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(71) **Applicant**: **EOLAS THERAPEUTICS, INC.** [US/US]; 7445 Trigo Lane, Carlsbad, California 92009 (US).

(72) **Inventors**: **KAMENECKA, Theodore**; 50 Stoney Drive, Palm Beach Gardens, Florida 33410 (US). **JIANG, Rong**; 427 Timber Meadow Lake Drive, Fuquay Varina, North Carolina 27526 (US). **SONG, Xinyi**; 7445 Trigo Lane, Carlsbad, California 92009 (US).

(74) **Agents**: **PERDOK SHONKA, Monique M.** et al.; Schwegman, Lundberg & Woessner, P.A., P.O. Box 2938, Minneapolis, Minnesota 55402 (US).

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(54) **Title**: SUBSTITUTED PROLINES / PIPERIDINES AS OREXIN RECEPTOR ANTAGONISTS

(57) **Abstract**: The present invention is directed to compounds that can modulate the bioactivity of an orexin receptor such as OX1 or OX2, or both; to pharmaceutical compositions and combinations comprising a compound of the invention; to methods of treatment of malconditions in patients wherein modulation of an orexin receptor is medically indicated; and to methods of preparation of compounds of the invention.

Substituted Prolines / Piperidines as Orexin Receptor Antagonists

STATEMENT OF GOVERNMENT SUPPORT

This work was supported by Grant Numbers 5 RO1 DA023915and 1 P01 DA033622 from the National Institutes of Health. The government has certain rights in this invention.

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the priority of U.S. provisional application serial number 61/596,062, filed February 7, 2012, the disclosure of which is incorporated herein by reference in its entirety.

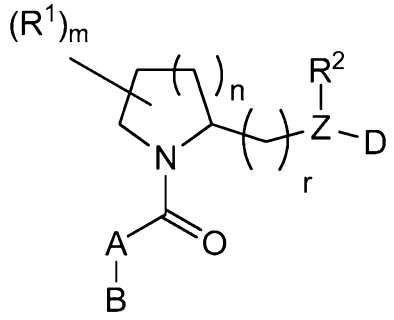
BACKGROUND

Orexins are a family of homologous peptides including species orexin A, or OR-A, and orexin B, or OR-B. Orexin A is a 33 amino acid peptide and orexin B is a 28 amino acid peptide (Sakurai T. et al., Cell (1998), 92, 573-585). Orexins are produced in neurons of the lateral hypothalamus and bind to at least two distinct G-protein-coupled receptors, termed OX_1 and OX_2 receptors. The receptor OX_1 is selective for OR-A, while the receptor OX_2 can bind both OR-A and OR-B. Orexins are found to stimulate food consumption, regulate states of sleep and wakefulness, and may be involved in neural mechanisms of drug abuse and addiction.

SUMMARY

The present invention is directed to compounds that can modulate the bioactivity of an orexin receptor such as OX_1 or OX_2, or both; to pharmaceutical compositions and combinations comprising a compound of the invention; to methods of treatment of malconditions in patients wherein modulation of an orexin receptor is medically indicated; and to methods of preparation of compounds of the invention.

In various embodiments, the invention provides receptor-modulatory non-peptidic small molecules that can activate or inhibit one or more classes of orexin receptors in the human nervous system. In various embodiments, the invention provides a compound of formula (I),



(I)

wherein

A comprises aryl or heteroaryl;

B is absent, or comprises aryl, aryloxy, heteroaryl, or heteroaryloxy;

wherein A or B or both can each independently be unsubstituted or can each independently be mono- or multi-substituted with J or with R', or both;

D comprises aryl, aroyl, heteroaryl, or heteroaroyl, wherein D can be unsubstituted or can be mono- or independently multi-substituted with J or with R', or with both;

Z is N or O, provided that when Z is O, R^2 is absent

R^1 comprises independently at each occurrence halo, oxo, hydroxy, cyano, (C_{1-4})alkyl, (C_{1-4})alkoxy, (C_{1-4})acyloxy, (C_{1-4})acylamido, haloalkyl, haloalkoxy, NR^aR^b, $C(=O)NR^aR^b$, $C(=O)OR^a$, SO_2R^a, $SO_2NR^aR^b$, cycloalkyl, heterocyclyl, aryl, aralkyl, or heteroaryl;

or one or more R^1 groups together with the ring to which they are bonded form a bicyclo[2.2.2], bicyclo[3.3.0], or bicyclo[4.3.0] ring system, wherein any bicyclo ring system can be *cis*-fused or *trans*-fused, wherein any alkyl, alkoxy, bicyclo ring system, cycloalkyl, heterocyclyl, aryl, aralkyl, or heteroaryl can be mono- or independently multi-substituted with J or with R', or with both;

R^a and R^b are independently at each occurrence H, (C_{1-4})alkyl, aralkyl, (C_{1-5})acyl, or R^a and R^b together with the nitrogen atom to which they are bonded form a 4-7 membered ring optionally further comprising 1 or 2 NR^c, O, S, SO, or SO_2, wherein R^c is H or (C_{1-4})alkyl, wherein any R^a, R^b, or R^c can be mono- or independently multi-substituted with J or with R', or both;

R^2 comprises H, (C_{1-4})alkyl, or (C_{1-5})acyl, or R^2 together with D and the nitrogen atom to which they are bonded form a phthalimido group, wherein any alkyl, acyl, or phthalimido group is optionally mono- or independently multi-substituted with J or with R', or with both;

J is halogen, (C1-C6)alkyl, OR', CN, CF_3, OCF_3, =O, =S, C(O), S(O), methylenedioxy, ethylenedioxy, $(CH_2)_{0-p}N(R')_2$, $(CH_2)_{0-p}SR'$, $(CH_2)_{0-p}S(O)R'$, $(CH_2)_{0-p}S(O)_2R'$, $(CH_2)_{0-p}S(O)_2N(R')_2$, $(CH_2)_{0-p}SO_3R'$, $(CH_2)_{0-p}C(O)R'$, $(CH_2)_{0-p}C(O)C(O)R'$, $(CH_2)_{0-p}C(O)CH_2C(O)R'$, $(CH_2)_{0-p}C(S)R'$, $(CH_2)_{0-p}C(O)OR'$, $(CH_2)_{0-p}OC(O)R'$, $(CH_2)_{0-p}C(O)N(R')_2$, $(CH_2)_{0-p}OC(O)N(R')_2$, $(CH_2)_{0-p}C(S)N(R')_2$, $(CH_2)_{0-p}NH\text{-}C(O)R'$, $(CH_2)_{0-p}N(R')N(R')C(O)R'$, $(CH_2)_{0-p}N(R')N(R')C(O)OR'$, $(CH_2)_{0-p}N(R')N(R')CON(R')_2$, $(CH_2)_{0-p}N(R')SO_2R'$, $(CH_2)_{0-p}N(R')SO_2N(R')_2$, $(CH_2)_{0-p}N(R')C(O)OR'$, $(CH_2)_{0-p}N(R')C(O)R'$, $(CH_2)_{0-p}N(R')C(S)R'$, $(CH_2)_{0-p}N(R')C(O)N(R')_2$, $(CH_2)_{0-p}N(R')C(S)N(R')_2$, $(CH_2)_{0-p}N(COR')COR'$, $(CH_2)_{0-p}N(OR')R'$, $(CH_2)_{0-p}C(=NH)N(R')_2$, $(CH_2)_{0-p}C(O)N(OR')R'$, or $(CH_2)_{0-p}C(=NOR')R'$;

wherein, each R' is independently at each occurrence hydrogen, $(C_1\text{-}C_{12})$-alkyl, $(C_2\text{-}C_{12})$-alkenyl, $(C_2\text{-}C_{12})$-alkynyl, $(C_3\text{-}C_{10})$-cycloalkyl, $(C_3\text{-}C_{10})$-cycloalkenyl, [$(C_3\text{-}C_{10})$cycloalkyl or $(C_3\text{-}C_{10})$-cycloalkenyl]-[$(C_1\text{-}C_{12})$-alkyl or $(C_2\text{-}C_{12})$-alkenyl or $(C_2\text{-}C_{12})$-alkynyl], $(C_6\text{-}C_{10})$-aryl, $(C_6\text{-}C_{10})$-aryl-[$(C_1\text{-}C_{12})$-alkyl or $(C_2\text{-}C_{12})$-alkenyl or $(C_2\text{-}C_{12})$-alkynyl], mono- or bicyclic 3-10 membered heterocyclyl, mono- or bicyclic 3-10 membered heterocyclyl-[$(C_1\text{-}C_{12})$-alkyl or $(C_2\text{-}C_{12})$-alkenyl or $(C_2\text{-}C_{12})$-alkynyl], mono- or bicyclic 5-10 membered heteroaryl, or mono- or bicyclic 5-10 membered heteroaryl-[$(C_1\text{-}C_{12})$-alkyl or $(C_2\text{-}C_{12})$-alkenyl or $(C_2\text{-}C_{12})$-alkynyl], wherein R' is substituted with 0-3 substituents selected independently from J^R;

or, when two R' are bound to a nitrogen atom or to two adjacent nitrogen atoms, the two R' groups together with the nitrogen atom or atoms to which they are bound can form a 3- to 8-membered monocyclic heterocyclic ring, or an 8- to 20-membered, bicyclic or tricyclic, heterocyclic ring system, wherein any ring or ring system can further contain 1-3 additional heteroatoms selected from the group consisting of N, NR', O, S, S(O) and $S(O)_2$, wherein each ring is substituted with 0-3 substituents selected independently from J^R; wherein, in any bicyclic or tricyclic ring system, each ring is linearly fused, bridged, or spirocyclic, wherein each ring is either aromatic or nonaromatic, wherein each ring can be fused to a $(C_6\text{-}C_{10})$aryl, mono- or bicyclic 5-10 membered heteroaryl, $(C_3\text{-}C_{10})$cycloalkyl or mono- or bicyclic 3-10 membered heterocyclyl;

J^R is halogen, OR, CN, CF_3, OCF_3, =O, =S, C(O), S(O), methylenedioxy, ethylenedioxy, $(CH_2)_{0-p}N(R)_2$, $(CH_2)_{0-p}SR$, $(CH_2)_{0-p}S(O)R$, $(CH_2)_{0-p}S(O)_2R$,

$(CH_2)_{0-p}S(O)_2N(R)_2$, $(CH_2)_{0-p}SO_3R$, $(CH_2)_{0-p}C(O)R$, $(CH_2)_{0-p}C(O)C(O)R$, $(CH_2)_{0-p}C(O)CH_2C(O)R$, $(CH_2)_{0-p}C(S)R$, $(CH_2)_{0-p}C(O)OR$, $(CH_2)_{0-p}OC(O)R$, $(CH_2)_{0-p}C(O)N(R)_2$, $(CH_2)_{0-p}OC(O)N(R)_2$, $(CH_2)_{0-p}C(S)N(R)_2$, $(CH_2)_{0-p}NH\text{-}C(O)R$, $(CH_2)_{0-p}N(R)N(R)C(O)R$, $(CH_2)_{0-p}N(R)N(R)C(O)OR$, $(CH_2)_{0-p}N(R)N(R)CON(R)_2$, $(CH_2)_{0-p}N(R)SO_2R$, $(CH_2)_{0-p}N(R)SO_2N(R)_2$, $(CH_2)_{0-p}N(R)C(O)OR$, $(CH_2)_{0-p}N(R)C(O)R$, $(CH_2)_{0-p}N(R)C(S)R$, $(CH_2)_{0-p}N(R)C(O)N(R)_2$, $(CH_2)_{0-p}N(R)C(S)N(R)_2$, $(CH_2)_{0-p}N(COR)COR$, $(CH_2)_{0-p}N(OR)R$, $(CH_2)_{0-p}C(=NH)N(R)_2$, $(CH_2)_{0-p}C(O)N(OR)R$, or $(CH_2)_{0-p}C(=NOR)R$; and,

R is independently at each occurrence hydrogen, $(C_1\text{-}C_{12})$-alkyl, $(C_2\text{-}C_{12})$-alkenyl, $(C_2\text{-}C_{12})$-alkynyl, $(C_3\text{-}C_{10})$-cycloalkyl, $(C_3\text{-}C_{10})$-cycloalkenyl, [$(C_3\text{-}C_{10})$cycloalkyl or $(C_3\text{-}C_{10})$-cycloalkenyl]-[$(C_1\text{-}C_{12})$-alkyl or $(C_2\text{-}C_{12})$-alkenyl or $(C_2\text{-}C_{12})$-alkynyl], $(C_6\text{-}C_{10})$-aryl, $(C_6\text{-}C_{10})$-aryl-[$(C_1\text{-}C_{12})$-alkyl or $(C_2\text{-}C_{12})$-alkenyl or $(C_2\text{-}C_{12})$-alkynyl], mono- or bicyclic 3-10 membered heterocyclyl, mono- or bicyclic 3-10 membered heterocyclyl-[$(C_1\text{-}C_{12})$-alkyl or $(C_2\text{-}C_{12})$-alkenyl or $(C_2\text{-}C_{12})$-alkynyl], mono- or bicyclic 5-10 membered heteroaryl, or mono- or bicyclic 5-10 membered heteroaryl-[$(C_1\text{-}C_{12})$-alkyl or $(C_2\text{-}C_{12})$-alkenyl or $(C_2\text{-}C_{12})$-alkynyl];

m is 0, 1, 2, 3, 4, 5, or 6; n is 1, 2, or 3; p = 0, 1, or 2; r = 0, 1, 2, or 3;

or any salt or hydrate thereof.

In various embodiments, the invention provides pharmaceutical compositions comprising a compound of the invention and a pharmaceutically acceptable excipient.

In various embodiments, the invention provides a method of modulating an orexin receptor, such as OX_1 or OX_2, or both, comprising contacting the receptor with an effective amount or concentration of a compound of the invention.

In various embodiments, the invention provides a method of treating a malcondition in a patient wherein modulation of an orexin receptor is medically indicating, comprising administering to the patient a compound of the invention in a dose, at a frequency, and for a duration to provide a beneficial effect to the patient. The orexin receptor can be OX_1, or can be OX_2. In various embodiments, the malcondition can comprise an eating disorder, obesity, alcoholism or an alcohol-related disorder, drug abuse or addiction, a sleep

disorder, a cognitive dysfunction in a psychiatric or neurologic disorder, depression, anxiety, panic disorder, schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's chorea, head ache, migraine, pain, gastrointestinal diseases, epilepsy, inflammations, immune-related diseases, endocrine-related diseases, cancer, hypertension, behavior disorder, mood disorder, manic depression, dementia, sex disorder, psychosexual disorder, and renal disease . Drug abuse and addiction can include abuse of or addiction to cocaine, opiates, amphetamines, or nicotine.

DETAILED DESCRIPTION

As used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise.

The term "about" as used herein, when referring to a numerical value or range, allows for a degree of variability in the value or range, for example, within 10%, or within 5% of a stated value or of a stated limit of a range.

As used herein, "individual" (as in the subject of the treatment) means both mammals and non-mammals. Mammals include, for example, humans; non-human primates, e.g. apes and monkeys; and non-primates, e.g. dogs, cats, cattle, horses, sheep, and goats. Non-mammals include, for example, fish and birds.

The term "disease" or "disorder" or "malcondition" are used interchangeably, and are used to refer to diseases or conditions wherein an orexin receptor plays a role in the biochemical mechanisms involved in the disease or malcondition such that a therapeutically beneficial effect can be achieved by acting on the receptor. "Acting on" an orexin receptor can include binding to the orexin receptor and/or inhibiting the bioactivity of the orexin receptor.

The expression "effective amount", when used to describe therapy to an individual suffering from a disorder, refers to the amount of a compound of the invention that is effective to inhibit or otherwise act on an orexin receptor in the individual's tissues wherein the orexin receptor involved in the disorder is active, wherein such inhibition or other action occurs to an extent sufficient to produce a beneficial therapeutic effect.

"Substantially" as the term is used herein means completely or almost completely; for example, a composition that is "substantially free" of a component either has none of the component or contains such a trace amount that any relevant functional property of the composition is unaffected by the presence of the trace amount, or a compound is "substantially pure" is there are only negligible traces of impurities present.

"Treating" or "treatment" within the meaning herein refers to an alleviation of symptoms associated with a disorder or disease, or inhibition of further progression or worsening of those symptoms, or prevention or prophylaxis of the disease or disorder, or curing the disease or disorder. Similarly, as used herein, an "effective amount" or a "therapeutically effective amount" of a compound of the invention refers to an amount of the compound that alleviates, in whole or in part, symptoms associated with the disorder or condition, or halts or slows further progression or worsening of those symptoms, or prevents or provides prophylaxis for the disorder or condition. In particular, a "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount is also one in which any toxic or detrimental effects of compounds of the invention are outweighed by the therapeutically beneficial effects.

By "chemically feasible" is meant a bonding arrangement or a compound where the generally understood rules of organic structure are not violated; for example a structure within a definition of a claim that would contain in certain situations a pentavalent carbon atom that would not exist in nature would be understood to not be within the claim. The structures disclosed herein, in all of their embodiments are intended to include only "chemically feasible" structures, and any recited structures that are not chemically feasible, for example in a structure shown with variable atoms or groups, are not intended to be disclosed or claimed herein.

When a substituent is specified to be an atom or atoms of specified identity, "or a bond", a configuration is referred to when the substituent is "a bond" that the groups that are immediately adjacent to the specified substituent are directly connected to each other in a chemically feasible bonding configuration.

All chiral, diastereomeric, racemic forms of a structure are intended, unless a particular stereochemistry or isomeric form is specifically indicated. Compounds used in the present invention can include enriched or resolved optical isomers at any or all asymmetric atoms as are apparent from the depictions, at any degree of enrichment. Both racemic and diastereomeric mixtures, as well as the individual optical isomers can be isolated or synthesized so as to be substantially free of their enantiomeric or diastereomeric partners, and these are all within the scope of the invention. In various embodiments, the invention can provide enantiomerically pure forms of the claimed compounds, or racemic mixtures, or enantionmerically enriched mixtures, or (when more than a single chiral center is present), diastereomerically pure compounds, or diastereomeric mixtures in any relative proportions.

The inclusion of an isotopic form of one or more atoms in a molecule that is different from the naturally occurring isotopic distribution of the atom in nature is referred to as an "isotopically labeled form" of the molecule. All isotopic forms of atoms are included as options in the composition of any molecule, unless a specific isotopic form of an atom is indicated. For example, any hydrogen atom or set thereof in a molecule can be any of the isotopic forms of hydrogen, i.e., protium (^{1}H), deuterium (^{2}H), or tritium (^{3}H) in any combination. Similarly, any carbon atom or set thereof in a molecule can be any of the isotopic form of carbons, such as ^{11}C, ^{12}C, ^{13}C, or ^{14}C, or any nitrogen atom or set thereof in a molecule can be any of the isotopic forms of nitrogen, such as ^{13}N, ^{14}N, or ^{15}N. A molecule can include any combination of isotopic forms in the component atoms making up the molecule, the isotopic form of every atom forming the molecule being independently selected. In a multi-molecular sample of a compound, not every individual molecule necessarily has the same isotopic composition. For example, a sample of a compound can include molecules containing various different isotopic compositions, such as in a tritium or ^{14}C radiolabeled sample where only some fraction of the set of molecules making up the macroscopic sample contains a radioactive atom. It is also understood that many elements that are not artificially isotopically enriched themselves are mixtures of naturally occurring isotopic forms, such as ^{14}N and ^{15}N, ^{32}S and ^{34}S, and so forth. A molecule as recited herein is defined as including isotopic forms of all its constituent elements at each position in the

molecule. As is well known in the art, isotopically labeled compounds can be prepared by the usual methods of chemical synthesis, except substituting an isotopically labeled precursor molecule. The isotopes, radiolabeled or stable, can be obtained by any method known in the art, such as generation by neutron absorption of a precursor nuclide in a nuclear reactor, by cyclotron reactions, or by isotopic separation such as by mass spectrometry. The isotopic forms are incorporated into precursors as required for use in any particular synthetic route. For example, ^{14}C and ^{3}H can be prepared using neutrons generated in a nuclear reactor. Following nuclear transformation, ^{14}C and ^{3}H are incorporated into precursor molecules, followed by further elaboration as needed.

The term "amino protecting group" or "N-protected" as used herein refers to those groups intended to protect an amino group against undesirable reactions during synthetic procedures and which can later be removed to reveal the amine. Commonly used amino protecting groups are disclosed in Protective Groups in Organic Synthesis, Greene, T.W.; Wuts, P. G. M., John Wiley & Sons, New York, NY, (3rd Edition, 1999). Amino protecting groups include acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl and the like; alkoxy- or aryloxy-carbonyl groups (which form urethanes with the protected amine) such as benzyloxycarbonyl (Cbz), p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl (Boc), diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl (Alloc), 2,2,2-trichloroethoxycarbonyl, 2-trimethylsilylethyloxycarbonyl (Teoc), phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl (Fmoc), cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl,

phenylthiocarbonyl and the like; aralkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. Amine protecting groups also include cyclic amino protecting groups such as phthaloyl and dithiosuccinimidyl, which incorporate the amino nitrogen into a heterocycle. Typically, amino protecting groups include formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, Alloc, Teoc, benzyl, Fmoc, Boc and Cbz. It is well within the skill of the ordinary artisan to select and use the appropriate amino protecting group for the synthetic task at hand.

The term "hydroxyl protecting group" or "O-protected" as used herein refers to those groups intended to protect an OH group against undesirable reactions during synthetic procedures and which can later be removed to reveal the amine. Commonly used hydroxyl protecting groups are disclosed in Protective Groups in Organic Synthesis, Greene, T.W.; Wuts, P. G. M., John Wiley & Sons, New York, NY, (3rd Edition, 1999). Hydroxyl protecting groups include acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl and the like; acyloxy groups (which form urethanes with the protected amine) such as benzyloxycarbonyl (Cbz), p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl (Boc), diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl (Alloc), 2,2,2-trichloroethoxycarbonyl, 2-trimethylsilylethyloxycarbonyl (Teoc), phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl (Fmoc), cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, phenylthiocarbonyl and the like; aralkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the

like. It is well within the skill of the ordinary artisan to select and use the appropriate hydroxyl protecting group for the synthetic task at hand.

A "carboxyl-activating" group or procedure, as the term is used herein, refers to a group replacing the hydroxyl group of a carboxyl to form a species that more readily undergoes reactions with nucleophilic reagents such as alcohols and amines. An example is an acyl halide, such as an acid chloride, that is activated for reactions leading to the formation of esters and amides. Another example is an N-hydroxy ester of a carboxylic acid, such as an N-hydroxysuccinimide ester, or an N-hydroxybenztriazole ester. Another example is a carbodiimide that reacts with the hydroxyl group of a carboxyl group to form an O-acylisourea, that is thus activated for subsequent reaction with a nucleophile.

In general, "substituted" refers to an organic group as defined herein in which one or more bonds to a hydrogen atom contained therein are replaced by one or more bonds to a non-hydrogen atom such as, but not limited to, a halogen (i.e., F, Cl, Br, and I); an oxygen atom in groups such as hydroxyl groups, alkoxy groups, aryloxy groups, aralkyloxy groups, oxo(carbonyl) groups, carboxyl groups including carboxylic acids, carboxylates, and carboxylate esters; a sulfur atom in groups such as thiol groups, alkyl and aryl sulfide groups, sulfoxide groups, sulfone groups, sulfonyl groups, and sulfonamide groups; a nitrogen atom in groups such as amines, hydroxylamines, nitriles, nitro groups, N-oxides, hydrazides, azides, and enamines; and other heteroatoms in various other groups. Non-limiting examples of substituents that can be bonded to a substituted carbon (or other) atom include F, Cl, Br, I, OR', $OC(O)N(R')_2$, CN, NO, NO_2, ONO_2, azido, CF_3, OCF_3, R', O (oxo), S (thiono), C(O), S(O), methylenedioxy, ethylenedioxy, $N(R')_2$, SR', SOR', SO_2R', $SO_2N(R')_2$, SO_3R', C(O)R', C(O)C(O)R', $C(O)CH_2C(O)R'$, C(S)R', C(O)OR', OC(O)R', $C(O)N(R')_2$, $OC(O)N(R')_2$, $C(S)N(R')_2$, $(CH_2)_{0-2}N(R')C(O)R'$, $(CH_2)_{0-2}N(R')N(R')_2$, N(R')N(R')C(O)R', N(R')N(R')C(O)OR', $N(R')N(R')CON(R')_2$, $N(R')SO_2R'$, $N(R')SO_2N(R')_2$, N(R')C(O)OR', N(R')C(O)R', N(R')C(S)R', $N(R')C(O)N(R')_2$, $N(R')C(S)N(R')_2$, N(COR')COR', N(OR')R', $C(=NH)N(R')_2$, C(O)N(OR')R', or C(=NOR')R' wherein R' can be hydrogen or a carbon-based moiety, and wherein the carbon-based moiety can itself be further substituted.

When a substituent is monovalent, such as, for example, F or Cl, it is bonded to the atom it is substituting by a single bond. When a substituent is more than monovalent, such as O, which is divalent, it can be bonded to the atom it is substituting by more than one bond, i.e., a divalent substituent is bonded by a double bond; for example, a C substituted with O forms a carbonyl group, C=O, which can also be written as "CO", "C(O)", or "C(=O)", wherein the C and the O are double bonded. When a carbon atom is substituted with a double-bonded oxygen (=O) group, the oxygen substituent is termed an "oxo" group. When a divalent substituent such as NR is double-bonded to a carbon atom, the resulting C(=NR) group is termed an "imino" group. When a divalent substituent such as S is double-bonded to a carbon atom, the results C(=S) group is termed a "thiocarbonyl" group.

Alternatively, a divalent substituent such as O, S, C(O), S(O), or $S(O)_2$ can be connected by two single bonds to two different carbon atoms. For example, O, a divalent substituent, can be bonded to each of two adjacent carbon atoms to provide an epoxide group, or the O can form a bridging ether group, termed an "oxy" group, between adjacent or non-adjacent carbon atoms, for example bridging the 1,4-carbons of a cyclohexyl group to form a [2.2.1]-oxabicyclo system. Further, any substituent can be bonded to a carbon or other atom by a linker, such as $(CH_2)_n$ or $(CR'_2)_n$ wherein n is 1, 2, 3, or more, and each R' is independently selected.

C(O) and $S(O)_2$ groups can be bound to one or two heteroatoms, such as nitrogen, rather than to a carbon atom. For example, when a C(O) group is bound to one carbon and one nitrogen atom, the resulting group is called an “amide” or “carboxamide.” When a C(O) group is bound to two nitrogen atoms, the functional group is termed a urea. When a $S(O)_2$ group is bound to one carbon and one nitrogen atom, the resulting unit is termed a “sulfonamide.” When a $S(O)_2$ group is bound to two nitrogen atoms, the resulting unit is termed a “sulfamate.”

Substituted alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl groups as well as other substituted groups also include groups in which one or more bonds to a hydrogen atom are replaced by one or more bonds, including double or triple bonds, to a carbon atom, or to a heteroatom such as, but not limited to, oxygen in carbonyl (oxo), carboxyl, ester, amide, imide, urethane, and urea

groups; and nitrogen in imines, hydroxyimines, oximes, hydrazones, amidines, guanidines, and nitriles.

Substituted ring groups such as substituted cycloalkyl, aryl, heterocyclyl and heteroaryl groups also include rings and fused ring systems in which a bond to a hydrogen atom is replaced with a bond to a carbon atom. Therefore, substituted cycloalkyl, aryl, heterocyclyl and heteroaryl groups can also be substituted with alkyl, alkenyl, and alkynyl groups as defined herein.

By a "ring system" as the term is used herein is meant a moiety comprising one, two, three or more rings, which can be substituted with non-ring groups or with other ring systems, or both, which can be fully saturated, partially unsaturated, fully unsaturated, or aromatic, and when the ring system includes more than a single ring, the rings can be fused, bridging, or spirocyclic. By "spirocyclic" is meant the class of structures wherein two rings are fused at a single tetrahedral carbon atom, as is well known in the art.

As to any of the groups described herein, which contain one or more substituents, it is understood, of course, that such groups do not contain any substitution or substitution patterns which are sterically impractical and/or synthetically non–feasible. In addition, the compounds of this disclosed subject matter include all stereochemical isomers arising from the substitution of these compounds.

Selected substituents within the compounds described herein are present to a recursive degree. In this context, “recursive substituent” means that a substituent may recite another instance of itself. Because of the recursive nature of such substituents, theoretically, a large number may be present in any given claim. One of ordinary skill in the art of medicinal chemistry and organic chemistry understands that the total number of such substituents is reasonably limited by the desired properties of the compound intended. Such properties include, by of example and not limitation, physical properties such as molecular weight, solubility or log P, application properties such as activity against the intended target, and practical properties such as ease of synthesis.

Recursive substituents are an intended aspect of the disclosed subject matter. One of ordinary skill in the art of medicinal and organic chemistry understands the versatility of such substituents. To the degree that recursive

substituents are present in a claim of the disclosed subject matter, the total number should be determined as set forth above.

Alkyl groups include straight chain and branched alkyl groups and cycloalkyl groups having from 1 to about 20 carbon atoms, and typically from 1 to 12 carbons or, in some embodiments, from 1 to 8 carbon atoms. Examples of straight chain alkyl groups include those with from 1 to 8 carbon atoms such as methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, and n-octyl groups. Examples of branched alkyl groups include, but are not limited to, isopropyl, iso-butyl, sec-butyl, t-butyl, neopentyl, isopentyl, and 2,2-dimethylpropyl groups. Representative substituted alkyl groups can be substituted one or more times with any of the groups listed above, for example, amino, hydroxy, cyano, carboxy, nitro, thio, alkoxy, and halogen groups.

Cycloalkyl groups are cyclic alkyl groups such as, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl groups. In some embodiments, the cycloalkyl group can have 3 to about 8-12 ring members, whereas in other embodiments the number of ring carbon atoms range from 3 to 4, 5, 6, or 7. Cycloalkyl groups further include polycyclic cycloalkyl groups such as, but not limited to, norbornyl, adamantyl, bornyl, camphenyl, isocamphenyl, and carenyl groups, and fused rings such as, but not limited to, decalinyl, and the like. Cycloalkyl groups also include rings that are substituted with straight or branched chain alkyl groups as defined above. Representative substituted cycloalkyl groups can be mono-substituted or substituted more than once, such as, but not limited to, 2,2-, 2,3-, 2,4- 2,5- or 2,6-disubstituted cyclohexyl groups or mono-, di- or tri-substituted norbornyl or cycloheptyl groups, which can be substituted with, for example, amino, hydroxy, cyano, carboxy, nitro, thio, alkoxy, and halogen groups. The term "cycloalkenyl" alone or in combination denotes a cyclic alkenyl group.

The terms "carbocyclic," "carbocyclyl," and "carbocycle" denote a ring structure wherein the atoms of the ring are carbon, such as a cycloalkyl group or an aryl group. In some embodiments, the carbocycle has 3 to 8 ring members, whereas in other embodiments the number of ring carbon atoms is 4, 5, 6, or 7. Unless specifically indicated to the contrary, the carbocyclic ring can be substituted with as many as N-1 substituents wherein N is the size of the carbocyclic ring with, for example, alkyl, alkenyl, alkynyl, amino, aryl, hydroxy,

cyano, carboxy, heteroaryl, heterocyclyl, nitro, thio, alkoxy, and halogen groups, or other groups as are listed above. A carbocyclyl ring can be a cycloalkyl ring, a cycloalkenyl ring, or an aryl ring. A carbocyclyl can be monocyclic or polycyclic, and if polycyclic each ring can be independently be a cycloalkyl ring, a cycloalkenyl ring, or an aryl ring.

(Cycloalkyl)alkyl groups, also denoted cycloalkylalkyl, are alkyl groups as defined above in which a hydrogen or carbon bond of the alkyl group is replaced with a bond to a cycloalkyl group as defined above.

Alkenyl groups include straight and branched chain and cyclic alkyl groups as defined above, except that at least one double bond exists between two carbon atoms. Thus, alkenyl groups have from 2 to about 20 carbon atoms, and typically from 2 to 12 carbons or, in some embodiments, from 2 to 8 carbon atoms. Examples include, but are not limited to vinyl, $-CH=CH(CH_3)$, $-CH=C(CH_3)_2$, $-C(CH_3)=CH_2$, $-C(CH_3)=CH(CH_3)$, $-C(CH_2CH_3)=CH_2$, cyclohexenyl, cyclopentenyl, cyclohexadienyl, butadienyl, pentadienyl, and hexadienyl among others.

Cycloalkenyl groups include cycloalkyl groups having at least one double bond between 2 carbons. Thus for example, cycloalkenyl groups include but are not limited to cyclohexenyl, cyclopentenyl, and cyclohexadienyl groups. Cycloalkenyl groups can have from 3 to about 8-12 ring members, whereas in other embodiments the number of ring carbon atoms range from 3 to 5, 6, or 7. Cycloalkyl groups further include polycyclic cycloalkyl groups such as, but not limited to, norbornyl, adamantyl, bornyl, camphenyl, isocamphenyl, and carenyl groups, and fused rings such as, but not limited to, decalinyl, and the like, provided they include at least one double bond within a ring. Cycloalkenyl groups also include rings that are substituted with straight or branched chain alkyl groups as defined above.

(Cycloalkenyl)alkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of the alkyl group is replaced with a bond to a cycloalkenyl group as defined above.

Alkynyl groups include straight and branched chain alkyl groups, except that at least one triple bond exists between two carbon atoms. Thus, alkynyl groups have from 2 to about 20 carbon atoms, and typically from 2 to 12 carbons or, in some embodiments, from 2 to 8 carbon atoms. Examples include, but are

not limited to –C≡CH, -C≡C(CH_3), -C≡C(CH_2CH_3), -CH_2C≡CH, -CH_2C≡C(CH_3), and -CH_2C≡C(CH_2CH_3) among others.

The term "heteroalkyl" by itself or in combination with another term means, unless otherwise stated, a stable straight or branched chain alkyl group consisting of the stated number of carbon atoms and one or two heteroatoms selected from the group consisting of O, N, and S, and wherein the nitrogen and sulfur atoms may be optionally oxidized and the nitrogen heteroatom may be optionally quaternized. The heteroatom(s) may be placed at any position of the heteroalkyl group, including between the rest of the heteroalkyl group and the fragment to which it is attached, as well as attached to the most distal carbon atom in the heteroalkyl group. Examples include: -O-CH_2-CH_2-CH_3, -CH_2-CH_2CH_2-OH, -CH_2-CH_2-NH-CH_3, -CH_2-S-CH_2-CH_3, -CH_2CH_2-S(=O)-CH_3, and -CH_2CH_2-O-CH_2CH_2-O-CH_3. Up to two heteroatoms may be consecutive, such as, for example, -CH_2-NH-OCH_3, or –CH_2-CH_2-S-S-CH_3.

A "cycloheteroalkyl" ring is a cycloalkyl ring containing at least one heteroatom. A cycloheteroalkyl ring can also be termed a "heterocyclyl," described below.

The term "heteroalkenyl" by itself or in combination with another term means, unless otherwise stated, a stable straight or branched chain monounsaturated or di-unsaturated hydrocarbon group consisting of the stated number of carbon atoms and one or two heteroatoms selected from the group consisting of O, N, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. Up to two heteroatoms may be placed consecutively. Examples include -CH=CH-O-CH_3, -CH=CH-CH_2-OH, -CH_2-CH=N-OCH_3, -CH=CH-N(CH_3)-CH_3, -CH_2-CH=CH-CH_2-SH, and and -CH=CH-O-CH_2CH_2-O-CH_3.

Aryl groups are cyclic aromatic hydrocarbons that do not contain heteroatoms in the ring. Thus aryl groups include, but are not limited to, phenyl, azulenyl, heptalenyl, biphenyl, indacenyl, fluorenyl, phenanthrenyl, triphenylenyl, pyrenyl, naphthacenyl, chrysenyl, biphenylenyl, anthracenyl, and naphthyl groups. In some embodiments, aryl groups contain about 6 to about 14 carbons in the ring portions of the groups. Aryl groups can be unsubstituted or

substituted, as defined above. Representative substituted aryl groups can be mono-substituted or substituted more than once, such as, but not limited to, 2-, 3-, 4-, 5-, or 6-substituted phenyl or 2-8 substituted naphthyl groups, which can be substituted with carbon or non-carbon groups such as those listed above.

Aralkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to an aryl group as defined above. Representative aralkyl groups include benzyl and phenylethyl groups and fused (cycloalkylaryl)alkyl groups such as 4-ethyl-indanyl. Aralkenyl group are alkenyl groups as defined above in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to an aryl group as defined above.

An "aroyl" group, as the term is used herein, refers to an aryl group bonded via an exocyclic carbonyl group, such as a benzoyl group.

Heterocyclyl groups or the term "heterocyclyl" includes aromatic and non-aromatic ring compounds containing 3 or more ring members, of which, one or more is a heteroatom such as, but not limited to, N, O, and S. Thus a heterocyclyl can be a cycloheteroalkyl, or a heteroaryl, or if polycyclic, any combination thereof. In some embodiments, heterocyclyl groups include 3 to about 20 ring members, whereas other such groups have 3 to about 15 ring members. A heterocyclyl group designated as a C_2-heterocyclyl can be a 5-ring with two carbon atoms and three heteroatoms, a 6-ring with two carbon atoms and four heteroatoms and so forth. Likewise a C_4-heterocyclyl can be a 5-ring with one heteroatom, a 6-ring with two heteroatoms, and so forth. The number of carbon atoms plus the number of heteroatoms sums up to equal the total number of ring atoms. A heterocyclyl ring can also include one or more double bonds. A heteroaryl ring is an embodiment of a heterocyclyl group. The phrase "heterocyclyl group" includes fused ring species including those comprising fused aromatic and non-aromatic groups. For example, a dioxolanyl ring and a benzdioxolanyl ring system (methylenedioxyphenyl ring system) are both heterocyclyl groups within the meaning herein. The phrase also includes polycyclic ring systems containing a heteroatom such as, but not limited to, quinuclidyl. Heterocyclyl groups can be unsubstituted, or can be substituted as discussed above. Heterocyclyl groups include, but are not limited to, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, pyrrolyl, pyrazolyl, triazolyl,

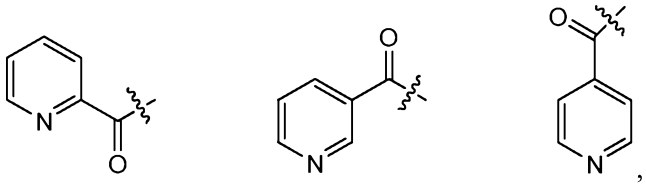
tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridinyl, thiophenyl, benzothiophenyl, benzofuranyl, dihydrobenzofuranyl, indolyl, dihydroindolyl, azaindolyl, indazolyl, benzimidazolyl, azabenzimidazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, imidazopyridinyl, isoxazolopyridinyl, thianaphthalenyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinoxalinyl, and quinazolinyl groups. Representative substituted heterocyclyl groups can be mono-substituted or substituted more than once, such as, but not limited to, piperidinyl or quinolinyl groups, which are 2-, 3-, 4-, 5-, or 6-substituted, or disubstituted with groups such as those listed above.

Heteroaryl groups are aromatic ring compounds containing 5 or more ring members, of which, one or more is a heteroatom such as, but not limited to, N, O, and S; for instance, heteroaryl rings can have 5 to about 8-12 ring members. A heteroaryl group is a variety of a heterocyclyl group that possesses an aromatic electronic structure. A heteroaryl group designated as a C_2-heteroaryl can be a 5-ring with two carbon atoms and three heteroatoms, a 6-ring with two carbon atoms and four heteroatoms and so forth. Likewise a C_4-heteroaryl can be a 5-ring with one heteroatom, a 6-ring with two heteroatoms, and so forth. The number of carbon atoms plus the number of heteroatoms sums up to equal the total number of ring atoms. Heteroaryl groups include, but are not limited to, groups such as pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridinyl, thiophenyl, benzothiophenyl, benzofuranyl, indolyl, azaindolyl, indazolyl, benzimidazolyl, azabenzimidazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, imidazopyridinyl, isoxazolopyridinyl, thianaphthalenyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinoxalinyl, and quinazolinyl groups. Heteroaryl groups can be unsubstituted, or can be substituted with groups as is discussed above. Representative substituted heteroaryl groups can be substituted one or more times with groups such as those listed above.

A "heteroaroyl" group, as the term is used herein, refers to a heteroaryl group bonded via an exocyclic carbonyl group, analogous to a benzoyl group but wherein the phenyl ring of the benzoyl group is replaced by a heteroaryl group.

Various synonyms can be used throughout in the naming of heteroaryl groups, among others. As used herein, the term "pyridyl" is synonymous with

"pyridinyl," the term "quinolyl" is synonymous with the term "quinolinyl," and so forth. The term "phthalimidoyl" or "phthalimido" refers to a phthalimide group bonded by its nitrogen atom. The term "pyridoyl" refers to a pyridylcarbonyl group; the term "quinoloyl" refers to a quinolylcarbonyl group, and so forth. The carbonyl group can be disposed at any position; for example, for "pyridoyl", any of the following structures are indicated:



, wherein a wavy line indicates a point of attachment. Similarly, the term "quinoloyl" refers to a quinoline ring bearing a carbonyl group at any chemically feasible position of substitution, the term "isoquinoloyl" refers to an isoquinoline ring bearing a carbonyl group at any chemically feasible position of substitution, and so forth.

Additional examples of aryl and heteroaryl groups include but are not limited to phenyl, biphenyl, indenyl, naphthyl (1-naphthyl, 2-naphthyl), N-hydroxytetrazolyl, N-hydroxytriazolyl, N-hydroxyimidazolyl, anthracenyl (1-anthracenyl, 2-anthracenyl, 3-anthracenyl), thiophenyl (2-thienyl, 3-thienyl), furyl (2-furyl, 3-furyl) , indolyl, oxadiazolyl, isoxazolyl, quinazolinyl, fluorenyl, xanthenyl, isoindanyl, benzhydryl, acridinyl, thiazolyl, pyrrolyl (2-pyrrolyl), pyrazolyl (3-pyrazolyl), imidazolyl (1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), triazolyl (1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl 1,2,3-triazol-4-yl, 1,2,4-triazol-3-yl), oxazolyl (2-oxazolyl, 4-oxazolyl, 5-oxazolyl), thiazolyl (2-thiazolyl, 4-thiazolyl, 5-thiazolyl), pyridyl (2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl), pyrazinyl, pyridazinyl (3- pyridazinyl, 4-pyridazinyl, 5-pyridazinyl), quinolyl (2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, 8-quinolyl), isoquinolyl (1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 6-isoquinolyl, 7-isoquinolyl, 8-isoquinolyl), benzo[b]furanyl (2-benzo[b]furanyl, 3-benzo[b]furanyl, 4-benzo[b]furanyl, 5-benzo[b]furanyl, 6-benzo[b]furanyl, 7-benzo[b]furanyl), 2,3-dihydro-benzo[b]furanyl (2-(2,3-dihydro-benzo[b]furanyl), 3-(2,3-dihydro-benzo[b]furanyl), 4-(2,3-dihydro-benzo[b]furanyl), 5-(2,3-dihydro-benzo[b]furanyl), 6-(2,3-dihydro-benzo[b]furanyl), 7-(2,3-dihydro-benzo[b]furanyl), benzo[b]thiophenyl (2-

benzo[b]thiophenyl, 3-benzo[b]thiophenyl, 4-benzo[b]thiophenyl, 5-benzo[b]thiophenyl, 6-benzo[b]thiophenyl, 7-benzo[b]thiophenyl), 2,3-dihydro-benzo[b]thiophenyl, (2-(2,3-dihydro-benzo[b]thiophenyl), 3-(2,3-dihydro-benzo[b]thiophenyl), 4-(2,3-dihydro-benzo[b]thiophenyl), 5-(2,3-dihydro-benzo[b]thiophenyl), 6-(2,3-dihydro-benzo[b]thiophenyl), 7-(2,3-dihydro-benzo[b]thiophenyl), indolyl (1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, 7-indolyl), indazole (1-indazolyl, 3-indazolyl, 4-indazolyl, 5-indazolyl, 6-indazolyl, 7-indazolyl), benzimidazolyl (1-benzimidazolyl, 2-benzimidazolyl, 4-benzimidazolyl, 5-benzimidazolyl, 6-benzimidazolyl, 7-benzimidazolyl, 8-benzimidazolyl), benzoxazolyl (1-benzoxazolyl, 2-benzoxazolyl), benzothiazolyl (1-benzothiazolyl, 2-benzothiazolyl, 4-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl, 7-benzothiazolyl), carbazolyl (1-carbazolyl, 2-carbazolyl, 3-carbazolyl, 4-carbazolyl), 5H-dibenz[b,f]azepine (5H-dibenz[b,f]azepin-1-yl, 5H-dibenz[b,f]azepine-2-yl, 5H-dibenz[b,f]azepine-3-yl, 5H-dibenz[b,f]azepine-4-yl, 5H-dibenz[b,f]azepine-5-yl), 10,11-dihydro-5H-dibenz[b,f]azepine (10,11-dihydro-5H-dibenz[b,f]azepine-1-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-2-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-3-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-4-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-5-yl), and the like.

Heterocyclylalkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of an alkyl group as defined above is replaced with a bond to a heterocyclyl group as defined above. Representative heterocyclyl alkyl groups include, but are not limited to, furan-2-yl methyl, furan-3-yl methyl, pyridine-3-yl methyl, tetrahydrofuran-2-yl ethyl, and indol-2-yl propyl.

Heteroarylalkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to a heteroaryl group as defined above.

The term “alkoxy" refers to an oxygen atom connected to an alkyl group, including a cycloalkyl group, as are defined above. Examples of linear alkoxy groups include but are not limited to methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy, and the like. Examples of branched alkoxy include but are not limited to isopropoxy, sec-butoxy, tert-butoxy, isopentyloxy, isohexyloxy, and the like. Examples of cyclic alkoxy include but are not limited to cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, and the like.

An alkoxy group can include one to about 12-20 carbon atoms bonded to the oxygen atom, and can further include double or triple bonds, and can also include heteroatoms. For example, an allyloxy group is an alkoxy group within the meaning herein. A methoxyethoxy group is also an alkoxy group within the meaning herein, as is a methylenedioxy group in a context where two adjacent atoms of a structures are substituted therewith.

The terms “halo” or “halogen” or "halide" by themselves or as part of another substituent mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom, preferably, fluorine, chlorine, or bromine.

A “haloalkyl” group includes mono-halo alkyl groups, poly-halo alkyl groups wherein all halo atoms can be the same or different, and per-halo alkyl groups, wherein all hydrogen atoms are replaced by halogen atoms, such as fluoro. Examples of haloalkyl include trifluoromethyl, 1,1-dichloroethyl, 1,2-dichloroethyl, 1,3-dibromo-3,3-difluoropropyl, perfluorobutyl, and the like.

A "haloalkoxy" group includes mono-halo alkoxy groups, poly-halo alkoxy groups wherein all halo atoms can be the same or different, and per-halo alkoxy groups, wherein all hydrogen atoms are replaced by halogen atoms, such as fluoro. Examples of haloalkoxy include trifluoromethoxy, 1,1-dichloroethoxy, 1,2-dichloroethoxy, 1,3-dibromo-3,3-difluoropropoxy, perfluorobutoxy, and the like.

The term “(C_x-C_y)perfluoroalkyl,” wherein x < y, means an alkyl group with a minimum of x carbon atoms and a maximum of y carbon atoms, wherein all hydrogen atoms are replaced by fluorine atoms. Preferred is -(C_1-C_6)perfluoroalkyl, more preferred is -(C_1-C_3)perfluoroalkyl, most preferred is $–CF_3$.

The term “(C_x-C_y)perfluoroalkylene,” wherein x < y, means an alkyl group with a minimum of x carbon atoms and a maximum of y carbon atoms, wherein all hydrogen atoms are replaced by fluorine atoms. Preferred is -(C_1-C_6)perfluoroalkylene, more preferred is -(C_1-C_3)perfluoroalkylene, most preferred is $–CF_2–$.

The terms "aryloxy" and “arylalkoxy” refer to, respectively, an aryl group bonded to an oxygen atom and an aralkyl group bonded to the oxygen atom at the alkyl moiety. Examples include but are not limited to phenoxy, naphthyloxy, and benzyloxy.

An “acyl” group as the term is used herein refers to a group containing a carbonyl moiety wherein the group is bonded via the carbonyl carbon atom. The carbonyl carbon atom is also bonded to another carbon atom, which can be part of an alkyl, aryl, aralkyl cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl group or the like. In the special case wherein the carbonyl carbon atom is bonded to a hydrogen, the group is a “formyl” group, an acyl group as the term is defined herein. An acyl group can include 0 to about 12-20 additional carbon atoms bonded to the carbonyl group. An acyl group can include double or triple bonds within the meaning herein. An acryloyl group is an example of an acyl group. An acyl group can also include heteroatoms within the meaning here. A nicotinoyl group (pyridyl-3-carbonyl) group is an example of an acyl group within the meaning herein. Other examples include acetyl, benzoyl, phenylacetyl, pyridylacetyl, cinnamoyl, and acryloyl groups and the like. When the group containing the carbon atom that is bonded to the carbonyl carbon atom contains a halogen, the group is termed a “haloacyl” group. An example is a trifluoroacetyl group.

The term “amine” includes primary, secondary, and tertiary amines having, e.g., the formula $N(group)_3$ wherein each group can independently be H or non-H, such as alkyl, aryl, and the like. Amines include but are not limited to $R\text{-}NH_2$, for example, alkylamines, arylamines, alkylarylamines; R_2NH wherein each R is independently selected, such as dialkylamines, diarylamines, aralkylamines, heterocyclylamines and the like; and R_3N wherein each R is independently selected, such as trialkylamines, dialkylarylamines, alkyldiarylamines, triarylamines, and the like. The term "amine" also includes ammonium ions as used herein.

An "amino" group is a substituent of the form $-NH_2$, -NHR, $-NR_2$, $-NR_3^+$, wherein each R is independently selected, and protonated forms of each, except for $-NR_3^+$, which cannot be protonated. Accordingly, any compound substituted with an amino group can be viewed as an amine. An "amino group" within the meaning herein can be a primary, secondary, tertiary or quaternary amino group. An "alkylamino" group includes a monoalkylamino, dialkylamino, and trialkylamino group.

An "ammonium" ion includes the unsubstituted ammonium ion NH_4^+, but unless otherwise specified, it also includes any protonated or quaternarized

forms of amines. Thus, trimethylammonium hydrochloride and tetramethylammonium chloride are both ammonium ions, and amines, within the meaning herein.

The term “amide” (or “amido”) includes C- and N-amide groups, i.e., -C(O)NR_2, and –NRC(O)R groups, respectively. Amide groups therefore include but are not limited to primary carboxamide groups (-C(O)NH_2) and formamide groups (-NHC(O)H). A "carboxamido" group is a group of the formula C(O)NR_2, wherein R can be H, alkyl, aryl, etc.

The term "azido" refers to an N_3 group. An "azide" can be an organic azide or can be a salt of the azide (N_3^-) anion. The term "nitro" refers to an NO_2 group bonded to an organic moiety. The term "nitroso" refers to an NO group bonded to an organic moiety. The term nitrate refers to an ONO_2 group bonded to an organic moiety or to a salt of the nitrate (NO_3^-) anion.

The term “urethane” (“carbamoyl” or “carbamyl”) includes N- and O-urethane groups, i.e., -NRC(O)OR and –OC(O)NR_2 groups, respectively.

The term “sulfonamide” (or “sulfonamido”) includes S- and N-sulfonamide groups, i.e., -SO_2NR_2 and –$NRSO_2R$ groups, respectively. Sulfonamide groups therefore include but are not limited to sulfamoyl groups (-SO_2NH_2). An organosulfur structure represented by the formula –S(O)(NR)– is understood to refer to a sulfoximine, wherein both the oxygen and the nitrogen atoms are bonded to the sulfur atom, which is also bonded to two carbon atoms.

The term “amidine” or “amidino” includes groups of the formula -C(NR)NR_2. Typically, an amidino group is –C(NH)NH_2.

The term “guanidine” or “guanidino” includes groups of the formula -NRC(NR)NR_2. Typically, a guanidino group is –NHC(NH)NH_2.

The invention can provide a salt form of a compound of the invention, i.e., a structure as shown, but in the form of a salt, such as a salt of an amine and an acid. Compounds of the invention can be amines, and as such can form salts with organic or inorganic acids. Salts can be used either as dosing forms for patients, in which case the salts are “pharmaceutically acceptable salts”, or can be salts formed with any acid that is useful, e.g., in chemical processing. A "salt" as is well known in the art includes an organic compound such as a carboxylic acid, a sulfonic acid, or an amine, in ionic form, in combination with a counterion. For example, acids in their anionic form can form salts with

cations such as metal cations, for example sodium, potassium, and the like; with ammonium salts such as NH_4^+ or the cations of various amines, including tetraalkyl ammonium salts such as tetramethylammonium, or other cations such as trimethylsulfonium, and the like. A "pharmaceutically acceptable" or "pharmacologically acceptable" salt is a salt formed from an ion that has been approved for human consumption and is generally non-toxic, such as a chloride salt or a sodium salt. A "zwitterion" is an internal salt such as can be formed in a molecule that has at least two ionizable groups, one forming an anion and the other a cation, which serve to balance each other. For example, amino acids such as glycine can exist in a zwitterionic form. A "zwitterion" is a salt within the meaning herein. The compounds of the present invention may take the form of salts. The term “salts” embraces addition salts of free acids or free bases which are compounds of the invention. Salts can be "pharmaceutically-acceptable salts." The term “pharmaceutically-acceptable salt” refers to salts which possess toxicity profiles within a range that affords utility in pharmaceutical applications. Pharmaceutically unacceptable salts may nonetheless possess properties such as high crystallinity, which have utility in the practice of the present invention, such as for example utility in process of synthesis, purification or formulation of compounds of the invention.

Suitable pharmaceutically-acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Examples of inorganic acids include hydrochloric, hydrobromic, hydriodic, nitric, carbonic, sulfuric, and phosphoric acids. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which include formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, trifluoromethanesulfonic, 2-hydroxyethanesulfonic, p-toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, stearic, alginic, β-hydroxybutyric, salicylic, galactaric and galacturonic acid. Examples of pharmaceutically unacceptable acid addition salts include, for example, perchlorates and tetrafluoroborates.

Suitable pharmaceutically acceptable base addition salts of compounds of the invention include, for example, metallic salts including alkali metal, alkaline earth metal and transition metal salts such as, for example, calcium, magnesium, potassium, sodium and zinc salts. Pharmaceutically acceptable base addition salts also include organic salts made from basic amines such as, for example, *N*,*N*'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Examples of pharmaceutically unacceptable base addition salts include lithium salts and cyanate salts. Although pharmaceutically unacceptable salts are not generally useful as medicaments, such salts may be useful, for example as intermediates in the synthesis of Formula (I) compounds, for example in their purification by recrystallization. All of these salts may be prepared by conventional means from the corresponding compound according to Formula (I) by reacting, for example, the appropriate acid or base with the compound according to Formula (I). The term "pharmaceutically acceptable salts" refers to nontoxic inorganic or organic acid and/or base addition salts, see, for example, Lit et al., Salt Selection for Basic Drugs (1986), *Int J. Pharm.*, **33**, 201-217, incorporated by reference herein.

A "hydrate" is a compound that exists in a composition with water molecules. The composition can include water in stoichiometic quantities, such as a monohydrate or a dihydrate, or can include water in random amounts. As the term is used herein a "hydrate" refers to a solid form, i.e., a compound in water solution, while it may be hydrated, is not a hydrate as the term is used herein.

A "solvate" is a similar composition except that a solvent other that water replaces the water. For example, methanol or ethanol can form an "alcoholate", which can again be stoichiometic or non-stoichiometric. As the term is used herein a "solvate" refers to a solid form, i.e., a compound in solution in a solvent, while it may be solvated, is not a solvate as the term is used herein.

A "prodrug" as is well known in the art is a substance that can be administered to a patient where the substance is converted in vivo by the action of biochemicals within the patients body, such as enzymes, to the active pharmaceutical ingredient. Examples of prodrugs include esters of carboxylic acid groups, which can be hydrolyzed by endogenous esterases as are found in

the bloodstream of humans and other mammals. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

In addition, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group. For example, if X is described as selected from the group consisting of bromine, chlorine, and iodine, claims for X being bromine and claims for X being bromine and chlorine are fully described. Moreover, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any combination of individual members or subgroups of members of Markush groups. Thus, for example, if X is described as selected from the group consisting of bromine, chlorine, and iodine, and Y is described as selected from the group consisting of methyl, ethyl, and propyl, claims for X being bromine and Y being methyl are fully described.

The present invention further embraces isolated compounds according to formula (I). The expression "isolated compound" refers to a preparation of a compound of formula (I), or a mixture of compounds according to formula (I), wherein the isolated compound has been separated from the reagents used, and/or byproducts formed, in the synthesis of the compound or compounds. "Isolated" does not mean that the preparation is technically pure (homogeneous), but it is sufficiently pure to compound in a form in which it can be used therapeutically. Preferably an "isolated compound" refers to a preparation of a compound of formula (I) or a mixture of compounds according to formula (I), which contains the named compound or mixture of compounds according to formula (I) in an amount of at least 10 percent by weight of the total weight. Preferably the preparation contains the named compound or mixture of compounds in an amount of at least 50 percent by weight of the total weight; more preferably at least 80 percent by weight of the total weight; and most preferably at least 90 percent, at least 95 percent or at least 98 percent by weight of the total weight of the preparation.

The compounds of the invention and intermediates may be isolated from their reaction mixtures and purified by standard techniques such as filtration,

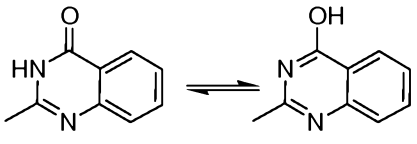
liquid-liquid extraction, solid phase extraction, distillation, recrystallization or chromatography, including flash column chromatography, or HPLC.

Isomerism and Tautomerism in Compounds of the Invention

Tautomerism

Within the present invention it is to be understood that a compound of the formula (I) or a salt thereof may exhibit the phenomenon of tautomerism whereby two chemical compounds that are capable of facile interconversion by exchanging a hydrogen atom between two atoms, to either of which it forms a covalent bond. Since the tautomeric compounds exist in mobile equilibrium with each other they may be regarded as different isomeric forms of the same compound. It is to be understood that the formulae drawings within this specification can represent only one of the possible tautomeric forms. However, it is also to be understood that the invention encompasses any tautomeric form, and is not to be limited merely to any one tautomeric form utilized within the formulae drawings. The formulae drawings within this specification can represent only one of the possible tautomeric forms and it is to be understood that the specification encompasses all possible tautomeric forms of the compounds drawn not just those forms which it has been convenient to show graphically herein. For example, tautomerism may be exhibited by a pyrazolyl group bonded as indicated by the wavy line. While both substituents would be termed a 4-pyrazolyl group, it is evident that a different nitrogen atom bears the hydrogen atom in each structure.

Such tautomerism can also occur with substituted pyrazoles such as 3-methyl, 5-methyl, or 3,5-dimethylpyrazoles, and the like. Another example of tautomerism is amido-imido (lactam-lactim when cyclic) tautomerism, such as is seen in heterocyclic compounds bearing a ring oxygen atom adjacent to a ring nitrogen atom. For example, the equilibrium:

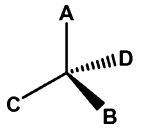


is an example of tautomerism. Accordingly, a structure depicted herein as one tautomer is intended to also include the other tautomer.

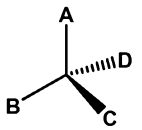
Optical Isomerism

It will be understood that when compounds of the present invention contain one or more chiral centers, the compounds may exist in, and may be isolated as pure enantiomeric or diastereomeric forms or as racemic mixtures. The present invention therefore includes any possible enantiomers, diastereomers, racemates or mixtures thereof of the compounds of the invention.

The isomers resulting from the presence of a chiral center comprise a pair of non-superimposable isomers that are called "enantiomers." Single enantiomers of a pure compound are optically active, *i.e.*, they are capable of rotating the plane of plane polarized light. Single enantiomers are designated according to the *Cahn-Ingold-Prelog* system. The priority of substituents is ranked based on atomic weights, a higher atomic weight, as determined by the systematic procedure, having a higher priority ranking. Once the priority ranking of the four groups is determined, the molecule is oriented so that the lowest ranking group is pointed away from the viewer. Then, if the descending rank order of the other groups proceeds clockwise, the molecule is designated *(R)* and if the descending rank of the other groups proceeds counterclockwise, the molecule is designated *(S)*. In the example in Scheme 14, the *Cahn-Ingold-Prelog* ranking is A > B > C > D. The lowest ranking atom, D is oriented away from the viewer.



(R) configuration



(S) configuration

The present invention is meant to encompass diastereomers as well as their racemic and resolved, diastereomerically and enantiomerically pure forms and salts thereof. Diastereomeric pairs may be resolved by known separation techniques including normal and reverse phase chromatography, and crystallization.

"Isolated optical isomer" means a compound which has been substantially purified from the corresponding optical isomer(s) of the same formula. Preferably, the isolated isomer is at least about 80%, more preferably at least 90% pure, even more preferably at least 98% pure, most preferably at least about 99% pure, by weight. Compounds of the present invention are provided in any of these degrees of enantiomeric purity, e.g., a racemic mixture of enantiomers (50% enantiomerically pure), or 80% enantiomerically pure, or 90% enantiomerically pure, or 98% enantiomerically pure, or 99+% enantiomerically pure.

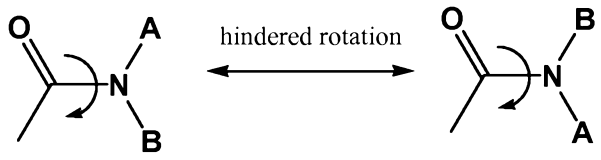
Isolated optical isomers may be purified from racemic mixtures by well-known chiral separation techniques. According to one such method, a racemic mixture of a compound of the invention, or a chiral intermediate thereof, is separated into 99% wt.% pure optical isomers by HPLC using a suitable chiral column, such as a member of the series of DAICEL® CHIRALPAK® family of columns (Daicel Chemical Industries, Ltd., Tokyo, Japan). The column is operated according to the manufacturer's instructions.

Isolated optical isomers (enantiomerically pure compounds) can also be prepared by the use of chiral intermediates or catalysts in synthesis. When a chiral synthetic intermediate is used, the optical center (chiral center) can be preserved without racemization throughout the remainder of the preparative procedure, as is well known in the art. Chiral catalyst can be used to impart at least some degree of enantiomeric purity to products of reactions catalyzed by the chiral catalyst. And, in some cases, compounds having at least some degree of enantiomeric enrichment can be obtained by physical processes such as selective crystallization of salts or complexes formed with chiral adjuvants.

Rotational Isomerism

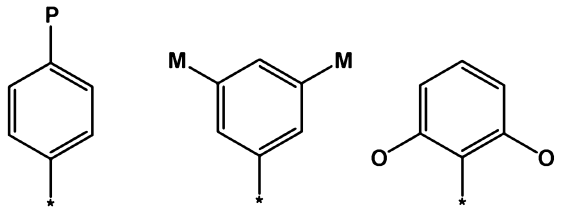
It is understood that due to chemical properties (*i.e.*, resonance lending some double bond character to the C-N bond) of restricted rotation about the amide bond linkage (as illustrated below) it is possible to observe separate rotamer species and even, under some circumstances, to isolate such species (see below). It is further understood that certain structural elements, including steric bulk or substituents on the amide nitrogen, may enhance the stability of a rotamer to the extent that a compound may be isolated as, and exist indefinitely, as a single stable rotamer. The present invention therefore includes any possible

stable rotamers of formula (I) which are biologically active in the treatment of cancer or other proliferative disease states.



Regioisomerism

The preferred compounds of the present invention have a particular spatial arrangement of substituents on the aromatic rings, which is related to the structure activity relationship demonstrated by the compound class. Often such substitution arrangement is denoted by a numbering system; however, numbering systems are often not consistent between different ring systems. In six-membered aromatic systems, the spatial arrangements are specified by the common nomenclature “para” for 1,4-substitution, “meta” for 1,3-substitution and “ortho” for 1,2-substitution as shown below.

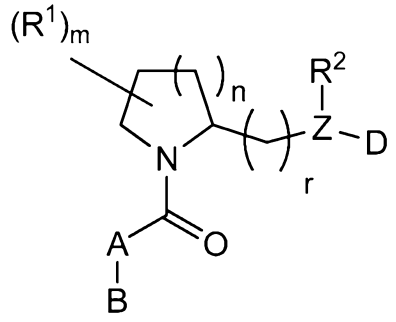


In various embodiments, a compound as shown in any of the Examples, or among the exemplary compounds, is provided. Provisos may apply to any of the disclosed categories or embodiments wherein any one or more of the other above disclosed embodiments or species may be excluded from such categories or embodiments.

In various embodiments, the compound or set of compounds, such as are used in the inventive methods, can be any one of any of the combinations and/or sub-combinations of the above-listed embodiments.

Description

In various embodiments, the invention provides a compound of formula (I),



(I)

wherein

A comprises aryl or heteroaryl;

B is absent, or comprises aryl, aryloxy, heteroaryl, or heteroaryloxy;

wherein A or B or both can each independently be unsubstituted or can each independently be mono- or multi-substituted with J or with R', or with both;

D comprises aryl, aroyl, heteroaryl, or heteroaroyl, wherein D can be unsubstituted or can be mono- or independently multi-substituted with J or with R', or with both;

Z is N or O, provided that when Z is O, R^2 is absent

R^1 comprises independently at each occurrence halo, oxo, hydroxy, cyano, (C_{1-4})alkyl, (C_{1-4})alkoxy, (C_{1-4})acyloxy, (C_{1-4})acylamido, haloalkyl, haloalkoxy, NR^aR^b, $C(=O)NR^aR^b$, $C(=O)OR^a$, SO_2R^a, $SO_2NR^aR^b$, cycloalkyl, heterocyclyl, aryl, aralkyl, or heteroaryl;

or one or more R^1 groups together with the ring to which they are bonded form a bicyclo[2.2.2], bicyclo[3.3.0], or bicyclo[4.3.0] ring system, wherein any bicyclo ring system can be *cis*-fused or *trans*-fused, wherein any alkyl, alkoxy, bicyclo ring system, cycloalkyl, heterocyclyl, aryl, aralkyl, or heteroaryl can be mono- or independently multi-substituted with J or with R', or with both;

R^a and R^b are independently at each occurrence H, (C_{1-4})alkyl, aralkyl, (C_{1-5})acyl, or R^a and R^b together with the nitrogen atom to which they are bonded form a 4-7 membered ring optionally further comprising 1 or 2 NR^c, O, S, SO, or SO_2, wherein R^c is H or (C_{1-4})alkyl, wherein any R^a, R^b, or R^c can be mono- or independently multi-substituted with J or with R', or with both;

R^2 comprises H, (C_{1-4})alkyl, or (C_{1-5})acyl, or R^2 together with D and the nitrogen atom to which they are bonded form a phthalimido group, wherein any alkyl, acyl, or phthalimido group is optionally mono- or independently multi-substituted with J or with R', or with both;

J is halogen, (C1-C6)alkyl, OR', CN, CF_3, OCF_3, =O, =S, C(O), S(O), methylenedioxy, ethylenedioxy, $(CH_2)_{0-p}N(R')_2$, $(CH_2)_{0-p}SR'$, $(CH_2)_{0-p}S(O)R'$, $(CH_2)_{0-p}S(O)_2R'$, $(CH_2)_{0-p}S(O)_2N(R')_2$, $(CH_2)_{0-p}SO_3R'$, $(CH_2)_{0-p}C(O)R'$, $(CH_2)_{0-p}C(O)C(O)R'$, $(CH_2)_{0-p}C(O)CH_2C(O)R'$, $(CH_2)_{0-p}C(S)R'$, $(CH_2)_{0-p}C(O)OR'$, $(CH_2)_{0-p}OC(O)R'$, $(CH_2)_{0-p}C(O)N(R')_2$, $(CH_2)_{0-p}OC(O)N(R')_2$, $(CH_2)_{0-p}C(S)N(R')_2$, $(CH_2)_{0-p}NH\text{-}C(O)R'$, $(CH_2)_{0-p}N(R')N(R')C(O)R'$, $(CH_2)_{0-p}N(R')N(R')C(O)OR'$, $(CH_2)_{0-p}N(R')N(R')CON(R')_2$, $(CH_2)_{0-p}N(R')SO_2R'$, $(CH_2)_{0-p}N(R')SO_2N(R')_2$, $(CH_2)_{0-p}N(R')C(O)OR'$, $(CH_2)_{0-p}N(R')C(O)R'$, $(CH_2)_{0-p}N(R')C(S)R'$, $(CH_2)_{0-p}N(R')C(O)N(R')_2$, $(CH_2)_{0-p}N(R')C(S)N(R')_2$, $(CH_2)_{0-p}N(COR')COR'$, $(CH_2)_{0-p}N(OR')R'$, $(CH_2)_{0-p}C(=NH)N(R')_2$, $(CH_2)_{0-p}C(O)N(OR')R'$, or $(CH_2)_{0-p}C(=NOR')R'$;

wherein, each R' is independently at each occurrence hydrogen, $(C_1\text{-}C_{12})$-alkyl, $(C_2\text{-}C_{12})$-alkenyl, $(C_2\text{-}C_{12})$-alkynyl, $(C_3\text{-}C_{10})$-cycloalkyl, $(C_3\text{-}C_{10})$-cycloalkenyl, [$(C_3\text{-}C_{10})$cycloalkyl or $(C_3\text{-}C_{10})$-cycloalkenyl]-[$(C_1\text{-}C_{12})$-alkyl or $(C_2\text{-}C_{12})$-alkenyl or $(C_2\text{-}C_{12})$-alkynyl], $(C_6\text{-}C_{10})$-aryl, $(C_6\text{-}C_{10})$-aryl-[$(C_1\text{-}C_{12})$-alkyl or $(C_2\text{-}C_{12})$-alkenyl or $(C_2\text{-}C_{12})$-alkynyl], mono- or bicyclic 3-10 membered heterocyclyl, mono- or bicyclic 3-10 membered heterocyclyl-[$(C_1\text{-}C_{12})$-alkyl or $(C_2\text{-}C_{12})$-alkenyl or $(C_2\text{-}C_{12})$-alkynyl], mono- or bicyclic 5-10 membered heteroaryl, or mono- or bicyclic 5-10 membered heteroaryl-[$(C_1\text{-}C_{12})$-alkyl or $(C_2\text{-}C_{12})$-alkenyl or $(C_2\text{-}C_{12})$-alkynyl], wherein R' is substituted with 0-3 substituents selected independently from J^R;

or, when two R' are bound to a nitrogen atom or to two adjacent nitrogen atoms, the two R' groups together with the nitrogen atom or atoms to which they are bound can form a 3- to 8-membered monocyclic heterocyclic ring, or an 8- to 20-membered, bicyclic or tricyclic, heterocyclic ring system, wherein any ring or ring system can further contain 1-3 additional heteroatoms selected from the group consisting of N, NR', O, S, S(O) and $S(O)_2$, wherein each ring is substituted with 0-3 substituents selected independently from J^R; wherein, in any bicyclic or tricyclic ring system, each ring is linearly fused, bridged, or spirocyclic, wherein each ring is either aromatic or nonaromatic, wherein each

ring can be fused to a (C_6-C_{10})aryl, mono- or bicyclic 5-10 membered heteroaryl, (C_3-C_{10})cycloalkyl or mono- or bicyclic 3-10 membered heterocyclyl;

J^R is halogen, OR, CN, CF_3, OCF_3, =O, =S, C(O), S(O), methylenedioxy, ethylenedioxy, $(CH_2)_{0-p}N(R)_2$, $(CH_2)_{0-p}SR$, $(CH_2)_{0-p}S(O)R$, $(CH_2)_{0-p}S(O)_2R$, $(CH_2)_{0-p}S(O)_2N(R)_2$, $(CH_2)_{0-p}SO_3R$, $(CH_2)_{0-p}C(O)R$, $(CH_2)_{0-p}C(O)C(O)R$, $(CH_2)_{0-p}C(O)CH_2C(O)R$, $(CH_2)_{0-p}C(S)R$, $(CH_2)_{0-p}C(O)OR$, $(CH_2)_{0-p}OC(O)R$, $(CH_2)_{0-p}C(O)N(R)_2$, $(CH_2)_{0-p}OC(O)N(R)_2$, $(CH_2)_{0-p}C(S)N(R)_2$, $(CH_2)_{0-p}NH\text{-}C(O)R$, $(CH_2)_{0-p}N(R)N(R)C(O)R$, $(CH_2)_{0-p}N(R)N(R)C(O)OR$, $(CH_2)_{0-p}N(R)N(R)CON(R)_2$, $(CH_2)_{0-p}N(R)SO_2R$, $(CH_2)_{0-p}N(R)SO_2N(R)_2$, $(CH_2)_{0-p}N(R)C(O)OR$, $(CH_2)_{0-p}N(R)C(O)R$, $(CH_2)_{0-p}N(R)C(S)R$, $(CH_2)_{0-p}N(R)C(O)N(R)_2$, $(CH_2)_{0-p}N(R)C(S)N(R)_2$, $(CH_2)_{0-p}N(COR)COR$, $(CH_2)_{0-p}N(OR)R$, $(CH_2)_{0-p}C(=NH)N(R)_2$, $(CH_2)_{0-p}C(O)N(OR)R$, or $(CH_2)_{0-p}C(=NOR)R$; and,

R is independently at each occurrence hydrogen, (C_1-C_{12})-alkyl, (C_2-C_{12})-alkenyl, (C_2-C_{12})-alkynyl, (C_3-C_{10})-cycloalkyl, (C_3-C_{10})-cycloalkenyl, [(C_3-C_{10})cycloalkyl or (C_3-C_{10})-cycloalkenyl]-[(C_1-C_{12})-alkyl or (C_2-C_{12})-alkenyl or (C_2-C_{12})-alkynyl], (C_6-C_{10})-aryl, (C_6-C_{10})-aryl-[(C_1-C_{12})-alkyl or (C_2-C_{12})-alkenyl or (C_2-C_{12})-alkynyl], mono- or bicyclic 3-10 membered heterocyclyl, mono- or bicyclic 3-10 membered heterocyclyl-[(C_1-C_{12})-alkyl or (C_2-C_{12})-alkenyl or (C_2-C_{12})-alkynyl], mono- or bicyclic 5-10 membered heteroaryl, or mono- or bicyclic 5-10 membered heteroaryl-[(C_1-C_{12})-alkyl or (C_2-C_{12})-alkenyl or (C_2-C_{12})-alkynyl];

m is 0, 1, 2, 3, 4, 5, or 6; n is 1, 2, or 3; p = 0, 1, or 2; r = 0, 1, 2, or 3;

or any salt or hydrate thereof.

In various embodiments, Z can be a nitrogen atom, substituted with R^2 as defined herein. When D comprises a carbonyl group (e.g., pyridoyl, quinoloyl, benzofuranoyl, and the like), then Z as a nitrogen atom forms an amide bond with the D group. When D does not comprise a carbonyl group in the bonding position (pyridyl, quinolyl, benzofuranyl, and the like), then Z as a nitrogen atom forms an amine bond with the D group.

In other embodiments, Z can be an oxygen atom, in which case R^2 is absent. When D comprises a carbonyl group (e.g., pyridoyl, quinoloyl, benzofuranoyl, and the like), Z as an oxygen atom forms an ester bond with the D group. When D does not comprise a carbonyl group in the bonding position

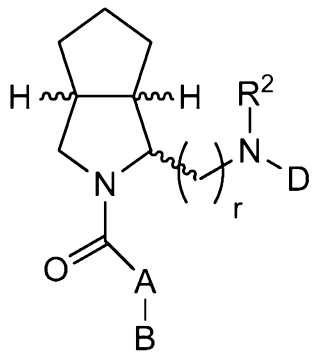
(pyridyl, quinolyl, benzofuranyl, and the like), then Z as an oxygen atom forms an ether bond with the D group.

In various embodiments, the invention provides a compound of formula (I) wherein A comprises phenyl, thiazolyl, pyrazolyl, pyridyl, or quinolyl, wherein A can each independently be unsubstituted or can each independently be mono- or multi-substituted with J or with R', or both; or any salt or hydrate thereof.

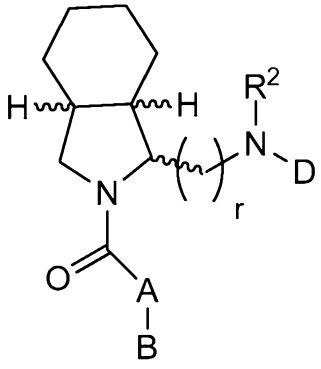
In various embodiments, the invention provides a compound of formula (I) wherein B comprises phenyl, pyridyl, pyrazidinyl, pyrimidinyl, pyrazinyl, pyrolyl, pyrazolyl, oxazolyl, imidazolyl, oxadiazolyl, {1,2,3)-triazolyl, (1,2,4)-triazolyl, wherein B can each independently be unsubstituted or can each independently be mono- or multi-substituted with J or with R', or both; or any salt or hydrate thereof.

In various embodiments, the invention provides a compound of formula (I) wherein D comprises pyridyl, pyridoyl, pyridazinyl, pyridazinoyl, pyrimidinyl, pyrimidinoyl, pyrazinyl, pyrazinoyl, quinolyl, quinoloyl, benzofuranyl, benzofuranoyl, benzoxazolyl, benzoxazoloyl, benzthiazolyl, or benzthiazoloyl; or wherein D combined with R^2 and the nitrogen atom to which they are bonded comprises phthalimidoyl, wherein D can be unsubstituted or can be mono- or independently multi-substituted with J or with R', or both; or any salt or hydrate thereof.

In various embodiments, the invention provides a compound of formula (I) comprising a bicyclic compound of any of formulas (IIA) or (IIB)

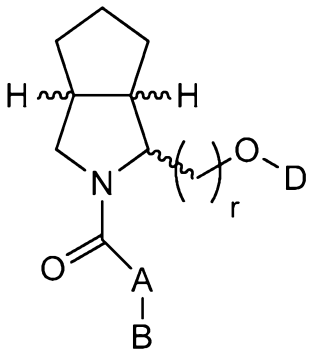


(IIA)

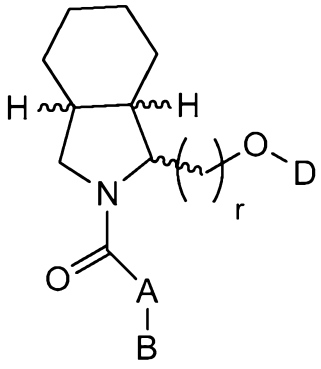


(IIB)

or any salt or hydrate thereof. Formula (IIA) is a bicyclo[3.3.0] system, and formula (IIB) is a bicyclo[4.3.0] system, and in both formulas (IIA) and (IIB), Z of formula (I) is nitrogen. The bicyclo ring junction can be *cis*-fused or *trans*-fused, and the sidechain can be of any relative orientation stereochemically in any of formulas (IIA) through (IID). The invention can provide mixed or pure diastereomeric forms, any one of which can be racemic or enantiomerically enriched. Alternatively, these bicyclo ring systems can be included in analogous structures wherein Z of formula (I) is oxygen. In various embodiments, the invention can provide a compound of formula (IIC), a bicyclo[3.3.0] system, or of formula (IID), a bicyclo[4.3.0] system:

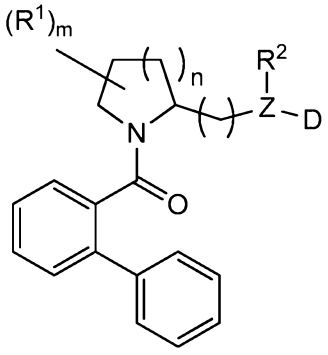


(IIC)

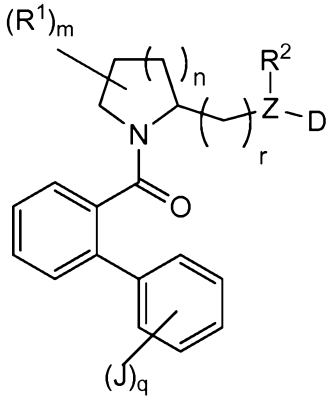


(IID)

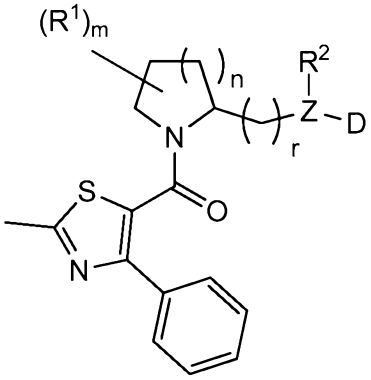
In various embodiments, the invention provides a compound of formula (I) comprising any of formulas (IIIA), (IIIB), (IIIC), (IIID), (IIIE), or (IIIF):



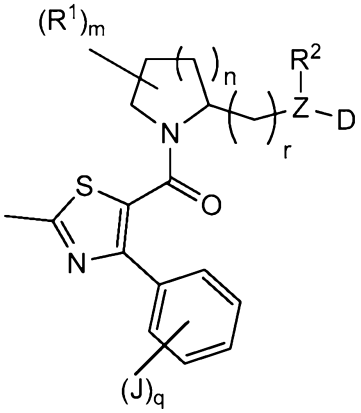
(IIIA)



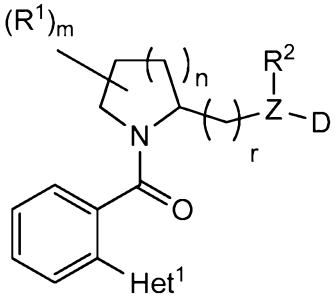
(IIIB)



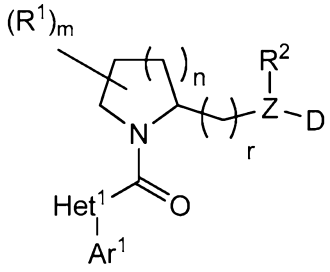
(IIIC)



(IIID)



(IIIE)

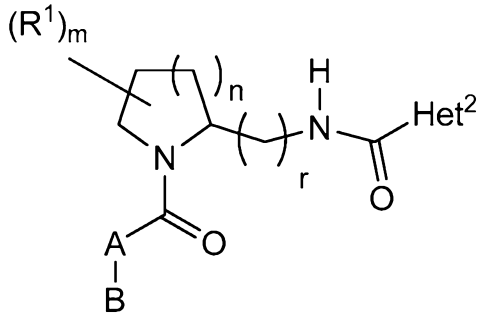


(IIIF);

wherein Z, D, R^1, m, and R^2 are as defined for Formula (I), n is 1 or 2, q = 1, 2, or 3, r = 1 or 2; Het^1 is an unsubstituted or J-substituted pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, trizolyl, pyrimidinyl, or pyridyl; Ar^1 is an unsubstituted or J-substituted phenyl; wherein J-substituted indicates the presence of 1-3 J substituents; or any salt or hydrate thereof. In various embodiments, each J is independently selected from the set consisting of F, Cl, and methoxy. More specifically, the invention provides a compound of any of formulas (IIIA), (IIIB), (IIIC), (IIID), (IIIE), or (IIIF), wherein n =1 or 2 (i.e., a pyrrolidine (proline), or a piperidine), and wherein m = 1 or 2. In various embodiments, R^1 is F, oxo, methyl, trifluoromethyl, hydroxy, acetoxy, methoxy, NH_2, N-methylamino, N-ethylamino, N,N-dimethylamino, N-isopropylamino, N-benzylamino, hydoxyethylamino, or acetamido; or any salt or hydrate thereof. More specifically, the invention provides in various embodiments a compound of any of formulas (IIIA), (IIIB), (IIIC), (IIID), (IIIE), or (IIIF) wherein D comprises pyridyl, pyridoyl, quinolyl, quinoloyl, or benzofuranyl, or wherein D

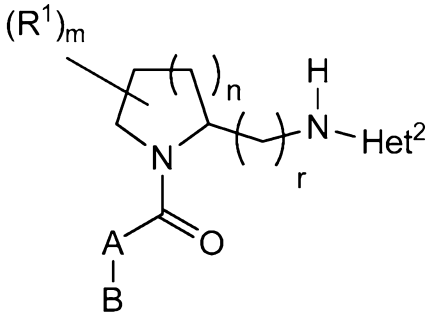
combined with R^2 and the nitrogen atom to which they are bonded comprises phthalimidoyl; or any salt or hydrate thereof.

In various embodiments, the invention provides a compound of formula (I) comprising a compound of formula (IVA)



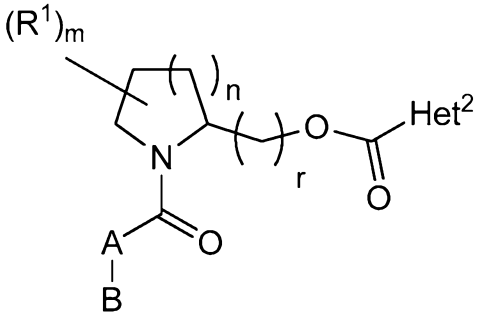
(IVA)

or a compound of formula (IVB)

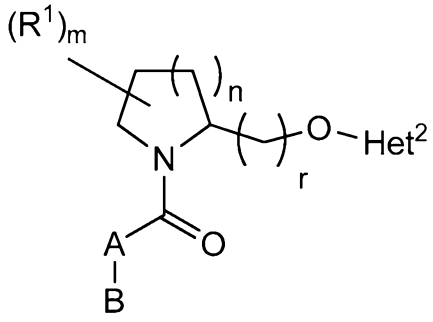


(IVB)

or a compound of formula (IVC)



or a compound of formula (IVD)

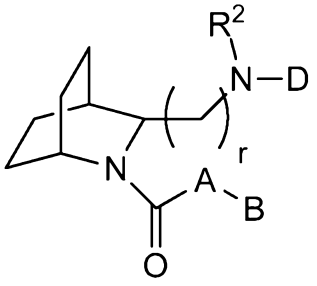


wherein A, B, and R^1, are as defined herein, wherein m = 1 or 2, n = 1 or 2; r = 1 or 2;

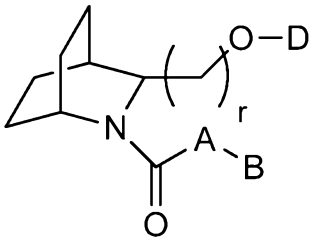
and r = 1 or 2; and Het^2 is an unsubstituted or J-substituted quinolyl, pyridyl, pyrimidyl, benzoxazolyl, benzimidazolyl, or benzthiazolyl; wherein J-substituted indicates the presence of 1-3 J substituents;

or any salt or hydrate thereof.

In various embodiments, the invention can provide a compound of formula (VA) or of formula (VB):



(VA)



(VB),

wherein A, B, D, R^2, are as defined herein, and r = 1 or 2; or any salt or hydrate thereof.

In various embodiments, the invention provides any of the compounds as listed below in "Table 1: Exemplary Compounds of the Invention," or any salt or hydrate thereof. Compounds of the invention can possess bioactivity as orexin receptor modulators, e.g., as orexin receptor antagonists, as described in greater detail below.

Pharmaceutical Methods and Uses

"Treating" or "treatment" within the meaning herein refers to an alleviation of symptoms associated with a disorder or disease, or inhibition of further progression or worsening of those symptoms, or prevention or prophylaxis of the disease or disorder. Similarly, as used herein, an "effective amount" or a "therapeutically effective amount" of a compound of the invention refers to an amount of the compound that alleviates, in whole or in part, symptoms associated with the disorder or condition, or halts or slows further progression or worsening of those symptoms, or prevents or provides prophylaxis for the disorder or condition. In particular, a "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount is also one in which any toxic or detrimental effects of

compounds of the invention are outweighed by the therapeutically beneficial effects.

Another aspect of an embodiment of the invention provides compositions of the compounds of the invention, alone or in combination with another medicament. As set forth herein, compounds of the invention include stereoisomers, tautomers, solvates, prodrugs, pharmaceutically acceptable salts and mixtures thereof. Compositions containing a compound of the invention can be prepared by conventional techniques, e.g. as described in Remington: *The Science and Practice of Pharmacy*, 19th Ed., 1995, incorporated by reference herein. The compositions can appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

Typical compositions include a compound of the invention and a pharmaceutically acceptable excipient which can be a carrier or a diluent. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which can be in the form of an ampoule, capsule, sachet, paper, or other container. When the active compound is mixed with a carrier, or when the carrier serves as a diluent, it can be solid, semi-solid, or liquid material that acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid carrier, for example contained in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatin, lactose, terra alba, sucrose, dextrin, magnesium carbonate, sugar, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent can include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax.

The formulations can be mixed with auxiliary agents which do not deleteriously react with the active compounds. Such additives can include wetting agents, emulsifying and suspending agents, salt for influencing osmotic pressure, buffers and/or coloring substances preserving agents, sweetening agents or flavoring agents. The compositions can also be sterilized if desired.

The route of administration can be any route which effectively transports the active compound of the invention to the appropriate or desired site of action, such as oral, nasal, pulmonary, buccal, subdermal, intradermal, transdermal or parenteral, e.g., rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment, the oral route being preferred.

If a solid carrier is used for oral administration, the preparation can be tabletted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. If a liquid carrier is used, the preparation can be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

Injectable dosage forms generally include aqueous suspensions or oil suspensions which can be prepared using a suitable dispersant or wetting agent and a suspending agent Injectable forms can be in solution phase or in the form of a suspension, which is prepared with a solvent or diluent. Acceptable solvents or vehicles include sterilized water, Ringer's solution, or an isotonic aqueous saline solution. Alternatively, sterile oils can be employed as solvents or suspending agents. Preferably, the oil or fatty acid is non-volatile, including natural or synthetic oils, fatty acids, mono-, di- or tri-glycerides.

For injection, the formulation can also be a powder suitable for reconstitution with an appropriate solution as described above. Examples of these include, but are not limited to, freeze dried, rotary dried or spray dried powders, amorphous powders, granules, precipitates, or particulates. For injection, the formulations can optionally contain stabilizers, pH modifiers, surfactants, bioavailability modifiers and combinations of these. The compounds can be formulated for parenteral administration by injection such as by bolus injection or continuous infusion. A unit dosage form for injection can be in ampoules or in multi-dose containers.

The formulations of the invention can be designed to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art. Thus, the formulations can also be formulated for controlled release or for slow release.

Compositions contemplated by the present invention can include, for example, micelles or liposomes, or some other encapsulated form, or can be

administered in an extended release form to provide a prolonged storage and/or delivery effect. Therefore, the formulations can be compressed into pellets or cylinders and implanted intramuscularly or subcutaneously as depot injections. Such implants can employ known inert materials such as silicones and biodegradable polymers, e.g., polylactide-polyglycolide. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides).

For nasal administration, the preparation can contain a compound of the invention, dissolved or suspended in a liquid carrier, preferably an aqueous carrier, for aerosol application. The carrier can contain additives such as solubilizing agents, e.g., propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabens.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet that can be prepared by conventional tabletting techniques can contain:

Core:		
	Active compound (as free compound or salt thereof)	250 mg
	Colloidal silicon dioxide (Aerosil)®	1.5 mg
	Cellulose, microcryst. (Avicel)®	70 mg
	Modified cellulose gum (Ac-Di-Sol)®	7.5 mg
	Magnesium stearate	Ad.
Coating:		
	HPMC approx.	9 mg
	*Mywacett 9-40 T approx.	0.9 mg

*Acylated monoglyceride used as plasticizer for film coating.

A typical capsule for oral administration contains compounds of the invention (250 mg), lactose (75 mg) and magnesium stearate (15 mg). The mixture is passed through a 60 mesh sieve and packed into a No. 1 gelatin capsule. A typical injectable preparation is produced by aseptically placing 250 mg of compounds of the invention into a vial, aseptically freeze-drying and sealing. For use, the contents of the vial are mixed with 2 mL of sterile physiological saline, to produce an injectable preparation.

In various embodiments, the invention provides a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable excipient, as described above.

In various embodiments, compounds of the invention can be used to modulate, such as to activate (agonist), or to block activation of (antagonist), an orexin receptor. Accordingly, in various embodiments, the invention provides a method of modulating an orexin receptor comprising contacting the receptor with an effective amount or concentration of a compound of the invention. The orexin receptor can be OX_1 or OX_2. In various embodiments, the compound of the invention is an antagonist of an orexin receptor such as OX_1 or OX_2, or both, and can be a selective inhibitor of one or the other. In various embodiments, contacting can take place *in vivo* within tissues of a patient, such as a human patient.

In various embodiments, the invention provides a method of treating a malcondition in a patient wherein modulation of an orexin receptor is medically indicating, comprising administering to the patient a compound of the invention in a dose, at a frequency, and for a duration to provide a beneficial effect to the patient. Modulation, such as agonism or antagonism, of an orexin receptor can be medically indicated in treatment of a malcondition wherein the orexin receptor plays a metabolic or regulatory role. Certain malconditions can be treated by selective modulation of a single class of orexin receptor, such as modulation of OX_1 while OX_2 is not influenced by administration of the compound of the invention at the dose provided. In various embodiments, compounds of the invention can be orexin-1 antagonists, and some of those are selective orexin-1 antagonists with respect to orexin-2. By "selective" is meant that one receptor is modulated at concentrations of the compound at least 10 times lower than the concentrations at which the comparative receptor is

modulated by that compound. Accordingly, in various embodiments, the compound of the invention can be a selective modulator, e.g., an antagonist, of orexin receptor OX_1. Or, the compound of the invention can be a selective modulator (e.g., antagonist) of an orexin receptor OX_2. Or the compound of the invention can further modulate other types or classes of receptors having affinity for one of more forms of the orexin class of natural peptidic ligands.

In various embodiments, modulation of an orexin receptor, for example, antagonism of orexin-1 by a compound of the invention can be used to treat a malcondition in a patient wherein the malcondition comprises an eating disorder, obesity, alcoholism or an alcohol-related disorder, drug abuse or addiction, a sleep disorder, a cognitive dysfunction in a psychiatric or neurologic disorder, depression, anxiety, panic disorder, schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's chorea, head ache, migraine, pain, gastrointestinal diseases, epilepsy, inflammations, immune-related diseases, endocrine-related diseases, cancer, hypertension, behavior disorder, mood disorder, manic depression, dementia, sex disorder, psychosexual disorder, and renal disease. Drug abuse and addiction can include abuse of or addiction to cocaine, opiates, amphetamines, or nicotine.

In various embodiments, the invention provides a use of a compound of the invention for treatment of a malcondition in a patient. For example, a compound of the invention can be used in the preparation of a medicament for administration to a patient suffering from a malcondition. More specifically, the malcondition can comprise an eating disorder, obesity, alcoholism or an alcohol-related disorder, drug abuse or addiction, a sleep disorder, a cognitive dysfunction in a psychiatric or neurologic disorder, depression, anxiety, panic disorder, schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's chorea, head ache, migraine, pain, gastrointestinal diseases, epilepsy, inflammations, immune-related diseases, endocrine-related diseases, cancer, hypertension, behavior disorder, mood disorder, manic depression, dementia, sex disorder, psychosexual disorder, and renal disease. Drug abuse and addiction can include abuse of or addiction to cocaine, opiates, amphetamines, or nicotine.

It is believed that antagonism of orexin-1, in particular, is medically indicated for the treatment of the above-listed conditions. By antagonism is meant blocking a receptor, in this case an orexin receptor, without causing it to

transduce a signal. That is, antagonism results in blocking an endogenous or exogenous ligand from activating, or causing agonism, of the receptor.

The compounds of the invention can be administered to a mammal, especially a human in need of such treatment, prevention, elimination, alleviation or amelioration of a malcondition. Such mammals include also animals, both domestic animals, e.g. household pets, farm animals, and non-domestic animals such as wildlife.

The compounds of the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.05 to about 5000 mg, preferably from about 1 to about 2000 mg, and more preferably between about 2 and about 2000 mg per day can be used. A typical dosage is about 10 mg to about 1000 mg per day. In choosing a regimen for patients it can frequently be necessary to begin with a higher dosage and when the condition is under control to reduce the dosage. The exact dosage will depend upon the activity of the compound, mode of administration, on the therapy desired, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

Generally, the compounds of the invention are dispensed in unit dosage form including from about 0.05 mg to about 1000 mg of active ingredient together with a pharmaceutically acceptable carrier per unit dosage.

Usually, dosage forms suitable for oral, nasal, pulmonal or transdermal administration include from about 125 μg to about 1250 mg, preferably from about 250 μg to about 500 mg, and more preferably from about 2.5 mg to about 250 mg, of the compounds admixed with a pharmaceutically acceptable carrier or diluent.

Dosage forms can be administered daily, or more than once a day, such as twice or thrice daily. Alternatively dosage forms can be administered less frequently than daily, such as every other day, or weekly, if found to be advisable by a prescribing physician.

It is within ordinary skill to evaluate any compound disclosed and claimed herein for effectiveness in modulation of an orexin receptor and in the various cellular assays using the procedures described above or found in the

scientific literature. Accordingly, the person of ordinary skill can prepare and evaluate any of the claimed compounds without undue experimentation.

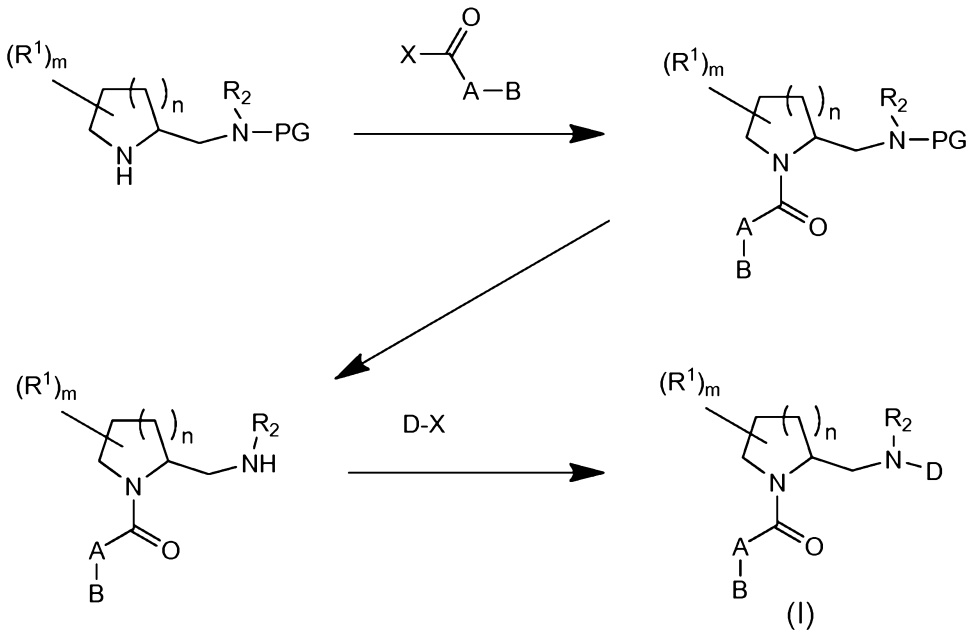
Any compound found to be an effective modulator, agonist or antagonist, can likewise be tested in animal models and in human clinical studies using the skill and experience of the investigator to guide the selection of dosages and treatment regimens.

Preparation of Compounds of the Invention

Compounds of the invention can be synthesized according to established literature procedures for analogous compounds and general techniques and reactions well known to persons of ordinary skill in the art.

As shown in General Synthetic Scheme A, below, a 2-(aminomethyl)pyrrolidine, 2-(aminomethyl)piperidine, or aminomethylaziridine precursor (i.e., wherein n = 1, 2, or 3), appropriately substituted with R^1 groups, can be coupled sequentially with the B-A-C(=O) fragment and the D fragment to provide a compound of the invention. The coupling steps can be carried out in either order, if necessary using appropriate protecting groups for functional R^1 or J groups with which the reactants can be substituted. General synthetic scheme I details a synthesis for compounds wherein group Z is nitrogen.

General Synthetic Scheme I



For a compound of formula (I) wherein R^2 is hydrogen, the compound can be prepared from an appropriately protected aminomethylpyrrolidine,

aminomethylpiperidine, or aminomethylaziridine, as shown. The group PG designates an N-protecting group, as are well-known in the art, to allow selective acylation of the ring nitrogen to occur for reaction with an activated B-A-C(=O)OH carboxylic acid, wherein X represents a carboxyl-activating group, e.g., an N-hydroxy ester, or a O-acylisourea, or a halogen. The carboxylic acid can be activated by any method known in the art, for example using HATU as is described below in General Synthetic Procedure A in the Examples, below. Then, the acylated intermediate can undergo deprotection of the aminomethyl protecting group (PG) using techniques suitable for the particular protecting group, and the amino group then reacted with an activated form of group D. For example, if D comprises a carboxylic acid group which is coupled with the aminomethyl group to form an amide, the carboxylic acid group can be activated using the techniques described above to form activated species D-X, which then forms the final product. For cases where D is an aryl, heteroaryl, or heterocyclic ring, the aminomethyl group can react with the corresponding aryl, heteroaryl or heterocyclic halide through a displacement reaction in the presence of a base or through standard metal mediated procedures (Buchwald, Ulmann) known to those skilled in the art. For further elaboration of R^2, the nitrogen atom can be reacted with an appropriate reagent; e.g. by alkylation, to provide compounds of formula (I) wherein R^2 is other than hydrogen.

It is understood that the synthesis can proceed in an alternative sequence by starting with an aminomethylpyrrolidine, aminomethylpiperidine, or aminomethylaziridine precursor wherein the protecting group is on the ring nitrogen atom and the exocyclic aminomethyl group is unprotected. Condensation with the D fragment, followed by deprotection of the ring nitrogen atom and coupling with the activated carboxylic acid B-A-C(=O)-X can provide the compound of formula (I).

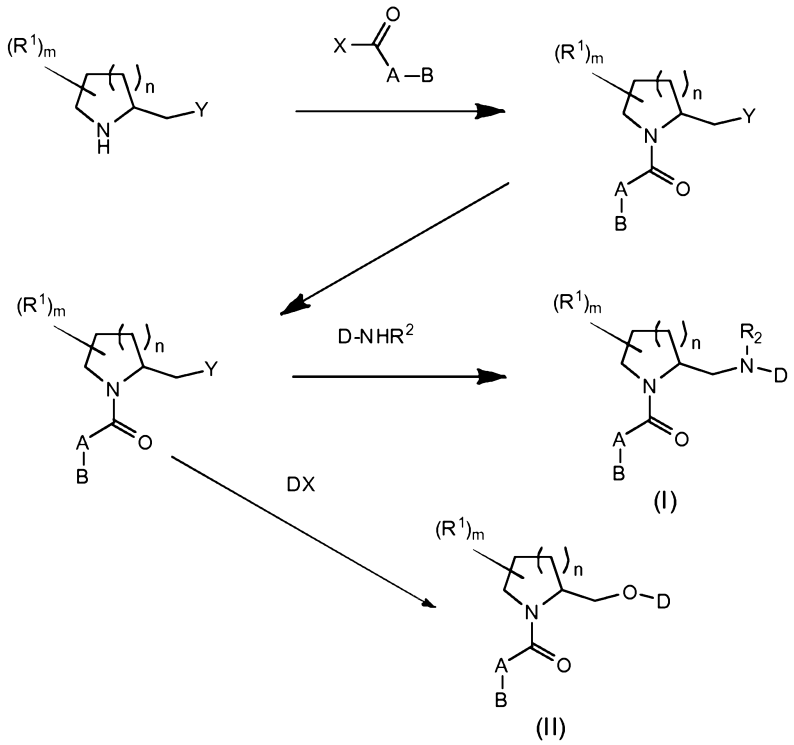
When the group Z of formula (I) is an oxygen atom, by coupling group D bearing an appropriate leaving group with a compound analogous to the penultimate intermediate shown in Scheme I, above, but bearing a hydroxyl group instead of an amino group on the sidechain.

Alternatively, synthesis of a compound of formula (I) can be achieved according General Synthetic Scheme II, below, wherein a D-NH2 fragment is coupled with an activated 2-methyl pyrrolidine or piperidine, which can be

derivatized with the B-A-C(=O)OH fragment either prior to or following the coupling.

For the embodimends of structure wherein group Z of formula (I) is an oxygen atom, a D-OH fragment can be coupled with an appropriately activated B-A-C fragment, either bearing a carboxyl group (to form an ester) or a leaving group (for form an ether).

General Synthetic Scheme II



An appropriately substituted pyrrolidine or piperidine or aziridine can bear a group Y for eventual displacement in a nucleophilic substitution reaction by amine D-NHR^2, particularly when the D group is not bonded to the nitrogen atom via a carbonyl group, e.g., when D is pyridyl instead of pyridoyl, quinolyl instead of quinoloyl, etc. For example, when D is pyridyl and R^2 is hydrogen, the D-NHR^2 reagent can be an aminopyridine, such as 2-, 3-, or 4-aminopyridine. For example Y can be a halo, or Y can be a hydroxyl. It is understood that Y can be in a protected form for the first step, if necessary, then deprotected and activated for the coupling with DNHR^2. For example, Y can be a protected hydroxyl group in the coupling of the first reagent with the activated B-A-C(=O)-X carboxylic acid, which is then converted to Y being a free hydroxyl group, followed by activation for nucleophilic displacement, e.g., as a

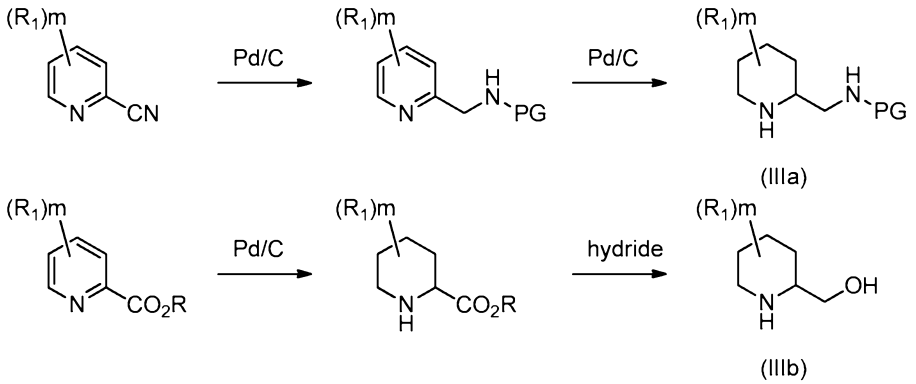
sulfonate ester, to provide the third reagent above that is then condensed with the D-NHR^2 reagent to provide the compound of formula (I). Y may also be a carboxaldehyde group and coupled with $DNHR^2$ by reductive amination. In the final product (I) or (II) in Synthetic Scheme II, above, the atom labeled Y becomes the Z group of formula (I).

In Synthetic Scheme II, it is also understood that the sequence can proceed in an alternative order of steps, i.e., coupling of the D-NHR^2 reagent with the activated Y-bearing ring system (with the ring nitrogen atom optionally protected as needed), followed by ring nitrogen deprotection and coupling with the activated B-A-C(=O)-X carboxylic acid.

Alternatively, when Y=OH, the alcohol may be coupled to DX (X=halogen or some other leaving group) to afford the ether product II. This can be done using any inorganic (for instance, Cs_2CO_3, K_2CO_3, etc.) or organic (for instance, Et_3N, iPr_2Net, DBU, etc) base in the appropriate solvent and at the appropriate temperature.

Appropriately substituted pyrrolidine, piperidine, and aziridine precursors can be prepared according to literature procedures and upon disclosed synthetic approaches described below in the Examples, using the knowledge of ordinary practitioners of organic synthetic chemistry.

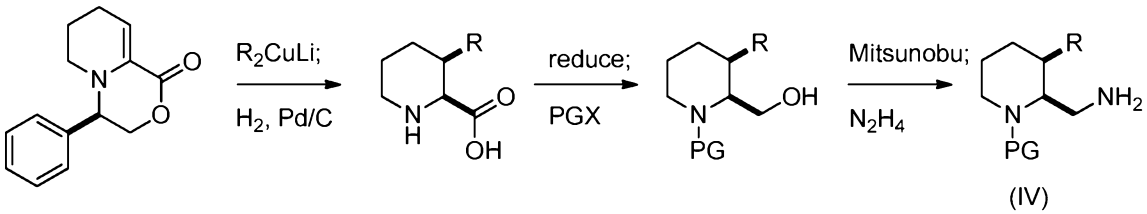
General Synthetic Scheme III



An appropriately substituted piperidine may be synthesized according to the protocol generally described in Synthetic Scheme III. A substituted 2-cyanopyridine can be reduced to the 2-aminomethyl pyridine and protected with a suitable protecting group. Further reduction of the ring provides the

differentially protected 2-aminomethyl piperidine IIIa. Alternatively, a 2-carboxypyridine (protected as the ester or as the acid) can be reduced to the substituted pipecolic acid and then reduced (using borane, or LAH, for instance) to the amino alcohol. Further functionalization to final products can follow protocols outlined in Schemes I and II above.

General Synthetic Scheme IV



(IV)

Enantiomerically pure 3-substituted 2-aminomethyl piperidines or 2-hydroxymethyl piperidines can be made as described in Synthetic Scheme IV. The 3-substituted pipecolic acids can be made as described in the literature in *J. Org. Chem.* **1994**, 59, p 3769, J. Royer et al. and *Tet. Lett.* **1999**, 40, 3699, J. Royer et al. R can be alkyl, alkenyl, alkynyl, haloalkyl, aryl, heteroaryl, etc. Reduction of the carboxylic acid with lithium aluminum hydride or borane or other suitable reducing agent provides the primary alcohol after protecting the piperidine nitrogen atom with a suitable protecting group. Conversion of the primary alcohol to the primary amine can be done by several standard approaches as described in the literature and known to those skilled in the art. One such way would be through Mitsunobu reaction with phthalamide and tripheylphosphine and diisopropylazodicarboxylate, followed by cleavage of the phthalimide group with hydrazine to give intermediate IV. Further functionalization to final products can follow protocols outlined in Schemes I and II above

Examples

The following examples of the compounds of the invention further demonstrate features and aspects of specific embodiments of the invention. The

parameters and characteristics of the compounds of the invention are set forth by the foregoing text.

Table 1: Exemplary Compounds of the Invention

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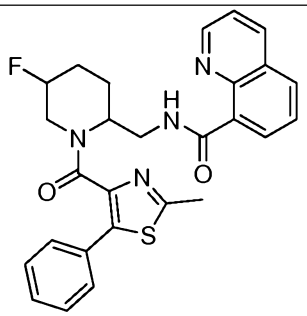
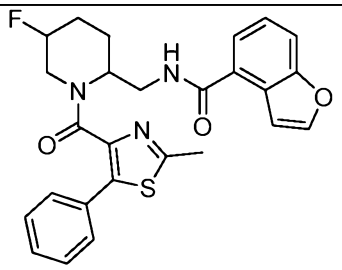
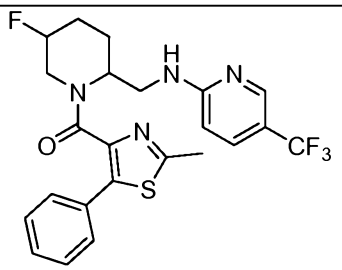
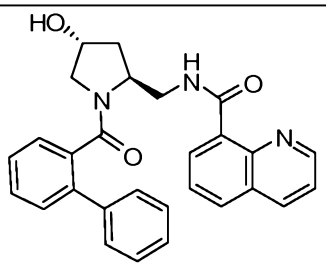
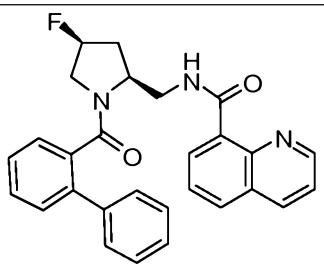
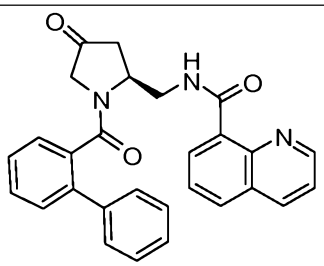
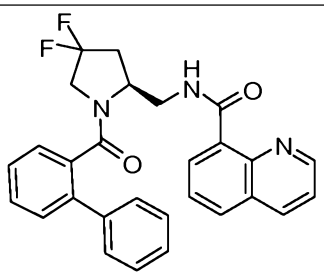
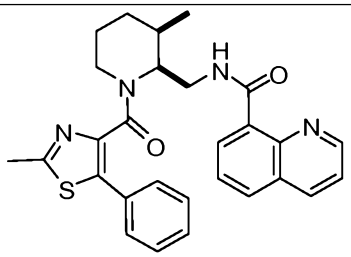
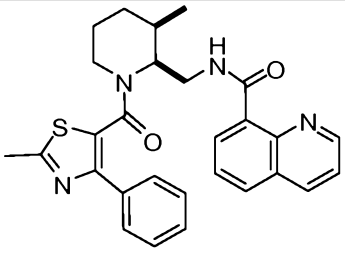
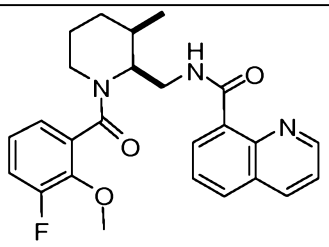
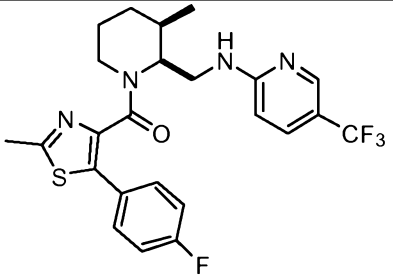
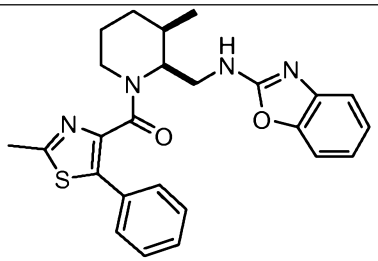
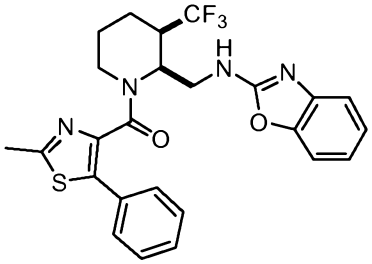
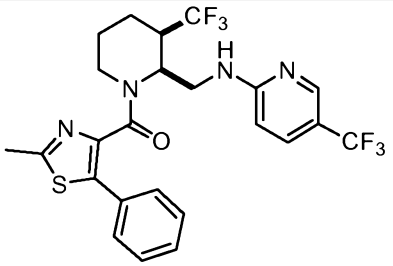
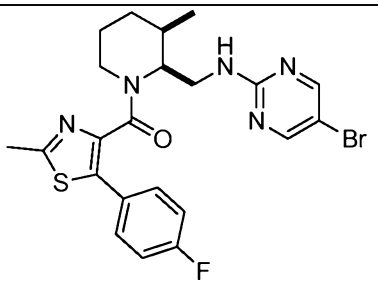
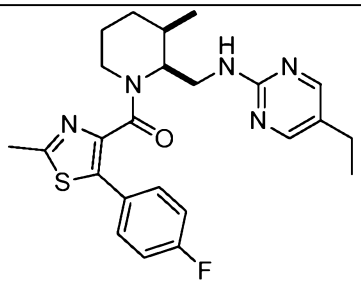
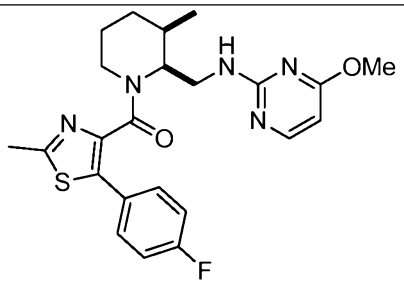
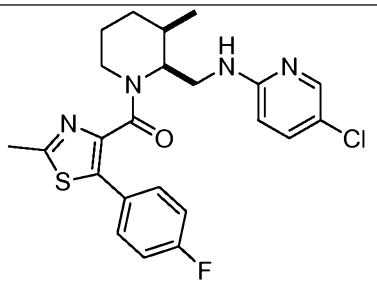
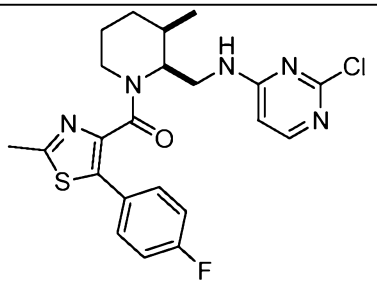
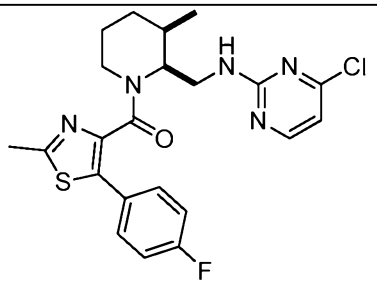
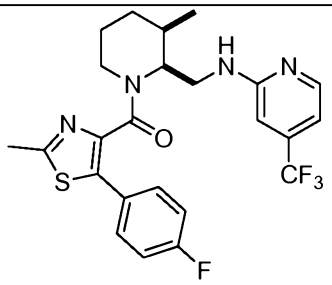
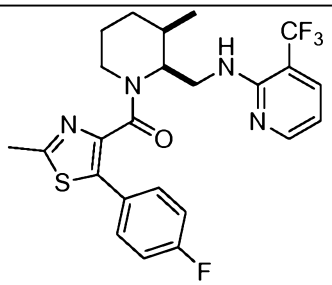
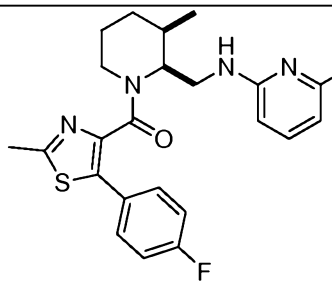
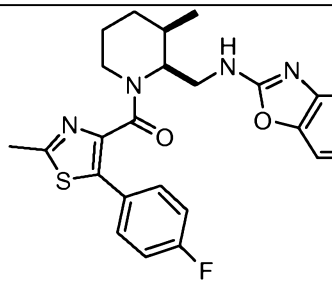
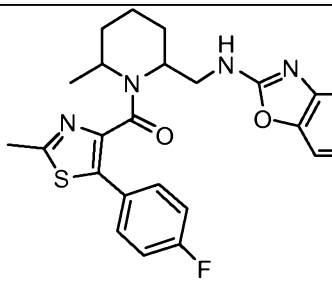
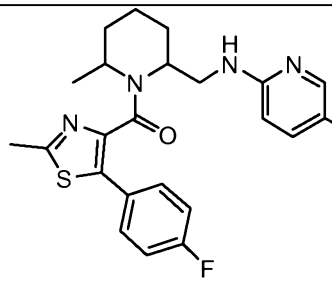
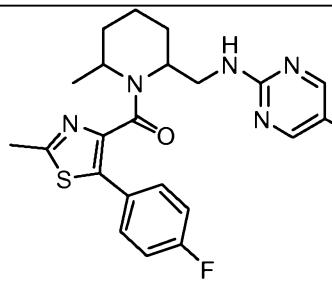
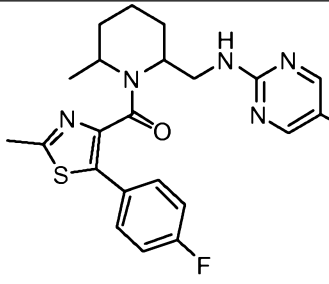
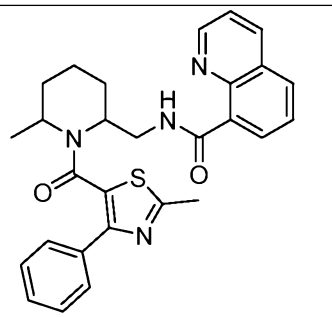
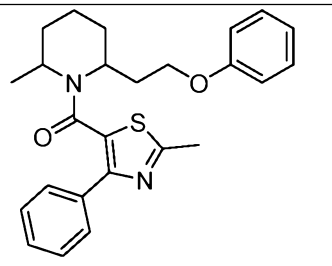
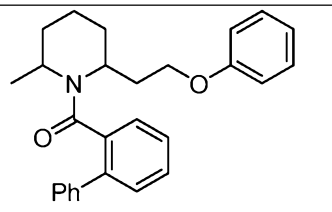
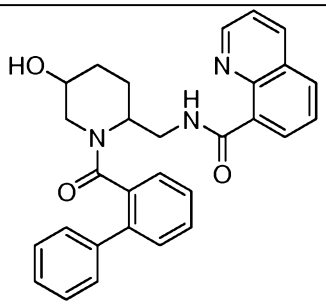
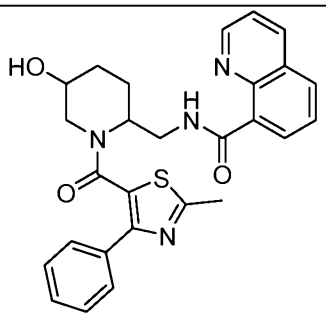
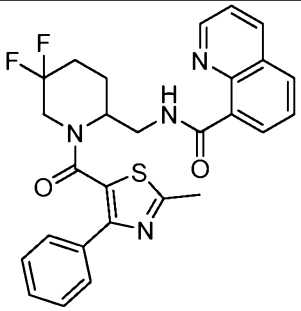
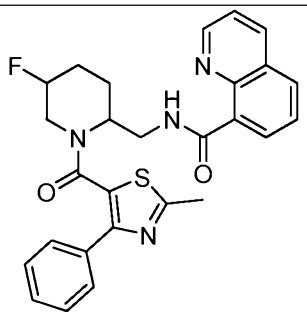
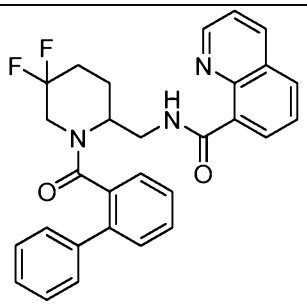
Example 1	
Example 2	
Example 3	
Example 4	
Example 5	
Example 6	
Example 7	
Example 8	
Example 9	

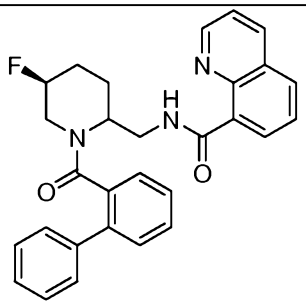
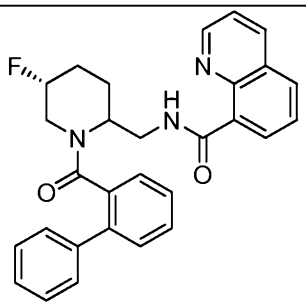
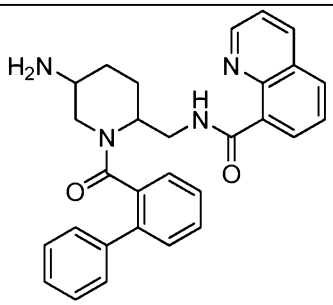
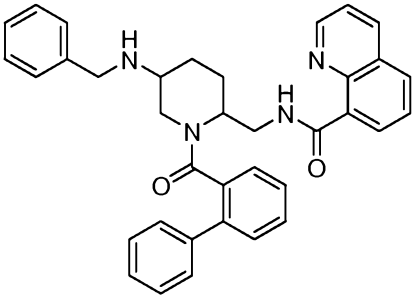
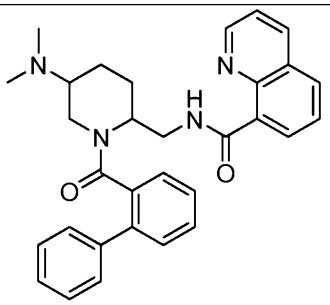
Example 10	
Example 11	
Example 12	
Example 13	
Example 14	
Example 15	

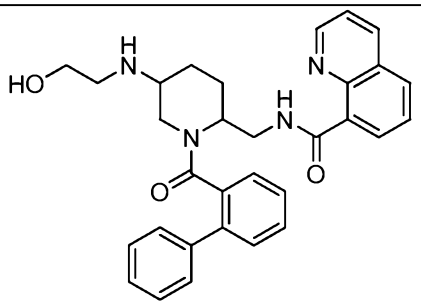
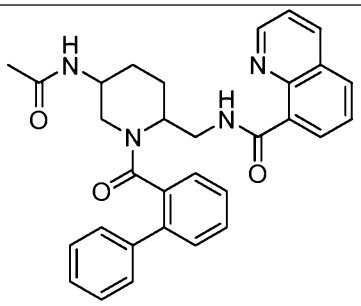
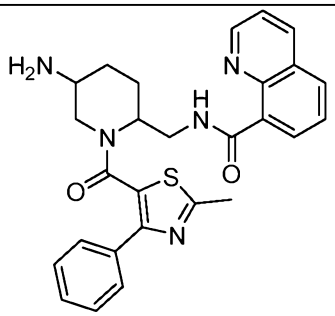
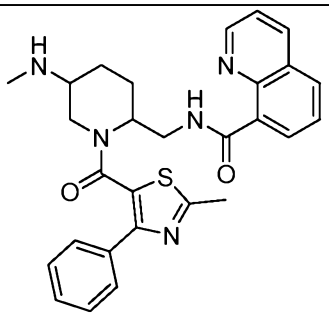
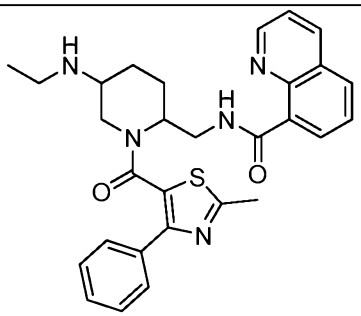
Example 16	
Example 17	
Example 18	
Example 19	
Example 20	

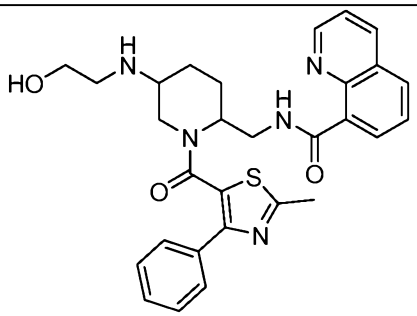
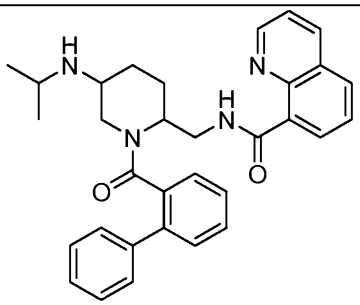
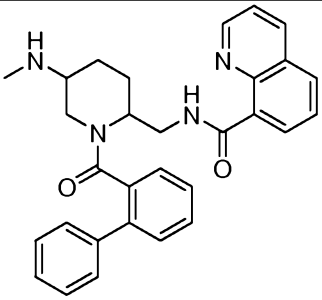
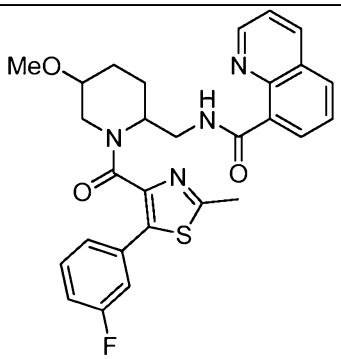
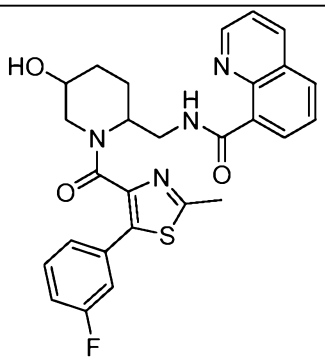
Example 21	
Example 22	
Example 23	
Example 24	
Example 25	

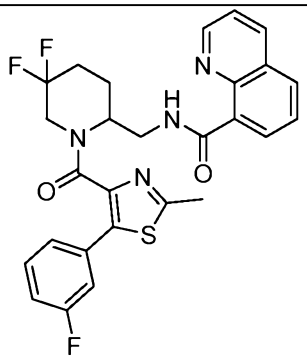
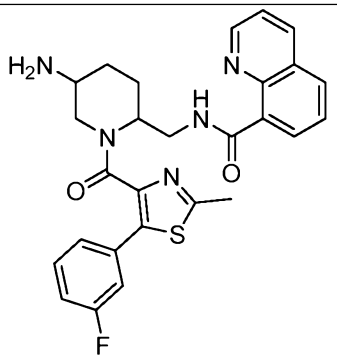
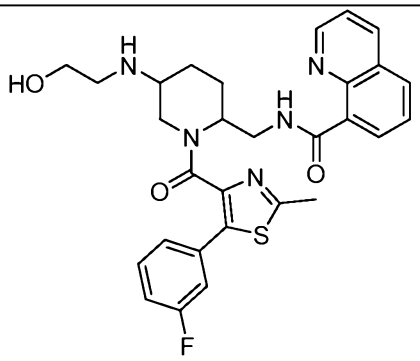
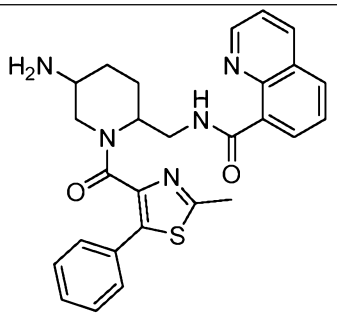
Example 26	
Example 27	
Example 28	
Example 29	
Example 30	
Example 31	

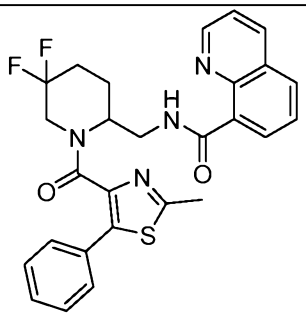
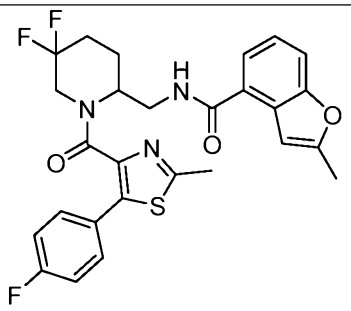
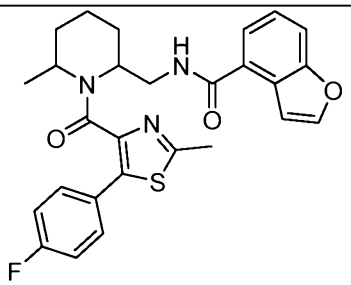
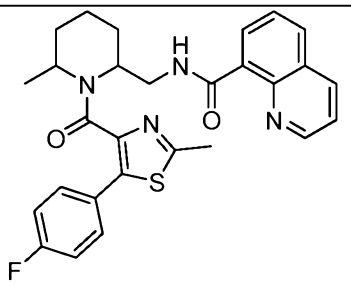
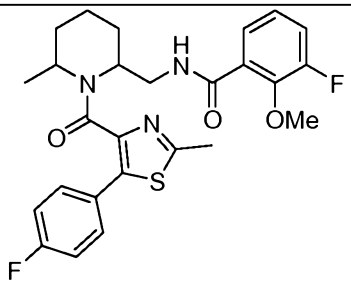
Example 32	
Example 33	
Example 34	
Example 35	
Example 36	

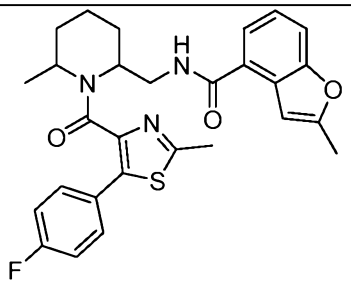
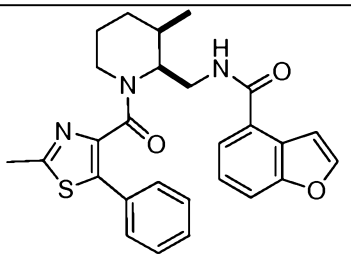
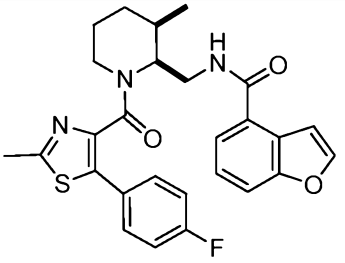
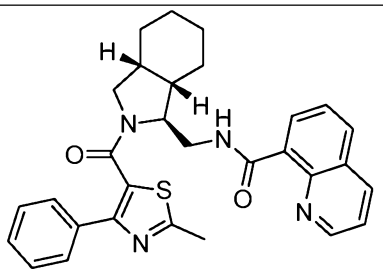
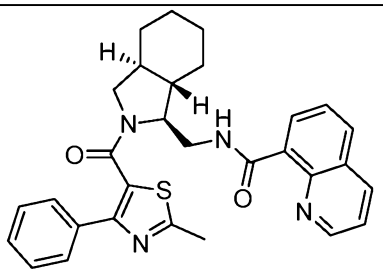
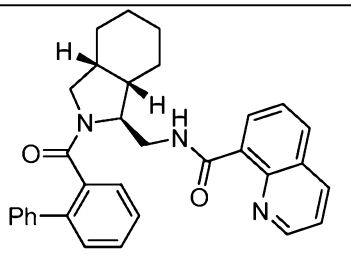
Example 37	
Example 38	
Example 39	
Example 40	
Example 41	

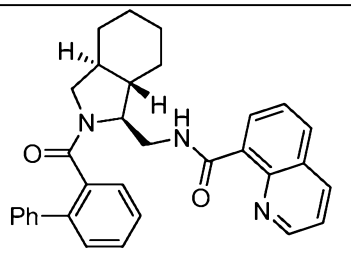
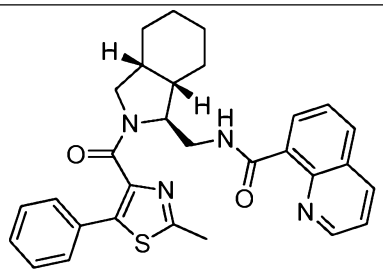
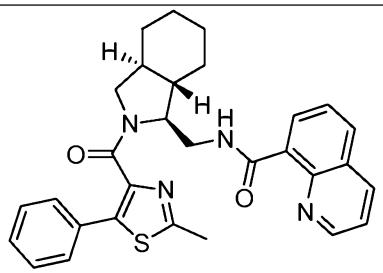
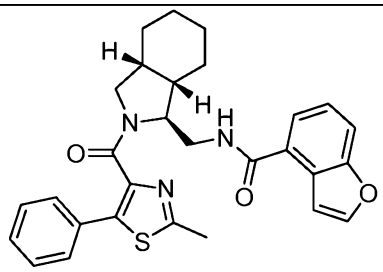
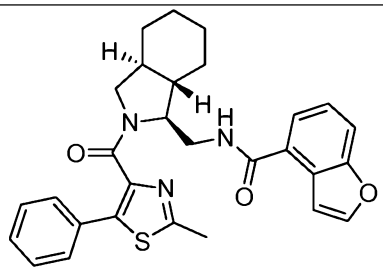
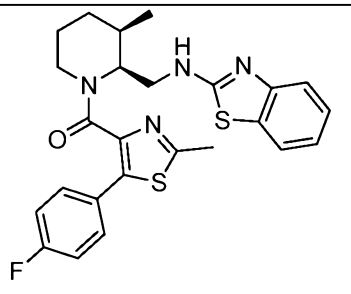
Example 42	
Example 43	
Example 44	
Example 45	
Example 46	

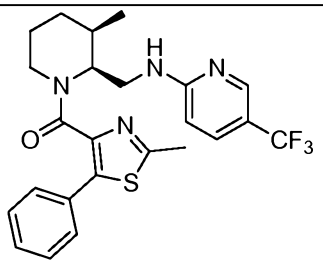
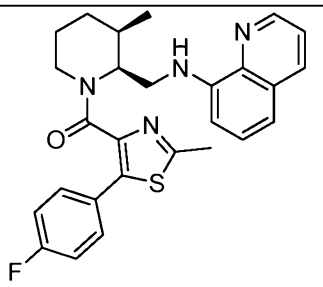
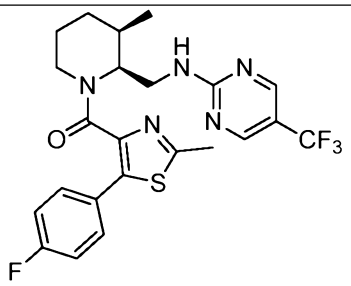
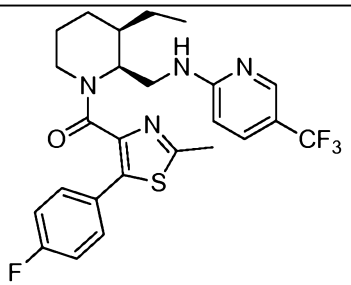
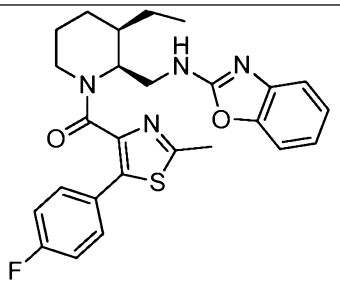
Example 47	
Example 48	
Example 49	
Example 50	
Example 51	

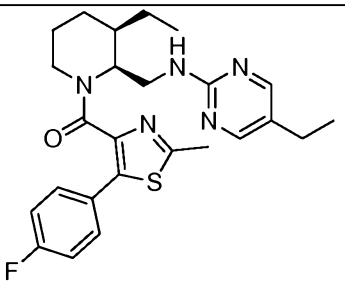
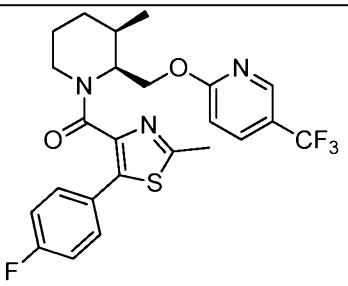
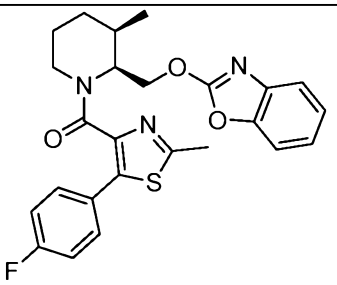
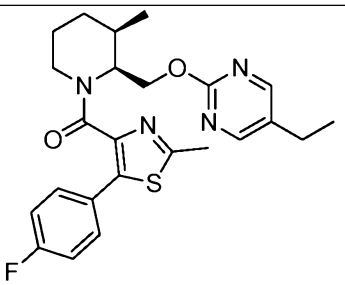
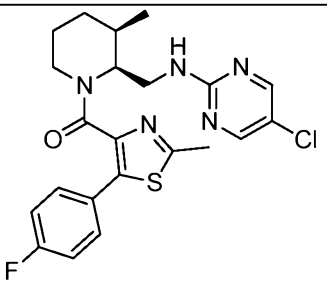
Example 52	
Example 53	
Example 54	
Example 55	

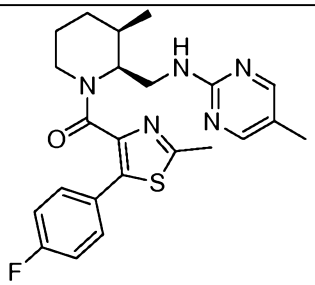
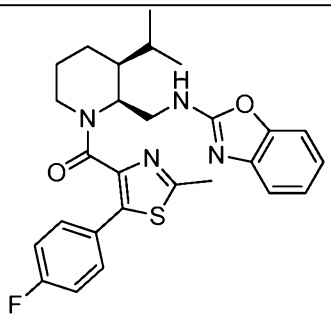
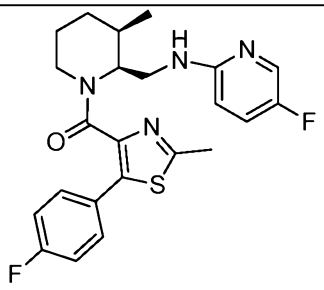
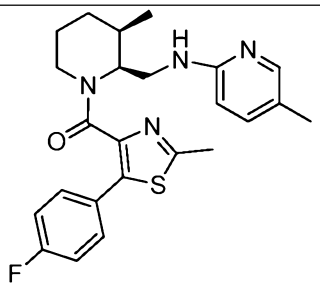
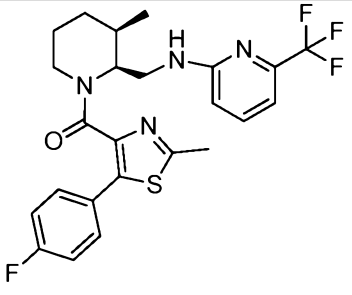
Example 56	
Example 57	
Example 58	
Example 59	
Example 60	

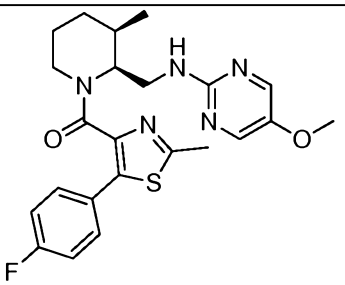
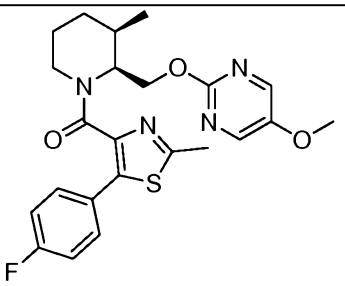
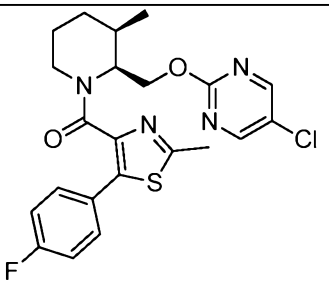
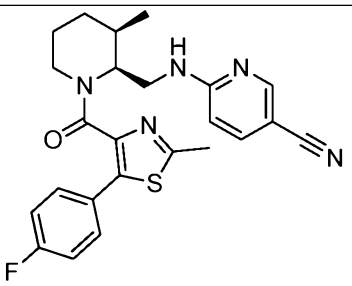
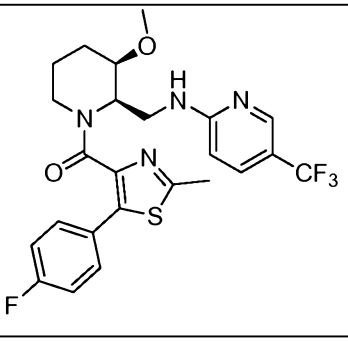
Example 61	
Example 62	
Example 63	
Example 64	
Example 65	
Example 66	

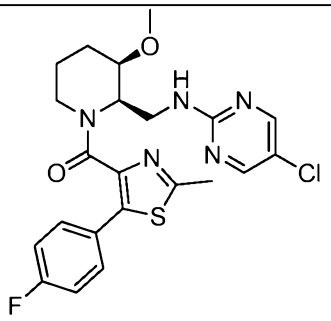
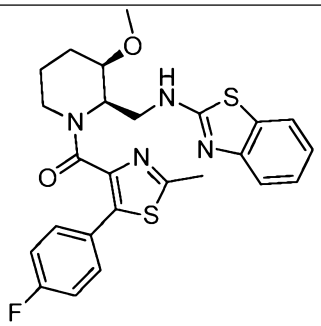
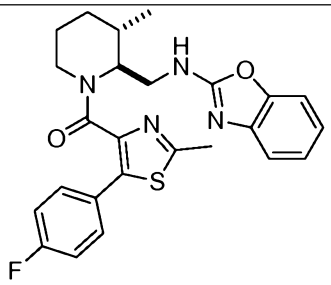
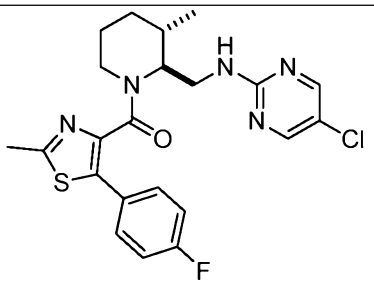
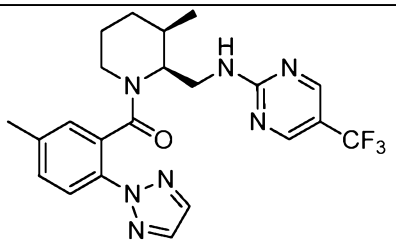
Example 67	
Example 68	
Example 69	
Example 70	
Example 71	
Example 72	

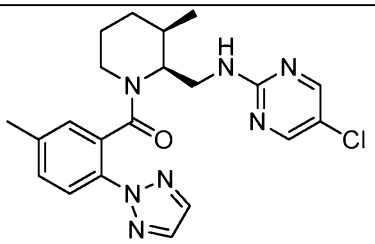
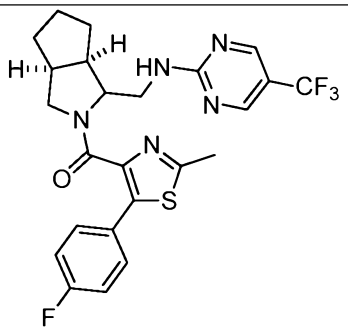
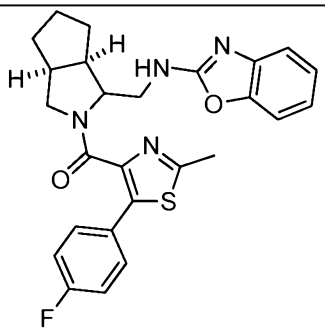
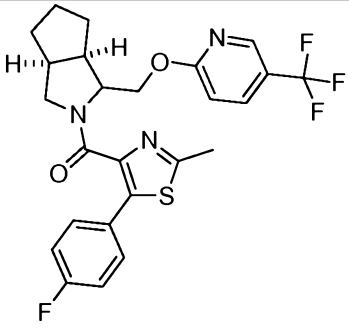
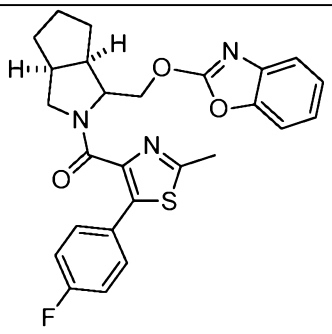
Example 73	
Example 74	
Example 75	
Example 76	
Example 77	

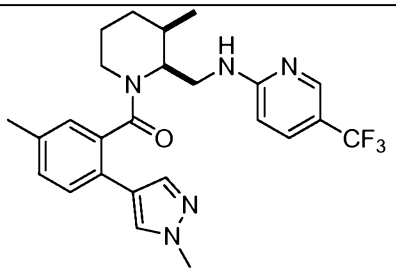
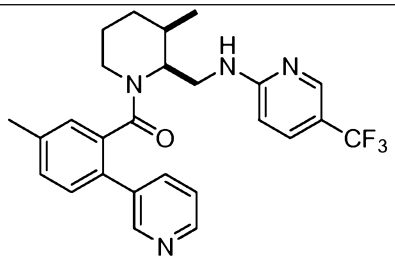
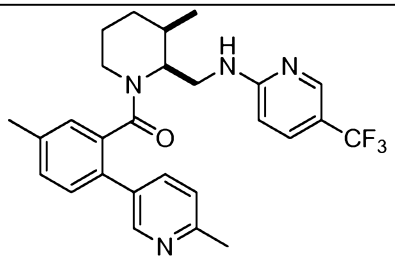
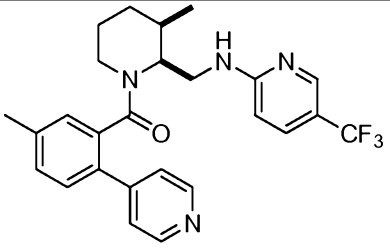
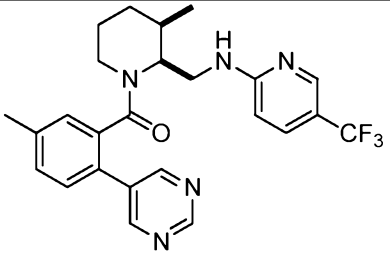
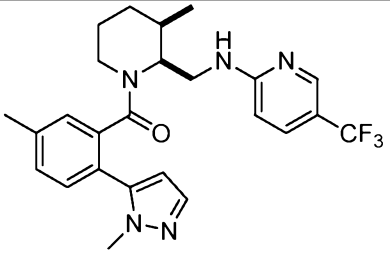
Example 78	
Example 79	
Example 80	
Example 81	
Example 82	

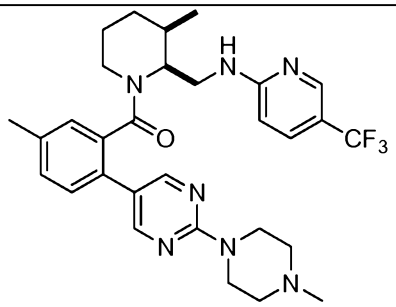
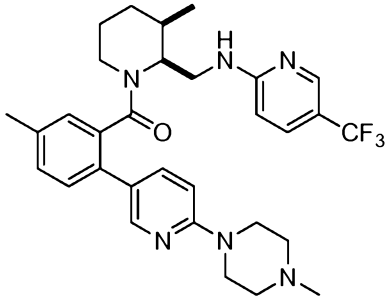
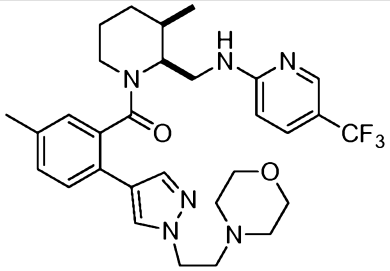
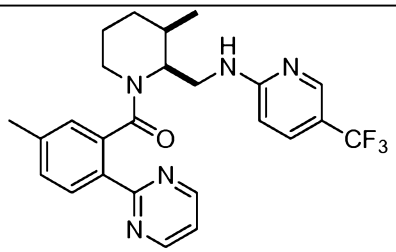
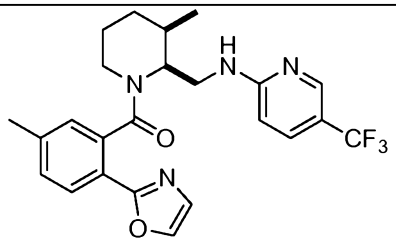
Example 83	
Example 84	
Example 85	
Example 86	
Example 87	

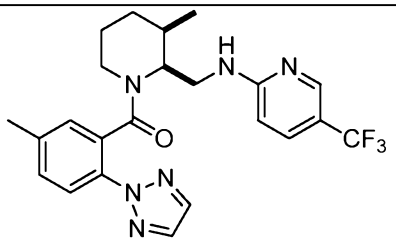
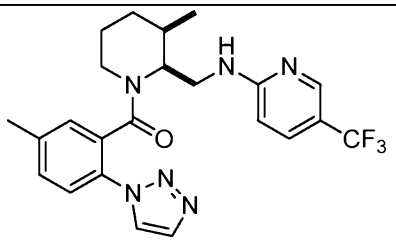
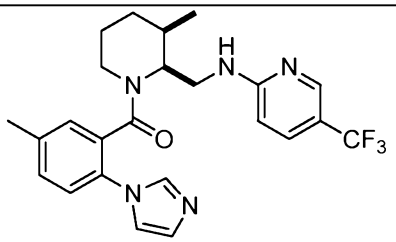
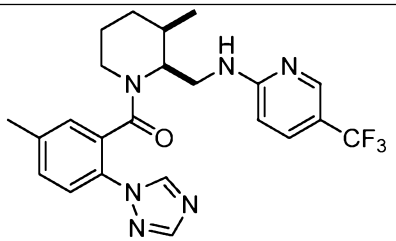
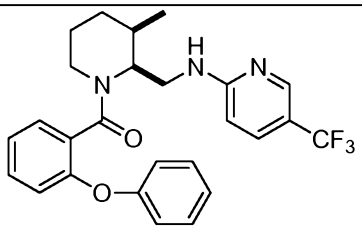
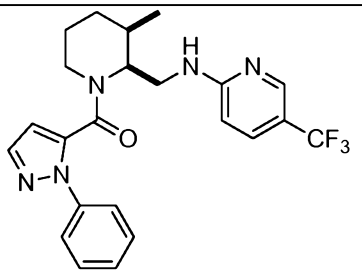
Example 88	
Example 89	
Example 90	
Example 91	
Example 92	

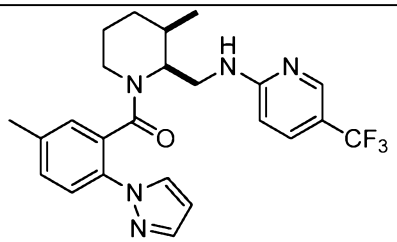
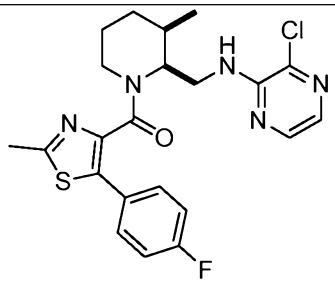
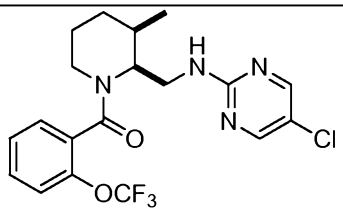
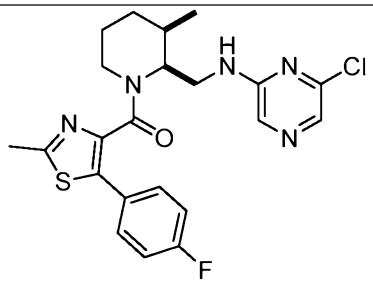
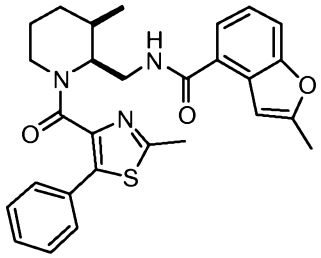
Example 93	
Example 94	
Example 95	
Example 96	
Example 97	

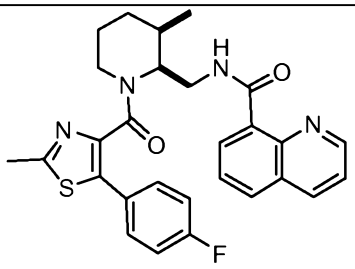
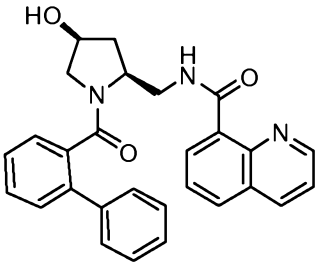
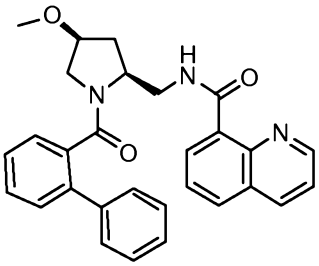
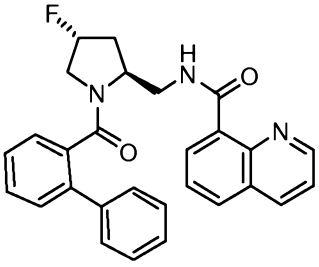
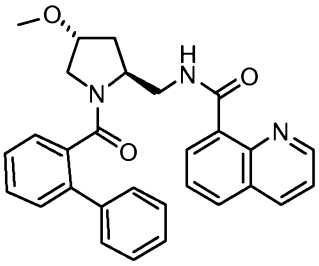
Example 98	
Example 99	
Example 100	
Example 101	
Example 102	

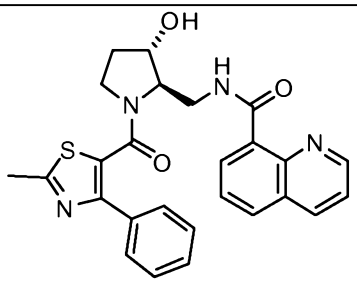
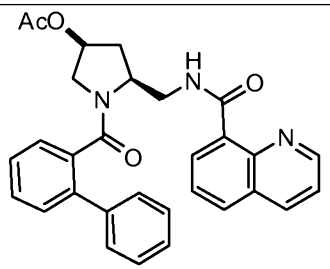
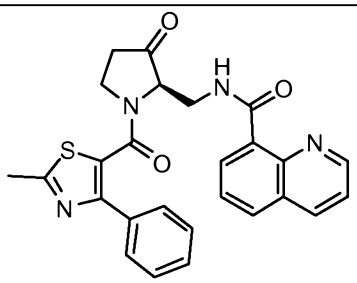
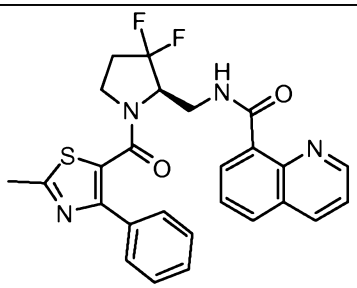
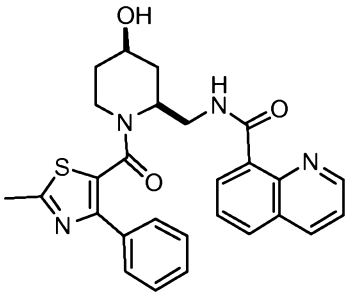
Example 103	
Example 104	
Example 105	
Example 106	
Example 107	
Example 108	

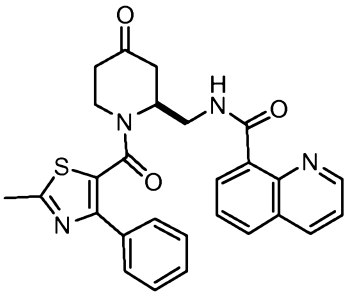
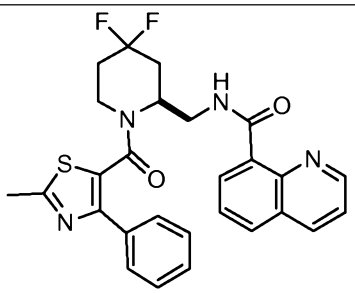
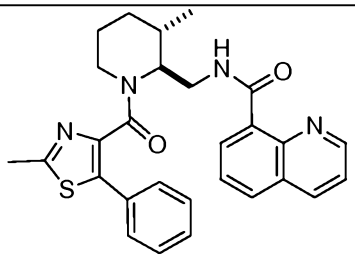
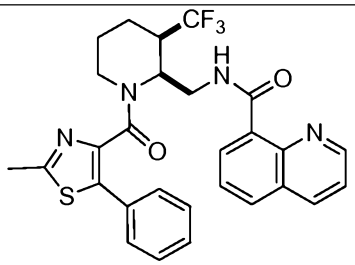
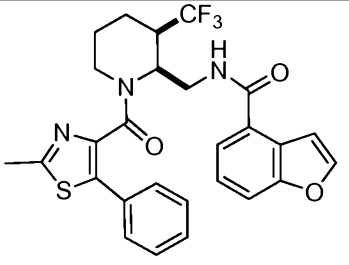
Example 109	
Example 110	
Example 111	
Example 112	
Example 113	

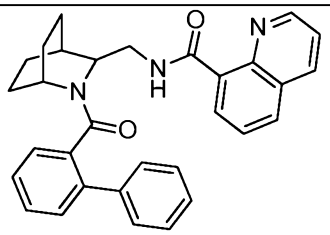
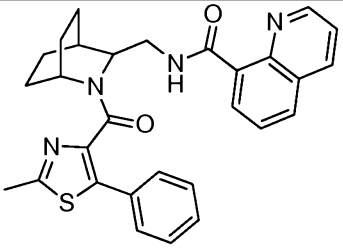
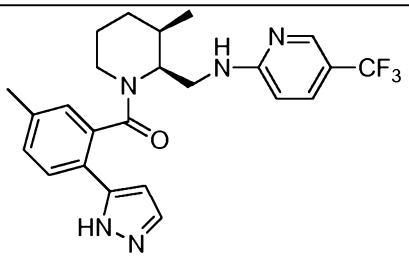
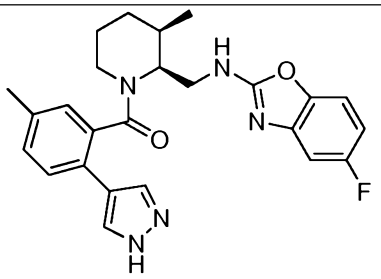
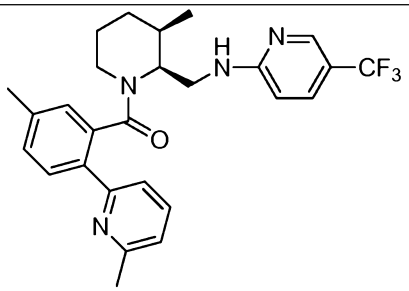
Example 114	
Example 115	
Example 116	
Example 117	
Example 118	
Example 119	

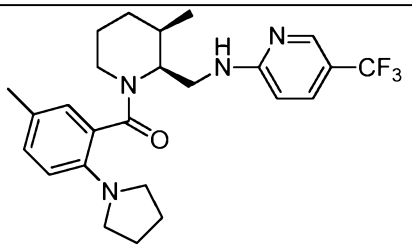
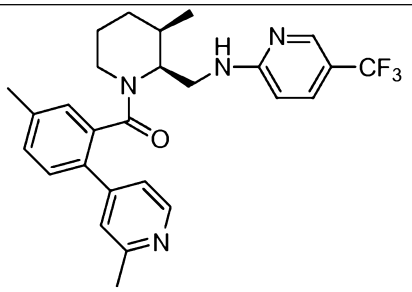
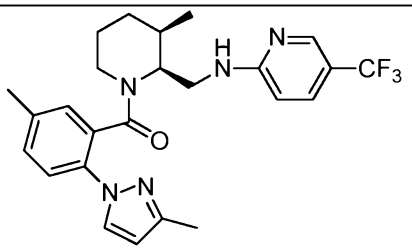
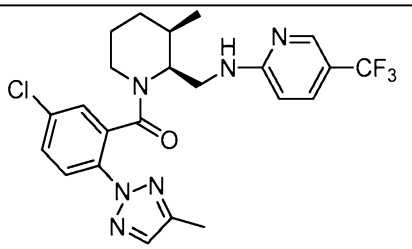
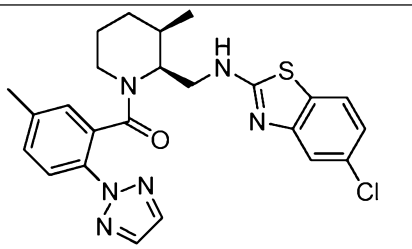
Example 120	
Example 121	
Example 122	
Example 123	
Example 124	

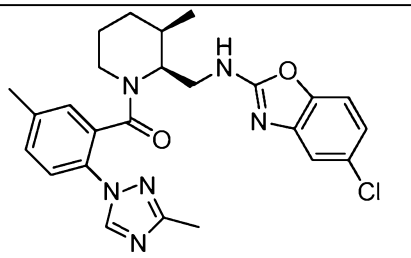
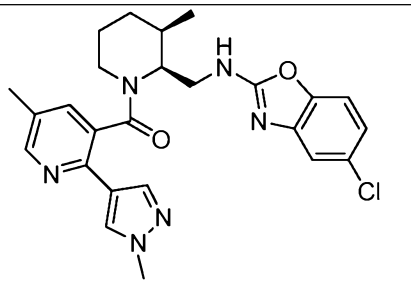
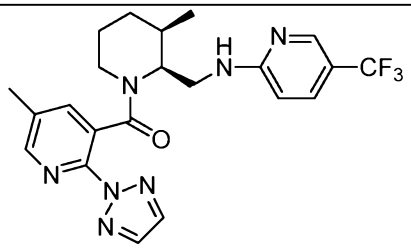
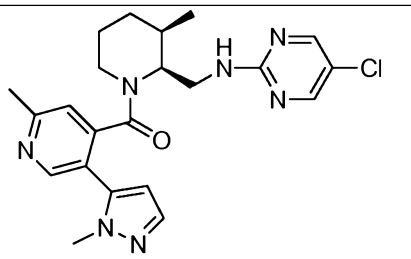
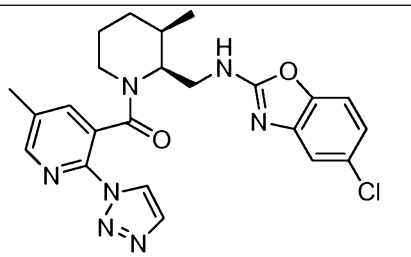
Example 125	
Example 126	
Example 127	
Example 128	
Example 129	

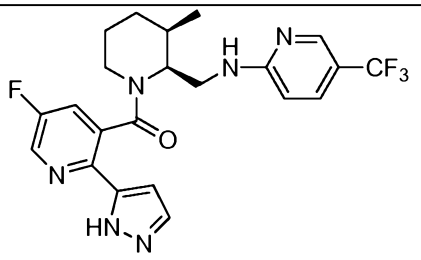
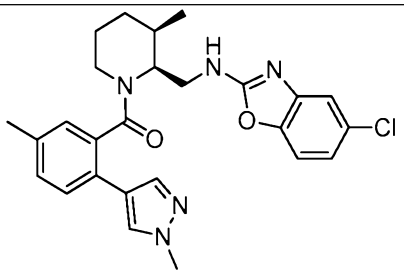
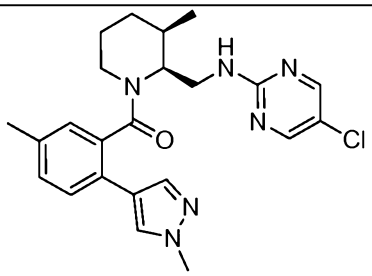
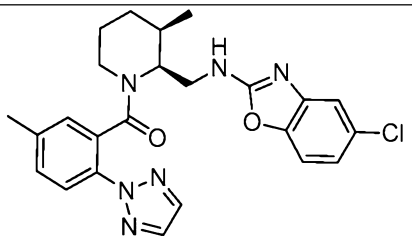
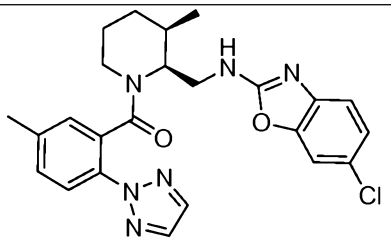
Example 130	
Example 131	
Example 132	
Example 133	
Example 134	

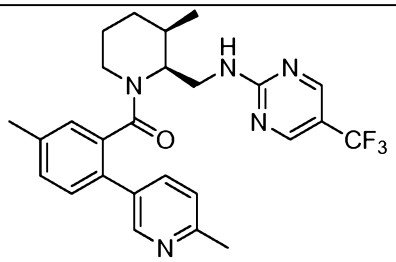
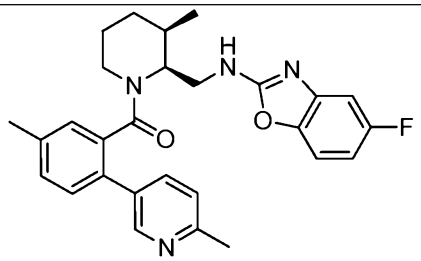
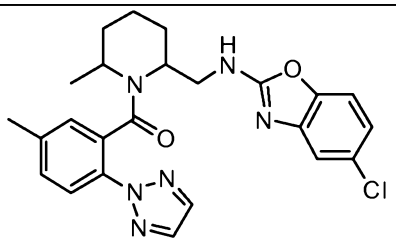
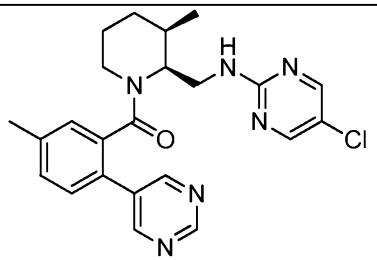
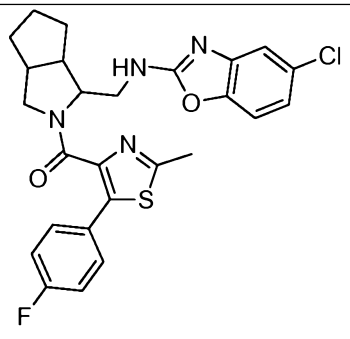
Example 135	
Example 136	
Example 137	
Example 138	
Example 139	

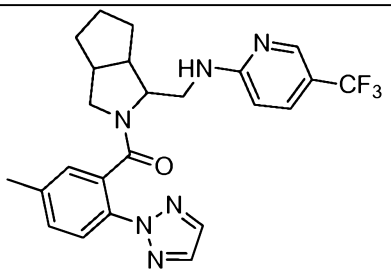
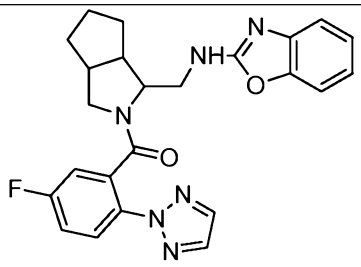
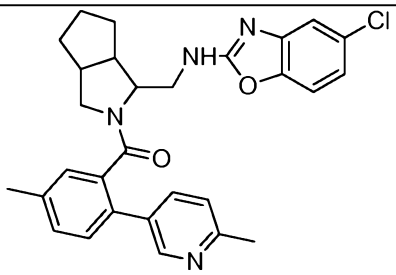
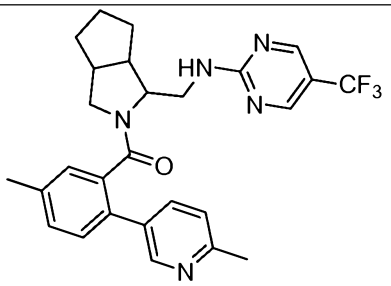
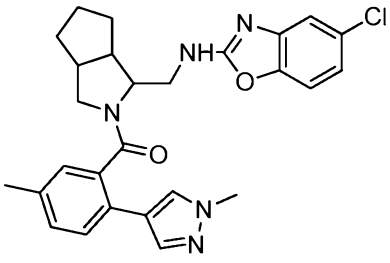
Example 140	
Example 141	
Example 142 P	
Example 143 P	
Example 144 P	

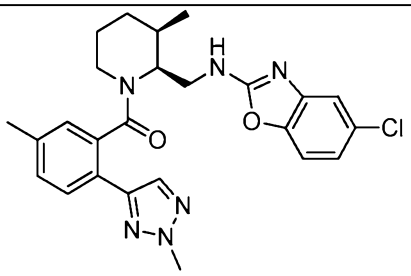
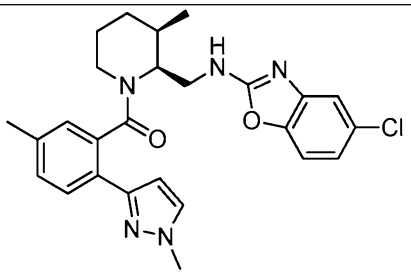
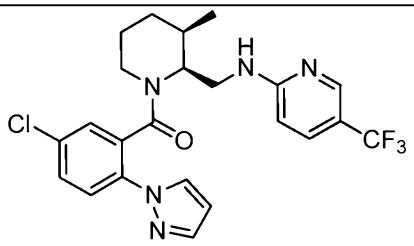
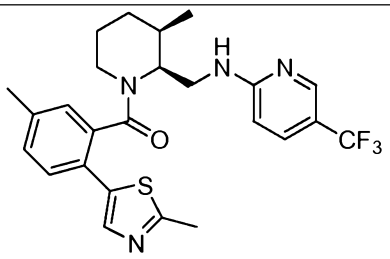
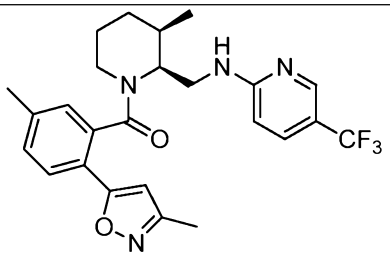
Example 145 P	
Example 146 P	
Example 147 P	
Example 148 P	
Example 149 P	

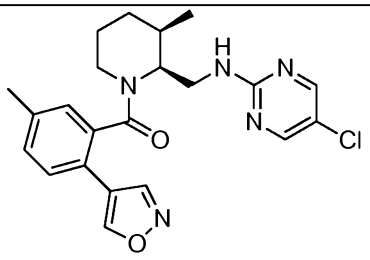
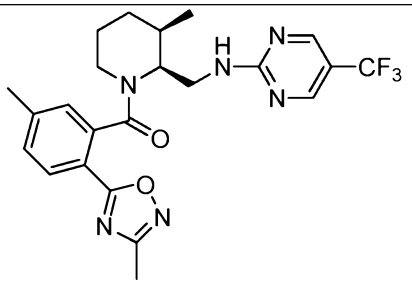
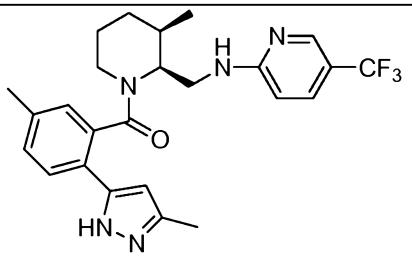
Example 150 P	
Example 151 P	
Example 152 P	
Example 153 P	
Example 154 P	

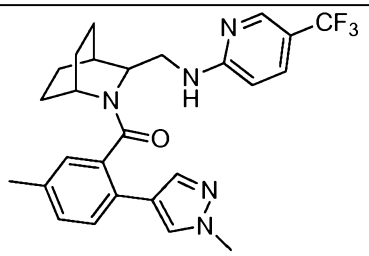
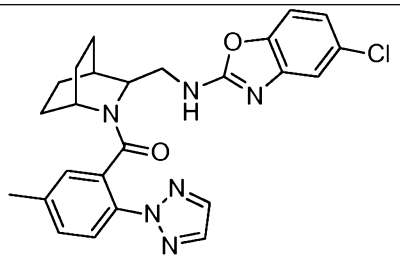
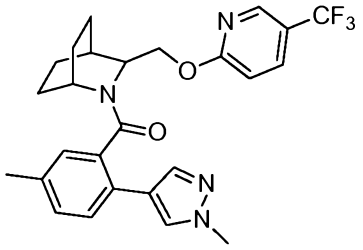
Example 155 P	
Example 156 P	
Example 157 P	
Example 158 P	
Example 159 P	

Example 160 P	
Example 161 P	
Example 162 P	
Example 163 P	
Example 164 P	

Example 165 P	
Example 166 P	
Example 167 P	
Example 168 P	
Example 169 P	

Example 170 P	
Example 171 P	
Example 172 P	
Example 173 P	
Example 174 P	

Example 175 P	
Example 176 P	
Example 177 P	

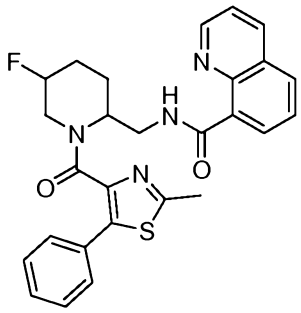
Example 178 P	
Example 179 P	
Example 180 P	

P = prophetic example

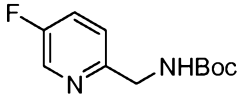
Synthetic Examples

Example 1

rac-N-((5-fluoro-1-(2-methyl-5-phenylthiazole-4-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide

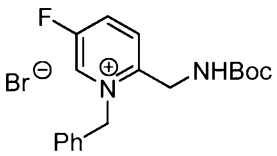


tert-Butyl (5-fluoropyridin-2-yl)methylcarbamate



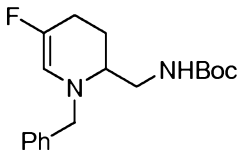
A solution of $(Boc)_2O$ (1.11 g, 5.16 mmol) in CH_2Cl_2 (3 mL) was added to a mixture of (5-fluoropyridin-2-yl)methanamine (0.64 g, 3.44 mmol) in CH_2Cl_2 dropwise at room temperature. The resulting mixture was stirred at room temperature overnight and quenched with saturated $NaHCO_3$. The organic portion was separated, dried with $MgSO_4$ and concentrated *in vacuo* to give desired *tert*-butyl (5-fluoropyridin-2-yl)methylcarbamate in 83% yield. ^1H NMR (MeOH-*d4*, 400 MHz) δ 8.39 (d, 1H), 7.63–7.58 (m, 1H), 7.44–7.40 (m, 1H), 4.35 (s, 2H), 1.53 (s, 2H), 1.48 (s, 7H). MS (ESI) 227 (M+H).

1-Benzyl-2-((*tert*-butoxycarbonylamino)methyl)-5-fluoropyridinium bromide



A mixture of benzyl bromide (4.21 mmol, 0.5 mL), tert-butyl (5-fluoropyridin-2-yl)methylcarbamate (3.49 mmol, 0.79 g) and acetone (4 mL) in a sealed tube was heated to 80 °C overnight. According to analytical HPLC, around 50% of the starting material remained. Additional benzyl bromide (33.68 mmol, 4.0 mL) was added and the reaction was continued for extra 8 hours. The reaction mixture was concentrated *in vacuo* and loaded on a pad of silica which was rinsed with ether until benzyl bromide was gone. Then, the silica pad was rinsed with MeOH. Removal of MeOH *in vacuo* afforded desired product 1-benzyl-2-((tert-butoxycarbonylamino)methyl)-5-fluoropyridinium bromide as light orange solid in 43% yield. MS (ESI) 317 (M+H)

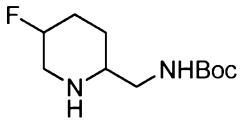
tert-Butyl (1-benzyl-5-fluoro-1,2,3,4-tetrahydropyridin-2-yl)methylcarbamate



$NaBH_4$ (5.56 mmol, 0.21 g) was added to a solution of 1-benzyl-2-((tert-butoxycarbonylamino)methyl)-5-fluoropyridinium bromide (1.40 mmol, 0.60g) in MeOH at 0 °C. The resulting mixture was stirred at 0 °C for 40 min. An aliquot was checked by analytical HPLC and some of the starting material remained. Additional $NaBH_4$ (5.56 mmol, 0.21 g) was added at 0 °C and the resulting mixture was stirred for extra 40 min. The reaction mixture was diluted with EtOAc and washed with brine. EtOAc layer was separated, dried with $MgSO_4$ and concentrated in vacuo to give desired tert-butyl (1-benzyl-5-fluoro-1,2,3,4-

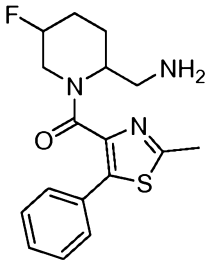
tetrahydropyridin-2-yl)methylcarbamate in 62% yield which was used for next step without further purification. MS (ESI) 321 (M+H).

tert-Butyl (5-fluoropiperidin-2-yl)methylcarbamate



The above described tert-butyl (1-benzyl-5-fluoro-1,2,3,4-tetrahydropyridin-2-yl)methylcarbamate and 10% Pd/C in MeOH was stirred at room temperature under a hydrogen balloon overnight. The reaction mixture was filtered through Celite and concentrated *in vacuo* to provide the desired product tert-butyl (5-fluoropiperidin-2-yl)methylcarbamate in quantitative yield which was used for next step without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.56–4.47 (m, 1H), 3.34–3.17 (m, 2H), 3.02–2.95 (m, 1H), 2.67–2.60 (m, 2H), 2.19–2.14 (m, 1H), 1.81–1.76 (m, 1H), 1.59–1.45 (m, 2H), 1.45 (s, 9H).

rac- (2-(Aminomethyl)-5-fluoropiperidin-1-yl)(2-methyl-5-phenylthiazol-4-yl)methanone



General procedure A: Amide Coupling using HATU as coupling agent.

A mixture of tert-butyl (5-fluoropiperidin-2-yl)methylcarbamate (0.43 mmol, 0.1 g), 2-methyl-5-phenyl-1,3-thiazole-4-carboxylic acid (made as described in the literature: see for instance, WO2008020405, 0.47 mmol, 0.1 g), diisopropyl ethyl amine (0.47 mmol, 0.08 mL) and HATU (0.47 mmol, 0.18 g) in dimethyl acetamide (2 mL) was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc and washed with 1N NaOH and brine successively. The organic layer was separated, dried with $MgSO_4$ and concentrated *in vacuo* to provide desired tert-butyl (5-fluoro-1-(2-methyl-5-phenylthiazole-4-carbonyl)piperidin-2-yl)methylcarbamate which was used for next step without further purification.

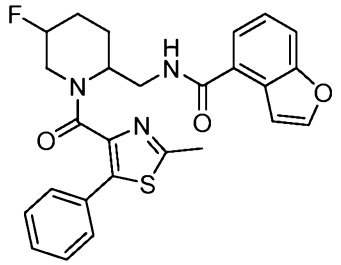
The above described tert-butyl (5-fluoro-1-(2-methyl-5-phenylthiazole-4-carbonyl)piperidin-2-yl)methylcarbamate was stirred in CH_2Cl_2 (5 mL) and TFA (5 mL)

overnight and concentrated *in vacuo*. The resulting residue was taken in EtOAc and washed with saturated $NaHCO_3$. EtOAc layer was separated, dried with $MgSO_4$ and concentrated *in vacuo* to afford desired (2-(aminomethyl)-5-fluoropiperidin-1-yl)(2-methyl-5-phenylthiazol-4-yl)methanone in 42% yield over two steps.

The final product *N*-((5-fluoro-1-(2-methyl-5-phenylthiazole-4-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide was prepared by following general procedure **A** using (2-(aminomethyl)-5-fluoropiperidin-1-yl)(2-methyl-5-phenylthiazol-4-yl)methanone and quinoline-8-carboxylic acid. The NMR of desired product indicated the presence of two rotamers in 1/2 ratio. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.02–10.99 (m, 0.33 H), 10.73–10.70 (m, 0.67 H), 9.05–9.03 (m, 0.33 H), 8.98–8.97 (m, 0.67 H), 8.62–8.59 (m, 1.33 H), 8.52–8.50 (M, 0.67 h), 8.24–8.19 (m, 1H), 7.81–7.74 (m, 1.33 H), 7.72–7.68 (m, 0.67 H), 7.47–7.43 (m, 0.67 H), 7.34–7.32 (m, 2.33 H), 7.19–7.10 (m, 2H), 5.08–4.67 (m, 2H) 3.98–3.34 (m, 4H), 2.65 (s, 1H), 2.23 (s, 2H), 2.12–1.69 (m, 2.67 H), 1.41–1.39 (m, 1.33 H). MS (ESI) 489 (M+H).

Example 2

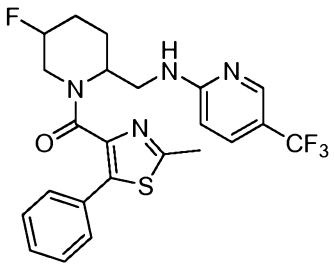
N-((5-fluoro-1-(2-methyl-5-phenylthiazole-4-carbonyl)piperidin-2-yl)methyl)benzofuran-4-carboxamide



N-((5-fluoro-1-(2-methyl-5-phenylthiazole-4-carbonyl)piperidin-2-yl)methyl)benzofuran-4-carboxamide was prepared by following general procedure A using (2-(aminomethyl)-5-fluoropiperidin-1-yl)(2-methyl-5-phenylthiazol-4-yl)methanone and benzofuran-4-carboxylic acid. MS (ESI) 478 (M+H).

Example 3

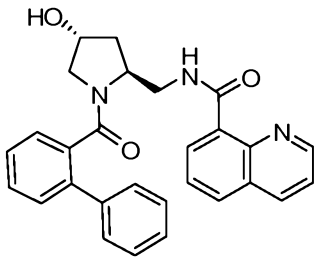
(5-Fluoro-2-((5-(trifluoromethyl)pyridin-2-ylamino)methyl)piperidin-1-yl)(2-methyl-5-phenylthiazol-4-yl)methanone



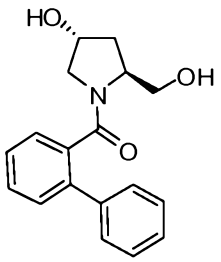
General procedure B: Amination of 2-chloro-5-(trifluoromethyl)pyridine. A mixture of (2-(aminomethyl)-5-fluoropiperidin-1-yl)(2-methyl-5-phenylthiazol-4-yl)methanone (0.18 mmol, 0.06 g), 2-chloro-5-(trifluoromethyl)pyridine (0.38 mmol, 0.07 g) and Cs_2CO_3 in DMF (1.5 mL) was stirred at 120 °C overnight. The reaction mixture was diluted with EtOAc and washed with brine. The organic layer was separated, dried with $MgSO_4$ and concentrated *in vacuo*. The desired (5-fluoro-2-((5-(trifluoromethyl)pyridin-2-ylamino)methyl)piperidin-1-yl)(2-methyl-5-phenylthiazol-4-yl)methanone was isolated by preparative HPLC. MS (ESI) 479 (M+H).

Example 4

N-(((2*S*,4*R*)-1-(Biphenylcarbonyl)-4-hydroxypyrrolidin-2-yl)methyl)quinoline-8-carboxamide



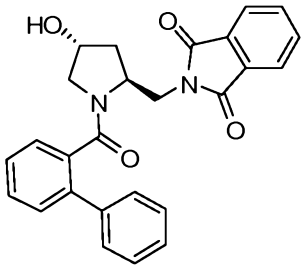
Biphenyl-2-yl((2*S*,4*R*)-4-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl)methanone



Formation of the amide bond was carried out using an adaptation of General Method A, above. A mixture of commercially available (2*S*,4*R*)-*tert*-butyl 4-hydroxy-2-(hydroxymethyl)pyrrolidine-1-carboxylate (3.26 g, 15 mmol) in 50 mL of DCM/TFA (3:2,

v/v) was stirred at r.t. for 4 hrs, concentrated *in vacuo* to give a brown oil as a crude TFA salt of (3*R*,5*S*)-5-(hydroxymethyl)pyrrolidin-3-ol, which was dissolved in DMF (28 mL), added with biphenyl-2-carboxylic acid (3.05 g, 15.4 mmol) and HATU (5.86 g, 15.4 mmol). The resulting solution was cooled to 0°C, added with Et_3N (8.8 mL, 63 mmol) dropwise and was allowed to warm to r.t. gradually and stirred overnight. 2M NaOH (aq.) was added and the mixture was extracted with EtOAc (3x). The combined EtOAc solution was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to a brown oil, which was purified by column chromatography on silica gel (10% MeOH in EtOAc) to provide biphenyl-2-yl((2*S*,4*R*)-4-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl)methanone as an off-white solid (2.0 g, 45% yield over two steps). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.59–7.57 (m, 2H), 7.54–7.40 (m, 7H), 4.44 (brs, 1H), 4.10 (s, 1H), 3.77–3.72 (m, 1H), 3.62 (brs, 1H), 3.32 (brs, 1H), 3.04–2.96 (m, 1H), 2.60 (brs, 1H), 2.00–1.95 (m,1H), 1.61 (brs, 2H). MS (ESI) 298.04 (M+H).

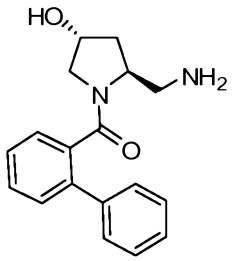
2-(((2*S*,4*R*)-1-(Biphenylcarbonyl)-4-hydroxypyrrolidin-2-yl)methyl)isoindoline-1,3-dione



General Procedure C: Converting hydroxyl group to amino group by Mitsunobu protocol and hydrazine cleavage

A solution of biphenyl-2-yl((2*S*,4*R*)-4-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl)methanone (1.67 g, 5.6 mmol), phthalimide (1.24 g, 8.4 mmol) and triphenylphosphine (2.20 g, 8.4 mmol) in THF (56 mL) was cooled to 0°C and added with DIAD (1.63 mL, 8.4 mmol) dropwise. The resulting suspension was allowed to warm to r.t. gradually and stirred overnight, concentrated *in vacuo* to a brown oil which was eluted on silica gel column (70% EtOAc in Hexanes) to provide 2-(((2*S*,4*R*)-1-(biphenylcarbonyl)-4-hydroxypyrrolidin-2-yl)methyl)isoindoline-1,3-dione as a white solid contaminated with triphenylphosphine oxide and used as-is.

((2*S*,4*R*)-2-(aminomethyl)-4-hydroxypyrrolidin-1-yl)(biphenyl-2-yl)methanone



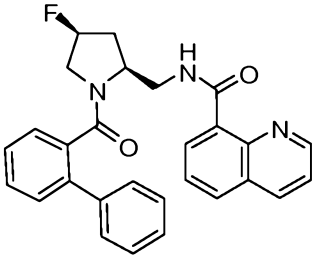
A mixture of the above mentioned 2-(((2*S*,4*R*)-1-(biphenylcarbonyl)-4-hydroxypyrrolidin-2-yl)methyl)isoindoline-1,3-dione (~5.6 mmol) and hydrazine monohydrate (0.65 mL, 10 mmol) in MeOH was stirred at 70°C for 4 hrs. The resulting white suspension was cooled to r.t., filtered and the filtrate was concentrated *in vacuo* to a white solid, which was purified by column chromatography on silica gel (100% MeOH) to provide ((2*S*,4*R*)-2-(aminomethyl)-4-hydroxypyrrolidin-1-yl)(biphenyl-2-yl)methanone as a white solid (1.1 g, 66% yield over two steps. MS (ESI) 297.05 (M+H).

N-(((2*S*,4*R*)-1-(Biphenylcarbonyl)-4-hydroxypyrrolidin-2-yl)methyl)quinoline-8-carboxamide

N-(((2*S*,4*R*)-1-(biphenylcarbonyl)-4-hydroxypyrrolidin-2-yl)methyl)quinoline-8-carboxamide was obtained as a 3:1 rotamer mixture by following the general procedure **A** using ((2*S*,4*R*)-2-(aminomethyl)-4-hydroxypyrrolidin-1-yl)(biphenyl-2-yl)methanone and quinoline-8-carboxylic acid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.28–11.01 (m, 1H), 8.84–8.70 (m, 1H), 8.60–8.40 (m, 1H), 8.13–8.08 (m, 1H), 7.80–7.77 (m, 1H), 7.50–7.03 (m, 11H), 4.41–4.30 (m 1H), 3.99–3.91 (m,1H), 3.54–3.28 (m, 2H), 2.86–2.56 (m, 3H), 1.99–1.70 (m, 2H). MS (ESI) 452.16 (M+H).

Example 5

N-(((2*S*,4*S*)-1-(Biphenylcarbonyl)-4-fluoropyrrolidin-2-yl)methyl)quinoline-8-carboxamide



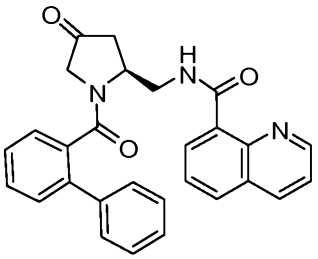
General Procedure D: Fluorination of hydroxyl group:

A mixture of *N*-(((2*S*,4*R*)-1-(biphenylcarbonyl)-4-hydroxypyrrolidin-2-yl)methyl)quinoline-8-carboxamide (0.045 g, 0.10 mmol) in DCM was cooled to -78 C,

added with bis(2-methoxyethyl)aminosulfur trifluoride (Aldrich) (41 μL, 0.22 mmol) dropwise. The resulting solution was stirred at -78°C for 0.5 hr, allowed to warm to r.t. gradually over 1.5 hrs and stirred at r.t. for 0.5 hr, which was quenched by slow addition of MeOH and purified by preparative HPLC using acetonitrile and water (0.1% TFA) as eluent to provide *N*-(((2*S*,4*S*)-1-(biphenylcarbonyl)-4-fluoropyrrolidin-2-yl)methyl)quinoline-8-carboxamide as a white solid. MS (ESI) 454.14 (M+H).

Example 6

(*S*)-*N*-((1-(Biphenylcarbonyl)-4-oxopyrrolidin-2-yl)methyl)quinoline-8-carboxamide

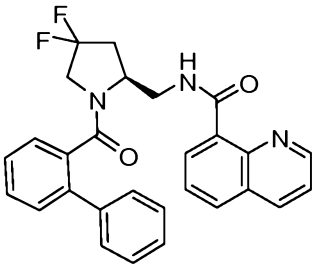


General Procedure E: Swern oxidation of alcohols to ketones:

To a solution of oxalyl chloride (39 μL, 0.45 mmol) in DCM (7 mL) at -78°C, was added a solution of DMSO (64 μL, 0.90 mmol) in DCM (4 mL). After stirring at -78°C for 15 min, a solution of *N*-(((2*S*,4*R*)-1-(biphenylcarbonyl)-4-hydroxypyrrolidin-2-yl)methyl)quinoline-8-carboxamide (0.135 g, 0.30 mmol) in DCM (4 mL) was added. The resulting mixture was stirred at -78°C for 1 hr, treated with Et_3N (0.25 mL, 1.8 mmol) dropwise and then allowed to warm to r.t. gradually over 1.5 hr. The mixture was then concentrated *in vacuo* to a beige solid and purified by column chromatography on silica gel (70% MeOH in EtOAc) to provide (*S*)-*N*-((1-(biphenylcarbonyl)-4-oxopyrrolidin-2-yl)methyl)quinoline-8-carboxamide as a white solid (0.071 g, 53% yield). MS (ESI) 450.12 (M+H).

Example 7

(*S*)-*N*-((1-(Biphenylcarbonyl)-4,4-difluoropyrrolidin-2-yl)methyl)quinoline-8-carboxamide

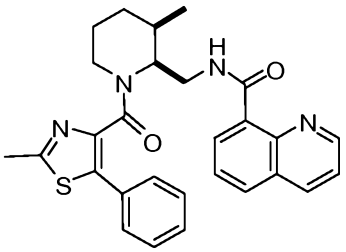


General Procedure F: Fluorination of carbonyl group:

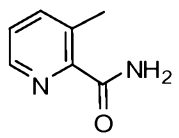
Bis(2-methoxyethyl)aminosulfur trifluoride (32 μL, 0.18 mmol) was added dropwise to a solution of (*S*)-*N*-((1-(biphenylcarbonyl)-4-oxopyrrolidin-2-yl)methyl)quinoline-8-carboxamide (0.036 g, 0.080 mmol) in DCM (80 μL), followed by addition of EtOH (1 μL) and stirred at r.t. overnight. The mixture was quenched with MeOH and purified by preparative HPLC using acetonitrile and water (0.1% TFA) as eluent to provide (*S*)-*N*-((1-(biphenylcarbonyl)-4,4-difluoropyrrolidin-2-yl)methyl)quinoline-8-carboxamide as a white solid. MS (ESI) 472.14 (M+H).

Example 8

rac-N-(((2*S*,3*R*)-3-Methyl-1-(2-methyl-5-phenylthiazole-4-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide



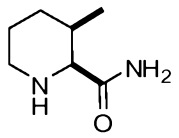
3-Methylpicolinamide



A mixture of 3-methylpicolinonitrile (2.36 g, 20 mmol) and conc. sulfuric acid (12.5 mL) was stirred at 80°C for 25 min. The solution was cooled to r.t., poured into water (80 mL), followed by addition of sat. Na_2CO_3 (aq.) until pH ~7. The resulting mixture was extracted with DCM (3x) and the combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to provide 3-methylpicolinamide as a white solid (2.65 g, 97%). ^1H

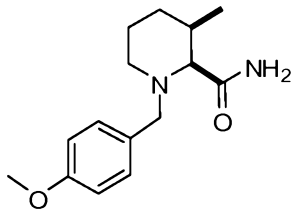
NMR ($CDCl_3$, 400 MHz) δ 8.43 (dd, 1H), 7.93 (brs, 1H), 7.62 (dd, 1H), 7.35 (dd, 1H), 5.44 (brs, 1H), 2.76 (s, 3H).

rac-(2*S*,3*R*)-3-Methylpiperidine-2-carboxamide



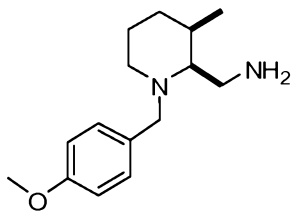
A mixture of 3-methylpicolinamide (2.23 g, 16.4 mmol) and PtO_2 (0.18 g, 0.8 mmol) in acetic acid (55 mL) was placed in a Parr shaker type hydrogenation apparatus, pressurized to 4.70 bar with H_2 and maintained at r.t. for 7 hrs. The mixture was filtered through Celite and the filtrate was concentrated *in vacuo* to a solid. A mixture of this crude solid and DCM and solid Na_2CO_3, were stirred at r.t. overnight. The resulting suspension was filtered and the filtrate was concentrated *in vacuo* to provide *rac*-(2*S*,3*R*)-3-methylpiperidine-2-carboxamide as a white solid (2.0 g, 86% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.51 (brs, 1H), 5.32 (brs, 1H), 3.37 (d, 1H), 3.14–3.10 (m, 1H), 2.70–2.63 (m, 1H), 2.33–2.28 (m, 1H), 1.73–1.58 (m,4H), 1.42–1.39 (m, 1H), 1.00 (d, 3H).

rac-(2*S*,3*R*)-1-(4-Methoxybenzyl)-3-methylpiperidine-2-carboxamide



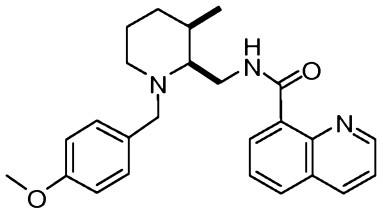
1-(Chloromethyl)-4-methoxybenzene (1.0 mL, 7.5 mmol) was added to a mixture of rac-(2S,3R)-3-methylpiperidine-2-carboxamide (0.71 g, 5.0 mmol) in sat. Na_2CO_3 (aq.)/DCM (15 mL, 1:2 v/v) and stirred vigorously at r.t. overnight. The resulting suspension was diluted with water and extracted with EtOAc (2x). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to a white residue, which was purified by column chromatography on silica gel (100% EtOAc) to provide rac-(2S,3R)-1-(4-methoxybenzyl)-3-methylpiperidine-2-carboxamide as a white solid (0.61 g, 41% yield. MS (ESI) 262.98 (M+H).

rac-((2*S*,3*R*)-1-(4-Methoxybenzyl)-3-methylpiperidin-2-yl)methanamine



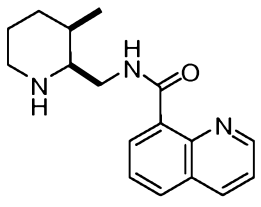
Rac-(2*S*,3*R*)-1-(4-methoxybenzyl)-3-methylpiperidine-2-carboxamide (0.61 g, 2.33 mmol) was added portionwise to a suspension of $LiAlH_4$ (0.30 g, 7.50 mmol) and THF (12 mL) and heated to reflux for 14 hrs. The reaction mixture was then cooled to 0°C and quenched with water and NaOH (aq.). The resulting mixture was stirred at r.t. for 1 hr, filtered and the filtrated was concentrated in vacuo to provide *rac*-((2*S*,3*R*)-1-(4-methoxybenzyl)-3-methylpiperidin-2-yl)methanamine as a colorless oil, used as-is without further purification.

rac-N-(((2*S*,3*R*)-1-(4-Methoxybenzyl)-3-methylpiperidin-2-yl)methyl)quinoline-8-carboxamide



Rac-N-(((2*S*,3*R*)-1-(4-methoxybenzyl)-3-methylpiperidin-2-yl)methyl)quinoline-8-carboxamide was obtained by following the general procedure A using the fore-mentioned crude *rac*-((2*S*,3*R*)-1-(4-methoxybenzyl)-3-methylpiperidin-2-yl)methanamine and quinoline-8-carboxylic acid. MS (ESI) 404.24 (M+H).

rac-N-(((2*S*,3*R*)-3-Methylpiperidin-2-yl)methyl)quinoline-8-carboxamide



Cerium ammonium nitrate (1.25 g, 2.28 mmol) was added portionwise to a mixture of rac-N-(((2S,3R)-1-(4-methoxybenzyl)-3-methylpiperidin-2-yl)methyl)quinoline-8-carboxamide (0.23 g, 0.57 mmol) in acetone/water (10 mL, 9:1 v/v) at 0°C and allowed to stir at r.t. for 5 hrs. Sat. $NaHCO_3$ (aq.) was added and the resulting suspension was stirred at r.t

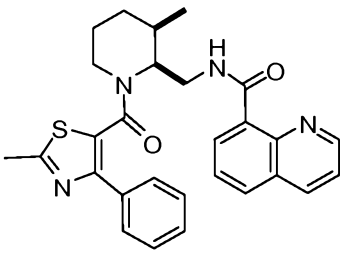
for 10 min, concentrated in vacuo to remove the acetone, then filtered through Celite and rinsed with EtOAc. The bi-layer filtrate was extracted with EtOAc and the combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to provide a brown oil as a 1:1 mixture of *rac-N*-(((2*S*,3*R*)-3-methylpiperidin-2-yl)methyl)quinoline-8-carboxamide / 4-methoxybenzaldehyde, which was used as-is without further purification. MS (ESI) 284.13 (M+H).

rac-N-(((2*S*,3*R*)-3-Methyl-1-(2-methyl-5-phenylthiazole-4-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide

Rac-N-(((2*S*,3*R*)-3-methyl-1-(2-methyl-5-phenylthiazole-4-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide was obtained as a 1:1 rotamer mixture by following the general procedure **A** using the fore-mentioned crude *rac-N*-(((2*S*,3*R*)-3-methylpiperidin-2-yl)methyl)quinoline-8-carboxamide and 2-methyl-5-phenylthiazole-4-carboxylic acid. MS (ESI) 485.12 (M+H).

Example 9.

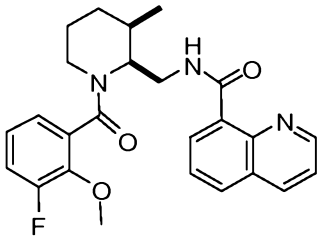
rac-N-(((2*S*,3*R*)-3-Methyl-1-(2-methyl-4-phenylthiazole-5-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide



Rac-N-(((2*S*,3*R*)-3-methyl-1-(2-methyl-4-phenylthiazole-5-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide was obtained by following the general procedure **A** using the fore-mentioned crude *rac-N*-(((2*S*,3*R*)-3-methylpiperidin-2-yl)methyl)quinoline-8-carboxamide and 2-methyl-4-phenylthiazole-5-carboxylic acid. MS (ESI) 485.15 (M+H).

Example 10.

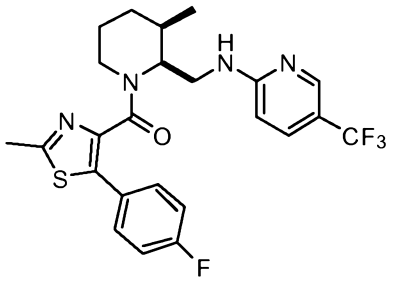
rac-N-(((2*S*,3*R*)-1-(3-Fluoro-2-methoxybenzoyl)-3-methylpiperidin-2-yl)methyl)quinoline-8-carboxamide



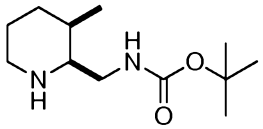
Rac-N-(((2*S*,3*R*)-1-(3-fluoro-2-methoxybenzoyl)-3-methylpiperidin-2-yl)methyl)quinoline-8-carboxamide was obtained by following the general procedure **A** using the fore-mentioned crude *rac-N*-(((2*S*,3*R*)-3-methylpiperidin-2-yl)methyl)quinoline-8-carboxamide and 3-fluoro-2-methoxybenzoic acid. MS (ESI) 436.14 (M+H).

Example 11.

rac- (5-(4-fluorophenyl)-2-methylthiazol-4-yl)((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)methanone



rac-tert-butyl (((2S,3R)-3-methylpiperidin-2-yl)methyl)carbamate



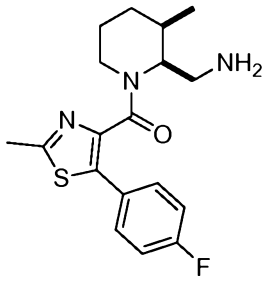
To a solution of 3-methyl-2-cyanopyridine (5g) in acetic acid was added 10% Pd/C. The parr shaker bottle was evacuated/H2 purged 3x, and then shaken at 50psi until starting material was consumed (typically <1h). The reaction was filtered through celite and concentrated to yield (3-methylpyridin-2-yl)methanamine acetic acid salt which was used without further purification.

To the crude salt in THF was added aq 1M NaOH, followed by BOC_2O (2eq). The reaction was allowed to stir at room temperature overnight. After ~16h, the reaction mixture was transferred to a seperatory funnel, diluted with EtOAc, and water, and the layers were separated. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated in

vacuo to give a crude residue which was purified by chromatography on silica gel (EtOAc/hex) to afford tert-butyl ((3-methylpyridin-2-yl)methyl)carbamate.

To a solution of the BOC-protected pyridylamine in MeOH was added Nishimura's catalyst. The parr shaker bottle was evacuated/purged with H_2 (3x) and then shaken at 50psi for 24h. The reaction was filtered through celite, and concentrated *in vacuo* to give the title compound as a near colorless oil, and was used without further purification. ^{1}H NMR (D_6-DMSO, 400 MHz) δ 6.7 (br s, NH), 4.0 (br s, 1H), 2.9-2.7 (m, 3H), 2.6-2.5 (m, 1H), 2.5-2.4 (m, 1H), 1.7-1.6 (br s, 1H), 1.6-1.45 (m, 3H), 1.4 (s, 9H), 1.3-1.2 (m, 1H), 0.8 (d,3H).

rac- ((2S,3R)-2-(aminomethyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



To a solution of tert-butyl (((2S,3R)-3-methylpiperidin-2-yl)methyl)carbamate (1.5g) from the previous step in CH_2Cl_2 was added DIEA (2eq) followed by 2-methyl-5-(4-fluorophenylthiazole)-4-carboxylic acid (2g) and HATU (3.3g). The reaction was allowed to stir at room temperature for 15h, and was then concentrated *in vacuo* to remove the CH_2Cl_2. The crude residue was taken up in EtOAc and washed with 1M HCl, sat aq. $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated. The crude residue was purified by chromatography on silica gel (EtOAc/hex) to give tert-butyl (((2S,3R)-1-(5-(4-fluorophenyl)-2-methylthiazole-4-carbonyl)-3-methylpiperidin-2-yl)methyl)carbamate as a light yellow oil which crystallized (2g).

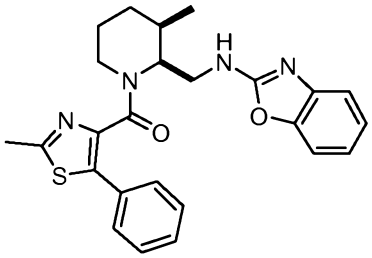
To a solution of this carbamate in CH_2Cl_2 was added TFA (1:1 v/v). The reaction was aged at room temperature and monitored for disappearance of starting material by analytical reverse-phase HPLC. When starting material was consumed, the reaction was concentrated in vacuo. The crude residue was taken up in EtOAc, and washed with sat aqueous $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated to afford the title compound as a pale yellow oil which crystallized. MS (ESI) 348.06 (M+H).

rac- (5-(4-fluorophenyl)-2-methylthiazol-4-yl)((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)methanone

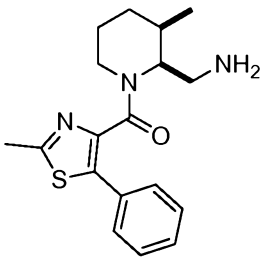
A mixture of ((2S,3R)-2-(aminomethyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone, 2-chloro-5-(trifluoromethyl)pyridine, and K_2CO_3 in DMAC was stirred at 120 °C overnight. The reaction mixture was diluted with EtOAc and washed with brine. The organic layer was separated, dried with $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by chromatography on silica gel (EtOAc/hex) to give the title compound as a pale yellow oil which solidified. MS (ESI) 493.01 (M+H).

Example 12.

rac- ((2S,3R)-2-((benzo[d]oxazol-2-ylamino)methyl)-3-methylpiperidin-1-yl)(2-methyl-5-phenylthiazol-4-yl)methanone



rac- ((2S,3R)-2-(aminomethyl)-3-methylpiperidin-1-yl)(2-methyl-5-phenylthiazol-4-yl)methanone



The title compound was synthesized following the same general protocol as described in Example 11 using tert-butyl (((2S,3R)-3-methylpiperidin-2-yl)methyl)carbamate and 2-methyl-5-phenylthiazole-4-carboxylic acid. MS (ESI) 330.08 (M+H).

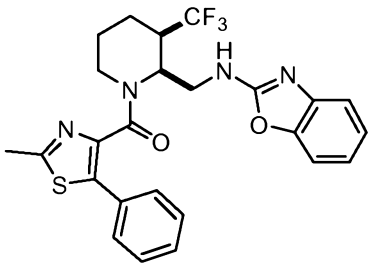
rac- ((2S,3R)-2-((benzo[d]oxazol-2-ylamino)methyl)-3-methylpiperidin-1-yl)(2-methyl-5-phenylthiazol-4-yl)methanone

A mixture of ((2S,3R)-2-(aminomethyl)-3-methylpiperidin-1-yl)(2-methyl-5-phenylthiazol-4-yl)methanone, 2-chlorobenzoxazole, and DIEA in CH_2Cl_2 was stirred at 60

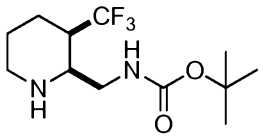
°C overnight. The reaction mixture was concentrated *in vacuo* to leave a near colorless solid. This solid was triturated with Et_2O/hexanes to leave the title compound as a colorless solid homogeneous by HPLC analysis. MS (ESI) 447.03 (M+H).

Example 13.

rac- ((2S,3R)-2-((benzo[d]oxazol-2-ylamino)methyl)-3-(trifluoromethyl)piperidin-1-yl)(2-methyl-5-phenylthiazol-4-yl)methanone



tert-butyl (((2S,3R)-3-(trifluoromethyl)piperidin-2-yl)methyl)carbamate



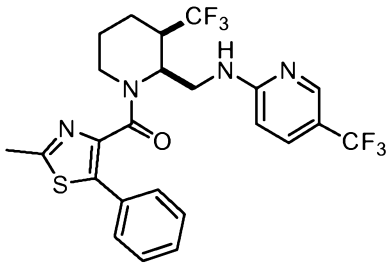
The title compound was synthesized following the same general protocol as described for *rac*-tert-butyl (((2S,3R)-3-methylpiperidin-2-yl)methyl)carbamate starting with 3-(trifluoromethyl)picolinonitrile. . ^{1}H NMR (D_6-DMSO, 400 MHz) δ 5.1 (br s, NH), 3.25 (br s, 2H), 3.1 (br s, 1H), 2.8 (br, 2H), 2.7 (br, 2H), 2.4 (br , 1H), 1.8-1.6 (m, 3H), 1.4 (s, 9H); MS (ESI) 283.2 (M+H).

rac- ((2S,3R)-2-((benzo[d]oxazol-2-ylamino)methyl)-3-(trifluoromethyl)piperidin-1-yl)(2-methyl-5-phenylthiazol-4-yl)methanone

The title compound was prepared following the same general protocol as described for Example's 11 and 12. MS (ESI) 501.05 (M+H).

Example 14.

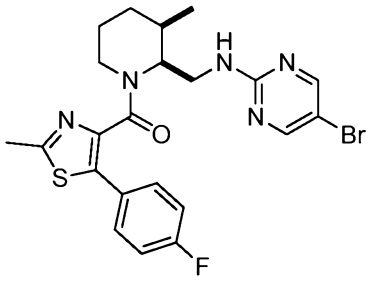
rac- (2-methyl-5-phenylthiazol-4-yl)((2S,3R)-3-(trifluoromethyl)-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)methanone



The title compound was prepared following the same general protocol as described for Example's 11 and 12 starting with 3-(trifluoromethyl)picolinonitrile. MS (ESI) 528.98 (M+H).

Example 15.

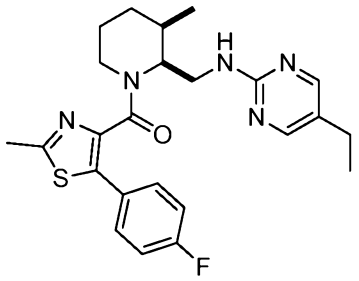
rac- ((2S,3R)-2-(((5-bromopyrimidin-2-yl)amino)methyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



A mixture of ((2S,3R)-2-(aminomethyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone, 5-bromo-2-chloropyrimidine, and DIEA in isopropanol was stirred at 120 °C for 1h in a microwave reactor. The reaction was complete as judged by reverse-phase analytical HPLC. The crude reaction mixture was purified by reverse-phase preparative HPLC to afford the title compound. MS (ESI) 505.88 (M+H).

Example 16.

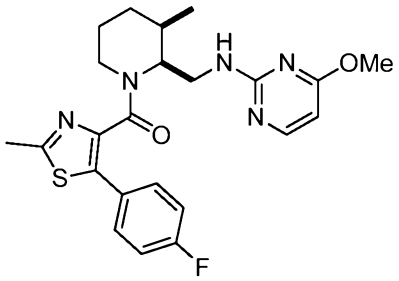
rac- ((2S,3R)-2-(((5-ethylpyrimidin-2-yl)amino)methyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



A mixture of ((2S,3R)-2-(aminomethyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone, 5-ethyl-2-chloropyrimidine, and DIEA in isopropanol was stirred at 110 °C for 18h. The reaction was cooled and concentrated *in vacuo*. The crude reaction mixture was purified by reverse-phase preparative HPLC to afford the title compound. MS (ESI) 454.02 (M+H).

Example 17.

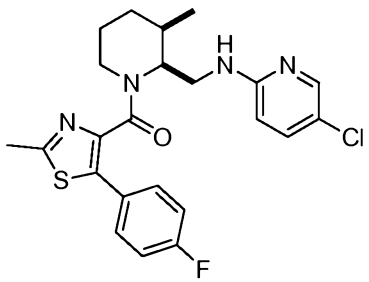
rac- (5-(4-fluorophenyl)-2-methylthiazol-4-yl)((2S,3R)-2-(((4-methoxypyrimidin-2-yl)amino)methyl)-3-methylpiperidin-1-yl)methanone



A mixture of ((2S,3R)-2-(aminomethyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone, 4-methoxy-2-chloropyrimidine, and DIEA in isopropanol was stirred at 110 °C for 18h. The reaction was cooled and concentrated *in vacuo*. The crude reaction mixture was purified by reverse-phase preparative HPLC to afford the title compound. MS (ESI) 456.02 (M+H).

Example 18.

rac- ((2S,3R)-2-(((5-chloropyridin-2-yl)amino)methyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone

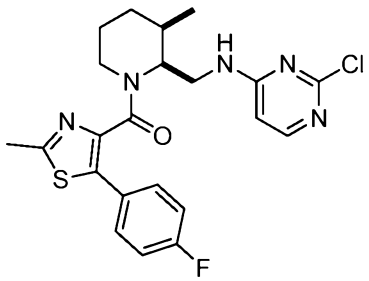


A mixture of ((2S,3R)-2-(aminomethyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone, 2-fluoro-5-chloropyridine, and K_2CO_3 in DMAC was

stirred at 120 °C for 16h. The reaction was cooled and concentrated *in vacuo*. The crude reaction mixture was purified by reverse-phase preparative HPLC to afford the title compound. MS (ESI) 458.95 (M+H).

Example 19

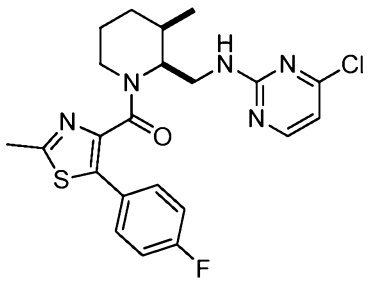
rac- ((2S,3R)-2-(((2-chloropyrimidin-4-yl)amino)methyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



A mixture of ((2S,3R)-2-(aminomethyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone, 2,4-dichloropyrimidine, and K_2CO_3 in DMAC was stirred at 120 °C for 18h. The reaction was cooled and concentrated *in vacuo*. The crude reaction mixture was purified by reverse-phase preparative HPLC to afford the title compound as the major isomer. MS (ESI) 459.94 (M+H).

Example 20.

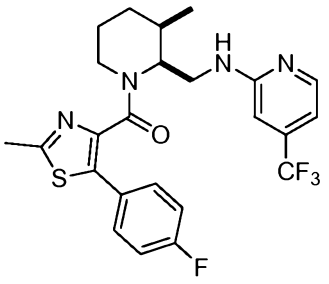
rac- ((2S,3R)-2-(((4-chloropyrimidin-2-yl)amino)methyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



The title compound was isolated as the minor isomer in the reaction described for Example 19. MS (ESI) 459.94 (M+H).

Example 21.

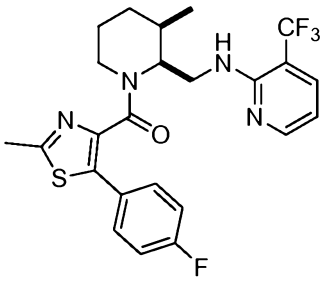
rac- (5-(4-fluorophenyl)-2-methylthiazol-4-yl)((2S,3R)-3-methyl-2-(((4-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)methanone



A mixture of ((2S,3R)-2-(aminomethyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone, 2-bromo-4-(trifluoromethyl)pyridine, Pd_2dba_3, BINAP, and NaOtBu in toluene was purged with argon, and then stirred at 70 °C for 12h. The reaction was cooled, filtered through a pad of silica gel and concentrated *in vacuo*. The crude reaction mixture was purified by reverse-phase preparative HPLC to afford the title compound. MS (ESI) 492.97 (M+H).

Example 22.

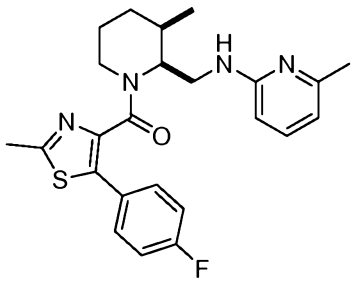
rac- (5-(4-fluorophenyl)-2-methylthiazol-4-yl)((2S,3R)-3-methyl-2-(((3-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)methanone



The title compound was prepared following the same general protocol as described for Example 21 using 2-bromo-3-(trifluoromethyl)pyridine. MS (ESI) 493.01 (M+H).

Example 23.

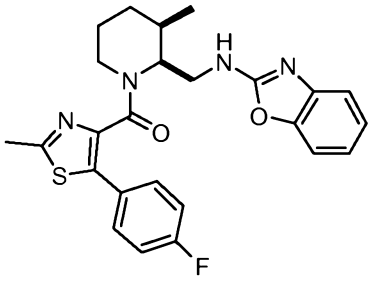
rac- (5-(4-fluorophenyl)-2-methylthiazol-4-yl)((2S,3R)-3-methyl-2-(((6-methylpyridin-2-yl)amino)methyl)piperidin-1-yl)methanone



The title compound was prepared following the same general protocol as described for Example 21 using 2-bromo-6-(methyl)pyridine. MS (ESI) 439.04 (M+H).

Example 24.

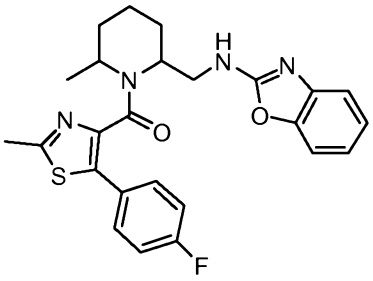
rac- ((2S,3R)-2-((benzo[d]oxazol-2-ylamino)methyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



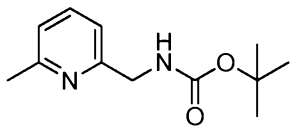
A mixture of ((2S,3R)-2-(aminomethyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone, 2-chlorobenzoxazole, and DIEA in CH_2Cl_2 was stirred at 60 ºC overnight. The reaction mixture was concentrated *in vacuo* to leave a near colorless solid. This solid was triturated with Et_2O/hex to leave the title compound as a colorless solid homogeneous by HPLC analysis. MS (ESI) 465.03 (M+H).

Example 25.

rac- (2-((benzo[d]oxazol-2-ylamino)methyl)-6-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone

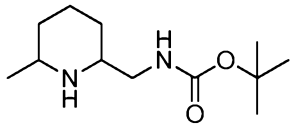


tert-butyl ((6-methylpyridin-2-yl)methyl)carbamate



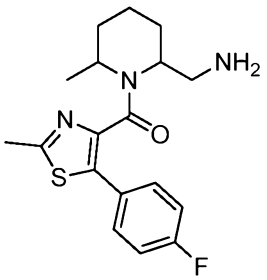
To a solution of 6-methyl-2-cyanopyridine (5g) and BOC_2O in EtOAc was added 10% Pd/C. The reaction mixture was stirred under a balloon of H_2 for 24h, and then filtered through celite and concentrated *in vacuo*. The crude residue was purified by chromatography on silica gel (EtOAc/hex) to give the title compound as a colorless oil. ^1H NMR (D_6-DMSO, 400 MHz) δ 7.6 (t, 1H), 7.4 (br s, NH), 7.2 (d, 1H), 7.1 (d, 1H), 4.2 (d, 2H), 2.4 (s, 3H), 1.4 (s, 9H).

rac-tert-butyl ((6-methylpiperidin-2-yl)methyl)carbamate



To a solution of the product from the previous step in MeOH was added Nishimura's catalyst. The parr shaker bottle was evacuated/purged with H_2 (3x) and then shaken at 50psi for 24h. The reaction was filtered through celite, and concentrated *in vacuo* to give the title compound as a near colorless oil, and was used without further purification. ^1H NMR (D_6-DMSO, 400 MHz) δ 6.75 (br s, NH), 3.3 (br s, 1H), 2.9-2.8 (m, 1H), 2.8-2.7 (m, 1H), 2.5-2.4 (m, 1H), 2.0-1.8 (br s, 1H), 1.75-1.65 (m, 1H), 1.55-1.45 (m, 2H), 1.4 (s, 9H), 1.3-1.2 (m, 1H), 0.95 (d,3H), 0.9-0.8 (m, 2H).

rac-(2-(aminomethyl)-6-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



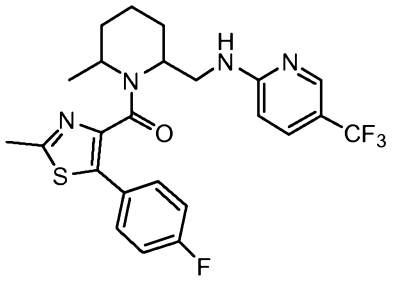
The title compound was made following the same general protocol as described for Example 11. MS (ESI) 348.11 (M+H).

rac- (2-((benzo[d]oxazol-2-ylamino)methyl)-6-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone

The title compound was made following the same general protocol as described for Example 12. MS (ESI) 465.08 (M+H).

Example 26.

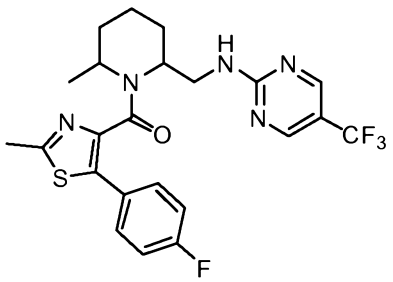
rac- (5-(4-fluorophenyl)-2-methylthiazol-4-yl)(2-methyl-6-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)methanone



The title compound was made following the same general protocol as described for Example 11. MS (ESI) 493.04 (M+H).

Example 27

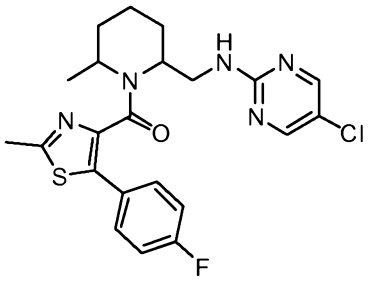
(5-(4-fluorophenyl)-2-methylthiazol-4-yl)(2-methyl-6-(((5-(trifluoromethyl)pyrimidin-2-yl)amino)methyl)piperidin-1-yl)methanone



The title compound was made following the same general protocol as described for Example 11. MS (ESI) 494.04 (M+H).

Example 28

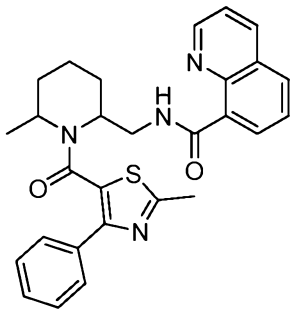
(2-(((5-chloropyrimidin-2-yl)amino)methyl)-6-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



The title compound was made following the same general protocol as described for Example 11. MS (ESI) 460.04 (M+H).

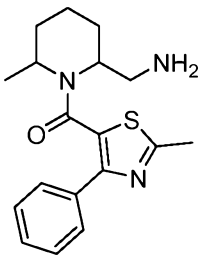
Example 29

N-((6-Methyl-1-(2-methyl-4-phenylthiazole-5-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide



Part I:

(2-(Aminomethyl)-6-methylpiperidin-1-yl)(2-methyl-4-phenylthiazol-5-yl)methanone



General Procedure G: Curtius Rearrangement of carboxylic acid. Ethyl chloroformate (0.28 mmol, 0.027 mL) and triethyl amine (0.28 mmol, 0.04 mL) were added to a solution of 2-(6-methyl-1-(2-methyl-4-phenylthiazole-5-carbonyl)piperidin-2-yl)acetic acid (0.14 mmol, 0.05 g) sequentially at 0 °C. The resulting mixture was stirred at room temperature for 1 hr. Then, an aqueous solution of NaN_3 (1.40 mmol, 0.045 g) in water (1 mL) was added at 0 °C with vigorously stirring. The reaction was tracked by analytical HPLC. The reaction mixture was diluted with EtOAc and washed with brine. The organic layer was separated, dried with

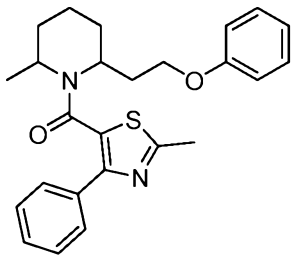
$MgSO_4$ and concentrated *in vacuo*. The resulting residue was mixed with toluene/ *t*BuOH (5 mL/5 mL) and refluxed at 110 °C overnight. The solvent was removed *in vacuo* to give *tert*-butyl (6-methyl-1-(2-methyl-4-phenylthiazole-5-carbonyl)piperidin-2-yl)methylcarbamate which was deprotected of Boc in TFA/CH_2Cl_2 (volume: 1/1) to give desired (2-(aminomethyl)-6-methylpiperidin-1-yl)(2-methyl-4-phenylthiazol-5-yl)methanone.

N-((6-Methyl-1-(2-methyl-4-phenylthiazole-5-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide

The title compound was prepared by following the general procedure **A** using (2-(aminomethyl)-6-methylpiperidin-1-yl)(2-methyl-4-phenylthiazol-5-yl)methanone and quinoline-8-carboxylic acid. MS (ESI) 485 (M+H).

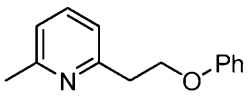
Example 30

(2-Methyl-4-phenylthiazol-5-yl)(2-methyl-6-(2-phenoxyethyl)piperidin-1-yl)methanone



Part I

2-Methyl-6-(2-phenoxyethyl)pyridine



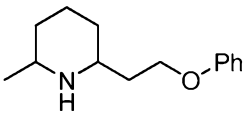
MsCl (6.7 mmol, 0.52 mL) was added to a solution of 6-methyl-2-pyridineethanol (6.7 mmol, 0.92 g) and triethyl amine (13.4 mmol, 1.88 mL) in toluene (6 mL) at 0 °C dropwise. The resulting mixture was stirred at 0 °C for 30 min. The precipitate generated from reaction was filtered off. The filtrate was concentrated *in vacuo* to give crude 2-(6-methylpyridin-2-yl)ethyl methanesulfonate which was used for next step without further purification.

A mixture of above described 2-(6-methylpyridin-2-yl)ethyl methanesulfonate, PhOH (13.4 mmol, 1.26 g) and NaOH (13.4 mmol, 0.54 g) in isopropanol (20 mL) was refluxed at 90 °C for 3 hr. The reaction mixture was concentrated *in vacuo* and dissolved in EtOAc

which was washed with water. The organic layer was separated, dried with $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by chromatography to give desired 2-methyl-6-(2-phenoxyethyl)pyridine as a colorless oil in 26% yield.

Part II

2-Methyl-6-(2-phenoxyethyl)piperidine

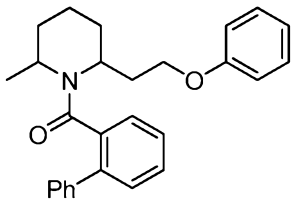


General Procedure H: Hydrogenation of pyridine to piperdine using Adam Catalyst. 2-Methyl-6-(2-phenoxyethyl)pyridine (0.19 mmol, 0.04 g) and Adam Catalyst (0.09 mmol, 0.02g) in MeOH was stirred at room temperature under a hydrogen balloon overnight. The reaction mixture was filtered through Celite and concentrated *in vacuo* to provide the desired product 2-methyl-6-(2-phenoxyethyl)piperidine in 30% conversion. This crude residue was used in the next step without further purification.

(2-Methyl-4-phenylthiazol-5-yl)(2-methyl-6-(2-phenoxyethyl)piperidin-1-yl)methanone was prepared according to general procedure **A** using 2-methyl-6-(2-phenoxyethyl)piperidine and 2-methyl-5-phenyl-1,3-thiazole-4-carboxylic acid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64–7.60 (m, 2H), 7.37–7.29 (m, 3H), 7.24–7.14 (m, 2H), 6.93–6.85 (m, 2H), 6.64–6.62 (m, 1H), 4.87–4.78 (m, 1H), 4.07–4.01 (m, 1H), 3.93–3.78 (m, 1H), 3.62–3.50 (m, 1H), 3.13–3.07 (m, 1H), 2.69 (s, 1H), 2.55 (s, 2H), 2.01–2.00 (m, 1H), 1.48–1.21 (m, 9H). MS (ESI) 421 (M+H).

Example 31

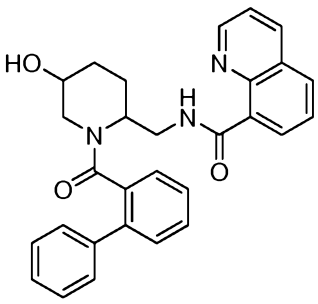
Biphenyl-2-yl(2-methyl-6-(2-phenoxyethyl)piperidin-1-yl)methanone



Biphenyl-2-yl(2-methyl-6-(2-phenoxyethyl)piperidin-1-yl)methanone was prepared according to general procedure **A** using 2-methyl-6-(2-phenoxyethyl)piperidine and biphenyl-2-carboxylic acid. MS (ESI) 400 (M+H).

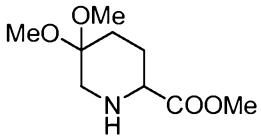
Example 32

N-((1-(biphenylcarbonyl)-5-hydroxypiperidin-2-yl)methyl)quinoline-8-carboxamide



Part I

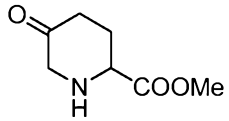
Methyl 5,5-dimethoxypiperidine-2-carboxylate



5-Oxopiperidine-2-carboxylic acid hydrochloride salt (41.1 mmol, 7.36 g) in MeOH was added thionyl chloride (206.7 mmol, 15 mL) dropwise by an additional funnel at -10 °C. The resulting mixture was refluxed at 60 °C overnight. The reaction mixture was concentrated *in vacuo* to give desired product methyl 5,5-dimethoxypiperidine-2-carboxylate as the HCl salt. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.28–4.20 (m, 1H), 3.78 (s, 3H), 3.35–3.32 (m, 1H), 3.16 (s, 3H), 3.14 (s, 3H), 3.31–1.98 (m, 2H), 1.82–1.69 (m, 2H).

Part II

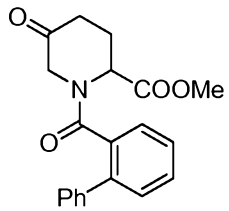
Methyl 5-oxopiperidine-2-carboxylate



The above described ketal was stirred in TFA at room temperature for 4 hr. An aliquot was taken for NMR which confirmed 100% conversion of starting material. The reaction mixture was diluted with water and extracted with DCM. The DCM layer was discarded and the water layer was concentrated in vacuo to give desired methyl 5-oxopiperidine-2-carboxylate as the TFA salt in quantitative yield.

Part III

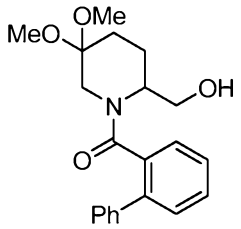
Methyl 1-(biphenylcarbonyl)-5-oxopiperidine-2-carboxylate



Methyl 1-(biphenylcarbonyl)-5-oxopiperidine-2-carboxylate was prepared according to general procedure **A** using methyl 5-oxopiperidine-2-carboxylate and biphenyl-2-carboxylic acid. MS (ESI) 338 (M+H).

Part IV

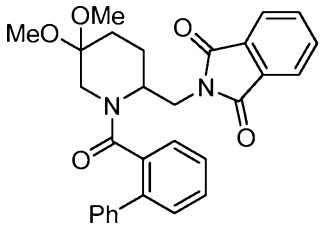
Biphenyl-2-yl(2-(hydroxymethyl)-5,5-dimethoxypiperidin-1-yl)methanone



Methyl 1-(biphenylcarbonyl)-5-oxopiperidine-2-carboxylate was converted to methyl 1-(biphenylcarbonyl)-5,5-dimethoxypiperidine-2-carboxylate (4.3 mmol, 1.65g) following the general protocol described in Part I above. To a solution of this ketal in anhydrous THF was added $LiBH_4$ (2M in THF) (9.4 mmol, 4.7 mL) at 0 °C under argon. The resulting mixture was stirred at room temperature and the reaction was tracked by analytical HPLC. The reaction was carefully quenched with saturated NH_4Cl and extracted with EtOAc. The organic layer was separated, dried with $MgSO_4$, and concentrated *in vacuo* to give desired biphenyl-2-yl(2-(hydroxymethyl)-5,5-dimethoxypiperidin-1-yl)methanone in quantitative yield which was used for next step without further purification.

Part V

2-((1-(Biphenylcarbonyl)-5,5-dimethoxypiperidin-2-yl)methyl)isoindoline-1,3-dione

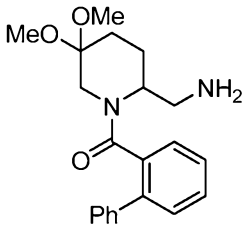


General Procedure I: Mitsunobu reaction of alcohol with phthalimide. DIAD (15.15 mmol, 2.93 mL) was added to a mixture of (biphenyl-2-yl(2-(hydroxymethyl)-5-methoxy-3,4-dihydropyridin-1(2H)-yl)methanone (4.5 mmol, 1.63 g), phthalimide (15.15 mmol, 2.23 g) and PPh_3 (15.15 mmol, 3.97 g) in anhydrous THF dropwise at 0 °C under argon. The resulting mixture was stirred at room temperature for overnight and concentrated *in vacuo* to give a crude residue which was purified by chromatography to give the desired 2-((1-(biphenylcarbonyl)-5,5-dimethoxypiperidin-2-yl)methyl)isoindoline-1,3-dione with slight

contamination of triphenylphosphine oxide. This contaminated product was used for next step without further purification.

Part VI

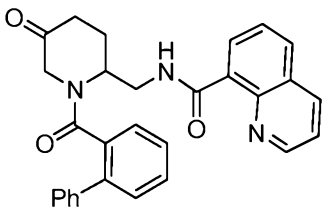
(2-(Aminomethyl)-5,5-dimethoxypiperidin-1-yl)(biphenyl-2-yl)methanone



General Procedure J. Conversion of phthalimide to primary amine using hydrazine. A mixture of the above described 2-((1-(biphenylcarbonyl)-5,5-dimethoxypiperidin-2-yl)methyl)isoindoline-1,3-dione (1.13 g, 2.3 mmol) and hydrazine monohydrate (10.0 mmol, 0.4 g) in MeOH (10 mL) was stirred at 60 °C. The reaction was tracked by analytical HPLC. MeOH was removed in vacuo and the reaction mixture was diluted with water followed by extraction with EtOAc. The organic layer was separated, dried with $MgSO_4$, and concentrated *in vacuo* to give desired (2-(aminomethyl)-5,5-dimethoxypiperidin-1-yl)(biphenyl-2-yl)methanone.

Part VII

N-((1-(biphenylcarbonyl)-5-oxopiperidin-2-yl)methyl)quinoline-8-carboxamide



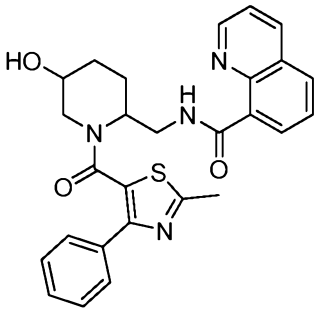
N-((1-(biphenylcarbonyl)-5-oxopiperidin-2-yl)methyl)quinoline-8-carboxamide was prepared according general procedure **A** using quinoline-8-carboxylic acid and N-((1-(biphenylcarbonyl)-5-methoxy-1,2,3,4-tetrahydropyridin-2-yl)methyl)quinoline-8-carboxamide which was synthesized from the product from Part VI above, following ketal cleavage using TFA and CH_2Cl_2. MS (ESI) 464 (M+H).

General procedure K. Reduction of ketone to alcohol. $NaBH_4$ (3.49 mmol, 0.13 g) was added to a solution of N-((1-(biphenylcarbonyl)-5-oxopiperidin-2-yl)methyl)quinoline-8-carboxamide TFA salt (0.46 mmol, 0.26 g) in MeOH (10 mL) at 0 °C in three portions. The resulting mixture was stirred at room temperature and the reaction was tracked by analytical HPLC. The reaction was quenched with water and extracted with EtOAc. The organic layer

was separated, dried with $MgSO_4$, and concentrated *in vacuo* to give crude residue which was purified by preparative HPLC to give desired N-((1-(biphenylcarbonyl)-5-hydroxypiperidin-2-yl)methyl)quinoline-8-carboxamide with unidentified stereochemistry (Y:75%). MS (ESI) 466 (M+H).

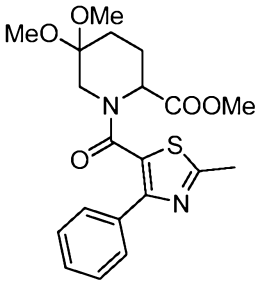
Example 33

N-((5-hydroxy-1-(2-methyl-4-phenylthiazole-5-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide



Part I

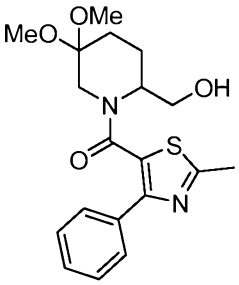
Methyl 5,5-dimethoxy-1-(2-methyl-4-phenylthiazole-5-carbonyl)piperidine-2-carboxylate



Methyl 5,5-dimethoxy-1-(2-methyl-4-phenylthiazole-5-carbonyl)piperidine-2-carboxylate was prepared according to general procedure **A** using methyl 5,5-dimethoxypiperidine-2-carboxylate and 2-methyl-4-phenylthiazole-5-carboxylic acid.

Part II

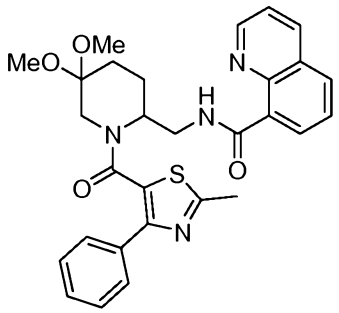
(2-(Hydroxymethyl)-5,5-dimethoxypiperidin-1-yl)(2-methyl-4-phenylthiazol-5-yl)methanone



The title compound was prepared from the product of Part I following the same general protocol as described for Example 32 Part IV.

Part III

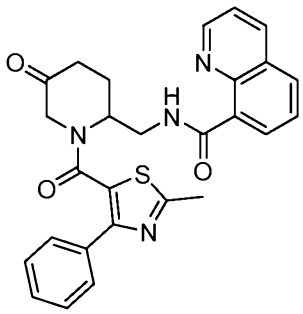
N-((5,5-dimethoxy-1-(2-methyl-4-phenylthiazole-5-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide



N-((5,5-dimethoxy-1-(2-methyl-4-phenylthiazole-5-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide was prepared according to general procedures I, J, and A using (2-(Hydroxymethyl)-5,5-dimethoxypiperidin-1-yl)(2-methyl-4-phenylthiazol-5-yl)methanone.

Part IV

N-((1-(2-methyl-4-phenylthiazole-5-carbonyl)-5-oxopiperidin-2-yl)methyl)quinoline-8-carboxamide

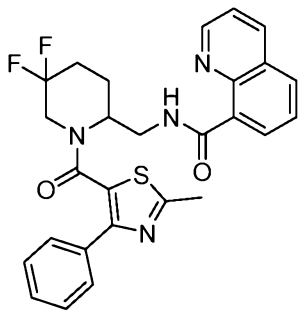


The title compound was prepared from the product of Part III above using TFA/CH_2Cl_2. MS (ESI) 485 (M+H).

N-((5-hydroxy-1-(2-methyl-4-phenylthiazole-5-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide was prepared according to general procedure **K** using N-((1-(2-methyl-4-phenylthiazole-5-carbonyl)-5-oxopiperidin-2-yl)methyl)quinoline-8-carboxamide. MS (ESI) 487 (M+H).

Example 34

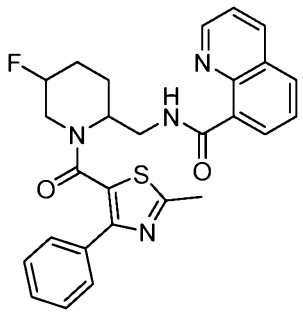
N-((5,5-difluoro-1-(2-methyl-4-phenylthiazole-5-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide



General Procedure L: Difluorination of ketone with Deoxo-fluo. Deoxo-fluo (0.17 mmol, 0.032 mL) in DCM (0.2 mL) was added to a solution of N-((1-(2-methyl-4-phenylthiazole-5-carbonyl)-5-oxopiperidin-2-yl)methyl)quinoline-8-carboxamide (0.10 mmol, 0.05 g) in DCM (0.2 mL) in a sealed tube at room temperature. Then EtOH (0.02 mmol, 0.0008 g) was added. The resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with DCM and quenched with saturated $NaHCO_3$. The organic layer was separated, dried with $MgSO_4$, and concentrated in vacuo to give crude residue which was purified by prep. HPLC to give desired N-((5,5-difluoro-1-(2-methyl-4-phenylthiazole-5-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide (Y:56%). MS (ESI) 507 (M+H).

Example 35

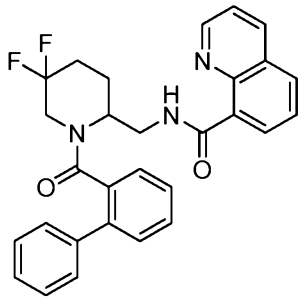
N-((5-fluoro-1-(2-methyl-4-phenylthiazole-5-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide



General Procedure M: Fluorination of alcohol with Deoxo-fluo. A solution of N-((5-hydroxy-1-(2-methyl-4-phenylthiazole-5-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide (0.07 mmol, 0.036 g) in DCM (0.3 mL) was added to a mixture of Deoxo-fluro (0.14 mmol, 0.027 mL) in DCM (0.2 mL) at -78 °C under argon. The resulting mixture was stirred at -78 °C for 1 hr and at room temperature for another 1.5 hr. The desired product was purified by preparative TLC to give N-((5-fluoro-1-(2-methyl-4-phenylthiazole-5-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide with unidentified stereochemistry (Y:16%). MS (ESI) 489 (M+H).

Example 36

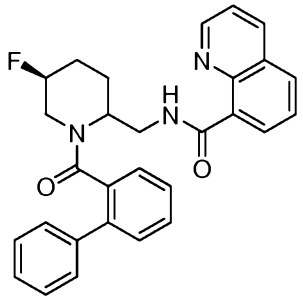
N-((1-(biphenylcarbonyl)-5,5-difluoropiperidin-2-yl)methyl)quinoline-8-carboxamide



N-((1-(biphenylcarbonyl)-5,5-difluoropiperidin-2-yl)methyl)quinoline-8-carboxamide was prepared according to general procedure **L** using N-((1-(biphenylcarbonyl)-5-oxopiperidin-2-yl)methyl)quinoline-8-carboxamide. MS (ESI) 486 (M+H).

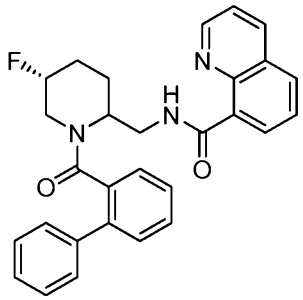
Example 37

N-(((5S)-1-(biphenylcarbonyl)-5-fluoropiperidin-2-yl)methyl)quinoline-8-carboxamide



Example 38

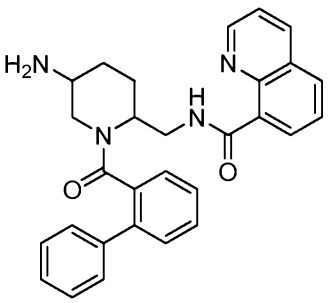
N-(((5R)-1-(biphenylcarbonyl)-5-fluoropiperidin-2-yl)methyl)quinoline-8-carboxamide



Example 37 and Example 38 were two different fractions isolated from the fluorination of N-((1-(biphenylcarbonyl)-5-oxopiperidin-2-yl)methyl)quinoline-8-carboxamide by following general procedure **M**. However, the stereochemistry of isomers has not been verified. MS (ESI) 468 (M+H).

Example 39

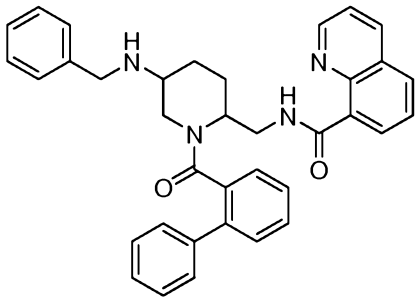
N-((5-amino-1-(biphenylcarbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide



General Procedure N: Reductive amination of ketone. $NaBH_3CN$ (0.18 mmol, 0.011 g) was added to a solution of N-((1-(biphenylcarbonyl)-5-oxopiperidin-2-yl)methyl)quinoline-8-carboxamide (0.06 mmol, 0.027 g) and NH_4OAc (0.6 mmol, 0.011 g) in MeOH. The resulting mixture was stirred at room temperature for overnight and quenched with saturated NH_4Cl. The aqueous solution was extracted with EtOAc and the organic layer was separated, dried with $MgSO_4$, and concentrated *in vacuo* to give crude residue which was purified by preparative HPLC to give desired N-((5-amino-1-(biphenylcarbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide. (ESI) 465 (M+H).

Example 40

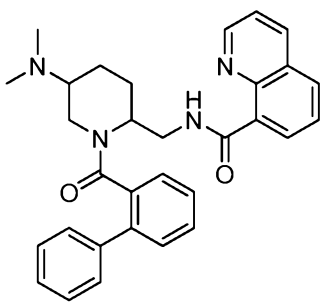
N-((5-(benzylamino)-1-(biphenylcarbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide



N-((5-(benzylamino)-1-(biphenylcarbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide was prepared according general procedure **N** using N-((1-(biphenylcarbonyl)-5-oxopiperidin-2-yl)methyl)quinoline-8-carboxamide and benzyl amine. (ESI) 555 (M+H).

Example 41

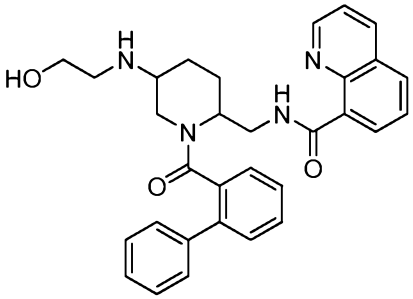
N-((1-(biphenylcarbonyl)-5-(dimethylamino)piperidin-2-yl)methyl)quinoline-8-carboxamide



N-((1-(biphenylcarbonyl)-5-(dimethylamino)piperidin-2-yl)methyl)quinoline-8-carboxamide was prepared according general procedure **N** using N-((1-(biphenylcarbonyl)-5-oxopiperidin-2-yl)methyl)quinoline-8-carboxamide and dimethyl amine. (ESI) 493 (M+H).

Example 42

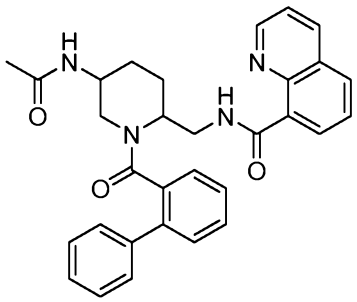
N-((1-(biphenylcarbonyl)-5-(2-hydroxyethylamino)piperidin-2-yl)methyl)quinoline-8-carboxamide



N-((1-(biphenylcarbonyl)-5-(2-hydroxyethylamino)piperidin-2-yl)methyl)quinoline-8-carboxamide was prepared according general procedure **N** using N-((1-(biphenylcarbonyl)-5-oxopiperidin-2-yl)methyl)quinoline-8-carboxamide and 2-aminoethanol. (ESI) 509 (M+H).

Example 43

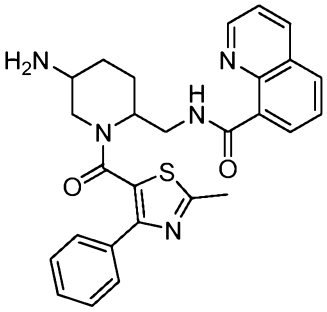
N-((5-acetamido-1-(biphenylcarbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide



Example 43 was isolated as a byproduct from the preparation of Example 39. (ESI) 507 (M+H).

Example 44

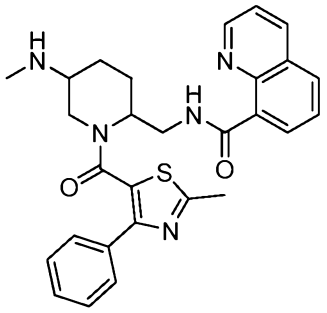
N-((5-amino-1-(2-methyl-4-phenylthiazole-5-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide



N-((5-amino-1-(2-methyl-4-phenylthiazole-5-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide was prepared according to general procedure **N** using N-((1-(2-methyl-4-phenylthiazole-5-carbonyl)-5-oxopiperidin-2-yl)methyl)quinoline-8-carboxamide. (ESI) 486 (M+H).

Example 45

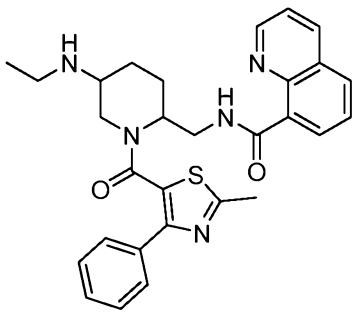
N-((1-(2-methyl-4-phenylthiazole-5-carbonyl)-5-(methylamino)piperidin-2-yl)methyl)quinoline-8-carboxamide



N-((1-(2-methyl-4-phenylthiazole-5-carbonyl)-5-(methylamino)piperidin-2-yl)methyl)quinoline-8-carboxamide was prepared according to general procedure **N** using N-((1-(2-methyl-4-phenylthiazole-5-carbonyl)-5-oxopiperidin-2-yl)methyl)quinoline-8-carboxamide and methyl amine. (ESI) 500 (M+H).

Example 46

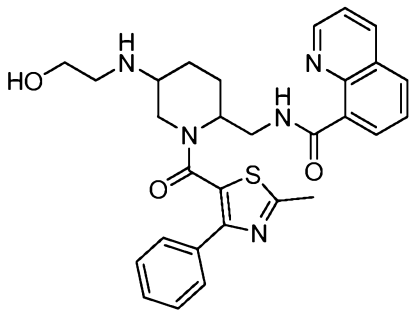
N-((5-(ethylamino)-1-(2-methyl-4-phenylthiazole-5-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide



N-((5-(ethylamino)-1-(2-methyl-4-phenylthiazole-5-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide was prepared according to general procedure **N** using N-((1-(2-methyl-4-phenylthiazole-5-carbonyl)-5-oxopiperidin-2-yl)methyl)quinoline-8-carboxamide and ethyl amine. (ESI) 514 (M+H)

Example 47

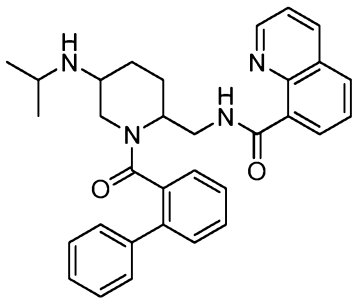
N-((5-(2-hydroxyethylamino)-1-(2-methyl-4-phenylthiazole-5-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide



N-((5-(2-hydroxyethylamino)-1-(2-methyl-4-phenylthiazole-5-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide was prepared according to general procedure **N** using N-((1-(2-methyl-4-phenylthiazole-5-carbonyl)-5-oxopiperidin-2-yl)methyl)quinoline-8-carboxamide and 2-aminoethanol. (ESI) 530 (M+H).

Example 48

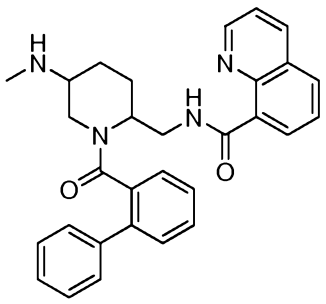
N-((5-(isopropylamino)-1-(2-methyl-4-phenylthiazole-5-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide



N-((5-(isopropylamino)-1-(2-methyl-4-phenylthiazole-5-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide was prepared according to general procedure **N** using N-((1-(2-methyl-4-phenylthiazole-5-carbonyl)-5-oxopiperidin-2-yl)methyl)quinoline-8-carboxamide and isopropyl amine. (ESI) 528 (M+H).

Example 49

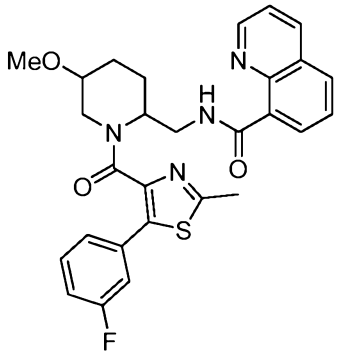
N-((1-(biphenylcarbonyl)-5-(methylamino)piperidin-2-yl)methyl)quinoline-8-carboxamide



N-((1-(biphenylcarbonyl)-5-(methylamino)piperidin-2-yl)methyl)quinoline-8-carboxamide was prepared according to general procedure **N** using N-((1-(biphenylcarbonyl)-5-oxopiperidin-2-yl)methyl)quinoline-8-carboxamide and methyl amine. (ESI) 479 (M+H)

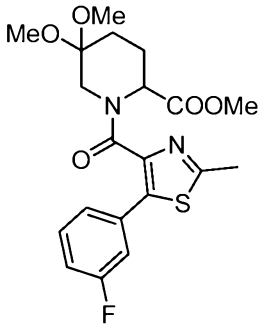
Example 50

N-((1-(5-(3-fluorophenyl)-2-methylthiazole-4-carbonyl)-5-methoxypiperidin-2-yl)methyl)quinoline-8-carboxamide



Part I

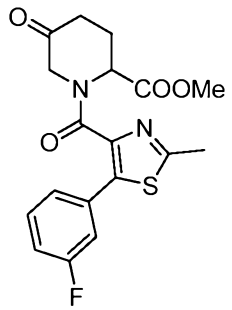
Methyl 1-(5-(3-fluorophenyl)-2-methylthiazole-4-carbonyl)-5,5-dimethoxypiperidine-2-carboxylate



Methyl 1-(5-(3-fluorophenyl)-2-methylthiazole-4-carbonyl)-5,5-dimethoxypiperidine-2-carboxylate was prepared according to general procedure **A** using product methyl 5,5-dimethoxypiperidine-2-carboxylate and 5-(3-fluorophenyl)-2-methylthiazole-4-carboxylic acid.

Part II

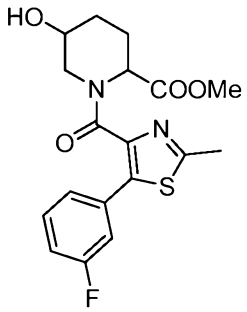
Methyl 1-(5-(3-fluorophenyl)-2-methylthiazole-4-carbonyl)-5-oxopiperidine-2-carboxylate



The title compound was prepared from the product of Part I above using TFA/CH_2Cl_2.

Part III

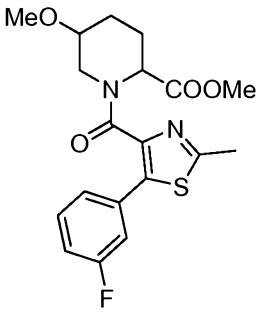
Methyl 1-(5-(3-fluorophenyl)-2-methylthiazole-4-carbonyl)-5-hydroxypiperidine-2-carboxylate



Methyl 1-(5-(3-fluorophenyl)-2-methylthiazole-4-carbonyl)-5-hydroxypiperidine-2-carboxylate was prepared according to general procedure **K** using methyl 1-(5-(3-fluorophenyl)-2-methylthiazole-4-carbonyl)-5-oxopiperidine-2-carboxylate.

Part IV

Methyl 1-(5-(3-fluorophenyl)-2-methylthiazole-4-carbonyl)-5-methoxypiperidine-2-carboxylate

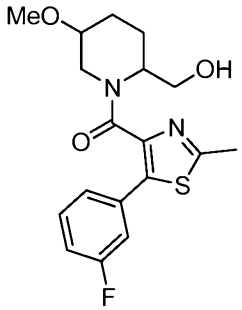


MeI (6.8 mmol, 0.43 mL) was added to a mixture of methyl 1-(5-(3-fluorophenyl)-2-methylthiazole-4-carbonyl)-5-hydroxypiperidine-2-carboxylate (0.68 mmol, 0.26 g) and Ag_2O (3.4 mmol, 0.8 g) in CH_3CN (3 mL) at room temperature. The resulting mixture was stirred at room temperature for two days. The reaction mixture was diluted with DCM and

filtered through a pad of celite. The filtrate was concentrated in vacuo to give desired product methyl 1-(5-(3-fluorophenyl)-2-methylthiazole-4-carbonyl)-5-methoxypiperidine-2-carboxylate which was used for next step without further purification (Y: 96%).

Part V

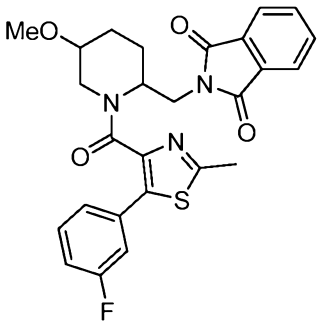
(5-(3-Fluorophenyl)-2-methylthiazol-4-yl)(2-(hydroxymethyl)-5-methoxypiperidin-1-yl)methanone



The title compound was prepared from the product of Part IV following the same general protocol as described for Example 32 Part IV.

Part VI

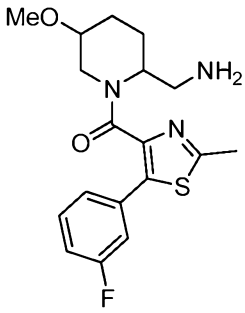
2-((1-(5-(3-Fluorophenyl)-2-methylthiazole-4-carbonyl)-5-methoxypiperidin-2-yl)methyl)isoindoline-1,3-dione



2-((1-(5-(3-Fluorophenyl)-2-methylthiazole-4-carbonyl)-5-methoxypiperidin-2-yl)methyl)isoindoline-1,3-dione was prepared according to general procedure **I** using (5-(3-fluorophenyl)-2-methylthiazol-4-yl)(2-(hydroxymethyl)-5-methoxypiperidin-1-yl)methanone and phthalimide.

Part VII

(2-(Aminomethyl)-5-methoxypiperidin-1-yl)(5-(3-fluorophenyl)-2-methylthiazol-4-yl)methanone



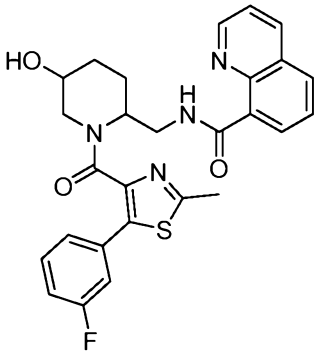
(2-(Aminomethyl)-5-methoxypiperidin-1-yl)(5-(3-fluorophenyl)-2-methylthiazol-4-yl)methanone was prepared according to general procedure **J** using 2-((1-(5-(3-fluorophenyl)-2-methylthiazole-4-carbonyl)-5-methoxypiperidin-2-yl)methyl)isoindoline-1,3-dione. (ESI) 364 (M+H).

N-((1-(5-(3-fluorophenyl)-2-methylthiazole-4-carbonyl)-5-methoxypiperidin-2-yl)methyl)quinoline-8-carboxamide

The title compound was prepared according to general procedure **A** using (2-(aminomethyl)-5-methoxypiperidin-1-yl)(5-(3-fluorophenyl)-2-methylthiazol-4-yl)methanone and quinoline-8-carboxylic acid. (ESI) 519 (M+H).

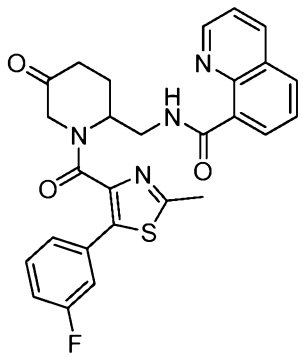
Example 51

N-((1-(5-(3-fluorophenyl)-2-methylthiazole-4-carbonyl)-5-hydroxypiperidin-2-yl)methyl)quinoline-8-carboxamide



Part I

N-((1-(5-(3-fluorophenyl)-2-methylthiazole-4-carbonyl)-5-oxopiperidin-2-yl)methyl)quinoline-8-carboxamide



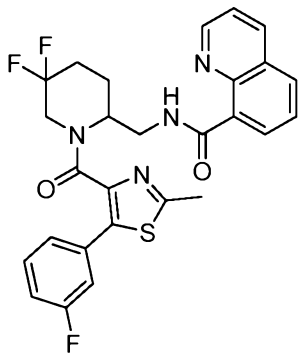
N-((1-(5-(3-fluorophenyl)-2-methylthiazole-4-carbonyl)-5-oxopiperidin-2-yl)methyl)quinoline-8-carboxamide was prepared in a similar fashion as N-((1-(2-methyl-4-phenylthiazole-5-carbonyl)-5-oxopiperidin-2-yl)methyl)quinoline-8-carboxamide.

N-((1-(5-(3-fluorophenyl)-2-methylthiazole-4-carbonyl)-5-hydroxypiperidin-2-yl)methyl)quinoline-8-carboxamide

The title compound was prepared according to general procedure K using N-((1-(5-(3-fluorophenyl)-2-methylthiazole-4-carbonyl)-5-oxopiperidin-2-yl)methyl)quinoline-8-carboxamide. (ESI) 505 (M+H).

Example 52

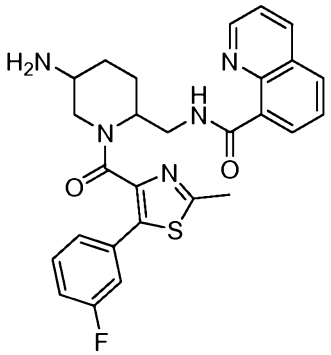
N-((5,5-difluoro-1-(5-(3-fluorophenyl)-2-methylthiazole-4-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide



N-((5,5-difluoro-1-(5-(3-fluorophenyl)-2-methylthiazole-4-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide was prepared according to general procedure **L** using N-((1-(5-(3-fluorophenyl)-2-methylthiazole-4-carbonyl)-5-oxopiperidin-2-yl)methyl)quinoline-8-carboxamide. (ESI) 525 (M+H).

Example 53

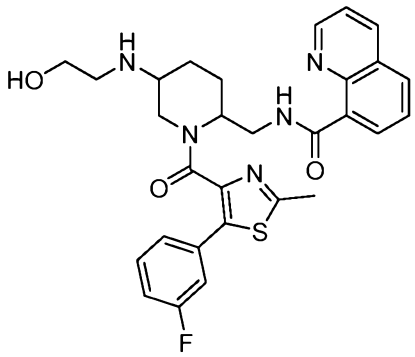
N-((5-amino-1-(5-(3-fluorophenyl)-2-methylthiazole-4-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide



N-((5-amino-1-(5-(3-fluorophenyl)-2-methylthiazole-4-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide was prepared according to general procedure **N** using N-((1-(5-(3-fluorophenyl)-2-methylthiazole-4-carbonyl)-5-oxopiperidin-2-yl)methyl)quinoline-8-carboxamide. (ESI) 504 (M+H).

Example 54

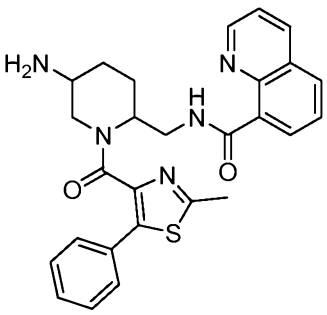
N-((1-(5-(3-fluorophenyl)-2-methylthiazole-4-carbonyl)-5-(2-hydroxyethylamino)piperidin-2-yl)methyl)quinoline-8-carboxamide



N-((1-(5-(3-fluorophenyl)-2-methylthiazole-4-carbonyl)-5-(2-hydroxyethylamino)piperidin-2-yl)methyl)quinoline-8-carboxamide was prepared according to general procedure **N** using N-((1-(5-(3-fluorophenyl)-2-methylthiazole-4-carbonyl)-5-oxopiperidin-2-yl)methyl)quinoline-8-carboxamide. (ESI) 548 (M+H).

Example 55

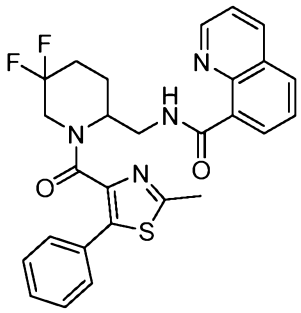
N-((5-amino-1-(2-methyl-5-phenylthiazole-4-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide



N-((5-amino-1-(2-methyl-5-phenylthiazole-4-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide was prepared according to general procedure **N** using N-((1-(2-methyl-5-phenylthiazole-4-carbonyl)-5-oxopiperidin-2-yl)methyl)quinoline-8-carboxamide which was obtained in a similar fashion as N-((1-(2-methyl-4-phenylthiazole-5-carbonyl)-5-oxopiperidin-2-yl)methyl)quinoline-8-carboxamide and NH_4OAC. (ESI) 486 (M+H).

Example 56

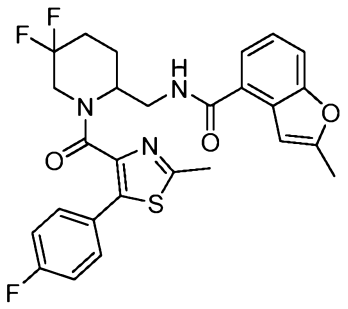
N-((5,5-difluoro-1-(2-methyl-5-phenylthiazole-4-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide



N-((5,5-difluoro-1-(2-methyl-5-phenylthiazole-4-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide was prepared according to general procedure **L** using N-((1-(2-methyl-5-phenylthiazole-4-carbonyl)-5-oxopiperidin-2-yl)methyl)quinoline-8-carboxamide. . (ESI) 507 (M+H).

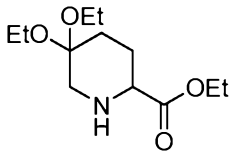
Example 57

N-((5,5-difluoro-1-(5-(4-fluorophenyl)-2-methylthiazole-4-carbonyl)piperidin-2-yl)methyl)-2-methylbenzofuran-4-carboxamide



Part I

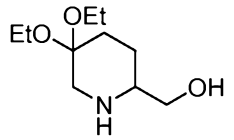
Ethyl 5,5-diethoxypiperidine-2-carboxylate



Ethyl 5,5-diethoxypiperidine-2-carboxylate was prepared according following the same general protocol as described in Example 32 Part I using 5-oxopiperidine-2-carboxylic acid and EtOH. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.22–4.17 (m, 2H), 3.74–3.42 (m, 4H), 3.82–3.35 (m, 1H), 3.23–3.13 (m, 1H), 2.62 (d, 1H), 2.10–2.05 (m, 1H), 1.98–1.93 (m, 1H), 1.92 (brs, 1H), 1.69–1.56 (m, 2H), 1.30–1.27 (m, 3H), 1.23–1.16 (m, 6H).

Part II

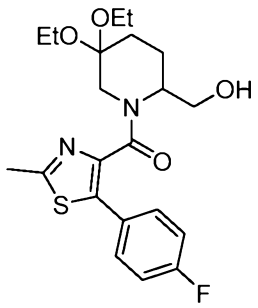
(5,5-Diethoxypiperidin-2-yl)methanol



General Procedure O: LAH reduction of amino ester to amino alcohol. A suspension of LAH (0.47 g, 12.25mmol) in anhydrous THF (5 mL) was added a solution of ethyl 5,5-diethoxypiperidine-2-carboxylate (0.6 g, 2.45 mmol) in anhydrous THF (5 mL) dropwise at room temperature. The resulting mixture was refluxed at 70 °C for overnight. The reaction mixture was cooled down to 0 °C and quenched sequentially with water (0.47 g), 15% NaOH (0.47 g) and water (1.41 g). The resulting suspension was stirred at room temperature for 1 hr and filtered. The filtrate was concentrated *in vacuo* to give desired (5,5-diethoxypiperidin-2-yl)methanol in 95% yield as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.54–3.32 (m, 6H), 3.11–3.04 (m, 1H), 2.56–2.46 (m, 2H), 2.05–2.00 (m, 1H), 1.52–1.23 (m, 3H), 1.15–1.07 (m, 6H).

Part III

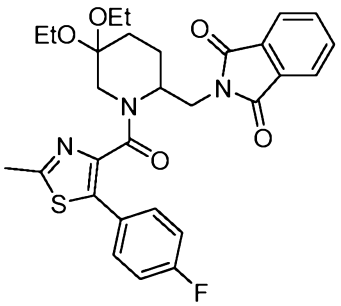
(5,5-Diethoxy-2-(hydroxymethyl)piperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



(5,5-Diethoxy-2-(hydroxymethyl)piperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone was prepared according to general procedure **A** using 5-(4-fluorophenyl)-2-methylthiazole-4-carboxylic acid and (5,5-diethoxypiperidin-2-yl)methanol.

Part IV

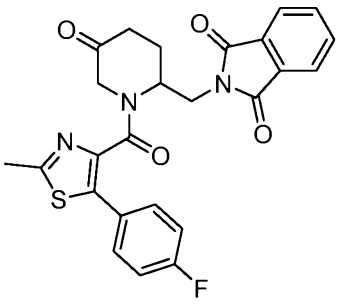
2-((5,5-Diethoxy-1-(5-(4-fluorophenyl)-2-methylthiazole-4-carbonyl)piperidin-2-yl)methyl)isoindoline-1,3-dione



2-((5,5-Diethoxy-1-(5-(4-fluorophenyl)-2-methylthiazole-4-carbonyl)piperidin-2-yl)methyl)isoindoline-1,3-dione was prepared according to general procedure **I** using (5,5-diethoxy-2-(hydroxymethyl)piperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73–7.71 (m, 2H), 7.63–7.62 (m, 2H), 7.38–7.35 (m, 2H), 7.21–6.91 (m, 2H), 4.86–4.81 (m, 1H), 4.10–4.03 (m, 2H), 3.10 (d, 1H), 2.27 (s, 3H), 1.89–1.83 (m, 1H), 1.70–1.61 (m, 1H), 1.32–1.28 (m, 2H), 1.19–1.03 (m, 6H). MS (ESI) 506 (M+H): desired product lost EtOH in LC/MS.

Part V

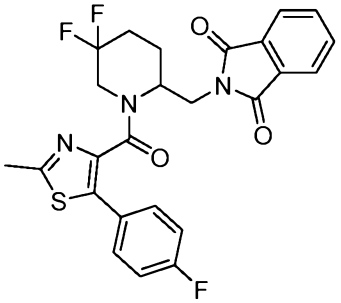
2-((1-(5-(4-fluorophenyl)-2-methylthiazole-4-carbonyl)-5-oxopiperidin-2-yl)methyl)isoindoline-1,3-dione



The title compound was prepared from the product of Part IV above using TFA/CH_2Cl_2. NMR reported as a mixture of two possible rotamers. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83–7.80 (m, 2H), 7.79–7.74 (m, 2H), 7.43–7.40 (m, 1H), 7.37–7.28 (m, 1H), 7.01–6.97 (m, 1H), 6.88–6.84 (m, 1H), 5.25–5.07 (m, 1H), 4.31–3.53 (m, 4H), 2.64 (s, 1.3 H), 2.47 (s, 1.7 H), 2.45–2.31 (m, 2H), 2.19–1.63 (m, 2H). MS (ESI) 478 (M+H).

Part VI

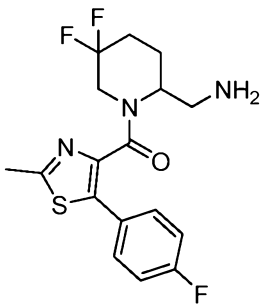
2-((5,5-Difluoro-1-(5-(4-fluorophenyl)-2-methylthiazole-4-carbonyl)piperidin-2-yl)methyl)isoindoline-1,3-dione



2-((5,5-Difluoro-1-(5-(4-fluorophenyl)-2-methylthiazole-4-carbonyl)piperidin-2-yl)methyl)isoindoline-1,3-dione was prepared according to general procedure **L** using 2-((1-(5-(4-fluorophenyl)-2-methylthiazole-4-carbonyl)-5-oxopiperidin-2-yl)methyl)isoindoline-1,3-dione. MS (ESI) 500 (M+H).

Part V

(2-(aminomethyl)-5,5-difluoropiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone

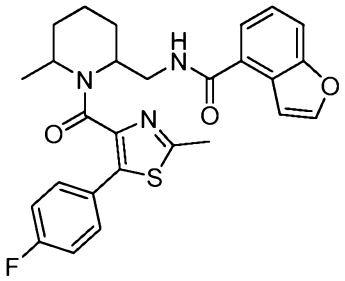


N-((5,5-difluoro-1-(2-methyl-5-phenylthiazole-4-carbonyl)piperidin-2-yl)methyl)-2-methylbenzofuran-4-carboxamide was prepared according to general procedure **J** using 2-((5,5-Difluoro-1-(5-(4-fluorophenyl)-2-methylthiazole-4-carbonyl)piperidin-2-yl)methyl)isoindoline-1,3-dione. MS (ESI) 370 (M+H).

N-((5,5-difluoro-1-(5-(4-fluorophenyl)-2-methylthiazole-4-carbonyl)piperidin-2-yl)methyl)-2-methylbenzofuran-4-carboxamide was prepared according to general procedure **A** using N-((5,5-difluoro-1-(2-methyl-5-phenylthiazole-4-carbonyl)piperidin-2-yl)methyl)-2-methylbenzofuran-4-carboxamide and 2-methylbenzofuran-4-carboxylic acid. The NMR was reported as a mixture of possible rotamers. ^{1}H NMR (MeOH-d4, 400 MHz) δ 7.61–7.54 (m, 2H), 7.49–7.29 (m, 2H), 7.29–7.25 (m, 1H), 7.05–7.01 (m, 2H), 6.88–6.83 (m, 1H), 4.19–4.17 (m, 1H), 3.86–3.70 (m, 2H), 3.50–3.35 (m, 2H), 2.50–2.48 (m, 3H), 2.25 (s, 3H), 2.10–1.99 (m, 2H), 1.69–1.65 (m, 1H), 1.33–1.25 (m, 1H). MS (ESI) 528 (M+H).

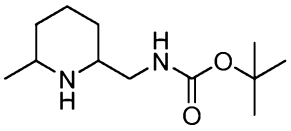
Example 58

N-((1-(5-(4-fluorophenyl)-2-methylthiazole-4-carbonyl)-6-methylpiperidin-2-yl)methyl)benzofuran-4-carboxamide



Part I

tert-Butyl (6-methylpiperidin-2-yl)methylcarbamate

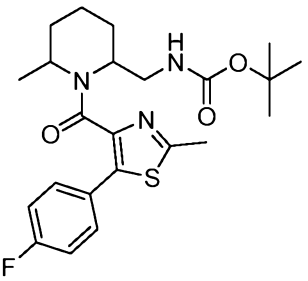


Nishimura catalyst (0.53 g) was added to a solution of tert-butyl (6-methylpyridin-2-yl)methylcarbamate (4.4 g, 0.02 mmol) in MeOH (60 mL) in a Parr Shaker high pressure vessel which was installed on Parr Shaker. The vessel was shaken under constant 5 bar hydrogen pressure for 30 min. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated *in vacuo* to give desired product *tert*-butyl (6-methylpiperidin-2-yl)methylcarbamate which was used for next step without further purification. ^{1}H NMR

($CDCl_3$, 400 MHz) δ 3.20–3.17 (m, 1H), 3.01–2.96 (m, 1H), 2.72–2.64 (m, 2H), 1.82–1.77 (m, 1H), 1.63–1.54 (m, 2H), 1.49 (s, 9H), 1.39–1.35 (m, 2H), 1.12–0.99 (m, 5H).

Part II

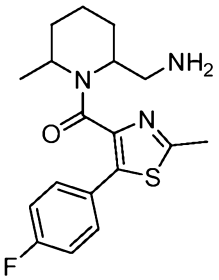
tert-Butyl (1-(5-(4-fluorophenyl)-2-methylthiazole-4-carbonyl)-6-methylpiperidin-2-yl)methylcarbamate



tert-Butyl (1-(5-(4-fluorophenyl)-2-methylthiazole-4-carbonyl)-6-methylpiperidin-2-yl)methylcarbamate was prepared according to general procedure **A** using *tert*-butyl (6-methylpiperidin-2-yl)methylcarbamate and 5-(4-fluorophenyl)-2-methylthiazole-4-carboxylic acid.

Part III

(2-(Aminomethyl)-6-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



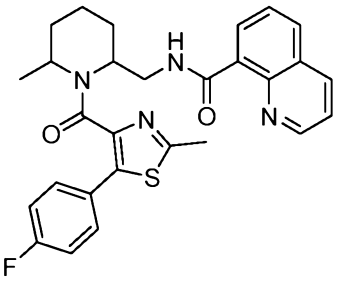
To a solution of *tert*-Butyl (1-(5-(4-fluorophenyl)-2-methylthiazole-4-carbonyl)-6-methylpiperidin-2-yl)methylcarbamate in DCM was added TFA. The solution was aged at room temperature until starting material was consumed as judged by reverse phase analytical HPLC analysis. The solution was then concentrated in vacuo to give the TFA salt of the title compound as an oil which was used without further purification. MS (ESI) 348 (M+H).

N-((1-(5-(4-fluorophenyl)-2-methylthiazole-4-carbonyl)-6-methylpiperidin-2-yl)methyl)benzofuran-4-carboxamide

The title compound was prepared by following the general procedure **A** using 2-(aminomethyl)-6-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone and benzofuran-4-carboxylic acid. MS (ESI) 492 (M+H).

Example 59

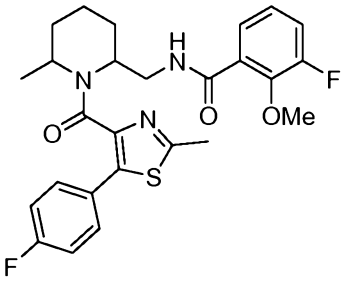
N-((1-(5-(4-fluorophenyl)-2-methylthiazole-4-carbonyl)-6-methylpiperidin-2-yl)methyl)quinoline-8-carboxamide



N-((1-(5-(4-fluorophenyl)-2-methylthiazole-4-carbonyl)-6-methylpiperidin-2-yl)methyl)quinoline-8-carboxamide was prepared according to general procedure **A** using 2-(aminomethyl)-6-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone and quinoline-8-carboxylic acid. MS (ESI) 503 (M+H).

Example 60

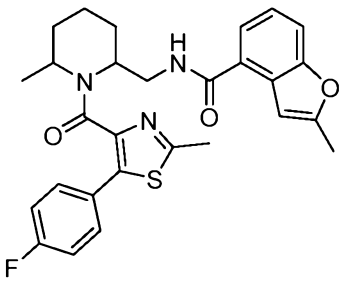
3-Fluoro-N-((1-(5-(4-fluorophenyl)-2-methylthiazole-4-carbonyl)-6-methylpiperidin-2-yl)methyl)-2-methoxybenzamide



3-Fluoro-N-((1-(5-(4-fluorophenyl)-2-methylthiazole-4-carbonyl)-6-methylpiperidin-2-yl)methyl)-2-methoxybenzamide was prepared according to general procedure **A** using 2-(aminomethyl)-6-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone and 3-fluoro-2-methoxybenzoic acid. MS (ESI) 500 (M+H).

Example 61

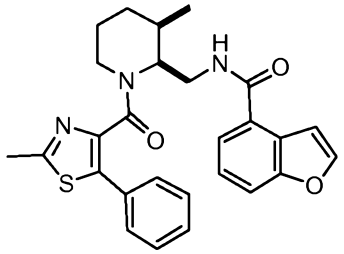
N-((1-(5-(4-fluorophenyl)-2-methylthiazole-4-carbonyl)-6-methylpiperidin-2-yl)methyl)-2-methylbenzofuran-4-carboxamide



N-((1-(5-(4-fluorophenyl)-2-methylthiazole-4-carbonyl)-6-methylpiperidin-2-yl)methyl)-2-methylbenzofuran-4-carboxamide was prepared according to general procedure **A** using 2-methylbenzofuran-4-carboxylic acid and (2-(aminomethyl)-6-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone which was obtained by removal of the BOC protecting group from *tert*-butyl (1-(5-(4-fluorophenyl)-2-methylthiazole-4-carbonyl)-6-methylpiperidin-2-yl)methylcarbamate following general procedure as described for Example 58. MS (ESI) 506 (M+H).

Example 62

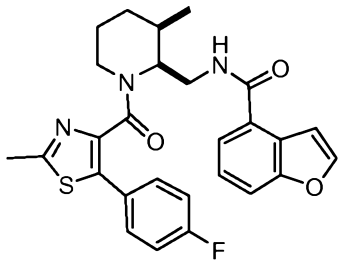
N-(((2S,3R)-3-methyl-1-(2-methyl-5-phenylthiazole-4-carbonyl)piperidin-2-yl)methyl)benzofuran-4-carboxamide



The title compound was obtained following the general protocol as described for the synthesis of Example 8 using benzofuran-4-carboxylic acid. MS (ESI) 474.1 (M+H).

Example 63

N-(((2S,3R)-1-(5-(4-fluorophenyl)-2-methylthiazole-4-carbonyl)-3-methylpiperidin-2-yl)methyl)benzofuran-4-carboxamide

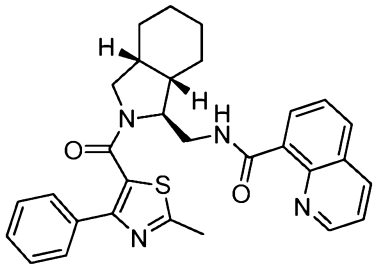


The title compound was obtained following the general protocol as described for the synthesis of Example 8 using benzofuran-4-carboxylic acid and 5-(4-fluorophenyl)-2-methylthiazole-4-carboxylic acid. MS (ESI) 492.1 (M+H).

Example 64 and Example 65

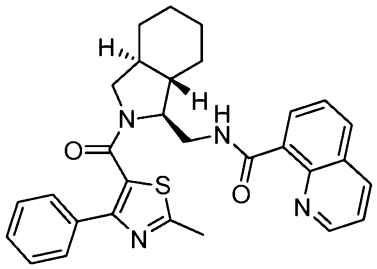
Example 64

N-(((1S,3aR,7aS)-2-(2-methyl-4-phenylthiazole-5-carbonyl)octahydro-1H-isoindol-1-yl)methyl)quinoline-8-carboxamide



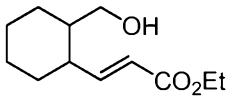
Example 65

N-(((1S,3aS,7aS)-2-(2-methyl-4-phenylthiazole-5-carbonyl)octahydro-1H-isoindol-1-yl)methyl)quinoline-8-carboxamide



Part I

(E)-ethyl 3-(2-(hydroxymethyl)cyclohexyl)acrylate



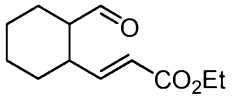
DIBAL-H (1M in toluene) (35.2 mmol, 35.2 mL) was added dropwise to a solution of hexahydroisobenzofuran-1(3H)-one (33.5mol, 4.7 g) in anhydrous ether (100 mL) at -10 °C under argon. The resulting mixture was stirred at -10 °C for 30 min under argon and quenched with MeOH (30 mL). The mixture was stirred at room temperature for overnight and the resulting suspension was added saturated Rochelle's salt aqueous solution and stirred for additional 30 min at room temperature. The organic layer was separated and washed with

saturated Rochelle's salt aqueous solution. The combined aqueous layer was extracted with ether (3X). The organic layer were combined, dried with dried with $MgSO_4$ and concentrated *in vacuo* to give lactol octahydroisobenzofuran-1-ol which was used for next step without further purification.

(Carbethoxymethylene)triphenylphosphorane (17.7 g, 50.7 mmol) was added to a solution of the above described octahydroisobenzofuran-1-ol in acetonitrile (100 mL) and the resulting mixture was refluxed at 85 °C overnight. Acetonitrile was removed in vacuo and the resulting residue was diluted with ether which was stirred at room temperature for 2 hr. The white precipitate was filtered off and washed with cold ether. All ether portion was combined and concentrated *in vacuo* to give crude product which was purified by chromatograph to afford desired (E)-ethyl 3-(2-(hydroxymethyl)cyclohexyl)acrylate as colorless oil (Y: 78.9 % over two steps). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.12–7.05 (m, 1H), 5.80 (d, 1H), 4.15–4.09 (m, 2H), 3.40–3.37 (m, 2H), 2.63–2.59 (m, 1H), 1.80–1.29 (m, 9H), 1.25–1.19 (m, 3H).

Part II

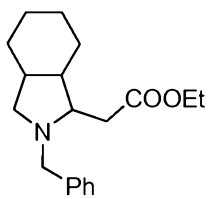
(E)-ethyl 3-(2-formylcyclohexyl)acrylate



General Procedure P: Oxidation of alcohol to aldhyde using PCC. A solution of (E)-ethyl 3-(2-(hydroxymethyl)cyclohexyl)acrylate (3.84 g, 18.1 mmol) in DCM (20 mL) was added to a suspension of PCC (5.86 g, 27.2 mmol) and celite (4.2 g) in DCM (40 mL). The resulting mixture was stirred under argon for 2 hr and filtered through a pad of silica which was rinsed with ether. The organic solvent was removed *in vacuo* to give desired product which was used for next step without further purification (Y: 85%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.67 (s, 1H), 7.16–7.09 (m, 1H), 5.88 (d, 1H), 4.22–4.17 (m, 2H), 2.83–2.81 (m, 1H), 2.60–2.57 (m, 1H), 1.96–1.90 (m, 1H), 1.80–1.55 (m, 8H), 1.33–1.26 (m, 3H).

Part III

Ethyl 2-(2-benzyloctahydro-1H-isoindol-1-yl)acetate

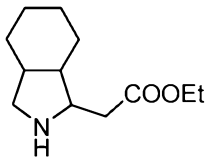


A mixture of (E)-ethyl 3-(2-formylcyclohexyl)acrylate, benzyl amine and $NaBH(OAc)_3$ in DCM was stirred at room temperature for 3 hr. The reaction mixture was

quenched with saturated $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with DCM (2X). All organic layers were combined, dried with dried with $MgSO_4$ and concentrated *in vacuo* to give the crude product which was purified by chromatography to afford desired ethyl 2-(2-benzyloctahydro-1H-isoindol-1-yl)acetate. MS (ESI) 302 (M+H).

Part IV

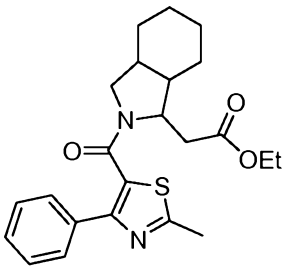
Ethyl 2-(octahydro-1H-isoindol-1-yl)acetate



Ethyl 2-(octahydro-1H-isoindol-1-yl)acetate was prepared following the same general protocol as described in Example 1 for debenzylation from ethyl 2-(2-benzyloctahydro-1H-isoindol-1-yl)acetate.

Part V

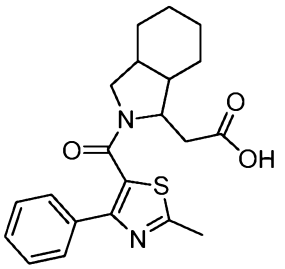
Ethyl 2-(2-(2-methyl-4-phenylthiazole-5-carbonyl)octahydro-1H-isoindol-1-yl)acetate



Ethyl 2-(2-(2-methyl-4-phenylthiazole-5-carbonyl)octahydro-1H-isoindol-1-yl)acetate was prepared according general procedure **A** from ethyl 2-(octahydro-1H-isoindol-1-yl)acetate and 2-methyl-4-phenylthiazole-5-carboxylic acid.

Part VI

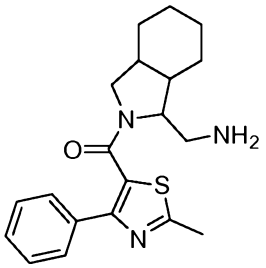
2-(2-(2-methyl-4-phenylthiazole-5-carbonyl)octahydro-1H-isoindol-1-yl)acetic acid



2-(2-(2-methyl-4-phenylthiazole-5-carbonyl)octahydro-1H-isoindol-1-yl)acetic acid was prepared according general procedure **B** from ethyl 2-(2-(2-methyl-4-phenylthiazole-5-carbonyl)octahydro-1H-isoindol-1-yl)acetate.

Part VII

(1-(Aminomethyl)-1H-isoindol-2(3H,3aH,4H,5H,6H,7H,7aH)-yl)(2-methyl-4-phenylthiazol-5-yl)methanone



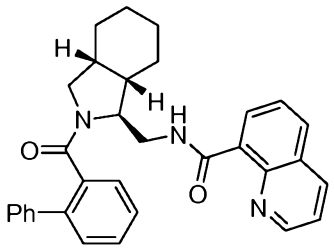
(1-(aminomethyl)-1H-isoindol-2(3H,3aH,4H,5H,6H,7H,7aH)-yl)(2-methyl-4-phenylthiazol-5-yl)methanone was prepared according to general procedure **G** using 2-(2-(2-methyl-4-phenylthiazole-5-carbonyl)octahydro-1H-isoindol-1-yl)acetic acid.

The pair of stereo isomers Examples 64 and 65 were isolated by prep HPLC from the coupling reaction according general procedure **A** using (1-(aminomethyl)-1H-isoindol-2(3H,3aH,4H,5H,6H,7H,7aH)-yl)(2-methyl-4-phenylthiazol-5-yl)methanone and quinoline-8-carboxylic acid. The assignment of stereochemistry is not verified. MS (ESI) 511 (M+H).

Example 66 and Example 67

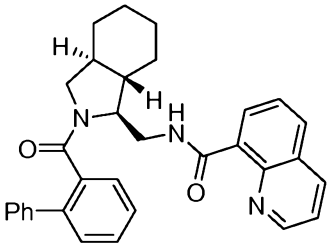
Example 66

N-(((1S,3aR,7aS)-2-(biphenylcarbonyl)octahydro-1H-isoindol-1-yl)methyl)quinoline-8-carboxamide



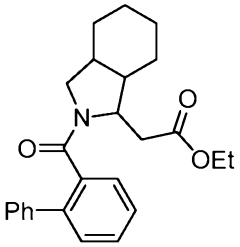
Example 67

N-(((1S,3aS,7aS)-2-(biphenylcarbonyl)octahydro-1H-isoindol-1-yl)methyl)quinoline-8-carboxamide



Part I

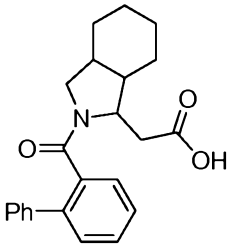
Ethyl 2-(2-(biphenylcarbonyl)octahydro-1H-isoindol-1-yl)acetate



Ethyl 2-(2-(biphenylcarbonyl)octahydro-1H-isoindol-1-yl)acetate was prepared according to general procedure **A** using ethyl 2-(octahydro-1H-isoindol-1-yl)acetate and biphenyl-2-carboxylic acid.

Part II

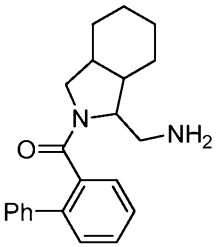
2-(2-(Biphenylcarbonyl)octahydro-1H-isoindol-1-yl)acetic acid



2-(2-(Biphenylcarbonyl)octahydro-1H-isoindol-1-yl)acetic acid was prepared by hydrolysis of ethyl 2-(2-(biphenylcarbonyl)octahydro-1H-isoindol-1-yl)acetate according to general procedure B.

Part III

(1-(Aminomethyl)-1H-isoindol-2(3H,3aH,4H,5H,6H,7H,7aH)-yl)(biphenyl-2-yl)methanone



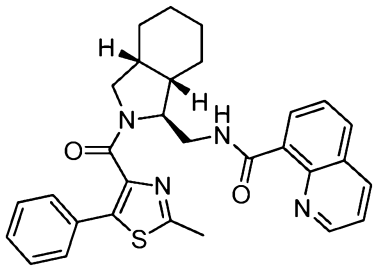
(1-(Aminomethyl)-1H-isoindol-2(3H,3aH,4H,5H,6H,7H,7aH)-yl)(biphenyl-2-yl)methanone was prepared by following general procedure **G** using 2-(2-(biphenylcarbonyl)octahydro-1H-isoindol-1-yl)acetic acid.

The pair of stereo isomers Examples 66 and 67 were isolated by prep HPLC from the coupling reaction according general procedure **A** using (1-(aminomethyl)-1H-isoindol-2(3H,3aH,4H,5H,6H,7H,7aH)-yl)(biphenyl-2-yl)methanone and quinoline-8-carboxylic acid. The assignment of stereochemistry is not verified. MS (ESI) (M+H).

Example 68 and Example 69

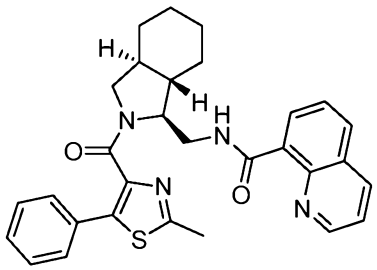
Example 68

N-(((1S,3aR,7aS)-2-(2-methyl-5-phenylthiazole-4-carbonyl)octahydro-1H-isoindol-1-yl)methyl)quinoline-8-carboxamide



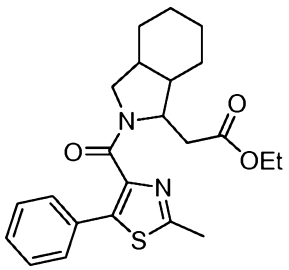
Example 69

N-(((1S,3aS,7aS)-2-(2-methyl-5-phenylthiazole-4-carbonyl)octahydro-1H-isoindol-1-yl)methyl)quinoline-8-carboxamide



Part I

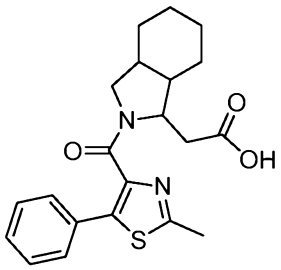
Ethyl 2-(2-(2-methyl-5-phenylthiazole-4-carbonyl)octahydro-1H-isoindol-1-yl)acetate



Ethyl 2-(2-(2-methyl-5-phenylthiazole-4-carbonyl)octahydro-1H-isoindol-1-yl)acetate was prepared according to general procedure **A** using ethyl 2-(octahydro-1H-isoindol-1-yl)acetate and 2-methyl-5-phenylthiazole-4-carboxylic acid.

Part II

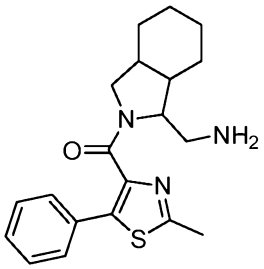
2-(2-(2-Methyl-5-phenylthiazole-4-carbonyl)octahydro-1H-isoindol-1-yl)acetic acid



2-(2-(2-Methyl-5-phenylthiazole-4-carbonyl)octahydro-1H-isoindol-1-yl)acetic acid was prepared according to general procedure **B** using ethyl 2-(2-(2-methyl-5-phenylthiazole-4-carbonyl)octahydro-1H-isoindol-1-yl)acetate

Part III

(1-(Aminomethyl)-1H-isoindol-2(3H,3aH,4H,5H,6H,7H,7aH)-yl)(2-methyl-5-phenylthiazol-4-yl)methanone



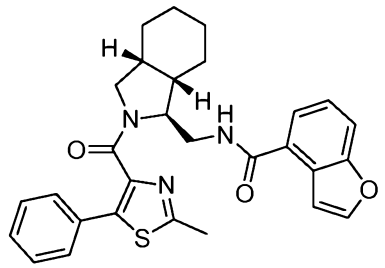
(1-(Aminomethyl)-1H-isoindol-2(3H,3aH,4H,5H,6H,7H,7aH)-yl)(2-methyl-5-phenylthiazol-4-yl)methanone was prepared according to general procedure **G** using 2-(2-(2-methyl-5-phenylthiazole-4-carbonyl)octahydro-1H-isoindol-1-yl)acetic acid.

The pair of stereo isomers Examples 68 and 69 were isolated by prep HPLC from the coupling reaction according general procedure **A** (1-(aminomethyl)-1H-isoindol-2(3H,3aH,4H,5H,6H,7H,7aH)-yl)(2-methyl-5-phenylthiazol-4-yl)methanone and quinoline-8-carboxylic acid. The assignment of stereochemistry is not verified. MS (ESI) 511 (M+H).

Example 70 and Example 71

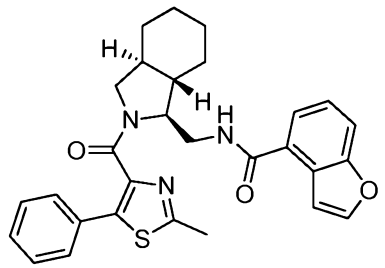
Example 70

N-(((1S,3aR,7aS)-2-(2-methyl-5-phenylthiazole-4-carbonyl)octahydro-1H-isoindol-1-yl)methyl)benzofuran-4-carboxamide



Example 71

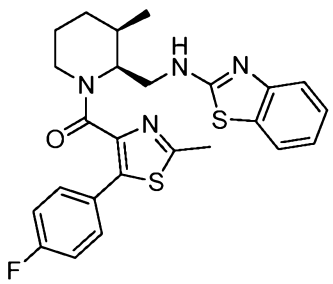
N-(((1S,3aS,7aS)-2-(2-methyl-5-phenylthiazole-4-carbonyl)octahydro-1H-isoindol-1-yl)methyl)benzofuran-4-carboxamide



The pair of stereo isomers Examples 70 and 71 were isolated by prep HPLC from the coupling reaction according general procedure **A** (1-(aminomethyl)-1H-isoindol-2(3H,3aH,4H,5H,6H,7H,7aH)-yl)(2-methyl-5-phenylthiazol-4-yl)methanone and benzofuran-4-carboxylic acid. The assignment of stereochemistry is not verified. MS (ESI) 500 (M+H).

Example 72

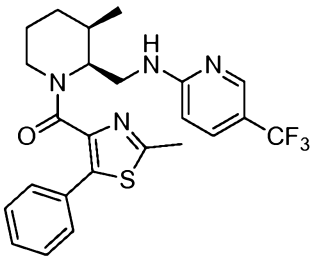
rac-((2S,3R)-2-((benzo[d]thiazol-2-ylamino)methyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



The title compound was prepared following the same general protocol as described for Example 12 using 2-chlorobenzothiazole. MS (ESI) 481.3 (M+H)

Example 73

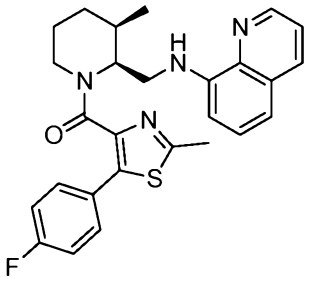
rac-((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)(2-methyl-5-phenylthiazol-4-yl)methanone



The title compound was prepared following the same general protocol as described for Example 11 using 2-methyl-5-phenylthiazole-4-carboxylic acid and tert-butyl (((2S,3R)-3-methylpiperidin-2-yl)methyl)carbamate. MS (ESI) 475.2 (M+H)

Example 74

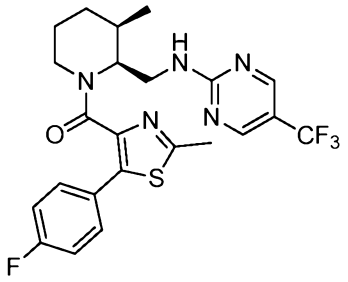
rac- ((2S,3R)-3-methyl-2-((quinolin-8-ylamino)methyl)piperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



The title compound was prepared following the same general protocol as described for Example 21 using 8-bromoquinoline. MS (ESI) 475.2 (M+H)

Example 75

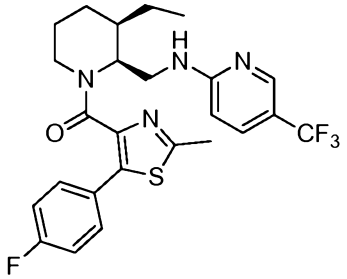
rac-((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyrimidin-2-yl)amino)methyl)piperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



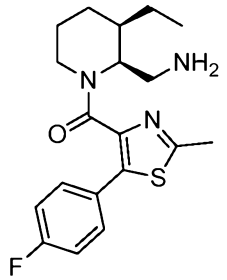
The title compound was prepared following the same general protocol as described for Example 18 using 2-chloro-5-(trifluoromethyl)pyrimidine. MS (ESI) 494.2 (M+H)

Example 76

((2S,3R)-3-ethyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



rac-((2S,3R)-2-(aminomethyl)-3-ethylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



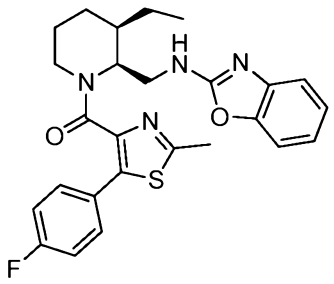
The title compound was synthesized following the same general protocol as described in Example 11 using 3-ethylpicolinonitrile and 5-(4-fluorophenyl)-2-methylthiazole-4-carboxylic acid. MS (ESI) 361.1 (M+H)

((2S,3R)-3-ethyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone

The title compound was prepared following the same general protocol as described for Example 11 using *rac*-((2S,3R)-2-(aminomethyl)-3-ethylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone. MS (ESI) 507.2 (M+H)

Example 77

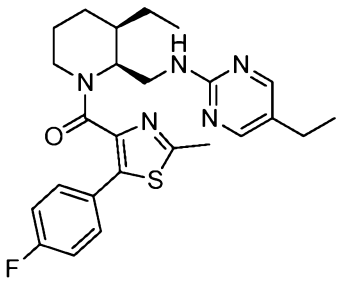
rac-((2S,3R)-2-((benzo[d]oxazol-2-ylamino)methyl)-3-ethylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



The title compound was prepared following the same general protocol as described for Example 12 using rac-((2S,3R)-2-(aminomethyl)-3-ethylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone. MS (ESI) 479.3 (M+H)

Example 78

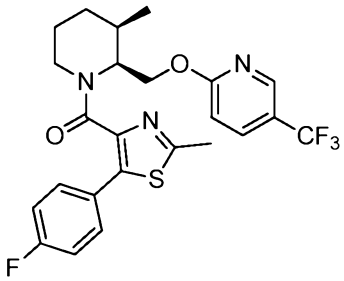
rac-((2S,3R)-3-ethyl-2-(((5-ethylpyrimidin-2-yl)amino)methyl)piperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



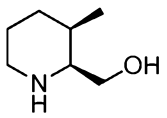
The title compound was prepared following the same general protocol as described for Example 16 using rac-((2S,3R)-2-(aminomethyl)-3-ethylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone. MS (ESI) 468.4 (M+H)

Example 79

rac-((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)oxy)methyl)piperidin-1-yl) (5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



rac-((2S,3R)-3-methylpiperidin-2-yl)methanol

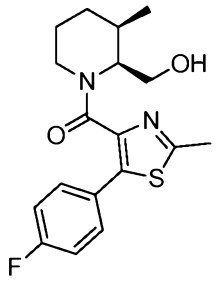


To a solution of methyl 3-methylpicolinate (5g) and 36% HCl (2 eq) in methanol was added 10% Pd/C. The parr shaker bottle was evacuated/H_2 purged 3x, and then shaken at 50psi until starting material was consumed (typically <1h). The reaction was filtered through celite and concentrated to yield (2S,3R)-methyl 3-methylpiperidine-2-carboxylate hydrochloride salt without further purification.

To a suspension of $LiAlH_4$ (4eq) in THF (40 ml) was added in portions the above crude salt at 0°C. The reaction was allowed to stir to room temperature overnight and then refluxed for 2h. The reaction mixture was then quenched with saturated Na_2SO_4 at 0°C and stirred for 1h. The reaction mixture was filtered and concentrated *in vacuo* to give the title compound as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.4 (m, 2H), 2.9 (m, 1H), 2.8 (m, 1H), 2.6 (m, 1H), 1.7 (m, 1H), 1.6 – 1.4 (m, 4H), 0.8 (d,3H).

rac-((2S,3R)-2-(hydroxymethyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



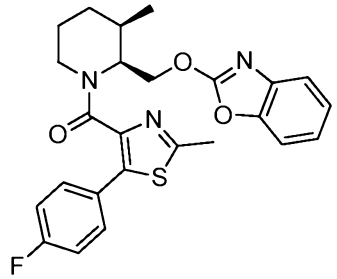
(1.4g) from the previous step in DMAC was added DIEA (2eq) followed by 5-(4-fluorophenyl)-2-methylthiazole-4-carboxylic acid (2.3g) and HATU (1.1eq). The reaction was allowed to stir at room temperature for 15h, and was then concentrated *in vacuo* to remove the DMAC. The crude residue was taken up in EtOAc and washed with 1M HCl, sat aq. $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated. The crude residue was purified by chromatography on silica gel (EtOAc/hex) to give the title compound as a brown oil which crystallized (2.6g). MS (ESI) 349.4 (M+H)

rac-((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)oxy)methyl)piperidin-1-yl) (5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone

To a stirred solution of *rac*-((2S,3R)-2-(hydroxymethyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone in THF was added NaH (4eq) at 0°C and stirred for 30 min at RT. 2-chloro-5-(trifluoromethyl)pyridine (2eq) was then added and solution refluxed for 2h. The reaction was cooled and quenched with saturated NH_4Cl and concentrated *in vacuo*. The crude reaction mixture was purified by reverse-phase preparative HPLC to afford the title compound. MS (ESI) 493.7 (M+H)

Example 80

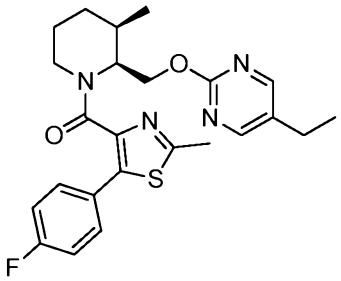
rac-((2S,3R)-2-((benzo[d]oxazol-2-yloxy)methyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



The title compound was prepared following the same general protocol as described for Example 79 using 2-chlorobenzoxazole. MS (ESI) 466.1 (M+H)

Example 81

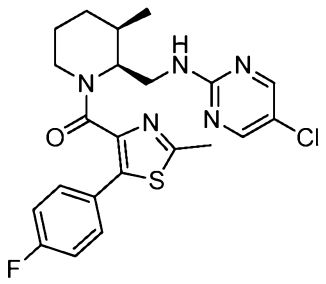
rac-((2S,3R)-2-(((5-ethylpyrimidin-2-yl)oxy)methyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



The title compound was prepared following the same general protocol as described for Example 79 using 2-chloro-5-ethylpyrimidine. MS (ESI) 454.8 (M+H)

Example 82

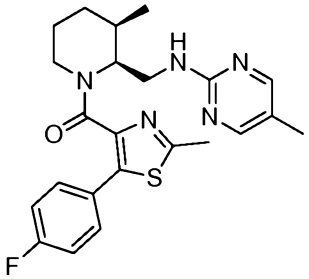
rac-((2S,3R)-2-(((5-chloropyrimidin-2-yl)amino)methyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



The title compound was prepared following the same general protocol as described for Example 16 using 2,5-dichloropyrimidine. MS (ESI) 460.0 (M+H)

Example 83

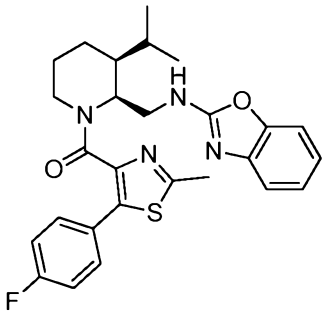
rac-((2S,3R)-3-methyl-2-(((5-methylpyrimidin-2-yl)amino)methyl)piperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



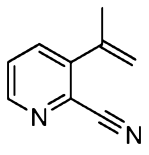
The title compound was prepared following the same general protocol as described for Example 16 using 2-chloro-5-methylpyrimidine. MS (ESI) 440.0 (M+H)

Example 84

rac-((2S,3S)-2-((benzo[d]oxazol-2-ylamino)methyl)-3-isopropylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone

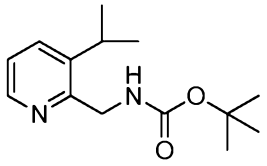


3-(prop-1-en-2-yl)picolinonitrile



A mixture of 3-bromopicolnonitrile, Isopropenylboronic acid pinacol ester, $Pd(PPh_3)_4$, and K_2CO_3 in dioxane/water (4:1) was stirred at 100 °C for 1h in a microwave reactor. The reaction mixture was transferred to a seperatory funnel, diluted with EtOAc, and water, and the layers were separated. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give a crude residue which was purified by chromatography on silica gel (EtOAc/hex) to afford the title compound. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.6 (m, 1H), 7.6 (m, 1H), 7.4 (m, 1H), 5.5 (s, 1H), 5.4 (s, 1H), 2.2 (s, 3H)

tert-butyl ((3-isopropylpyridin-2-yl)methyl)carbamate

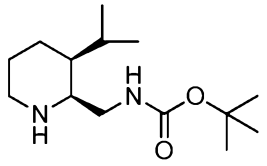


To a solution of 3-(prop-1-en-2-yl)picolinonitrile in acetic acid was added 10% Pd/C. The parr shaker bottle was evacuated/H2 purged 3x, and then shaken at 50psi until starting material was consumed (typically <1h). The reaction was filtered through celite and concentrated to yield (3-isopropylpyridin-2-yl)methanamine_acetic acid salt which was used without further purification.

To the crude salt in THF was added aq 1M NaOH, followed by BOC_2O (2eq). The reaction was allowed to stir at room temperature overnight. After ~16h, the reaction mixture was transferred to a seperatory funnel, diluted with EtOAc, and water, and the layers were separated. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give a crude residue which was purified by chromatography on silica gel (EtOAc/hex) to afford the title compound as a clear oil.

^1H NMR ($CDCl_3$, 400 MHz) δ 8.4 (m, 1H), 7.5 (m, 1H), 7.2 (m, 1H), 4.5 (s, 2H), 3.1 (s, 1H), 1.4 (s, 9H), 1.2 (d, J = 3.5 Hz, 6H)

rac-tert-butyl (((2S,3S)-3-isopropylpiperidin-2-yl)methyl)carbamate



To a solution of the BOC-protected pyridylamine prepared above in MeOH was added Nishimura's catalyst. The parr shaker bottle was evacuated/purged with H_2 (3x) and then

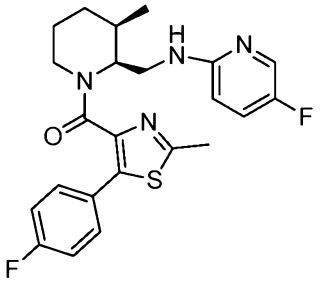
shaken at 50psi for 24h. The reaction was filtered through celite, and concentrated *in vacuo* to give the title compound as a near colorless oil, and was used without further purification. MS (ESI) 251.3 (M+H)

rac-((2S,3S)-2-((benzo[d]oxazol-2-ylamino)methyl)-3-isopropylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone

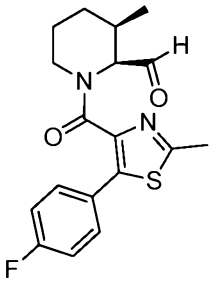
The title compound was prepared following the same general protocol as described for Example's 11 and 12 using *rac*-((2S,3S)-2-((benzo[d]oxazol-2-ylamino)methyl)-3-isopropylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone. MS (ESI) 493.3 (M+H)

Example 85

rac-((2S,3R)-2-(((5-fluoropyridin-2-yl)amino)methyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



rac-(2S,3R)-1-(5-(4-fluorophenyl)-2-methylthiazole-4-carbonyl)-3-methylpiperidine-2-carbaldehyde



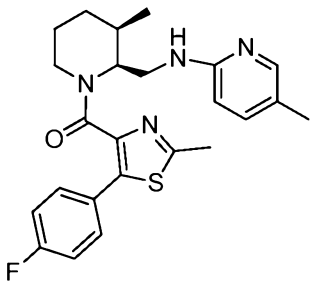
To a stirred solution of *rac*-((2S,3R)-2-(hydroxymethyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone in DCM was added Dess–Martin periodinane (1.5eq) and stirred at room temperature for 4h. The reaction mixture was transferred to a seperatory funnel, diluted with more DCM, water and the layers were separated. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give a crude residue which was purified by chromatography on silica gel (EtOAc/hex) to afford the title compound. MS (ESI) 347.1 (M+H)

rac-((2S,3R)-2-(((5-fluoropyridin-2-yl)amino)methyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone

To a stirred solution of *rac*-(2S,3R)-1-(5-(4-fluorophenyl)-2-methylthiazole-4-carbonyl)-3-methylpiperidine-2-carbaldehyde and 5-fluoropyridin-2-amine in methanol/acetic acid (50:1) was added sodium cyanoborohydride at 0°C. The reaction was then stirred at room temperature overnight. After ~16h, the reaction mixture was transferred to a seperatory funnel, diluted with EtOAc, saturated $NaHCO_3$ and the layers separated. The organic layer was washed with water, brine, dried ($MgSO_4$), and concentrated in vacuo. The crude reaction mixture was purified by reverse-phase preparative HPLC to afford the title compound. MS (ESI) 443.2 (M+H)

Example 86

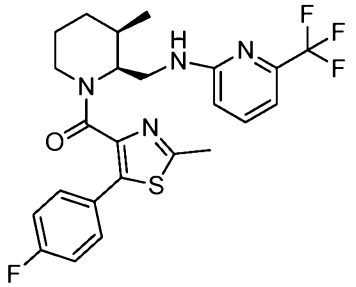
rac-((2S,3R)-3-methyl-2-(((5-methylpyridin-2-yl)amino)methyl)piperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



The title compound was prepared following the same general protocol as described for Example 85 using 5-methylpyridin-2-amine. MS (ESI) 439.2 (M+H)

Example 87

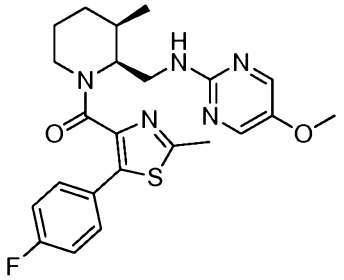
rac-((2S,3R)-3-methyl-2-(((6-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



The title compound was prepared following the same general protocol as described for Example 85 using 6-(trifluoromethyl)pyridin-2-amine. MS (ESI) 493.2 (M+H)

Example 88

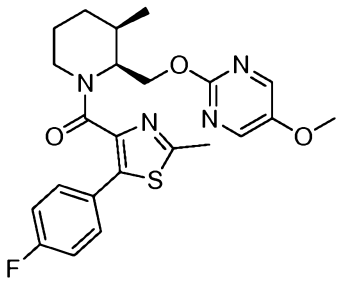
rac-((2S,3R)-2-(((5-methoxypyrimidin-2-yl)amino)methyl)-3-methylpiperidin-1-yl) (5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



A mixture of ((2S,3R)-2-(aminomethyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone, 2-chloro-5-methoxypyrimidine, Pd_2dba_3, BINAP, and NaOtBu in toluene was purged with argon, and then stirred at 70 °C for 72h. The reaction was cooled, filtered through a pad of silica gel and concentrated *in vacuo*. The crude reaction mixture was purified by reverse-phase preparative HPLC to afford the title compound. MS (ESI) 456.2 (M+H)

Example 89

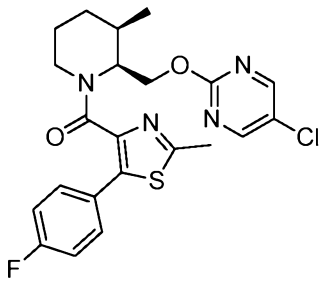
rac-((2S,3R)-2-(((5-methoxypyrimidin-2-yl)oxy)methyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



The title compound was prepared following the same general protocol as described for Example 81 using 2-chloro-5-methoxypyrimidine. MS (ESI) 457.2 (M+H)

Example 90

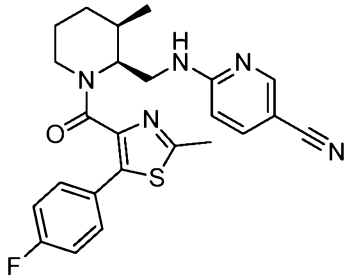
rac-((2S,3R)-2-(((5-chloropyrimidin-2-yl)oxy)methyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



The title compound was prepared following the same general protocol as described for Example 81 using 2,5-dichloropyrimidine. MS (ESI) 461.1 (M+H)

Example 91

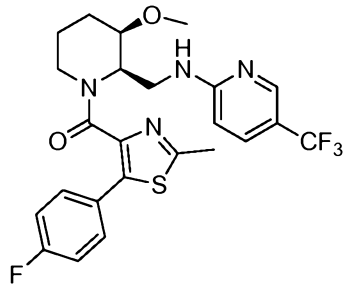
rac-6-((((2S,3R)-1-(5-(4-fluorophenyl)-2-methylthiazole-4-carbonyl)-3-methylpiperidin-2-yl)methyl)amino)nicotinonitrile



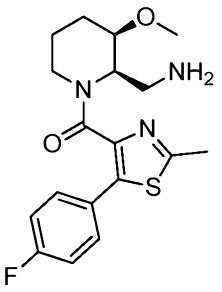
The title compound was prepared following the same general protocol as described for Example 18 using 6-chloronicotinonitrile. MS (ESI) 450.2 (M+H)

Example 92

rac-((2R,3R)-3-methoxy-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



rac-((2R,3R)-2-(aminomethyl)-3-methoxypiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



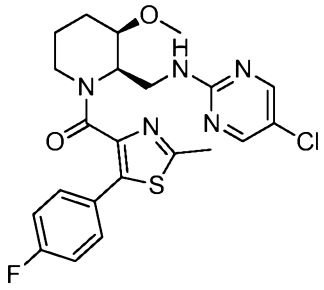
The title compound was synthesized following the same general protocol as described in Example 11 using 3-methoxypicolinonitrile and 5-(4-fluorophenyl)-2-methylthiazole-4-carboxylic acid. MS (ESI) 464.4 (M+H)

rac-((2R,3R)-3-methoxy-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone

The title compound was prepared following the same general protocol as described for Example 11 using *rac*-((2R,3R)-2-(aminomethyl)-3-methoxypiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone. MS (ESI) 509.4 (M+H)

Example 93

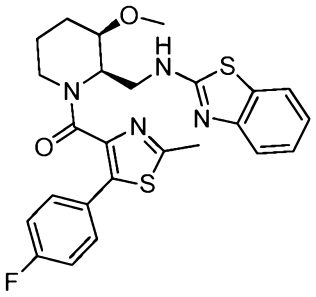
rac-((2R,3R)-2-(((5-chloropyrimidin-2-yl)amino)methyl)-3-methoxypiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



The title compound was prepared following the same general protocol as described for Example 16 using 2,5-dichloropyrimidine and *rac*-((2R,3R)-2-(aminomethyl)-3-methoxypiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone. MS (ESI) 476.0 (M+H)

Example 94

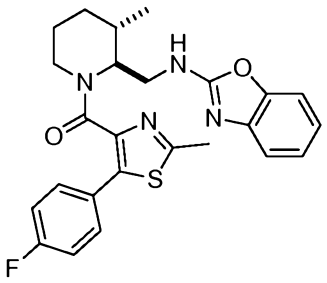
rac-((2R,3R)-2-((benzo[d]thiazol-2-ylamino)methyl)-3-methoxypiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



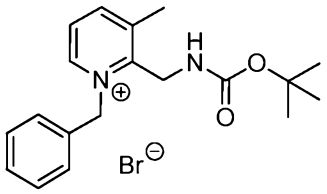
The title compound was prepared following the same general protocol as described for Example 12 using 2-chlorobenzothiazole and *rac*-((2R,3R)-2-(aminomethyl)-3-methoxypiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone. MS (ESI) 497.0 (M+H)

Example 95

((2R,3R)-2-((benzo[d]oxazol-2-ylamino)methyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone

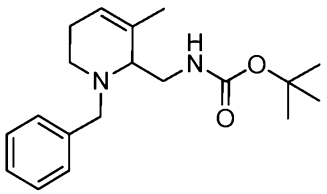


1-benzyl-2-(((tert-butoxycarbonyl)amino)methyl)-3-methylpyridin-1-ium bromide



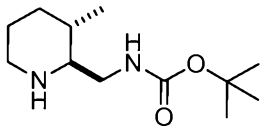
Tert-butyl ((3-methylpyridin-2-yl)methyl)carbamate (4.5g) and Benzylbromide (2eq) in 80ml of acetonitrile was heated in a sealed tube at reflux overnight and then concentrated *in vacuo* to give the title compound and was used without further purification. MS (ESI) 313 (M+H)

rac-tert-butyl ((1-benzyl-3-methyl-1,2,5,6-tetrahydropyridin-2-yl)methyl)carbamate



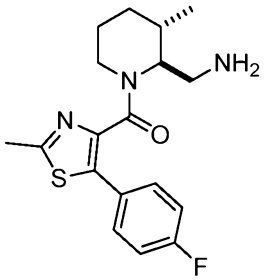
To a solution of 1-benzyl-2-(((tert-butoxycarbonyl)amino)methyl)-3-methylpyridin-1-ium bromide (1.5g) in MeOH (100 ml) was added $NaBH_4$ (3eq) in three portions at 0°C . The solution was then stirred for 3h at room temperature and then concentrated *in vacuo*. The crude residue was taken up in EtOAc and washed with sat aq. $NaHCO_3$, dried ($MgSO_4$), and concentrated. The crude residue was purified by chromatography on silica gel (EtOAc/hex) to give the title compound as a pale yellow oil in 63% yield. MS (ESI) 317 (M+H)

rac-tert-butyl (((2R,3R)-3-methylpiperidin-2-yl)methyl)carbamate



A mixture of *rac*-tert-butyl ((1-benzyl-3-methyl-1,2,5,6-tetrahydropyridin-2-yl)methyl)carbamate and $Pd(OH)_2/C$ (20% wt, 0.1eq) was pressurized to 4 bar with H_2 and maintained at room temperature for 5 h. The mixture was filtered through Celite and the filtrate was concentrated *in vacuo* to yield the title compound as a colorless oil. MS (ESI) 229.2 (M+H)

rac-((2S,3R)-2-(aminomethyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



To a solution of *rac*-tert-butyl (((2R,3R)-3-methylpiperidin-2-yl)methyl)carbamate (1eq) from the previous step in DMF was added DIEA (2eq) followed by 5-(4-fluorophenyl)-2-methylthiazole-4-carboxylic acid (1.5eq) and HATU (2eq). The reaction was allowed to stir at room temperature for 15h, and was then concentrated *in vacuo* to remove the DMF. The crude residue was taken up in EtOAc and washed with 1M HCl, sat aq. $NaHCO_3$, brine,

dried ($MgSO_4$), and concentrated. The crude residue was purified by chromatography on silica gel (EtOAc/hex) to give tert-butyl (((2R,3R)-1-(5-(4-fluorophenyl)-2-methylthiazole-4-carbonyl)-3-methylpiperidin-2-yl)methyl)carbamate as a light yellow oil.

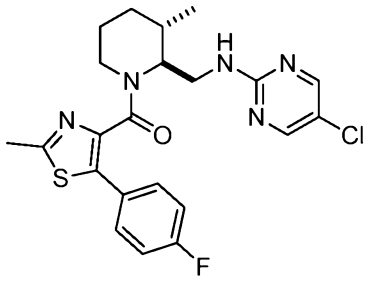
To a solution of this carbamate in CH_2Cl_2 was added TFA (1:1 v/v). The reaction was aged at room temperature and monitored for disappearance of starting material by analytical reverse-phase HPLC. When starting material was consumed, the reaction was concentrated in vacuo. The crude residue was taken up in EtOAc, and washed with sat aqueous $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated to afford the title compound as a pale yellow oil which crystallized. MS (ESI) 348.2 (M+H).

rac-((2R,3R)-2-((benzo[d]oxazol-2-ylamino)methyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone

A mixture of ((2R,3R)-2-(aminomethyl)-3-methylpiperidin-1-yl)(2-methyl-5-phenylthiazol-4-yl)methanone, 2-chlorobenzoxazole, and DIEA in ACN was stirred at 60 °C overnight. The reaction mixture was concentrated *in vacuo*. The crude reaction mixture was purified by reverse-phase preparative HPLC to afford the title compound. MS (ESI) 465.1 (M+H).

Example 96

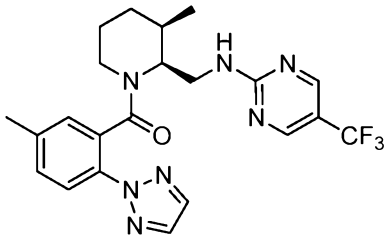
rac-((2R,3R)-2-(((5-chloropyrimidin-2-yl)amino)methyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



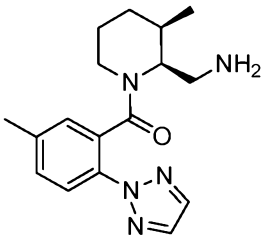
The title compound was prepared following the same general protocol as described for Example 16 using 2,5-dichloropyrimidine and *rac*-((2S,3R)-2-(aminomethyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone. MS (ESI) 460.4 (M+H).

Example 97

rac-((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyrimidin-2-yl)amino)methyl)piperidin-1-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone



rac-((2S,3R)-2-(aminomethyl)-3-methylpiperidin-1-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone



To a solution of *rac*-tert-butyl (((2S,3R)-3-methylpiperidin-2-yl)methyl)carbamate (1eq) from Example 11 in DMF was added DIEA (2eq) followed by 5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoic acid (1.5eq) and HATU (2eq). The reaction was allowed to stir at room temperature for 15h, and was then concentrated *in vacuo* to remove the DMF. The crude residue was taken up in EtOAc and washed with 1M HCl, sat aq. $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated. The crude residue was purified by chromatography on silica gel (EtOAc/hex) to give *rac*-tert-butyl (((2S,3R)-3-methyl-1-(5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoyl)piperidin-2-yl)methyl)carbamateas a light yellow oil.

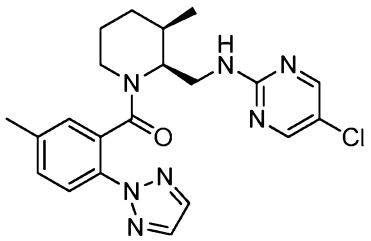
To a solution of this carbamate in CH_2Cl_2 was added TFA (1:1 v/v). The reaction was aged at room temperature and monitored for disappearance of starting material by analytical reverse-phase HPLC. When starting material was consumed, the reaction was concentrated in vacuo. The crude residue was taken up in EtOAc, and washed with sat aqueous $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated to afford the title compound as a pale yellow oil which crystallized. MS (ESI) 314.1 (M+H).

rac-((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyrimidin-2-yl)amino)methyl)piperidin-1-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound was prepared following the same general protocol as described for Example 18 using ((2S,3R)-2-(aminomethyl)-3-methylpiperidin-1-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone and 2-chloro-5-(trifluoromethyl)pyrimidine. MS (ESI) 460.0 (M+H).

Example 98

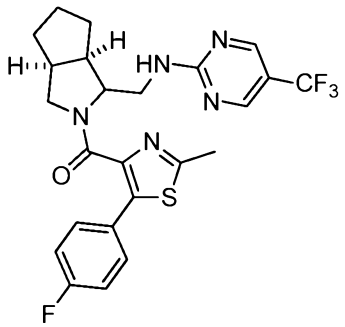
rac-((2S,3R)-2-(((5-chloropyrimidin-2-yl)amino)methyl)-3-methylpiperidin-1-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone



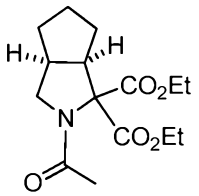
The title compound was prepared following the same general protocol as described for Example 16 starting with *rac*-((2S,3R)-2-(aminomethyl)-3-methylpiperidin-1-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone and 2,5-dichloropyrimidine. MS (ESI) 426.4 (M+H).

Example 99

(5-(4-fluorophenyl)-2-methylthiazol-4-yl)(1-(hydroxymethyl)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)methanone

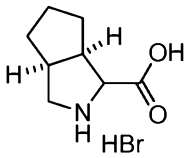


diethyl 2-acetylhexahydrocyclopenta[c]pyrrole-1,1(2H)-dicarboxylate



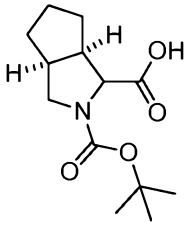
The title compound was prepared from cyclopenten-1-aldehyde (1eq) and diethyl acetamidomalonate (1eq) using the procedure by Chung et al (J. Org. Chem. 1990, 55,270). MS (ESI) 298 (M+H)

octahydrocyclopenta[c]pyrrole-1-carboxylic acid hydrobromide



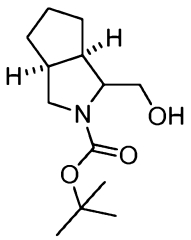
A solution of the diethyl 2-acetylhexahydrocyclopenta[c]pyrrole-1,1(2H)-dicarboxylate prepared above in 48% aqueous HBr 48% and AcOH (4:1) was heated at 120°C overnight for 16h. The reaction mixture was cooled, concentrated in vacuo and lyophilized to yield the title compound. MS (ESI) 156 (M+H).

2-(tert-butoxycarbonyl)octahydrocyclopenta[c]pyrrole-1-carboxylic acid



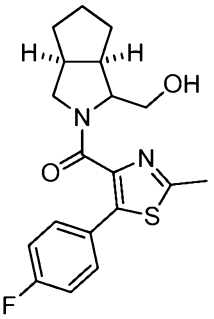
The amino acid prepared above and $NaHCO_3$ (2eq.) were dissolved in water/dioxane (1:1, v/v) and Boc_2O (1.5 eq.) was added. After stirring overnight at room temperature, water was added and the resulting solution was washed with EtOAc (4 times). The aqueous solution was then acidified with 1N HCl to pH 1-2 and extracted with EtOAc (4 times), dried ($MgSO_4$), and concentrated. The crude residue was purified by chromatography on silica gel (EtOAc : CH_2Cl_2 = 1 : 3) to give the title compound as a creamy white solid. MS (ESI) 256 (M+H)

tert-butyl (((2S,3R)-3- tert-butyl 1-(hydroxymethyl)hexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate



To a stirred solution of 2-(tert-butoxycarbonyl)octahydrocyclopenta[c]pyrrole-1-carboxylic acid (1eq) in THF was added BH_3SMe_2 (10M,2eq) dropwise over 5 mins at 0°C. The reaction was then allowed to stir overnight at room temperature and then quenched with cooled water at 0°C. The reaction mixture was diluted with EtOAc and washed with water, brine, dried ($MgSO_4$), and concentrated. The crude residue was concentrated in vacuo to give the title compound as a clear oil. MS (ESI) 242.2 (M+H)

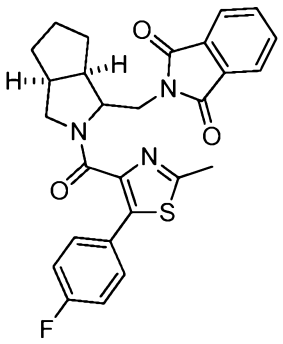
(5-(4-fluorophenyl)-2-methylthiazol-4-yl)(1-(hydroxymethyl)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)methanone



To a solution of the carbamate above in CH_2Cl_2 was added TFA (1:1 v/v). The reaction was stirred at room temperature for 30 minutes before being concentrated in vacuo. The crude residue was taken up in EtOAc, and washed with sat aqueous $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated to afford (octahydrocyclopenta[c]pyrrol-1-yl)methanol as a pale yellow oil.

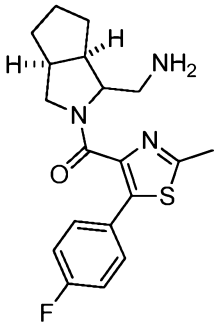
To a solution of (octahydrocyclopenta[c]pyrrol-1-yl)methanol (1eq) in DMF was added DIEA (2eq) followed by 5-(4-fluorophenyl)-2-methylthiazole-4-carboxylic acid (1.5eq) and HATU (2eq). The reaction was allowed to stir at room temperature for 15h, and was then concentrated *in vacuo* to remove the DMF. The crude residue was taken up in EtOAc and washed with 1M HCl, sat aq. $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated. The crude residue was purified by chromatography on silica gel (EtOAc/hex) to give the title compound as a clear oil. MS (ESI) 361.1 (M+H)

2-((2-(5-(4-fluorophenyl)-2-methylthiazole-4-carbonyl)octahydrocyclopenta[c]pyrrol-1-yl)methyl)isoindoline-1,3-dione



A solution of (5-(4-fluorophenyl)-2-methylthiazol-4-yl)(1-(hydroxymethyl)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)methanone (1eq), phthalimide (2eq) and triphenylphosphine (3eq) in THF (56 mL) was cooled to 0°C and added with DIAD (5eq) dropwise. The resulting suspension was allowed to warm to r.t. gradually and stirred overnight, concentrated *in vacuo* to a brown oil. The reaction mixture was diluted with EtOAc and washed with water, brine, dried ($MgSO_4$), and concentrated. The crude residue was purified by chromatography on silica gel (EtOAc/hex) to give the title compound as a clear oil. MS (ESI) 490.4 (M+H)

(1-(aminomethyl)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



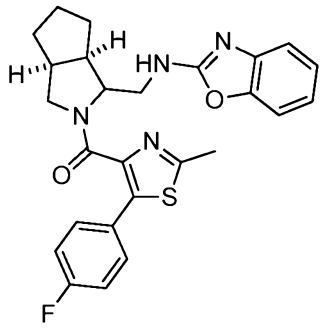
2-((-2-(5-(4-fluorophenyl)-2-methylthiazole-4-carbonyl)octahydrocyclopenta[c]pyrrol-1-yl)methyl)isoindoline-1,3-dione (1eq) and hydrazine monohydrate (4eq) in MeOH was stirred at 70°C for 3 hrs and then concentrated *in vacuo* to a yellow oil. The reaction mixture was diluted with EtOAc and washed with water, brine, dried ($MgSO_4$), and concentrated. The crude residue was purified by chromatography on silica gel (20% MeOH in EtOAc) to firstly remove the impurities and then (2:8:1 MeOH/EtOAc/TEA) to elute the title compound which was concentrated to yield a yellow oil. MS (ESI) 360.3 (M+H)

(5-(4-fluorophenyl)-2-methylthiazol-4-yl)(1-(hydroxymethyl)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)methanone

The title compound was prepared following the same general protocol as described for Example 18 using (1-(aminomethyl)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone and 2-chloro-5-(trifluoromethyl)pyrimidine. MS (ESI) 506.4 (M+H)

Example 100

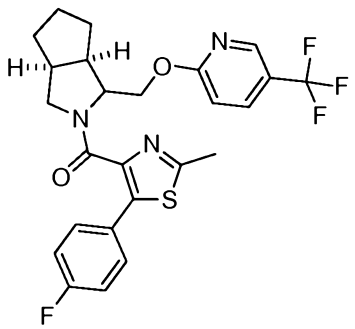
(1-((benzo[d]oxazol-2-ylamino)methyl)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



A mixture of (1-(aminomethyl)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone, 2-chlorobenzoxazole, and DIEA in ACN was stirred at 60 °C overnight. The reaction mixture was concentrated *in vacuo*. The crude reaction mixture was purified by reverse-phase preparative HPLC to afford the title compound. MS (ESI) 477.4 (M+H)

Example 101

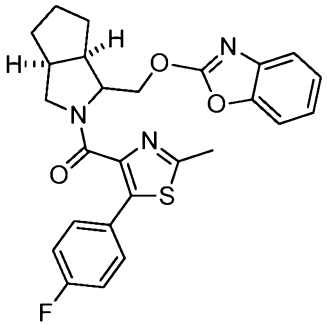
(5-(4-fluorophenyl)-2-methylthiazol-4-yl)(1-(((5-(trifluoromethyl)pyridin-2-yl)oxy)methyl)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)methanone



The title compound was prepared following the same general protocol as described for Example 79 using (5-(4-fluorophenyl)-2-methylthiazol-4-yl)(1-(hydroxymethyl)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)methanone. MS (ESI) 506.2 (M+H)

Example 102

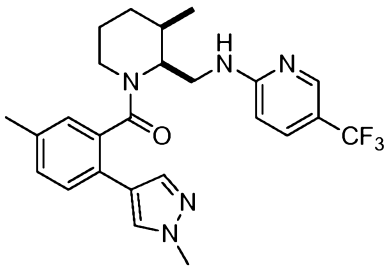
(1-((benzo[d]oxazol-2-yloxy)methyl)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



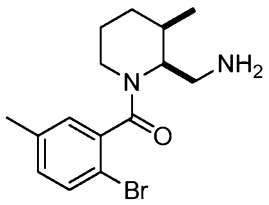
The title compound was prepared following the same general protocol as described for Example 80 using (5-(4-fluorophenyl)-2-methylthiazol-4-yl)(1-(hydroxymethyl)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)methanone and 2-chlorobenzoxazole. MS (ESI) 478.2 (M+H)

Example 103

rac- ((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)(5-methyl-2-(1-methyl-1H-pyrazol-4-yl)phenyl)methanone



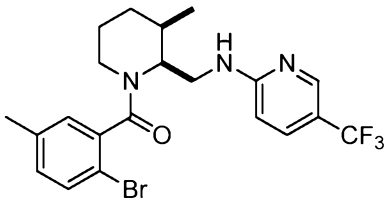
rac- ((2S,3R)-2-(aminomethyl)-3-methylpiperidin-1-yl)(2-bromo-5-methylphenyl)methanone



The title compound was synthesized following the same general protocol as described in Example 11 using tert-butyl (((2S,3R)-3-methylpiperidin-2-yl)methyl)carbamate and 2-bromo-5-methylbenzoic acid. ESI-MS (m/z): 325, 327, $[M]^+$, $[M+2]^+$.

5

<u>*rac*- (2-bromo-5-methylphenyl)((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)methanone</u>



The title compound was prepared following the same general protocol as described for
10 Example 11 starting with *rac*- ((2S,3R)-2-(aminomethyl)-3-methylpiperidin-1-yl)(2-bromo-5-methylphenyl)methanone and 2-chloro-5-(trifluoromethyl)pyridine. ESI-MS (m/z): 470, 472, $[M]^+$, $[M+2]^+$.

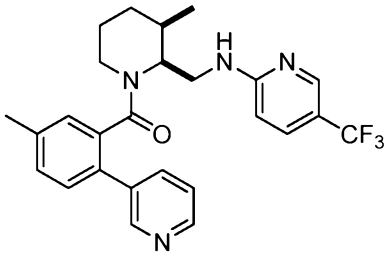
<u>*rac*- ((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)(5-
15 methyl-2-(1-methyl-1H-pyrazol-4-yl)phenyl)methanone</u>

The mixture of *rac*- (2-bromo-5-methylphenyl)((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)methanone (0.045 g, 0.097mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.024 g, 0.116 mmol), $P(PPh_3)_4$ (0.017 g, 0.015 mmol), K_2CO_3 (0.4 g, 0.291 mmol) and dioxane /H_2O (4:1,
20 3 mL) was degassed for 5 min and heated overnight at 100° C oil bath. The completion of reaction was monitored by analytical HPLC. The mixture was cooled and extracted with EtOAc. The combined organic layers were washed with saturated $NaHCO_3$ and dried over Na_2SO_4. The solvent was removed in vacuo to obtain a crude residue, which was purified by preparative-HPLC to obtain the title compound as TFA salt. ESI-MS (m/z): 472, $[M+1]^+$.

25

Example 104

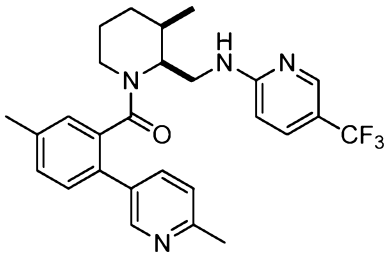
rac- ((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)(5-methyl-2-(pyridin-3-yl)phenyl)methanone



The title compound as TFA salt was prepared following the same general protocol as described for Example 103 starting with pyridin-3-ylboronic acid. ESI-MS (m/z): 469, $[M+1]^+$.

Example 105

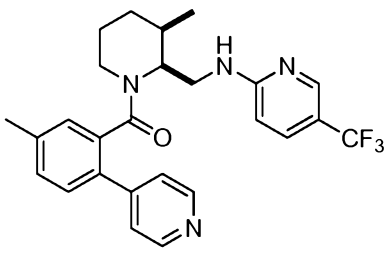
rac- ((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)(5-methyl-2-(6-methylpyridin-3-yl)phenyl)methanone



The title compound as TFA salt was prepared following the same general protocol as described for Example 103 starting with (6-methylpyridin-3-yl)boronic acid. ESI-MS (m/z): 483, $[M+1]^+$.

Example 106

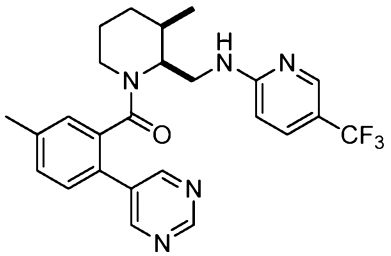
rac- ((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)(5-methyl-2-(pyridin-4-yl)phenyl)methanone



The title compound as TFA salt was prepared following the same general protocol as described for Example 103 starting with pyridin-4-ylboronic acid. ESI-MS (m/z): 469, $[M+1]^+$.

Example 107

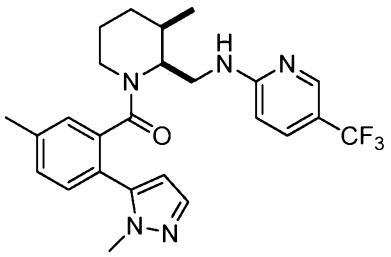
rac- ((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)(5-methyl-2-(pyrimidin-5-yl)phenyl)methanone



The title compound as TFA salt was prepared following the same general protocol as described for Example 103 starting with pyrimidin-5-ylboronic acid. ESI-MS (m/z): 470, $[M+1]^+$.

Example 108

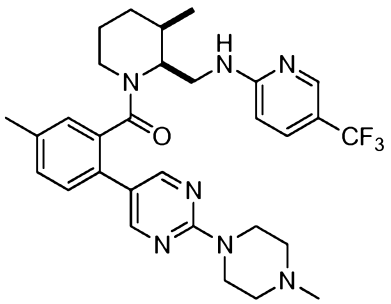
rac- ((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)(5-methyl-2-(1-methyl-1H-pyrazol-5-yl)phenyl)methanone



The title compound as TFA salt was prepared following the same general protocol as described for Example 103 starting with 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole. ESI-MS (m/z): 472, $[M+1]^+$.

Example 109

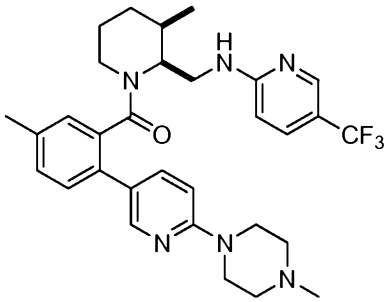
rac- ((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)(5-methyl-2-(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)phenyl)methanone



The title compound as TFA salt was prepared following the same general protocol as described for Example 103 starting with 2-(4-methylpiperazin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine. ESI-MS (m/z): 568, $[M+1]^+$.

Example 110

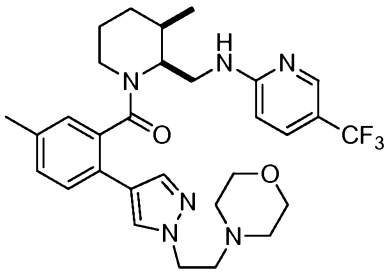
rac- ((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)(5-methyl-2-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)phenyl)methanone



The title compound as TFA salt was prepared following the same general protocol as described for Example 103 starting with 1-methyl-4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine. ESI-MS (m/z): 567, $[M+1]^+$.

Example 111

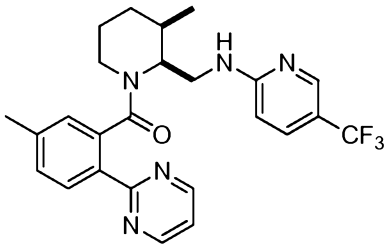
rac- ((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)(5-methyl-2-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)phenyl)methanone



The title compound as TFA salt was prepared following the same general protocol as described for Example 103 starting with 4-(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)ethyl)morpholine. ESI-MS (m/z): 571, $[M+1]^+$.

Example 112

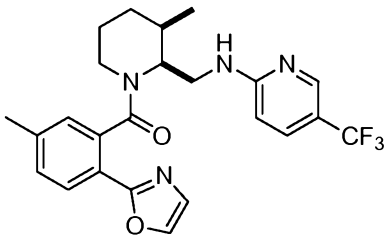
rac- ((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)(5-methyl-2-(pyrimidin-2-yl)phenyl)methanone



The mixture of *rac*- (2-bromo-5-methylphenyl)((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)methanone (0.03 g, 0.0638 mmol), 2-(tributylstannyl)pyrimidine (0.028 g, 0.0766 mmol), $P(PPh_3)_4$ (0.011 g, 0.01 mmol), Cs_2CO_3 (0.42 g, 0.13 mmol) and dioxane (1 mL) was degassed for 5 min and heated overnight at 140 °C oil bath. The completion of reaction was monitored by analytical HPLC. The mixture was cooled and extracted with EtOAc. The combine organic layers were washed with saturated $NaHCO_3$ and dried over Na_2SO_4. The solvent was removed in vacuo to obtain the crude, which was purified by preparative-HPLC to obtain the title compound as TFA salt. . ESI-MS (m/z): 470, $[M+1]^+$.

Example 113

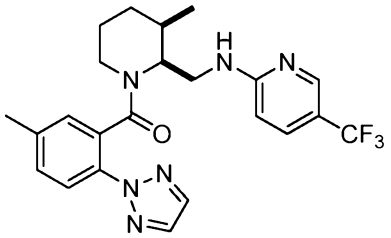
rac- ((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)(5-methyl-2-(oxazol-2-yl)phenyl)methanone



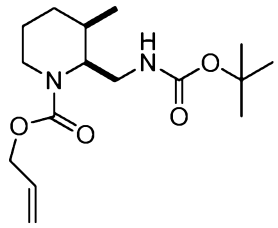
The title compound as TFA salt was prepared following the same general protocol as described for Example 112 starting with 2-(tributylstannyl)oxazole. ESI-MS (m/z): 459, $[M+1]^+$.

Example 114

rac- ((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

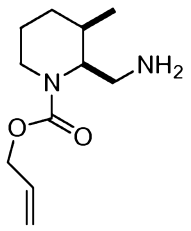


rac- (2S,3R)-allyl 2-(((tert-butoxycarbonyl)amino)methyl)-3-methylpiperidine-1-carboxylate



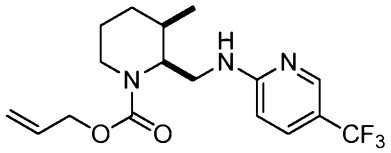
To the mixture of *rac*-tert-butyl (((2S,3R)-3-methylpiperidin-2-yl)methyl)carbamate (9.48 g, 41.53 mmol) in THF (25 mL) was added NaOH (2 M, 25 mL), followed by allyl chloroformate (6.65 mL, 62.3 mmol). The mixture was stirred at RT overnight. The mixture was diluted with EtOAc, washed with H_2O and Brine. The solvent was removed in vacuo and the resulting crude residue was purified by chromatography on silica gel (0~100% DCM/EtOAc) to obtain the title compound as a colorless oil.

rac- (2S,3R)-allyl 2-(aminomethyl)-3-methylpiperidine-1-carboxylate



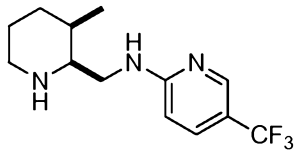
To a solution of this carbamate in CH_2Cl_2 was added TFA (1:1 v/v). The reaction was aged at room temperature and monitored for disappearance of starting material thin layer chromatography (tlc). When starting material was consumed, the reaction was concentrated in vacuo. The crude residue was taken up in EtOAc, and washed with sat aqueous $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated to afford the title compound.

rac- (2S,3R)-allyl 3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidine-1-carboxylate



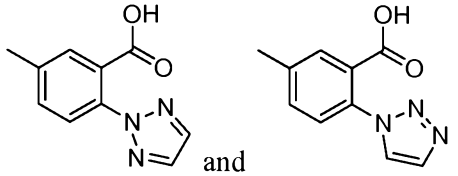
A mixture of *rac*- (2S,3R)-allyl 2-(aminomethyl)-3-methylpiperidine-1-carboxylate (1.36 g, 6.43 mmol), 2-chloro-5-(trifluoromethyl)pyridine (1.75 g, 9.645 mmol), and Cs_2CO_3 (4.2 g, 12.86 mmol) in DMF (20 mL) was stirred at 80 °C for 2 days. The reaction mixture was diluted with EtOAc and washed with brine. The organic layer was separated, dried with $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by chromatography on silica gel (EtOAc/hex) to give the title compound. ESI-MS (m/z): 358, $[M+1]^+$.

rac- N-(((2S,3R)-3-methylpiperidin-2-yl)methyl)-5-(trifluoromethyl)pyridin-2-amine



To a mixture of *rac*- (2S,3R)-allyl 3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidine-1-carboxylate (1.18 g, 3.32 mmol), $Pd(PPh_3)_4$ (0.384 g, 0.003 mmol) and THF (20 mL) was added morpholine (3.0 mL, 33.2 mmol). The mixture was degassed for 5 min and stirred at room temperature. The reaction was monitored for disappearance of starting material by analytical reverse-phase HPLC. After ~1h, the reaction was concentrated in vacuo. The crude residue was taken up in EtOAc, and washed with sat aqueous $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated and the resulting crude residue was purified by silica gel chromatography (0~100% DCM/EtOAc) to afford the title compound ESI-MS (m/z): 472, $[M+1]^+$.

5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoic acid and 5-methyl-2-(1H-1,2,3-triazol-1-yl)benzoic acid



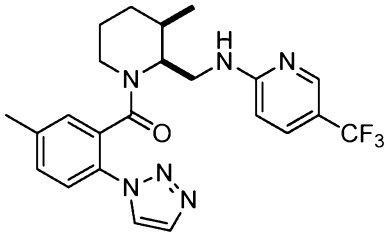
The mixture of 2-bromo-5-methylbenzoic acid (1 g, 4.65 mmol), 1,2,3-triazole (0.58 g, 8.37 mmol), (1S,2S)-N1,N2-dimethylcyclohexane-1,2-diamine (0.265 g, 1.86 mmol), Cs_2CO_3 (3.0 g, 9.3 mmol) and CuI (0.089 g, 0.465 mmol) in DMF (15 mL) was degassed and heated at 120 °C for 1h in a microwave reactor. The reaction was cooled to RT, diluted with MeOH, and acidified with AcOH to pH4~5. The solvent was removed in vacuo to obtain the crude which was purified by silica gel chromatography (0~100% DCM/EtOAc) to obtain the faster eluting acid 5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoic acid as the major product and the second eluting 5-methyl-2-(1H-1,2,3-triazol-1-yl)benzoic acid as the minor product. ESI-MS (m/z): 204, $[M+1]^+$.

rac- ((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound was synthesized following the same general protocol as described in Example 11 using 5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoic acid and *rac*- N-(((2S,3R)-3-methylpiperidin-2-yl)methyl)-5-(trifluoromethyl)pyridin-2-amine. ESI-MS (m/z): 459, $[M+1]^+$.

Example 115

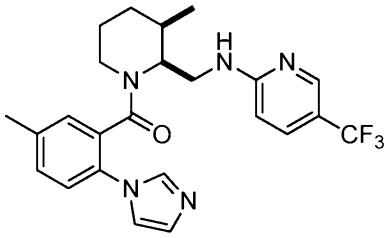
rac- ((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)(5-methyl-2-(1H-1,2,3-triazol-1-yl)phenyl)methanone



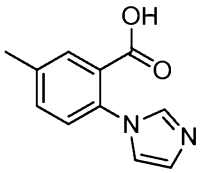
The title compound was synthesized following the same general protocol as described in Example 11 using 5-methyl-2-(1H-1,2,3-triazol-1-yl)benzoic acid and *rac*- N-(((2S,3R)-3-methylpiperidin-2-yl)methyl)-5-(trifluoromethyl)pyridin-2-amine. ESI-MS (m/z): 459, $[M+1]^+$.

Example 116

rac- (2-(1H-imidazol-1-yl)-5-methylphenyl)((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)methanone



2-(1H-imidazol-1-yl)-5-methylbenzoic acid



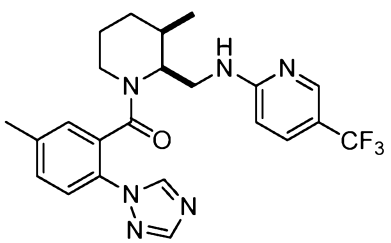
The title compound was synthesized following the same general protocol as described in Example 114 using imidazole instead of 1,2,3-triazole. ESI-MS (m/z): 203, $[M+1]^+$.

rac- (2-(1H-imidazol-1-yl)-5-methylphenyl)((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)methanone

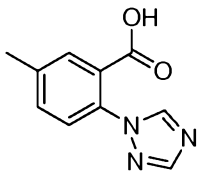
The title compound was synthesized following the same general protocol as described in Example 11 using 2-(1H-imidazol-1-yl)-5-methylbenzoic acid and *rac*- N-(((2S,3R)-3-methylpiperidin-2-yl)methyl)-5-(trifluoromethyl)pyridin-2-amine. ESI-MS (m/z): 458, $[M+1]^+$.

Example 117

rac- ((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)(5-methyl-2-(1H-1,2,4-triazol-1-yl)phenyl)methanone



5-methyl-2-(1H-1,2,4-triazol-1-yl)benzoic acid



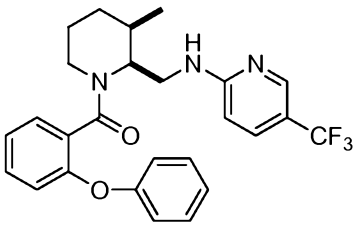
The title compound was synthesized following the same general protocol as described in Example 114 using 1H-1,2,4-triazole instead of 1,2,3-triazole. ESI-MS (m/z): 204, $[M+1]^+$.

rac- (2-(1H-imidazol-1-yl)-5-methylphenyl)((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)methanone

The title compound was synthesized following the same general protocol as described in Example 11 using 5-methyl-2-(1H-1,2,4-triazol-1-yl)benzoic acid and *rac*- N-(((2S,3R)-3-methylpiperidin-2-yl)methyl)-5-(trifluoromethyl)pyridin-2-amine. ESI-MS (m/z): 459, $[M+1]^+$.

Example 118

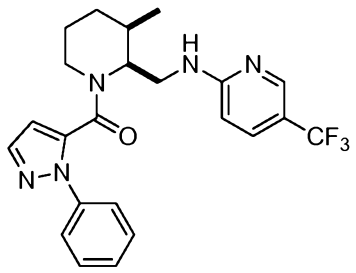
rac- ((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)(2-phenoxyphenyl)methanone



The title compound was synthesized following the same general protocol as described in Example 11 using 2-phenoxybenzoic acid and *rac*- N-(((2S,3R)-3-methylpiperidin-2-yl)methyl)-5-(trifluoromethyl)pyridin-2-amine. ESI-MS (m/z): 470, $[M+1]^+$.

Example 119

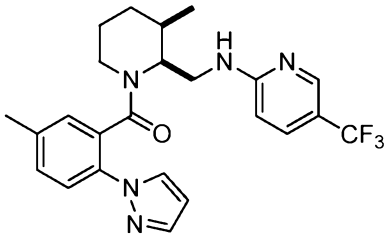
rac- ((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)(1-phenyl-1H-pyrazol-5-yl)methanone



The title compound was synthesized following the same general protocol as described in Example 11 using 1-phenyl-1H-pyrazole-5-carboxylic acid and *rac*- N-(((2S,3R)-3-methylpiperidin-2-yl)methyl)-5-(trifluoromethyl)pyridin-2-amine. ESI-MS (m/z): 444, $[M+1]^+$.

Example 120

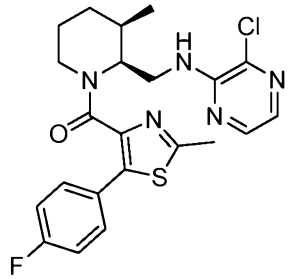
rac- ((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone



A mixture of *rac*- (2-bromo-5-methylphenyl)((2S,3R)-3-methyl-2-(((5-(trifluoromethyl)pyridin-2-yl)amino)methyl)piperidin-1-yl)methanone (0.0326 g, 0.0693 mmol), pyrazole (0.0094 g, 0.139 mmol), (1S,2S)-N1,N2-dimethylcyclohexane-1,2-diamine (0.004 g, 0.0277 mmol), Cs_2CO_3 (0.045 g, 0.139 mmol) and CuI (0.003 g, 0.0139 mmol) and dioxane (1.0 mL) was degassed and heated overnight at 140 °C. The reaction was cooled to RT, and acidified with TFA to pH4~5. The solvent was removed in vacuo to obtain the crude which as purified by preparative-HPLC to obtain the title compound as a TFA salt. ESI-MS (m/z): 458, $[M+1]^+$.

Example 121

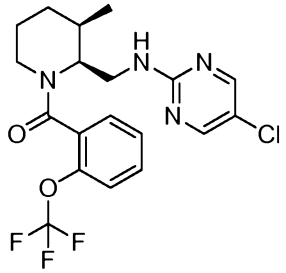
rac-((2S,3R)-2-(((3-chloropyrazin-2-yl)amino)methyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



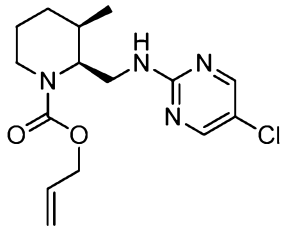
The title compound was prepared following the same general protocol as described for Example 18 using 2,3-dichloropyrazine. MS (ESI) 460.2 (M+H)

Example 122

rac-((2S,3R)-2-(((5-chloropyrimidin-2-yl)amino)methyl)-3-methylpiperidin-1-yl)(2-(trifluoromethoxy)phenyl)methanone

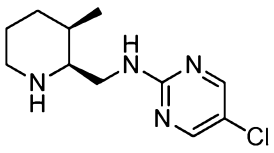


rac-(2S,3R)-allyl 2-(((5-chloropyrimidin-2-yl)amino)methyl)-3-methylpiperidine-1-carboxylate



The title compound was prepared following the same general protocol as described for Example 16 using 2,5-dichloropyrimidine and *rac*-(2S,3R)-allyl 2-(aminomethyl)-3-methylpiperidine-1-carboxylate. MS (ESI) 325.2 (M+H)

rac-5-chloro-N-(((2S,3R)-3-methylpiperidin-2-yl)methyl)pyrimidin-2-amine



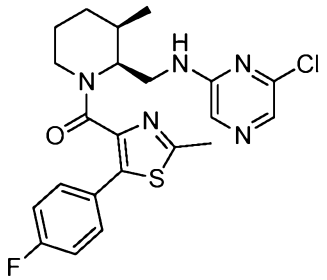
The title compound was prepared following the same general protocol as described for Example 114 using *rac*-(2S,3R)-allyl 2-(((5-chloropyrimidin-2-yl)amino)methyl)-3-methylpiperidine-1-carboxylate from the previous step. (ESI) 241.4 (M+H)

rac-((2S,3R)-2-(((5-chloropyrimidin-2-yl)amino)methyl)-3-methylpiperidin-1-yl)(2-(trifluoromethoxy)phenyl)methanone

To a solution of the forementioned *rac*-5-chloro-N-(((2S,3R)-3-methylpiperidin-2-yl)methyl)pyrimidin-2-amine and diisopropylamine (3eq) in DCM was added 2-(trifluoromethoxy)benzoyl chloride (1.2eq) dropwise. The reaction was stirred at reflux for 3h and concentrated *in vacuo*. The crude reaction mixture was purified by reverse-phase preparative HPLC to afford the title compound. (ESI) 429.1 (M+H)

Example 123

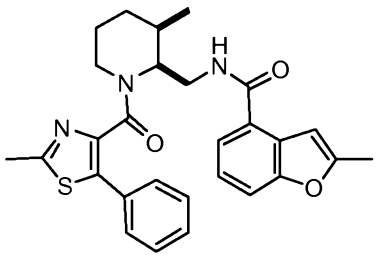
rac-((2S,3R)-2-(((6-chloropyrazin-2-yl)amino)methyl)-3-methylpiperidin-1-yl)(5-(4-fluorophenyl)-2-methylthiazol-4-yl)methanone



The title compound was prepared following the same general protocol as described for Example 18 using 2,6-dichloropyrazine. MS (ESI) 460.2 (M+H)

Example 124

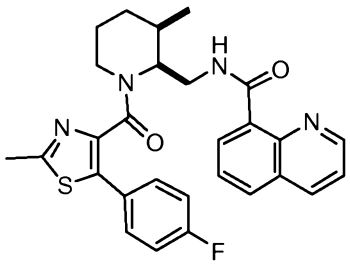
2-methyl-N-(((2S,3R)-3-methyl-1-(2-methyl-5-phenylthiazole-4-carbonyl)piperidin-2-yl)methyl)benzofuran-4-carboxamide



The title compound was obtained following the general protocol as described for the synthesis of Example 8 using 2-methylbenzofuran-4-carboxylic acid. MS (ESI) 488.1 (M+H).

Example 125

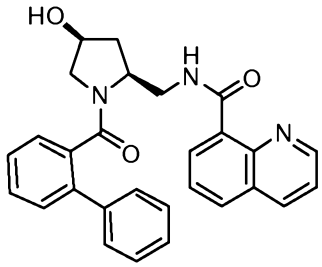
N-(((2S,3R)-1-(5-(4-fluorophenyl)-2-methylthiazole-4-carbonyl)-3-methylpiperidin-2-yl)methyl)quinoline-8-carboxamide



The title compound was obtained following the general protocol as described for the synthesis of Example 8 using 5-(4-fluorophenyl)-2-methylthiazole-4-carboxylic acid. MS (ESI) 503.1 (M+H).

Example 126

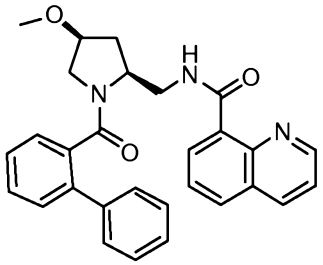
N-(((2S,4S)-1-([1,1'-biphenyl]-2-carbonyl)-4-hydroxypyrrolidin-2-yl)methyl)quinoline-8-carboxamide



The title compound was synthesized following the same standard protocol as described in Examples 4 starting with (2*S*,4*S*)-*tert*-butyl 4-hydroxy-2-(hydroxymethyl)pyrrolidine-1-carboxylate. MS (ESI) 452.2 (M+H).

Example 127

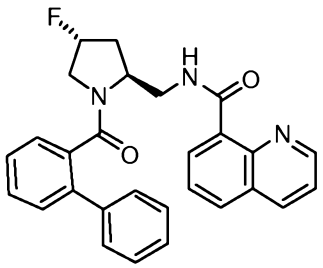
N-(((2S,4S)-1-([1,1'-biphenyl]-2-carbonyl)-4-methoxypyrrolidin-2-yl)methyl)quinoline-8-carboxamide



To a vigorously stirred suspension of the product from the previous example in CH_2Cl_2 and 45% HBF_4(aq) at 0° C was added in three portions 0.1mL 2M TMS-CH_2N_2 hexane solution dropwise over 10 minutes. The reaction was allowed to stir at room temperature overnight. The crude mixture was loaded directly onto a reverse-phase prep-HPLC and two peaks were collected, the first being the desired product, the second being recovered starting material. MS (ESI) 466.2 (M+H).

Example 128

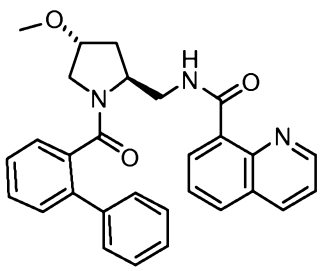
N-(((2*S*,4*R*)-1-(Biphenylcarbonyl)-4-fluoropyrrolidin-2-yl)methyl)quinoline-8-carboxamide



The title compound was synthesized following the same standard protocol as described in Examples 5 starting with *N-(((2S,4S)*-1-([1,1'-biphenyl]-2-carbonyl)-4-hydroxypyrrolidin-2-yl)methyl)quinoline-8-carboxamide. MS (ESI) 454.1 (M+H).

Example 129

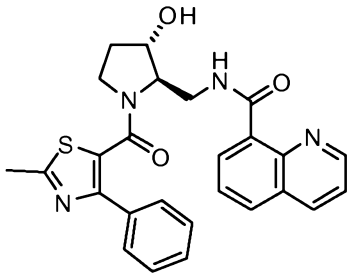
N-(((2S,4R)- 1-([1,1'-biphenyl]-2-carbonyl)-4-methoxypyrrolidin-2-yl)methyl)quinoline-8-carboxamide



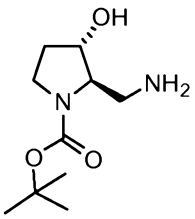
The title compound was made following the same general protocol as described for Example 127 using the product from Example 4. MS (ESI) 466.2 (M+H).

Example 130

N-(((2R,3S)-3-hydroxy-1-(2-methyl-4-phenylthiazole-5-carbonyl)pyrrolidin-2-yl)methyl)quinoline-8-carboxamide



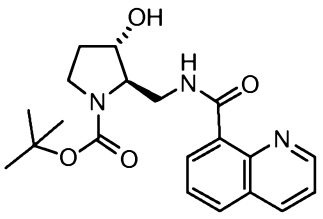
(2R,3S)-tert-butyl 2-(aminomethyl)-3-hydroxypyrrolidine-1-carboxylate



To a solution of (2S,3S)-1-(tert-butoxycarbonyl)-3-hydroxypyrrolidine-2-carboxylic acid in THF at 0° C was added BH_3-DMS. The reaction was allowed to warm to room temperature overnight, and then quenched by the careful addition of MeOH. The reaction was concentrated in vacuo to give (2R,3S)-tert-butyl 3-hydroxy-2-(hydroxymethyl)pyrrolidine-1-carboxylate as a near colorless oil which was used without further purification.

(2R,3S)-tert-butyl 3-hydroxy-2-(hydroxymethyl)pyrrolidine-1-carboxylate was converted to the title compound following the same general protocol for Mitsunobu reaction with phthalimide followed by hydrazine cleavage as described for Example 32 Part V and Part VI.

(2R,3S)-tert-butyl 3-hydroxy-2-((quinoline-8-carboxamido)methyl)pyrrolidine-1-carboxylate



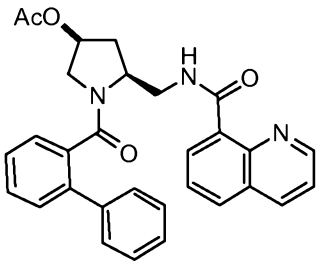
The title compound was prepared according general procedure **A** using quinoline-8-carboxylic acid and the product from the previous step. MS (ESI) 371.93 (M+H).

N-(((2R,3S)-3-hydroxy-1-(2-methyl-4-phenylthiazole-5-carbonyl)pyrrolidin-2-yl)methyl)quinoline-8-carboxamide

To a solution of the product from the previous step in CH_2Cl_2 was added TFA. The reaction was aged at room temperature for 1h, and then concentrated in vacuo to give the crude amine as a TFA salt. This crude amine was coupled with 2-methyl-4-phenylthiazole-5-carboxylic acid according to general procedure **A** to give the title compound as a pale yellow solid. MS (ESI) 473.1 (M+H).

Example 131

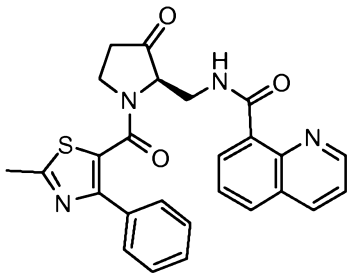
(3S,5S)-1-([1,1'-biphenyl]-2-carbonyl)-5-((quinoline-8-carboxamido)methyl)pyrrolidin-3-yl acetate



To a 0° C solution of the product from Example 4 in THF was added Ph_3P, acetic acid, followed by diisopropylazodicarboxylate (DIAD). The reaction was allowed to warm to room temperature overnight. After 18h, the reaction mixture was directly loaded onto a reverse-phase preparative HPLC, and the desired product was isolated as a colorless solid. MS (ESI) 494.1 (M+H).

Example 132

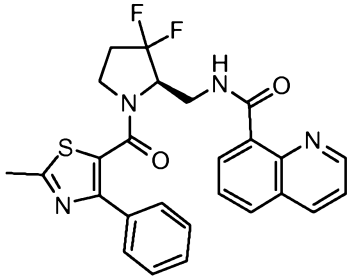
(R)-N-((1-(2-methyl-4-phenylthiazole-5-carbonyl)-3-oxopyrrolidin-2-yl)methyl)quinoline-8-carboxamide



To a -78° C solution of $(COCl)_2$ in CH_2Cl_2 was added a solution of DMSO in CH_2Cl_2. After 20min, a solution of the product from Example 130 in CH_2Cl_2 was added dropwise. The reaction was aged at -78° C for 3h, and then allowed to warm to room temperature over 1h. The reaction mixture was concentrated *in vacuo* to give a beige solid which was purified by chromatography on silica gel to give the title compound as a colorless solid. MS (ESI) 471.1 (M+H).

Example 133

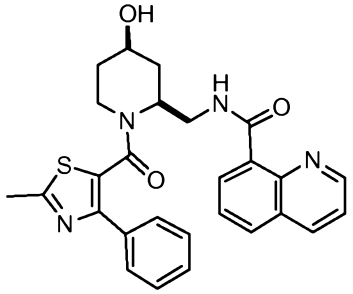
(R)-N-((3,3-difluoro-1-(2-methyl-4-phenylthiazole-5-carbonyl)pyrrolidin-2-yl)methyl)quinoline-8-carboxamide



The title compound was prepared following the same general protocol as described for Example 7. MS (ESI) 493.1 (M+H).

Example 134

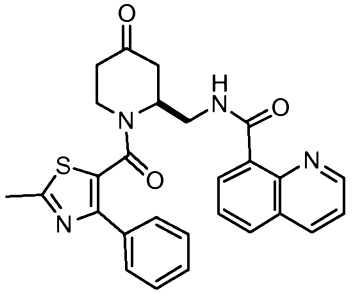
N-(((2S,4R)-4-hydroxy-1-(2-methyl-4-phenylthiazole-5-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide



The title compound was prepared following the same standard protocols as described for Example 130 starting with (2S,4R)-1-(tert-butoxycarbonyl)-4-hydroxypiperidine-2-carboxylic acid. MS (ESI) 487.1 (M+H).

Example 135

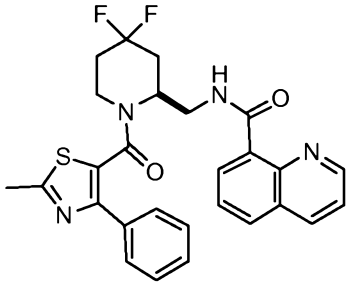
(S)-N-((1-(2-methyl-4-phenylthiazole-5-carbonyl)-4-oxopiperidin-2-yl)methyl)quinoline-8-carboxamide



The title compound was prepared following the same standard protocol as described for Example 132 starting with the product from Example 134. MS (ESI) 485.1 (M+H).

Example 136

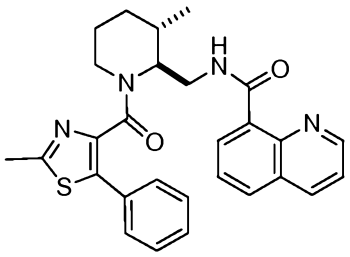
(S)-N-((4,4-difluoro-1-(2-methyl-4-phenylthiazole-5-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide



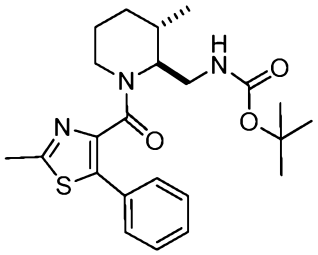
The title compound was prepared following the same standard protocol as described for Example 133 starting with the product from Example 135. MS (ESI) 507.1 (M+H).

Example 137

N-(((2S,3S)-3-methyl-1-(2-methyl-5-phenylthiazole-4-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide



tert-butyl (((2S,3S)-3-methyl-1-(2-methyl-5-phenylthiazole-4-carbonyl)piperidin-2-yl)methyl)carbamate



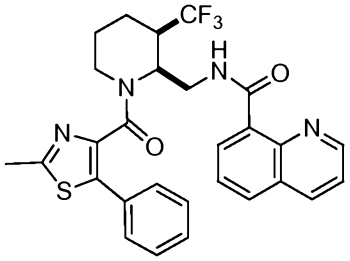
The title compound was made following General Procedure A using tert-butyl (((2S,3S)-3-methylpiperidin-2-yl)methyl)carbamate from Example 95 and 2-methyl-5-phenylthiazole-4-carboxylic acid. MS (ESI) 429.83 (M+H).

N-(((2S,3S)-3-methyl-1-(2-methyl-5-phenylthiazole-4-carbonyl)piperidin-2-yl)methyl)quinoline-8-carboxamide

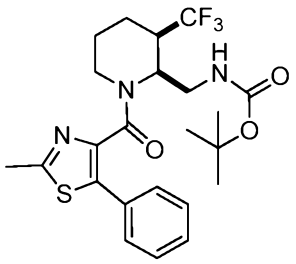
The title compound was made following BOC-deprotection of the compound from the previous step using TFA/CH_2Cl_2, followed by coupling to quinoline-8-carboxylic acid using the standard protocol as describe in General Procedure A. The product was isolated as a beige solid. MS (ESI) 485.1 (M+H).

Example 138

N-(((2S,3R)-1-(2-methyl-5-phenylthiazole-4-carbonyl)-3-(trifluoromethyl)piperidin-2-yl)methyl)quinoline-8-carboxamide



tert-butyl (((2S,3R)-1-(2-methyl-5-phenylthiazole-4-carbonyl)-3-(trifluoromethyl)piperidin-2-yl)methyl)carbamate



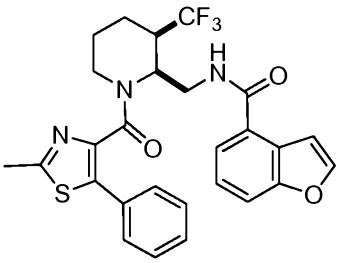
The title compound was made following General Procedure A using tert-butyl (((2S,3R)-3-(trifluoromethyl)piperidin-2-yl)methyl)carbamate from Example 13 and 2-methyl-5-phenylthiazole-4-carboxylic acid. MS (ESI) 483.8 (M+H).

N-(((2S,3R)-1-(2-methyl-5-phenylthiazole-4-carbonyl)-3-(trifluoromethyl)piperidin-2-yl)methyl)quinoline-8-carboxamide

The title compound was made following BOC-deprotection of the compound from the previous step using TFA/CH_2Cl_2, followed by coupling to quinoline-8-carboxylic acid using the standard protocol as describe in General Procedure A. The product was isolated as a near colorless solid. MS (ESI) 539.14 (M+H).

Example 139

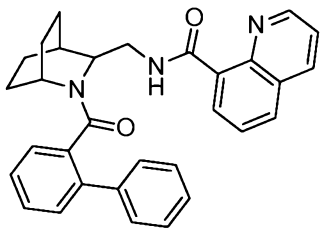
N-(((2S,3R)-1-(2-methyl-5-phenylthiazole-4-carbonyl)-3-(trifluoromethyl)piperidin-2-yl)methyl)benzofuran-4-carboxamide



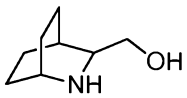
The title compound was made following the same general protocol as described for Example 138 using benzofuran-4-carboxylic acid. MS (ESI) 528.1 (M+H).

Example 140

N-(((1s,4s)-2-([1,1'-biphenyl]-2-carbonyl)-2-azabicyclo[2.2.2]octan-3-yl)methyl)quinoline-8-carboxamide

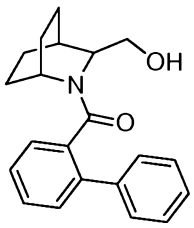


(1s,4s)-2-azabicyclo[2.2.2]octan-3-ylmethanol



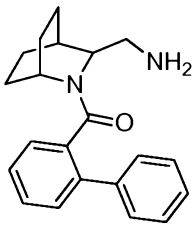
The title compound was prepared following General Procedure O starting with commercially available (1s,4s)-ethyl 2-azabicyclo[2.2.2]octane-3-carboxylate. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.7-3.6 (m, 1H), 3.6-3.48 (m, 2H), 3.2 (t, 1H), 2.6-2.35 (m, 2H), 1.8-1.4 (m, 5H), 1.3-1.1 (m, 2H), 1.1-0.9 (m, 1H).

[1,1'-biphenyl]-2-yl((1s,4s)-3-(hydroxymethyl)-2-azabicyclo[2.2.2]octan-2-yl)methanone



The title compound was prepared following General Procedure A starting with the product from the previous step and [1,1'-biphenyl]-2-carboxylic acid.

[1,1'-biphenyl]-2-yl((1s,4s)-3-(aminomethyl)-2-azabicyclo[2.2.2]octan-2-yl)methanone



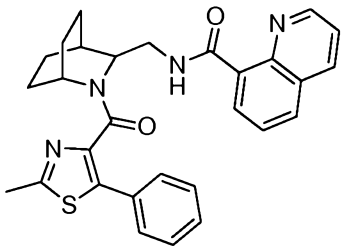
The title compound was prepared following General Procedure C starting with the product from the previous step. MS (ESI) 321.1 (M+H).

N-(((1s,4s)-2-([1,1'-biphenyl]-2-carbonyl)-2-azabicyclo[2.2.2]octan-3-yl)methyl)quinoline-8-carboxamide

The title compound was prepared following General Procedure A starting with the product from the previous step and quinoline-8-carboxylic acid. MS (ESI) 476.2 (M+H).

Example 141

N-(((1s,4s)-2-(2-methyl-5-phenylthiazole-4-carbonyl)-2-azabicyclo[2.2.2]octan-3-yl)methyl)quinoline-8-carboxamide



The title compound was prepared following same general protocol as described for Example 140, but using 2-methyl-5-phenylthiazole-4-carboxylic acid. MS (ESI) 497.2 (M+H).

Orexin Receptor Cell-based Functional Assay.

Measurement of $[Ca^{2+}]i$ using a FLIPR: CHO-OX_1 or CHO-OX_2 cells are seeded into black-walled clear-base 384-well plates (Costar) at a density of 20,000 cells per well in F12-K medium supplemented with 10% FBS and selection antibiotic (500ug/ml G418 or 15ug/ml Blasticidin) and cultured overnight. The cells are incubated with equal volume of calcium4 loading buffer (Molecular Devices, Inc.) containing 2.5 mM probenecid at 37°C for 30 min, followed by putative OX_1 or OX_2 receptor antagonists (dose-range 0.1 nM – 10 μM) for another 30 min. The plates are then placed into a FLIPR (Molecular Devices, Inc.) to monitor fluorescence (l excitation 488 nm, l emission 540 nm) before and after the addition of EC_{90} of [OXA].

Table 2: IC_{50} Bioactivity of Exemplary Compounds of the Invention with Respect to OX_1 and OX_2

Compound	OX_1 (μM)	OX_2 (μM)
1	0.001	0.008
2	0.001	0.007
3	0.002	0.036
4	0.088	1.0
5	0.006	0.040
6	0.030	0.70
7	0.15	0.075
8	0.003	0.060
9	0.015	0.085
10	<3.0	NT

11	0.008	4.9
12	0.004	0.45
13	0.009	0.22
14	0.009	0.46
15	0.001	>5.0
16	0.008	>10.0
17	0.052	1.8
18	0.016	1.5
19	0.27	>10
20	1.3	>10
21	0.024	0.52
22	0.082	>10
23	0.06	1.4
24	0.004	0.34
25	0.008	0.13
26	0.018	0.091
27	<0.10	NT
28	<0.01	NT
29	0.20	NT
30	0.22	NT
31	0.010	NT
32	0.002	0.014
33	0.020	NT
34	0.005	0.005
35	0.002	0.004
36	0.002	0.002
37	0.001	0.003
38	0.004	NT
39	0.030	0.16
40	0.60	1.5
41	1.5	NT
42	0.027	0.14

43	2.0	NT
44	NT	1.0
45	<10	NT
46	<10	NT
47	<10	NT
48	<10	NT
49	0.025	0.6
50	0.007	0.025
51	0.010	0.075
52	0.001	0.010
53	0.065	0.75
54	0.18	1.2
55	0.12	2.0
56	<0.10	NT
57	<0.10	NT
58	0.001	0.008
59	0.040	1.2
60	0.001	0.37
61	0.007	0.38
62	0.001	0.008
63	0.002	0.048
64	3.0	NT
65	>2.0	NT
66	0.35	NT
67	1.0	NT
68	0.12	NT
69	0.13	NT
70	0.17	NT
71	0.04	NT
72	0.006	>4.0
73	<0.010	>3.0
74	0.058	>5.0

75	0.003	3.3
76	0.30	>4.0
77	0.070	>10
78	0.002	>10
79	0.001	>10
80	0.14	>10
81	<0.010	>10
82	0.004	>10
83	0.030	>10
84	0.035	>10
85	0.100	>10
86	0.022	>10
87	0.22	0.070
88	0.042	>10
89	NT	NT
90	NT	NT
91	0.14	>10
92	0.56	>4.0
93	0.100	>1.0
94	0.076	1.0
95	0.029	0.253
96	0.018	1.4
97	0.009	>10
98	0.006	>10
99	0.082	5.0
100	0.008	>10
101	3.0	>10
102	>1.0	NT
103	0.004	6.0
104	0.001	8.8
105	0.109	1.6
106	0.040	>1.0

107	0.078	>10
108	0.013	>10
109	>1.0	NT
110	>1.0	NT
111	>1.0	NT
112	0.017	>10
113	0.025	0.190
114	0.003	>10
115	0.010	>10
116	<0.10	NT
117	0.038	>10
118	0.262	>10
119	0.400	>10
120	0.003	0.50
121	>1.0	NT
122	3.5	5
123	3.6	3.2
124	0.015	0.237
125	0.010	0.095
126	0.006	0.008
127	0.008	0.025
128	0.035	0.030
129	0.12	0.32
130	0.006	NT
131	0.053	0.040
132	0.23	1.4
133	0.012	1.4
134	0.005	>10
135	NT	NT
136	<1.0	NT
137	0.003	0.10
138	0.008	0.040

139	0.003	0.017
140	<0.1	NT

141	0.002	NT

NT=not tested

Compounds of the invention are found to have bioactivity as modulators, e.g, as antagonists of both OX_1 and OX_2. Certain compounds, e.g., compound 49, are seen to be selective inhibitors of the OX_1 receptor (~25-fold selectivity).

While the invention has been described and exemplified in sufficient detail for those skilled in this art to make and use it, various alternatives, modifications, and improvements will be apparent to those skilled in the art without departing from the spirit and scope of the claims.

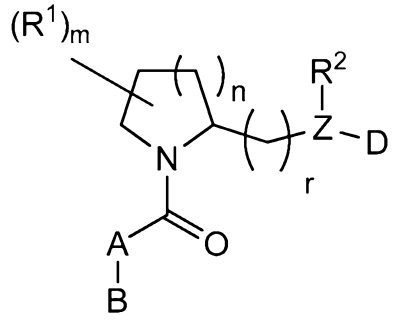
All patents and publications referred to herein are incorporated by reference herein to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference in its entirety.

The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims.

CLAIMS

What is claimed is:

1. A compound of formula (I),



(I)

wherein

A comprises aryl or heteroaryl;

B is absent, or comprises aryl, aryloxy, heteroaryl, or heteroaryloxy;

wherein A or B or both can each independently be unsubstituted or can each independently be mono- or multi-substituted with J or with R', or both;

D comprises aryl, aroyl, heteroaryl, or heteroaroyl, wherein D can be unsubstituted or can be mono- or independently multi-substituted with J or with R', or both;

Z is N or O, provided that when Z is O, R^2 is absent

R^1 comprises independently at each occurrence halo, oxo, hydroxy, cyano, (C_{1-4})alkyl, (C_{1-4})alkoxy, (C_{1-4})acyloxy, (C_{1-4})acylamido, haloalkyl, haloalkoxy, NR^aR^b, $C(=O)NR^aR^b$, $C(=O)OR^a$, SO_2R^a, $SO_2NR^aR^b$, cycloalkyl, heterocyclyl, aryl, aralkyl, or heteroaryl;

or one or more R^1 groups together with the ring to which they are bonded form a bicyclo[2.2.2], bicyclo[3.3.0], or bicyclo[4.3.0] ring system, wherein any bicyclo ring system can be *cis*-fused or *trans*-fused, wherein any alkyl, alkoxy, bicyclo ring system, cycloalkyl, heterocyclyl, aryl, aralkyl, or heteroaryl can be mono- or independently multi-substituted with J or with R', or both;

R^a and R^b are independently at each occurrence H, (C_{1-4})alkyl, aralkyl, (C_{1-5})acyl, or R^a and R^b together with the nitrogen atom to which they are bonded form a 4-7 membered ring optionally further comprising 1 or 2 NR^c, O, S, SO, or SO_2, wherein R^c is H or (C_{1-4})alkyl, wherein any R^a, R^b, or R^c can be mono- or independently multi-substituted with J or with R', or both;

R^2 comprises H, (C_{1-4})alkyl, or (C_{1-5})acyl, or R^2 together with D and the nitrogen atom to which they are bonded form a phthalimido group, wherein any alkyl, acyl, or phthalimido group is optionally mono- or independently multi-substituted with J or with R', or both;

J is halogen, (C1-C6)alkyl, OR', CN, CF_3, OCF_3, =O, =S, C(O), S(O), methylenedioxy, ethylenedioxy, $(CH_2)_{0-p}N(R')_2$, $(CH_2)_{0-p}SR'$, $(CH_2)_{0-p}S(O)R'$, $(CH_2)_{0-p}S(O)_2R'$, $(CH_2)_{0-p}S(O)_2N(R')_2$, $(CH_2)_{0-p}SO_3R'$, $(CH_2)_{0-p}C(O)R'$, $(CH_2)_{0-p}C(O)C(O)R'$, $(CH_2)_{0-p}C(O)CH_2C(O)R'$, $(CH_2)_{0-p}C(S)R'$, $(CH_2)_{0-p}C(O)OR'$, $(CH_2)_{0-p}OC(O)R'$, $(CH_2)_{0-p}C(O)N(R')_2$, $(CH_2)_{0-p}OC(O)N(R')_2$, $(CH_2)_{0-p}C(S)N(R')_2$, $(CH_2)_{0-p}NH\text{-}C(O)R'$, $(CH_2)_{0-p}N(R')N(R')C(O)R'$, $(CH_2)_{0-p}N(R')N(R')C(O)OR'$, $(CH_2)_{0-p}N(R')N(R')CON(R')_2$, $(CH_2)_{0-p}N(R')SO_2R'$, $(CH_2)_{0-p}N(R')SO_2N(R')_2$, $(CH_2)_{0-p}N(R')C(O)OR'$, $(CH_2)_{0-p}N(R')C(O)R'$, $(CH_2)_{0-p}N(R')C(S)R'$, $(CH_2)_{0-p}N(R')C(O)N(R')_2$, $(CH_2)_{0-p}N(R')C(S)N(R')_2$, $(CH_2)_{0-p}N(COR')COR'$, $(CH_2)_{0-p}N(OR')R'$, $(CH_2)_{0-p}C(=NH)N(R')_2$, $(CH_2)_{0-p}C(O)N(OR')R'$, or $(CH_2)_{0-p}C(=NOR')R'$;

wherein, each R' is independently at each occurrence hydrogen, $(C_1\text{-}C_{12})$-alkyl, $(C_2\text{-}C_{12})$-alkenyl, $(C_2\text{-}C_{12})$-alkynyl, $(C_3\text{-}C_{10})$-cycloalkyl, $(C_3\text{-}C_{10})$-cycloalkenyl, [$(C_3\text{-}C_{10})$cycloalkyl or $(C_3\text{-}C_{10})$-cycloalkenyl]-[$(C_1\text{-}C_{12})$-alkyl or $(C_2\text{-}C_{12})$-alkenyl or $(C_2\text{-}C_{12})$-alkynyl], $(C_6\text{-}C_{10})$-aryl, $(C_6\text{-}C_{10})$-aryl-[$(C_1\text{-}C_{12})$-alkyl or $(C_2\text{-}C_{12})$-alkenyl or $(C_2\text{-}C_{12})$-alkynyl], mono- or bicyclic 3-10 membered heterocyclyl, mono- or bicyclic 3-10 membered heterocyclyl-[$(C_1\text{-}C_{12})$-alkyl or $(C_2\text{-}C_{12})$-alkenyl or $(C_2\text{-}C_{12})$-alkynyl], mono- or bicyclic 5-10 membered heteroaryl, or mono- or bicyclic 5-10 membered heteroaryl-[$(C_1\text{-}C_{12})$-alkyl or $(C_2\text{-}C_{12})$-alkenyl or $(C_2\text{-}C_{12})$-alkynyl], wherein R' is substituted with 0-3 substituents selected independently from J^R;

or, when two R' are bound to a nitrogen atom or to two adjacent nitrogen atoms, the two R' groups together with the nitrogen atom or atoms to which they are bound can form a 3- to 8-membered monocyclic heterocyclic ring, or an 8- to 20-membered, bicyclic or tricyclic, heterocyclic ring system, wherein any ring or ring system can further contain 1-3 additional heteroatoms selected from the group consisting of N, NR', O, S, S(O) and $S(O)_2$, wherein each ring is substituted with 0-3 substituents selected independently from J^R;

wherein, in any bicyclic or tricyclic ring system, each ring is linearly fused, bridged, or spirocyclic, wherein each ring is either aromatic or nonaromatic, wherein each ring can be fused to a $(C_6\text{-}C_{10})$aryl, mono- or bicyclic 5-10 membered heteroaryl, $(C_3\text{-}C_{10})$cycloalkyl or mono- or bicyclic 3-10 membered heterocyclyl;

J^R is halogen, OR, CN, CF_3, OCF_3, =O, =S, C(O), S(O), methylenedioxy, ethylenedioxy, $(CH_2)_{0-p}N(R)_2$, $(CH_2)_{0-p}SR$, $(CH_2)_{0-p}S(O)R$, $(CH_2)_{0-p}S(O)_2R$, $(CH_2)_{0-p}S(O)_2N(R)_2$, $(CH_2)_{0-p}SO_3R$, $(CH_2)_{0-p}C(O)R$, $(CH_2)_{0-p}C(O)C(O)R$, $(CH_2)_{0-p}C(O)CH_2C(O)R$,

$(CH_2)_{0-p}C(S)R$, $(CH_2)_{0-p}C(O)OR$, $(CH_2)_{0-p}OC(O)R$, $(CH_2)_{0-p}C(O)N(R)_2$, $(CH_2)_{0-p}OC(O)N(R)_2$, $(CH_2)_{0-p}C(S)N(R)_2$, $(CH_2)_{0-p}NH\text{-}C(O)R$, $(CH_2)_{0-p}N(R)N(R)C(O)R$, $(CH_2)_{0-p}N(R)N(R)C(O)OR$, $(CH_2)_{0-p}N(R)N(R)CON(R)_2$, $(CH_2)_{0-p}N(R)SO_2R$, $(CH_2)_{0-p}N(R)SO_2N(R)_2$, $(CH_2)_{0-p}N(R)C(O)OR$, $(CH_2)_{0-p}N(R)C(O)R$, $(CH_2)_{0-p}N(R)C(S)R$, $(CH_2)_{0-p}N(R)C(O)N(R)_2$, $(CH_2)_{0-p}N(R)C(S)N(R)_2$, $(CH_2)_{0-p}N(COR)COR$, $(CH_2)_{0-p}N(OR)R$, $(CH_2)_{0-p}C(=NH)N(R)_2$, $(CH_2)_{0-p}C(O)N(OR)R$, or $(CH_2)_{0-p}C(=NOR)R$; and,

R is independently at each occurrence hydrogen, $(C_1\text{-}C_{12})$-alkyl, $(C_2\text{-}C_{12})$-alkenyl, $(C_2\text{-}C_{12})$-alkynyl, $(C_3\text{-}C_{10})$-cycloalkyl, $(C_3\text{-}C_{10})$-cycloalkenyl, [$(C_3\text{-}C_{10})$cycloalkyl or $(C_3\text{-}C_{10})$-cycloalkenyl]-[$(C_1\text{-}C_{12})$-alkyl or $(C_2\text{-}C_{12})$-alkenyl or $(C_2\text{-}C_{12})$-alkynyl], $(C_6\text{-}C_{10})$-aryl, $(C_6\text{-}C_{10})$-aryl-[$(C_1\text{-}C_{12})$-alkyl or $(C_2\text{-}C_{12})$-alkenyl or $(C_2\text{-}C_{12})$-alkynyl], mono- or bicyclic 3-10 membered heterocyclyl, mono- or bicyclic 3-10 membered heterocyclyl-[$(C_1\text{-}C_{12})$-alkyl or $(C_2\text{-}C_{12})$-alkenyl or $(C_2\text{-}C_{12})$-alkynyl], mono- or bicyclic 5-10 membered heteroaryl, or mono- or bicyclic 5-10 membered heteroaryl-[$(C_1\text{-}C_{12})$-alkyl or $(C_2\text{-}C_{12})$-alkenyl or $(C_2\text{-}C_{12})$-alkynyl];

m is 0, 1, 2, 3, 4, 5, or 6; n is 1, 2, or 3; p = 0, 1, or 2; r = 0, 1, 2, or 3;

or any salt or hydrate thereof.

2. The compound of claim 1 wherein A comprises phenyl, thiazolyl, pyrazolyl, pyridyl, or quinolyl, wherein A can each independently be unsubstituted or can each independently be mono- or multi-substituted with J or with R', or both; or any salt or hydrate thereof.

3. The compound of claim 1 wherein B comprises phenyl, pyridyl, pyrazidinyl, pyrimidinyl, pyrazinyl, pyrolyl, pyrazolyl, oxazolyl, imidazolyl, oxadiazolyl, {1,2,3)-triazolyl, (1,2,4)-triazolyl, wherein B can each independently be unsubstituted or can each independently be mono- or multi-substituted with J or with R', or both; or any salt or hydrate thereof.

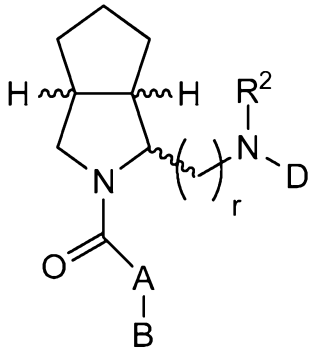
4. The compound of claim 1 wherein D comprises pyridyl, pyridoyl, pyridazinyl, pyridazinoyl, pyrimidinyl, pyrimidinoyl, pyrazinyl, pyrazinoyl, quinolyl, quinoloyl, benzofuranyl, benzofuranoyl, benzoxazolyl, benzoxazoloyl, benzthiazolyl, or benzthiazoloyl; or wherein D combined with R^2 and the nitrogen atom to which they are bonded comprises phthalimidoyl, wherein D can be unsubstituted or can be mono- or independently multi-substituted with J or with R', or both; or any salt or hydrate thereof.

5. The compound of claim 1, wherein Z is N.

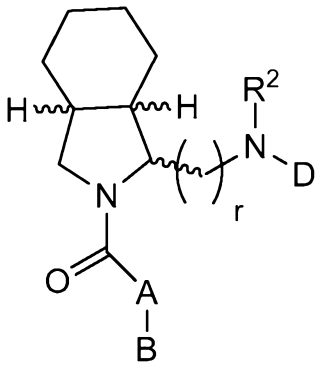
6. The compound of claim 5, wherein R^2 comprises H, (C_{1-4})alkyl, or (C_{1-5})acyl.

7. The compound of claim 1, wherein Z is O and R^2 is absent.

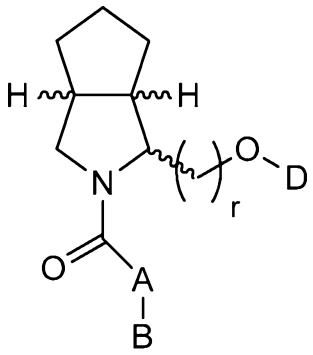
8. The compound of claim 1 comprising a bicyclic compound of any of formulas (IIA), (IIB), (IIC), or (IID)



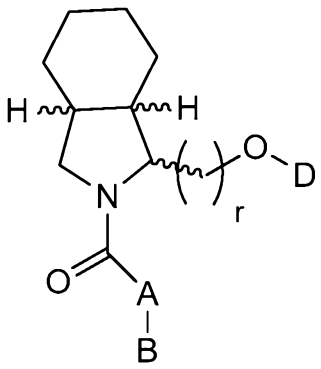
(IIA)



(IIB)



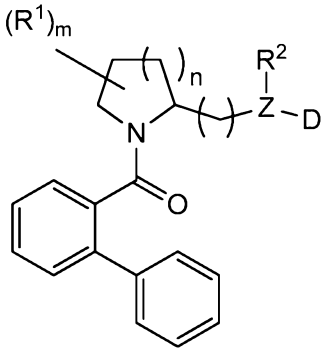
(IIC)



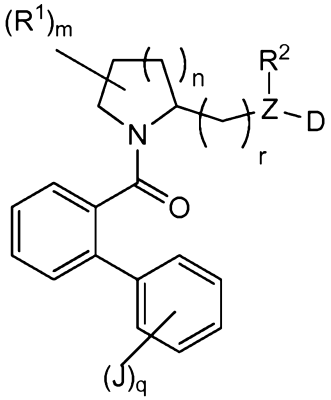
(IID);

or any salt or hydrate thereof.

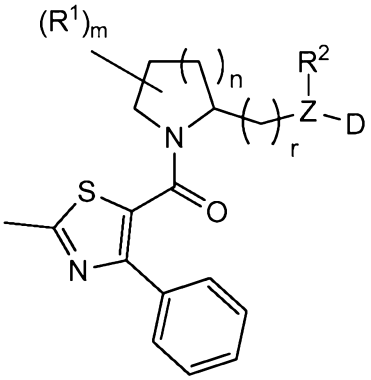
9. The compound of formula (I) comprising any of formulas (IIIA), (IIIB), (IIIC), (IIID), (IIIE), or (IIIF):



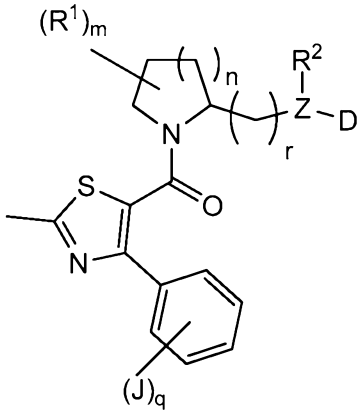
(IIIA)



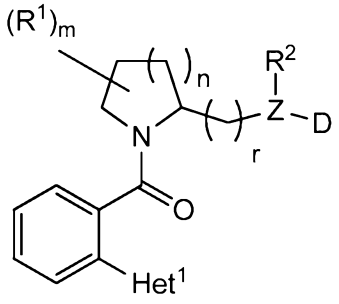
(IIIB)



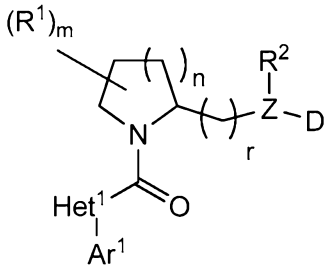
(IIIC)



(IIID)



(IIIE)



(IIIF);

wherein Z, D, R^1, m, and R^2 are as defined for Formula (I);

n is 1 or 2, q = 1, 2, or 3, r = 1 or 2;

Het^1 is an unsubstituted or J-substituted pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, trizolyl, pyrimidinyl, or pyridyl;

Ar^1 is an unsubstituted or J-substituted phenyl;

wherein J-substituted indicates the presence of 1-3 J substituents; and each J is independently selected from the set consisting of F, Cl, and methoxy;

or any salt or hydrate thereof.

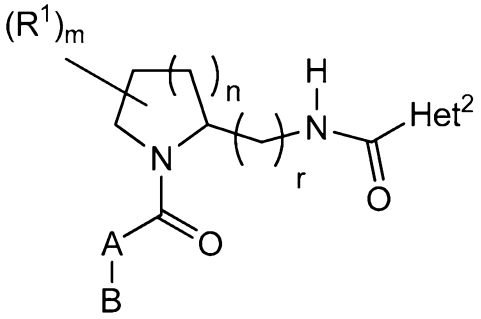
10. The compound of claim 9 wherein n =1 or 2, m = 1 or 2, and R^1 is F, oxo, methyl, trifluoromethyl, hydroxy, acetoxy, methoxy, NH_2, N-methylamino, N-ethylamino, N,N-dimethylamino, N-isopropylamino, N-benzylamino, hydoxyethylamino, or acetamido,

or any salt or hydrate thereof.

11. The compound of claim 9 wherein D comprises pyridyl, pyridoyl, quinolyl, quinoloyl, or benzofuranyl, or wherein D combined with R^2 and the nitrogen atom to which they are bonded comprises phthalimidoyl;

or any salt or hydrate thereof.

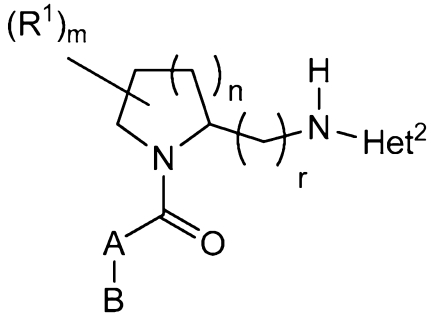
12. The compound of formula (I) comprising a compound of formula (IVA)



(IVA)

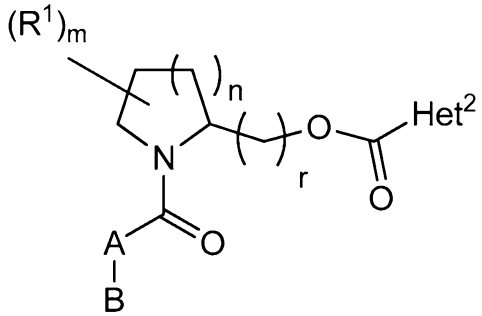
wherein m = 1 or 2, n = 1 or 2; r = 1 or 2;

or a compound of formula (IVB)

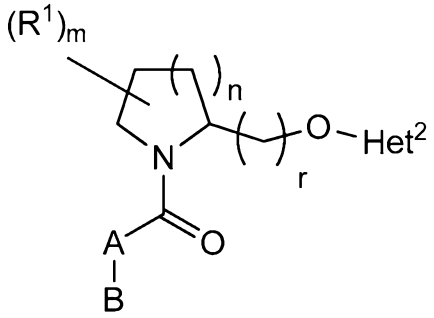


(IVB)

or a compound of formula (IVC)



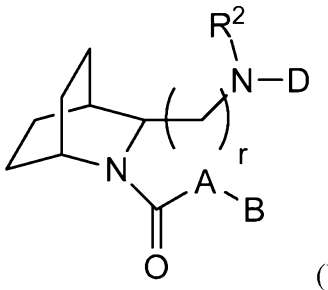
or a compound of formula (IVD)



wherein A, B, R^1, and m are as defined herein, and r = 1 or 2; and Het^2 is an unsubstituted or J-substituted quinolyl, pyridyl, pyrimidyl, benzoxazolyl, benzimidazolyl, or benzthiazolyl; wherein J-substituted indicates the presence of 1-3 J substituents;

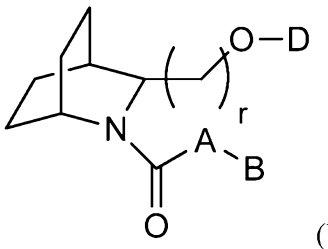
or any salt or hydrate thereof.

13. The compound of claim 1, of formula (VA)



(VA)

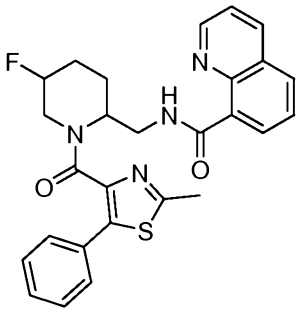
or of formula (VB)

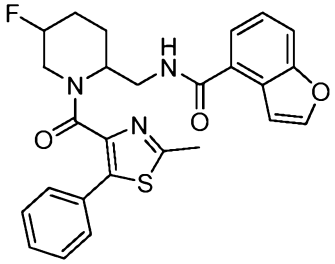


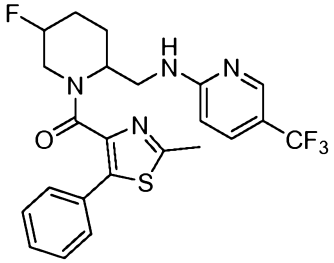
(VB),

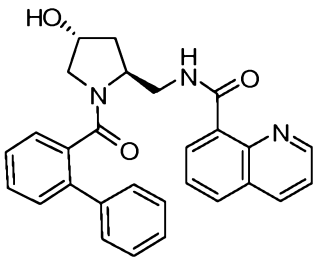
or any salt or hydrate thereof.

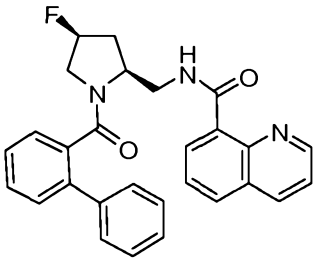
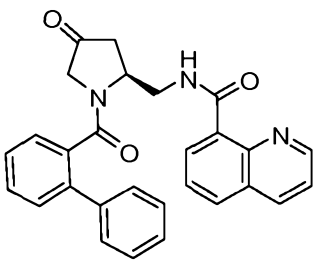
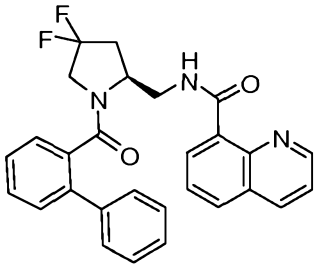
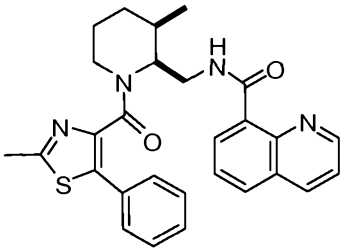
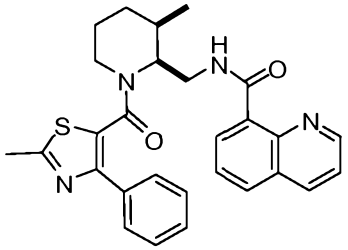
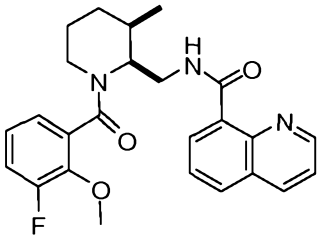
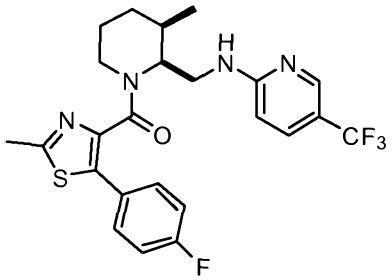
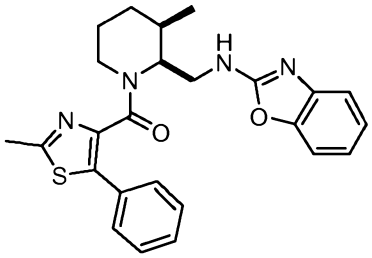
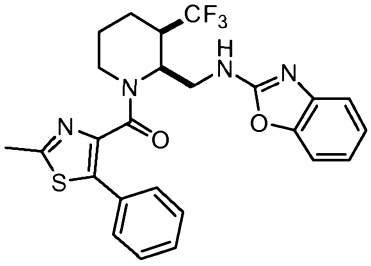
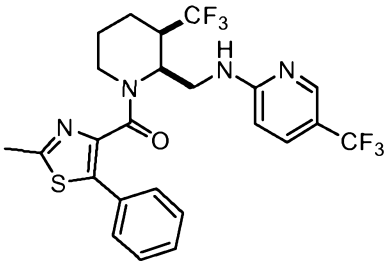
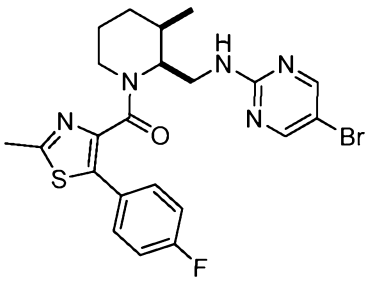
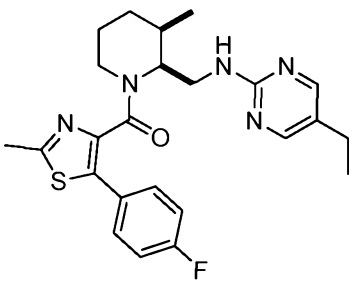
14. The compound of claim 1 comprising any of the following:









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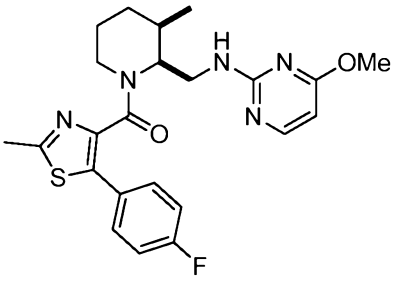
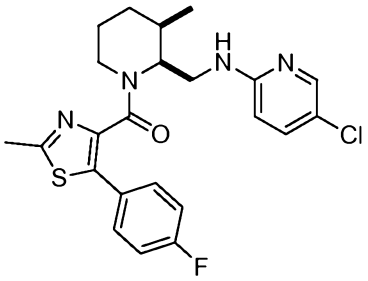
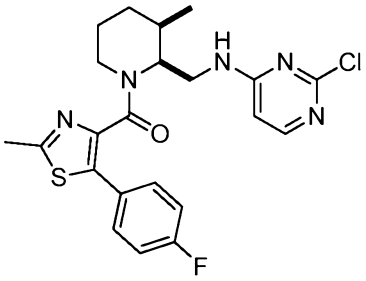
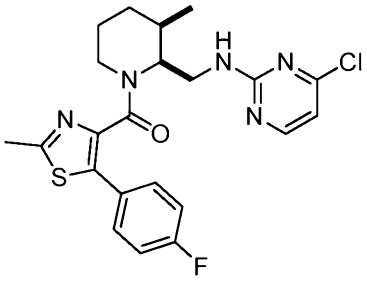

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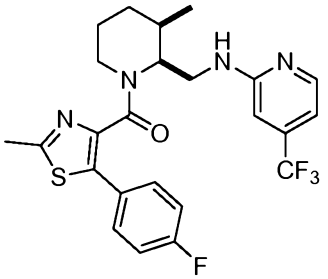
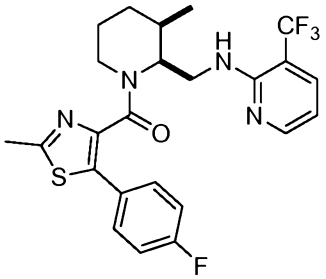
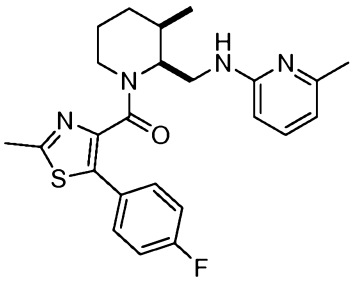
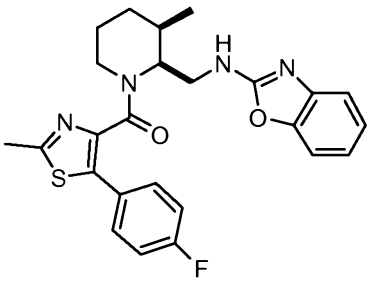

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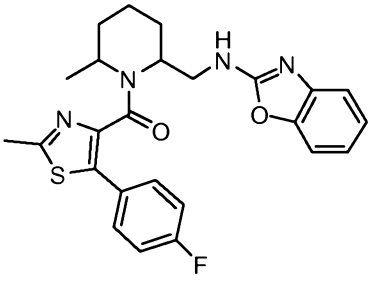
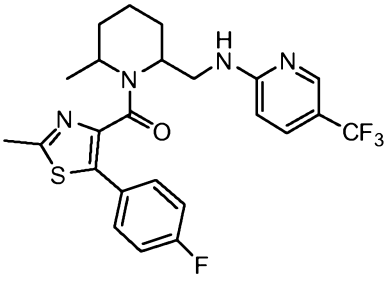

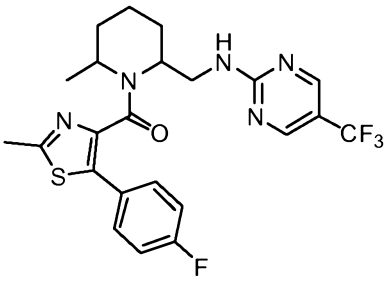

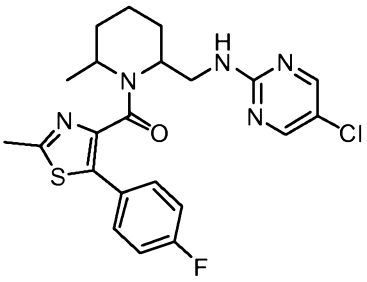

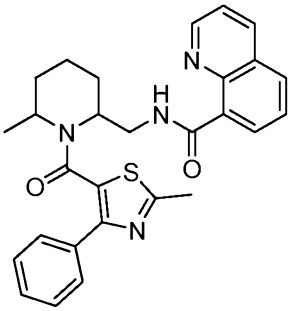

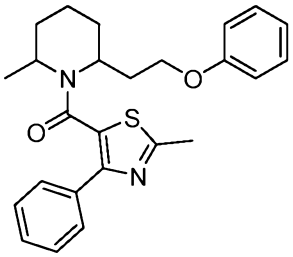

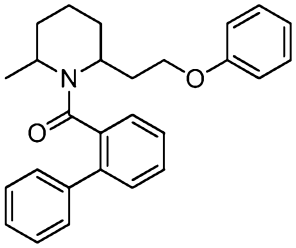

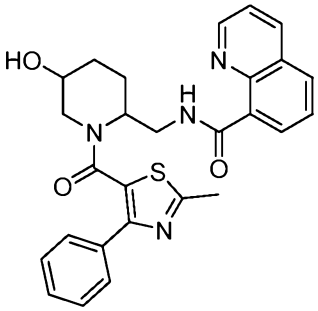

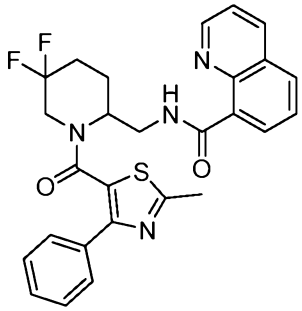

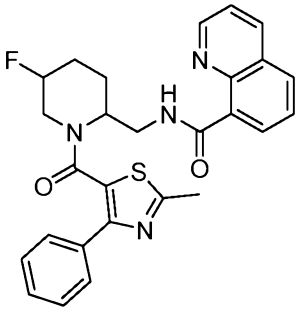

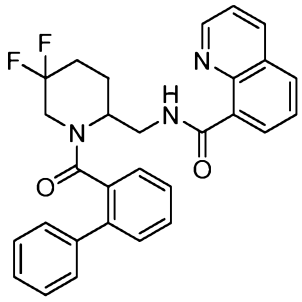

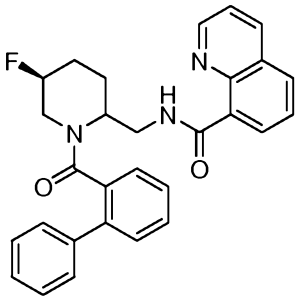

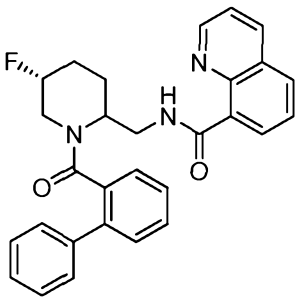

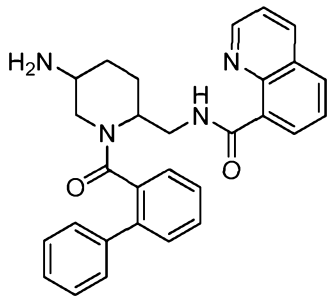

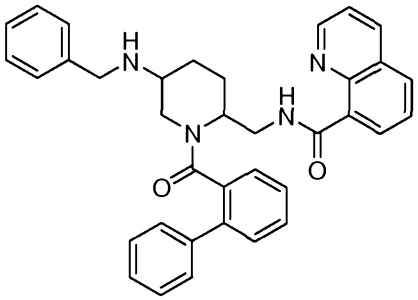

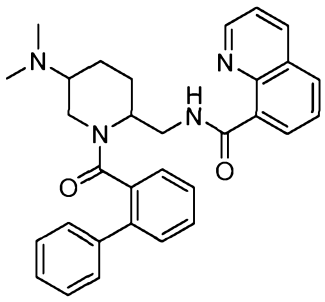

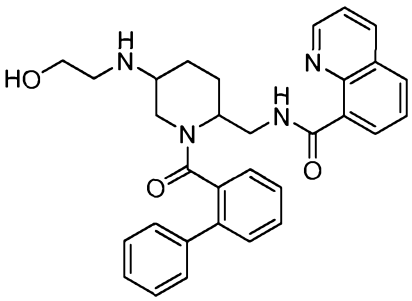

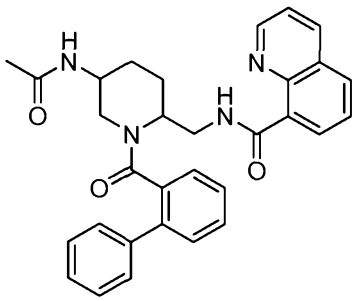

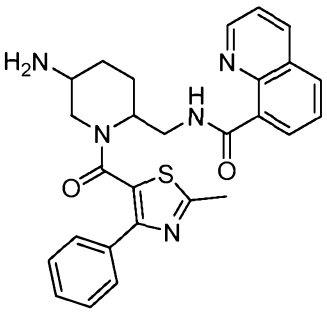

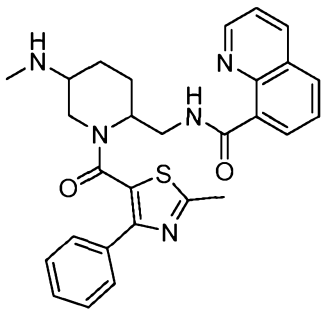

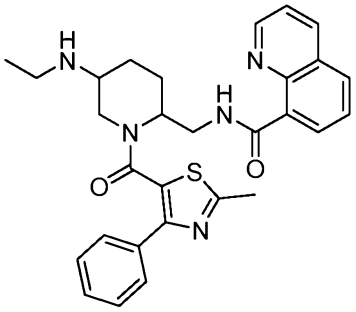

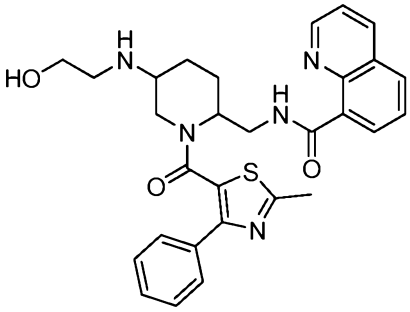

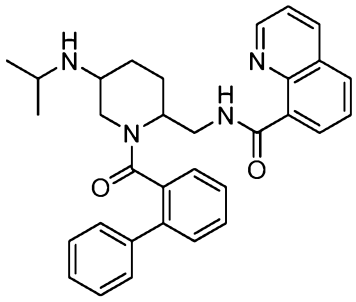

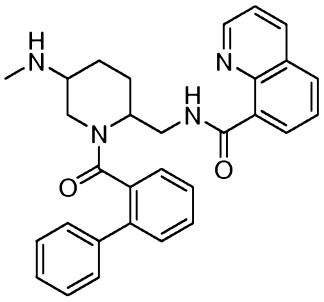

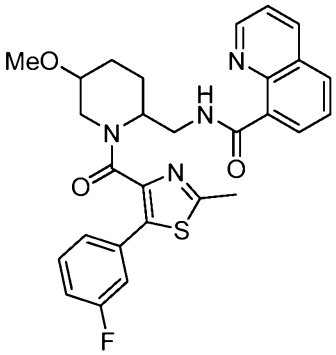

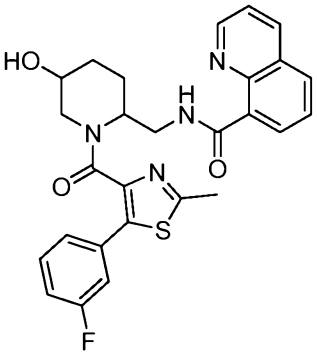

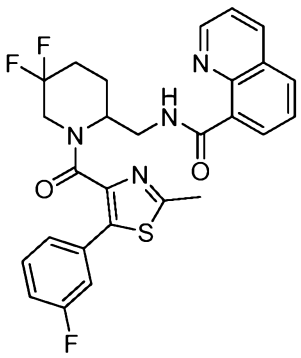

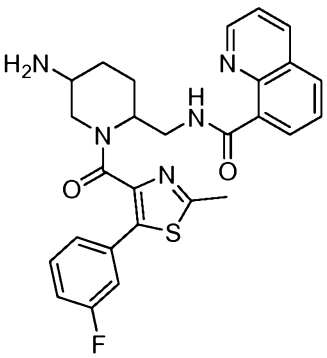

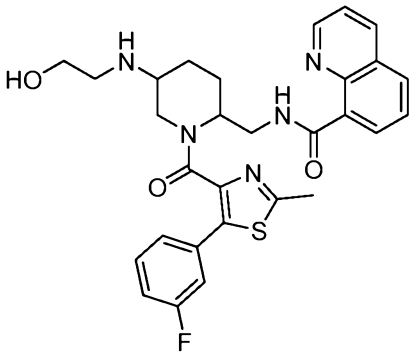

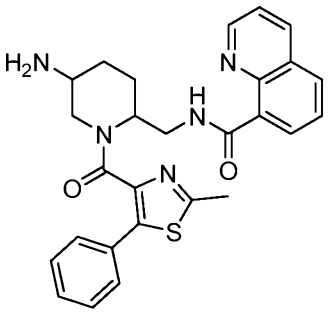

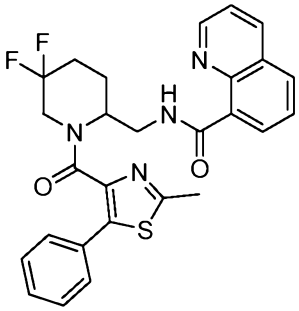

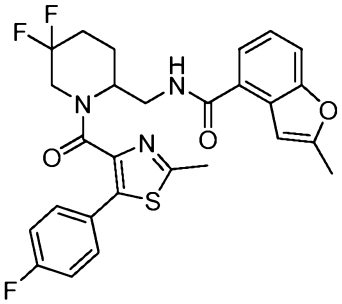

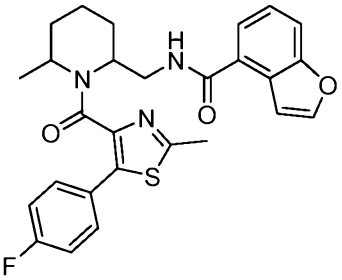

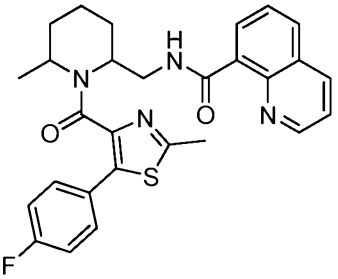

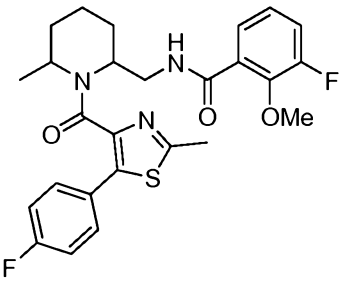

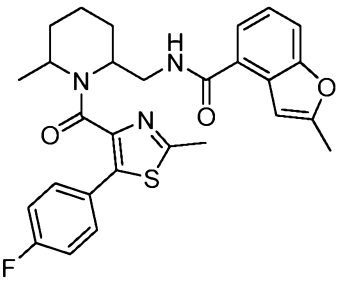

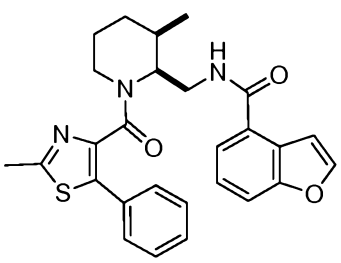

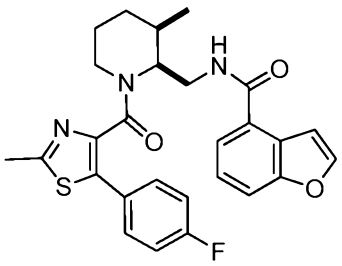

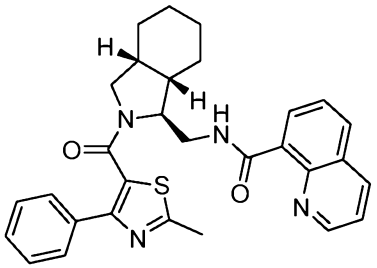

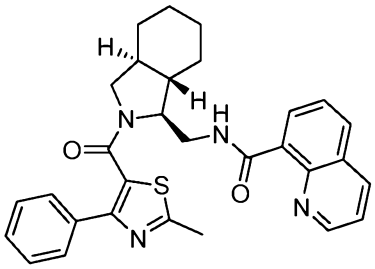

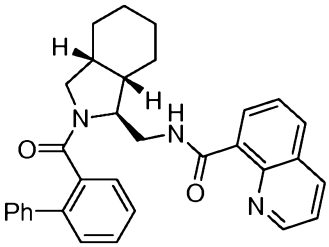

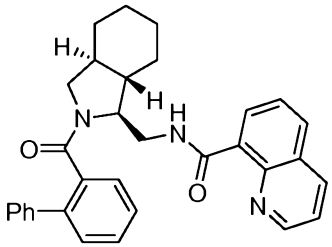

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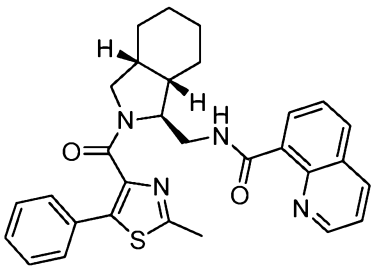

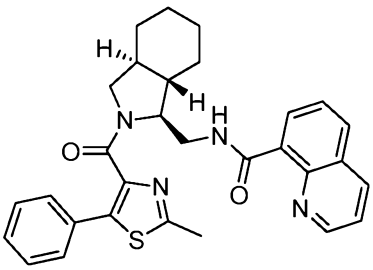

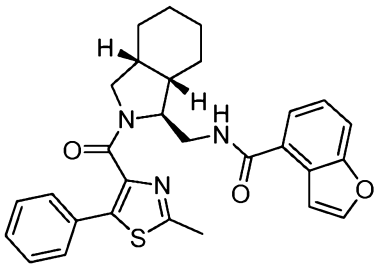

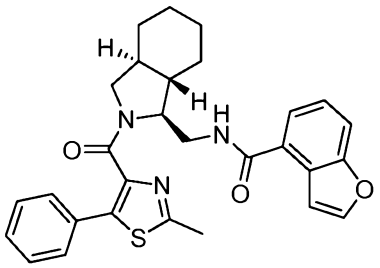

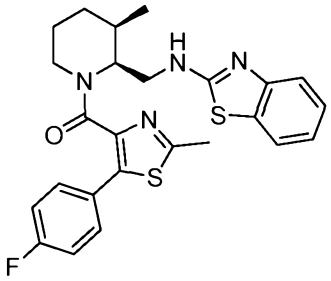

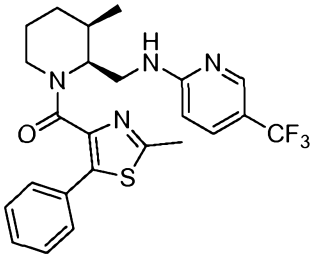

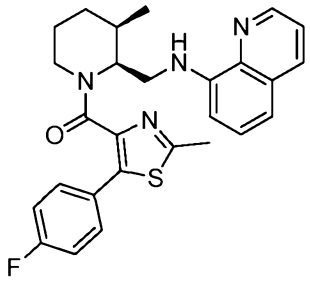

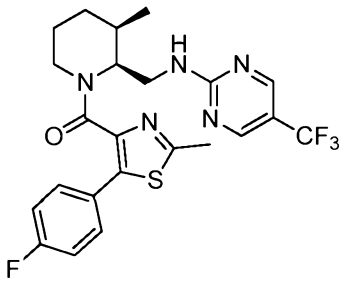

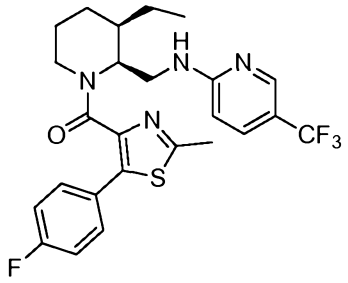

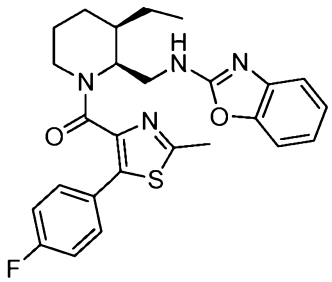

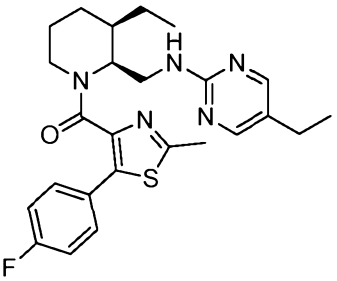

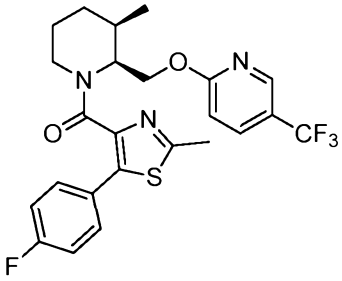

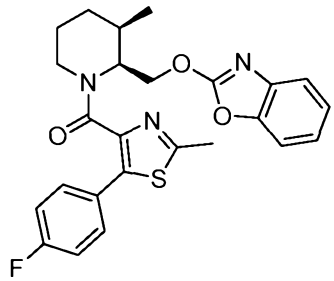

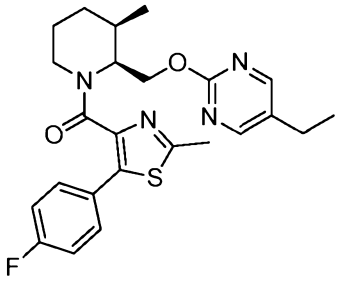

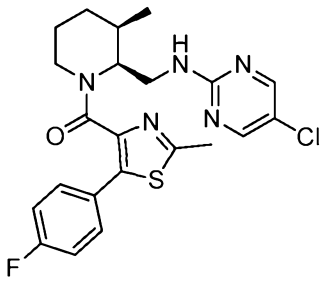

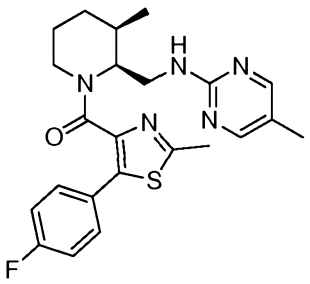

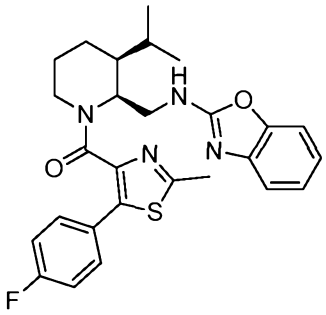

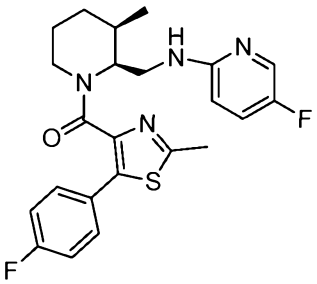

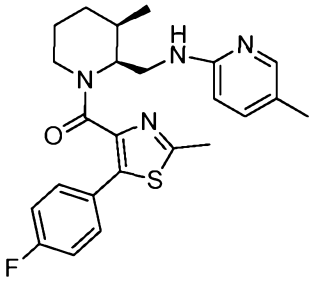

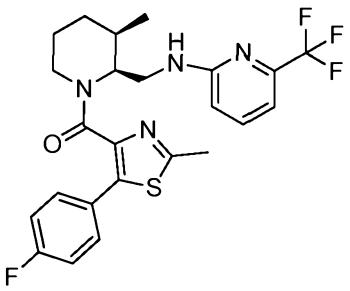

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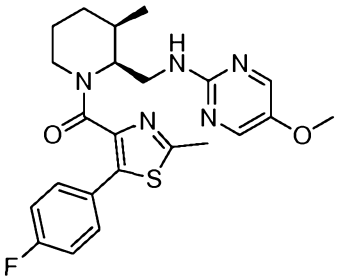

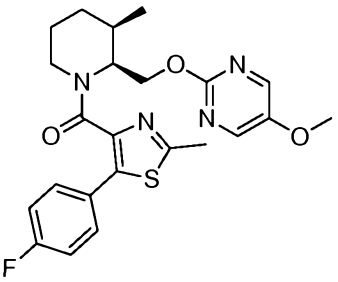

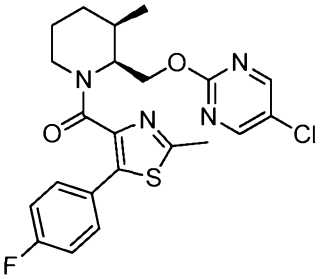

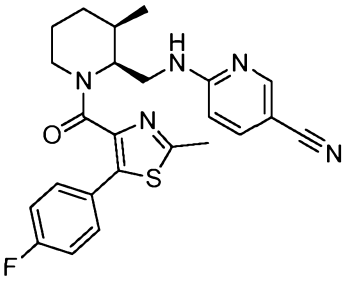

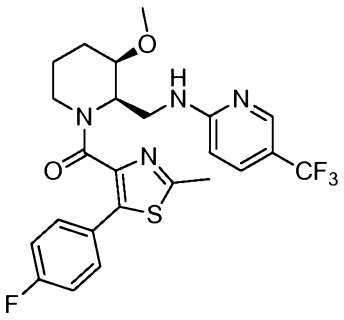

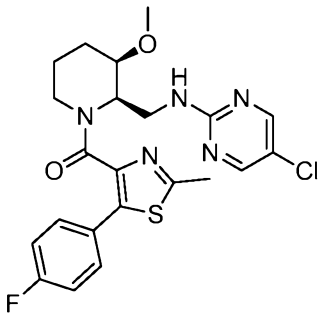

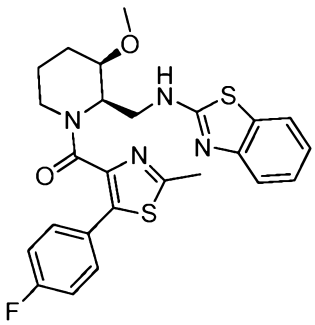

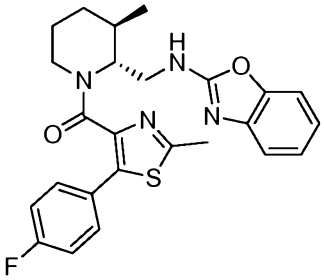

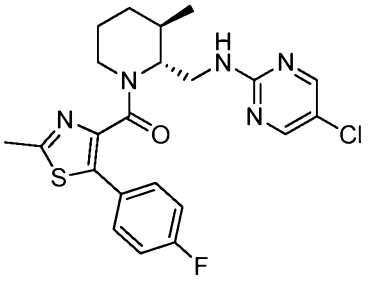

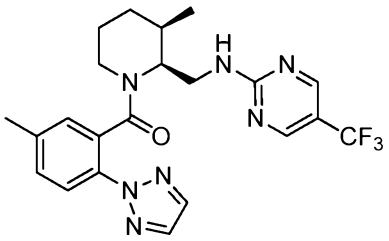

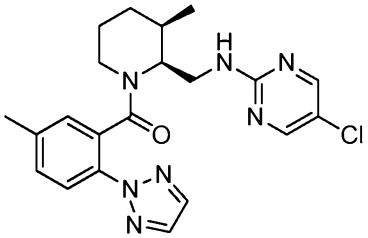

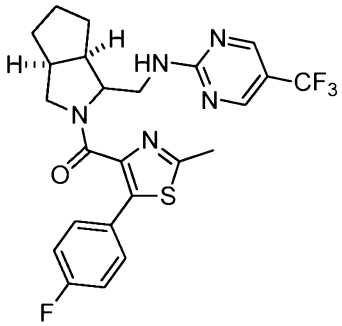

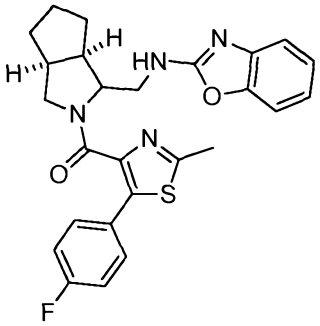

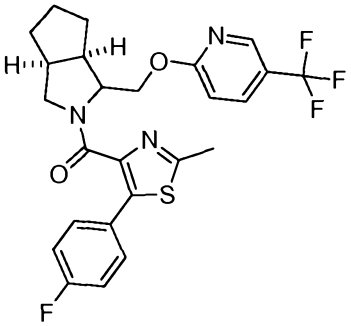

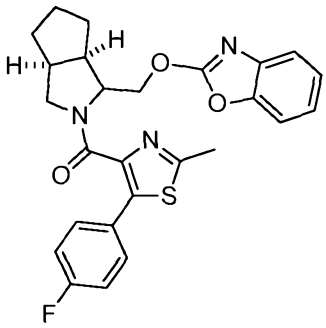

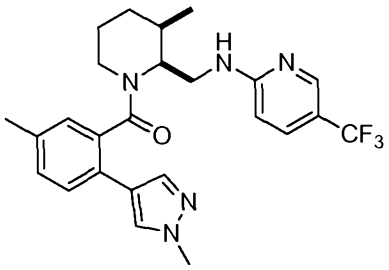

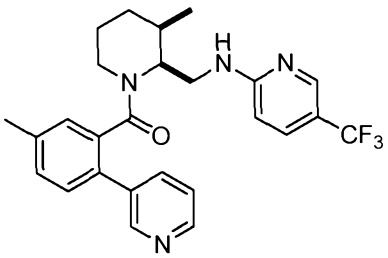

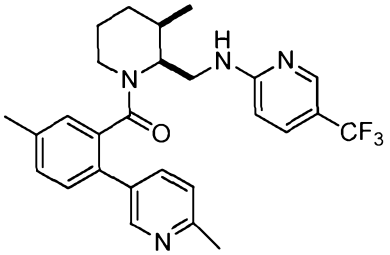

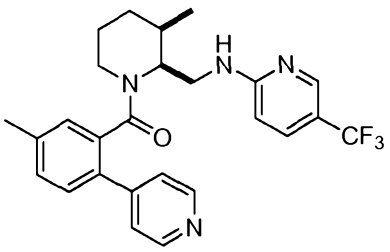

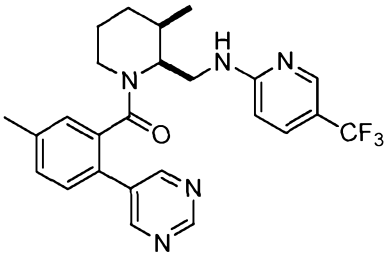

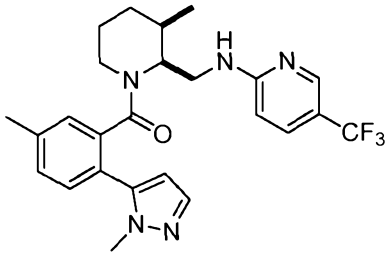

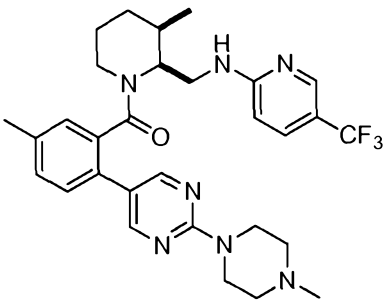

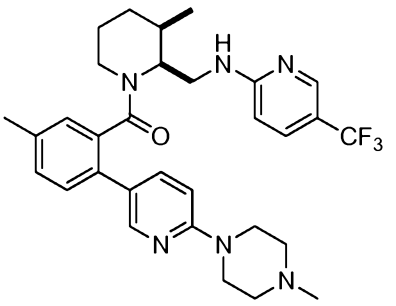
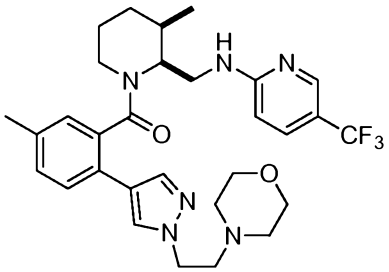
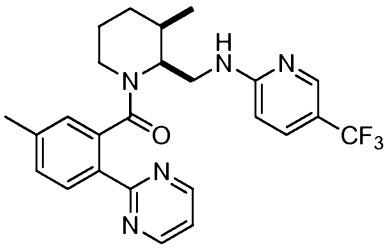
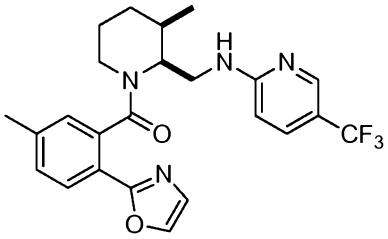
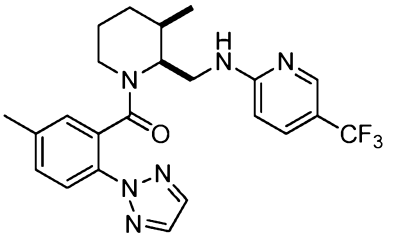
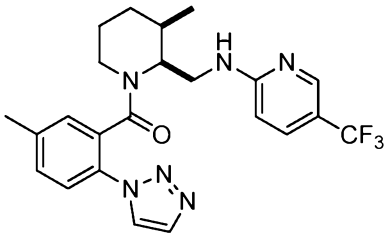
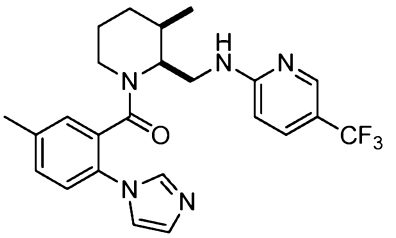
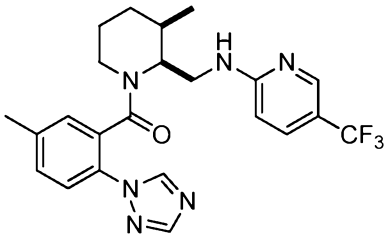
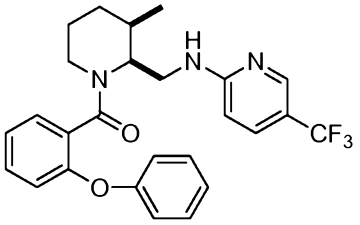
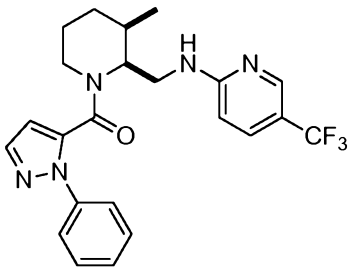
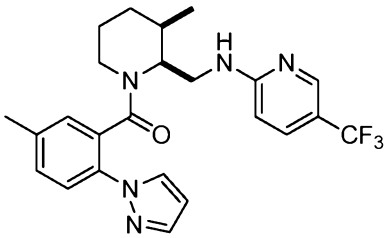
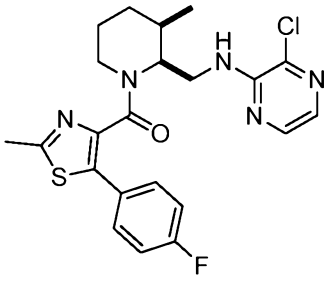

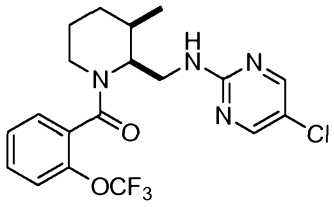

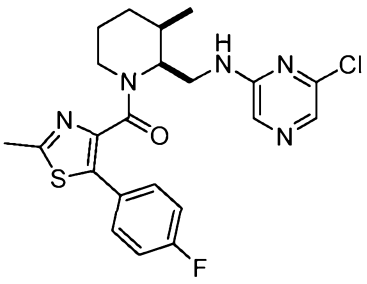

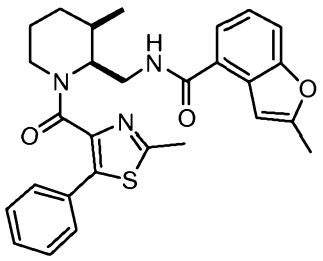

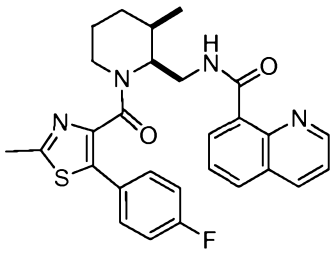

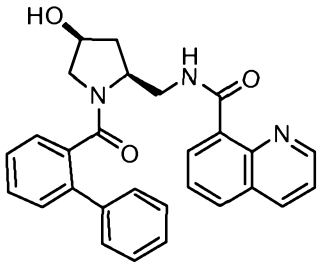

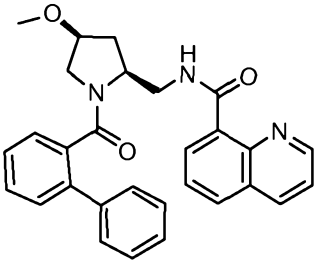

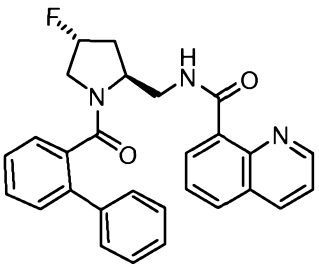

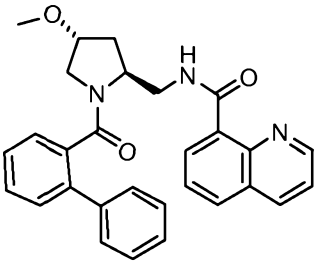

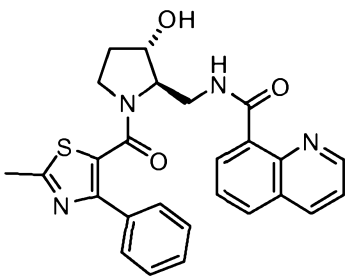

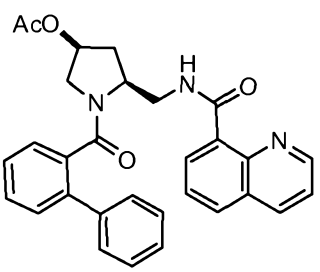

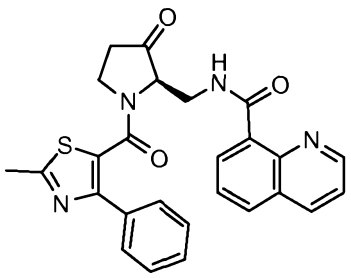

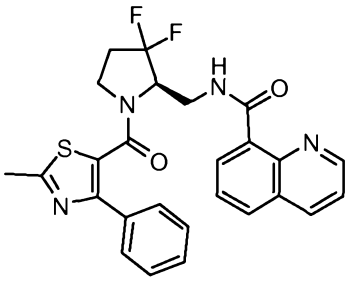

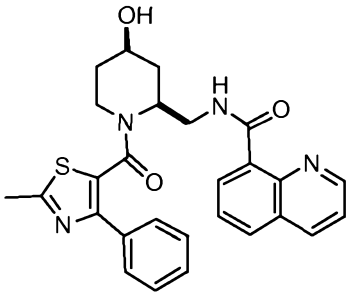

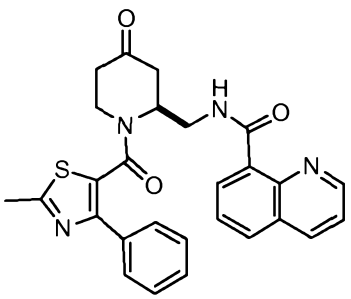

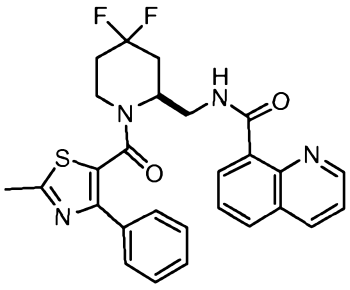

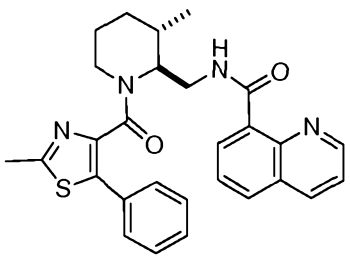

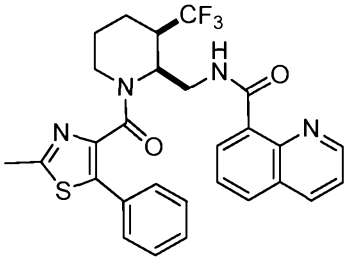

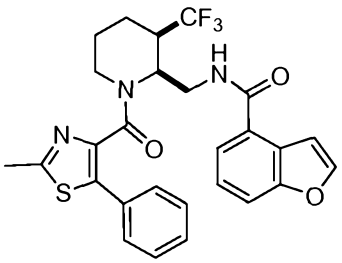

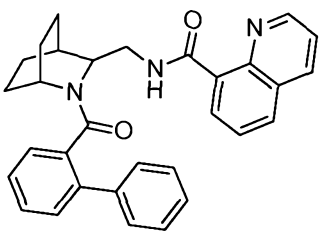

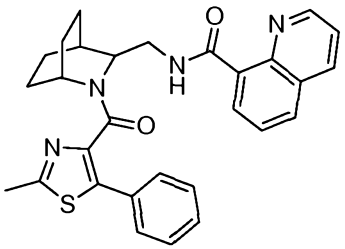

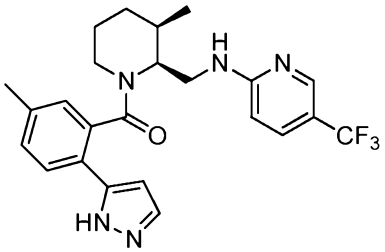

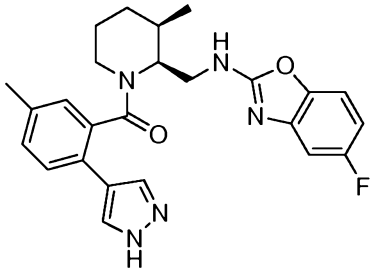

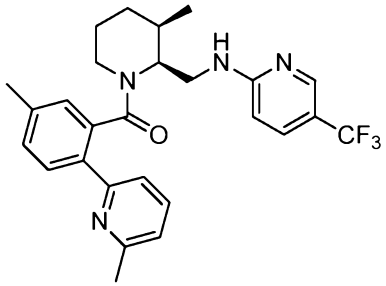

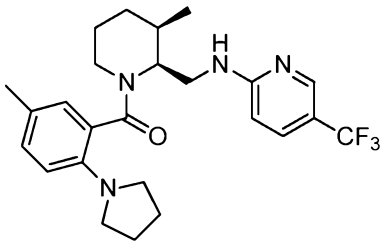

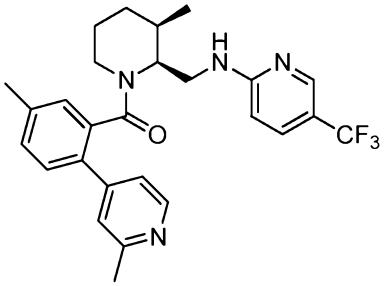

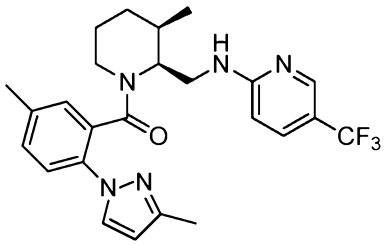

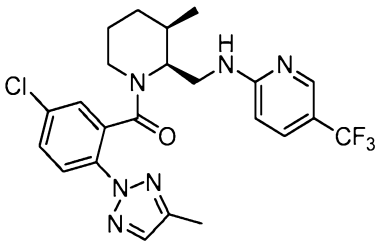

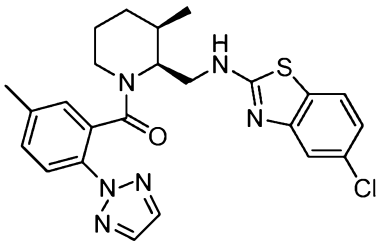

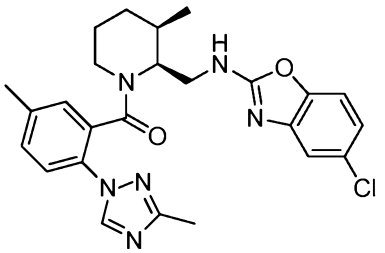

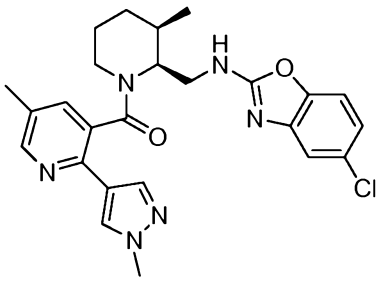

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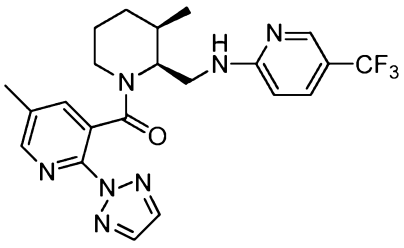

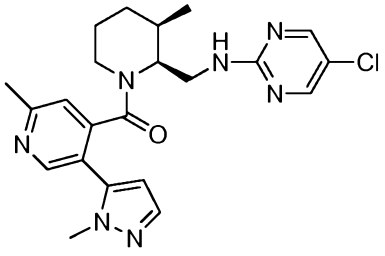

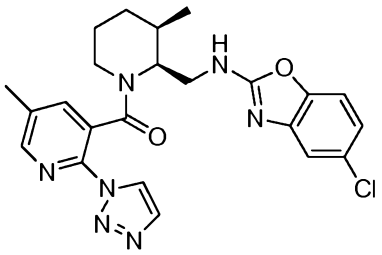

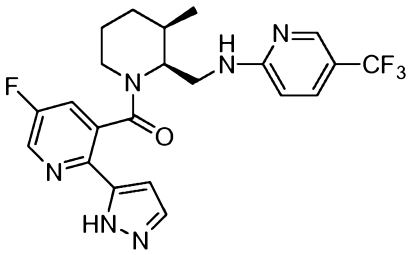

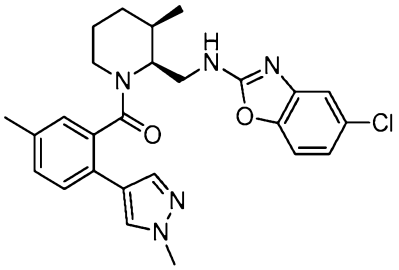

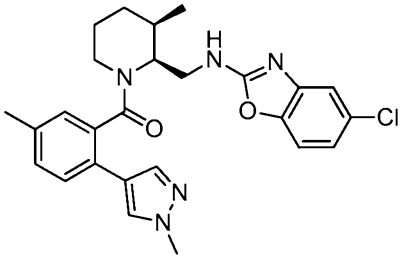

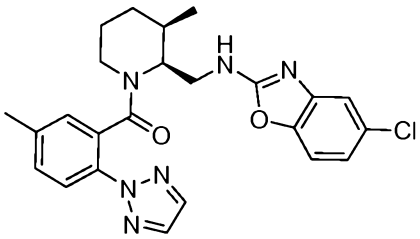

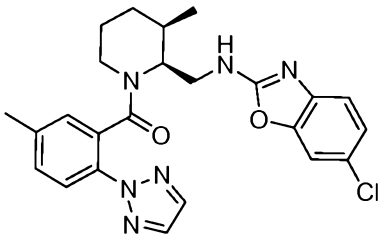

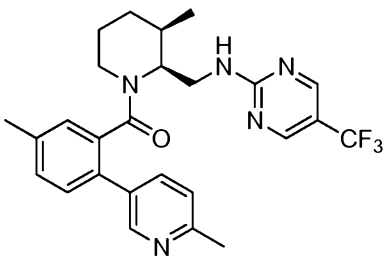

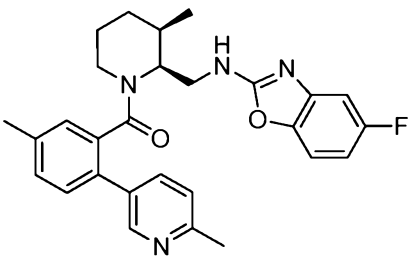

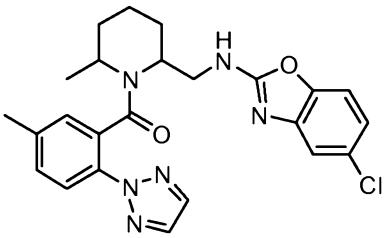

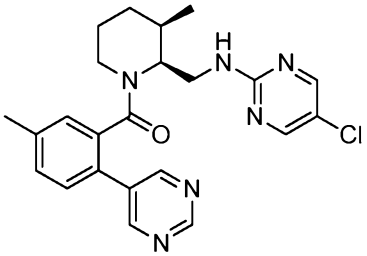

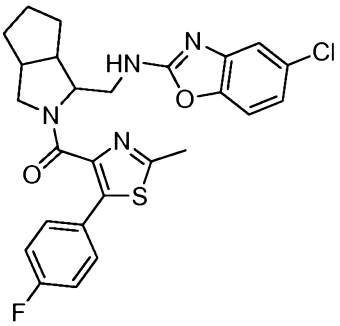

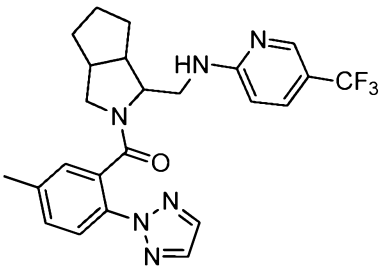

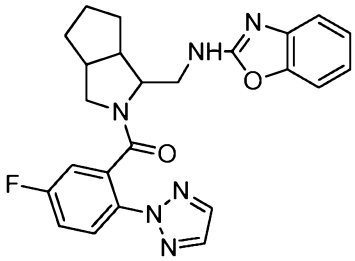

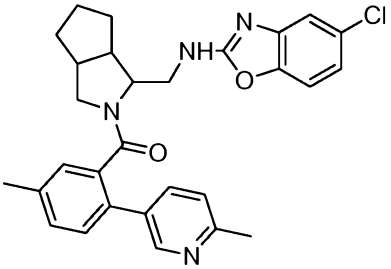

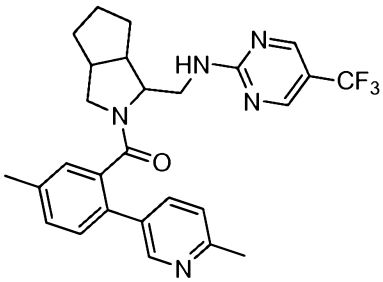

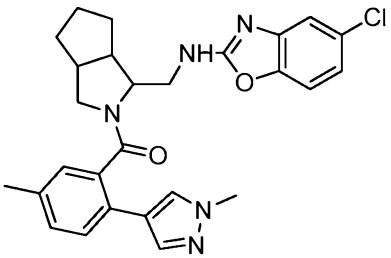

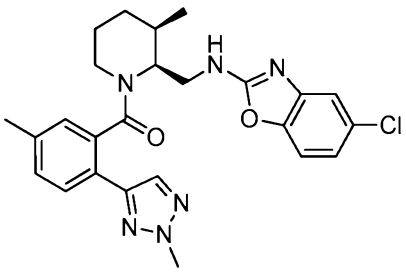

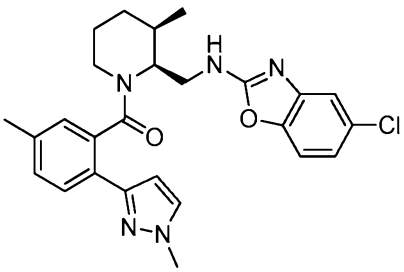

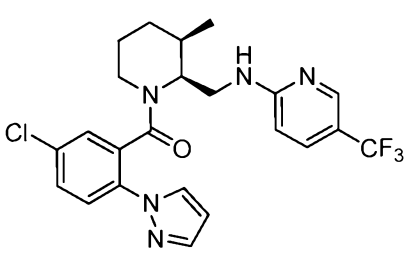
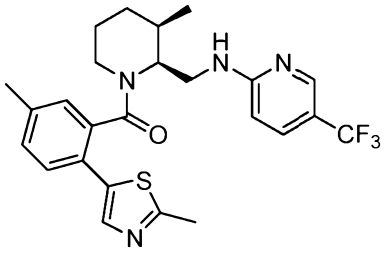
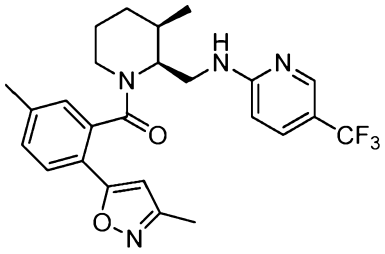
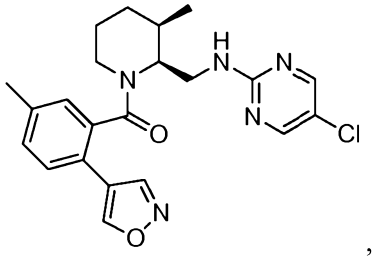
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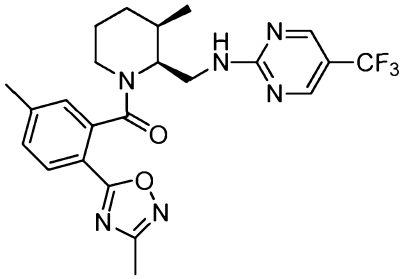
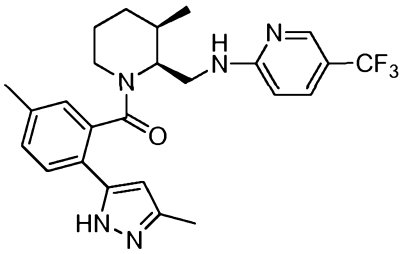

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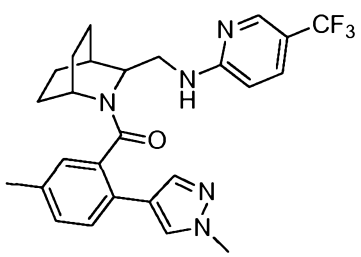
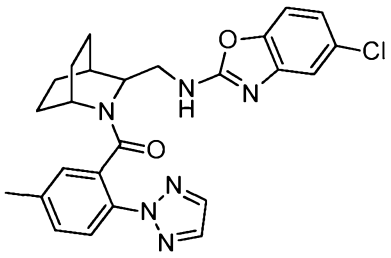
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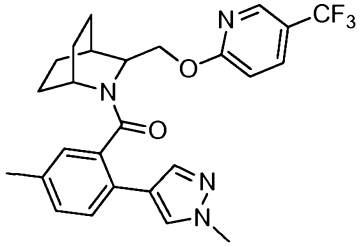

10 or any salt or hydrate thereof.

15. A pharmaceutical composition comprising a compound of any one of claims 1-14 and a pharmaceutically acceptable excipient.

16. A method of modulating an orexin receptor comprising contacting the receptor with an effective amount or concentration of a compound of any one of claims 1-14.

17. The method of claim 16 wherein modulating an orexin receptor is antagonism of the orexin receptor.

18. The method of claim 16 wherein contacting is *in vivo* in a tissue or system of a patient.

19. A method of treating a malcondition in a patient wherein modulation of an orexin receptor is medically indicating, comprising administering to the patient a compound of any one of claims 1-14 in a dose, at a frequency, and for a duration to provide a beneficial effect to the patient.

20. The method of claim 19 wherein modulating an orexin receptor is antagonism of the orexin receptor.

21. The method of claim 19 wherein the compound is a selective modulator of an orexin receptor OX_1.

22. The method of claim 19 wherein the compound is a selective modulator of an orexin receptor OX_2.

23. The method of claim 19 wherein the malcondition comprises an eating disorder, obesity, alcoholism or an alcohol-related disorder, drug abuse or addiction, a sleep disorder, a cognitive dysfunction in a psychiatric or neurologic disorder, depression, anxiety, panic disorder, schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's chorea, head ache, migraine, pain, gastrointestinal diseases, epilepsy, inflammations, immune-related diseases, endocrine-related diseases, hypertension, behavior disorder, mood disorder, manic depression, dementia, sex disorder, psychosexual disorder, or renal disease.

24. The method of claim 23 wherein the drug addiction comprises addiction to cocaine, opiates, or nicotine.

25. The method of claim 23 wherein modulating an orexin receptor is antagonism of the orexin receptor.

26. Use of a compound of any of claims 1-14 for treatment of a malcondition in a patient.

27. The use of claim 26 wherein the malcondition comprises an eating disorder, obesity, alcoholism or an alcohol-related disorder, drug abuse or addiction, a sleep disorder, a cognitive dysfunction in a psychiatric or neurologic disorder, depression, anxiety, panic disorder, schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's chorea, head ache, migraine, pain, gastrointestinal diseases, epilepsy, inflammations, immune-related diseases, endocrine-related diseases, cancer, hypertension, behavior disorder, mood disorder, manic depression, dementia, sex disorder, psychosexual disorder, or renal disease.

28. The use of claim 27 wherein the drug addiction comprises addiction to cocaine, opiates, or nicotine.