Pharmacologically active heterocyclic-substituted pyrazolo[1,5-*a*]pyrimidine derivatives

FIELD OF THE INVENTION

The present invention relates to new pyrazolo[1,5-*a*]pyrimidine derivatives of formula (I) or pharmaceutically acceptable salts, biologically active metabolites, pro-drugs, racemates, enantiomers, diastereomers, solvates and hydrates thereof that serve as $GABA_B$ receptor positive allosteric modulators. The invention also relates to the process for producing such compounds as well as key intermediates of the process. The invention further relates to pharmaceutical compositions comprising such compounds optionally in combination with two or more different therapeutic agents and the use of such compounds in methods for treating diseases and conditions mediated and modulated by the $GABA_B$ receptor positive allosteric mechanism. The invention also provides a method for manufacture of medicaments useful in the treatment of such disorders.

BACKGROUND OF THE INVENTION

Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the central nervous system and plays a key role in modulating neuronal activity. It exerts its action via three receptor systems, the related ionotropic $GABA_A$ and $GABA_C$ receptors, and the distinct metabotropic $GABA_B$ receptors (Hill and Bowery, *Nature* 1981, 290, 149-152). The latter $GABA_B$ receptors are widespreadly distributed within the mammalian central nervous system with various expression levels in different brain regions (Bovery et al, *Neuroscience* 1987, 20, 365-385). $GABA_B$ receptors can be found both pre- and postsynaptically and play an important role in the fine-tuning of neurotransmission. Most $GABA_B$ receptors cluster around excitatory synapses, either at the edge of the presynaptic terminal or on dendritic spines opposite to glutamatergic boutons (Ulrich and Bettler, *Curr. Opin. Neurobiol.* 2007, 17, 298-303).

$GABA_B$ receptors belong to the Family 3 (C) of G-protein coupled receptors (GPCRs) together with metabotropic glutamate receptors (mGluRs), calcium-sensing receptors, taste receptors and a number of orphan receptors, showing highest, approximately 30% homology to mGluRs (Bettler et al, *Physiol. Rev.* 2004, 84, 835-867). $GABA_B$ receptors are heterodimers consisting of two similar, yet different subunits, B1 and B2. The B1 subunit has multiple splice

variants with only two (B1a and B1b) having clear physiological significance. These isoforms differ only in their extracellular domain containing two Sushi motifs that regulate the subcellular localization of the receptor (Vigot et al, *Neuron* 2006, 50, 589-601; Biermann et al, J. Neurosci. 2010, 30, 1385-1394). The B1 subunit binds the endogenous neurotransmitter ligand GABA as well as other orthosteric agonists (such as baclofen, SKF97541) and antagonists (such as phaclofen, saclofen). The B2 subunit is responsible for G-protein activation-mediated intracellular signal transduction and is believed to bind allosteric modulators (Binet et al, *J. Biol. Chem.* 2004, 279, 29085-29091; Dupuis et al, *Mol. Pharmacol.* 2006, 70, 2027-2036). The site of action for the Novartis $GABA_B$ positive allosteric modulator compounds CGP7930 and GS39783 is the heptahelical transmembrane domain of the B2 subunit; the exact binding site for other, unrelated positive allosteric modulator chemotypes is not known.

The main synaptic effects of $GABA_B$ receptors are the presynaptic blockade of neurotransmitter release (GABA as well as glutamate) and postsynaptic hyperpolarization (Gassmann and Bettler, in Handbook of Contemporary Neuropharmacology 2007). These effects are the result of inhibition of presynaptic calcium influx and stimulation of postsynaptic inwardly rectifying potassium (GIRK) channels, respectively. Ion channel functions are mediated in a membrane-delimited manner through the activation of $\beta\gamma$ subunits of G_i/G_o proteins. In addition to these, $GABA_B$ receptors also signal via the α subunit of the same G-proteins that inhibits adenylate cyclase and retards the recruitment of synaptic vesicles (Chalifoux and Carter, *Curr. Opin. Neurobiol.* 2011, 21, 339-442). Beside these fast cellular events, $GABA_B$ receptors also regulate cytoplasmic kinases including mitogen-acivated protein kinase and thereby influence synaptic plasticity on the longer-term.

In order to better understand the physiological significance of $GABA_B$ receptors at the behavioral level, knockout mice have been generated with mutations selectively in the B1, B1a, B1b and the B2 subunits. Mice without B1 subunits displayed increased anxiety in explorative-like situations (light-dark box, staircase assays), increased panic, spontaneous seizures, hyperalgesia, hyperlocomotion, and memory impairment (Schuler et al, *Neuron* 2001, 31, 47-58). Mice that do not express $GABA_{B2}$ subunits behave similarly to B1 subunit knockouts; these animals are overanxious, show spontaneous seizure activity, hyperalgesia, hyperlocomotion, and memory impairment (Mombereau et al, *Eur. J. Pharmacol.* 2004, 497, 119-120; Mombereau et al, *Neuroreport* 2005, 16, 307-310; Gassmann et al, *J. Neurosci.* 2004, 24, 6086-6097). Based on the above, the $GABA_B$ receptor system seems to play a general role in the regulation of neuronal excitability with consequences on various aspects of overt behavior.

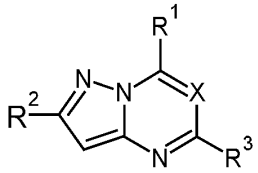
The only approved and commercialized selective $GABA_B$ receptor ligand is the orthosteric agonist racemic baclofen. Baclofen was approved as a centrally acting muscle relaxant used to reduce spasticity associated with cerebral palsy, multiple sclerosis, and spinal cord injuries. Beside these applications, baclofen may have potential therapeutic benefits in treating conditions including asthma, pain, obesity, binge eating, drug and alcohol abuse, anxiety, posttraumatic stress disorder, cough, inflammation, gastroeasophageal reflux and urinary incontinence (eg., Breslow et al, *Am. J. Psychiatry* 1989, 146, 353-356; Drake et al, *Ann. Pharmacother.* 2003, 37, 1177-1181; Leggio et al, *CNS Neurol. Disord. Drug Targets* 2010, 9, 33-44). Although baclofen has beneficial potential in a number of therapeutic indications, unfortunately it also has a range of unwanted properties including poor blood-brain-barrier penetration, narrow therapeutic window, receptor desensitization, development of tolerance against the main effects, and withdrawal upon termination of use (Vacher and Bettler, *Curr. Drug Targets CNS Neurol. Disord.* 2003, 2, 248-259; Ross et al, *Neurocrit. Care* 2011, 14, 103-108; Keegan et al, *Neuropharmacology* 2015, 95, 492-502).

Allosteric modulation is an alternative way to selectively stimulate GPCRs without the unwanted properties of orthosteric ligands (Conn et al, *Nat Rev* 2009, 8, 41-54; Wang et al, J. *Pharmacol. Exp. Ther.* 2009, 331, 340-348). Allosteric modulators bind to the receptors at sites that are different from the binding site of the endogenous (orthosteric) ligands and are effective predominantly if an agonist is also bound to the receptor. This has consequences on the temporal and spacial pattern of efficacy which in turn affects the behavioral and adaptive responses the organism gives to allosteric stimulation. In contrast to orthosteric agonism, allosteric modulation of targets is expected to show less side effects, desensitization and development of tolerance. Indeed, it has been shown for the $GABA_B$ receptor positive allosteric modulator GS39783 in preclinical models, that this compound can have a favourable side effect profile (Cryan et al, *J. Pharmacol. Exp. Ther.* 2004, 310, 952-963), desensitization of the receptor can be prevented (Gjoni and Urwyler, *Neuropharmacology* 2008, 55:1293-1299) and tolerance may not develop upon chronic administration (Mombereau et al, *Neuropsychopharmacology* 2004, 29, 1050-1062). These results suggest that positive allosteric modulators of the $GABA_B$ receptor may be useful novel chemical entities without the unwanted properties of the orthosteric ligands such as baclofen.

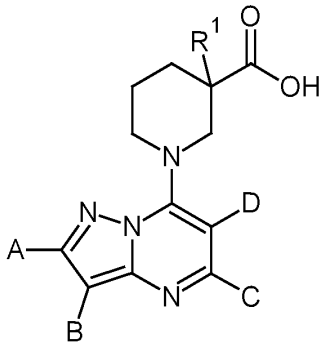
Several patents and patent applications describe positive allosteric $GABA_B$ modulators which have different chemical structures. Pyrimidine derivatives as positive allosteric modulators of the $GABA_B$ receptor have been disclosed in WO 2005/094828 and WO 2006/136442. Thieno[3,2-*b*]pyrimidine and [1,3]thiazolo[5,4-*d*]pyrimidine derivatives as positive allosteric

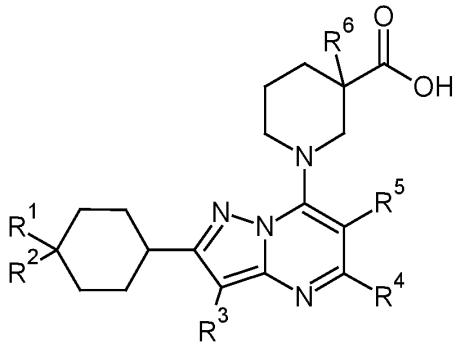
modulators of the $GABA_B$ receptor have been disclosed in WO 2015/056771 (US 2015/0111876). Pyrazolo[1,5-*a*]pyrimidine derivatives have been disclosed in US 2016/0304527 A1.

In WO2017069270 Taisho Pharmaceutical Co., Ltd. described pyrazolo[1,5-*a*]pyrimidine and pyrazolo[1,5-*a*][1,3,5]triazine derivatives, as positive allosteric modulators at the $GABA_B$ receptors. In most of the examples the R_1 substituent connects through a carbon-nitrogen bond to the core.



Two recent patent applications by Richter Gedeon Nyrt. (WO2018167629 and WO2018167630) describe pyrazolo-pyrimidines with positive allosteric activity at the $GABA_B$ receptors. These examples are carboxylic acids, and the heterocycle is connected to the pyrazolo[1,5-*a*]pyrimidine core through a nitrogen atom.





The purpose of the present invention is to provide further compounds with high affinity to $GABA_B$ receptors. Unexpectedly, we found in the present invention that compounds in which the central aromatic bicycle at position 7 is connected through a carbon atom to an optionally substituted six- membered saturated heterocyclic ring containing 1 or 2 heteroatom selected from N, O or S, show nanomolar potency. There is no suggestion in WO2018167629, WO2018167630 or WO2017069270 to undertake such structural modification to obtain the compounds of formula (I).

The structurally closest compounds disclosed in WO2017069270 by Taisho Pharmaceutical Co., Ltd. are examples A148, A225, B14, B23, B30, B31, B35. This patent suggests, that the sufficiently active compounds have a carbon-nitrogen bond between the core and the R_1 substituent,

or in the case of a carbon-carbon bond, the core needs an additional N atom at position X. These compounds (examples A148, A225, B14, B23, B30, B31, B35) are the less active compounds.

The skilled person would not expect that the present substitution on the pyrazolo[1,5-*a*]pyrimidine core keeps the excellent pharmaceutical activity.

The above described in vitro advantages are further strengthened by the unexpected finding that certain examples of the present invention possessed great behavioural benefit in the prenatal valproate disease model that recapitulates the core symptoms of autism spectrum disorder. The inventors therefore showed that the compounds of the invention has therapeutic potential for the core symptoms of autism spectrum disorder in humans.

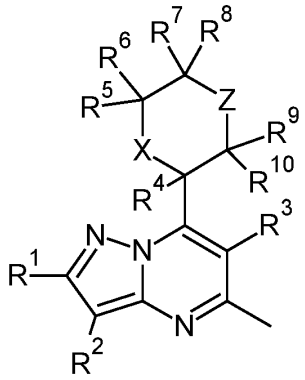
SUMMARY OF THE INVENTION

Our invention discloses heterocyclic derivatives with a carbocyclic-pyrazolo-pyrimidine scaffold. We found that these compounds show mostly nanomolar potency.

We have identified a class of pyrazolo[1,5-*a*]pyrimidine derivatives which have high affinity for $GABA_B$ receptors providing unique role in the treatment of psychiatric, neurodevelopmental, neurological and other central nervous system disorders as well as peripheral conditions where stimulation of the $GABA_B$ receptor may offer therapeutic benefit.

We identified new compounds that are brain penetrant. The present invention relates to compounds being $GABA_B$ receptor positive allosteric modulators and the synthesis thereof. Compounds of the present invention are useful for the treatment of psychiatric, neurodevelopmental, neurological and other central nervous system disorders as well as peripheral conditions where stimulation of the $GABA_B$ receptor may offer therapeutic benefit.

The present invention relates to the pyrazolo[1,5-*a*] pyrimidine derivatives of formula (I)



(I)

R^1 represents phenyl- or cyclohexyl group substituted by C_1-C_6alkyl or halo-C_1-C_6alkyl;

R^2 represents H or halogen;

R^3 represents H or C_1-C_6alkyl;

R^4 represents H; C_1-C_6alkyl or halo- C_1-C_6alkyl;

R^5 and R^6 may be each, independently H; C_1-C_6alkyl or halogen;

R^7 and R^8 may be each, independently H or C_1-C_6alkyl;

R9 and R10 may be each, independently H or C_1-C_6alkyl or R^9 and R^{10} together may form oxo group;

X represents $–CR^xR^y$ or -O- or -$S(O)_n$- group, wherein R^x and R^y may be each, independently H or C_1-C_6alkyl group and wherein n is 0 or 1 or 2;

Z represents -NR-; or -O-; or -$S(O)_2$- group wherein

R may be H or -$C(O)R^{11}$ or -$S(O)_2R^{12}$ group; aminocarbonyl-C_1-C_3alkyl; carboxy-C_1-C_3alkyl; cyano-C_1-C_3alkyl; C_1-C_5(cyclo)alkyl; saturated 4-6 membered heterocyclic ring with one O, or -$C(NH)(NH_2)$ group;

wherein R^{11} may be H; C_1-C_3alkyl; C_1-C_3alkoxy; C_1-C_3alkoxy-C_1-C_3alkyl; C_1-C_3alkoxy-C_1-C_3alkoxy; methanesulphonyl-C_1-C_3alkyl; or R^{11} may be a saturated 3-6 membered carbocyclic ring, or a 4-6 membered saturated or unsaturated heterocyclic ring with one to three hetero atoms selected from N, O or S; or amino, mono- or dialkylamino group; amino- C_1-C_3alkyl; hydroxy-C_1-C_3alkyl substituted by NH_2-group;

wherein R^{12} may be C_1-C_3 alkyl; amino or dialkylamino group;

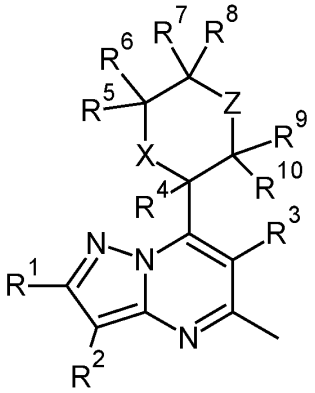
R^4 and CR^x may form a cycloalkyl ring; or pharmaceutically acceptable salts, biologically active metabolites, pro-drugs, racemates, enantiomers, diastereomers, solvates and hydrates thereof.

The invention also relates to the pharmaceutical compositions containing the compounds of formula (I) or pharmaceutically acceptable salts, biologically active metabolites, pro-drugs, racemates, enantiomers, diastereomers, solvates and hydrates thereof.

Furthermore, the present invention relates to the synthesis of the compounds of formula (I) and optical antipodes or racemates and/or salts thereof, the pharmaceutical compositions comprising thereof and the chemical and pharmaceutical manufacture of medicaments containing these compounds, as well as the methods of treatment with these compounds, which means administering to a mammal to be treated – including human – suffering from psychiatric, neurodevelopmental, neurological and other central nervous system disorders as well as peripheral conditions where stimulation of the $GABA_B$ receptor may offer therapeutic benefit, effective amount of compounds of formula (I) and optical antipodes or racemates and/or salts thereof of the present invention as such or as medicament.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to the pyrazolo[1,5-*a*]pyrimidine derivatives of formula (I)



(I)

R^1 represents phenyl- or cyclohexyl group substituted by C_1-C_6alkyl or halo-C_1-C_6alkyl;

R^2 represents H or halogen;

R^3 represents H or C_1-C_6alkyl;

R^4 represents H; C_1-C_6alkyl or halo-C_1-C_6alkyl;

R^5 and R^6 may be each, independently H; C_1-C_6alkyl or halogen;

R^7 and R^8 may be each, independently H or C_1-C_6alkyl;

R^9 and R^{10} may be each, independently H or C_1-C_6alkyl or R^9 and R^{10} together may form oxo group;

X represents -CR^xR^y or -O- or -$S(O)_n$- group, wherein R^x and R^y may be each, independently H or C_1-C_6alkyl group and wherein n is 0 or 1 or 2;

Z represents -NR-; or -O-; or -$S(O)_2$- group wherein

R may be H or -$C(O)R^{11}$ or -$S(O)_2R^{12}$ group; aminocarbonyl-C_1-C_3alkyl; carboxy-C_1-C_3alkyl; cyano-C_1-C_3alkyl; C_1-C_5(cyclo)alkyl; saturated 4-6 membered heterocyclic ring with one O, or -$C(NH)(NH_2)$ group;

wherein R^{11} may be H; C_1-C_3alkyl; C_1-C_3alkoxy; deutero-C_1-C_3alkoxy; C_1-C_3alkoxy-C_1-C_3alkyl; C_1-C_3alkoxy-C_1-C_3alkoxy; methanesulphonyl-C_1-C_3alkyl; or R^{11} may be a saturated 3-6 membered carbocyclic ring, or a 4-6 membered saturated or unsaturated heterocyclic ring with one to three hetero atoms selected from N, O or S; or amino, mono- or dialkylamino group; amino-C_1-C_3alkyl; hydroxy-C_1-C_3alkyl substituted by NH_2 –group;

wherein R^{12} may be C_1-C_3alkyl; amino or dialkylamino group;

R^4 and CR^x may form a cycloalkyl ring;

or pharmaceutically acceptable salts, biologically active metabolites, pro-drugs, racemates, enantiomers, diastereomers, solvates and hydrates thereof.

The term “halogen” or “halo” as used herein alone or as a part of another group refers to chlorine, bromine, fluorine and iodine.

The term “C_1-C_6alkyl” as used herein refers to branched or straight chain alkyl groups comprising one to six carbon atoms, including but not limited to methyl, ethyl, propyl, normal- and isopropyl and different butyl groups.

The term “C_1-C_6alkoxy” as used herein refers to branched or straight chain alkyl groups comprising one to six carbon atoms bonded through an oxygen atom, including but not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, and t-butoxy.

The term “mammal” as used herein refers to any members of the class “Mammalia” including, but not limited to human.

The term “salt” means nontoxic base addition salts of the compounds of the invention which are generally prepared by reacting the acid with a suitable organic or inorganic base.

Included within the scope of the present invention are all stereoisomers, geometric isomers and tautomeric forms of the compounds of formula (I), including compounds exhibiting more than one type of isomerism and mixtures of one or more thereof.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from the suitable optically pure precursor or resolution of the racemate (or racemate of a salt or derivative) using, for example chiral high pressure liquid chromatography (HPLC).

The term “pharmaceutically acceptable” describes an ingredient that is useful in preparing a pharmaceutical composition and is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes those acceptable for veterinary use as well as human pharmaceutical use.

The term “pharmaceutical composition” refers to a mixture of a compound of the invention with other chemical components, such as pharmaceutically acceptable auxiliary materials, e.g. diluents or carriers. The pharmaceutical composition facilitates administration of the compound to the subject.

The term "excipient" defines a chemical compound that facilitates the incorporation of a compound into cells or tissues.

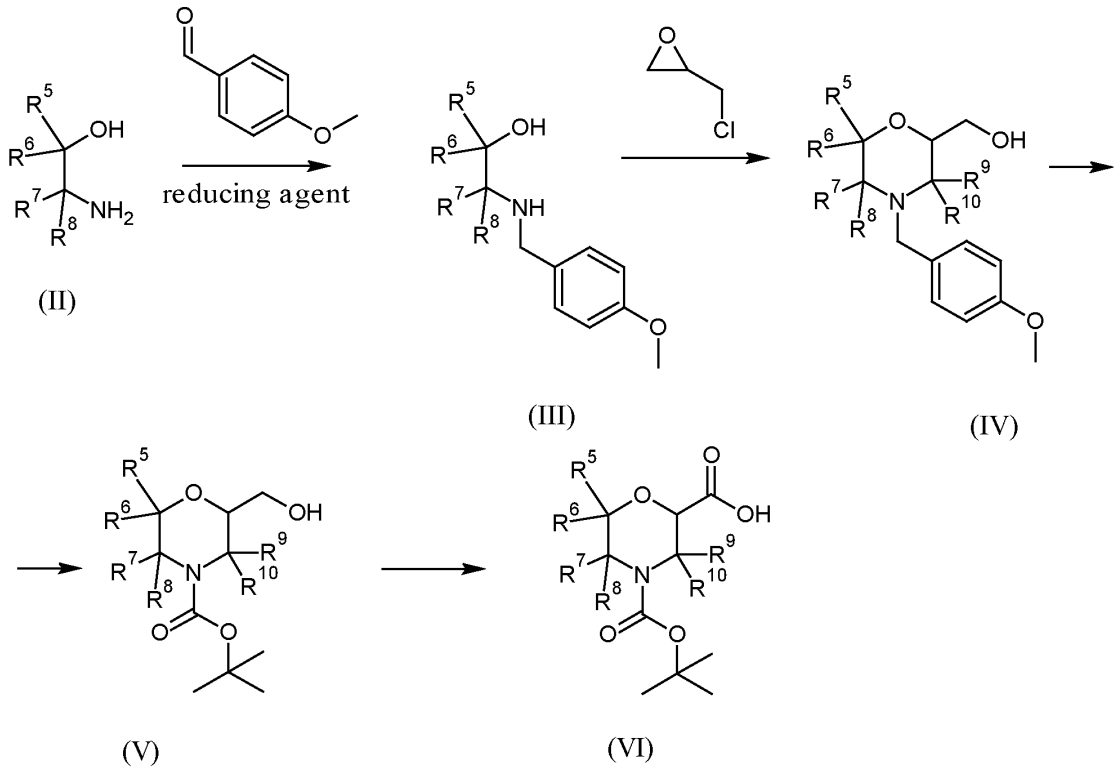
As used herein, the term “treatment” means using an effective therapy to reduce, alleviate or eliminate the symptoms associated with diseases and conditions mediated and modulated by the $GABA_B$ receptor positive allosteric mechanism.

As a further aspect of the present invention there is provided the synthesis of compounds of formula (I).

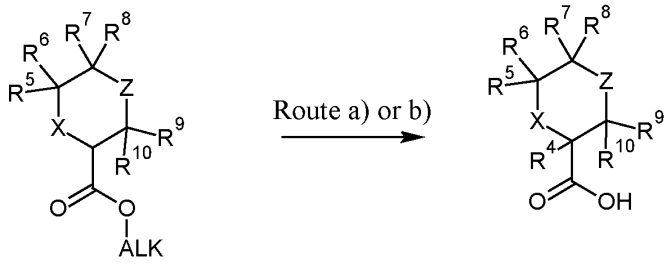
Compounds according to the present invention were synthesized in line with the synthetic routes and schemes described below.

Accordingly, the compounds of formula (I) of the invention can be synthesized by one of the following routes:

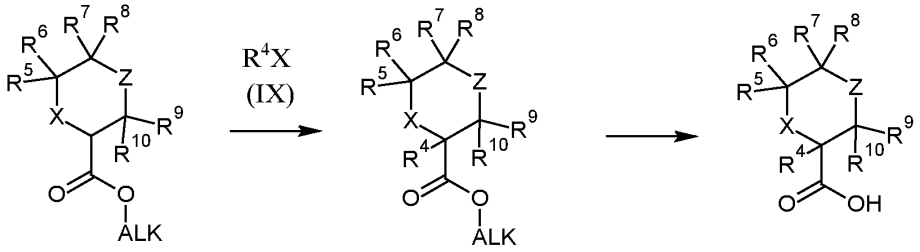
<u>If R^9=R^{10}=H; X=O and Z=NR then</u>



If R^4 is not H

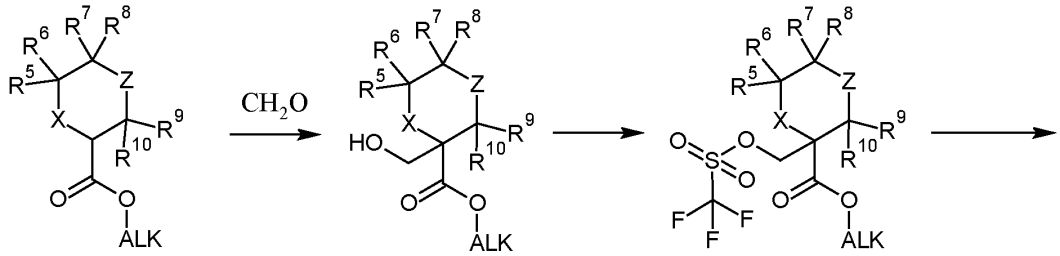


Route a):

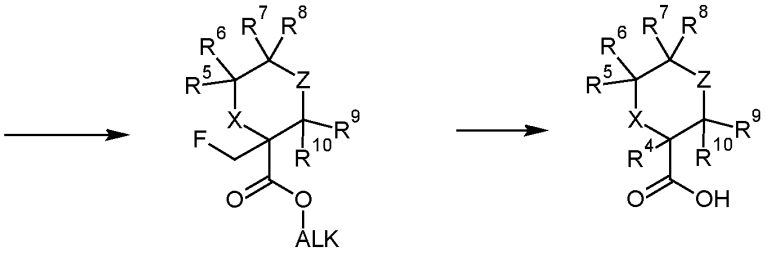


(VII) (X) (VIII)

Route b):

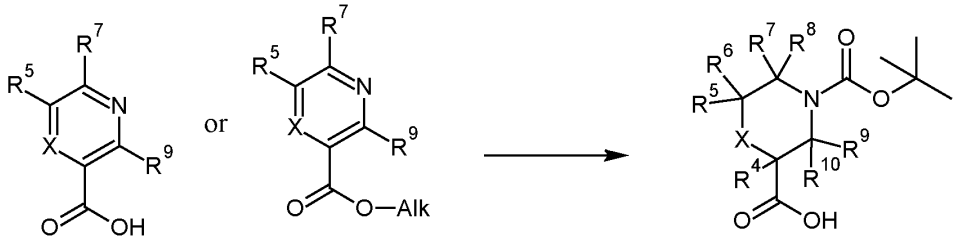


(VII) (XI) (XII)



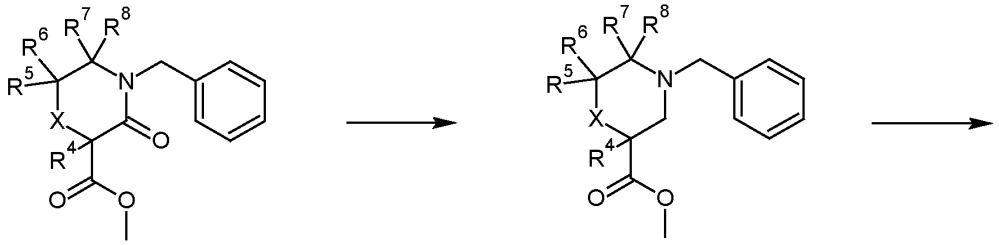
(XIII) (VIII)

If R^4=R^6=R^8=R^{10}=H; X=CR^xR^y; R^y=H and Z=NR then

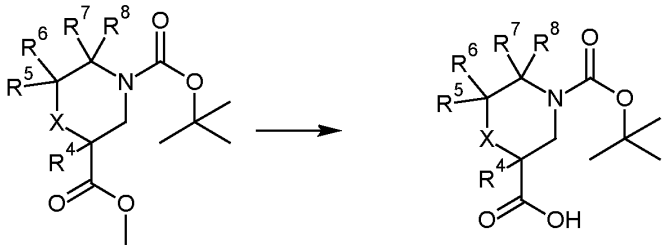


(XIV) (XV) (XVI)

If R^4=H; X=CR^xR^y and Z=NR then



(XVII) (XVIII)



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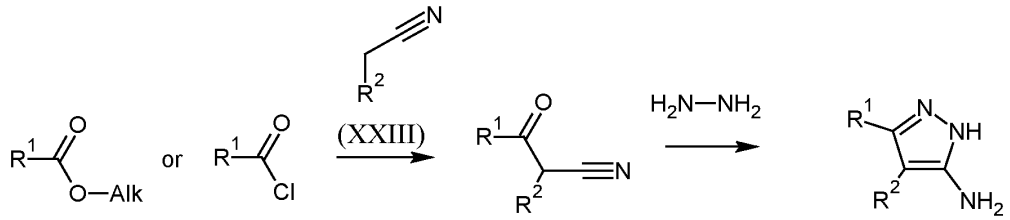
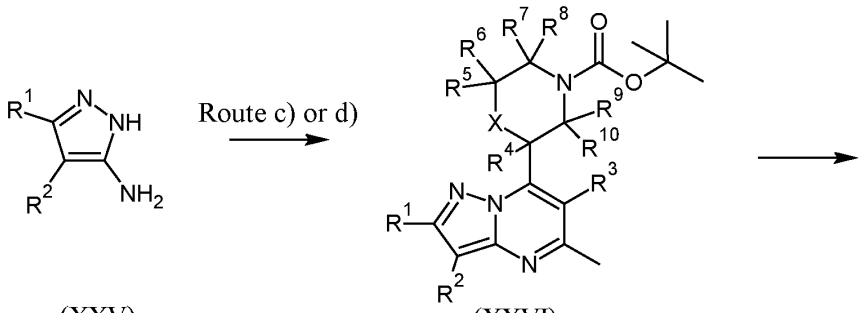
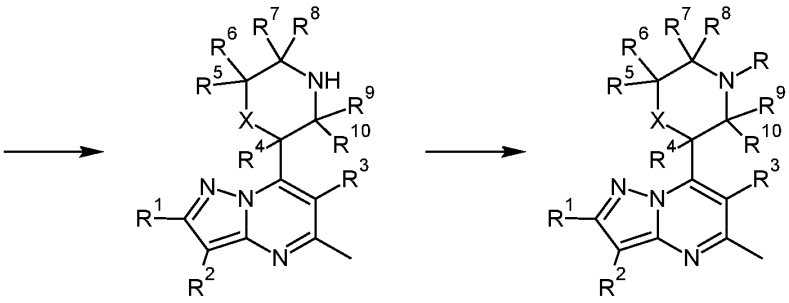


(XXI) (XXII) (XXIII) (XXIV) (XXV)

If Z=NR and X is not -S(O)$_n$- then

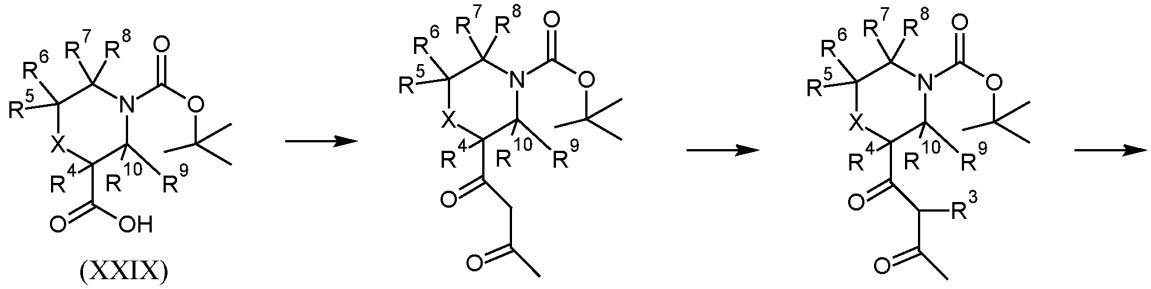


(XXV) (XXVI)

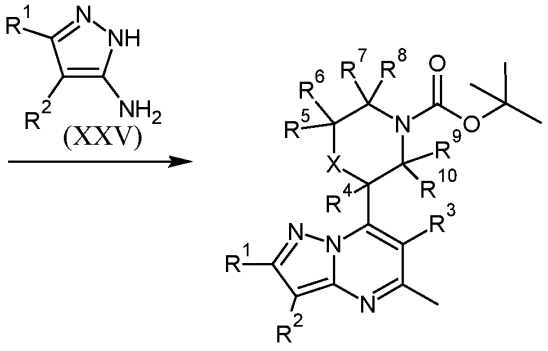


(XXVII) (XXVIII)

Route c)



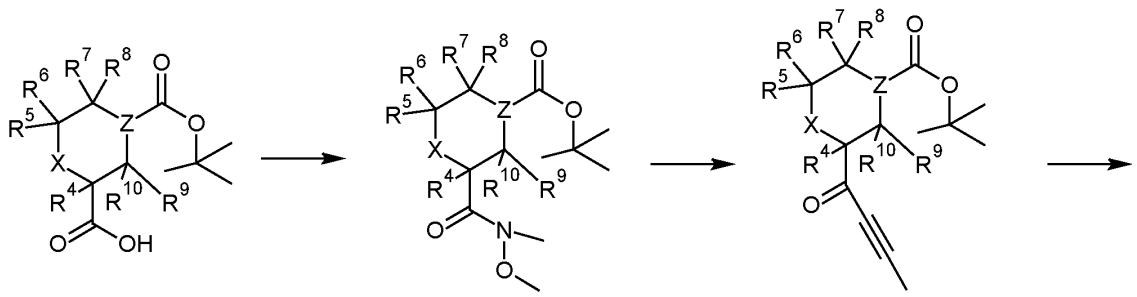
(XXIX) (XXX) (XXXI)



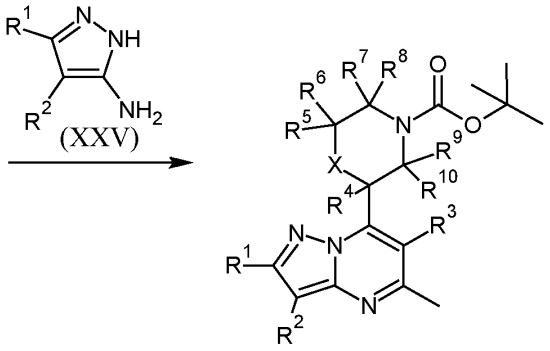
(XXV)

(XXVI)

Route d)



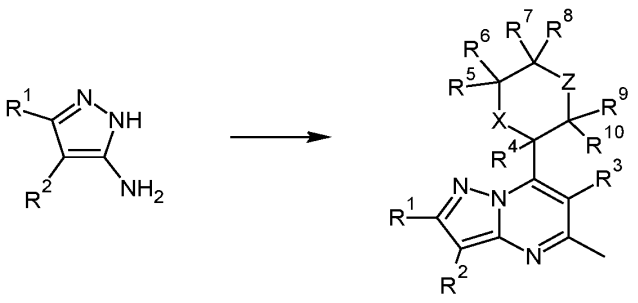
(XXIX) (XXXII) (XXXIII)



(XXV)

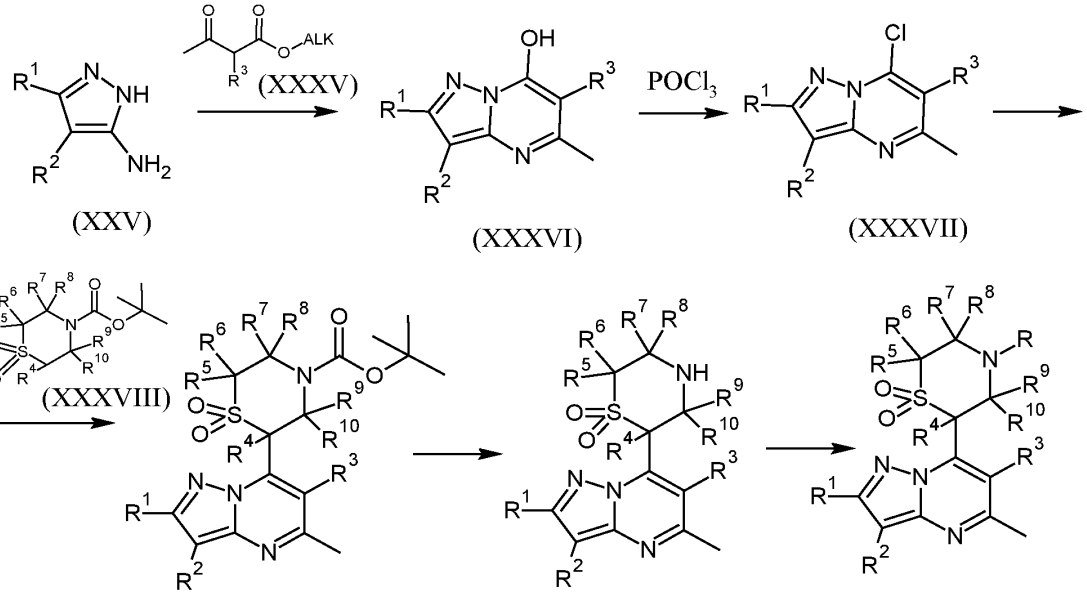
(XXVI)

If Z=O or -S(O)$_2$- then



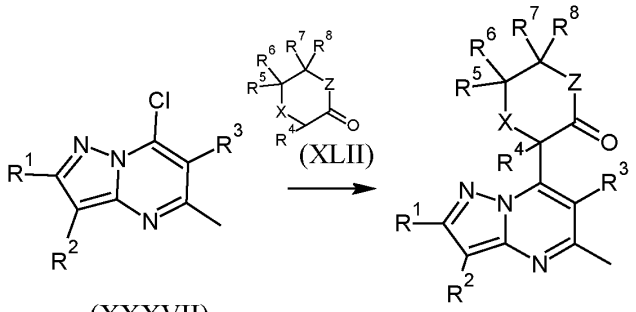
(XXV) (XXXIV)

If X=S(O)$_2$ and Z=NR then



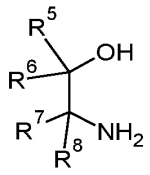
(XXV) (XXXV) (XXXVI) (XXXVII) (XXXVIII) (XXXIX) (XL) (XLI)

If R^9 and R^{10} together form an oxo group:



(XXXVII) (XLII) (XLIII)

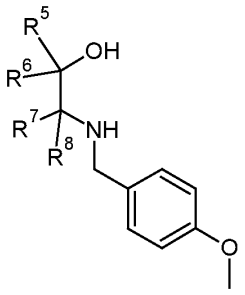
If R^9=R^{10}=H; X=O and Z=NR then: reacting β-amino-alcohol derivative of formula (II)



(II)

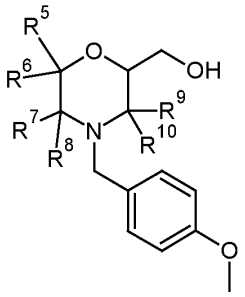
- wherein the meaning of R^5, R^6, R^7, R^8, R is described above for compound of formula (I) with 4-Methoxybenzaldehyde, then with a reducing agent

The so obtained β-amino-alcohol derivative of formula (III) is reacted with



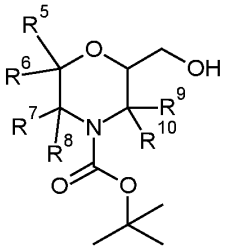
(III)

epichlorohydrin to provide a compound of formula (IV)



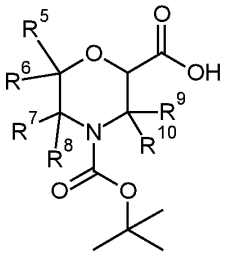
(IV)

The so obtained morpholine derivative of formula (IV) is reacted with hydrogen and then with di-*tert*-butyl dicarbonate to provide a compound of formula (V)



(V)

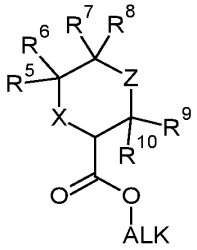
The so obtained morpholine derivative of formula (V) is oxidized to carboxylic acid derivative of formula (VI)



(VI)

If R^4 is not H then:

Route a): reacting carboxylic acid ester derivative of formula (VII)



(VII)

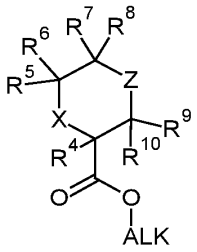
- wherein the meaning of R^5, R^6, R^7, R^8, R^9, R^{10}, X, Z is described above for compound of formula (I) with an alkyl halide of formula (IX)

R^4X

(IX)

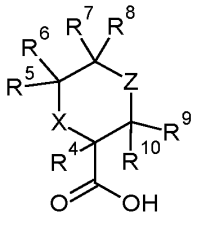
- wherein the meaning of R^4 is described above for compound of formula (I)

The so obtained heterocycle of formula (X) is hydrolyzed



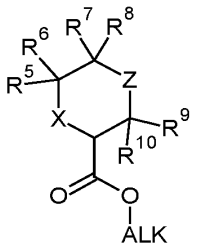
(X)

to provide the carboxylic acid derivative of formula (VII)



(VIII)

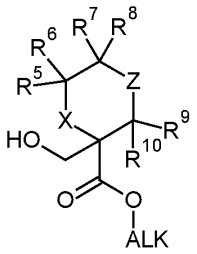
Route b): reacting carboxylic acid ester derivative of formula (VII)



(VII)

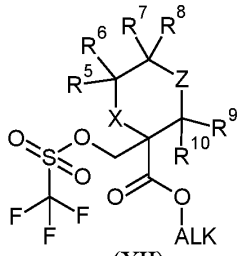
- wherein the meaning of R^5, R^6, R^7, R^8, R^9, R^{10}, X, Z is described above for compound of formula (I) with formaldehyde

The so obtained hydroxymethyl derivative of formula (XI) is reacted with



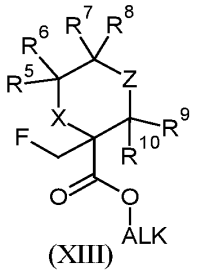
(XI)

trifluoromethanesulfonic anhydride to provide a compound of formula (XII)



(XII)

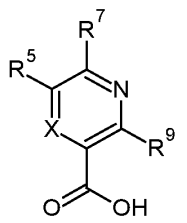
The so obtained triflate derivative of formula (XII) is reacted with tetrabutylammonium fluoride to provide a compound of formula (XIII).



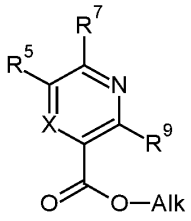
(XIII)

The so obtained fluoromethyl derivative of formula (XIII) is hydrolyzed to provide the carboxylic acid derivative of formula (VIII)

If R^4=R^6=R^8=R^{10}=H; X=CR^xR^y; R^y=H and Z=NR then reacting nicotinic acid derivative of formula (XIV) or nicotinic acid ester derivative of formula (XV)

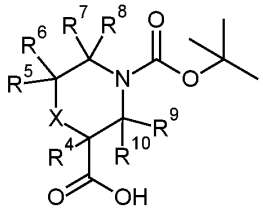


or



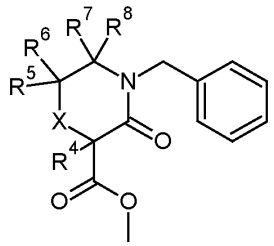
(XIV) (XV)

- wherein the meaning of R^5, R^7, R^9 is described above for compound of formula (I) with hydrogen, then with di-*tert*-butyl dicarbonate. If the product is a carboxylic acid ester, it is hydrolysed to furnish the piperidine derivative of formula (XVI)



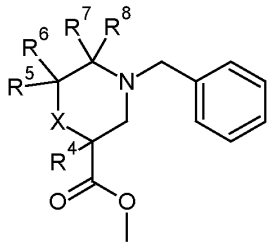
(XVI)

If R^4=H; X=CR^xR^y and Z=NR then reacting lactame derivative of formula (XVII)



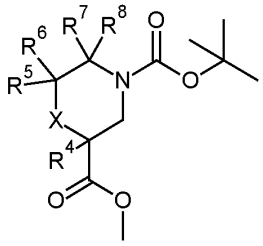
(XVII)

- wherein the meaning of R^4, R^5, R^6, R^7, R^8 is described above for compound of formula (I) with a reducing agent to provide the piperidine derivative of formula (XVIII)



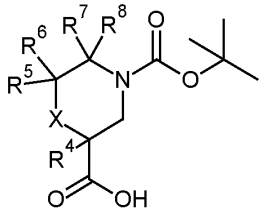
(XVIII)

The so obtained piperidine derivative of formula (XVIII) is reacted with hydrogen, then with di-*tert*-butyl dicarbonate to furnish piperidine derivative of formula (XIX)



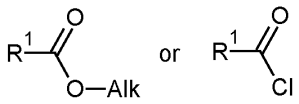
(XIX)

The carboxylic acid ester is hydrolysed to provide piperidine derivative (XX).



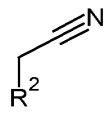
(XX)

Reacting a carboxylic acid ester derivative of formula (XXI) or carboxylic acid chloride derivative of formula (XXII)



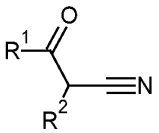
(XXI) (XXII)

- wherein the meaning of R^1 is described above for compound of formula (I) – with an acetonitrile derivative of formula (XXIII)



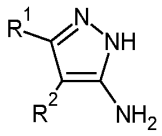
(XXIII)

- wherein the meaning of R^2 is described above for compound of formula (I), then the so obtained acylacetonitrile derivative of formula (XXIV) is reacted with



(XXIV)

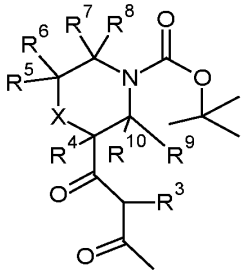
hydrazine hydrate to provide a compound of formula (XXV)



(XXV)

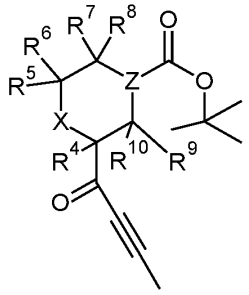
If Z=NR and X is not $S(O)_n$ then reacting aminopyrazole derivative of formula (XXV) with either

c) acetylacetone derivative of formula (XXXI)



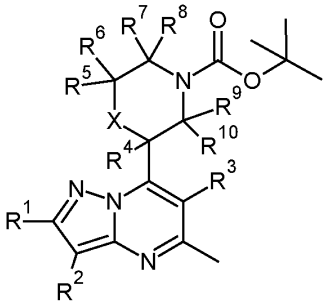
- wherein the meaning of R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10} is described above for compound of formula (I), or

d) alkyne derivative of formula (XXXIII)



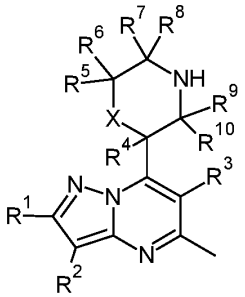
(XXXIII)

- wherein the meaning of R^4, R^5, R^6, R^7, R^8, R^9, R^{10} is described above for compound of formula (I) to furnish pyrazolo[1,5-*a*]pyrimidine derivative of formula (XXVI)



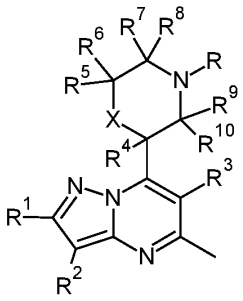
(XXVI)

The so obtained compound is treated with strong acid to furnish the amine derivative of formula (XXVII).



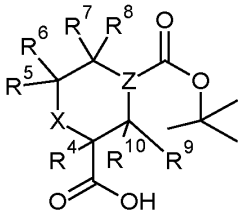
(XXVII)

The so obtained compound is treated with the appropriate reagents to furnish examples of formula (XXVIII)



(XXVIII)

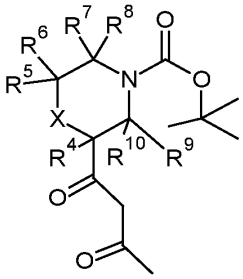
Route c): reacting carboxylic acid derivative of formula (XXIX)



(XXIX)

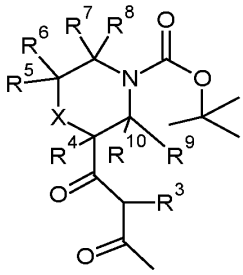
- wherein the meaning of R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10} is described above for compound of formula (I) with acetone

The so obtained acetylacetone derivative of formula (XXX)



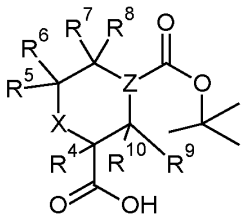
(XXX)

is reacted with the appropriate alkyl halide to furnish the acetylacetone derivative of formula (XXXI)



(XXXI)

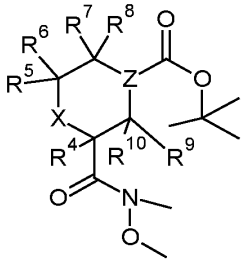
Route d): reacting carboxylic acid derivative of formula (XXIX)



(XXIX)

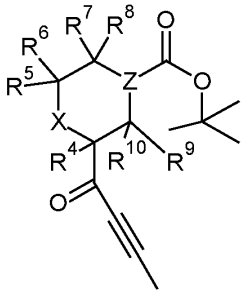
- wherein the meaning of R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10} is described above for compound of formula (I) with N,O-dimethylamine

The so obtained Weinreb amide derivative of formula (XXXII)



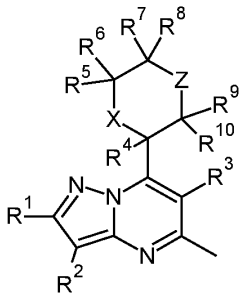
(XXXII)

is reacted with 1-Propynylmagnesium bromide to furnish alkyne derivative of formula (XXXIII).



(XXXIII)

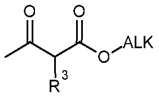
If Z=O os $S(O)_2$: reacting aminopyrazole derivative of formula (XXV) with the appropriate acetylacetone derivative or the appropriate alkyne derivative to furnish the pyrazolo[1,5-*a*]pyrimidine derivative of formula (XXXIV)



(XXXIV)

- wherein the meaning of R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, X, Z is described above for compound of formula (I)

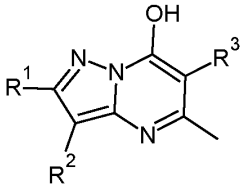
If X=S(O)$_2$ and Z=NR then: reacting aminopyrazole derivative of formula (XXV) with acylacetic ester derivative of formula (XXXV)



(XXXV)

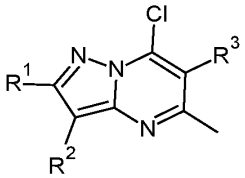
- wherein the meaning of R^3 is described above for compound of formula (I)

The so obtained compound of formula (XXXVI)



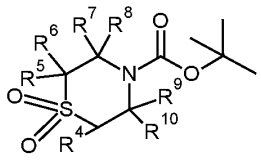
(XXXVI)

is chlorinated to furnish a chloro derivative of formula (XXXVII)



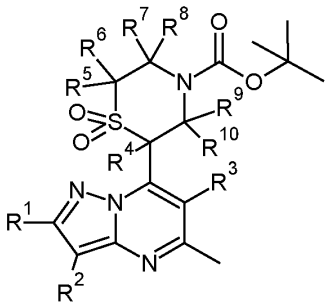
(XXXVII)

The so obtained compound is reacted with sulfone derivative of compound (XXXVII)



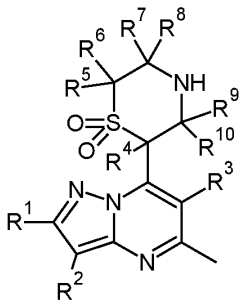
(XXXVIII)

- wherein the meaning of R^4, R^5, R^6, R^7, R^8, R^9, R^{10} is described above for compound of formula (I) to furnish the sulfone derivative of compound (XXXIX).



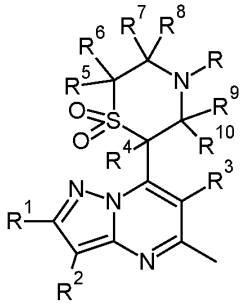
(XXXIX)

The so obtained compound is treated with strong acid to furnish the amine derivative of formula (XL).



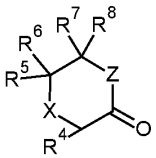
(XL)

The so obtained compound is treated with the appropriate reagents to furnish examples of formula (XLI)



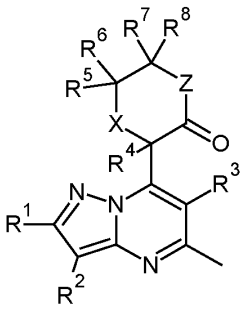
(XLI)

If R^9 and R^{10} together form an oxo group: reacting chloro derivative of formula (XXXVII) with heterocycle of formula (XLII)



(XLII)

- wherein the meaning of R^4, R^5, R^6, R^7, R^8 is described above for compound of formula (I) to furnish examples of formula (XLIII)



(XLIII)

The synthesis of carboxylic acid derivative of formula (VI) can be carried out in the following way:

The reaction of β-amino-alcohol derivative of formula (II) with 4-Methoxybenzaldehyde is preferably carried out in a proper solvent, e.g. methanol. The reducing agent is preferably $NaBH_4$. The reaction is carried out at a temperature in the range of 0 °C to room temperature. The necessary reaction time is 1-16 h. The reactions are followed by thin layer chromatography. The reaction is quenched by the addition of water. The product (III) is isolated by extraction with a proper organic solvent.

The ring closure of β-amino-alcohol derivative of formula (III) is preferably carried out in a suitable solvent, e.g. toluene with epichlorohydrin, suitable Lewis acid, e.g. $LiClO_4$, and a suitable base, e.g. NaOMe in MeOH. The reaction is carried out at a temperature in the range of 0 °C to room temperature. The necessary reaction time is 24-48 h. The reactions are followed by thin layer chromatography. The reaction is quenched by the addition of saturated NH_4Cl solution. The crude product is isolated by extraction with a proper organic solvent. The product (IV) is purified by column chromatography. The column chromatography is carried out on normal phase using Kieselgel 60 as adsorbent and different solvent systems, e.g. cyclohexane/ethyl acetate.

The hydrogenation of morpholine derivative of formula (IV) is preferably carried out in a suitable solvent, e.g. ethanol, in the presence of a suitable catalyst, e.g. palladium on carbon, in the presence of di-*tert*-butyl dicarbonate. The reaction is preferably carried out at room temperature, preferably at 5-10 bar. The necessary reaction time is 24-72 h. The reactions are followed by thin layer chromatography. The crude product is isolated after filtration over Celite pad. The product (V) is purified by column chromatography. The column chromatography is carried out on normal phase using Kieselgel 60 as adsorbent and different solvent systems, e.g. cyclohexane/ethyl acetate.

The oxidation of morpholine derivative of formula (V) is preferably carried out in a suitable solvent system, e.g. dichloromethane/water, preferably in the presence of TEMPO radical and (Diacetoxyiodo)benzene. The reaction is carried out at a temperature in the range of 0 °C to room temperature. The necessary reaction time is 1-16 h. The reactions are followed by thin layer chromatography. The crude product is isolated by extraction with a proper organic solvent. The product (VI) is crystallized from a suitable solvent, preferably hexane.

The synthesis of carboxylic acid derivative of formula (VIII) can be carried out by different routes:

Route a):

The reaction of a carboxylic acid ester derivative of formula (VII) with an alkyl halide derivative of formula (IX) is preferably carried out in a proper solvent e.g. tetrahydrofuran, preferably in the presence of a strong base, e.g. lithium bis(trimethylsilyl)amide. The reaction is carried out at a temperature in the range of -78 °C to room temperature. The necessary reaction time is 1-16 h. The reactions are followed by thin layer chromatography. The reaction is quenched by the addition of saturated NH_4Cl solution. The product (X) is isolated by extraction with a proper organic solvent.

The obtained carboxylic acid ester derivative of formula (X) is hydrolyzed in a suitable solvent mixture, e.g. ethanol/water, in the presence of an alkali, e.g. sodium hydroxide. The reaction is carried out at a temperature in the range of 0 °C to room temperature. The necessary reaction time is 1-16 h. The reactions are followed by thin layer chromatography. The reaction mixture is acidified to pH=3 with a suitable acid, e.g. citric acid. The product (VIII) is isolated by extraction with a proper organic solvent.

Route b):

The reaction of a carboxylic acid ester derivative of formula (VII) with formaldehyde is preferably carried out in a proper solvent e.g. tetrahydrofuran, preferably in the presence of a strong base, e.g. lithium bis(trimethylsilyl)amide. The reaction is carried out at a temperature in the range of -78 °C to room temperature. The necessary reaction time is 1-16 h. The reactions are followed by thin layer chromatography. The reaction is quenched by the addition of saturated NH_4Cl solution. The product (XI) is isolated by extraction with a proper organic solvent.

The triflation of hydroxymethyl derivative of formula (XI) with e.g. trifluoromethanesulfonic anhydride is preferably carried out in a proper solvent e.g. dichloromethane, preferably in the presence of a base, e.g. pyridine. The reaction is carried out at a temperature in the range of -78 °C to room temperature. The necessary reaction time is 1-16 h. The reactions are followed by thin layer chromatography. The reaction is quenched by the addition of 1M HCl solution. The product (XII) is isolated by extraction with a proper organic solvent.

The fluorination of triflate derivative of formula (XII) with tetrabutylammonium fluoride is preferably carried out in a proper solvent, e.g. tetrahydrofuran. The reaction is preferably carried out at room temperature. The necessary reaction time is 1-16 h. The reactions are followed by thin layer chromatography. The reaction is quenched by the addition of water. The crude product is isolated by extraction with a proper organic solvent. The product (XIII) is purified by column chromatography. The column chromatography is carried out on normal phase using Kieselgel 60 as adsorbent and different solvent systems, e.g. cyclohexane/ethyl acetate.

The obtained carboxylic acid ester derivative of formula (XIII) is hydrolyzed in a suitable solvent mixture, e.g. ethanol/water, in the presence of an alkali, e.g. sodium hydroxide. The reaction is carried out at a temperature in the range of 0 °C to room temperature. The necessary reaction time is 1-16 h. The reactions are followed by thin layer chromatography. The reaction mixture is acidified to pH=3 with a suitable acid, e.g. citric acid. The product (VIII) is isolated by extraction with a proper organic solvent.

The synthesis of carboxylic acid derivative of formula (XVI) can be carried out in the following way:

The reaction of nicotinic acid derivative of formula (XIV) or nicotinic acid ester derivative of formula with hydrogen is preferably carried out in a proper solvent, e.g. water or alcohol, in the presence of a proper catalyst, e.g. platinum(IV) oxide. The reaction is preferably carried out at room temperature, preferably at 5-10 bar. The necessary reaction time is 24-72 h. The reactions are followed by thin layer chromatography. The product is isolated after filtration over Celite pad. The reaction with di-*tert*-butyl dicarbonate is preferably carried out in a proper solvent or solvent system, e.g. tetrahydrofuran with water, optionally in the presence of a base, e.g. sodium bicarbonate. The product is isolated by extraction with a proper organic solvent. If the product is a carboxylic acid ester, it is hydrolyzed in a proper solvent system, e.g. ethanol/water, in the presence of an alkali, e.g. sodium hydroxide. The reaction is carried out at a temperature in the range of 0 °C to room temperature. The necessary reaction time is 1-16 h. The reactions are followed by thin layer chromatography. The reaction mixture is acidified to pH=3 with a suitable acid, e.g. citric acid. The product (XVI) is isolated by extraction with a proper organic solvent.

The synthesis of carboxylic acid derivative of formula (XX) can be carried out in the following way:

The reaction of lactam derivative of formula (XVII) with a proper reducing agent, e. g. $NaBH_4$ with boron trifluoride diethyl etherate is preferably carried out in a proper solvent e.g. tetrahydrofuran. The reaction is carried out at a temperature in the range of -15 °C to room temperature. The necessary reaction time is 1-16 h. The reactions are followed by thin layer chromatography. The reaction is quenched by the addition of water. The product (XVIII) is isolated by extraction with a proper organic solvent.

The hydrogenation of piperidine derivative of formula (XVIII) is preferably carried out in a suitable solvent, e.g. methanol, in the presence of a suitable catalyst, e.g. palladium on carbon, in the presence of di-*tert*-butyl dicarbonate. The reaction is preferably carried out at room temperature, preferably at 5-10 bar. The necessary reaction time is 24-72 h. The reactions are followed by thin layer chromatography. The crude product is isolated after filtration over Celite pad. The product (XIX) is purified by column chromatography. The column chromatography is carried out on normal phase using Kieselgel 60 as adsorbent and different solvent systems, e.g. cyclohexane/ethyl acetate.

The obtained carboxylic acid ester derivative of formula (XIX) is preferably hydrolyzed in a suitable solvent, e.g. tetrahydrofuran, in the presence of potassium trimethylsilanolate. The

reaction is carried out at a reflux temperature. The necessary reaction time is 1-16 h. The reactions are followed by thin layer chromatography. The reaction mixture is acidified to pH=4 with a suitable acid, e.g. citric acid. The product (XX) is isolated by extraction with a proper organic solvent.

The synthesis of aminopyrazole derivative of formula (XXV) can be carried out in the following way:

The reaction of a carboxylic acid ester derivative of formula (XXI) or carboxylic acid chloride derivative of formula (XXII) with an acetonitrile derivative of formula (XXIII) is preferably carried out in a proper solvent, e.g. tetrahydrofuran, preferably in the presence of a strong base e.g. *n*-butyllithium, lithium bis(trimethylsilyl)amide. The reaction carried out at a temperature in the range of -78 °C to room temperature. The necessary reaction time is 1-16 h. The reactions are followed by thin layer chromatography. The reaction mixture is quenched by addition of water and hydrochloric acid (~pH 2-3) or saturated ammonium chloride solution. The product acylacetonitrile derivative of formula (XXIV) is isolated by extraction with a proper organic solvent.

The cyclocondensation reaction of the acylacetonitrile derivative of formula (XXIV) with hydrazine hydrate to aminopyrazole derivatives of formula (XXV) is preferably carried out in a suitable solvent, e.g. ethanol. The reaction is preferably carried out at boiling point of the solvent. The necessary reaction time is 1-6 h. The reactions are followed by thin layer chromatography. The reaction is quenched by the addition of water. The product (XXV) is isolated by extraction with a proper organic solvent.

The synthesis of pyrazolo[1,5-*a*]pyrimidine derivative of formula (XXVI) can be carried out in the following ways:

Route c):

The cyclocondensation reaction of the aminopyrazole derivative of formula (XXV) with acetylacetone derivatives of formula (XXXI) is preferably carried out in a suitable solvent, e.g. toluene, in the presence of a proper catalyst, e.g. p- Toluenesulfonic acid monohydrate. The reaction is preferably carried out at boiling point of the solvent. The necessary reaction time is 1-16 h. The reactions are followed by thin layer chromatography. The product (XXVI) is purified by column chromatography. The column chromatography is carried out on normal phase using Kieselgel 60 as adsorbent and different solvent systems, e.g. cyclohexane/ethyl acetate.

Route d):

The cyclocondensation reaction of the aminopyrazole derivative of formula (XXV) with alkyne derivatives of formula (XXXIII) is preferably carried out in a suitable solvent, e.g. ethanol, in the presence of a proper base, e.g. pyrrolidine, and a suitable acid, e.g. acetic acid. The reaction is preferably carried out at 60 °C. The necessary reaction time is 4-16 h. The reactions are followed by thin layer chromatography. The product (XXVI) is purified by column chromatography. The column chromatography is carried out on normal phase using Kieselgel 60 as adsorbent and different solvent systems, e.g. cyclohexane/ethyl acetate.

The synthesis of pyrazolo[1,5-*a*]pyrimidine derivative of formula (XXVIII) can be carried out in the following way:

The reaction of pyrazolo[1,5-*a*]pyrimidine derivative of formula (XXVI) with a strong acid, e.g. trifluoroacetic acid is preferably carried out in a proper solvent, e.g. dichloromethane. The reaction carried out at a temperature in the range of 0 °C to room temperature. The necessary reaction time is 1-16 h. The reactions are followed by thin layer chromatography. The reaction mixture is quenched by addition of 2M sodium hydroxide solution (~pH 12-14). The product pyrazolo[1,5-*a*]pyrimidine derivative of formula (XXVII) is isolated by extraction with a proper organic solvent.

The compound pyrazolo[1,5-*a*]pyrimidine derivative of formula (XXVII) can be transformed to pyrazolo[1,5-*a*]pyrimidine derivative of formula (XXVIII) in the following ways:

In certain embodiments the reaction of pyrazolo[1,5-*a*]pyrimidine derivative of formula (XXVII) with methyl bromoacetate, in the presence of a base, e.g. *N,N*-Diisopropylethylamine, is preferably carried out in a proper solvent, e.g. toluene. The reaction is preferably carried out at room temperature. The necessary reaction time is 4-16 h. The reactions are followed by thin layer chromatography. The reaction is quenched by the addition of water. The crude product is isolated by extraction with a proper organic solvent. The crude product is purified by column chromatography. The column chromatography is carried out on normal phase using Kieselgel 60 as adsorbent and different solvent systems, e.g. acetone/dichloromethane. The product is hydrolyzed in the presence of hydrochloric acid, in a suitable solvent, e.g. water, to furnish pyrazolo[1,5-*a*]pyrimidine derivative of formula (XXVIII).

In certain embodiments the reaction of pyrazolo[1,5-*a*]pyrimidine derivative of formula (XXVII) with *N*-Boc protected amino acids, in the presence of a base, e.g. *N,N*-

Diisopropylethylamine, is carried out in a proper solvent, e.g. dimethylformamide, using a proper coupling agent, e.g. HBTU. The reaction is preferably carried out at room temperature. The necessary reaction time is 1-16 h. The reactions are followed by thin layer chromatography. The reaction is quenched by the addition of water. The crude product is isolated by extraction with a proper organic solvent. The product is purified by column chromatography. The column chromatography is carried out on normal phase using Kieselgel 60 as adsorbent and different solvent systems, e.g. methanol/dichloromethane. The product is reacted with strong acid, e.g. Trifluoroacetic acid, in a proper solvent, e.g. dichloromethane. The reaction is preferably carried out at 0 °C to room temperature. The necessary reaction time is 1-16 h. The reactions are followed by thin layer chromatography. The product (XXVIII) is purified by column chromatography. The column chromatography is carried out on normal phase using Kieselgel 60 as adsorbent and different solvent systems, e.g. methanol/dichloromethane.

In certain embodiments the reaction of pyrazolo[1,5-*a*]pyrimidine derivative of formula (XXVII) with acyl chlorides, in the presence of a base, e.g. triethylamine, is preferably carried out in a proper solvent, e.g. dichloromethane. The reaction is preferably carried out at 0 °C to room temperature. The necessary reaction time is 1-16 h. The reactions are followed by thin layer chromatography. The reaction is quenched by the addition of water. The crude product is isolated by extraction with a proper organic solvent. The product (XXVIII) is purified by column chromatography. The column chromatography is carried out on normal phase using Kieselgel 60 as adsorbent and different solvent systems, e.g. methanol/dichloromethane.

In certain embodiments the reaction of pyrazolo[1,5-*a*]pyrimidine derivative of formula (XXVII) with formic acid, is preferably carried out in a proper solvent, e.g. toluene. The reaction is preferably carried out at boiling point of the solvent. The necessary reaction time is 4-16 h. The reactions are followed by thin layer chromatography. The reaction is quenched by the addition of water. The crude product is isolated by extraction with a proper organic solvent. The product (XXVIII) is purified by column chromatography. The column chromatography is carried out on normal phase using Kieselgel 60 as adsorbent and different solvent systems, e.g. methanol/dichloromethane.

In certain embodiments the reaction of pyrazolo[1,5-*a*]pyrimidine derivative of formula (XXVII) with carboxylic acids, in the presence of a base, e.g. *N,N*-Diisopropylethylamine, is carried out in a proper solvent, e.g. dimethylformamide, using a proper coupling agent, e.g. HBTU. The reaction is preferably carried out at room temperature. The necessary reaction time is 1-16 h. The reactions are followed by thin layer chromatography. The reaction is quenched by the addition of water. The crude product is isolated by extraction with a proper organic solvent. The product

(XXVIII) is purified by column chromatography. The column chromatography is carried out on normal phase using Kieselgel 60 as adsorbent and different solvent systems, e.g. methanol/dichloromethane.

In certain embodiments the reaction of pyrazolo[1,5-*a*]pyrimidine derivative of formula (XXVII) with 1-Amidinopyrazole Hydrochloride, in the presence of a base, e.g. *N,N*-Diisopropylethylamine, is preferably carried out in a proper solvent, e.g. dimethylformamide. The reaction is preferably carried out at room temperature. The necessary reaction time is 1-16 h. The reactions are followed by thin layer chromatography. The product (XXVIII) is isolated by filtration.

In certain embodiments the reaction of pyrazolo[1,5-*a*]pyrimidine derivative of formula (XXVII) with the proper aldehyde or ketone, in the presence of a reducing agent, e.g. Sodium triacetoxyborohydride, in the presence of acetic acid, is preferably carried out in a proper solvent, e.g. 1,2-Dichloroethane. The reaction is preferably carried out at room temperature. The necessary reaction time is 1-16 h. The reactions are followed by thin layer chromatography. The reaction is quenched by the addition of water. The crude product is isolated by extraction with a proper organic solvent. The product (XXVIII) is purified by column chromatography. The column chromatography is carried out on normal phase using Kieselgel 60 as adsorbent and different solvent systems, e.g. methanol/dichloromethane.

In certain embodiments the reaction of pyrazolo[1,5-*a*]pyrimidine derivative of formula (XXVII) with (Trimethylsilyl)isocyanate, is preferably carried out in a proper solvent, e.g. dichloromethane. The reaction is preferably carried out at room temperature. The necessary reaction time is 1-16 h. The reactions are followed by thin layer chromatography. The reaction is quenched by the addition of water. The crude product is isolated by extraction with a proper organic solvent. The product (XXVIII) is purified by column chromatography. The column chromatography is carried out on normal phase using Kieselgel 60 as adsorbent and different solvent systems, e.g. methanol/dichloromethane.

In certain embodiments the reaction of pyrazolo[1,5-*a*]pyrimidine derivative of formula (XXVII) with sulfamide, is preferably carried out in a proper solvent, e.g. dioxane. The reaction is preferably carried out at boiling point of the solvent. The necessary reaction time is 1-16 h. The reactions are followed by thin layer chromatography. The reaction is quenched by the addition of water. The crude product is isolated by extraction with a proper organic solvent. The product (XXVIII) is purified by column chromatography. The column chromatography is carried out on normal phase using Kieselgel 60 as adsorbent and different solvent systems, e.g. methanol/dichloromethane.

The compounds of the present invention and optical antipodes or racemates and/or salts thereof can be used as such or suitably in the form of pharmaceutical compositions.

The invention also relates to the pharmaceutical compositions containing the compounds of formula (I) or optical antipodes or racemates and/or salts thereof as active ingredient for the treatment of certain disorders associated with $GABA_B$ receptor positive allosteric modulator activity.

The present compounds may be co-adminstered to a subject in combination with two or more different therapeutic agents (eg. most preferably antipsychotics and psychostimulants; and preferably antidepressants, anxiolytics, antihypertensives, anticonvulsants, sedatives, and narcotics).

Suitable routes of administration may, for example, include oral, rectal, transmucosal, transdermal or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intraarticular, intrathecal, direct intraventricular, intraperitoneal, intranasal, or intraocular injections and eye drops.

Alternatively, one may administer the compound in a local rather than systemic manner, for example, via injection of the compound directly in the renal or cardiac area, often in a depot or sustained release formulation. Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome coated with a tissue-specific antibody. The liposomes will be targeted to and taken up selectively by the organ.

The pharmaceutical compositions can be administered through via a variety of routes and dosages forms. The compound of the invention may be administered either alone or in combination with pharmaceutically acceptable carriers, in either single or multiple doses. The dosage required to exert the therapeutic effect can vary within wide limits and will be fitted to the individual requirements in each of the particular case, depending on the stage of the disease, the condition and the bodyweight of the patient to be treated, as well as the sensitivity of the patient against the active ingredient, route of administration and number of daily treatments.

For the sake of a simple administration it is suitable if the pharmaceutical compositions comprise dosage units containing the amount of the active ingredient to be administered once, or a few multiples or a half, third or fourth part thereof. Such dosage units are e.g. tablets, which can be powdered with grooves promoting the halving or quartering of the tablet in order to exactly administer the required amount of the active ingredient.

The pharmaceutical compositions containing the active ingredient according to the present invention usually contain 0.01 to 500 mg of active ingredient in a single dosage unit. It is, of course possible that the amount of the active ingredient in some compositions exceeds the upper or lower limits defined above.

As a further aspect of the invention there is provided the pharmaceutical manufacture of medicaments containing the compounds of formula (I) or optical antipodes or racemates and/or salts thereof.

The pharmaceutical compositions of the present invention may be formulated as different pharmaceutical dosage forms, such as but not limited to, solid oral dosage forms like tablets (e.g. buccal, sublingual, effervescents, chewable, orodispersible, freeze dried), capsules, lozenges, pastilles, pills, orodispersible films, granules, powders; liquid oral dosage forms like solutions, emulsions, suspensions, syrups, elixirs, oral drops; parenteral dosage forms like intravenous injections, intramuscular injections, subcutaneous injections; other dosage forms like eye drops, semi-solid eye preparations, transdermal dosage forms, suppositories, rectal capsules, rectal solutions, emulsions and suspensions, etc.

In one embodiment the invention relates to pharmaceutical dosage forms specifically intended for pediatric use, such as but not limited to, solutions, syrups, elixirs, suspensions, powders for reconstitution as suspension, dispersible or effervescent tablets, chewable tablets, orally disintegrating tablets, tablets or coated tablets, sprinkle oral powder or granules, capsules.

The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, emulsifying, suspending, entrapping, freeze-drying, extrusion, laminating, film-casting, granulating, grinding, encapsulating, dragee-making or tableting processes.

Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art.

Suitable excipients for the preparation of the dosage forms may be selected from the following categories, such as but not limited to, tablet and capsule fillers, tablet and capsule binders, modified-release agents, disintegrants, glidants, lubricants, sweetening agents, taste-masking agents, flavoring agents, coating agents, surfactants, antioxidants, buffering agents, complexing

agents, emulsifying agents, lyophilization aids, microencapsulating agents, ointment bases, penetration enhancers, solubilizing agents, solvents, suppository bases, suspending agents.

In one embodiment the invention relates to the using of specific excipients which are able to improve the solubility, dissolution, penetration, adsorption or bioavailability of the active ingredient(s), such as but not limited to, hydrophilic polymers, hot melt extrusion excipients, surfactants, buffering agents, complexing agents, emulsifying agents, lyophilization aids, superdisintegrants, microencapsulating agents, penetration enhancers, solubilizing agents, co-solvents, suspending agents.

The above described ingredients and different routes of manufacture are merely representative. Other materials as well as processing techniques and the like well known in the art can also be used.

The compounds are effective in the treatment of psychiatric, neurodevelopmental, neurological and other central nervous system disorders as well as peripheral conditions where stimulation of the $GABA_B$ receptor may offer therapeutic benefit

BIOLOGICAL EVALUATION

***In vitro* [^{35}S]GTPγS binding assay in rat cortical membranes**

Cortices of freshly harvested rat brains were dissected on an ice-cold surface and homogenized by a glass Dounce homogeniser immediately in ice-cold buffer containing 50 mM Tris, 5 mM $MgCl_2$ and 1 mM EDTA (pH=7.6). Tissue homogenates were centrifuged at 40000 g for 15 min at 4°C. Membrane pellets were resuspended in the same buffer and membranes were incubated for 10 min at 30°C in a shaking water bath to eliminate endogenous GABA. Homogenates were centrifuged again under the same conditions. The final pellets were resuspended in ice-cold buffer (pH=7.6) containing 50 mM Tris, 100 mM NaCl, 7 mM $MgCl_2$, 1 mM EDTA and 1 mM dithiotreithol (DTT) to yield a concentration of 20 mg tissue weight/ml and frozen at -70°C until use. The assay was done in a buffer containing 50 mM Tris (pH=7.4), 100 mM NaCl, 7 mM $MgCl_2$, 1 mM EDTA and 1 mM DTT. Each assay tube contained 150 µL GDP (in a final concentration of 50 µM), 100 µL ligand and 125 µL of the membrane suspension (250 µg tissue/tube). The assay tubes were preincubated for 10 min at 30°C to assure equilibrium. Nonspecific binding was determined in the presence of 10 µM GTPγS; basal binding was determined in the presence of buffer only. After addition of 50 pM [^{35}S]GTPγS in a volume of 25 µL to the tubes, membranes were incubated for an additional 60 min at 30°C. The assay was terminated by rapid filtration through Packard UniFilter GF/B using a Packard harvester and washed four times with 1 ml ice-cold buffer.

After drying the filters at 40°C for 1 h, 40 µL Microscint (Packard) was added to the filters and radioactivity of the filters was determined by a TopCount NXT (PerkinElmer, Waltham, MA; Alper and Nelson, *Eur. J. Pharmacol.* 1998, 343, 303-312; Rinken et al, *Biochem. Pharmacol.* 1999, 57, 155-162). Data thus gathered were used to determine PAM EC_{50} values for each compound as primary in vitro activity end point.

In Table 1 compounds of this invention measured in the [^{35}S]GTPγS binding assay are listed.

Table 1

Example	In vitro PAM potency	Example	In vitro PAM potency	Example	In vitro PAM potency
1	++	50	++	93	+++
2	++	51	++	94	+++
3	+++	52	+++	95	+++
4	++	53	+++	96	+++
5	+	54	++	97	++
6	++	55	++	98	+++
7	++	56	+++	99	++
8	+++	57	++	100	++
9	+	58	+	101	-
10	+++	59	++	102	+
11	++	60	++	103	++
12	+++	61	++	104	++
17	+++	62	++	105	+++
18	++	63	++	106	++
19	++	64	+++	107	+++
21	+++	65	+++	108	++
22	++	66	+	109	++
23	++	67	++	110	+++
24	+++	68	+	111	++
25	+	69	++	112	++
26	++	70	++	113	++
27	++	71	+++	114	++
28	+	72	++	116	++
29	++	73	+++	117	+
30	+++	74	++	118	++
32	++	75	+	119	++
33	++	76	++	120	++
34	+	77	+	121	++
35	+	78	++	122	++
36	+++	79	++	123	++
37	++	80	++	124	++++
38	++	81	++	125	++
39	++	82	+	126	++
40	+	83	++	127	++
41	+	84	++	128	+++
42	+	85	++	129	++

43	++	86	++	130	++
44	+	87	++++	132	+
45	++	88	++	158	++
46	++	89	++	159	++
47	++	90	++++	160	++
48	++	91	+	161	++
49	+++	92	+		

+ PAM EC_{50} < 100 nM

++ 100 nM ≤ PAM EC_{50} < 1000 nM

+++ 1000 nM ≤ PAM EC_{50} < 10000 nM

++++ 10000 nM ≤ PAM EC_{50}

Foot shock-induced ultrasonic vocalization (USV) in adult rats

Under stressful conditions, adult rats emit 22 kHz ultrasounds that can be reduced by various pharmacological treatments (De Vry et al, *Eur. J. Pharmacol.* 1993, 249, 331–339; Sanchez, *Eur. J. Pharmacol.* 2003, 463, 133–143). Previous unpublished experiments indicated that $GABA_B$ receptor ligands can also inhibit vocalizations that are induced by electric footshocks as stressor. Therefore, a foot shock-induced vocalization paradigm in adult rats was used to assess in vivo efficacy of centrally acting $GABA_B$ receptor ligands. Behavioral measurements were carried out on male Wistar rats (200-250 g, Toxicoop, Hungary or Janvier, France). Rats were housed in groups of four in plastic cages with a wire grid top in a temperature and light-controlled laboratory animal care unit (22 ± 2 °C, 12-h light/dark cycle, lights on at 6:00 AM) with ad libitum access to commercial pellet rat food and tap water. Investigations were approved by the Local Ethical Committee of Gedeon Richter Plc. and were carried out in strict compliance with the European Directive 2010/63/EU regarding the care and use of laboratory animals for experimental procedures and all efforts were made to minimize the number of animals as well as their suffering. In order to evoke emission of ultrasounds, animals were footshocked after a habituation period of 30 s (6 shocks, 1 s, 0.8 mA each, inter-shock interval 10 s) in a sound attenuated shocking chamber (Experimetria, 40x40x80 cm). Investigational compounds were administered at the dose of 10 mg/kg in a solid dispersion formulation or Tween80 suspension in distilled water 1 h before shocking per os. Vocalizations were measured right after the last footshock for 10 min with a Metris Sonotrack system and the total time of vocalizations was registered. Vocalization of parallel vehicle treated animals was considered as control value and inhibition percent was calculated for each compound.

In Table 2 compounds of this invention measured in the USV assay are listed.

Table 2

Example	USV inhibition %	Investigated dose (mg/kg, p.o.)
5	88%	1
9	71%	1
32	68%	3
39	33%	3
42	91%	10
43	41%	10
47	63%	10
58	44%	1
66	49%	1
68	39%	1
75	19%	1
82	86%	1
91	89%	1
111	44%	1
112	72%	1
113	66%	1
116	0%	1
117	73%	1
132	65%	1
158	35%	3

Prenatal valproate model of autism spectrum disorder (ASD)

The prenatal valproate model has excellent construct and face validity, therefore it is a widely accepted disease model of ASD (Christensen et al, *JAMA* 2013, 309, 1696-1703; Roullet et al, *Neurotox. Teratol.* 2013, 36, 45-56). In this method, time-mated female Wistar rats (Harlan UK) were administered a single dose of valproic acid (VPA, 600 mg/kg, i.p.) on gestational day 12.5. Male offspring were housed according to standard laboratory conditions until time of testing at postnatal day 59. Animals were housed in groups of 4 in conventional cages and maintained at 22–24°C on a standard 12 hour light/dark cycle (07.30-19.30), with food and water available ad libitum. After investigational drug treatment, offspring were examined behaviorally in the social preference assay at postnatal day 59. The social preference test is a highly accepted assay to assess autistic behavior in rodents (Nadler et al, *Genes Brain Behav.* 2007, 3, 303-314; Bambini-Junior et al, *Brain Res.* 2011, 1408, 8-16). Briefly, in this assay a test animal is allowed to investigate a conspecific separated by a dividing perforated wall or a similar area however, without a target conspecific. An

autistic animal (such as a prenatally valproate-exposed rat) spends little time with social investigation during a test session.

The inventors unexpectedly found that examples of the present invention were of great behavioral benefit in the present preclinical disease model that recapitulates the core symptoms of ASD. The inventors therefore showed that these compounds may be of therapeutic potential for the core symptoms of ASD in humans.

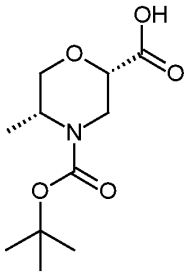
EXAMPLES

The invention is further defined in the following Examples. It should be understood that the Examples are given by way of illustration only. From the above discussion and the Examples, one skilled in the art can ascertain the essential characteristics of the invention, and without departing from the spirit and scope thereof, can make various changes and modifications to adapt the invention to various uses and conditions. As a result, the invention is not limited by the illustrative examples set forth herein below, but rather defined by the claims appended hereto.

In general, the compounds of formula (I) can be prepared according to the general knowledge of one skilled in the art and/or using methods set forth in the Example and/or Intermediate sections that follow. Solvents, temperatures, pressures, and other reaction conditions can readily be selected by one of ordinary skill in the art. Starting materials are commercially available and/or readily prepared by one skilled in the art.

The present invention will be now illustrated by the following not limiting examples.

Intermediate 1



(2*S*,5*R*)-4-[(*tert*-butoxy)carbonyl]-5-methylmorpholine-2-carboxylic acid

a) (2*R*)-2-{[(4-methoxyphenyl)methyl]amino}propan-1-ol

Under nitrogen to a solution of 6.00 g (80 mmol) (*R*)-2-Amino-1-propanol in 60 ml methanol was added 10.3 g (75.9 mmol) 4-Methoxybenzaldehyde. After addition the mixture was stirred at RT for 3 hours, then 3.02 g (80 mmol) $NaBH_4$ was added in portions at 0 °C. The obtained mixture was allowed to warm to RT and stirred at this temperature for 18 hours.

The reaction mixture was quenched by slow addition of 70 ml distilled water at 0 °C. Methanol was evaporated, and the resulting mixture was extracted with dichloromethane. The combined organic layer was washed with distilled water, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield 13.77 g (88%) of the title compound. GC-MS (EI) m/z 196.2 [MH^+]

b) [(2*S*,5*R*)-4-[(4-methoxyphenyl)methyl]-5-methylmorpholin-2-yl]methanol

The above obtained (2*R*)-2-{[(4-methoxyphenyl)methyl]amino}propan-1-ol was suspended in 100 ml toluene and 3.98 g (43 mmol) (*R*)-Epichlorohydrin was added, followed by the addition of 4.58 g (43 mmol) $LiClO_4$. The reaction mixture was stirred at RT for 18 hours, then 30 ml sodium methoxide solution was added (25 wt% in CH_3OH). The reaction mixture was stirred at RT for 18 hours. 100 ml saturated aqeous NH_4Cl was added, followed by the addition of 30 ml distilled water. The mixture was extracted with ethyl acetate. The combined organic layer was washed with distilled water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography eluting with 0-100% ethyl acetate in cyclohexane to yield 4.01 g (52%) of the title compound. GC-MS (EI) m/z 252.2 [MH^+]

c) *tert*-butyl (2*S*,5*R*)-2-(hydroxymethyl)-5-methylmorpholine-4-carboxylate

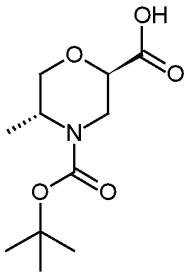
The above obtained [(2*S*,5*R*)-4-[(4-methoxyphenyl)methyl]-5-methylmorpholin-2-yl]methanol was dissolved in 100 ml ethanol, and hydrogenated at 10 bar in the presence of 500 mg 10% Pd/C and 5.22 g (23.9 mmol) BOC_2O for 2 days at RT. The reaction mixture was filtered through Celite, concentrated *in vacuo*, and purified by silica gel chromatography eluting with 0-100% ethyl acetate in cyclohexane to yield 1.55 g (42%) of the title compound. GC-MS (EI) m/z 232.2 [MH^+]

d) (2*S*,5*R*)-4-[(*tert*-butoxy)carbonyl]-5-methylmorpholine-2-carboxylic acid

The above obtained *tert*-butyl (2*S*,5*R*)-2-(hydroxymethyl)-5-methylmorpholine-4-carboxylate was dissolved in 50 ml dichloromethane and 25 ml distilled water. To the reaction mixture was added 210 mg (1.34 mmol) TEMPO and 4.97 g (15.4 mmol) (Diacetoxyiodo)benzene at 0 °C. The obtained mixture was allowed to warm to RT and stirred at this temperature for 18 hours. The reaction was quenched by the addition of 10 ml methanol. The mixture was extracted with dichloromethane. The combined organic layer was washed with distilled water, brine, dried

over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was triturated with hexane and filtered to yield 1.02 g (62%) of the title compound. GC-MS (EI) m/z 246.1 [MH^+]

Intermediate 2



(2*R*,5*R*)-4-[(*tert*-butoxy)carbonyl]-5-methylmorpholine-2-carboxylic acid

a) [(2*R*,5*R*)-4-[(4-methoxyphenyl)methyl]-5-methylmorpholin-2-yl]methanol

The title compound is prepared from (2*R*)-2-{[(4-methoxyphenyl)methyl]amino}propan-1-ol and (*S*)-Epichlorohydrin according to the method described in Intermediate 1b.

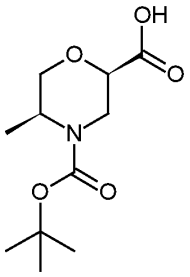
b) *tert*-butyl (2*R*,5*R*)-2-(hydroxymethyl)-5-methylmorpholine-4-carboxylate

The title compound is prepared from [(2*R*,5*R*)-4-[(4-methoxyphenyl)methyl]-5-methylmorpholin-2-yl]methanol according to the method described in Intermediate 1c.

c) (2*R*,5*R*)-4-[(*tert*-butoxy)carbonyl]-5-methylmorpholine-2-carboxylic acid

The title compound is prepared from *tert*-butyl (2*R*,5*R*)-2-(hydroxymethyl)-5-methylmorpholine-4-carboxylate according to the method described in Intermediate 1d.

Intermediate 3



(2*R*,5*S*)-4-[(*tert*-butoxy)carbonyl]-5-methylmorpholine-2-carboxylic acid

a) (2*S*)-2-{[(4-methoxyphenyl)methyl]amino}propan-1-ol

The title compound is prepared from (*S*)-2-Amino-1-propanol according to the method described in Intermediate 1a.

b) [(2*R*,5*S*)-4-[(4-methoxyphenyl)methyl]-5-methylmorpholin-2-yl]methanol

The title compound is prepared from (2*S*)-2-{[(4-methoxyphenyl)methyl]amino}propan-1-ol and (*S*)-Epichlorohydrin according to the method described in Intermediate 1b.

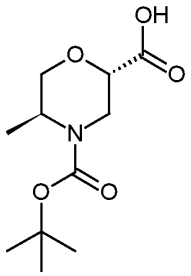
c) *tert*-butyl (2*R*,5*S*)-2-(hydroxymethyl)-5-methylmorpholine-4-carboxylate

The title compound is prepared from *tert*-butyl [(2*R*,5*S*)-4-[(4-methoxyphenyl)methyl]-5-methylmorpholin-2-yl]methanol according to the method described in Intermediate 1c.

d) (2*R*,5*S*)-4-[(*tert*-butoxy)carbonyl]-5-methylmorpholine-2-carboxylic acid

The title compound is prepared from *tert*-butyl (2*R*,5*S*)-2-(hydroxymethyl)-5-methylmorpholine-4-carboxylate according to the method described in Intermediate 1d.

Intermediate 4



(2*S*,5*S*)-4-[(*tert*-butoxy)carbonyl]-5-methylmorpholine-2-carboxylic acid

a) [(2*S*,5*S*)-4-[(4-methoxyphenyl)methyl]-5-methylmorpholin-2-yl]methanol

The title compound is prepared from (2*S*)-2-{[(4-methoxyphenyl)methyl]amino}propan-1-ol and (*R*)-Epichlorohydrin according to the method described in Intermediate 1b.

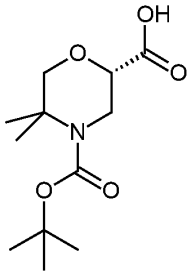
b) *tert*-butyl (2*S*,5*S*)-2-(hydroxymethyl)-5-methylmorpholine-4-carboxylate

The title compound is prepared from [(2*S*,5*S*)-4-[(4-methoxyphenyl)methyl]-5-methylmorpholin-2-yl]methanol according to the method described in Intermediate 1c.

c) (2*R*,5*R*)-4-[(*tert*-butoxy)carbonyl]-5-methylmorpholine-2-carboxylic acid

The title compound is prepared from *tert*-butyl (2*S*,5*S*)-2-(hydroxymethyl)-5-methylmorpholine-4-carboxylate according to the method described in Intermediate 1d.

Intermediate 5



(2*S*)-4-[(*tert*-butoxy)carbonyl]-5,5-dimethylmorpholine-2-carboxylic acid

a) 2-(benzylamino)-2-methylpropan-1-ol

The title compound is prepared from 2-amino-2-methylpropan-1-ol according to the method described in Intermediate 1a.

b) [(2*S*)-4-benzyl-5,5-dimethylmorpholin-2-yl]methanol

The title compound is prepared from 2-(benzylamino)-2-methylpropan-1-ol and (*R*)-Epichlorohydrin according to the method described in Intermediate 1b.

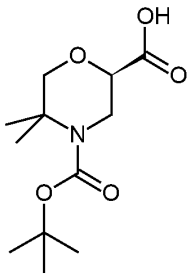
c) *tert*-butyl (2*S*)-2-(hydroxymethyl)-5,5-dimethylmorpholine-4-carboxylate

The title compound is prepared from *tert*-butyl [(2*S*)-4-benzyl-5,5-dimethylmorpholin-2-yl]methanol according to the method described in Intermediate 1c.

e) (2*S*)-4-[(*tert*-butoxy)carbonyl]-5,5-dimethylmorpholine-2-carboxylic acid

The title compound is prepared from *tert*-butyl (2*S*)-2-(hydroxymethyl)-5,5-dimethylmorpholine-4-carboxylate according to the method described in Intermediate 1d.

Intermediate 6



(2*R*)-4-[(*tert*-butoxy)carbonyl]-5,5-dimethylmorpholine-2-carboxylic acid

a) [(2*R*)-4-benzyl-5,5-dimethylmorpholin-2-yl]methanol

The title compound is prepared from 2-(benzylamino)-2-methylpropan-1-ol and (*S*)-Epichlorohydrin according to the method described in Intermediate 1b.

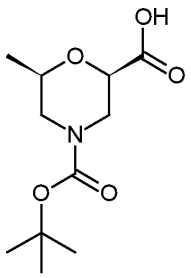
b) *tert*-butyl (2*R*)-2-(hydroxymethyl)-5,5-dimethylmorpholine-4-carboxylate

The title compound is prepared from *tert*-butyl [(2*R*)-4-benzyl-5,5-dimethylmorpholin-2-yl]methanol according to the method described in Intermediate 1c.

c) (2*R*)-4-[(*tert*-butoxy)carbonyl]-5,5-dimethylmorpholine-2-carboxylic acid

The title compound is prepared from *tert*-butyl (2*R*)-2-(hydroxymethyl)-5,5-dimethylmorpholine-4-carboxylate according to the method described in Intermediate 1d.

Intermediate 7



(2*R*,6*R*)-4-[(*tert*-butoxy)carbonyl]-6-methylmorpholine-2-carboxylic acid

a) (2*R*)-1-{[(4-methoxyphenyl)methyl]amino}propan-2-ol

The title compound is prepared from (*R*)-1-Amino-2-propanol according to the method described in Intermediate 1a.

b) [(2*R*,6*R*)-4-[(4-methoxyphenyl)methyl]-6-methylmorpholin-2-yl]methanol

The title compound is prepared from (2*R*)-1-{[(4-methoxyphenyl)methyl]amino}propan-2-ol and (*S*)-Epichlorohydrin according to the method described in Intermediate 1b.

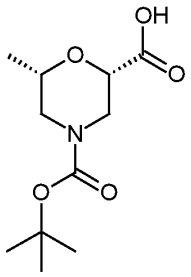
c) *tert*-butyl (2*R*,6*R*)-2-(hydroxymethyl)-6-methylmorpholine-4-carboxylate

The title compound is prepared from *tert*-butyl [(2*R*,6*R*)-4-[(4-methoxyphenyl)methyl]-6-methylmorpholin-2-yl]methanol methanol according to the method described in Intermediate 1c.

d) (2*R*,6*R*)-4-[(*tert*-butoxy)carbonyl]-6-methylmorpholine-2-carboxylic acid

The title compound is prepared from *tert*-butyl (2*R*,6*R*)-2-(hydroxymethyl)-6-methylmorpholine-4-carboxylate according to the method described in Intermediate 1d.

Intermediate 8



(2*S*,6*S*)-4-[(*tert*-butoxy)carbonyl]-6-methylmorpholine-2-carboxylic acid

a) (2*S*)-1-{[(4-methoxyphenyl)methyl]amino}propan-2-ol

The title compound is prepared from (*S*)-1-Amino-2-propanol according to the method described in Intermediate 1a.

b) [(2*S*,6*S*)-4-[(4-methoxyphenyl)methyl]-6-methylmorpholin-2-yl]methanol

The title compound is prepared from (2*S*)-1-{[(4-methoxyphenyl)methyl]amino}propan-2-ol and (*R*)-Epichlorohydrin according to the method described in Intermediate 1b.

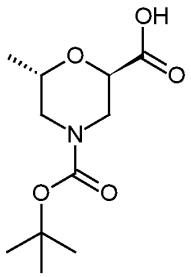
c) *tert*-butyl (2*S*,6*S*)-2-(hydroxymethyl)-6-methylmorpholine-4-carboxylate

The title compound is prepared from *tert*-butyl [(2*S*,6*S*)-4-[(4-methoxyphenyl)methyl]-6-methylmorpholin-2-yl]methanol methanol according to the method described in Intermediate 1c.

d) (2*S*,6*S*)-4-[(*tert*-butoxy)carbonyl]-6-methylmorpholine-2-carboxylic acid

The title compound is prepared from *tert*-butyl (2*S*,6*S*)-2-(hydroxymethyl)-6-methylmorpholine-4-carboxylate according to the method described in Intermediate 1d.

Intermediate 9



(2*R*,6*S*)-4-[(*tert*-butoxy)carbonyl]-6-methylmorpholine-2-carboxylic acid

a) [(2*R*,6*S*)-4-[(4-methoxyphenyl)methyl]-6-methylmorpholin-2-yl]methanol

The title compound is prepared from (2*S*)-1-{[(4-methoxyphenyl)methyl]amino}propan-2-ol and (*S*)-Epichlorohydrin according to the method described in Intermediate 1b.

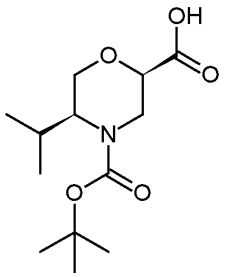
b) *tert*-butyl (2*R*,6*S*)-2-(hydroxymethyl)-6-methylmorpholine-4-carboxylate

The title compound is prepared from [(2*R*,5*S*)-4-[(4-methoxyphenyl)methyl]-6-methylmorpholin-2-yl]methanol according to the method described in Intermediate 1c.

c) (2*R*,6*S*)-4-[(*tert*-butoxy)carbonyl]-6-methylmorpholine-2-carboxylic acid

The title compound is prepared from *tert*-butyl (2*R*,6*S*)-2-(hydroxymethyl)-6-methylmorpholine-4-carboxylate according to the method described in Intermediate 1d.

Intermediate 10



(2*R*,5*S*)-4-[(*tert*-butoxy)carbonyl]-5-(propan-2-yl)morpholine-2-carboxylic acid

a) (2*S*)-2-{[(4-methoxyphenyl)methyl]amino}-3-methylbutan-1-ol

The title compound is prepared from (*S*)-2-Amino-3-methyl-1-butanol according to the method described in Intermediate 1a.

b) [(2*R*,5*S*)-4-[(4-methoxyphenyl)methyl]-5-(propan-2-yl)morpholin-2-yl]methanol

The title compound is prepared from (2*S*)-2-{[(4-methoxyphenyl)methyl]amino}-3-methylbutan-1-ol and (*S*)-Epichlorohydrin according to the method described in Intermediate 1b.

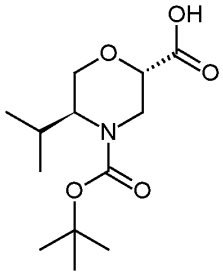
c) *tert*-butyl (2*R*,5*S*)-2-(hydroxymethyl)-5-(propan-2-yl)morpholine-4-carboxylate

The title compound is prepared from [(2*R*,5*S*)-4-[(4-methoxyphenyl)methyl]-5-(propan-2-yl)morpholin-2-yl]methanol according to the method described in Intermediate 1c.

d) (2*R*,5*S*)-4-[(*tert*-butoxy)carbonyl]-5-(propan-2-yl)morpholine-2-carboxylic acid

The title compound is prepared from *tert*-butyl (2*R*,5*S*)-2-(hydroxymethyl)-5-(propan-2-yl)morpholine-4-carboxylate according to the method described in Intermediate 1d.

Intermediate 11



(2*S*,5*S*)-4-[(*tert*-butoxy)carbonyl]-5-(propan-2-yl)morpholine-2-carboxylic acid

a) [(2*S*,5*S*)-4-[(4-methoxyphenyl)methyl]-5-(propan-2-yl)morpholin-2-yl]methanol

The title compound is prepared from (2*S*)-2-{[(4-methoxyphenyl)methyl]amino}propan-1-ol and (*R*)-Epichlorohydrin according to the method described in Intermediate 1b.

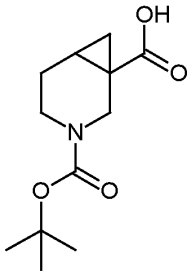
b) *tert*-butyl (2*S*,5*S*)-2-(hydroxymethyl)-5-(propan-2-yl)morpholine-4-carboxylate

The title compound is prepared from [(2*S*,5*S*)-4-[(4-methoxyphenyl)methyl]-5-methylmorpholin-2-yl]methanol according to the method described in Intermediate 1c.

c) (2*S*,5*S*)-4-[(*tert*-butoxy)carbonyl]-5-(propan-2-yl)morpholine-2-carboxylic acid

The title compound is prepared from *tert*-butyl (2*S*,5*S*)-2-(hydroxymethyl)-5-(propan-2-yl)morpholine-4-carboxylate according to the method described in Intermediate 1d.

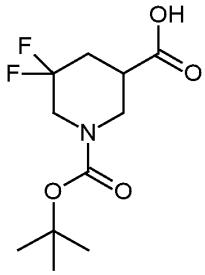
Intermediate 12



3-[(*tert*-butoxy)carbonyl]-3-azabicyclo[4.1.0]heptane-1-carboxylic acid

The title compound is prepared as described in *Tetrahedron*, **2010**, *66*, 5492-5497.

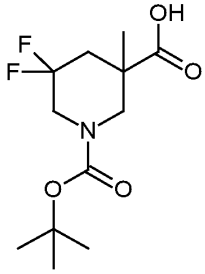
Intermediate 13



1-[(*tert*-butoxy)carbonyl]-5,5-difluoropiperidine-3-carboxylic acid

The title compound is prepared as described in WO2015/164508.

Intermediate 14



1-[(*tert*-butoxy)carbonyl]-5,5-difluoro-3-methylpiperidine-3-carboxylic acid

a) 1-*tert*-butyl 3-methyl 5,5-difluoro-3-methylpiperidine-1,3-dicarboxylate

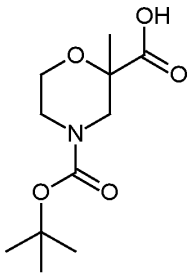
Under nitrogen to a solution of 2.18 g (7.8 mmol) 1-*tert*-butyl 3-methyl 5,5-difluoropiperidine-1,3-dicarboxylate (prepared as described in WO2015/164508) in 50 ml dry tetrahydrofuran 8.6 mL 1 M lithium bis(trimethylsilyl)amide in tetrahydrofuran solution (8.6 mmol) was added dropwise at (-78) °C - (-65) °C. After addition the mixture was stirred at -78 °C for 1 hour, 0.73 mL (11.7 mmol) of Iodomethane was added dropwise. The so obtained mixture was allowed to warm to RT and stirred at this temperature for 18 h. The reaction mixture was quenched by addition of 25 ml saturated ammonium chloride solution and 10 ml distilled water. The reaction mixture was extracted with ethyl acetate, the combined organic layer was washed with distilled water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield 2.22 g (97%) of the title compound. GC-MS (EI) m/z 294.1 [MH^+]

b) 1-[(*tert*-butoxy)carbonyl]-5,5-difluoro-3-methylpiperidine-3-carboxylic acid

The above obtained *tert*-butyl 1-*tert*-butyl 3-methyl 5,5-difluoro-3-methylpiperidine-1,3-dicarboxylate was dissolved in 30 ml methanol. 30.3 ml 2 M aqeous sodium hydroxide (15.1 mmol)

was added dropwise at 0 °C. The obtained mixture was allowed to warm to RT and stirred at this temperature for 18 hours. The reaction mixture was acidified to pH=3 with citric acid, and methanol was evaporated. The mixture was extracted with ethyl acetate. The combined organic layer was washed with distilled water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield 2.20 g (100%) of the title compound. GC-MS (EI) m/z 280.1 [MH^+]

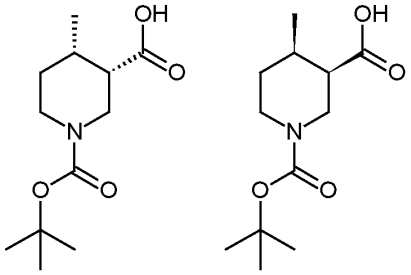
Intermediate 15



4-[(*tert*-butoxy)carbonyl]-2-methylmorpholine-2-carboxylic acid

The title compound is prepared as described in WO2011/26917.

Intermediate 16



***cis*-1-[(*tert*-butoxy)carbonyl]-4-methylpiperidine-3-carboxylic acid**

a) *cis*-4-methylpiperidine-3-carboxylic acid hydrochloride

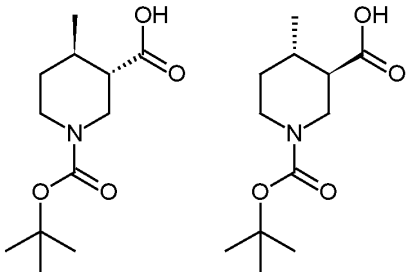
A solution of 15 g (86.6 mmol) 4-methylpyridine-3-carboxylic acid hydrochloride in 100 ml distilled water was hydrogenated at 10 bar in the presence of 1.5 g PtO_2 x H_2O for 12 hours at RT. The mixture was filtered through Celite and concentrated *in vacuo* to yield 16.6 g (100%) of the title compound.

b) *cis*-1-[(*tert*-butoxy)carbonyl]-4-methylpiperidine-3-carboxylic acid

33.29 g (185.3 mmol) of *cis*-4-methylpiperidine-3-carboxylic acid was dissolved 300 ml distilled water and 200 ml tetrahydrofuran. 39.3 g (371 mmol) Na_2CO_3 was added, followed by the

addition of 40.4 g (185 mmol) BOC_2O dissolved in 100 ml tetrahydrofuran, at 0 °C. The obtained mixture was allowed to warm to RT and stirred at this temperature for 18 hours. The reaction mixture was acidified to pH=3 with citric acid. The mixture was extracted with ethyl acetate. The combined organic layer was washed with distilled water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield 29.40 g (65%) of the title compound. GC-MS (EI) m/z 243.2 [MH^+]

Intermediate 17



***trans*-1-[(*tert*-butoxy)carbonyl]-4-methylpiperidine-3-carboxylic acid**

a) 1-*tert*-butyl 3-methyl *cis*-4-methylpiperidine-1,3-dicarboxylate

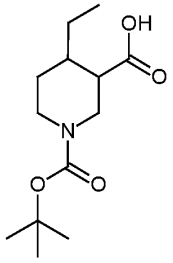
To a solution of 1.22 g (5 mmol) *cis*-1-[(*tert*-butoxy)carbonyl]-4-methylpiperidine-3-carboxylic acid (Intermediate 15) in 6 ml dimethylformamide was added 6.52 g (20 mmol) Cs_2CO_3 and 2.5 ml (40 mmol) iodomethane. The obtained mixture was stirred at RT for 18 hours. 50 ml distilled water was added. The mixture was extracted with ethyl acetate. The combined organic layer was washed with distilled water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield 1.29 g (100%) of the title compound. GC-MS (EI) m/z 258.2 [MH^+]

b) *trans*-1-[(*tert*-butoxy)carbonyl]-4-methylpiperidine-3-carboxylic acid

Under nitrogen to a solution of 0.76 g (3 mmol) 1-*tert*-butyl 3-methyl *cis*-4-methylpiperidine-1,3-dicarboxylate in 25 ml dry tetrahydrofuran 10 mL 1 M potassium *tert*-butoxy in tetrahydrofuran solution (10 mmol) was added dropwise at (-78) °C - (-65) °C. After addition the mixture was stirred at -78 °C for 2 hours, 8 mL distilled water, 8 ml methanol, 5 ml 10 M aqeous sodium hydroxide (50 mmol) was added dropwise. The reaction mixture was allowed to warm to RT, and stirred for 2 hours. The reaction mixture was acidified to pH=3 with citric acid, and methanol was evaporated. The obtained mixture was extracted with ethyl acetate. The combined organic layer was washed with distilled water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was dissolved in ethyl acetate and ethanolic ammonia was added. The precipitated crystals were filtered, partitioned between 10% citric acid solution and ethyl acetate. The mixture

was extracted with ethyl acetate. The combined organic layer was washed with distilled water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield 0.59 g (82%) of the title compound. GC-MS (EI) m/z 244.1 [MH^+]

Intermediate 18



1-[(*tert*-butoxy)carbonyl]-4-ethylpiperidine-3-carboxylic acid

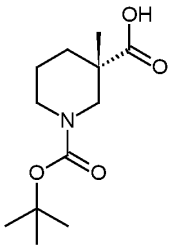
a) 4-ethylpiperidine-3-carboxylic acid hydrochloride

The title compound is prepared from 4-ethylpyridine-3-carboxylic acid according to the method described in Intermediate16a.

b) 1-[(*tert*-butoxy)carbonyl]-4-ethylpiperidine-3-carboxylic acid

The title compound is prepared from 4-ethylpiperidine-3-carboxylic acid hydrochloride according to the method described in Intermediate16b.

Intermediate 19



(3*S*)-1-[(*tert*-butoxy)carbonyl]-3-methylpiperidine-3-carboxylic acid

a) 1-*tert*-butyl 3-ethyl (3*S*)-3-methylpiperidine-1,3-dicarboxylate

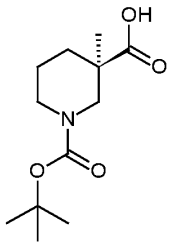
To a suspension of 7.1 g (34.2 mmol) ethyl (3*S*)-3-methylpiperidine-3-carboxylate hydrochloride (prepared as described in WO 2018/167631) in 100 ml dichloromethane was added 10.5 ml (75.2 mmol) triethylamine, and 8.21 g (37.6 mmol) BOC_2O at 0 °C. The resulting mixture was allowed to warm to RT and stirred for 3 hours. The reaction mixture was washed with distilled

water, 10% citric acid solution, brine, and concentrated *in vacuo* to yield 9.68 g (104%) of the title compound. GC-MS (EI) m/z 272.2 [MH^+]

b) (3*S*)-1-[(*tert*-butoxy)carbonyl]-3-methylpiperidine-3-carboxylic acid

The above obtained 1-*tert*-butyl 3-ethyl (3*S*)-3-methylpiperidine-1,3-dicarboxylate was dissolved in 200 ml ethanol and 65 ml 4 M aqeous sodium hydroxide (300 mmol) was added dropwise at 0 °C. The reaction mixture was allowed to warm to RT, and stirred for 18 hours. The reaction mixture was acidified to pH=3 with citric acid, and ethanol was evaporated. The obtained mixture was extracted with ethyl acetate. The combined organic layer was washed with distilled water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield 8.0 g (96%) of the title compound. GC-MS (EI) m/z 244.1 [MH^+]

Intermediate 20



(3*R*)-1-[(*tert*-butoxy)carbonyl]-3-methylpiperidine-3-carboxylic acid

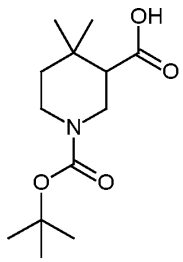
a) 1-*tert*-butyl 3-ethyl (3*R*)-3-methylpiperidine-1,3-dicarboxylate

The title compound is prepared from (3*R*)-3-methylpiperidine-3-carboxylate hydrochloride (prepared as described in WO 2018/167631) according to the method described in Intermediate19a.

b) (3*R*)-1-[(*tert*-butoxy)carbonyl]-3-methylpiperidine-3-carboxylic acid

The title compound is prepared from 1-*tert*-butyl 3-ethyl (3*R*)-3-methylpiperidine-1,3-dicarboxylate according to the method described in Intermediate19a.

Intermediate 21



1-[(*tert*-butoxy)carbonyl]-4,4-dimethylpiperidine-3-carboxylic acid

a) methyl 1-benzyl-4,4-dimethylpiperidine-3-carboxylate

Under nitrogen to a solution of 2.20 g (8 mmol) methyl 1-benzyl-4,4-dimethyl-6-oxopiperidine-3-carboxylate (prepared as described in *J. Org. Chem.* **2005**, *70*, 3957-3962.) in 22 ml dry tetrahydrofuran was added 0.92 g (24.4 mmol) $NaBH_4$ and 3.96 ml boron trifluoride diethyl etherate dropwise at -15 °C. The reaction mixture was allowed to warm to RT, and stirred for 3 hours. 15 ml distilled water was added and the reaction mixture was extracted with ethyl acetate, the combined organic layer was washed with distilled water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield 1.87 g (89%) of the title compound. GC-MS (EI) m/z 262.2 [MH^+]

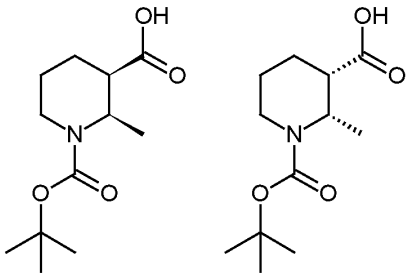
b) 1-*tert*-butyl 3-methyl 4,4-dimethylpiperidine-1,3-dicarboxylate

The above obtained methyl 1-benzyl-4,4-dimethylpiperidine-3-carboxylate was dissolved in 20 ml methanol and hydrogenated at 10 bar in the presence of 0.4 g 10% Pd/C and 1.60 g (7.1 mmol) BOC_2O at RT for 18 hours. The reaction mixture was filtered through Celite, concentrated *in vacuo*, and purified by silica gel chromatography eluting with 20% ethyl acetate in cyclohexane to yield 0.89 g (47%) of the title compound. GC-MS (EI) m/z 271.2 [MH^+]

c) 1-[(*tert*-butoxy)carbonyl]-4,4-dimethylpiperidine-3-carboxylic acid

To a solution of 0.48 g (1.9 mmol) 1-*tert*-butyl 3-methyl 4,4-dimethylpiperidine-1,3-dicarboxylate in 15 ml dry tetrahydrofuran 0.49 g (3.7 mmol) Potassium trimethylsilanolate was added, and the reaction mixture was refluxed for 1 hour. Distilled water was added, and the reaction mixture was acidified to pH=4 with acetic acid. The obtained mixture was extracted with ethyl acetate. The combined organic layer was washed with distilled water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield 0.39 g (85%) of the title compound. GC-MS (EI) m/z 258.2 [MH^+]

Intermediate 22



***cis*-1-[(*tert*-butoxy)carbonyl]-2-methylpiperidine-3-carboxylic acid**

a) ethyl *cis*-2-methylpiperidine-3-carboxylate

A solution of 4.27 g (25.8 mmol) ethyl 2-methylpyridine-3-carboxylate in 40 ml distilled water was hydrogenated at 10 bar in the presence of 0.3 g PtO_2 x H_2O for 12 hours at RT. The mixture was filtered through Celite and concentrated *in vacuo* to yield 3.94 g (89%) of the title compound. GC-MS (EI) m/z 172.1 [MH^+]

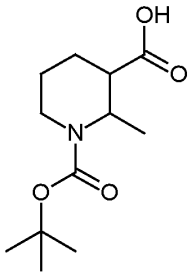
b) 1-*tert*-butyl 3-ethyl *cis*-2-methylpiperidine-1,3-dicarboxylate

The above obtained ethyl *cis*-2-methylpiperidine-3-carboxylate was dissolved in 20 ml distilled water and 40 ml tetrahydrofuran. 2.00 g (23.8 mmol) $NaHCO_3$ and 5.00 g (22.9 mmol) BOC_2O was added at 0 °C. The reaction mixture was allowed to warm to RT, and stirred for 3 hours. 30 ml distilled water was added. The mixture was extracted with ethyl acetate. The combined organic layer was washed with distilled water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield 3.57 g (57%) of the title compound. GC-MS (EI) m/z 272.2 [MH^+]

c) *cis*-1-[(*tert*-butoxy)carbonyl]-2-methylpiperidine-3-carboxylic acid

The above obtained 1-*tert*-butyl 3-ethyl *cis*-2-methylpiperidine-1,3-dicarboxylate was dissolved in 50 ml ethanol. 10 ml 6 M aqeous sodium hydroxide (60 mmol) was added dropwise at 0 °C. The obtained mixture was allowed to warm to RT and stirred at this temperature for 18 hours. The reaction mixture was acidified to pH=3 with 1M HCl solution, and ethanol was evaporated. The mixture was extracted with ethyl acetate. The combined organic layer was washed with distilled water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield 2.81 g (88%) of the title compound. GC-MS (EI) m/z 244.1 [MH^+]

Intermediate 23



1-[(*tert*-butoxy)carbonyl]-2-methylpiperidine-3-carboxylic acid

a) ethyl 2-methylpiperidine-3-carboxylate

Under nitrogen to a solution of 23.00 g (160.63 mmol) ethyl *cis*-2-methylpiperidine-3-carboxylate (Intermediate 22a) in 50 ml ethanol was added 2.00 g (87 mmol) sodium dissolved in 50 ml ethanol. The reaction mixture was refluxed for 16 hours. The mixture is concentrated *in vacuo* to obtain the title compound as an oil. The crude product is used in the next step.

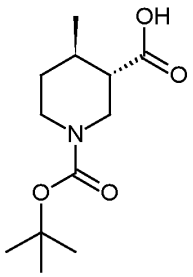
b) 1-*tert*-butyl 3-ethyl 2-methylpiperidine-1,3-dicarboxylate

The above obtained ethyl 2-methylpiperidine-3-carboxylate was dissolved in 200 ml tetrahydrofuran and 200 ml distilled water and 13.00 g (60 mmol) BOC_2O was added. The reaction mixture was stirred for 16 hours at RT. The reaction mixture was acidified to pH=3 with 1M HCl solution and extracted with ethyl acetate. The combined organic layer was washed with distilled water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with 33% ethyl acetate in cyclohexane, then again with dichloromethane to yield 2.3 g (16%) of the title compound.

c) 1-[(*tert*-butoxy)carbonyl]-2-methylpiperidine-3-carboxylic acid

The title compound is prepared from 1-*tert*-butyl 3-ethyl 2-methylpiperidine-1,3-dicarboxylate according to the method described in Intermediate 22c.

Intermediate 24



(3*S*,4*R*)-1-[(*tert*-butoxy)carbonyl]-4-methylpiperidine-3-carboxylic acid

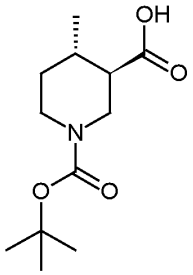
a) 1-*tert*-butyl 3-methyl (3*S*,4*R*)-4-methylpiperidine-1,3-dicarboxylate

The title compound is prepared from methyl (3*S*,4*R*)-4-methylpiperidine-3-carboxylate (prepared as described in US2010/0093706) according to the method described in Intermediate 22b.

b) (3*S*,4*R*)-1-[(*tert*-butoxy)carbonyl]-4-methylpiperidine-3-carboxylic acid

The title compound is prepared from methyl 1-*tert*-butyl 3-methyl (3*S*,4*R*)-4-methylpiperidine-1,3-dicarboxylate according to the method described in Intermediate 22c.

Intermediate 25



(3*R*,4*S*)-1-[(*tert*-butoxy)carbonyl]-4-methylpiperidine-3-carboxylic acid

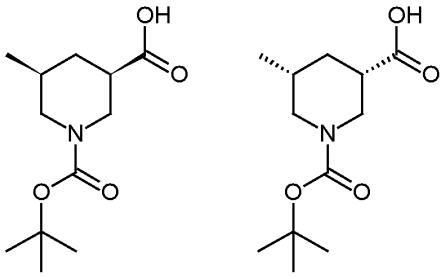
a) 1-*tert*-butyl 3-methyl (3*R*,4*S*)-4-methylpiperidine-1,3-dicarboxylate

The title compound is prepared from methyl (3*R*,4*S*)-4-methylpiperidine-3-carboxylate (prepared as described in US2010/0093706) according to the method described in Intermediate 22b.

b) (3*R*,4*S*)-1-[(*tert*-butoxy)carbonyl]-4-methylpiperidine-3-carboxylic acid

The title compound is prepared from methyl 1-*tert*-butyl 3-methyl (3*R*,4*S*)-4-methylpiperidine-1,3-dicarboxylate according to the method described in Intermediate 22c.

Intermediate 26



***cis*-1-[(*tert*-butoxy)carbonyl]-5-methylpiperidine-3-carboxylic acid**

a) *cis*-5-methylpiperidine-3-carboxylic acid

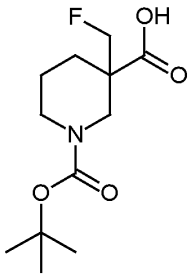
A solution of 1.00 g (7.3 mmol) 5-methylpyridine-3-carboxylic acid in 20 ml acetic acid was hydrogenated at 10 bar in the presence of 0.2 g PtO_2 x H_2O for 12 hours at RT. The mixture was filtered through Celite and concentrated *in vacuo* to yield 1.00 g (96%) of the title compound. GC-MS (EI) m/z 144.1 [MH^+]

b) *cis*-1-[(*tert*-butoxy)carbonyl]-5-methylpiperidine-3-carboxylic acid

The above obtained *cis*-5-methylpiperidine-3-carboxylic acid was dissolved in 10 ml distilled water and 10 ml tetrahydrofuran. 1.52 g (7 mmol) BOC_2O was added at 0 °C. The reaction

mixture was allowed to warm to RT, and stirred for 3 hours. 30 ml distilled water was added. The mixture was extracted with ethyl acetate. The combined organic layer was washed with distilled water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield 0.45 g (25%) of the title compound. GC-MS (EI) m/z 244.1 [MH^+]

Intermediate 27



1-[(*tert*-butoxy)carbonyl]-3-(fluoromethyl)piperidine-3-carboxylic acid

a) 1-*tert*-Butyl 3-ethyl 3-(hydroxymethyl)piperidine-1,3-dicarboxylate

The title compound is prepared from 1-*tert*-butyl 3-ethyl piperidine-1,3-dicarboxylate and paraformaldehyde according to the method described in Intermediate 14a.

b) 1-*tert*-Butyl 3-ethyl 3-{[(1,1,2-trifluoroethanesulfonyl)oxy]methyl}piperidine-1,3-dicarboxylate

Under nitrogen, to a stirred solution of 0.296 g (1.03 mmol) ethyl 3-(hydroxymethyl) piperidine-3-carboxylate and 0.120 ml (1.48 mmol) pyridine in 5 ml of dichloromethane 0.230 ml (1.48 mmol) trifluoromethanesulfonic anhydride was added dropwise at (-78) °C - (-65) °C. After addition the mixture was stirred at -78 °C for 5 min and allowed to warm to room temperature and stirred at this temperature for 18 h. The reaction mixture was quenched by addition of 1M hydrochloric acid solution. The reaction mixture was extracted with dichloromethane, the combined organic layer was washed with distilled water, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to obtain the title compound as oil. The crude product is used in the next step.

c) 1-*tert*-Butyl 3-ethyl 3-(fluoromethyl)piperidine-1,3-dicarboxylate

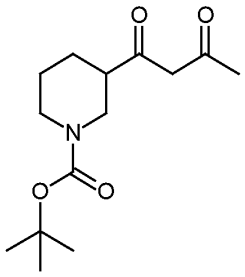
The above obtained 1-*tert*-butyl 3-ethyl 3-{[(1,1,2-trifluoroethanesulfonyl)oxy] methyl}piperidine-1,3-dicarboxylate was solved in 4 ml tetrahydrofuran and 1.25 ml (1.25 mmol) 1M tetrabutylammonium fluoride in tetrahydrofuran was added. The reaction mixture was stirred for 1 h at room temperature, diluted with water and extracted with ethyl acetate. The combined organic layer was washed with distilled water, dried over anhydrous sodium sulfate, filtered and

concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with 33% ethyl acetate in cyclohexane to yield 0.121 g (40%) of the title compound.

d) 1-[(*tert*-butoxy)carbonyl]-3-(fluoromethyl)piperidine-3-carboxylic acid

The title compound is prepared from 1-*tert*-Butyl 3-ethyl 3-(fluoromethyl)piperidine-1,3-dicarboxylate according to the method described in Intermediate 22c.

Intermediate 28

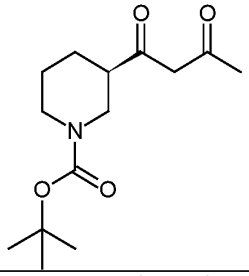
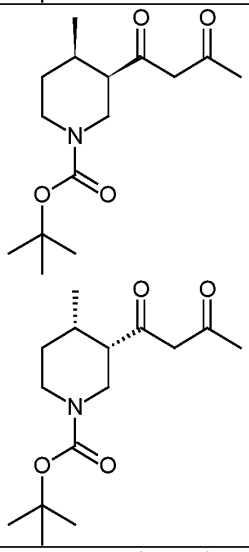
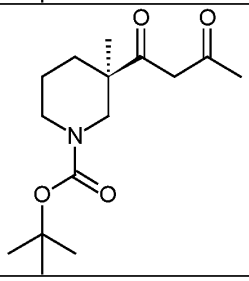
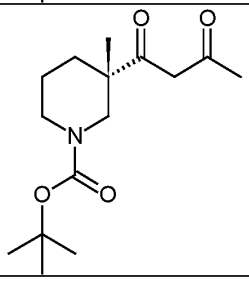


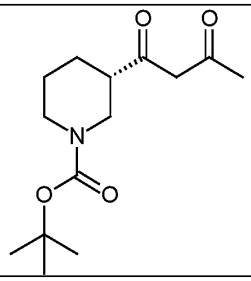
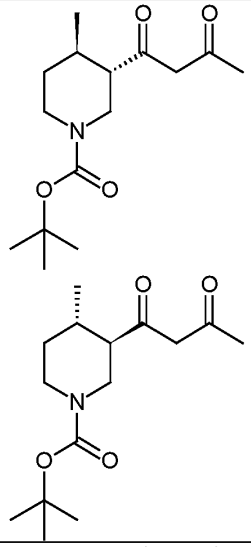
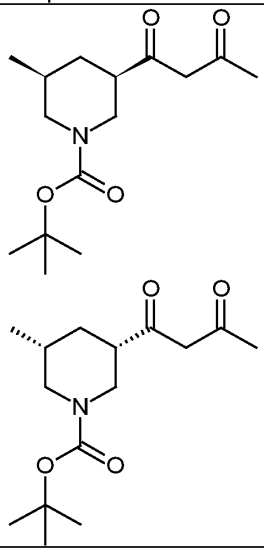
***tert*-butyl 3-(3-oxobutanoyl)piperidine-1-carboxylate**

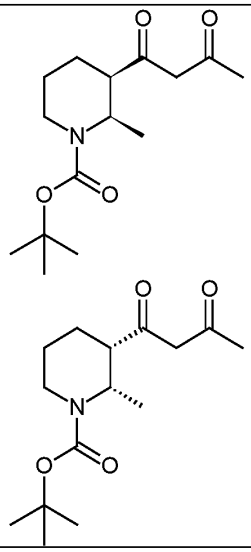
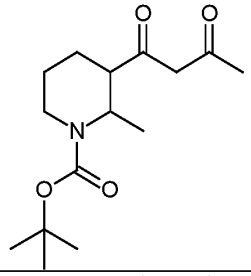
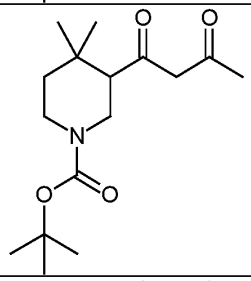
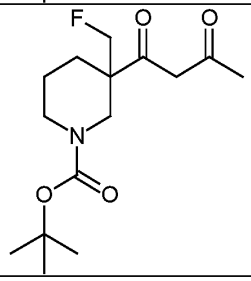
To a solution of 5.00 g (21.8 mmol) 1-[(*tert*-butoxy)carbonyl]piperidine-3-carboxylic acid in 30 ml dry tetrahydrofuran 3.89 g (24 mmol) CDI was added at 0 °C, and the reaction mixture was allowed to warm to RT and stirred for 2 hours. In a separate flask, under nitrogen, to a solution of 24 ml 2 M lithium diisopropylamide in tetrahydrofuran/heptane/ethylbenzene (48 mmol) in 30 ml dry tetrahydrofuran, 3.2 ml (43.6 mmol) acetone was added dropwise at (-78) °C - (-65) °C. After addition the mixture was stirred at -78 °C for 1 hour, and the solution of the activated acid was added dropwise at (-78) °C - (-65) °C. After addition, the mixture was stirred at -78 °C for 10 minutes, and quenched by the addition of 10% citric acid. The mixture was extracted with ethyl acetate. The combined organic layer was washed with distilled water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography eluting with dichloromethane to yield 2.28 g (39%) of the title compound. GC-MS (EI) m/z 270.2 [MH^+]

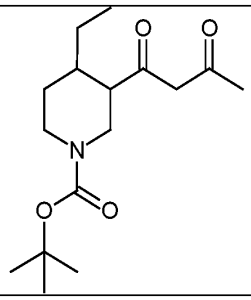
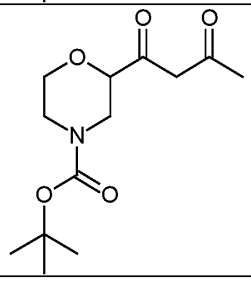
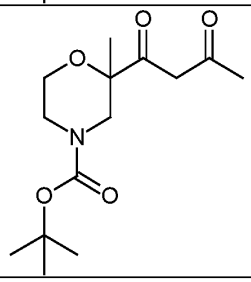
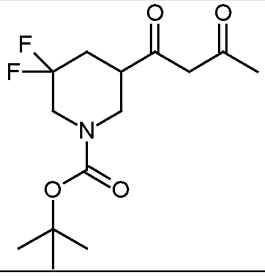
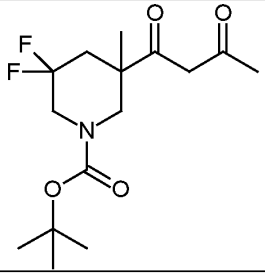
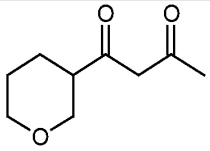
Compounds of Table 3 were prepared from the appropriate carboxylic acid and acetone according to the method described in Intermediate 28.

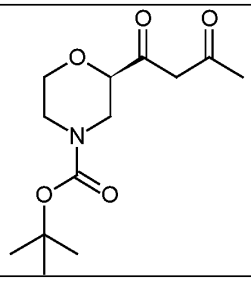
Table 3

Intermediate	Structure	Intermediate (starting material)	GC-MS (EI) m/z [MH^+]
29		(3*R*)-1-[(*tert*-butoxy)carbonyl]piperidine-3-carboxylic acid	270.2
30		16	284.2
31		20	284.2
32		19	284.2

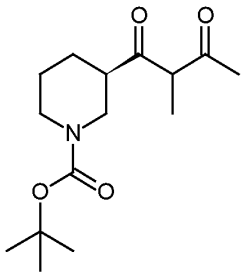
33		(3*S*)-1-[(*tert*-butoxy)carbonyl]piperidine-3-carboxylic acid	270.2
34		17	284.2
35		26	284.2

36		22	284.2
37		23	284.2
38		21	298.2
39		27	302.2

40		18	298.2
41		4-[(*tert*-butoxy)carbonyl]morpholine-2-carboxylic acid	272.1
42		15	286.2
43		13	306.1
44		14	320.1
45		oxane-3-carboxylic acid	171.1

46		(2*R*)-4-[(*tert*-butoxy)carbonyl]morpholine-2-carboxylic acid	272.1

Intermediate 47

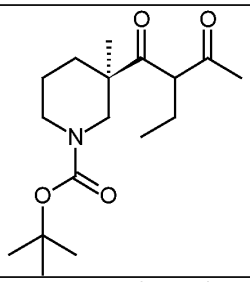
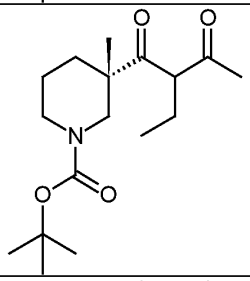
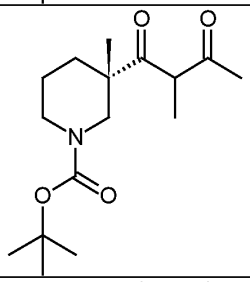
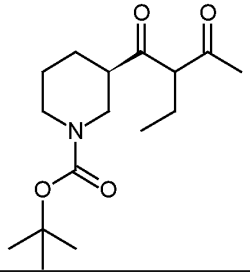
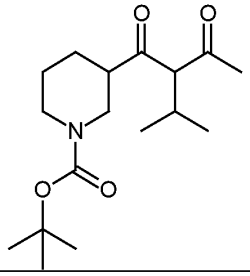


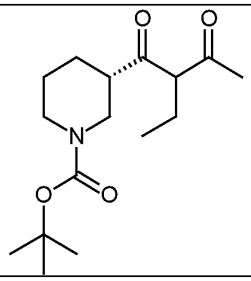
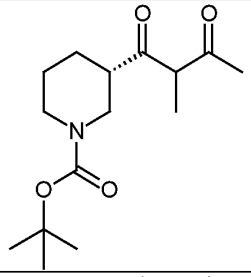
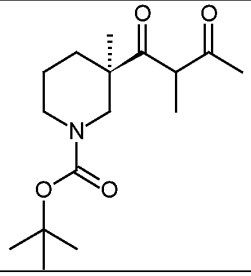
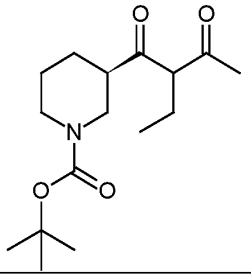
***tert*-butyl (3*R*)-3-(2-methyl-3-oxobutanoyl)piperidine-1-carboxylate**

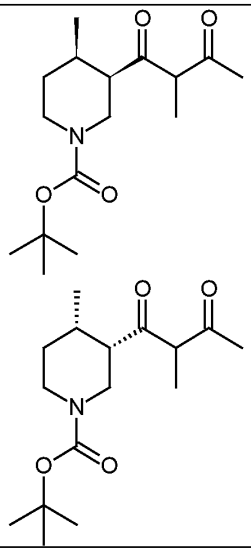
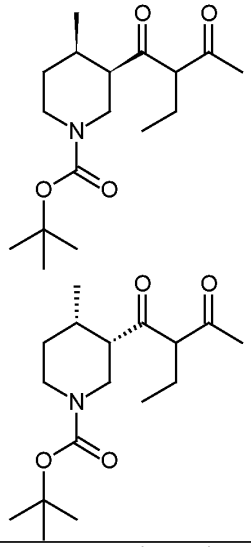
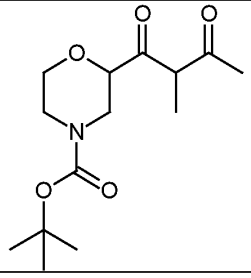
To a solution of 0.80 g (2.97 mmol) *tert*-butyl (3*R*)-3-(3-oxobutanoyl)piperidine-1-carboxylate (Intermediate 29) in 20 ml acetone was added 0.56 ml (8.91 mmol) iodomethane and 1.23 g (8.91 mmol) K_2CO_3. The reaction mixture was refluxed for 3 hours. The reaction mixture was allowed to cool to RT, acetone was evaporated, and the residue was partitioned between distilled water and ethyl acetate. The mixture was extracted with ethyl acetate. The combined organic layer was washed with distilled water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield 0.70 g (83%) of the title compound. GC-MS (EI) m/z 284.2 [MH^+]

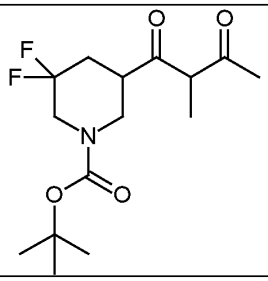
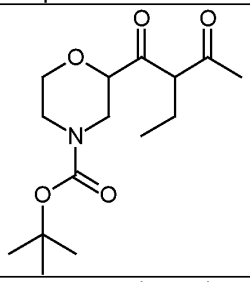
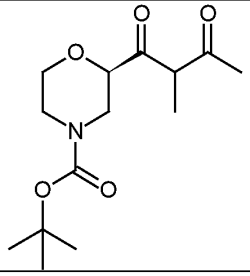
Compounds of Table 4 were prepared from the appropriate diketone and iodoalkane according to the method described in Intermediate 47.

Table 4

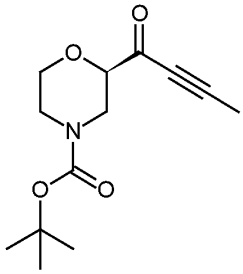
Intermediate	Structure	Intermediate (starting material)	GC-MS (EI) m/z [MH^+]
48		31	312.2
49		32	312.2
50		32	298.2
51		29	298.2
52		28	312.2

53		33	298.2
54		33	284.2
55		20	298.2
56		29	298.2

57		30	298.2
58		30	312.2
59		41	286.1

60		43	320.1
61		41	300.1
62		46	286.1

Intermediate 63



***tert*-butyl (2*R*)-2-(but-2-ynoyl)morpholine-4-carboxylate**

a) *tert*-butyl (2*R*)-2-[methoxy(methyl)carbamoyl]morpholine-4-carboxylate

Under nitrogen to a solution of 1.00 g (4.32 mmol) (2*R*)-4-[(*tert*-butoxy)carbonyl]morpholine-2-carboxylic acid in 10 ml dimethylformamide was added 1.27 g (13 mmol) N,O-Dimethylhydroxylamine hydrochloride, 3.77 ml (21.6 mmol) *N,N*-Diisopropylethylamine, 1.8 g (4.76 mmol) HBTU, 0.73 g (4.76 mmol) HOBt*H_2O at 0 °C. The reaction mixture was allowed to warm to RT and stirred for 16 hours. Distilled water was added, and the mixture was extracted with ethyl acetate. The combined organic layer was washed with 1M

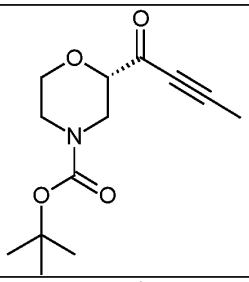
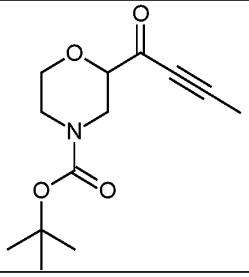
HCl solution, 1M NaOH solution, distilled water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield 1.00 g (84%) of the title compound. GC-MS (EI) m/z 275.2 [MH^+]

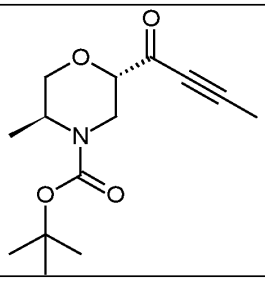
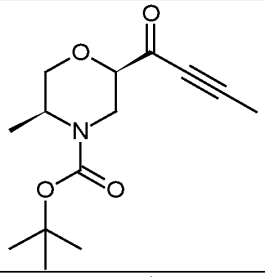
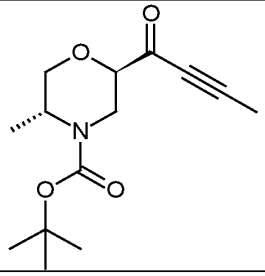
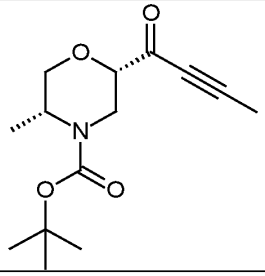
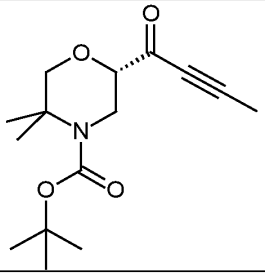
b) *tert*-butyl (2*R*)-2-(but-2-ynoyl)morpholine-4-carboxylate

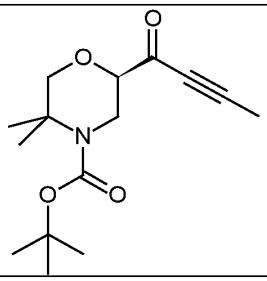
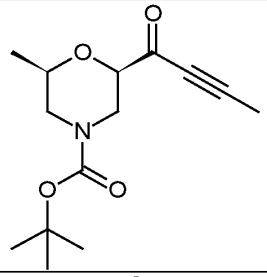
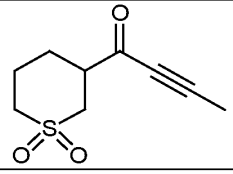
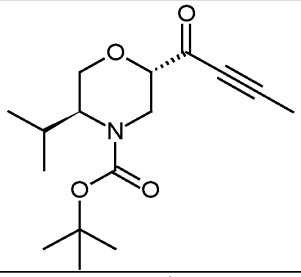
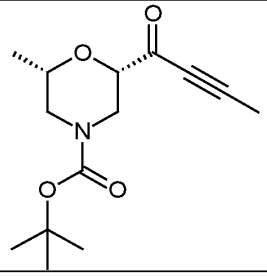
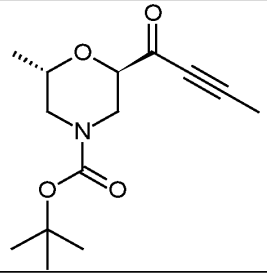
Under nitrogen the above obtained *tert*-butyl (2*R*)-2-[methoxy(methyl)carbamoyl]morpholine-4-carboxylate was dissolved in 20 ml dry tetrahydrofuran, and 11 ml 0.5 M 1-Propynyl magnesium bromide in tetrahydrofuran (5.5 mmol) was added dropwise at 0 °C. The reaction mixture was stirred for 20 minutes at 0 °C, and quenched by the addition of 10 ml saturated NH_4Cl solution and 5 ml distilled water. The mixture was extracted with ethyl acetate. The combined organic layer was washed with distilled water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield 0.83 g (90%) of the title compound. GC-MS (EI) m/z 254.1 [MH^+]

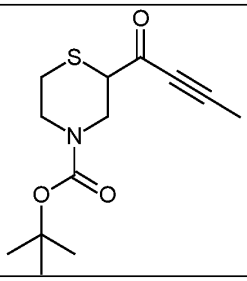
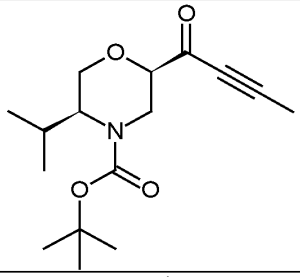
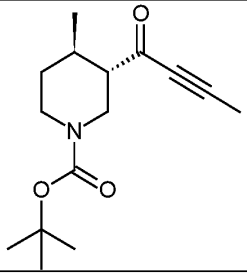
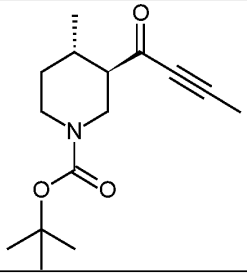
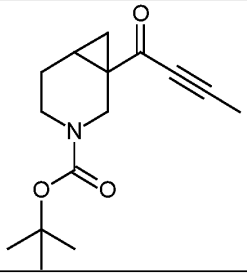
Compounds of Table 5 were prepared from the appropriate Weinreb amide and 1-Propynyl magnesium bromide according to the method described in Intermediate 63.

Table 5

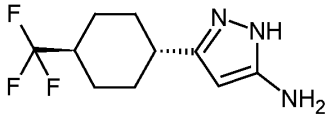
Intermediate	Structure	Intermediate (starting material)	GC-MS (EI) m/z [MH^+]
64		(2*S*)-4-[(*tert*-butoxy)carbonyl]morpholine-2-carboxylic acid	254.1
65		4-[(*tert*-butoxy)carbonyl]morpholine-2-carboxylic acid	254.1

66		4	268.1
67		3	268.1
68		2	268.1
69		1	268.1
70		5	282.1

71		6	282.1
72		7	268.1
73		1,1-dioxo-1λ⁶-thiane-3-carboxylic acid	201.1
74		11	296.2
75		8	268.1
76		9	268.1

77		4-[(*tert*-butoxy)carbonyl]thiomorpholine-2-carboxylic acid	248.1
78		10	296.2
79		24	266.2
80		25	266.2
81		12	264.3

Intermediate 82



3-[*trans*-4-(Trifluoromethyl)cyclohexyl]-1H-pyrazol-5-amine

a) Methyl *trans*-4-(trifluoromethyl)cyclohexane-1-carboxylate

To a solution of 10 g (51 mmol) *trans* 4-(trifluoromethyl)cyclohexane-1-carboxylic acid in 150 ml methanol 10 ml (137 mmol) thionyl chloride was added dropwise at -10 °C. After addition the mixture was allowed to warm to room temperature and stirred at this temperature for 16 h, then concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water. The combined organic layer was washed with $NaHCO_3$ solution and water, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield 8.96 g (84%) of the title compound. GC-MS (EI) m/z 211.2 [MH^+]

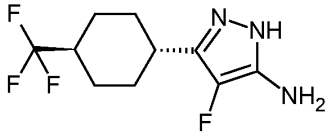
b) 3-Oxo-3-[*trans*-4-(trifluoromethyl)cyclohexyl]propanenitrile

Under nitrogen to a mixture of 9.1 ml (174 mmol) acetonitrile in 260 ml dry tetrahydrofuran 51 ml 2.5 M *n*-butyllithium in *n*-hexane solution (127 mmol) was added dropwise at (-78) °C - (-65) °C. After addition the mixture was stirred at -78°C for 1 h, 8.96 g (42.6 mmol) methyl *trans*-4-(trifluoromethyl)cyclohexane-1-carboxylate was added dropwise. The so obtained mixture was allowed to warm to room temperature and stirred at this temperature for 1 h. The reaction mixture was quenched by addition of 150 mL of saturated ammonium chloride solution. The tetrahydrofuran was evaporated and the mixture was extracted with ethyl acetate. The combined organic layer was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product is used in the next step.

c) 3-[*trans*-4-(Trifluoromethyl)cyclohexyl]-1H-pyrazol-5-amine

The above obtained 3-oxo-3-[*trans*-4-(trifluoromethyl)cyclohexyl]propanenitrile was solved in 187 ml of ethanol and 4.4 ml (167 mmol) of hydrazine monohydrate was added. Under inert gas atmosphere, the reaction mixture was refluxed for 16 h. The solvent was removed *in vacuo* and dry toluene was evaporated from the residue several times to yield 11.15 g of the title compound. LC-MS (ESI) m/z 234.2 [MH^+]

Intermediate 83



4-fluoro-3-[*trans*-4-(trifluoromethyl)cyclohexyl]-1H-pyrazol-5-amine

a) *trans*-4-(Trifluoromethyl)cyclohexane-1-carbonyl chloride

A mixture of 5 g (25.5 mmol) *trans* 4-(trifluoromethyl)cyclohexane-1-carboxylic acid, 100 ml dichloromethane, 5 ml (68.5 mmol) thionyl chloride and 0.1 ml dimethyformamide was refluxed for 6 h. The reaction mixture was concentrated *in vacuo* and dry tetrahydrofuran was evaporated from the residue several times. The crude product is used in the next step.

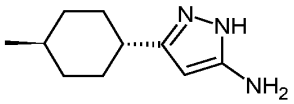
b) 2-Fluoro-3-oxo-3-[*trans*-4-(trifluoromethyl)cyclohexyl]propanenitrile

Under inert gas atmosphere, to a solution of the above obtained *trans*-4-(trifluoromethyl) cyclohexane-1-carbonyl chloride and 1.5 ml (26.96 mmol) fluoroacetonitrile in 50 ml dry tetrahydrofuran 50 ml (50 mmol) 1M lithium bis(trimethylsilyl)amide was added dropwise at - 78 °C. After addition the mixture was stirred at -78°C for 1 h, then the mixture was allowed to warm to room temperature and poured into 200 ml of water. The pH of the mixture was adjusted to 2 by the addition of 1M hydrochloric acid. The mixture was extracted with ethyl acetate, the combined organic layer was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product is used in the next step.

c) 4-Fluoro-3-[*trans*-4-(trifluoromethyl)cyclohexyl]-1H-pyrazol-5-amine

The above obtained 2-fluoro-3-oxo-3-[*trans*-4-(trifluoromethyl)cyclohexyl]propanenitrile was dissolved in 65 ml of ethanol and 4.4 ml (77 mmol) of hydrazine monohydrate was added. Under inert gas atmosphere, the reaction mixture was refluxed for 16 h. The solvent was removed *in vacuo* to obtain the title compound as oil. LC-MS (ESI) m/z 252.2 [MH^+]

Intermediate 84



3-(*trans*-4-methylcyclohexyl)-1H-pyrazol-5-amine

a) Methyl *trans*-4-methylcyclohexane-1-carboxylate

The title compound is prepared from *trans*-4-methylcyclohexane-1-carboxylic acid according to the method described in Intermediate 82a.

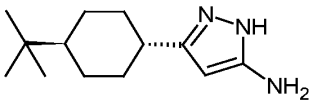
b) 3-Oxo-3-(*trans*-4-methylcyclohexyl)propanenitrile

The title compound is prepared from Methyl *trans*-4-methylcyclohexane-1-carboxylate according to the method described in Intermediate 82b.

c) 3-(*trans*-4-methylcyclohexyl)-1H-pyrazol-5-amine

The title compound is prepared from 3-Oxo-3-(*trans*-4-methylcyclohexyl)propanenitrile according to the method described in Intermediate 82c.

Intermediate 85



3-[(*trans*-4-*tert*-butylcyclohexyl]-1H-pyrazol-5-amine

a) Methyl *trans*-4-*tert*-butylcyclohexane-1-carboxylate

The title compound is prepared from *trans*-4-*tert*-butylcyclohexane-1-carboxylic acid according to the method described in Intermediate 82a.

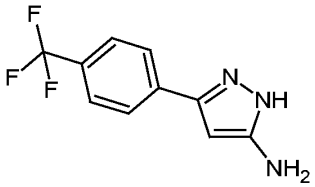
b) 3-Oxo-3-(*trans*-4-*tert*-butylcyclohexyl)propanenitrile

The title compound is prepared from Methyl *trans*-4-*tert*-butylcyclohexane-1-carboxylate according to the method described in Intermediate 82b.

c) 3-(*trans*-4-*tert*-butylcyclohexyl)-1H-pyrazol-5-amine

The title compound is prepared from 3-Oxo-3-(*trans*-4-*tert*-butylcyclohexyl)propanenitrile according to the method described in Intermediate 82c.

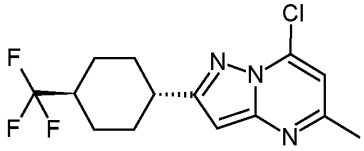
Intermediate 86



3-[4-(trifluoromethyl)phenyl]-1H-pyrazol-5-amine

The title compound is prepared as described in WO2018/167629.

Intermediate 87



7-chloro-5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidine

a) 5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-ol

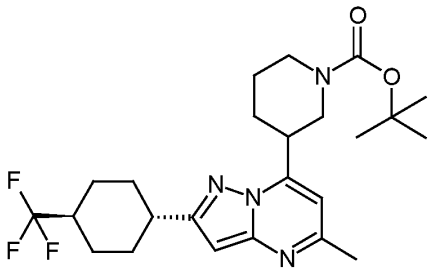
To a solution 0.50 g (2.14 mmol) 3-[*trans*-4-(Trifluoromethyl)cyclohexyl]-1H-pyrazol-5-amine (Intermediate 82) in 30 ml toluene was added 0.30 ml (2.37 mmol) ethyl acetoacetate and a catalytic amount of p-Toluenesulfonic acid monohydrate. The reaction mixture was refluxed for 16 hours, and allowed to warm to RT. The precipitated crystals were filtered to yield 0.51 g (79%) of the title compound. LC-MS (ESI) m/z 300.1 [MH^+]

b) 7-chloro-5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidine

The above obtained 5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-ol was suspended in 10 ml toluene, 0.59 ml (3.40 mmol) *N,N*-Diisopropylethylamine and 0.80 ml (8.50 mmol) phosphoryl chloride was added. The reaction mixture was refluxed for 2 hours and then quenched the by the addition of ice. The reaction mixture was neutralized by the addition of saturated $NaHCO_3$ solution. The resulting mixture was extracted with ethyl acetate. The combined organic layer was washed with distilled water, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield 0.53 g (99%) of the title compound. LC-MS (ESI) m/z 318.1 [MH^+]

Route c)

Intermediate 88

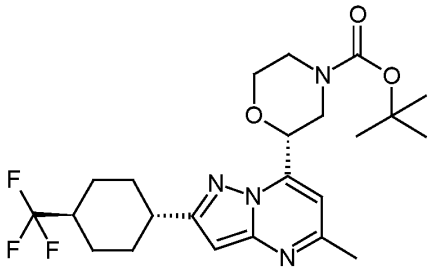


***tert*-butyl 3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidine-1-carboxylate**

To a solution of 0.81 g (3 mmol) *tert*-butyl 3-(3-oxobutanoyl)piperidine-1-carboxylate (Intermediate 28) in 25 ml toluene was added 0.50 g (2.14 mmol) 3-[*trans*-4-(Trifluoromethyl)cyclohexyl]-1H-pyrazol-5-amine (Intermediate 82) and 0.02 g (0.1 mmol) p-Toluenesulfonic acid monohydrate. The reaction mixture was refluxed for 16 hours and the solvent was evaporated. The residue was purified by silica gel chromatography eluting with 0-30% ethyl acetate in cyclohexane to yield 0.26 g (26%) of the title compound. LC-MS (ESI) m/z 467.2 [MH^+]

Route d)

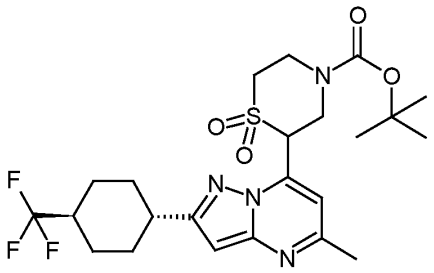
Intermediate 89



***tert*-butyl (2*R*)-2-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}morpholine-4-carboxylate**

To a solution of 0.83 g (3.28 mmol) *tert*-butyl (2*R*)-2-(but-2-ynoyl)morpholine-4-carboxylate (Intermediate 63) in 10 ml ethanol was added 0.27 ml (3.28 mmol) pyrrolidine. The reaction mixture was stirred at RT for 30 minutes and 0.77 g (3.28 mmol) 3-[*trans*-4-(Trifluoromethyl)cyclohexyl]-1H-pyrazol-5-amine (Intermediate 82) and 1.5 ml acetic acid was added. The reaction mixture was stirred at 60 °C for 4 hours, and the solvent was evaporated. The residue was purified by silica gel chromatography eluting with 0-50% ethyl acetate in cyclohexane to yield 1.45 g (95%) of the title compound. LC-MS (ESI) m/z 469.2 [MH^+]

Intermediate 90



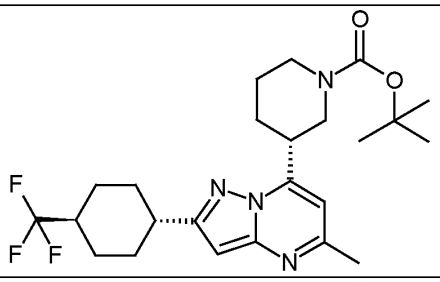
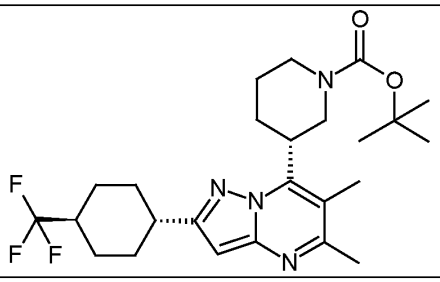
***tert*-butyl 2-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-1,1-dioxo-1λ⁶-thiomorpholine-4-carboxylate**

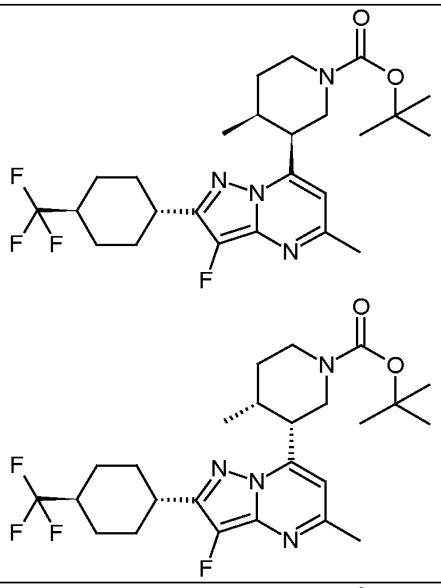
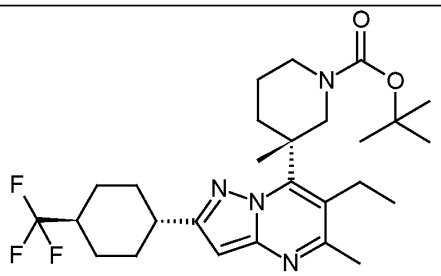
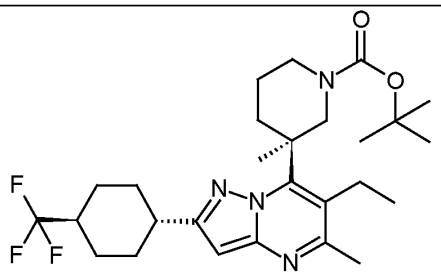
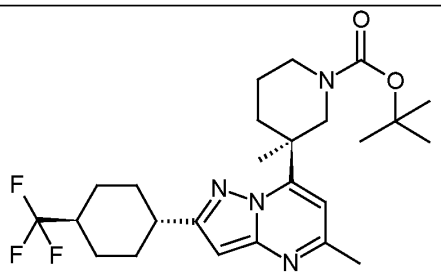
To a solution of 1.12 g (4.75 mmol) *tert*-butyl 1,1-dioxo-1λ⁶-thiomorpholine-4-carboxylate (prepared as described in EP1140904) in 30 ml dry tetrahydrofuran 4.8 mL 1 M lithium bis(trimethylsilyl)amide in tetrahydrofuran solution (4.8 mmol) was added dropwise at (-78) °C - (-65) °C. After addition the mixture was stirred at -78 °C for 1 hour, 1.26 g (3.96 mmol) 7-chloro-5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidine (Intermiediate 87) was added. The so

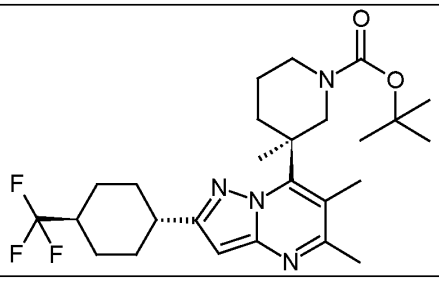
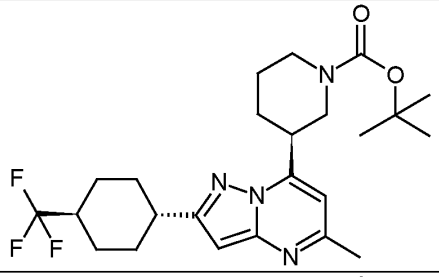
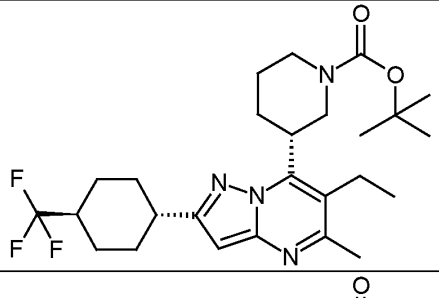
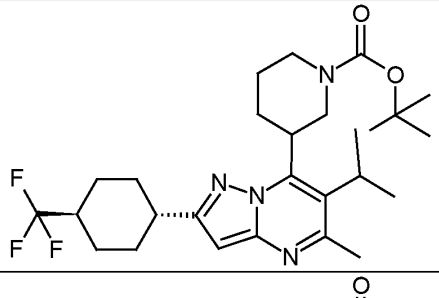
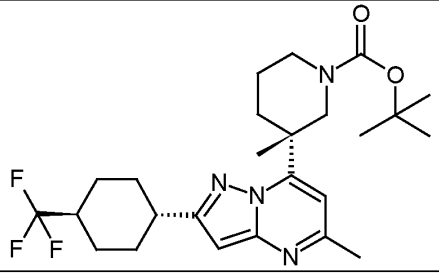
obtained mixture was allowed to warm to RT and stirred at this temperature for 18 h. The reaction mixture was quenched by addition of 20 ml saturated ammonium chloride solution and 10 ml distilled water. The reaction mixture was extracted with ethyl acetate, the combined organic layer was washed with distilled water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 0-35% ethyl acetate in cyclohexane to yield 0.63 g (31%) of the title compound. LC-MS (ESI) m/z 517.2 [MH^+]

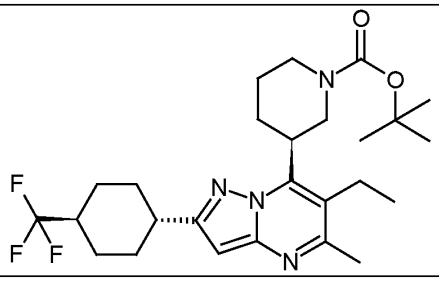
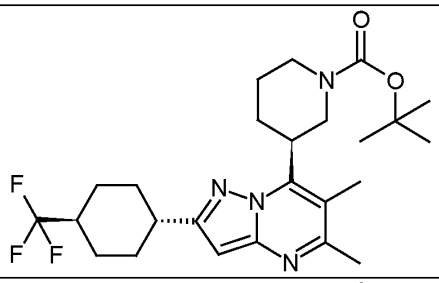
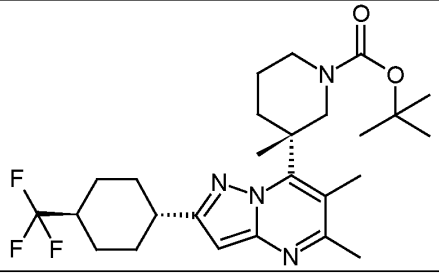
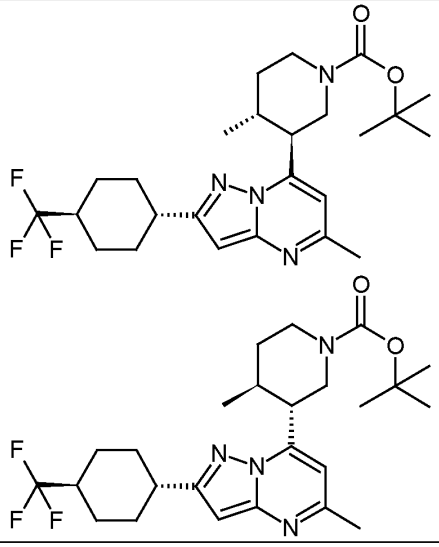
Intermediates 91 - 155 were prepared using analogues methods to those Intermediates described above and are exemplified below in Table 6.

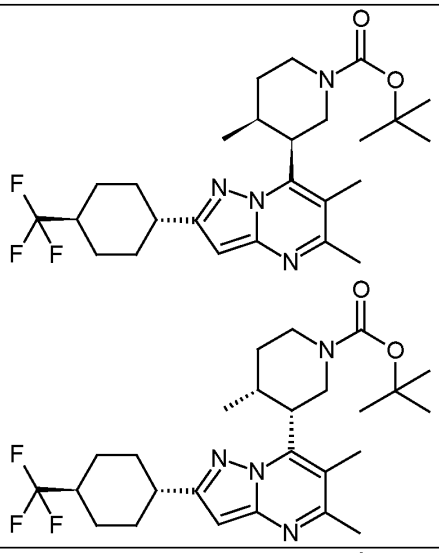
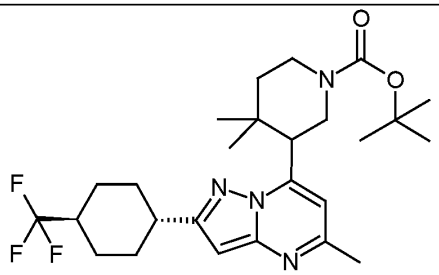
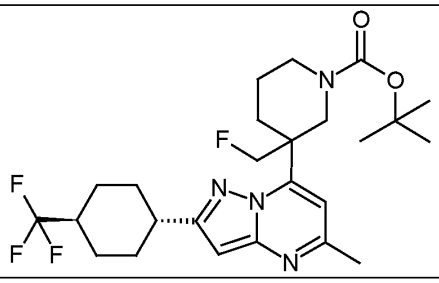
Table 6

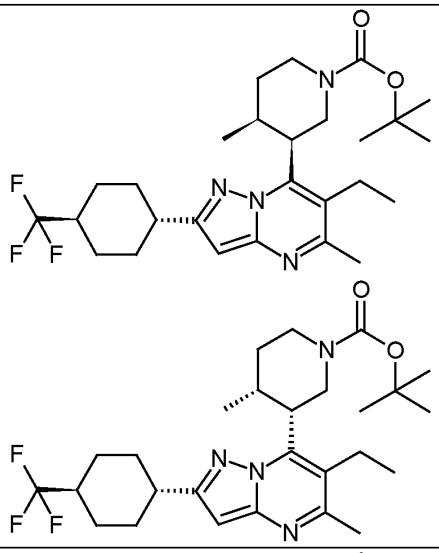
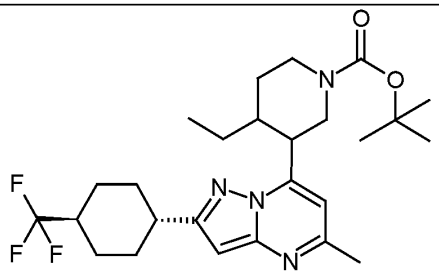
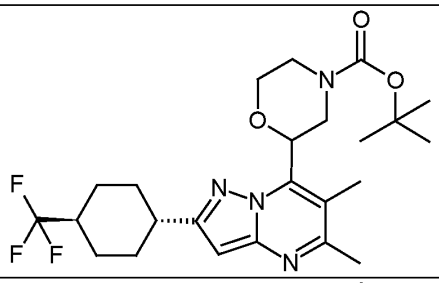
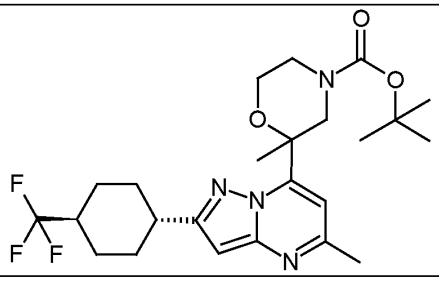
Intermediate	Structure	LC-MS (ESI) m/z [MH^+]	Intermediates (starting materials)	Route
91		467.2	82+29	c
92		481.2	82+47	c

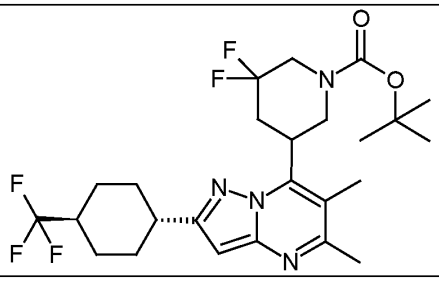
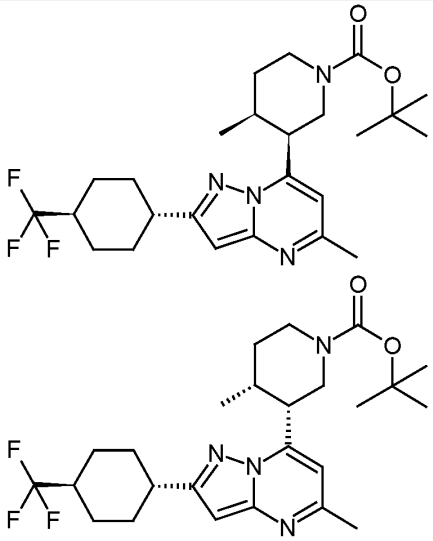
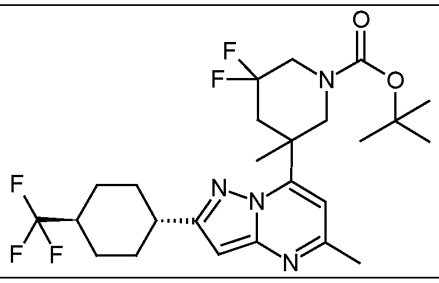
93		499.3	83+30	c
94		509.3	82+48	c
95		509.3	82+49	c
96		481.3	82+32	c

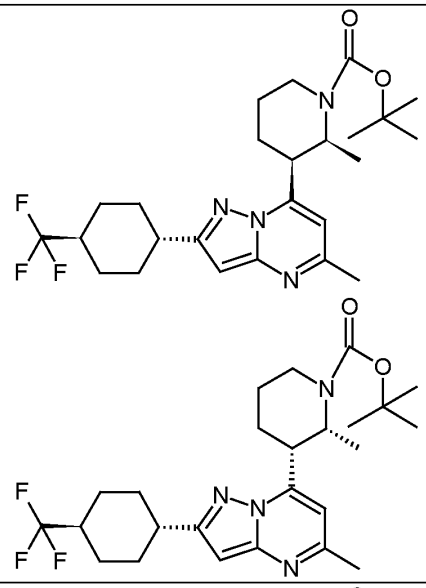
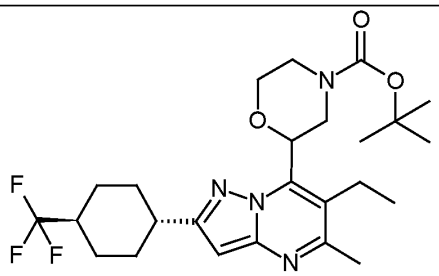
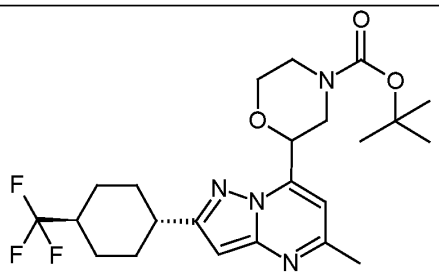
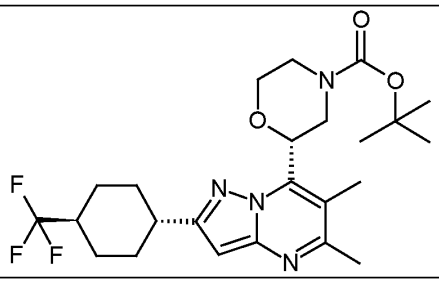
97		495.3	82+50	c
98		467.2	82+33	c
99		495.2	82+29	c
100		509.3	82+52	c
101		481.3	82+31	c

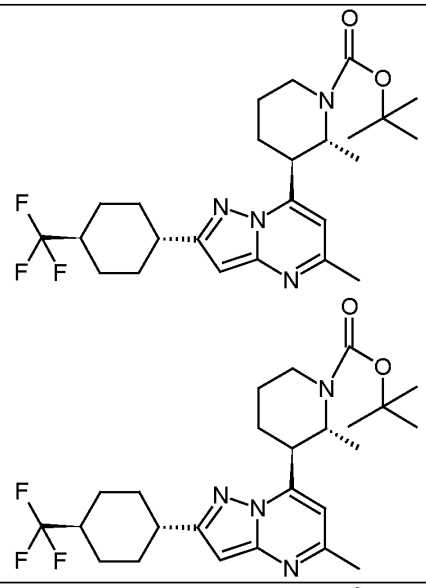
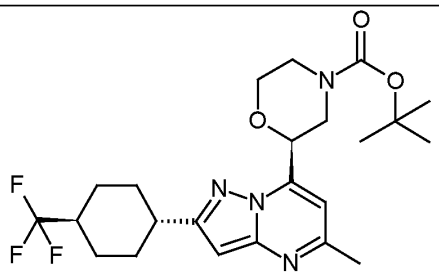
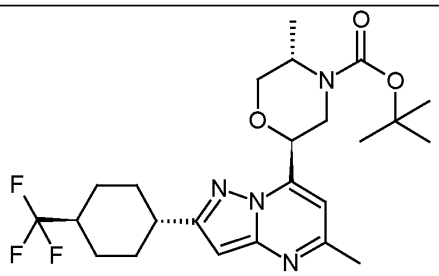
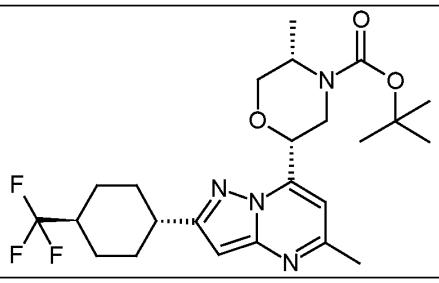
102		495.2	82+53	c
103		481.2	82+54	c
104		495.3	82+55	c
105		481.3	82+34	c

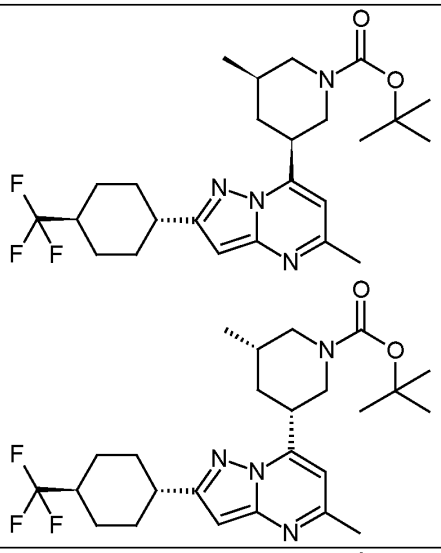
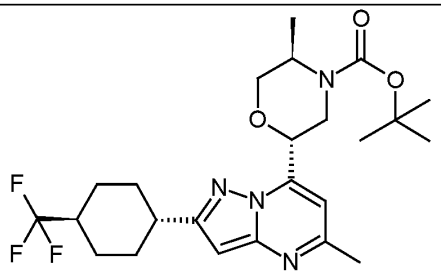
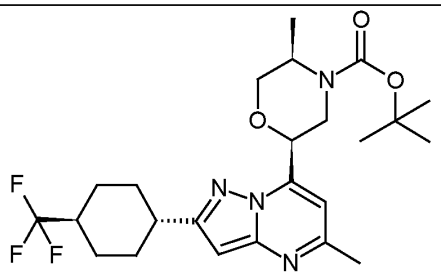
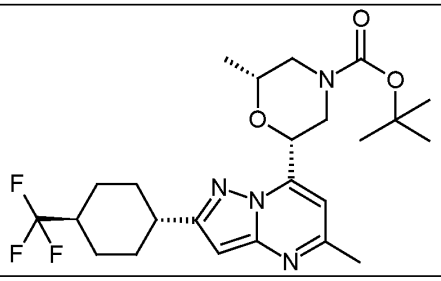
106		495.3	82+57	c
107		495.3	82+38	c
108		499.3	82+39	c

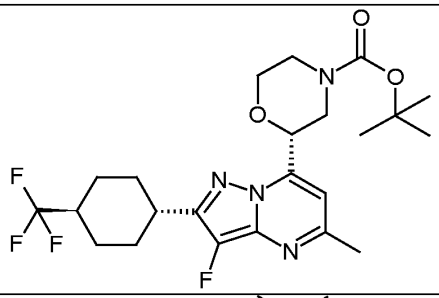
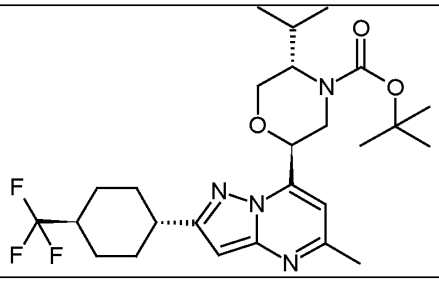
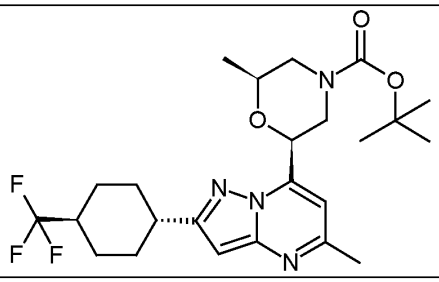
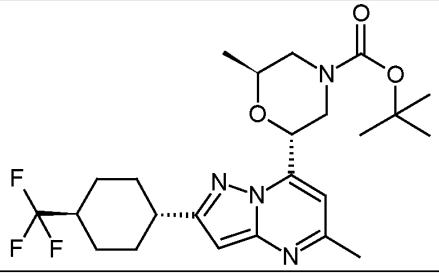
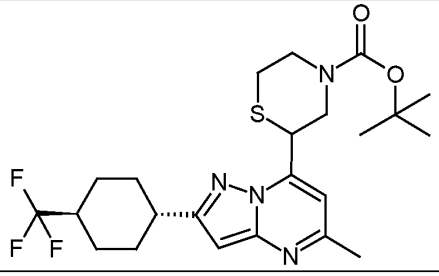
109		509.3	82+58	c
110		495.3	82+40	c
111		483.3	82+59	c
112		483.3	82+42	c

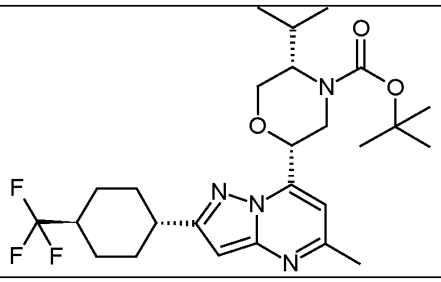
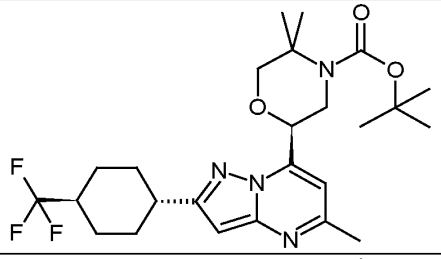
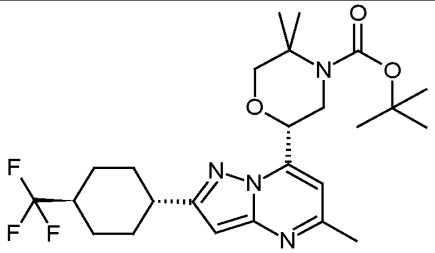
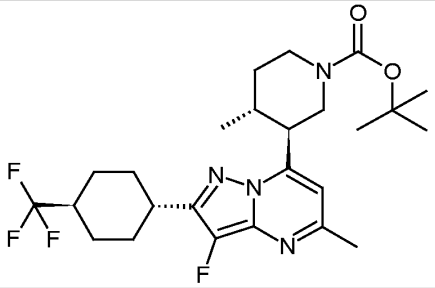
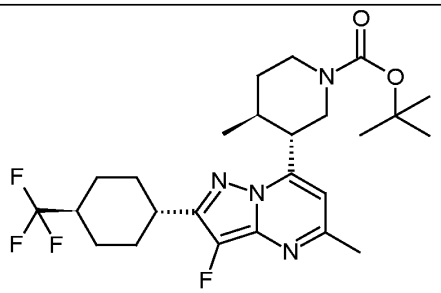
113		517.3	82+60	c
114		481.2	82+30	c
115		517.3	82+44	c

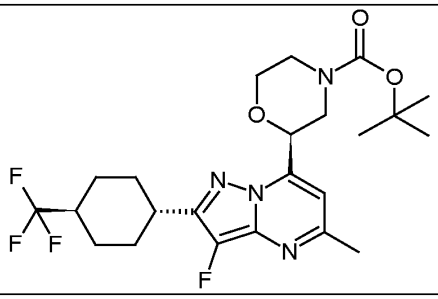
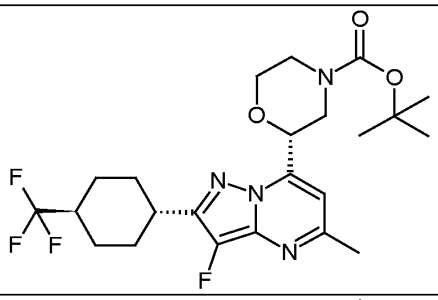
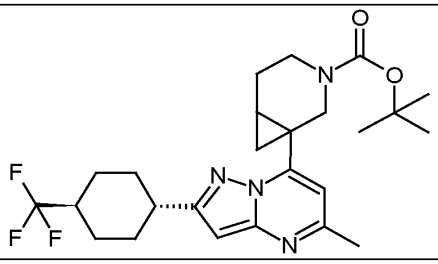
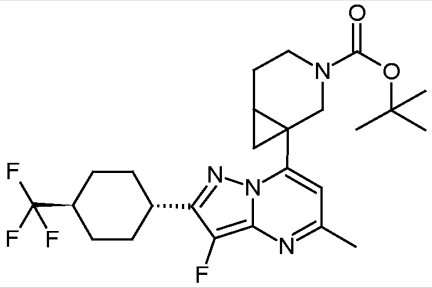
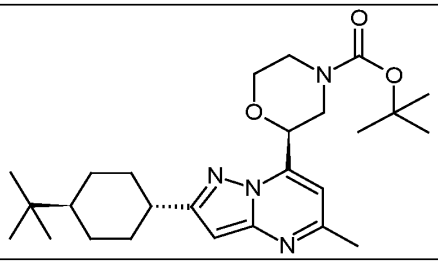
116		481.3	82+36	c
117		497.3	82+61	c
118		469.3	82+41	c
119		483.3	82+62	c

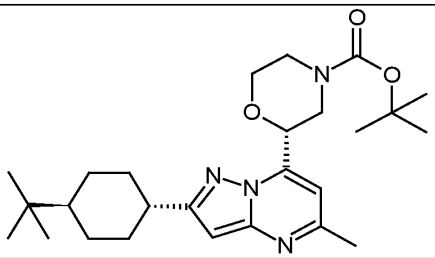
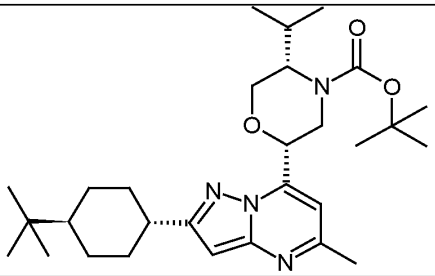
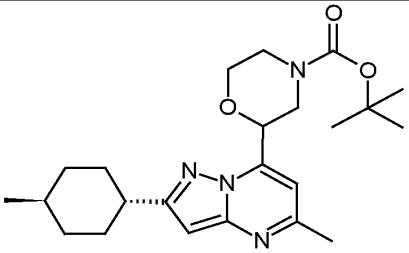
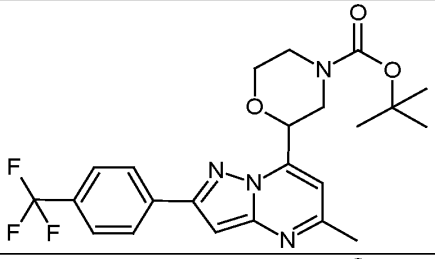
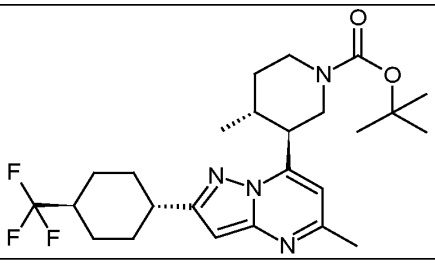
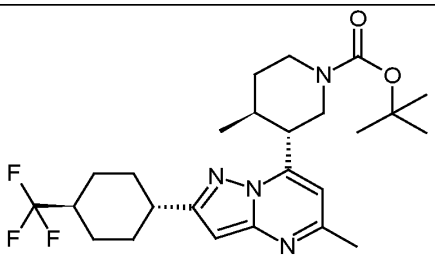
120		481.3	82+37	c
121		469.3	82+64	d
122		474.3	82+66	d
123		474.3	82+67	d

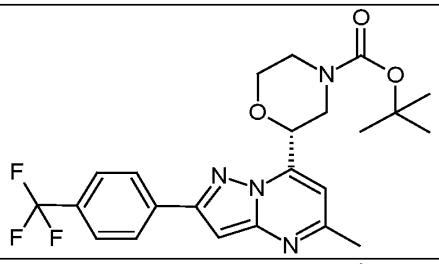
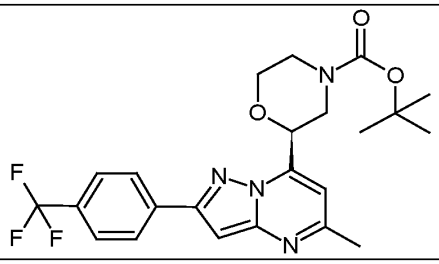
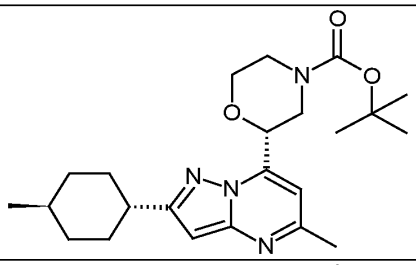
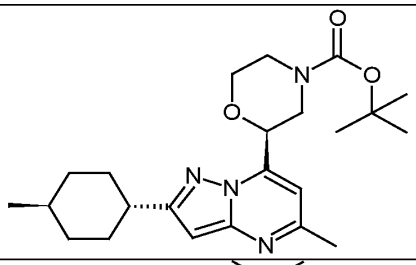
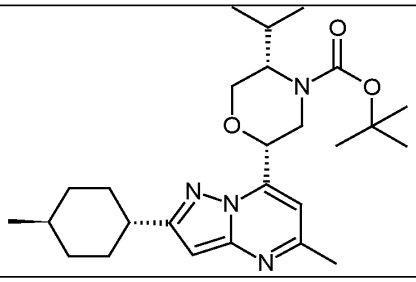
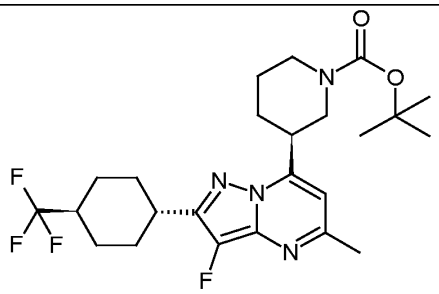
124		481.2	82+35	c
125		474.3	82+68	d
126		474.3	82+69	d
127		474.3	82+72	d

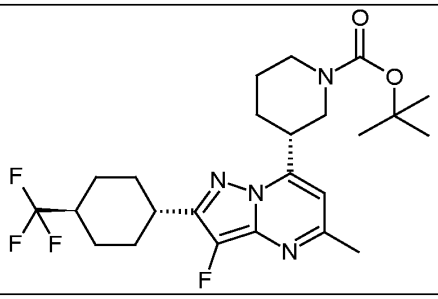
128		487.2	83+63	d
129		511.3	82+74	d
130		474.3	82+75	d
131		474.3	82+76	d
132		485.2	82+77	d

133		511.3	82+78	d
134		497.3	82+70	d
135		497.3	82+71	d
136		499.2	83+79	d
137		499.2	83+80	d

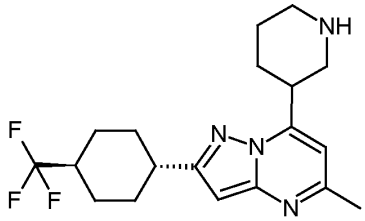
138		487.2	83+64	d
139		487.2	83+63	d
140		479.3	82+81	d
141		497.3	83+81	d
142		457.2	85+64	d

143		457.2	85+63	d
144		499.5	85+78	d
145		415.4	84+65	d
146		463.4	86+65	d
147		481.2	82+79	d
148		481.2	82+80	d

149		463.4	86+63	d
150		463.4	86+64	d
151		415.4	84+63	d
152		415.4	84+64	d
153		457.4	84+78	d
154		485.4	83+33	c

155		485.4	83+29	c

Intermediate 156

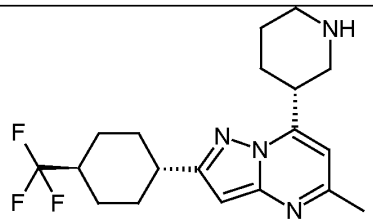
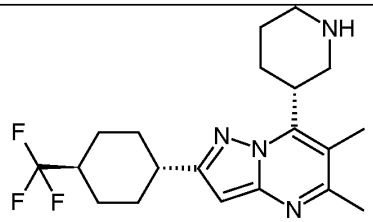
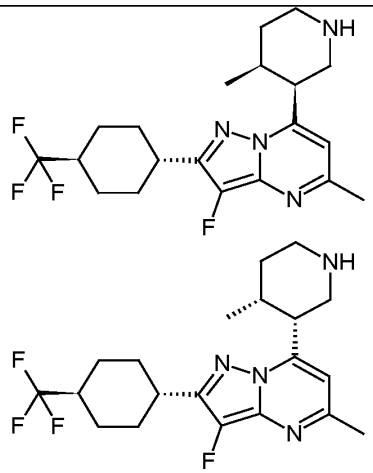
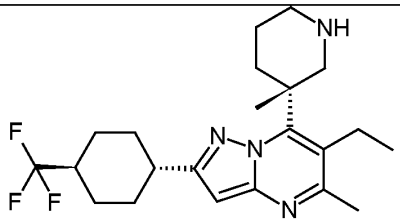
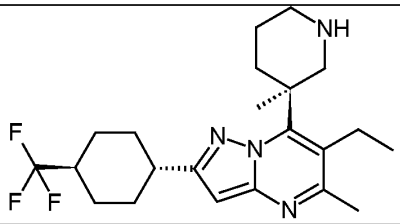


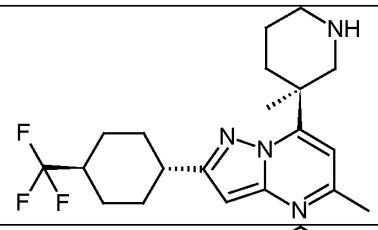
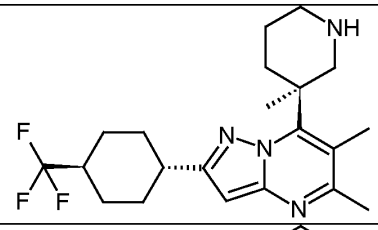
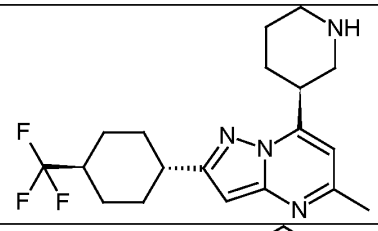
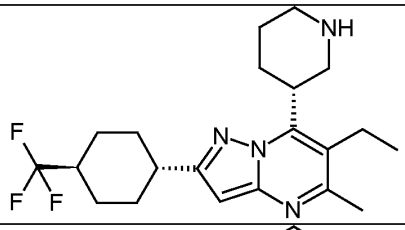
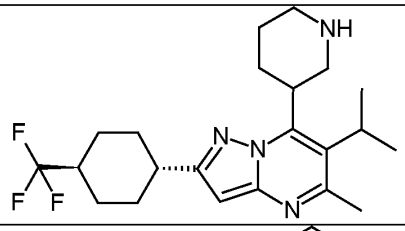
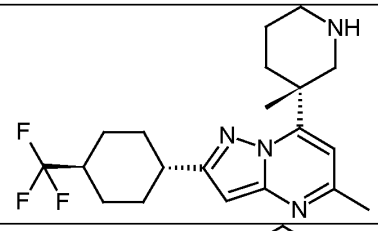
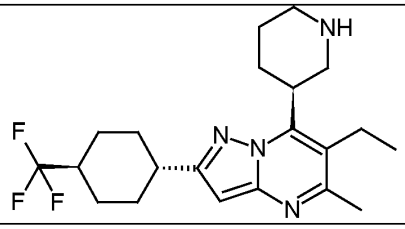
3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidine

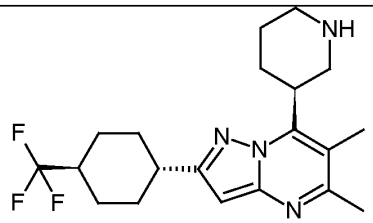
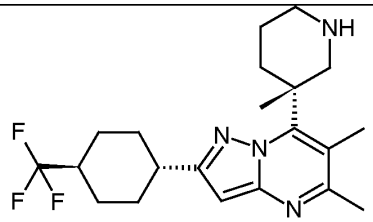
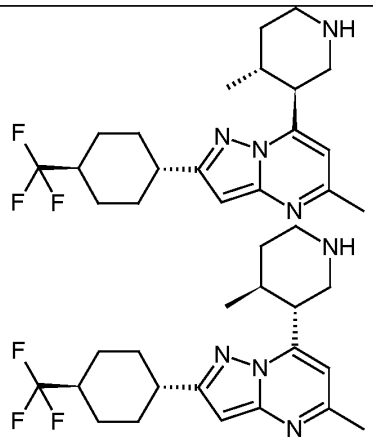
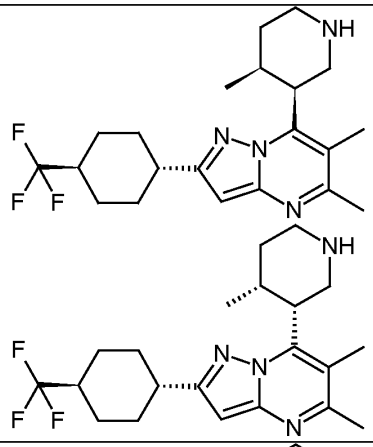
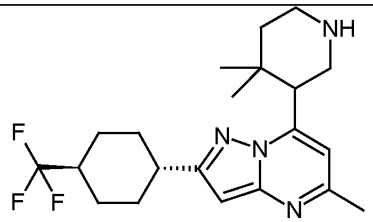
To a solution of 1.00 g (2.14 mmol) *tert*-butyl 3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidine-1-carboxylate (Intermediate 88) in 20 ml dichloromethane was added 3.3 ml (42.8 mmol) trifluoroacetic acid dropwise at 0 °C. The reaction mixture was allowed to warm to RT and stirred for 16 hours. 10 ml distilled water was added, and the pH was adjusted to 10 by the addition of 2 M aqeous sodium hydroxide. The mixture was extracted with dichloromethane. The combined organic layer was washed with distilled water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield 0.70 g (89%) of the title compound. LC-MS (ESI) m/z 367.2 [MH^+]

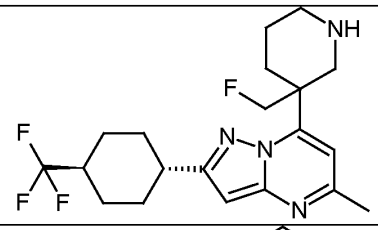
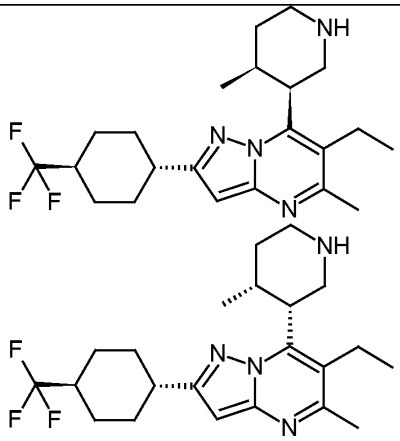
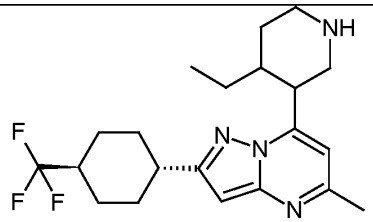
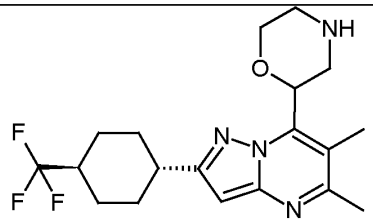
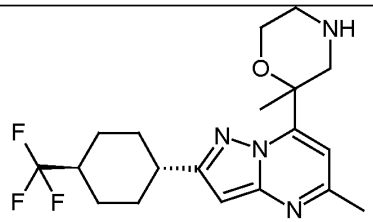
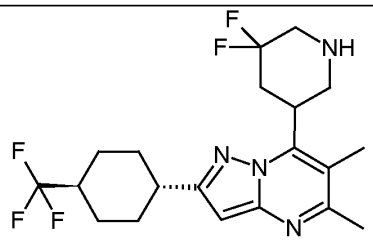
Intermediates 157 - 221 were prepared using analogues methods to those Intermediates described above and are exemplified below in Table 7.

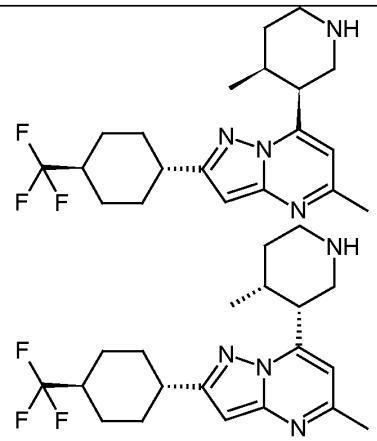
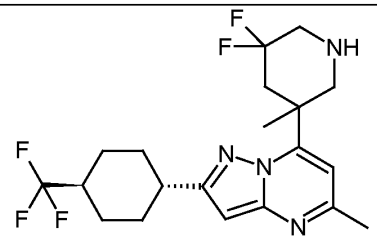
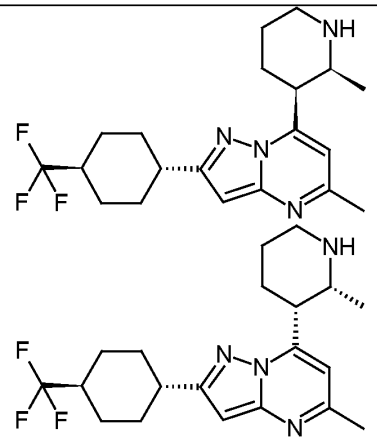
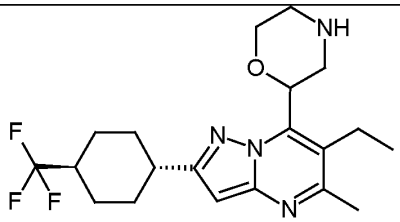
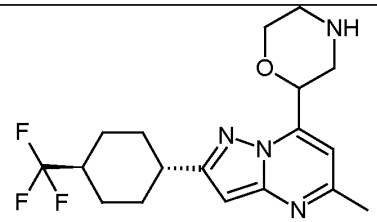
Table 7

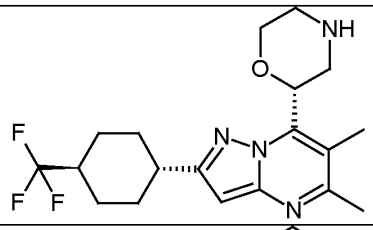
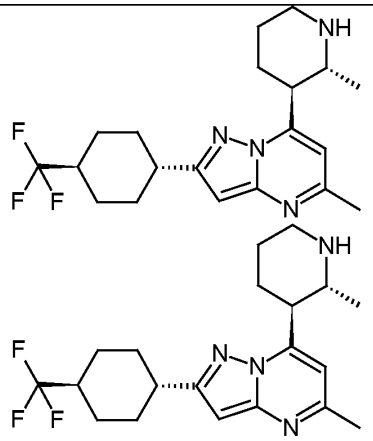
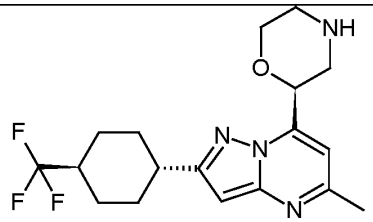
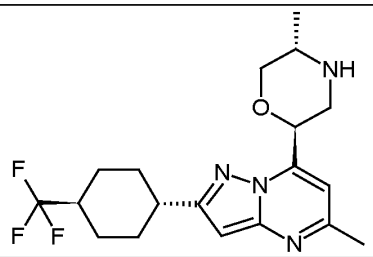
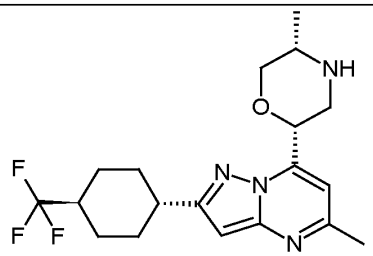
Intermediate	Structure	LC-MS (ESI) m/z [MH^+]	Intermediate (starting material)
157		367.2	91
158		381.2	92
159		399.3	93
160		409.3	94
161		409.3	95

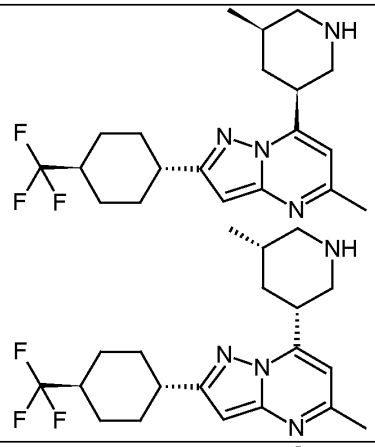
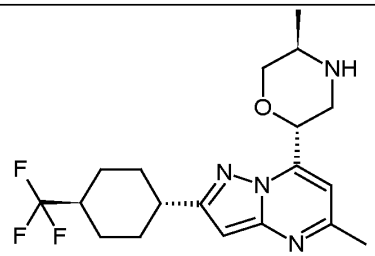
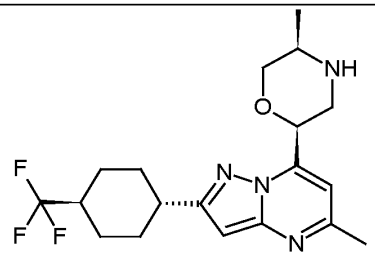
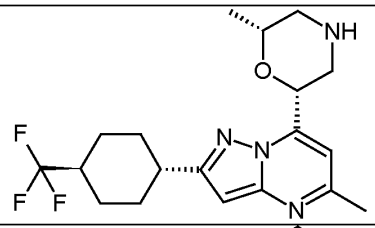
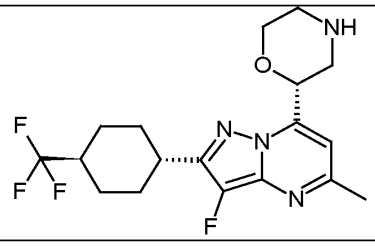
162		381.3	96
163		395.3	97
164		367.2	98
165		395.2	99
166		409.3	100
167		381.3	101
168		395.2	102

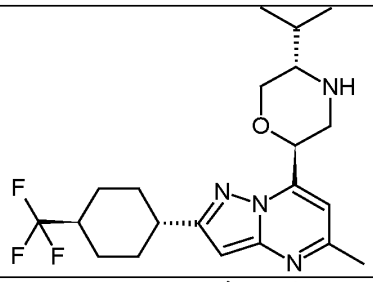
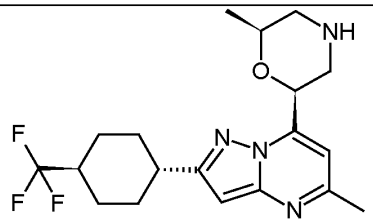
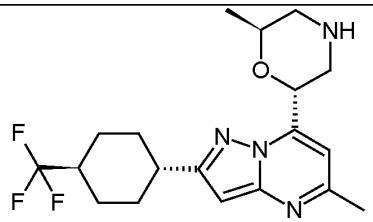
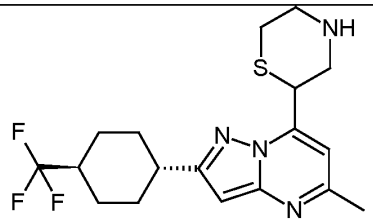
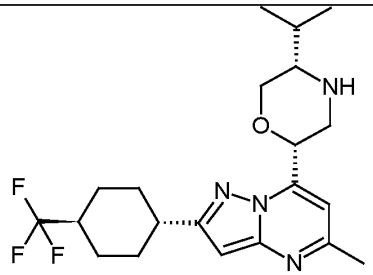
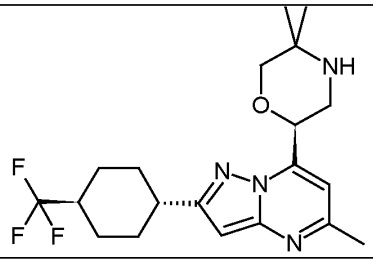
169		381.2	103
170		395.3	104
171		381.3	105
172		395.3	106
173		395.3	107

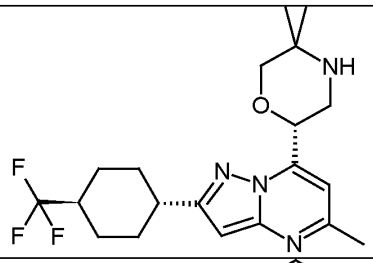
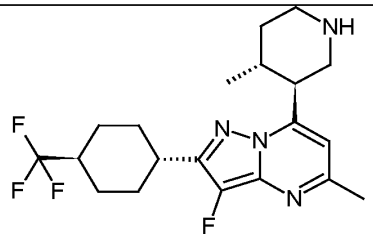
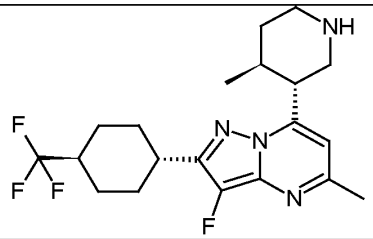
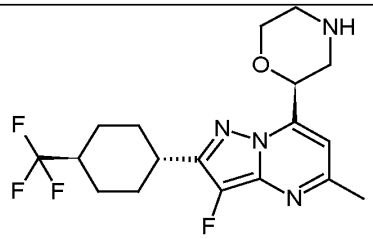
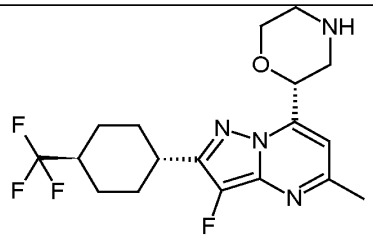
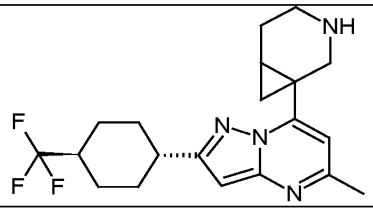
174		399.3	108
175		409.3	109
176		395.3	110
177		383.3	111
178		383.3	112
179		417.3	113

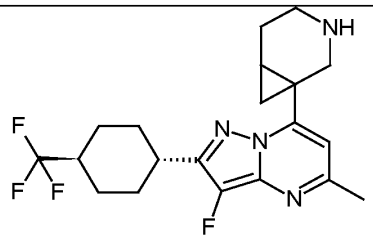
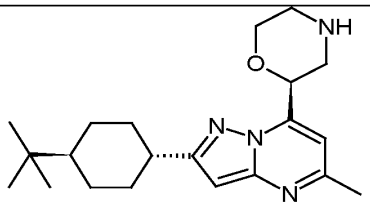
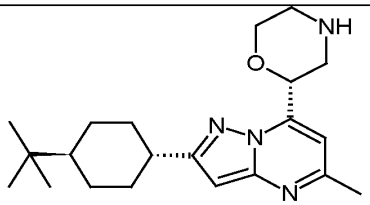
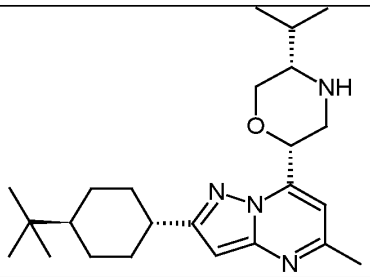
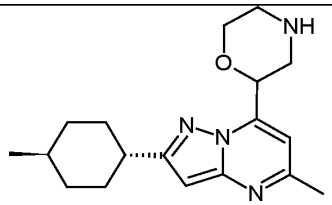
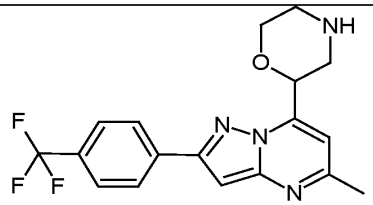
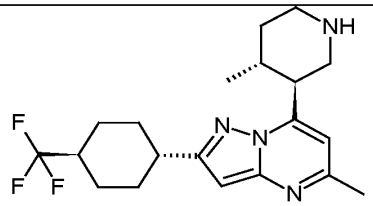
180		381.2	114
181		417.3	115
182		381.3	116
183		397.3	117
184		369.3	118

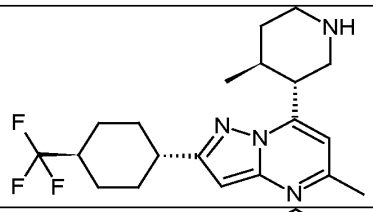
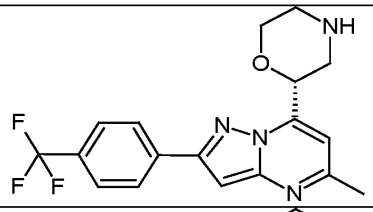
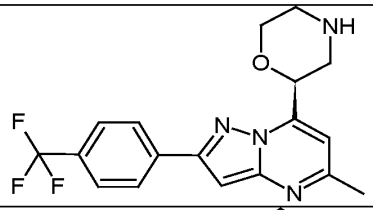
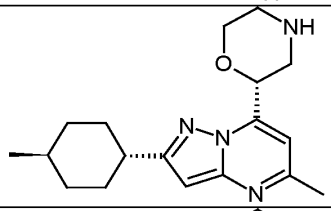
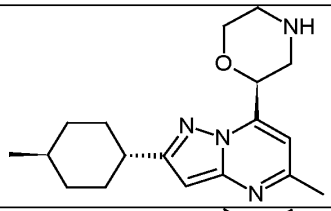
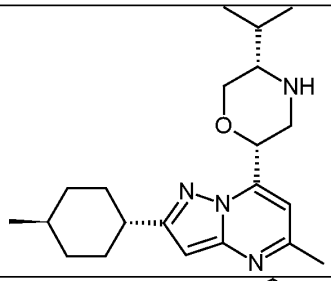
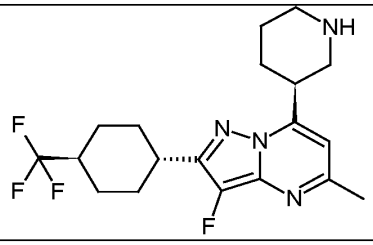
185		383.3	119
186		381.3	120
187		369.3	121
188		374.3	122
189		374.3	123

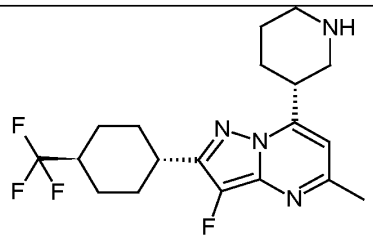
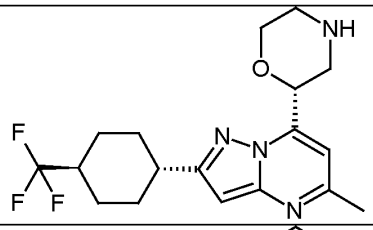
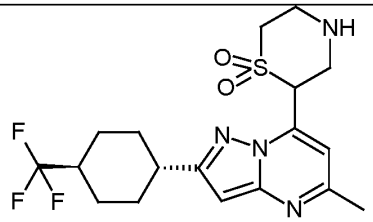
190		381.2	124
191		374.3	125
192		374.3	126
193		374.3	127
194		387.2	128

195		411.3	129
196		374.3	130
197		374.3	131
198		385.2	132
199		411.3	133
200		397.3	134

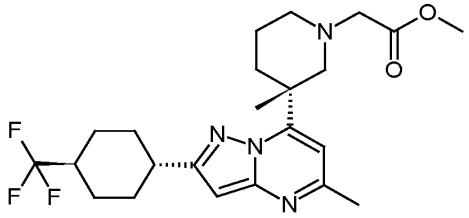
201		397.3	135
202		399.2	136
203		399.2	137
204		387.2	138
205		387.2	139
206		379.4	140

207		397.4	141
208		357.2	142
209		357.2	143
210		399.5	144
211		315.2	145
212		363.5	146
213		381.2	147

214		381.2	148
215		363.5	149
216		363.5	150
217		315.2	151
218		315.2	152
219		357.6	153
220		385.2	154

221		385.2	155
222		369.3	89
223		417.2	89

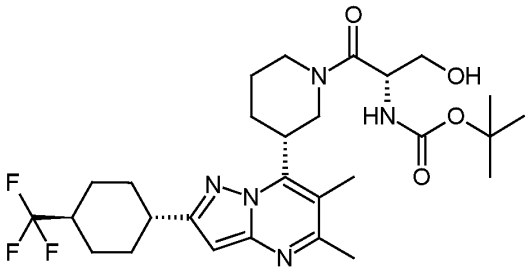
Intermediate 224



methyl 2-[(3*R*)-3-methyl-3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidin-1-yl]acetate

To a solution of 0.07 g (0.18 mmol) (3*R*)-3-methyl-3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidine (Intermediate 167) in 2 ml toluene was added 0.03 ml (0.28 mmol) methyl bromoacetate and 0.1 ml (0.57 mmol) *N,N*-Diisopropylethylamine. The reaction mixture was stirred for 16 hours at RT and diluted with toluene. The mixture was washed with distilled water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography eluting with 5% acetone in dichloromethane to yield 0.06 g (80%) of the title compound. LC-MS (ESI) m/z 453.2 [MH^+]

Intermediate 225

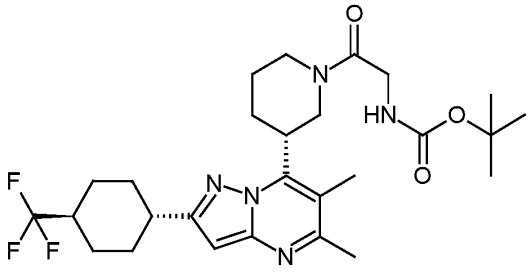
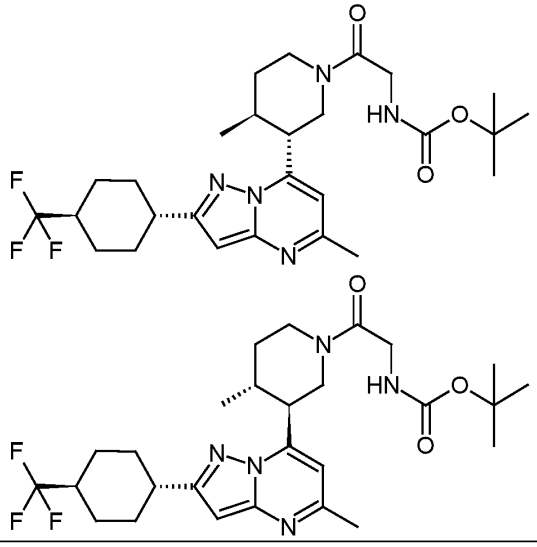


***tert*-butyl *N*-[(2*S*)-1-[(3*R*)-3-{5,6-dimethyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidin-1-yl]-3-hydroxy-1-oxopropan-2-yl]carbamate**

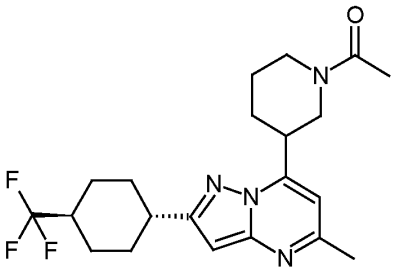
Under nitrogen to a solution of 0.17 g (0.45 mmol) (3*R*)-3-{5,6-dimethyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidine (Intermediate 158) in 10 ml dimethylformamide was added 0.09 g (0.46 mmol) Boc-Ser-OH, 0.08 g (0.54 mmol) 1-Hydroxybenzotriazole hydrate, 0.2 ml (1.12 mmol) *N,N*-Diisopropylethylamine and 0.1 g (0.54 mmol) EDC at 0 °C. The reaction mixture was allowed to warm to RT, and stirred for 16 hours. The reaction mixture was diluted with distilled water. The resulting mixture was extracted with ethyl acetate. The combined organic layer was washed with distilled water, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 4% methanol in dichloromethane to yield 0.12 g (46%) of the title compound. LC-MS (ESI) m/z 568.3 [MH^+]

Intermediates 225 - 226 were prepared using analogues methods to those Intermediates described above and are exemplified below in Table 8.

Table 8

Intermediate	Structure	LC-MS (ESI) m/z [MH^+]	Intermediate (starting material)
226		538.2	158
227		538.2	171

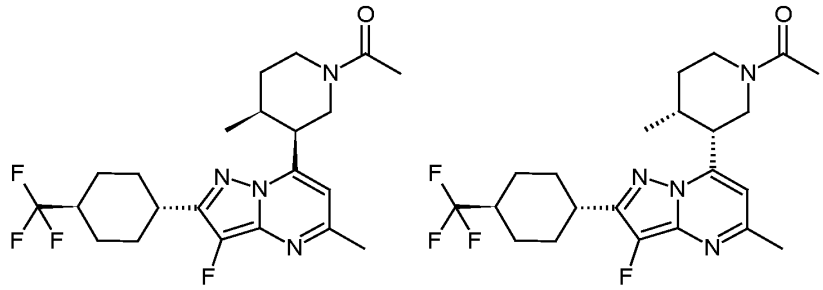
Example 1



1-(3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidin-1-yl)ethan-1-one

To a solution of 0.18 g (0.47 mmol) 3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidine (Intermediate 156) in 15 ml dichloromethane was added 0.1 ml (0.7 mmol) triethylamine and 0.04 ml (0.56 mmol) acetyl chloride. The reaction mixture was stirred for 2 hours at RT and washed with distilled water, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography eluting with 0-10% methanol in dichloromethane to yield 0.17 g (85%) of the title compound. LC-MS (ESI) m/z 409.2 [MH^+]

Example 2 and Example 3



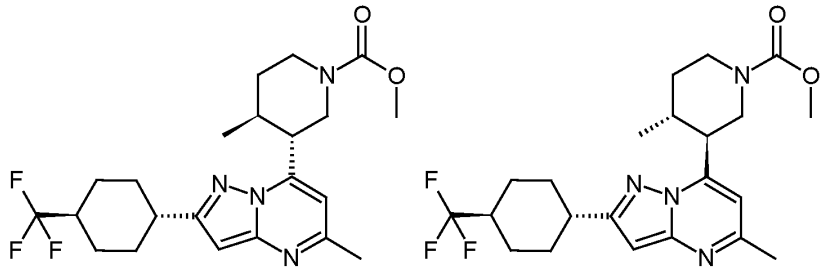
1-[(3*S*,4*S*)-3-{3-fluoro-5-methyl-2-[(*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-4-methylpiperidin-1-yl]ethan-1-one

and

1-[(3*R*,4*R*)-3-{3-fluoro-5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-4-methylpiperidin-1-yl]ethan-1-one

The racemic form of the title compounds (Example 158) were prepared from *cis*-3-{3-fluoro-5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-4-methylpiperidine (Intermediate 159) according to the method described in Example 1. LC-MS (ESI) m/z 441.2 [MH^+]. The A and B enantiomers were separated using chiral preparative HPLC (Lux i-Amylose-1 5µm 250x21.2mm; F=21.34ml/min; eluents:A: *n*-heptane B: 2-propanol; isocratic5%B t=25°C) obtaining **enantiomer A** (T_r 13.625, Example 2), and **enantiomer B** (T_r 20.089, Example 3). Their absolute configuration is not determined.

Example 4 and Example 5



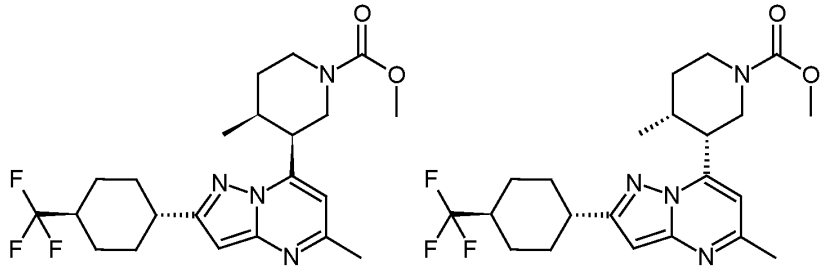
methyl (3*R*,4*S*)-4-methyl-3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidine-1-carboxylate

and

methyl (3*S*,4*R*)-4-methyl-3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidine-1-carboxylate

The racemic form of the title compounds (Example 159) were prepared from *trans*-4-methyl-3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidine (Intermediate 171) and methyl chloroformate according to the method described in Example 1. LC-MS (ESI) m/z 439.2 [MH^+]. The A and B enantiomers were separated using chiral preparative HPLC (Lux i-Amylose-1 5µm 150x21.1mm; F=10ml/min; eluents:A: water B: 2-propanol; isocratic55%B t=40°C) obtaining **enantiomer A** (T_r 18.886, Example 4), and **enantiomer B** (T_r 24.444, Example 5). Their absolute configuration was determined with VCD spectroscopy. Example 4 is (3*R*,4*S*) and Example 5 is (3*S*,4*R*).

Example 6 and Example 7



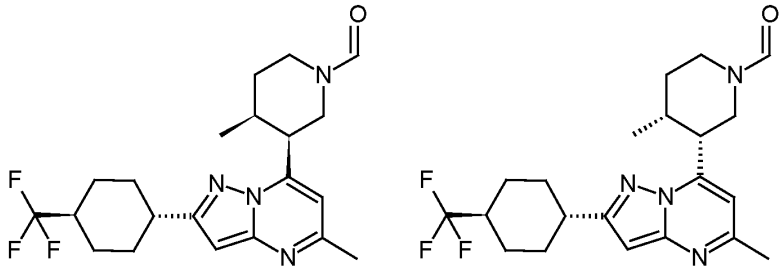
methyl (3*S*,4*S*)-4-methyl-3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidine-1-carboxylate

and

methyl (3*R*,4*R*)-4-methyl-3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidine-1-carboxylate

The racemic form of the title compounds (Example 76) were prepared from *cis*-4-methyl-3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidine (Intermediate 180) and methyl chloroformate according to the method described in Example 1. LC-MS (ESI) m/z 439.2 [MH^+]. The A and B enantiomers were separated using chiral preparative HPLC (Lux i-Amylose-1 5µm 150x21.1mm; F=10ml/min; eluents:A: water B: 2-propanol; isocratic 55%B t=40°C) obtaining **enantiomer A** (T_r 18.886, Example 6), and **enantiomer B** (T_r 29.748, Example 7). Their absolute configuration is not determined.

Example 8 and Example 9



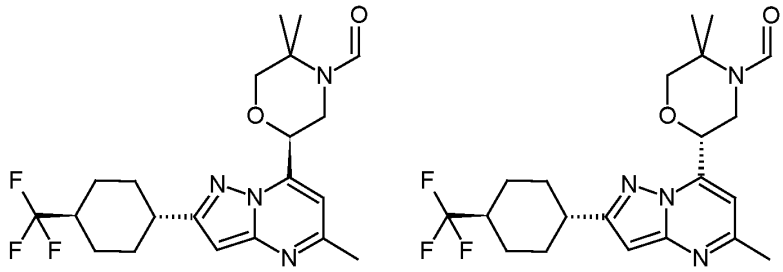
(3*S*,4*S*)-4-methyl-3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidine-1-carbaldehyde

and

(3*R*,4*R*)-4-methyl-3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidine-1-carbaldehyde

The racemic form of the title compounds (Example 160) were prepared from *cis*-4-methyl-3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidine (Intermediate 180) and formic acid according to the method described in Example 22. LC-MS (ESI) m/z 409.2 [MH^+]. The A and B enantiomers were separated using chiral preparative HPLC (Chiral Pak IG 20µm 200x50mm; F=50ml/min; eluents:A: *n*-heptane B: dichloromethane; isocratic 50%B t=25°C) obtaining **enantiomer A** (T_r 27, Example 8), and **enantiomer B** (T_r 51, Example 9). Their absolute configuration is not determined.

Example 10 and Example 11



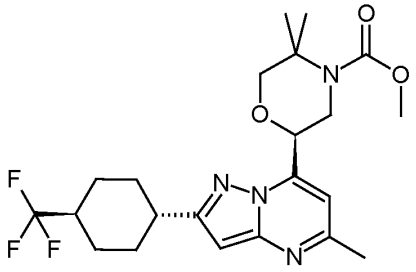
(2*S*)-5,5-dimethyl-2-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}morpholine-4-carbaldehyde

and

(2*R*)-5,5-dimethyl-2-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}morpholine-4-carbaldehyde

The enantiomerically enriched form of the title compounds were prepared from (2*S*)-5,5-dimethyl-2-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}morpholine or (2*R*)-5,5-dimethyl-2-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}morpholine (Intermediate 200 or Intermediate 201) and formic acid according to the method described in Example 22. LC-MS (ESI) m/z 425.2 [MH^+]. The A and B enantiomers were separated using chiral preparative HPLC (Reprosil Chiral MIX 5µm 150x20mm; F=20ml/min; eluents:A: water B: acetonitrile; isocratic 50%B t=40°C) obtaining **enantiomer A** (T_r 12.783, Example 10), and **enantiomer B** (T_r 15.088, Example 11).

Example 12

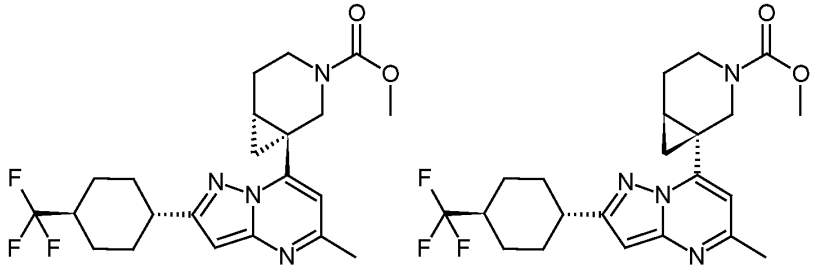


methyl (2*S*)-5,5-dimethyl-2-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}morpholine-4-carboxylate

The enantiomerically enriched form of the title compound were prepared from (2*S*)-5,5-dimethyl-2-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-

yl}morpholine (Intermediate 200) and methyl chloroformate according to the method described in Example 1. LC-MS (ESI) m/z 455.2 [MH^+]. The A and B enantiomers were separated using chiral preparative HPLC (Lux Cellulose-3 5µm 250x21.1mm; F=20ml/min; eluents:A: *n*-heptane B: 2-propanol ; isocratic 10%B t=40°C) obtaining **enantiomer A** (T_r 4.788, Example 12).

Example 13 and Example 14



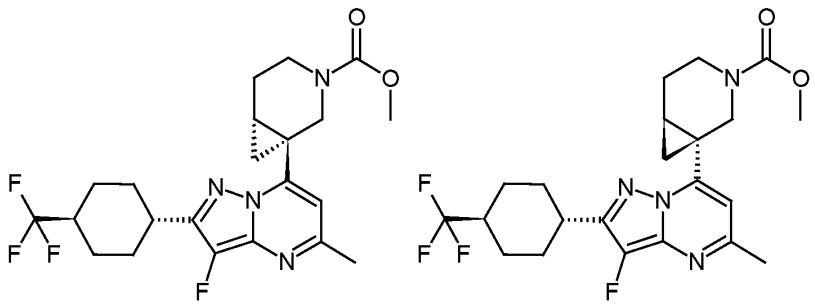
methyl (1*S*,6*R*)-1-{5-methyl-2-[trans-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-3-azabicyclo[4.1.0]heptane-3-carboxylate

and

methyl (1*R*,6*S*)-1-{5-methyl-2-[trans-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-3-azabicyclo[4.1.0]heptane-3-carboxylate

The racemic form of the title compounds were prepared from 1-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-3-azabicyclo[4.1.0]heptane (Intermediate 206) and methyl chloroformate according to the method described in Example 1. LC-MS (ESI) m/z 437.2 [MH^+]. The A and B enantiomers were separated using chiral preparative HPLC (Lux Cellulose-3 5µm 250x21.2mm; F=25ml/min; eluents:A: water B: acetonitrile; isocratic 50%B t=40°C) obtaining **enantiomer A** (T_r 6.811, Example 13), and **enantiomer B** (T_r 7.479, Example 14). Their absolute configuration is not determined.

Example 15 and Example 16



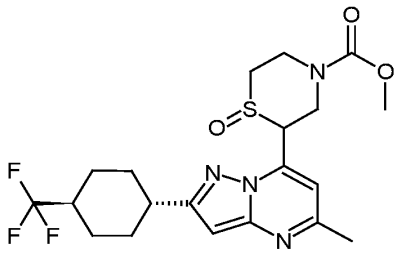
methyl (1*S*,6R)-1-{3-fluoro-5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-3-azabicyclo[4.1.0]heptane-3-carboxylate

and

methyl (1*R*,6S)-1-{3-fluoro-5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-3-azabicyclo[4.1.0]heptane-3-carboxylate

The racemic form of the title compounds were prepared from 1-{3-fluoro-5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-3-azabicyclo[4.1.0]heptane (Intermediate 207) and methyl chloroformate according to the method described in Example 1. LC-MS (ESI) m/z 455.2 [MH^+]. The A and B enantiomers were separated using chiral preparative HPLC (Lux Cellulose-3 5µm 250x21.2mm; F=25ml/min; eluents:A: water B: acetonitrile; isocratic 50%B t=40°C) obtaining **enantiomer A** (T_r 8.811, Example 15), and **enantiomer B** (T_r 10.414, Example 16). Their absolute configuration is not determined.

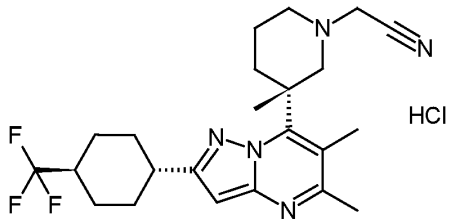
Example 17



methyl 2-{5-methyl-2-[(*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-1-oxo-1λ⁴-thiomorpholine-4-carboxylate

To a solution of 0.16 g (0.73 mmol) Sodium periodate in 10 ml distilled water was added 0.1 g (0.23 mmol) methyl 2-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}thiomorpholine-4-carboxylate (Example 126), 10 ml methanol and 10 ml dioxane at 0 °C. The reaction mixture was allowed to warm to RT and stirred for 16 hours. The organic solvents were evaporated, and the mixture was filtered to yield 0.07 g (66%) of the title compound. LC-MS (ESI) m/z 459.2 [MH^+].

Example 18



2-[(3*R*)-3-{5,6-dimethyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-3-methylpiperidin-1-yl]acetonitrile hydrochloride

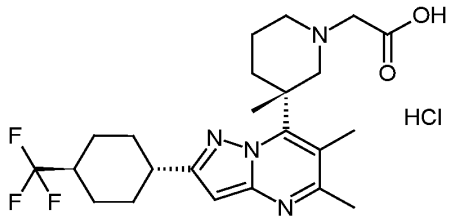
a) 2-[(3*R*)-3-{5,6-dimethyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-3-methylpiperidin-1-yl]acetonitrile

The title compound is prepared from (3*R*)-3-{5,6-dimethyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-3-methylpiperidine (Intermediate 170) and bromoacetonitrile according to the method described in Intermediate 224.

b) 2-[(3*R*)-3-{5,6-dimethyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-3-methylpiperidin-1-yl]acetonitrile hydrochloride

To a solution of 0.05 g (0.12 mmol) 2-[(3*R*)-3-{5,6-dimethyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-3-methylpiperidin-1-yl]acetonitrile in 5 ml diethyl ether was added 1 ml hydrochloric acid in ethyl acetate was added. The precipitate was filtered to yield 0.04 g (67%) of the title compound. LC-MS (ESI) m/z 434.3 [MH^+].

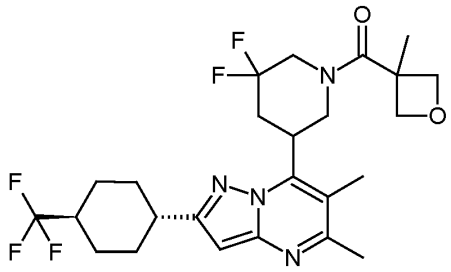
Example 19



2-[(3*R*)-3-{5,6-dimethyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-3-methylpiperidin-1-yl]acetic acid hydrochloride

To a suspension of 0.06 g methyl 2-[(3*R*)-3-methyl-3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidin-1-yl]acetate (Intermediate 224) in 0.5 ml distilled water was added 0.5 ml 37% hydrochloric acid. The mixture was refluxed for 16 hours. The reaction mixture was concentrated *in vacuo*, and triturated with diethyl ether. The mixture was filtered to yield 0.04 g (73%) of the title compound. LC-MS (ESI) m/z 439.2 [MH^+].

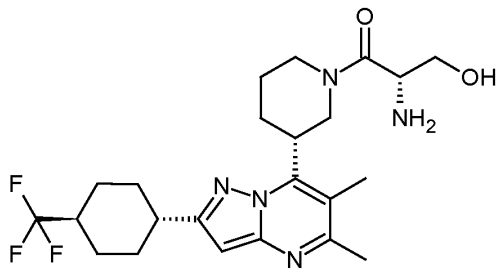
Example 20



5-{5,6-dimethyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-3,3-difluoro-1-(3-methyloxetane-3-carbonyl)piperidine

Under nitrogen to a solution of 0.08 g (0.19 mmol) 5-{5,6-dimethyl-2-[-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-3,3-difluoropiperidine (Intermediate 179) in 1 ml dimethylformamide was added 0.03 g (0.23 mmol) 3-Methyloxetane-3-carboxylic acid, 0.07 g (0.19 mmol) HBTU and 0.11 ml (0.634 mmol) N,N-Diisopropylethylamine. The reaction mixture was stirred for 16 hours. The reaction mixture was diluted with distilled water. The resulting mixture was extracted with ethyl acetate. The combined organic layer was washed with distilled water, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 5% methanol in dichloromethane to yield 0.05 g (50%) of the title compound. LC-MS (ESI) m/z 515.2 [MH^+]

Example 21

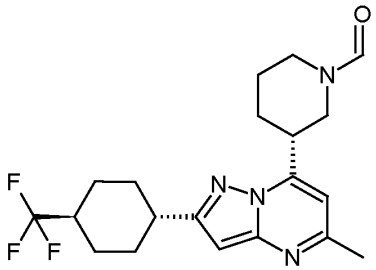


(2*S*)-2-amino-1-[(3*R*)-3-{5,6-dimethyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidin-1-yl]-3-hydroxypropan-1-one

To a solution of 0.12 g (0.21 mmol) *tert*-butyl N-[(2*S*)-1-[(3*R*)-3-{5,6-dimethyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidin-1-yl]-3-hydroxy-1-oxopropan-2-yl]carbamate (Intermediate 225) in 5 ml dichloromethane was added 1 ml (10 mmol) trifluoroacetic acid. The reaction mixture was stirred at RT for 16 hours and the pH was adjusted to

8 by the addition of saturated $NaHCO_3$ solution. The mixture was extracted with dichloromethane. The combined organic layer was washed with distilled water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 10% methanol in dichloromethane to yield 0.04 g (43%) of the title compound. LC-MS (ESI) m/z 468.2 [MH^+]

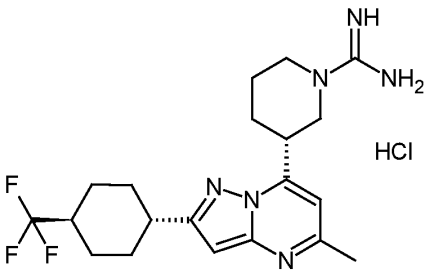
Example 22



(3*R*)-3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidine-1-carbaldehyde

To a solution of 0.16 g (0.45 mmol) (3*R*)-3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidine (Intermediate 157) in 10 ml toluene was added 0.2 ml (53.4 mmol) formic acid. The reaction mixture was refluxed for 3 hours and evaporated. The crude product was purified by silica gel chromatography eluting with 0-100% ethyl acetate in cyclohexane to yield 0.14 g (78%) of the title compound. LC-MS (ESI) m/z 395.2 [MH^+]

Example 23

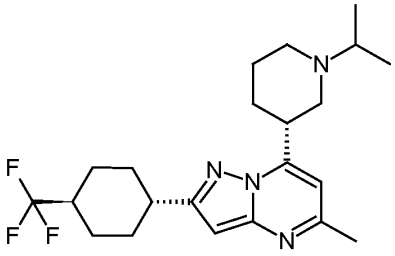


(3*R*)-3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidine-1-carboximidamide hydrochloride

To a solution of 0.08 g (0.2 mmol) (3*R*)-3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidine (Intermediate 157) in 1 ml

dimethylformamide was added 0.06 g (0.4 mmol) 1-Amidinopyrazole Hydrochloride and 0.07 ml (0.4 mmol) *N,N*-Diisopropylethylamine. The reaction mixture was stirred for 16 hours at RT and filtered to yield 0.09 g (97%) of the title compound. LC-MS (ESI) m/z 409.3 [MH^+]

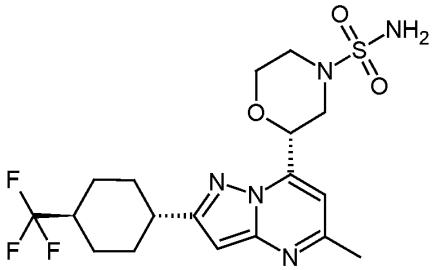
Example 24



(3*R*)-3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-1-(propan-2-yl)piperidine

To a solution of 0.13 g (0.34 mmol) (3*R*)-3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidine (Intermediate 157) in 5 ml 1,2-dichloroethane was added 0.03 ml (0.34 mmol) acetone, 0.1 g (0.48 mmol) Sodium triacetoxyborohydride and 0.02 ml (0.34 mmol) acetic acid. The reaction mixture was stirred for 16 hours at RT and washed with 1M NaOH solution. The organic layer was washed with distilled water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography eluting with 0-10% methanol in dichloromethane to yield 0.05 g (38%) of the title compound. LC-MS (ESI) m/z 409.3 [MH^+]

Example 25

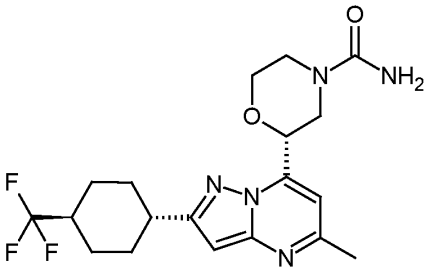


(2*R*)-2-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}morpholine-4-sulfonamide

To a solution of 0.12 g (0.33 mmol) (2*R*)-2-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}morpholine (Intermediate 222) in 15

ml dioxane was added 0.31 g (3.23 mmol) sulfamide. The reaction mixture was refluxed for 1 hour and evaporated. The crude product was purified by silica gel chromatography eluting with 0-100% ethyl acetate in cyclohexane to yield 0.03 g (21%) of the title compound. LC-MS (ESI) m/z 448.2 [MH^+]

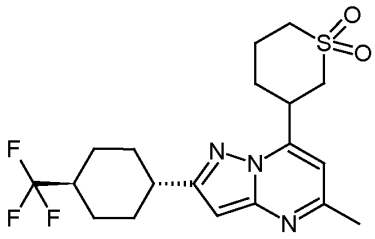
Example 26



(2*R*)-2-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}morpholine-4-carboxamide

To a solution of 0.12 g (0.33 mmol) (2*R*)-2-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}morpholine (Intermediate 222) in 10 ml dichloromethane was added 0.1 ml (0.72 mmol) (Trimethylsilyl)isocyanate. The reaction mixture was stirred for 3 hours at RT. The reaction mixture was washed with distilled water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography eluting with 0-10% methanol in dichloromethane to yield 0.06 g (48%) of the title compound. LC-MS (ESI) m/z 412.2 [MH^+]

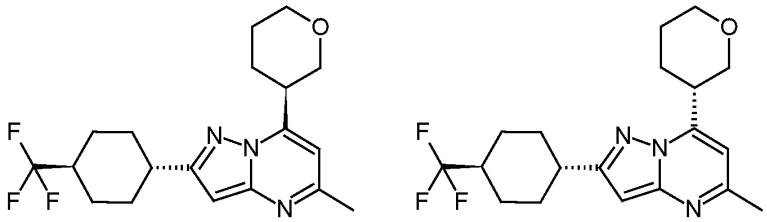
Example 27



3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-1λ⁶-thiane-1,1-dione

The title compound is prepared from 3-[*trans*-4-(trifluoromethyl)cyclohexyl]-1H-pyrazol-5-amine (Intermediate 82) and 3-(but-2-ynoyl)-1λ⁶-thiane-1,1-dione (Intermediate 73) according to the method described in Intermediate 89. LC-MS (ESI) m/z 416.2 [MH^+]

Example 28 and Example 29



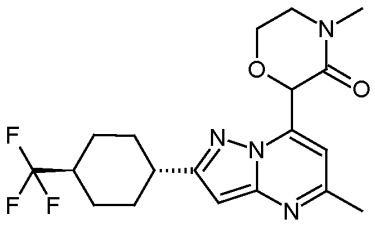
5-methyl-7-[(3*R*)-oxan-3-yl]-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidine

and

5-methyl-7-[(3*S*)-oxan-3-yl]-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidine

The racemic form of the title compounds (Example 161) were prepared from 3-[*trans*-4-(trifluoromethyl)cyclohexyl]-1H-pyrazol-5-amine (Intermediate 82) and 1-(oxan-3-yl)butane-1,3-dione (Intermediate 45) according to the method described in Intermediate 88. LC-MS (ESI) m/z 368.2 [MH^+]. The A and B enantiomers were separated using chiral preparative HPLC (Lux i-Amylose-1 5µm 150x21.1mm; F=20ml/min; eluents:A: water B: acetonitrile; isocratic50%B t=40°C) obtaining **enantiomer A** (T_r 26.148, Example 28), and **enantiomer B** (T_r 30.798, Example 29).

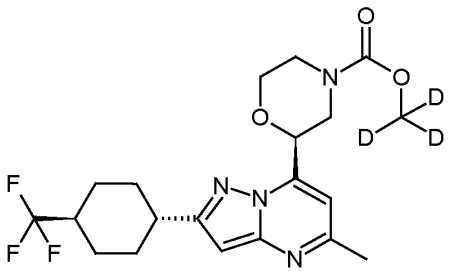
Example 30



4-methyl-2-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}morpholin-3-one

The title compound is prepared from 7-chloro-5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidine (Intermediate 87) and 4-methylmorpholin-3-one according to the method described in Intermediate 90. LC-MS (ESI) m/z 397.2 [MH^+]

Example 31

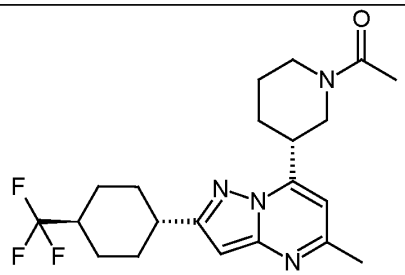


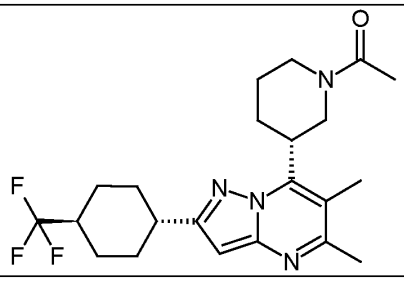
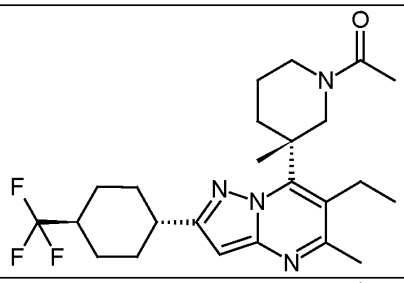
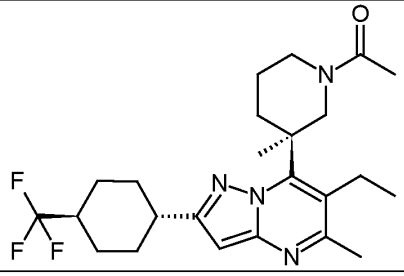
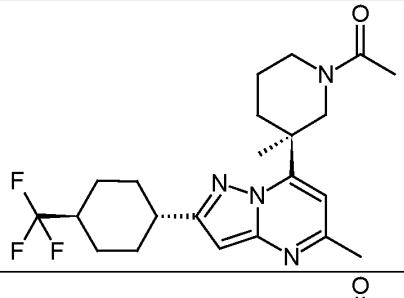
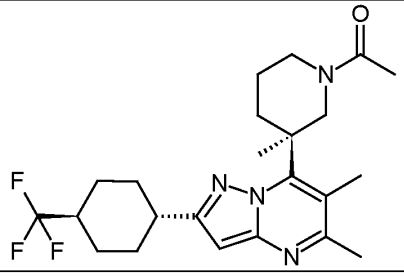
($^2H_3$)methyl (2S)-2-{5-methyl-2-[(*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}morpholine-4-carboxylate

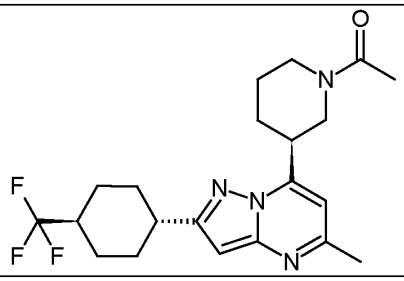
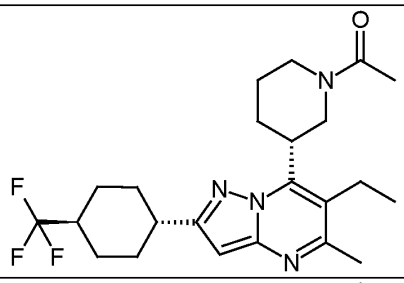
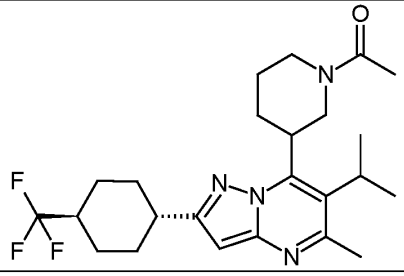
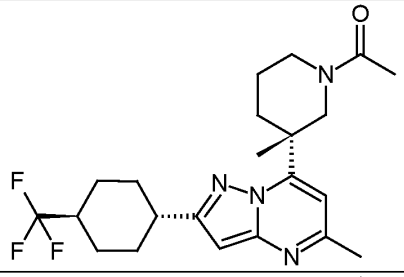
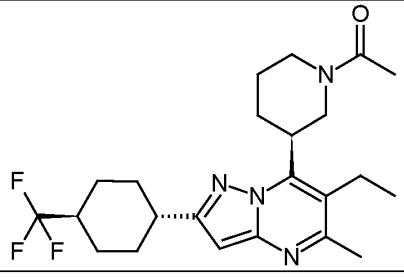
To a solution of 0.39 g (2.42 mmol) Carbonyldiimidazole in 20 ml dichloromethane was added 0.1 ml (2.42 mmol) CD_3OD at 0 °C. The reaction mixture was stirred for 1 hours at RT. To this mixture, 0.89 g (2.42 mmol) (2*S*)-2-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}morpholine (Intermediate 187) dissolved in 10 ml dichloromethane was added. The reaction mixture was stirred at RT for 16 hours. The reaction mixture was washed with distilled water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography eluting with 0-10% methanol in dichloromethane to yield 0.09 g (8%) of the title compound. LC-MS (ESI) m/z 430.4 [MH^+]

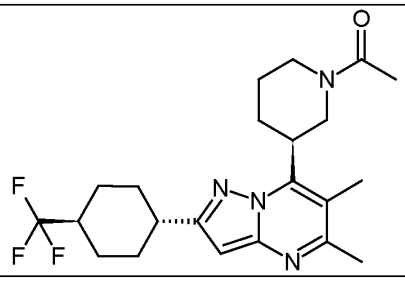
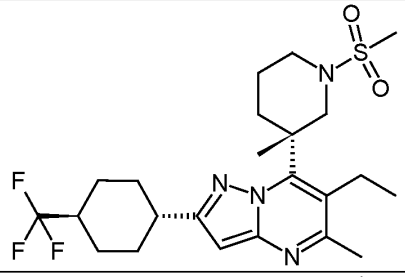
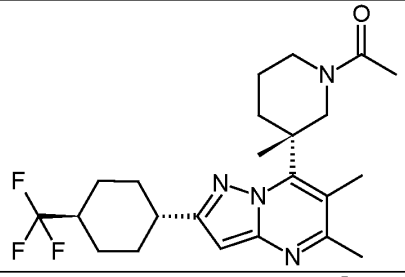
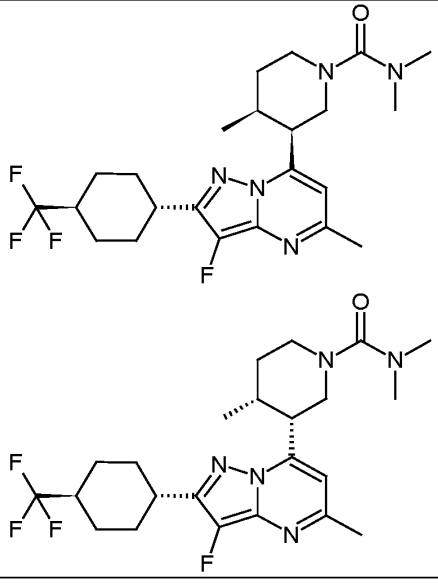
Examples 32 - 161 were prepared using analogues methods to those Examples described above and are exemplified below in Table 9.

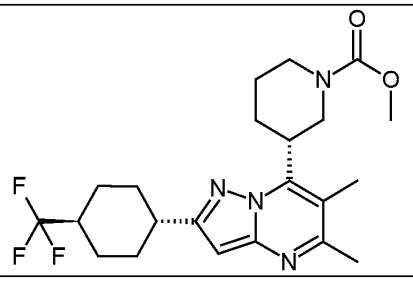
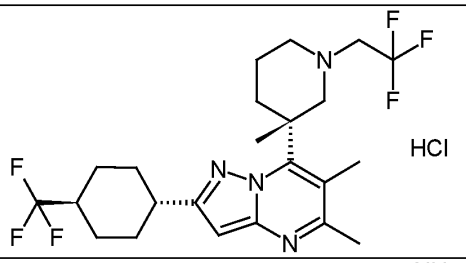
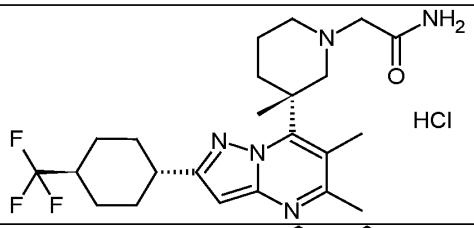
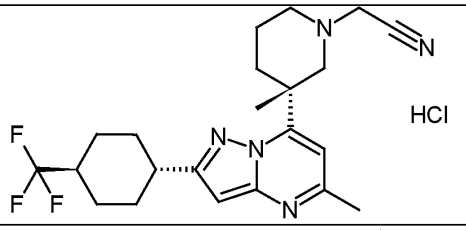
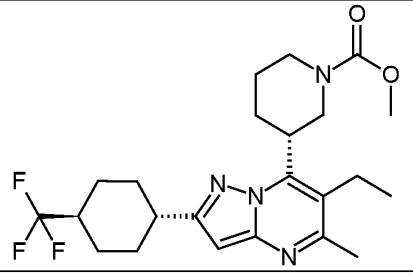
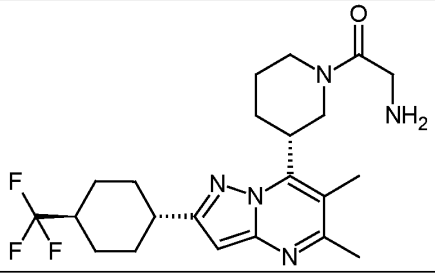
Table 9

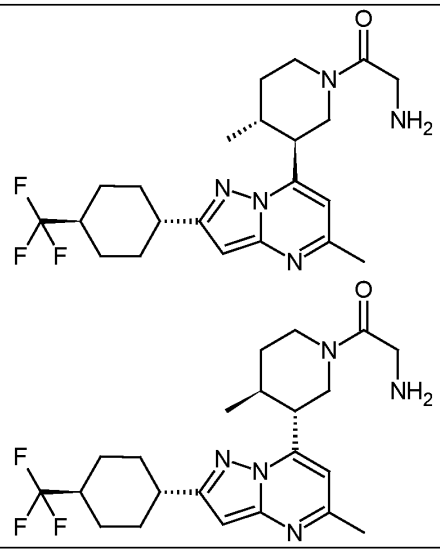
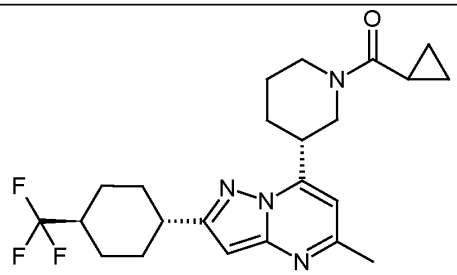
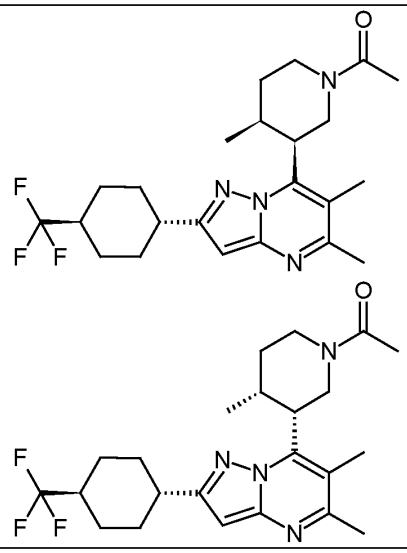
Example	Structure	LC-MS (ESI) m/z [MH^+]	Intermediate
32		409.2	157

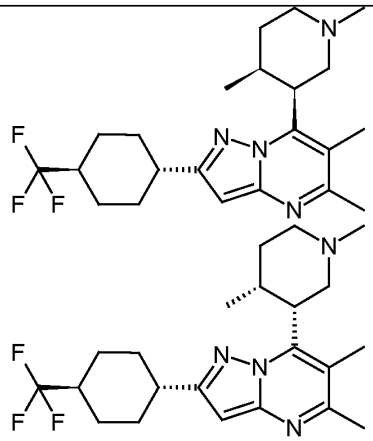
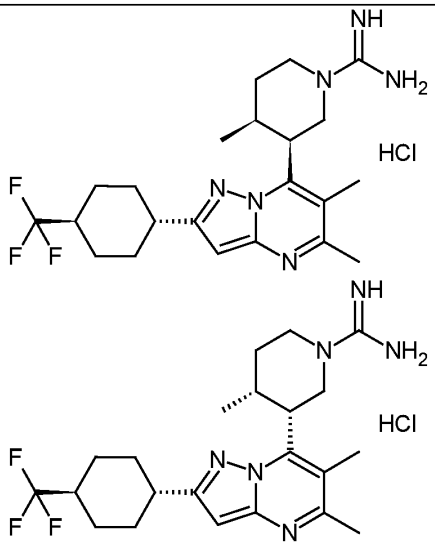
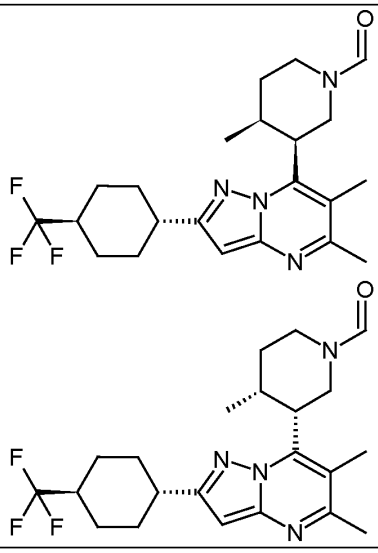
33		423.2	158
34		451.2	160
35		451.2	161
36		423.2	162
37		437.2	163

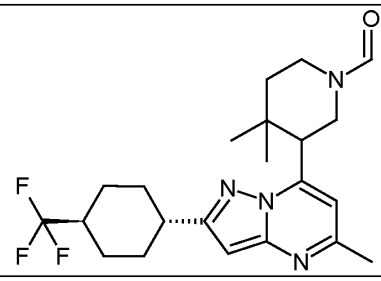
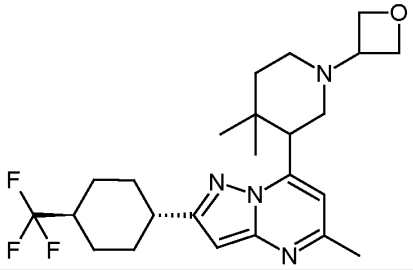
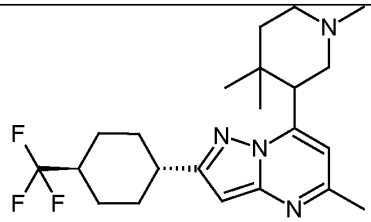
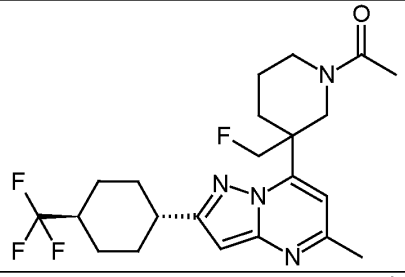
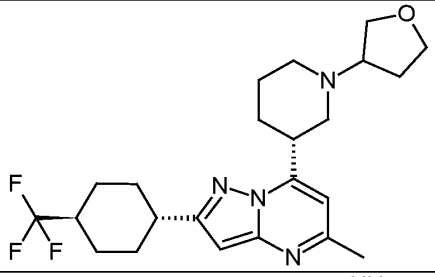
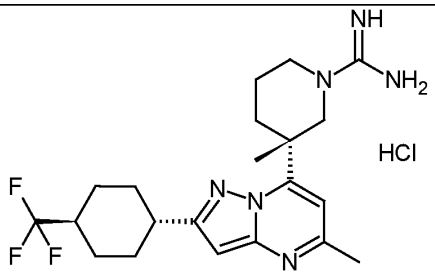
38		423.2	164
39		437.2	165
40		451.2	166
41		423.2	167
42		437.2	168

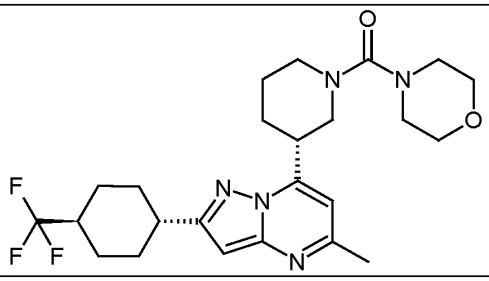
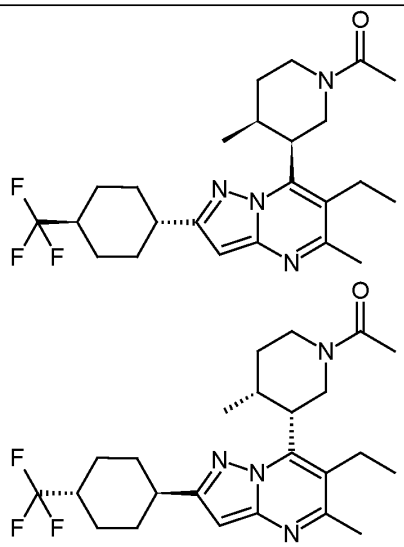
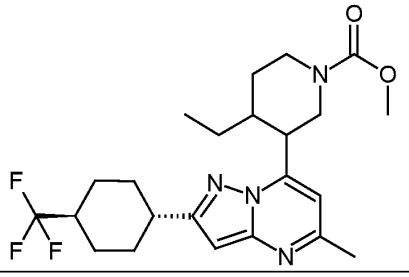
43		423.2	169
44		487.2	160
45		437.2	170
46		470.2	159

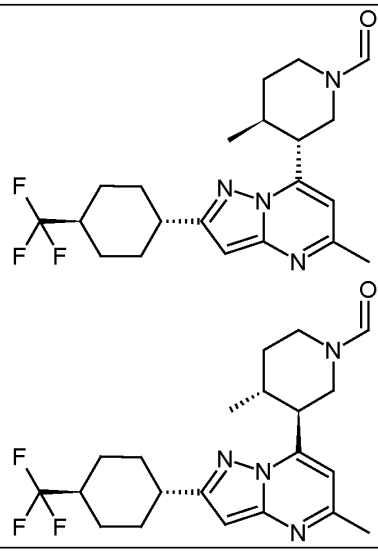
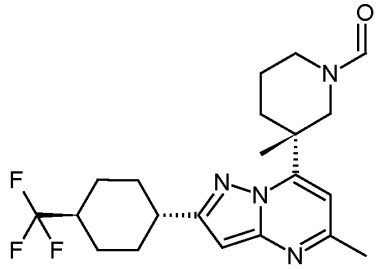
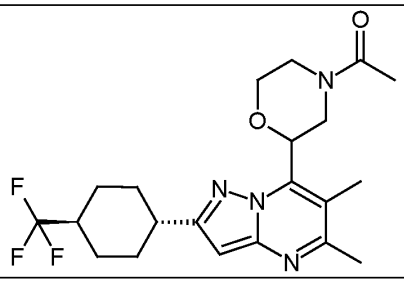
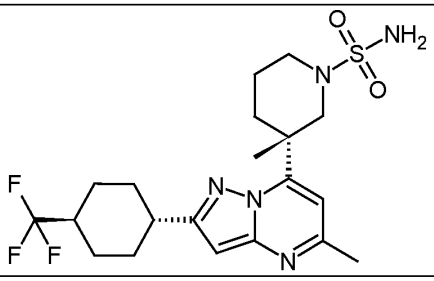
47		439.2	158
48		477.2	170
49		452.2	170
50		420.2	167
51		453.2	165
52		438.2	225

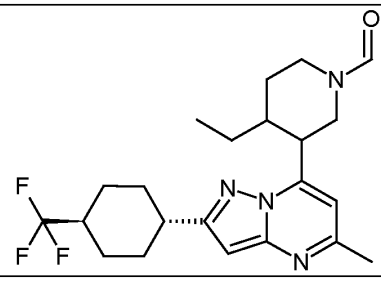
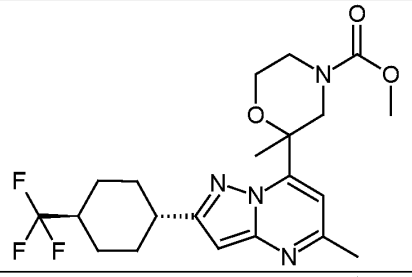
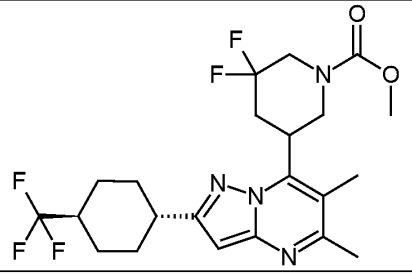
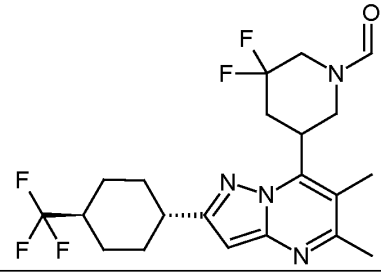
53		438.2	171
54		435.2	157
55		437.2	172

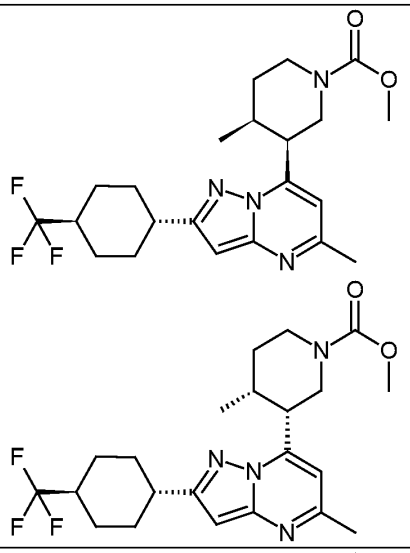
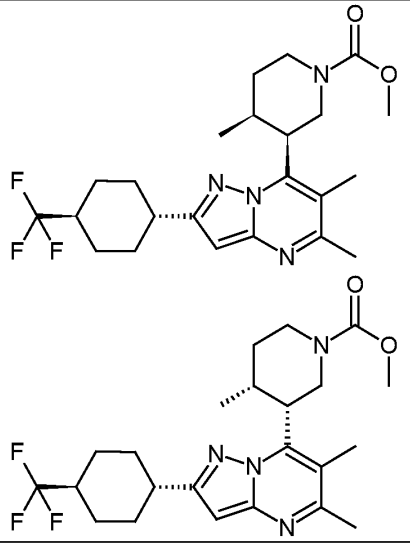
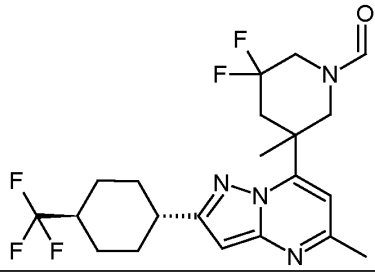
56		409.2	172
57		437.2	172
58		423.2	172

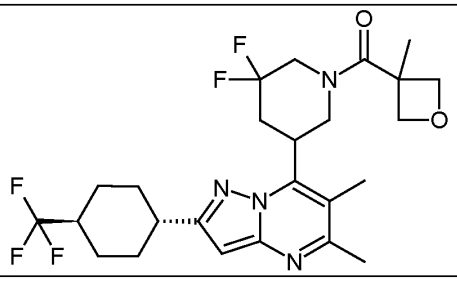
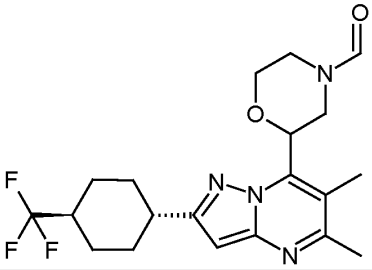
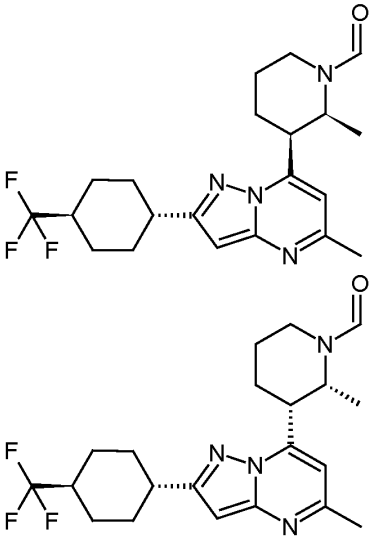
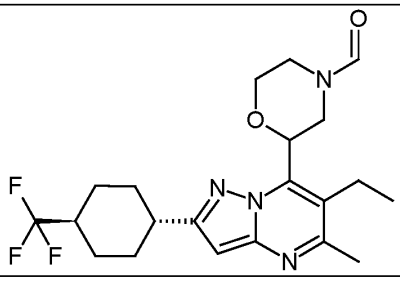
59		423.2	173
60		451.2	173
61		409.2	173
62		441.2	174
63		437.2	157
64		423.2	167

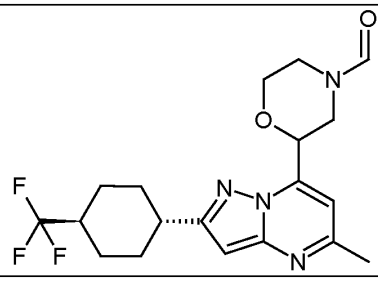
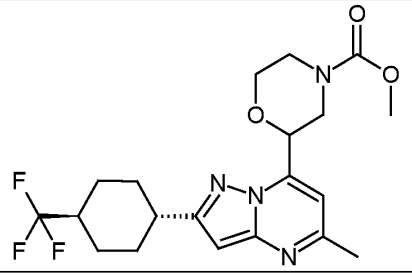
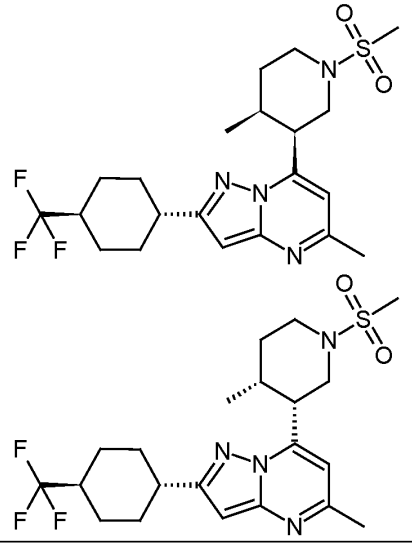
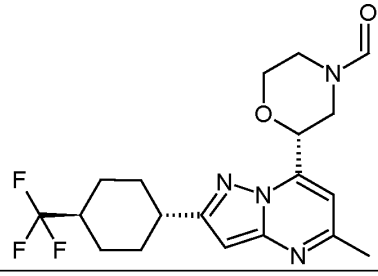
65		480.2	157
66		451.2	175
67		453.2	176

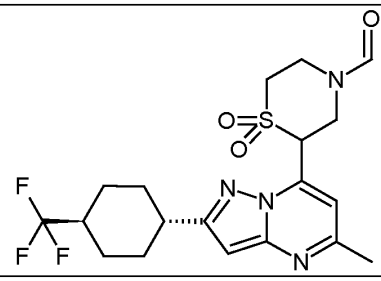
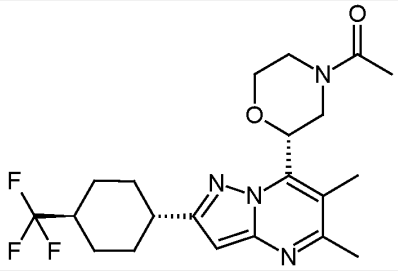
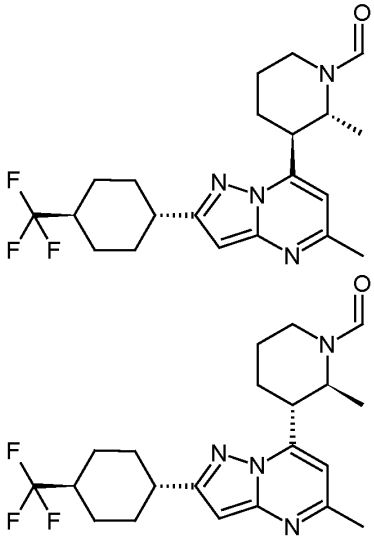
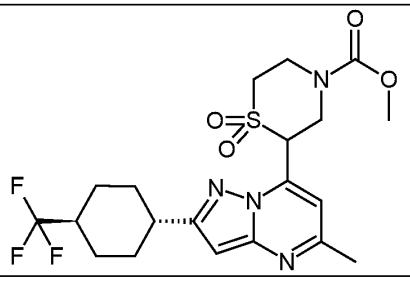
68		409.2	171
69		409.2	167
70		425.3	177
71		460.2	167

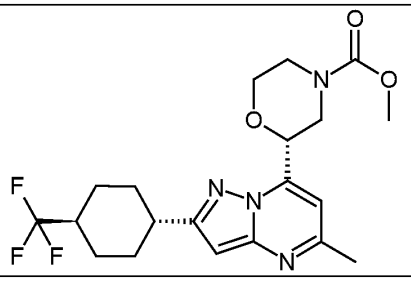
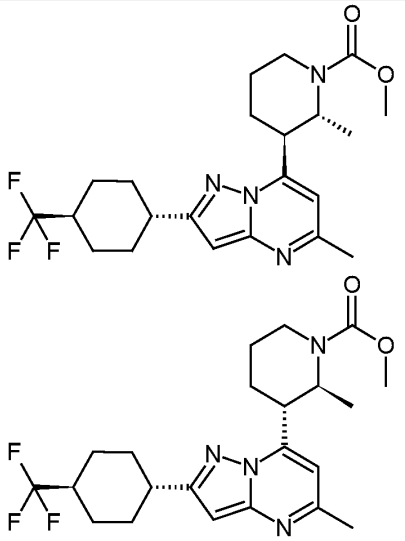
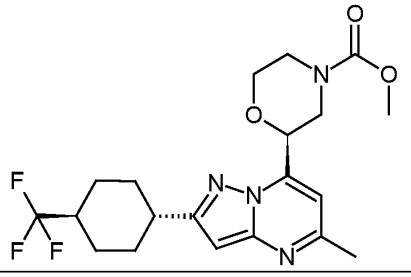
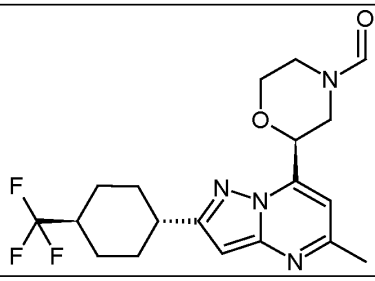
72		423.3	176
73		441.2	178
74		475.2	179
75		445.2	179

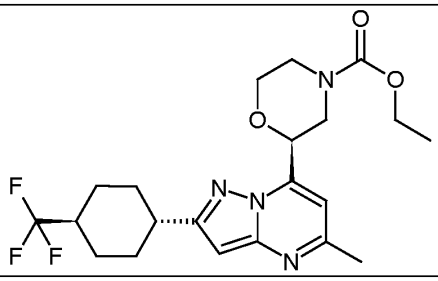
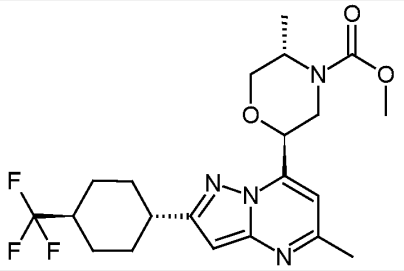
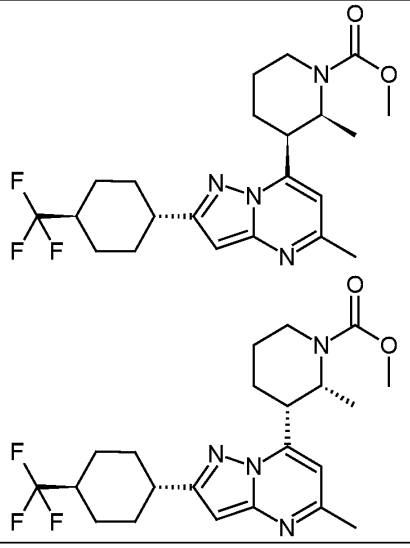
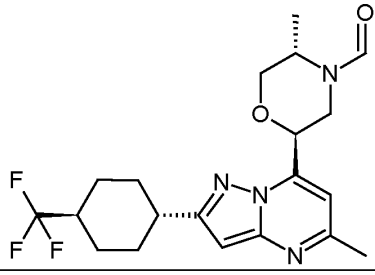
76		439.3	180
77		453.2	172
78		445.3	181

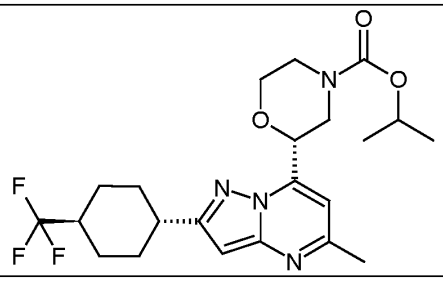
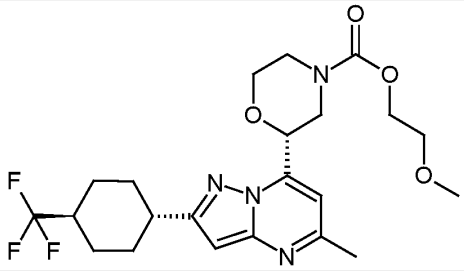
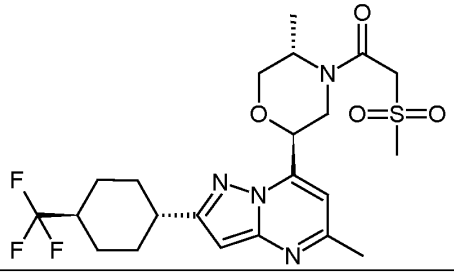
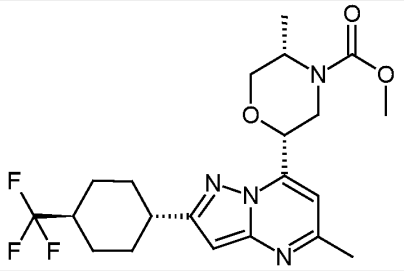
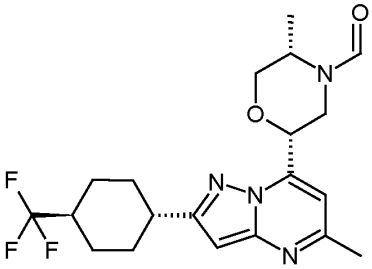
79		515.2	75
80		411.2	177
81		409.2	182
82		425.2	183

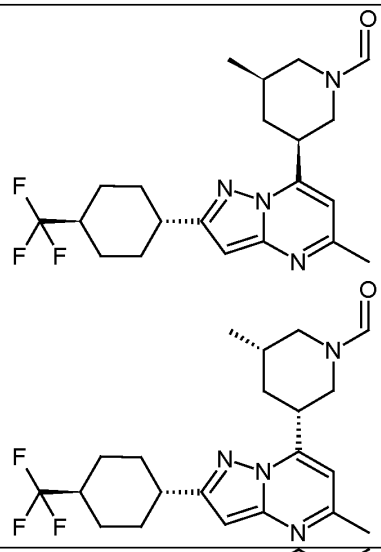
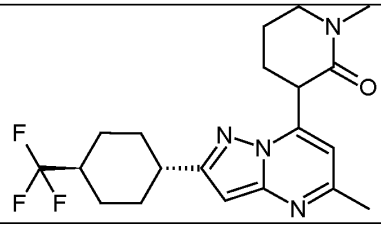
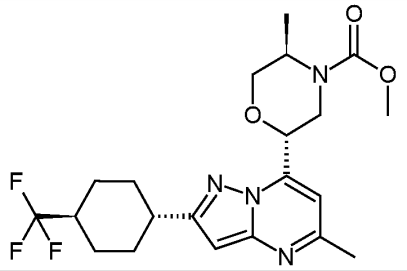
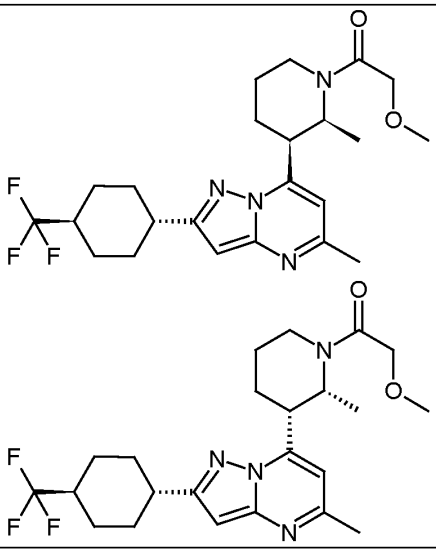
83		397.2	184
84		427.2	184
85		459.2	180
86		397.2	222

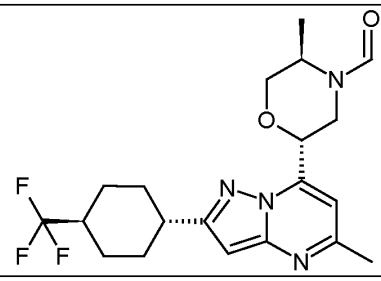
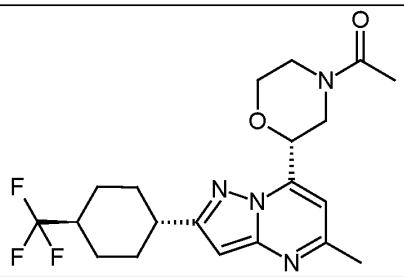
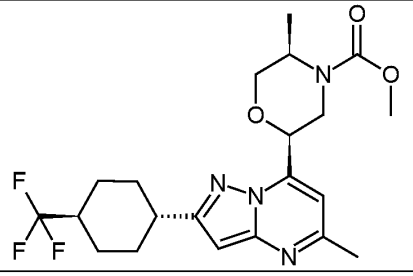
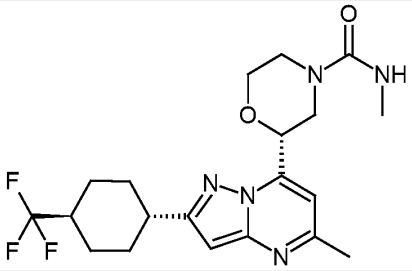
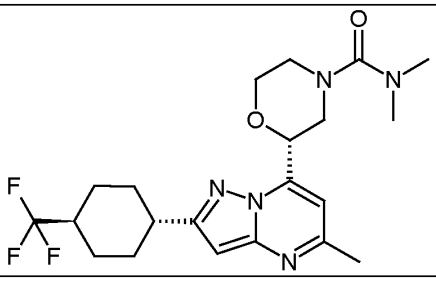
87		445.3	223
88		425.2	185
89		409.3	186
90		475.3	223

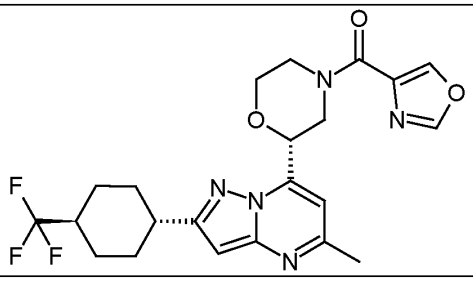
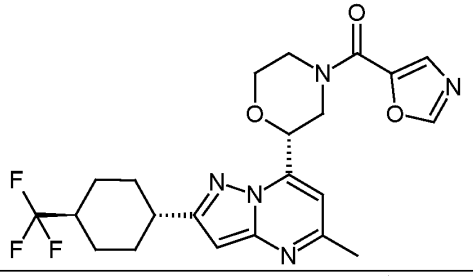
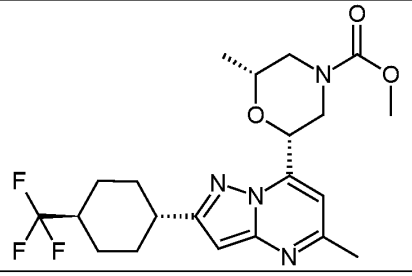
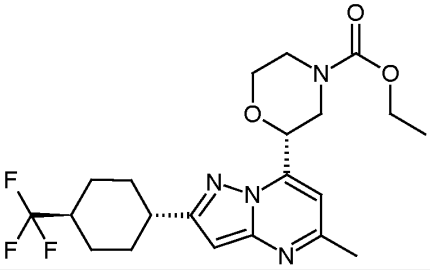
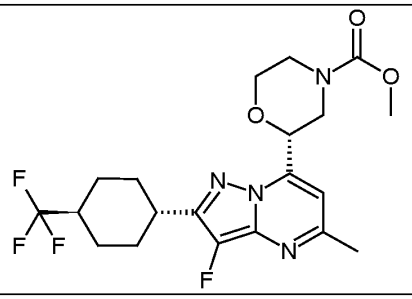
91		427.2	222
92		439.3	186
93		427.3	187
94		397.3	187

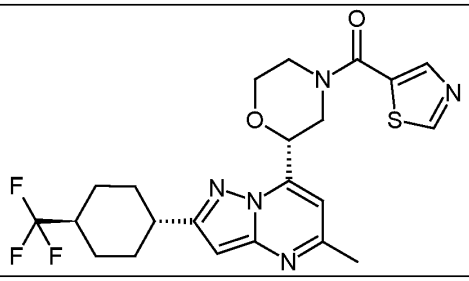
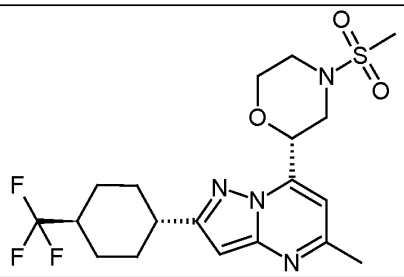
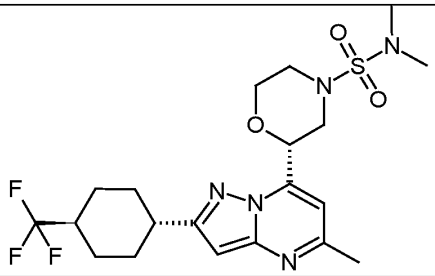
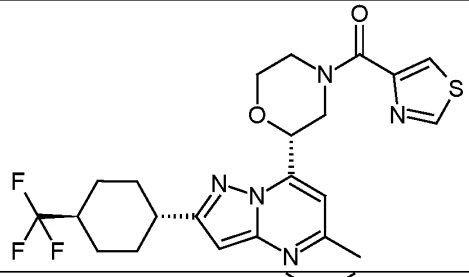
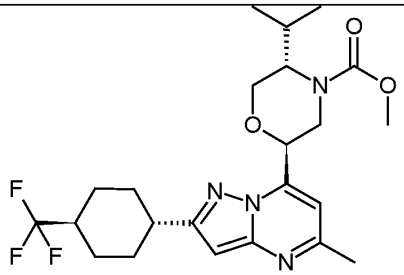
95		441.2	187
96		441.2	188
97		439.3	182
98		411.3	188

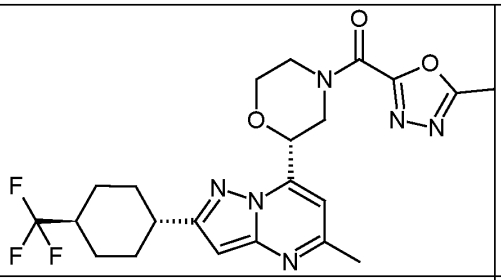
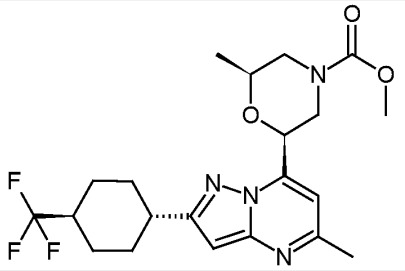
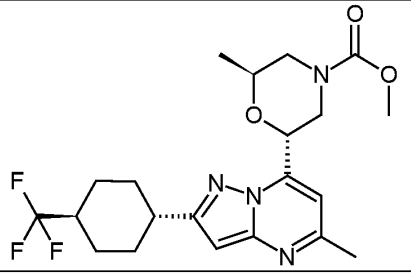
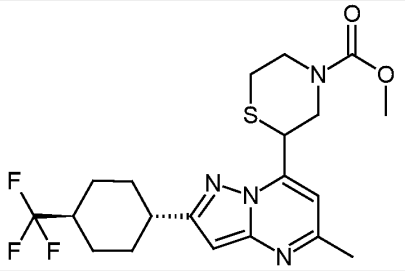
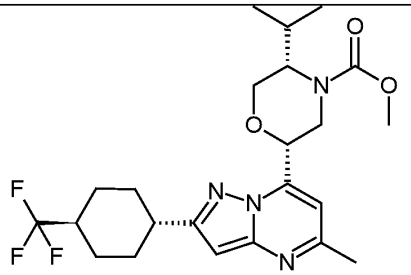
99		455.2	222
100		471.2	222
101		503.3	188
102		441.2	189
103		411.2	189

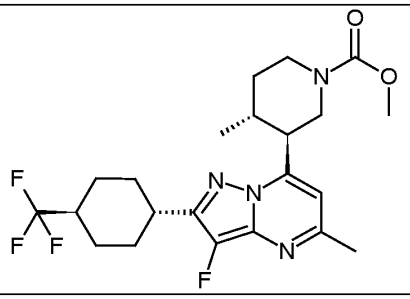
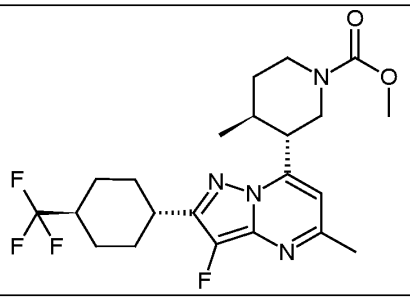
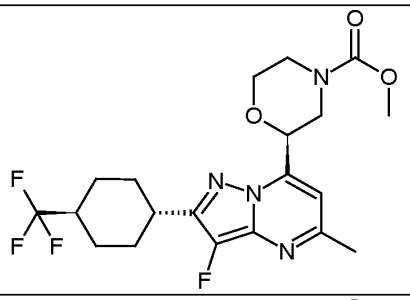
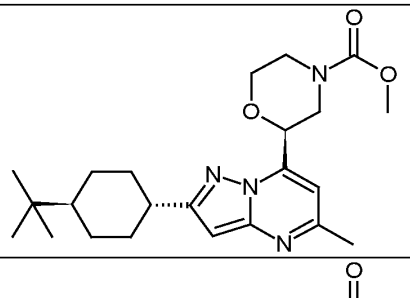
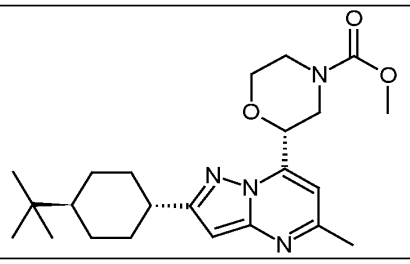
104		409.3	190
105		395.2	87
106		441.2	191
107		453.2	182

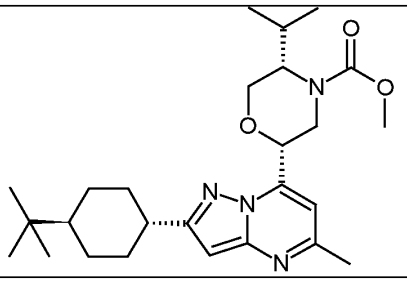
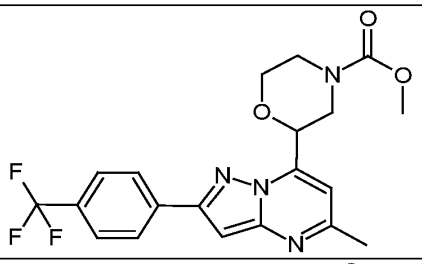
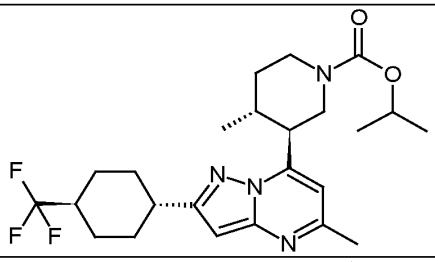
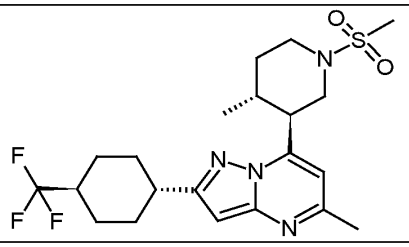
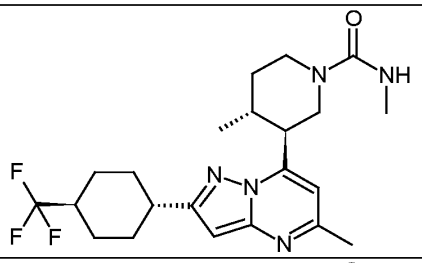
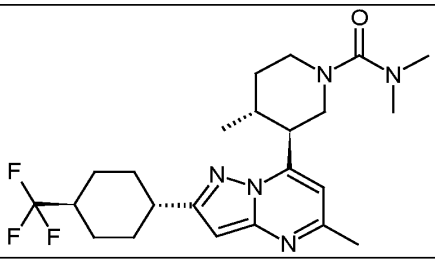
108		411.2	191
109		411.2	222
110		441.2	192
111		426.2	222
112		440.1	222

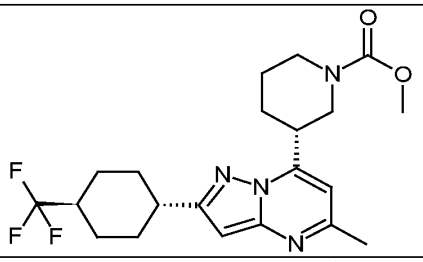
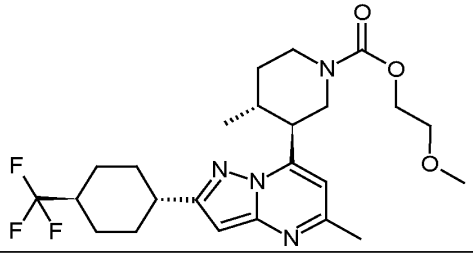
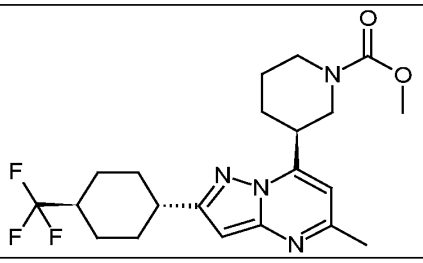
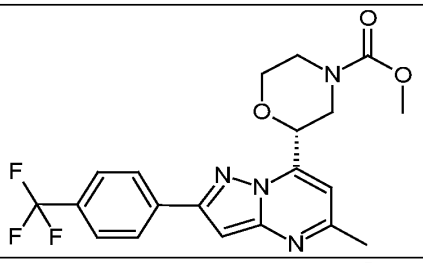
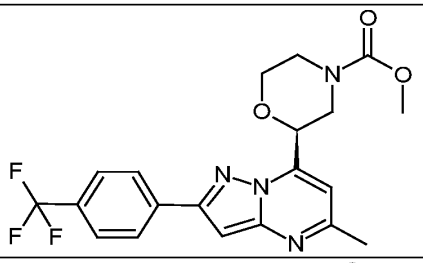
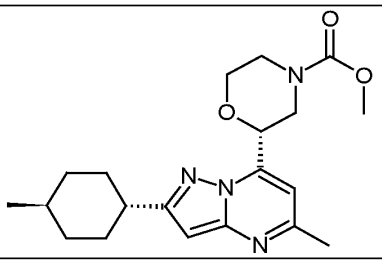
113		464.3	222
114		464.3	222
115		441.3	193
116		441.2	222
117		445.3	194

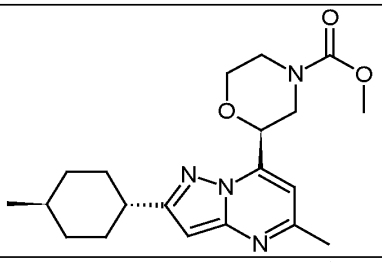
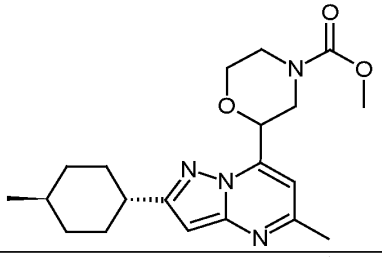
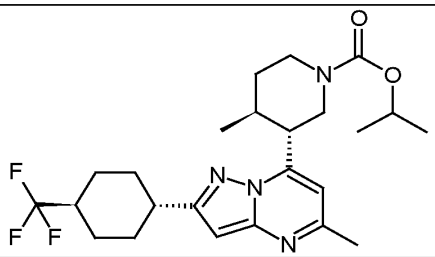
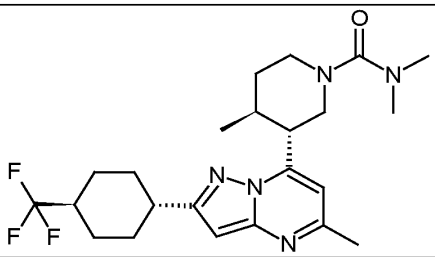
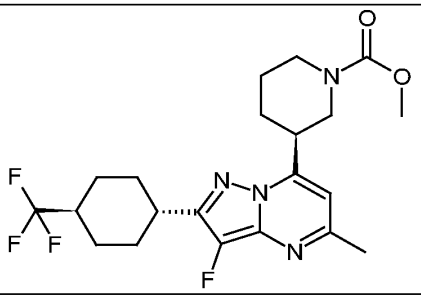
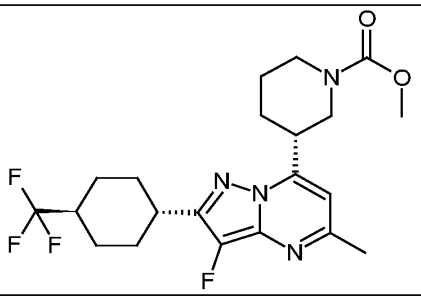
118		480.3	222
119		447.2	222
120		476.2	222
121		480.3	222
122		469.2	195

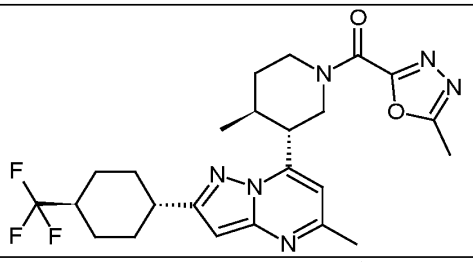
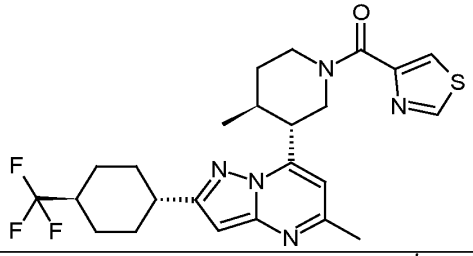
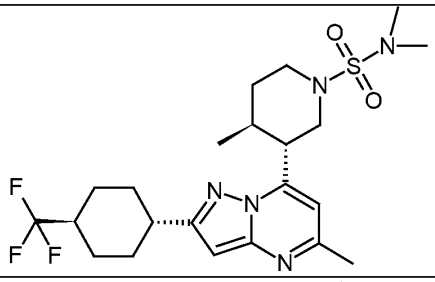
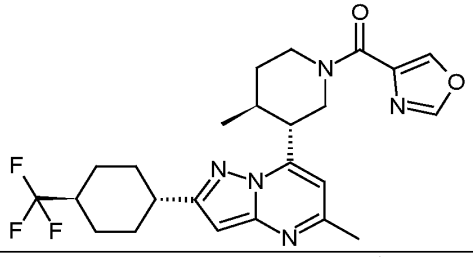
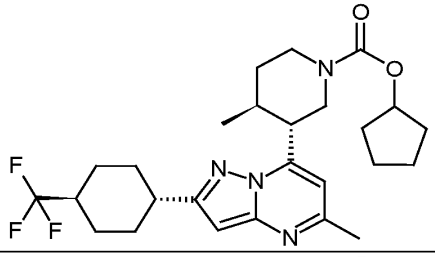
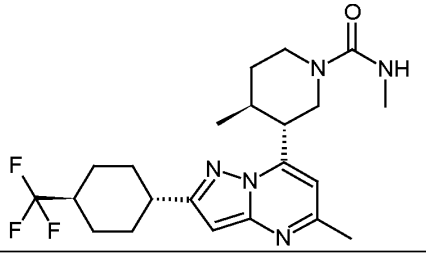
123		479.2	222
124		441.3	196
125		441.2	197
126		443.2	198
127		469.2	219

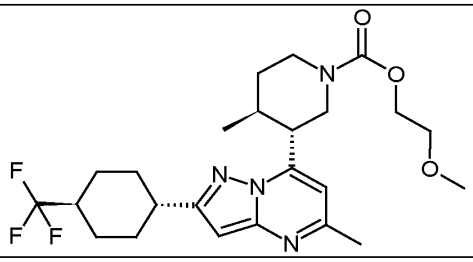
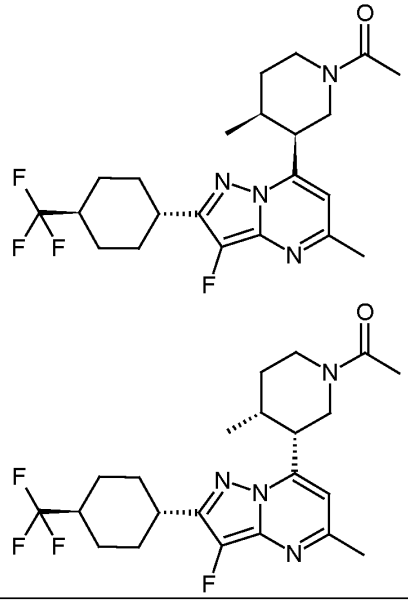
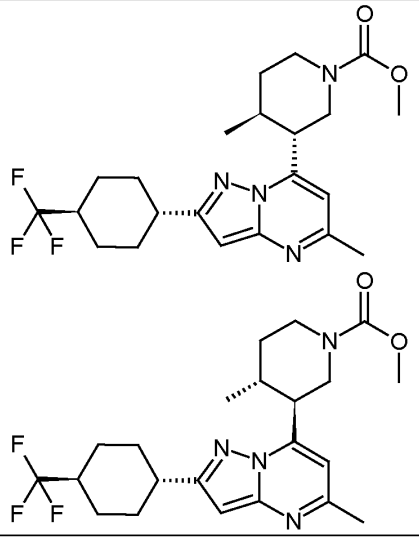
128		457.2	202
129		457.2	203
130		445.2	204
131		415.4	208
132		415.4	209

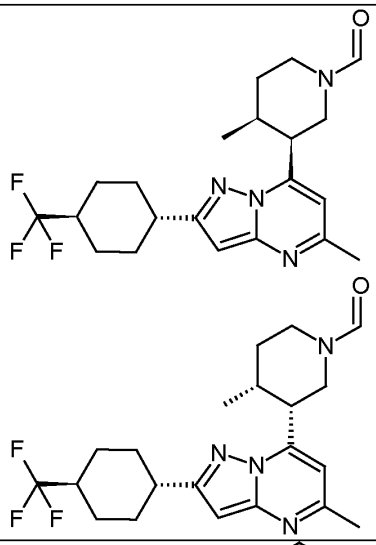
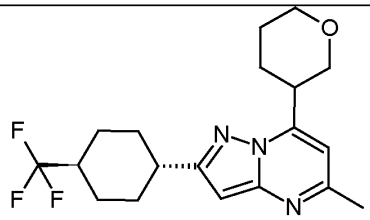
133		457.3	210
134		421.4	212
135		467.4	213
136		459.2	213
137		438.5	213
138		452.5	213

139		425.2	157
140		483.4	213
141		425.2	164
142		421.4	215
143		421.4	216
144		373.6	217

145		373.6	218
146		373.6	211
147		467.4	214
148		452.5	214
149		443.3	220
150		443.3	221

151		491.5	214
152		492.6	214
153		488.8	214
154		476.6	214
155		493.5	214
156		438.2	214

157		483.5	214
158		441.2	159
159		439.2	171

160		409.2	180
161		368.2	82+45

Preparation of pharmaceutical compositions

The following formulation examples illustrate representative pharmaceutical compositions of this invention. The present invention however is not limited to the following pharmaceutical compositions.

A) Solid oral dosage forms

I., Tablets

Active ingredient(s)	0.01 – 90%
Filler	1 – 99.9%
Binder	0 – 20%
Disintegrant	0 – 20%
Lubricant	0 – 10%
Other specific excipient(s)	0 – 50%

II., Orodispersible films

Active ingredient(s)	0.01 – 90%
Film forming agent	1 – 99.9%
Plasticizer	0 – 40%
Other specific excipient(s)	0 – 50%

B) Liquid oral dosage forms

III., Oral suspensions

Active ingredient(s)	0.01 – 50%
Liquid vehicle	10 – 99.9%
Wetting agent	0 – 50%
Thickener	0 – 50%
Buffering agent	q.s.
Osmotic agent	0 – 50%
Preservatives	q.s.

IV., Syrups

Active ingredient(s)	0.01 – 50%
Solvent	10 – 99.9%
Sugar component	1 – 20%
Flavouring agents	0 – 10%

C) Parenteral dosage forms

V., Intravenous injections

Active ingredient(s)	0.01 – 50%
Solvent	10 – 99.9%
Co-solvent	0 – 99.9%
Osmotic agent	0 – 50%
Buffering agent	q.s.

D) Other dosage forms

VI., Suppositories

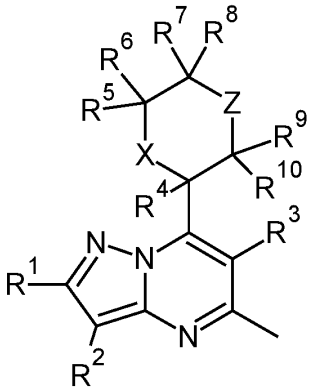
Active ingredient(s)	0.01 – 50%
Suppository base	1 – 99.9%
Surface-active agents	0 – 20%
Lubricants	0 – 20%
Preservatives	q.s.

VII., Eye drops

Active ingredient(s)	0.01 – 50%
Water	0 – 99.9%
Solvent	0 – 99.9%
Osmotic agent	0 – 20%
Viscosity enhancer	0 – 20%
Buffering agent	q.s.
Preservatives	q.s.

Claims

1. A compound of formula (I)



(I)

wherein

R^1 represents phenyl- or cyclohexyl group substituted by C_1-C_6alkyl or halo-C_1-C_6alkyl;

R^2 represents H or halogen;

R^3 represents H or C_1-C_6alkyl;

R^4 represents H; C_1-C_6alkyl or halo-C_1-C_6alkyl;

R^5 and R^6 may be each, independently H; C_1-C_6alkyl or halogen;

R^7 and R^8 may be each, independently H or C_1-C_6alkyl;

R^9 and R^{10} may be each, independently H or C_1-C_6alkyl or R^9 and R^{10} together may form oxo group;

X represents -CR^xR^y or -O- or -$S(O)_n$- group, wherein R^x and R^y may be each, independently H or C_1-C_6alkyl group and wherein n is 0 or 1 or 2;

Z represents -NR-; or -O-; or -$S(O)_2$- group wherein

R may be H or -$C(O)R^{11}$ or -$S(O)_2R^{12}$ group; aminocarbonyl-C_1-C_3alkyl; carboxy-C_1-C_3alkyl; cyano-C_1-C_3alkyl; C_1-C_5(cyclo)alkyl; saturated 4-6 membered heterocyclic ring with one O, or -$C(NH)(NH_2)$ group;

wherein R^{11} may be H; C_1-C_3alkyl; C_1-C_3alkoxy; deutero-C_1-C_3alkoxy; C_1-C_3alkoxy-C_1-C_3alkyl; C_1-C_3alkoxy-C_1-C_3alkoxy; methanesulphonyl-C_1-C_3alkyl; or R^{11} may be a saturated 3-6 membered carbocyclic ring, or a 4-6 membered saturated or unsaturated heterocyclic ring with one to three

hetero atoms selected from N, O or S; or amino, mono- or dialkylamino group; amino- C_1-C_3alkyl; hydroxy-C_1-C_3alkyl substituted by NH_2-group;

wherein R^{12} may be C_1-C_3alkyl; amino or dialkylamino group;

R^4 and CR^x may form a cycloalkyl ring;

or pharmaceutically acceptable salts, biologically active metabolites, pro-drugs, racemates, enantiomers, diastereomers, solvates and hydrates thereof.

2. A compound according to claim 1 wherein

if X represents -CR^xR^y then Z represents -NR- group; or

if X represents -O-; or -S(O)n- group then Z represents -NR- group; or

if X represents -CR^xR^y group then Z represents -O-; or -$S(O)_2$- group.

3. A compound according to claim 2 wherein X represents -CR^xR^y and Z represents -NR- group, wherein R may be -$C(O)R^{11}$.

4. A compound according to claim 2 wherein X represents -O- or -$S(O)_2$- group and Z represents -NR- group, where R may be -$C(O)R^{11}$ or -$S(O)_2R^{12}$ group.

5. A compound according to claim 1 selected from the group of

1-[(3*R*)-3-{6-ethyl-5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-3-methylpiperidin-1-yl]ethan-1-one,

1-[(3*S*)-3-{6-ethyl-5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-3-methylpiperidin-1-yl]ethan-1-one,

1-{3-[5-methyl-6-(propan-2-yl)-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl]piperidin-1-yl}ethan-1-one,

1-[(3*R*)-3-methyl-3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidin-1-yl]ethan-1-one,

1-[(3*S*)-3-{6-ethyl-5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidin-1-yl]ethan-1-one,

(3*R*)-3-{6-ethyl-5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-1-methanesulfonyl-3-methylpiperidine,

methyl (3*R*,4*S*)-4-methyl-3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidine-1-carboxylate,

methyl (3*S*,4*R*)-4-methyl-3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidine-1-carboxylate,

trans-3-{5,6-dimethyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-4-methylpiperidine-1-carbaldehyde,

1-[*trans*-3-{6-ethyl-5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-4-methylpiperidin-1-yl]ethan-1-one,

trans-4-methyl-3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidine-1-carbaldehyde,

methyl *trans*-3-{5,6-dimethyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-4-methylpiperidine-1-carboxylate,

5-{5,6-dimethyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-3,3-difluoropiperidine-1-carbaldehyde,

2-{6-ethyl-5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}morpholine-4-carbaldehyde,

methyl (2*R*)-2-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}morpholine-4-carboxylate,

methyl *trans*-2-methyl-3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidine-1-carboxylate,

(2*R*)-2-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}morpholine-4-sulfonamide,

methyl (2*R*,5*S*)-5-methyl-2-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}morpholine-4-carboxylate,

methyl (2*R*)-2-{3-fluoro-5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}morpholine-4-carboxylate,

5-methyl-7-[(3*R*)-oxan-3-yl]-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidine, and

5-methyl-7-[(3*S*)-oxan-3-yl]-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidine.

6. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) or pharmaceutically acceptable salts, biologically active metabolites, pro-drugs, racemates, enantiomers, diastereomers, solvates and hydrates thereof according to claim 1 as active ingredient and pharmaceutically acceptable carrier.

7. A combination comprising a therapeutically effective amount of a compound of formula (I) or pharmaceutically acceptable salts, biologically active metabolites, pro-drugs, racemates, enantiomers, diastereomers, solvates and hydrates thereof according to claim 1 and one or more therapeutically active co-agents.

8. A process for manufacturing pharmaceutical composition having $GABA_B$ receptor positive allosteric modulator effect characterized by mixing a therapeutically effective amount of a compound of formula (I) or pharmaceutically acceptable salts, biologically active metabolites, pro-drugs, racemates, enantiomers, diastereomers, solvates and hydrates thereof according to claim 1 and optical antipodes or racemates and/or salts thereof as active ingredients and pharmaceutically acceptable excipients.

9. A compound of formula (I) or pharmaceutically acceptable salts, biologically active metabolites, pro-drugs, racemates, enantiomers, diastereomers, solvates and hydrates thereof according to claim 1 for use as $GABA_B$ receptor positive allosteric modulator.

10. A compound of formula (I) or pharmaceutically acceptable salts, biologically active metabolites, pro-drugs, racemates, enantiomers, diastereomers, solvates and hydrates thereof according to claim 1 for use in the treatment or prevention of disorders associated with $GABA_B$ receptor positive allosteric modulator activity.

11. The compound for use according to claim 10 wherein the disorder associated with $GABA_B$ receptor positive allosteric modulator activity is selected from the group of psychiatric disorders (such as anxiety, panic disorder, posttraumatic disorder, depression, schizophrenia), neurodevelopmental disorders (such as autism spectrum disorder, obsessive-compulsive disorder, Fragile X syndrome), cognitive disorders, epilepsy, spasticity, skeletal muscle rigidity, spinal cord

injury, multiple sclerosis, amyotrophic lateral sclerosis, cerebral palsy, essential tremor, pain (neuropathic, visceral, osteoarthritic), substance abuse (cocaine, nicotine, alcohol), obesity, binge eating, asthma, cough, urinary incontinence, gastroesophageal reflux disease, transient lower esophageal sphincter relaxation, and irritable bowel syndrome.

12. A method of treatment and/or prevention of a disorder which requires positive allosteric modulation of the $GABA_B$ receptor characterized by administering an effective amount of a compound of formula (I) as claimed in claim 1 and optical antipodes or racemates and/or salts thereof as such or combined with pharmaceutically acceptable auxiliary materials and the like usually applied in pharmaceuticals to the mammal to be treated.

13. The method according to claim 12 wherein disorder which requires positive allosteric modulation of the $GABA_B$ receptor is selected from the group of psychiatric disorders (such as anxiety, panic disorder, posttraumatic disorder, depression, schizophrenia), neurodevelopmental disorders (such as autism spectrum disorder, obsessive-compulsive disorder, Fragile X syndrome), cognitive disorders, epilepsy, spasticity, skeletal muscle rigidity, spinal cord injury, multiple sclerosis, amyotrophic lateral sclerosis, cerebral palsy, essential tremor, pain (neuropathic, visceral, osteoarthritic), substance abuse (cocaine, nicotine, alcohol), obesity, binge eating, asthma, cough, urinary incontinence, gastroesophageal reflux disease, transient lower esophageal sphincter relaxation, and irritable bowel syndrome.

14. The following compounds as an intermediate in the synthesis of the compounds of Formula (I):

(3S,4R)-4-methyl-3-{5-methyl-2-[trans-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-a]pyrimidin-7-yl}piperidine (Intermediate 213),

(3S)-3-{5-methyl-2-[trans-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-a]pyrimidin-7-yl}morpholine (Intermediate 222),

(3R)-3-{6-ethyl-5-methyl-2-[trans-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-a]pyrimidin-7-yl}-3-methylpiperidine (Intermediate 160),

(3S)-3-{6-ethyl-5-methyl-2-[trans-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-a]pyrimidin-7-yl}piperidine (Intermediate 168),

(2R,5S)-5-methyl-2-{5-methyl-2-[trans-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-a]pyrimidin-7-yl}morpholine (Intermediate 189).