl,

3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazinyl,

morpholinyl, or

piperazinyl unsubstituted or substituted by substituents independently selected from C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, morpholinylC_{1-6}alkyl, oxetanyl, oxopyrrolidinylC_{1-6}alkyl and tetrahydrofuranyloxyC_{1-6}alkyl;

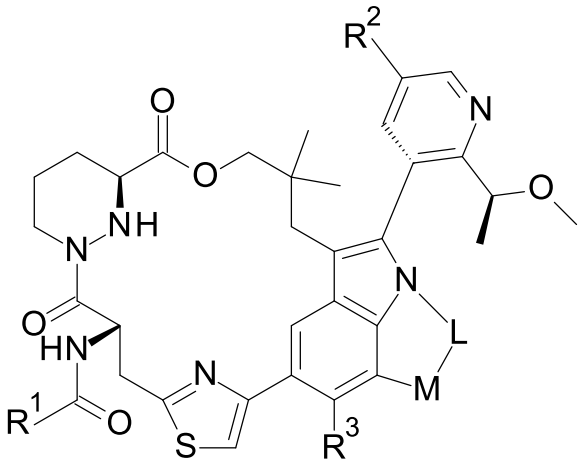
R^3 is H or halogen;

M is C_{1-6}alkylene or O;

L is C_{1-6}alkylene, hydroxyC_{1-6}alkylene or haloC_{1-6}alkylene;

or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure relates to a compound of formula (Ic),



(Ic),

wherein

R^1 is 2-oxabicyclo[2.1.1]hexanyl,

3-oxabicyclo[3.1.0]hexanyl,

6-bicyclo[3.1.0]hexanyl substituted twice by halogen,

6-tricyclo[3.1.1.$0^{3,6}$]heptanyl,

C_{3-7}cycloalkyl substituted once, twice or three times by the substituents independently selected from C_{1-6}alkyl, C_{1-6}alkylpyridinyl, C_{1-6}alkylpyrimidinyl, C_{1-6}alkyltetrazolyl, C_{3-7}cycloalkyl, haloC_{1-6}alkyl, halogen, halophenyl, hydroxy, phenyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl and thiazolyl, or

tetrahydropyranyl;

R^2 is 1,3,4,6,7,8,9,9a-octahydropyrido[1,2-a]pyrazinyl,

3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazinyl,

morpholinyl, or

piperazinyl unsubstituted or substituted by substituents independently selected from C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, morpholinylC_{1-6}alkyl, oxetanyl, oxopyrrolidinylC_{1-6}alkyl and tetrahydrofuranyloxyC_{1-6}alkyl;

R^3 is H or halogen;

M is C_{1-6}alkylene or O;

L is C_{1-6}alkylene, hydroxyC_{1-6}alkylene or haloC_{1-6}alkylene;

or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure relates to a compound selected from:

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.$1^{2,5}$.$1^{9,13}$.$0^{19,27}$.$0^{21,26}$]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-methyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.$1^{2,5}$.$1^{9,13}$.$0^{19,27}$.$0^{21,26}$]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-methyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-methyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-methyl-cyclopropanecarboxamide;

(1*S*,2*S*)-2-(difluoromethyl)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]cyclopropanecarboxamide;

(1*S*,5*R,6r*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-3-oxabicyclo[3.1.0]hexane-6-carboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-methyl-cyclopropanecarboxamide;

(1*S*,2*S*)-2-(difluoromethyl)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]cyclopropanecarboxamide;

(1*S*,5*R,6r*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-3-oxabicyclo[3.1.0]hexane-6-carboxamide;

(1*S*,2*S*)-2-(difluoromethyl)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]cyclopropanecarboxamide;

(1*S*,5*R*,6*r*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-3-oxabicyclo[3.1.0]hexane-6-carboxamide;

(1*S*,5*R*,6*r*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-3-oxabicyclo[3.1.0]hexane-6-carboxamide;

(1*S*,2*S*)-2-(difluoromethyl)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]cyclopropanecarboxamide;

(1*S*,5*R*,6*r*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-3-oxabicyclo[3.1.0]hexane-6-carboxamide;

(1*R*,2*S*)-2-cyclopropyl-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-methyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-23,23-difluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-methyl-cyclopropanecarboxamide;

2,2-difluoro-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-1-methyl-cyclopropanecarboxamide;

(1*S*,2*S*)-2-(difluoromethyl)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-phenyl-cyclopropanecarboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[5-[(9*aS*)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[2,1-c][1,4]oxazin-8-yl]-2-[(1*S*)-1-methoxyethyl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-methyl-cyclopropanecarboxamide;

(1*R*,2*R*)-2-(2-fluorophenyl)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]cyclopropanecarboxamide;

(1*S*,2*S*)-2-(2-fluorophenyl)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(2-pyridyl)cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-23,23-difluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(29),2,5(31),19,25,27-hexaen-7-yl]-2-(difluoromethyl)cyclopropanecarboxamide;

(1*S*,2*R*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-methyl-cyclopropanecarboxamide;

(1*S*,2*S*)-2-(difluoromethyl)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]cyclopropanecarboxamide;

(1*S*,5*R,6r*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-3-oxabicyclo[3.1.0]hexane-6-carboxamide;

(1*R*,2*S*)-2-cyclopropyl-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(29),2,5(31),19,25,27-hexaen-7-yl]cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17,23,23-tetramethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-methyl-cyclopropanecarboxamide;

(1*S*,5*R*,6*r*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[5-[(9*aS*)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[2,1-c][1,4]oxazin-8-yl]-2-[(1*S*)-1-methoxyethyl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-3-oxabicyclo[3.1.0]hexane-6-carboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[5-[(9*aS*)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[2,1-c][1,4]oxazin-8-yl]-2-[(1*S*)-1-methoxyethyl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(difluoromethyl)cyclopropanecarboxamide;

(1*R*,5*S*,6*s*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-3-oxabicyclo[3.1.0]hexane-6-carboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(29),2,5(31),19,25,27-hexaen-7-yl]-2-phenyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(29),2,5(31),19,25,27-hexaen-7-yl]-2-phenyl-cyclopropanecarboxamide;

(1*r*,2*S*,3*R*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(29),2,5(31),19,25,27-hexaen-7-yl]-2-phenyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-pyrimidin-5-yl-cyclopropanecarboxamide;

(1*S*,5*R*)-3,3-difluoro-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]bicyclo[3.1.0]hexane-6-carboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[5-[(9*aR*)-1,3,4,6,7,8,9,9*a*-octahydropyrido[1,2-a]pyrazin-2-yl]-2-[(1*S*)-1-methoxyethyl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-methyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-pyrimidin-4-yl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(29),2,5(31),19,25,27-hexaen-7-yl]-2-phenyl-cyclopropanecarboxamide;

(1*R*,5*S*,6*s*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-3-oxabicyclo[3.1.0]hexane-6-carboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*,22*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17,22-trimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-methyl-cyclopropanecarboxamide;

2,2-difluoro-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(29),2,5(31),19,25,27-hexaen-7-yl]-1-methyl-cyclopropanecarboxamide;

N-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(29),2,5(31),19,25,27-hexaen-7-yl]-1,2-dimethyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(3-pyridyl)cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(4-pyridyl)cyclopropanecarboxamide;

(1*R*,2*R*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(4-pyridyl)cyclopropanecarboxamide;

2-(4-fluorophenyl)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(29),2,5(31),19,25,27-hexaen-7-yl]cyclopropanecarboxamide;

(1*S*,5*R*,6*r*)-*N*-[(7*S*,13*S*)-23,23-difluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-3-oxabicyclo[3.1.0]hexane-6-carboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17,23,23-tetramethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-pyridazin-3-yl-cyclopropanecarboxamide;

(1*R*,2*S*)-2-cyclopropyl-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(29),2,5(31),19,25,27-hexaen-7-yl]cyclopropanecarboxamide;

3,3-difluoro-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]cyclopentanecarboxamide;

N-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-oxabicyclo[2.1.1]hexane-1-carboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-23,23-difluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-methyl-cyclopropanecarboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(29),2,5(31),19,25,27-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*r*,2*S*,3*R*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17,23,23-tetramethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

trans-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(29),2,5(31),19,25,27-hexaen-7-yl]-4-(1-methyltetrazol-5-yl)cyclohexanecarboxamide;

trans-4-hydroxy-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-4-methyl-cyclohexanecarboxamide;

N-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]tricyclo[3.1.1.0^{3,6}]heptane-6-carboxamide;

(1*r*,2*S*,3*R*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-23,23-difluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-methyl-cyclopropanecarboxamide;

(1*r*,2*S*,3*R*)-*N*-[(7*S*,13*S*)-23,23-difluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

N-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]tetrahydropyran-4-carboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-23,23-difluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-phenyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-23,23-difluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-phenyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-pyrimidin-2-yl-cyclopropanecarboxamide;

(1*R*,2*R*)-*N*-[(7*S*,13*S*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-pyrimidin-2-yl-cyclopropanecarboxamide;

(1*r*,2*S*,3*R*)-*N*-[(7*S*,13*S*)-23,23-difluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(29),2,5(31),19,25,27-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*r*,2*S*,3*R*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*r*,2*S*,3*R*)-*N*-[(7*S*,13*S*)-23,23-difluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-pyrimidin-5-yl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(3-pyridyl)cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(3-pyridyl)cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-23,23-difluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(3-pyridyl)cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-23,23-difluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(3-pyridyl)cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-pyrimidin-5-yl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-pyrimidin-5-yl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-23,23-difluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-pyrimidin-5-yl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(3-pyridyl)cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(3-pyridyl)cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(3-pyridyl)cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-pyrazin-2-yl-cyclopropanecarboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,25-dioxa-4-thia-9,21,31,32-tetrazahexacyclo[24.3.1.1^{2,5}.1^{9,13}.0^{19,28}.0^{21,27}]dotriaconta-1(29),2,5(32),19,26(30),27-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*r*,2*S*,3*R*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[5-[(9*aR*)-1,3,4,6,7,8,9,9*a*-octahydropyrido[1,2-a]pyrazin-2-yl]-2-[(1*S*)-1-methoxyethyl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[5-[(9*aR*)-1,3,4,6,7,8,9,9*a*-octahydropyrido[1,2-a]pyrazin-2-yl]-2-[(1*S*)-1-methoxyethyl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(3-pyridyl)cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[5-[(9*aR*)-1,3,4,6,7,8,9,9*a*-octahydropyrido[1,2-a]pyrazin-2-yl]-2-[(1*S*)-1-methoxyethyl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-pyrimidin-5-yl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[5-[(9*aS*)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[2,1-c][1,4]oxazin-8-yl]-2-[(1*S*)-1-methoxyethyl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(3-pyridyl)cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[5-[(9*aS*)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[2,1-c][1,4]oxazin-8-yl]-2-[(1*S*)-1-methoxyethyl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-pyrimidin-5-yl-cyclopropanecarboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[5-(4-cyclopropylpiperazin-1-yl)-2-[(1*S*)-1-methoxyethyl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*,23*S*)-23-hydroxy-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-piperazin-1-yl-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*)-20-[5-[4-(2,2-difluoroethyl)piperazin-1-yl]-2-[(1*S*)-1-methoxyethyl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[5-[4-(2-fluoroethyl)piperazin-1-yl]-2-[(1*S*)-1-methoxyethyl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[5-[4-(3-hydroxypropyl)piperazin-1-yl]-2-[(1*S*)-1-methoxyethyl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*R*,2*R*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(4-methylpyrimidin-5-yl)cyclopropanecarboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[5-(4-ethylpiperazin-1-yl)-2-[(1*S*)-1-methoxyethyl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*R*,2*R*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-thiazol-4-yl-cyclopropanecarboxamide;

(1*r*,2*S*,3*R*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2-methoxyethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*R*,2*R*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(2-methyl-3-pyridyl)cyclopropanecarboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-tetrahydropyran-4-ylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(oxetan-3-yl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*r*,2*S*,3*R*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-[[(2*S*)-morpholin-2-yl]methyl]piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*R*,2*R*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(5-methyl-3-pyridyl)cyclopropanecarboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-[2-(2-oxopyrrolidin-1-yl)ethyl]piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2-tetrahydrofuran-3-yloxyethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(3-methoxy-3-methyl-butyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*r*,2*S*,3*R*)-*N*-[(7*S*,13*S*)-29-fluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

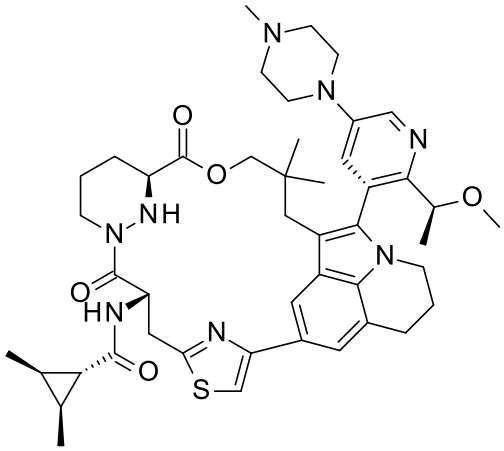
(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17,22,22-tetramethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(29),2,5(31),19,25,27-hexaen-7-yl]-2-methyl-cyclopropanecarboxamide;

(1r,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,31,32-tetrazahexacyclo[24.3.1.1^{2,5}.1^{9,13}.0^{19,28}.0^{21,27}]dotriaconta-1(29),2,5(32),19,26(30),27-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide; and

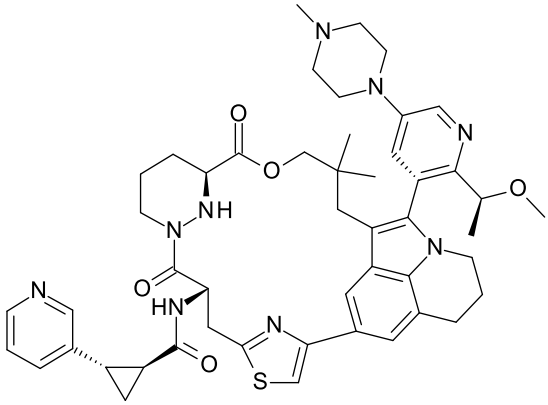
(1r,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,32,33-tetrazahexacyclo[25.3.1.1^{2,5}.1^{9,13}.0^{19,29}.0^{21,28}]tritriaconta-1(30),2,5(33),19,27(31),28-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

or a pharmaceutically acceptable salt thereof.

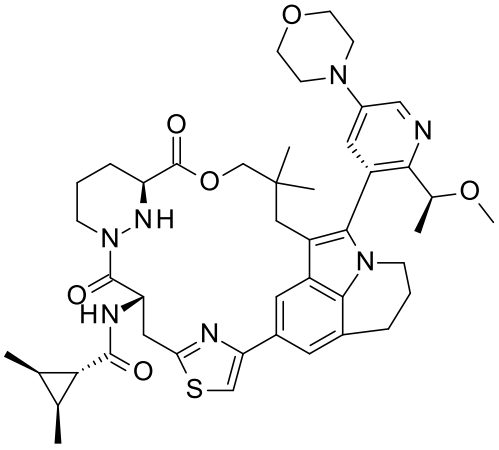
In another aspect, the present disclosure relates to a compound selected from:



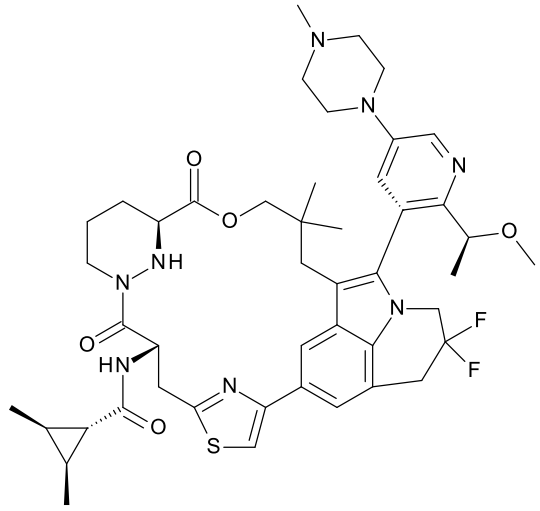
(Example 24);



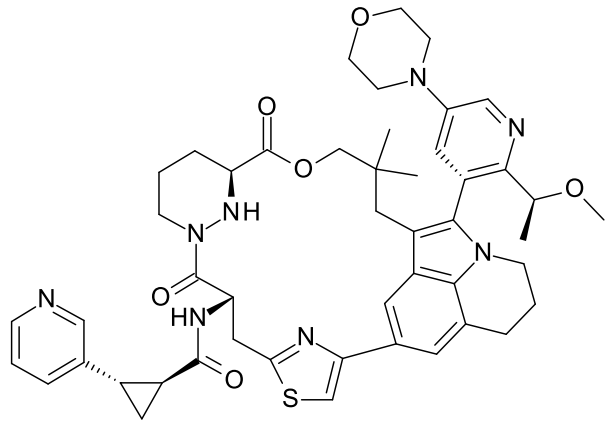
(Example 56);



(Example 73);



(Example 83); and



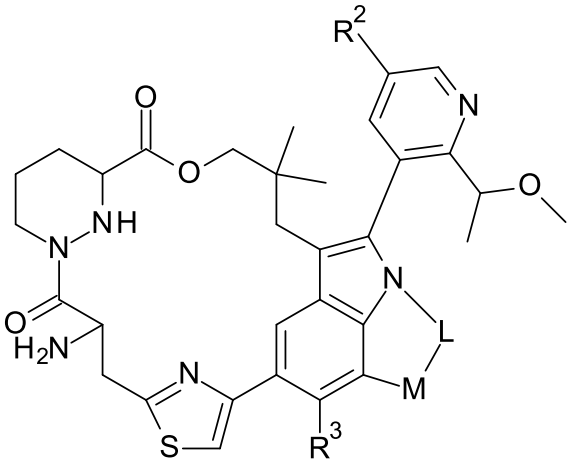
(Example 89);

or a pharmaceutically acceptable salt thereof.

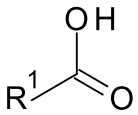
The disclosure also relates to their manufacture medicaments based on a compound in accordance with the disclosure and their production as well as the use of compounds of formula (I), (Ia), (Ib) or (Ic) thereof as inhibitor of KRAS.

In another aspect, the present disclosure relates to a process for the preparation of a compound as described herein comprising the following step:

a) coupling reaction between compound of formula (IIb),



(IIb), and acid (III),



(III),

in the presence of a coupling reagent and a base to form the compound of formula (Ib);

wherein R^1, R^2, M and L are as described herein; the coupling reagent is T_3P, HATU, PyBOP or EDCI/HOBt; the base is TEA, DIEPA or DMAP.

In another aspect, the present disclosure relates to a compound or pharmaceutically acceptable salt as described herein for use as therapeutically active substance.

In another aspect, the present disclosure relates to a pharmaceutical composition comprising a compound as described herein and a pharmaceutically acceptable excipient.

In another aspect, the present disclosure relates to a compound as described herein for use in treating a KRAS G12C protein-related disease.

In another aspect, the present disclosure relates to a compound as described herein for use in treating a KRAS G12C, G12D and G12V protein-related disease.

In another aspect, the present disclosure relates to a compound as described herein for use in inhibiting RAS interaction with downstream effectors, wherein the downstream effectors are RAF and PI3K.

In another aspect, the present disclosure relates to a compound as described herein for use in inhibiting the propagating oncogenic MAPK and PI3K signaling.

In another aspect, the present disclosure relates to a compound as described herein for use in the treatment or prophylaxis of cancers in a subject in need thereof, wherein the cancer comprises a first RAS mutation that is G12C and a second RAS mutation at a position selected from the group consisting of V8A, V9Y, S17E, A59T, T58I, D69P, M72I, S65W, R68S, D92R, H95N, Y96D, Q99W and F156L.

In another aspect, the present disclosure relates to the use of a compound as described herein in the preparation of a medicament for the treatment or prophylaxis of cancers in a subject in need thereof, wherein the cancer comprises a first RAS mutation that is G12C and a second RAS mutation at a position selected from the group consisting of V8A, V9Y, S17E, A59T, T58I, D69P, M72I, S65W, R68S, D92R, H95N, Y96D, Q99W and F156L.

In another aspect, the present disclosure relates to the use of a compound as described herein in the preparation of a medicament for the treatment or prophylaxis of KRAS mutation driven cancers, wherein the cancer is selected from pancreatic cancer, colorectal cancer, lung cancer, esophageal cancer, gallbladder cancer, melanoma ovarian cancer and endometrial cancer.

In another aspect, the present disclosure relates to a compound as described herein for use in the treatment or prophylaxis of KRAS mutation driven cancers, wherein the cancer is selected from pancreatic cancer, colorectal cancer, lung cancer, esophageal cancer, gallbladder cancer, melanoma ovarian cancer and endometrial cancer.

In another aspect, the present disclosure relates to the use of a compound as described herein in the preparation of a medicament for the treatment or prophylaxis of primary central nervous system (CNS) tumors harboring RAS mutations or RAS driven cancers with brain metastases; wherein the CNS tumor is primary melanocytic tumors of the CNS harboring NRAS mutation; wherein the cancer is selected from pancreatic adenocarcinoma, colorectal cancer, non-small cell lung cancer.

In another aspect, the present disclosure relates to a compound as described herein for use in the treatment or prophylaxis of primary central nervous system (CNS) tumors harboring RAS mutations or RAS driven cancers with brain metastases; wherein the CNS tumor is primary melanocytic tumors of the CNS harboring NRAS mutation; wherein the cancer is selected from pancreatic adenocarcinoma, colorectal cancer, non-small cell lung cancer.

In another aspect, the present disclosure relates to a compound or pharmaceutically acceptable salt as described herein for use in the treatment or prophylaxis of KRAS mutation driven cancers, wherein the cancer is selected from pancreatic adenocarcinoma, colorectal cancer and non-small cell lung cancer.

In another aspect, the present disclosure relates to the use of a compound as described herein in the preparation of a medicament for the treatment or prophylaxis of KRAS mutation driven cancers, wherein the cancer is selected from pancreatic adenocarcinoma, colorectal cancer and non-small cell lung cancer.

In another aspect, the present disclosure relates to a compound or pharmaceutically acceptable salt as described herein, when manufactured according to a process as described herein.

The compounds of formula (I), (Ia), (Ib) or (Ic) showed good KRAS inhibition for G12C, G12D and G12V.

In another example, the compounds of current disclosure have significantly improved single dose pharmacokinetics (PK) properties comparing with the reference compounds suggesting that compounds of this disclosure are more suitable for treating cancers with RAS mutation as an orally therapeutic active ingredient in clinic (Example 128).

In another example, the compounds of this disclosure showed superior human hepatocyte stability which is advantageous to improve in vivo performance of the compound, such as dose reduction, exposure enhancement, and half-life prolongation (Example 129).

In another example, the compounds of this disclosure exhibited less inhibitory effect on hERG potassium channel compared to reference compound, suggesting that compounds of this disclosure could have less concern regarding cardiovascular toxicity associated with hERG channel blockade (Example 138).

In another example, the compounds of this disclosure showed better selectivity compared to reference compounds on WT KRAS/HRAS/NRAS potentially indicating an improved tolerability and safety profile (Example 132).

In another example, the compounds of this disclosure consistently exhibited more potent anti-proliferative activity across 119 cell panels, significantly differentiated from reference compound treated group, that potentially could result in more robust anti-tumor responses in clinic (Example 131).

In another example, the compounds of this disclosure exhibited longer and sustained pathway inhibition over treatment period, and demonstrated significantly enhanced anti-tumor activities compared with reference compound that potentially could result in more durable anti-tumor responses in clinic (Example 130).

In another example, the compounds of this disclosure showed much higher binding affinity to CYPA and an obviously much lower dissociation rate that revealed a stronger stability of formed CYPA-compound binary complex. This result is consistent with the less potency shift of Example 24 observed in washout assay in Example 140, which further suggesting more persistent cell growth inhibition that would be advantageous for achieving durable efficacy in clinic (Example 139 and 140).

In addition, the compounds of current disclosure showed excellent tumor growth inhibition (TGI) in brain metastasis intracranial model, improved toxicity and solubility profiles. Furthermore, the compounds of current disclosure avoided generating unfavorable or even toxic metabolite in vivo compared to reference compounds.

BRIEF DESCRIPTION OF THE FIGURES

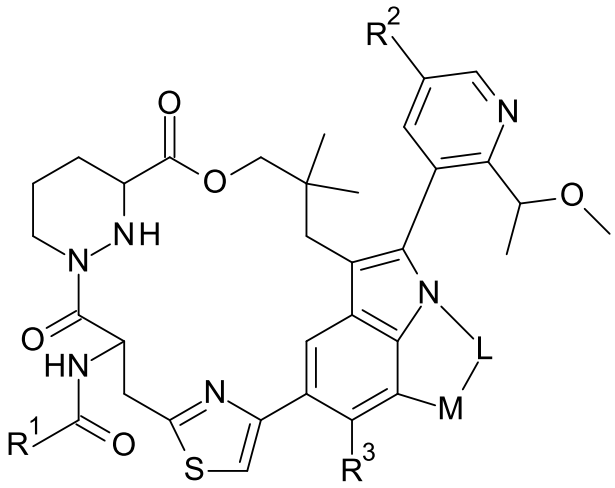
Figure 1. Absolute configuration structure of compound F6 in the form of its (2S,3S)-2,3-bis[(4-methylbenzoyl)oxy]butanedioic acid salt acetonitrile solvate.

Figure 2. Bioluminescence signal changes and body weight change after administering vehicle or test articles to female BALB/c nude mice bearing NCI-H1373-luc intracranial tumors. Data points represent mean ± SEM.

Figure 3. Tumor bioluminescence picture of each group from Figure 2.

CLAIMS

1. A compound of formula (Ib),



(Ib),

wherein

R^1 is 2-oxabicyclo[2.1.1]hexanyl,

3-oxabicyclo[3.1.0]hexanyl,

6-bicyclo[3.1.0]hexanyl substituted twice by halogen,

6-tricyclo[3.1.1.$0^{3,6}$]heptanyl,

C_{3-7}cycloalkyl substituted once, twice or three times by the substituents independently selected from C_{1-6}alkyl, C_{1-6}alkylpyridinyl, C_{1-6}alkylpyrimidinyl, C_{1-6}alkyltetrazolyl, C_{3-7}cycloalkyl, haloC_{1-6}alkyl, halogen, halophenyl, hydroxy, phenyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl and thiazolyl, or

tetrahydropyranyl;

R^2 is 1,3,4,6,7,8,9,9a-octahydropyrido[1,2-a]pyrazinyl,

3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazinyl,

morpholinyl, or

piperazinyl unsubstituted or substituted by substituents independently selected from C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, morpholinylC_{1-6}alkyl, oxetanyl, oxopyrrolidinylC_{1-6}alkyl and tetrahydrofuranyloxyC_{1-6}alkyl;

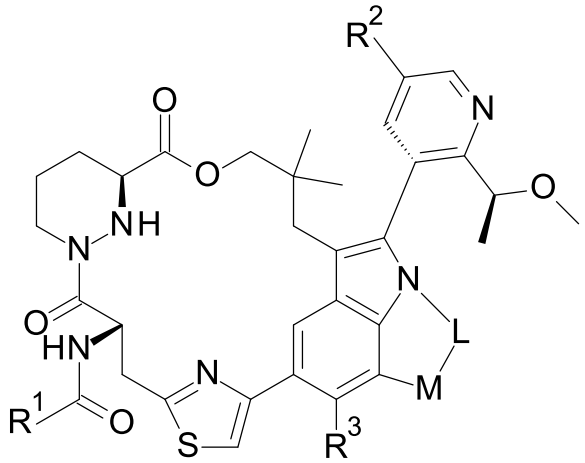
R^3 is H or halogen;

M is C_{1-6}alkylene or O;

L is C_{1-6}alkylene, hydroxyC_{1-6}alkylene or haloC_{1-6}alkylene;

or a pharmaceutically acceptable salt thereof.

2. A compound of formula (Ic),



(Ic),

wherein

R^1 is 2-oxabicyclo[2.1.1]hexanyl,

3-oxabicyclo[3.1.0]hexanyl,

6-bicyclo[3.1.0]hexanyl substituted twice by halogen,

6-tricyclo[3.1.1.$0^{3,6}$]heptanyl,

C_{3-7}cycloalkyl substituted once, twice or three times by the substituents independently selected from C_{1-6}alkyl, C_{1-6}alkylpyridinyl, C_{1-6}alkylpyrimidinyl, C_{1-6}alkyltetrazolyl, C_{3-7}cycloalkyl, haloC_{1-6}alkyl, halogen, halophenyl, hydroxy, phenyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl and thiazolyl, or

tetrahydropyranyl;

R^2 is 1,3,4,6,7,8,9,9a-octahydropyrido[1,2-a]pyrazinyl,

3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazinyl,

morpholinyl, or

piperazinyl unsubstituted or substituted by substituents independently selected from C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, morpholinylC_{1-6}alkyl, oxetanyl, oxopyrrolidinylC_{1-6}alkyl and tetrahydrofuranyloxyC_{1-6}alkyl;

R^3 is H or halogen;

M is C_{1-6}alkylene or O;

L is C_{1-6}alkylene, hydroxyC_{1-6}alkylene or haloC_{1-6}alkylene;

or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 or 2, wherein R^1 is C_{3-7}cycloalkyl substituted once or twice by the substituents independently selected from C_{1-6}alkyl and pyridinyl.

4. A compound according to any one of claims 1-3, wherein R^1 is cyclopropyl once substituted by pyridinyl or twice substituted by methyl.

5. A compound according to any one of claims 1-4, wherein R^1 is 2,3-dimethyl-cyclopropyl or 2-(3-pyridinyl)cyclopropyl.

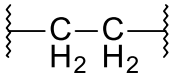
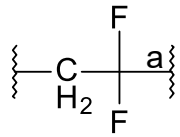
6. A compound according to any one of claims 1-5, wherein R^2 is morpholinyl or C_{1-6}alkylpiperazinyl.

7. A compound according to any one of claims 1-6, wherein R^2 is morpholinyl or 4-methylpiperazin-1-yl.

8. A compound according to any one of claims 1-7, wherein M is C_{1-6}alkylene.

9. A compound according to any one of claims 1-8, wherein M is CH_2.

10. A compound according to any one of claims 1-9, wherein L is ethylene or difluoroethylene.

11. A compound according to any one of claims 1-10, wherein L is  or , wherein bond “a” connects to M.

12. A compound according to claim 1 or 2, wherein

R^1 is C_{3-7}cycloalkyl substituted once or twice by the substituents independently selected from C_{1-6}alkyl and pyridinyl;

R^2 is morpholinyl or $C_{1\text{-}6}$alkylpiperazinyl;

R^3 is H;

M is $C_{1\text{-}6}$alkylene;

L is $C_{1\text{-}6}$alkylene or halo$C_{1\text{-}6}$alkylene;

or a pharmaceutically acceptable salt thereof.

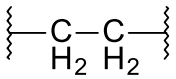
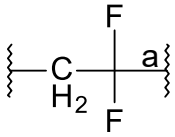
13. A compound according to claim 12, wherein

R^1 is 2,3-dimethyl-cyclopropyl or 2-(3-pyridinyl)cyclopropyl;

R^2 is morpholinyl or 4-methylpiperazin-1-yl;

R^3 is H;

M is CH_2;

L is  or , wherein bond "a" connects to M;

or a pharmaceutically acceptable salt thereof.

14. A compound selected from:

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-methyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-methyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-methyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-methyl-cyclopropanecarboxamide;

(1*S*,2*S*)-2-(difluoromethyl)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]cyclopropanecarboxamide;

(1*S*,5*R,6r*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-3-oxabicyclo[3.1.0]hexane-6-carboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-methyl-cyclopropanecarboxamide;

(1*S*,2*S*)-2-(difluoromethyl)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]cyclopropanecarboxamide;

(1*S*,5*R,6r*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-3-oxabicyclo[3.1.0]hexane-6-carboxamide;

(1*S*,2*S*)-2-(difluoromethyl)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]cyclopropanecarboxamide;

(1*S*,5*R,6r*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-3-oxabicyclo[3.1.0]hexane-6-carboxamide;

(1*S*,5*R,6r*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-3-oxabicyclo[3.1.0]hexane-6-carboxamide;

(1*S*,2*S*)-2-(difluoromethyl)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-

tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]cyclopropanecarboxamide;

(1*S*,5*R,6r*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-3-oxabicyclo[3.1.0]hexane-6-carboxamide;

(1*R*,2*S*)-2-cyclopropyl-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-methyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-23,23-difluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-methyl-cyclopropanecarboxamide;

2,2-difluoro-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-1-methyl-cyclopropanecarboxamide;

(1*S*,2*S*)-2-(difluoromethyl)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-phenyl-cyclopropanecarboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[5-[(9*aS*)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[2,1-c][1,4]oxazin-8-yl]-2-[(1*S*)-1-methoxyethyl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-methyl-cyclopropanecarboxamide;

(1*R*,2*R*)-2-(2-fluorophenyl)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]cyclopropanecarboxamide;

(1*S*,2*S*)-2-(2-fluorophenyl)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(2-pyridyl)cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-23,23-difluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(29),2,5(31),19,25,27-hexaen-7-yl]-2-(difluoromethyl)cyclopropanecarboxamide;

(1*S*,2*R*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-methyl-cyclopropanecarboxamide;

(1*S*,2*S*)-2-(difluoromethyl)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]cyclopropanecarboxamide;

(1*S*,5*R*,6*r*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-3-oxabicyclo[3.1.0]hexane-6-carboxamide;

(1*R*,2*S*)-2-cyclopropyl-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-

tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(29),2,5(31),19,25,27-hexaen-7-yl]cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17,23,23-tetramethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-methyl-cyclopropanecarboxamide;

(1*S*,5*R,*6*r*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[5-[(9*aS*)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[2,1-c][1,4]oxazin-8-yl]-2-[(1*S*)-1-methoxyethyl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-3-oxabicyclo[3.1.0]hexane-6-carboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[5-[(9*aS*)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[2,1-c][1,4]oxazin-8-yl]-2-[(1*S*)-1-methoxyethyl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(difluoromethyl)cyclopropanecarboxamide;

(1*R*,5*S,*6*s*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-3-oxabicyclo[3.1.0]hexane-6-carboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(29),2,5(31),19,25,27-hexaen-7-yl]-2-phenyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(29),2,5(31),19,25,27-hexaen-7-yl]-2-phenyl-cyclopropanecarboxamide;

(1*r*,2*S*,3*R*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(29),2,5(31),19,25,27-hexaen-7-yl]-2-phenyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-pyrimidin-5-yl-cyclopropanecarboxamide;

(1*S*,5*R*)-3,3-difluoro-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]bicyclo[3.1.0]hexane-6-carboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[5-[(9*aR*)-1,3,4,6,7,8,9,9*a*-octahydropyrido[1,2-a]pyrazin-2-yl]-2-[(1*S*)-1-methoxyethyl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-methyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-pyrimidin-4-yl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(29),2,5(31),19,25,27-hexaen-7-yl]-2-phenyl-cyclopropanecarboxamide;

(1*R*,5*S,*6*s*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-3-oxabicyclo[3.1.0]hexane-6-carboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*,22*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17,22-trimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-methyl-cyclopropanecarboxamide;

2,2-difluoro-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(29),2,5(31),19,25,27-hexaen-7-yl]-1-methyl-cyclopropanecarboxamide;

N-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-

tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(29),2,5(31),19,25,27-hexaen-7-yl]-1,2-dimethyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(3-pyridyl)cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(4-pyridyl)cyclopropanecarboxamide;

(1*R*,2*R*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(4-pyridyl)cyclopropanecarboxamide;

2-(4-fluorophenyl)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(29),2,5(31),19,25,27-hexaen-7-yl]cyclopropanecarboxamide;

(1*S*,5*R,6r*)-*N*-[(7*S*,13*S*)-23,23-difluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-3-oxabicyclo[3.1.0]hexane-6-carboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17,23,23-tetramethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-pyridazin-3-yl-cyclopropanecarboxamide;

(1*R*,2*S*)-2-cyclopropyl-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(29),2,5(31),19,25,27-hexaen-7-yl]cyclopropanecarboxamide;

3,3-difluoro-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]cyclopentanecarboxamide;

N-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-oxabicyclo[2.1.1]hexane-1-carboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-23,23-difluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-methyl-cyclopropanecarboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(29),2,5(31),19,25,27-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*r*,2*S*,3*R*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17,23,23-tetramethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

trans-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(29),2,5(31),19,25,27-hexaen-7-yl]-4-(1-methyltetrazol-5-yl)cyclohexanecarboxamide;

trans-4-hydroxy-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-4-methyl-cyclohexanecarboxamide;

N-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]tricyclo[3.1.1.0^{3,6}]heptane-6-carboxamide;

(1*r*,2*S*,3*R*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-

tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-23,23-difluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-methyl-cyclopropanecarboxamide;

(1*r*,2*S*,3*R*)-*N*-[(7*S*,13*S*)-23,23-difluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

N-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]tetrahydropyran-4-carboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-23,23-difluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-phenyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-23,23-difluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-phenyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-pyrimidin-2-yl-cyclopropanecarboxamide;

(1*R*,2*R*)-*N*-[(7*S*,13*S*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-pyrimidin-2-yl-cyclopropanecarboxamide;

(1*r*,2*S*,3*R*)-*N*-[(7*S*,13*S*)-23,23-difluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(29),2,5(31),19,25,27-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*r*,2*S*,3*R*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*r*,2*S*,3*R*)-*N*-[(7*S*,13*S*)-23,23-difluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-pyrimidin-5-yl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(3-pyridyl)cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(3-pyridyl)cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-23,23-difluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(3-pyridyl)cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-23,23-difluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(3-pyridyl)cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-

tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-pyrimidin-5-yl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-pyrimidin-5-yl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-23,23-difluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-pyrimidin-5-yl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(3-pyridyl)cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(3-pyridyl)cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(3-pyridyl)cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-pyrazin-2-yl-cyclopropanecarboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,25-dioxa-4-thia-9,21,31,32-tetrazahexacyclo[24.3.1.1^{2,5}.1^{9,13}.0^{19,28}.0^{21,27}]dotriaconta-1(29),2,5(32),19,26(30),27-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*r*,2*S*,3*R*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[5-[(9*aR*)-1,3,4,6,7,8,9,9*a*-octahydropyrido[1,2-a]pyrazin-2-yl]-2-[(1*S*)-1-methoxyethyl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-

thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[5-[(9*aR*)-1,3,4,6,7,8,9,9*a*-octahydropyrido[1,2-a]pyrazin-2-yl]-2-[(1*S*)-1-methoxyethyl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(3-pyridyl)cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[5-[(9*aR*)-1,3,4,6,7,8,9,9*a*-octahydropyrido[1,2-a]pyrazin-2-yl]-2-[(1*S*)-1-methoxyethyl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-pyrimidin-5-yl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[5-[(9*aS*)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[2,1-c][1,4]oxazin-8-yl]-2-[(1*S*)-1-methoxyethyl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(3-pyridyl)cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[5-[(9*aS*)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[2,1-c][1,4]oxazin-8-yl]-2-[(1*S*)-1-methoxyethyl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-pyrimidin-5-yl-cyclopropanecarboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[5-(4-cyclopropylpiperazin-1-yl)-2-[(1*S*)-1-methoxyethyl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15,24-dioxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*,23*S*)-23-hydroxy-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-piperazin-1-yl-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*)-20-[5-[4-(2,2-difluoroethyl)piperazin-1-yl]-2-[(1*S*)-1-methoxyethyl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[5-[4-(2-fluoroethyl)piperazin-1-yl]-2-[(1*S*)-1-methoxyethyl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[5-[4-(3-hydroxypropyl)piperazin-1-yl]-2-[(1*S*)-1-methoxyethyl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*R*,2*R*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(4-methylpyrimidin-5-yl)cyclopropanecarboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[5-(4-ethylpiperazin-1-yl)-2-[(1*S*)-1-methoxyethyl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*R*,2*R*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-thiazol-4-yl-cyclopropanecarboxamide;

(1*r*,2*S*,3*R*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2-methoxyethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*R*,2*R*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(2-methyl-3-pyridyl)cyclopropanecarboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-tetrahydropyran-4-ylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(oxetan-3-yl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-

tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*r*,2*S*,3*R*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-[[(2*S*)-morpholin-2-yl]methyl]piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*R*,2*R*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2-(5-methyl-3-pyridyl)cyclopropanecarboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-[2-(2-oxopyrrolidin-1-yl)ethyl]piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2-tetrahydrofuran-3-yloxyethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*r*,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(3-methoxy-3-methyl-butyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*r*,2*S*,3*R*)-*N*-[(7*S*,13*S*)-29-fluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(28),2,5(31),19,25(29),26-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

(1*S*,2*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17,22,22-tetramethyl-8,14-dioxo-15-oxa-4-thia-9,21,30,31-tetrazahexacyclo[23.3.1.1^{2,5}.1^{9,13}.0^{19,27}.0^{21,26}]hentriaconta-1(29),2,5(31),19,25,27-hexaen-7-yl]-2-methyl-cyclopropanecarboxamide;

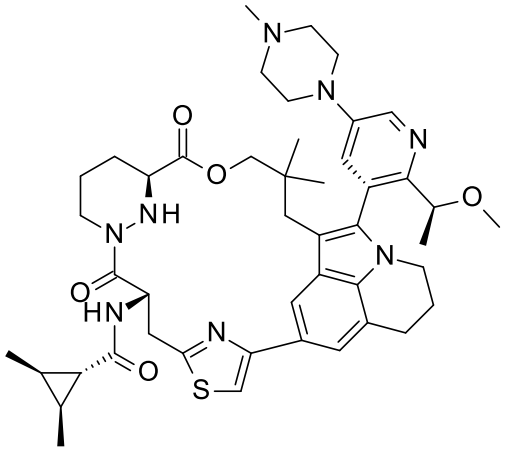
(1r,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,31,32-

tetrazahexacyclo[24.3.1.1^{2,5}.1^{9,13}.0^{19,28}.0^{21,27}]dotriaconta-1(29),2,5(32),19,26(30),27-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide; and

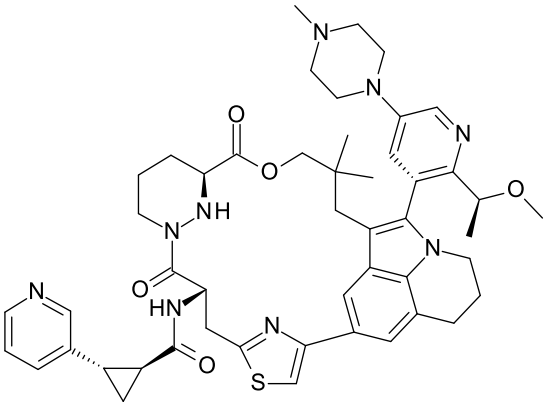
(1r,2*R*,3*S*)-*N*-[(7*S*,13*S*)-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,32,33-tetrazahexacyclo[25.3.1.1^{2,5}.1^{9,13}.0^{19,29}.0^{21,28}]tritriaconta-1(30),2,5(33),19,27(31),28-hexaen-7-yl]-2,3-dimethyl-cyclopropanecarboxamide;

or a pharmaceutically acceptable salt thereof.

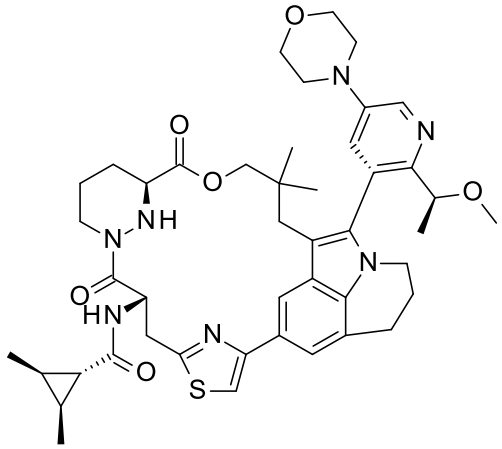
15. A compound selected from:



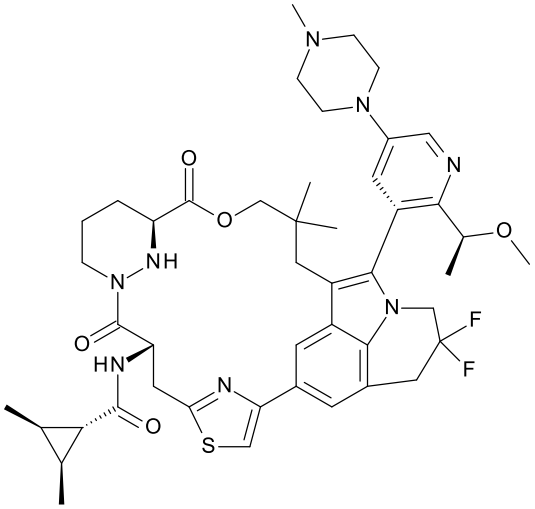
(Example 24);



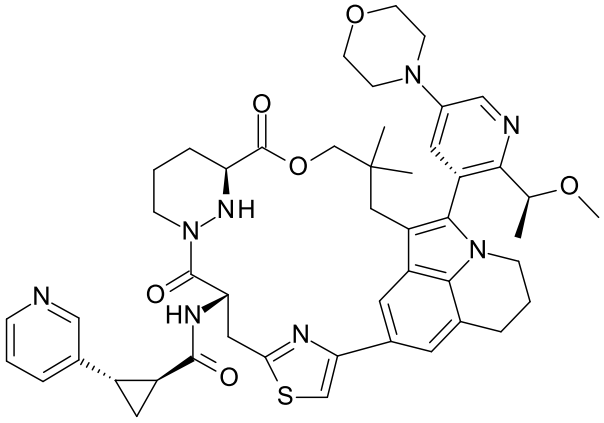
(Example 56);



(Example 73);



(Example 83); and

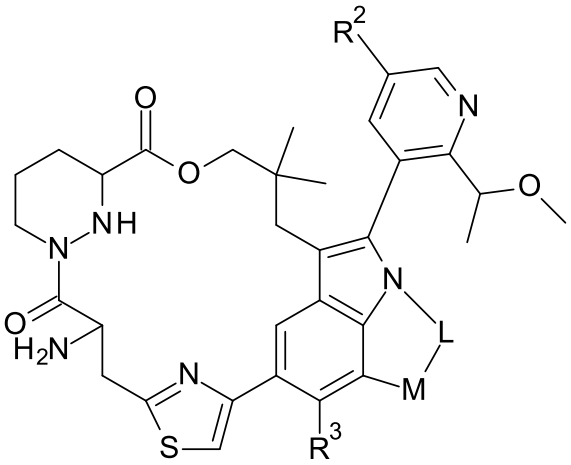


(Example 89);

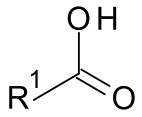
or a pharmaceutically acceptable salt thereof.

16. A process for the preparation of a compound according to any one of claims 1 to 15 comprising the following step:

a) coupling reaction between compound of formula (IIb),



(IIb), and acid (III),



(III), in the presence of a coupling reagent and a base to form the compound of formula (Ib);

wherein R^1, R^2, M and L are defined as in any one of claims 1 to 13; the coupling reagent is T_3P, HATU, PyBOP or EDCI/HOBt; the base is TEA, DIEPA or DMAP.

17. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 15 for use as therapeutically active substance.

18. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 15 and a pharmaceutically acceptable excipient.

19. A compound according to any one of claims 1 to 15 for use in treating a KRAS G12C protein-related disease.

20. A compound according to any one of claims 1 to 15 for use in treating a KRAS G12C, G12D and G12V protein-related disease.

21. A compound according to any one of claims 1 to 15 for use in inhibiting RAS interaction with downstream effectors, wherein the downstream effectors are RAF and PI3K.

22. A compound according to any one of claims 1 to 15 for use in inhibiting the propagating oncogenic MAPK and PI3K signaling.

23. A compound according to any one of claims 1 to 15 for use in the treatment or prophylaxis of cancers in a subject in need thereof, wherein the cancer comprises a first RAS mutation that is G12C and a second RAS mutation at a position selected from the group consisting of V8A, V9Y, S17E, A59T, T58I, D69P, M72I, S65W, R68S, D92R, H95N, Y96D, Q99W and F156L.

24. The use of a compound according to any one of claims 1 to 15 in the preparation of a medicament for the treatment or prophylaxis of cancers in a subject in need thereof, wherein the cancer comprises a first RAS mutation that is G12C and a second RAS mutation at a position selected from the group consisting of V8A, V9Y, S17E, A59T, T58I, D69P, M72I, S65W, R68S, D92R, H95N, Y96D, Q99W and F156L.

25. The use of a compound according to any one of claims 1 to 15 in the preparation of a medicament for the treatment or prophylaxis of KRAS mutation driven cancers, wherein the cancer is selected from pancreatic cancer, colorectal cancer, lung cancer, esophageal cancer, gallbladder cancer, melanoma ovarian cancer and endometrial cancer.

26. A compound according to any one of claims 1 to 15 for use in the treatment or prophylaxis of KRAS mutation driven cancers, wherein the cancer is selected from pancreatic cancer, colorectal cancer, lung cancer, esophageal cancer, gallbladder cancer, melanoma ovarian cancer and endometrial cancer.

27. The use of a compound according to any one of claims 1 to 15 in the preparation of a medicament for the treatment or prophylaxis of primary central nervous system (CNS) tumors harboring RAS mutations or RAS driven cancers with brain metastases; wherein the CNS tumor is primary melanocytic tumors of the CNS harboring NRAS mutation; wherein the cancer is selected from pancreatic adenocarcinoma, colorectal cancer, non-small cell lung cancer.

28. A compound according to any one of claims 1 to 15 for use in the treatment or prophylaxis of primary central nervous system (CNS) tumors harboring RAS mutations or RAS driven cancers with brain metastases; wherein the CNS tumor is primary melanocytic tumors of the CNS harboring NRAS mutation; wherein the cancer is selected from pancreatic adenocarcinoma, colorectal cancer, non-small cell lung cancer.

29. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 15 for use in the treatment or prophylaxis of KRAS mutation driven cancers, wherein the cancer is selected from pancreatic adenocarcinoma, colorectal cancer and non-small cell lung cancer.

30. The use of a compound according to any one of claims 1 to 15 in the preparation of a medicament for the treatment or prophylaxis of KRAS mutation driven cancers, wherein the cancer is selected from pancreatic adenocarcinoma, colorectal cancer and non-small cell lung cancer.

31. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 15, when manufactured according to a process of claim 16.