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(54) **Title**: BICYCLIC PYRIMIDONE COMPOUNDS AS INHIBITORS OF LP-PLA2

(57) **Abstract**: The present invention relates to novel pyrimido[1,6-a]pyrimidin-6(2H)-one compounds that inhibit Lp-PLA$_2$ activity, processes for their preparation, to compositions containing them and to their use in the treatment of diseases associated with the activity of Lp-PLA$_2$, for example atherosclerosis, Alzheimer's disease.

BICYCLIC PYRIMIDONE COMPOUNDS AS INHIBITORS OF LP-PLA2

RELATED APPLICATION

The present application claims priority from PCT International Application No. PCT/CN2013/070977 filed on January 25, 2013 at the State Intellectual Property Office of the People's Republic of China, the entire contents of which is incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to novel pyrimido[1,6-a]pyrimidin-6(2H)-one compounds, processes for their preparation, intermediates useful in their preparation, pharmaceutical compositions containing them, and their use in therapy for the treatment of diseases or conditions mediated by Lp-PLA_2.

BACKGROUND OF THE INVENTION

Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) previously known as platelet-activating factor acetylhydrolase (PAF-AH), is a phospholipase A2 enzyme involved in hydrolysis of lipoprotein lipids or phospholipids. Lp-PLA_2 travels with low-density lipoprotein (LDL) and rapidly cleaves oxidized phosphatidylcholine molecules derived from the oxidation of LDL. (*See* e.g. , Zalewski A, et al., *Arterioscler. Thromb. Vasc. Biol.,* 25, 5, 923–31(2005)). Lp-PLA_2 hydrolyzes the sn-2 ester of the oxidized phosphatidylcholines to give lipid mediators, lyso-phosphatidylcholine (lysoPC) and oxidized nonesterified fatty acids (NEFAs). It has been observed that lysoPC and NEFAs elicit inflammatory responses. (*See* e.g., Zalewski A, et al. (2005)).

A number of Lp-PLA_2 inhibitors and/or uses thereof have been previously described. (*See.* for example, published patent application nos. WO96/13484, WO96/19451, WO97/02242, WO97/12963, WO97/21675, WO97/21676, WO 97/41098, WO97/41099, WO99/24420, WO00/10980, WO00/66566, WO00/66567, WO00/68208, WO01/60805, WO02/30904, WO02/30911, WO03/015786, WO03/016287, WO03/041712, WO03/042179, WO03/042206, WO03/042218, WO03/086400, WO03/87088, WO08/048867, US 2008/0103156, US 2008/0090851, US 2008/0090852, and WO08/048866.) Disclosed uses include treating disease that involves or is associated with endothelial dysfunction, disease that involves lipid oxidation in conjunction with Lp-PLA_2 activity (e.g., associated with the formation of lysophosphatidylcholine and oxidized free fatty acids), and disease that involves activated monocytes, macrophages or lymphocytes or which is associated with increased involvement of monocytes, macrophages or lymphocytes. Examples of diseases or conditions include atherosclerosis (e.g. peripheral vascular atherosclerosis and cerebrovascular atherosclerosis), diabetes, hypertension, angina pectoris, after ischaemia and reperfusion, rheumatoid arthritis, stroke, inflammatory conditions of the brain such

as Alzheimer's Disease, various neuropsychiatric disorders such as schizophrenia, myocardial infarction, ischaemia, reperfusion injury, sepsis, acute and chronic inflammation, and psoriasis.

Lp-PLA_2 inhibitors and/or uses thereof are also reported, for example, in PCT Publication Nos. WO05/003118 (and its Canadian family member CA 2530816A1); WO06/063811; WO06/063813 and WO 2008/141176; JP 200188847; and US Published Patent Application Nos. US 2008/0279846 A1, US 2010/0239565 A1, and US 2008/0280829 A1.

Other researchers have studied the effects related to Lp-PLA_2 and inhibitors thereof. For example, research data has also indicated that LysoPC promotes atherosclerotic plaque development, which can ultimately lead to the formation of a necrotic core. (*See* e.g., Wilensky et al., *Current Opinion in Lipidology*, 20, 415–420 (2009)). In addition, the effect of Lp-PLA_2 inhibitors on atherosclerotic plaque composition was demonstrated in a diabetic and hypercholesterolemic porcine model of accelerated coronary atherosclerosis. (*See* e.g., Wilensky et al., *Nature Medicine,* 10, 1015-1016 (2008)). These research results provided further evidence that Lp-PLA_2 inhibitors may be used to treat atherosclerosis.

Additional research has found that high Lp-PLA_2 activity is associated with high risk of dementia, including Alzheimer's disease (AD) (*See* e.g., Van Oijen, *et al.* Annals of Neurology, 59,139 (2006)). Higher level of oxidized LDL has also been observed in AD patients (*See* e.g., Kassner et al. *Current Alzheimer Research*, 5, 358-366 (2008); Dildar, et al., *Alzheimer Dis Assoc Disord,* 24, April–June (2010); Sinem, et al. *Current Alzheimer Research,* 7, 463-469 (2010)). Further, research data has shown that neuroinflammation is present in AD patients and multiple cytotoxic inflammatory cytokines are up-regulated in AD patients. (*See* e.g., Colangelo, et al., *Journal of Neuroscience Research*, 70, 462–473 (2002); Wyss-Coray, *Nature Medicine,* 12, Sept. (2006)). Research has shown that LysoPC function is a pro-inflammatory factor inducing multiple cytotoxic inflammatory cytokine release (*See* Shi, et al. *Atherosclerosis*, 191, 54–62 (2007)). Therefore, this recent research has provided additional evidence that that the inhibitors of Lp-PLA_2 can be used to treat AD by inhibiting activity of Lp-PLA_2 and reducing lysoPC production.

In addition, the treatment of an Lp-PLA_2 inhibitor on a diabetic and hypercholesterolemia swine model demonstrated that the blood-brain-barrier leakage and the brain amyloid beta protein (Aβ) burden, the pathological hallmarks of Alzheimer's disease, were reduced. (*See* U.S. Patent Application Publication No. 2008/0279846). This publication describes several uses of Lp-PLA_2 inhibitors for treating diseases associated with blood-brain-barrier leakage, including, e.g., Alzheimer's disease and vascular dementia.

Further, neuroinflammation, including multiple cytotoxic cytokine release, is a common feature of all neurodegenerative diseases including multiple sclerosis, amyotrophic lateral sclerosis, Parkinson's disease, Alzheimer's disease, etc. (*See* e.g., Perry, *Acta Neuropathol*, 120, 277–286 (2010)). As discussed above, Lp-PLA_2 inhibitors can reduce inflammation, for example, reducing

multiple cytokine release by suppressing lysoPC production. (*See* e.g., Shi, et al. *Atherosclerosis* 191, 54–62 (2007)). Thus, inhibiting Lp-PLA_2 is a potential therapeutic treatment for neurodegenerative diseases including multiple sclerosis, amyotrophic lateral sclerosis, Parkinson's disease, etc.

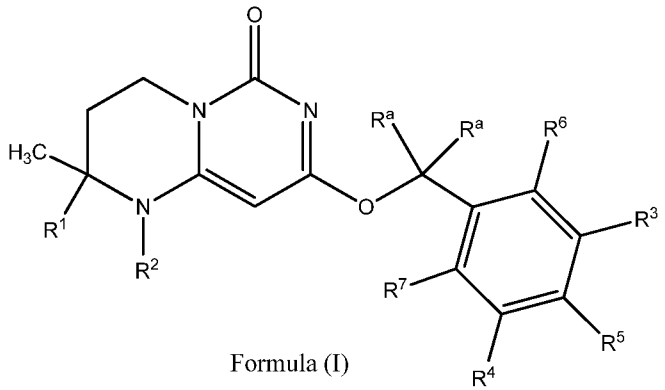
In addition to the inflammatory effect, LysoPC has been implicated in leukocyte activation, induction of apoptosis and mediation of endothelial dysfunction (*See*, e.g., Wilensky et al., *Current Opinion in Lipidology*, 20, 415–420 (2009)). Therefore, it is believed that Lp-PLA_2 inhibitors can be used to treat tissue damage associated with diabetes by reducing the production of lysoPC, which can cause a continuous cycle of vascular inflammation and increased reactive oxygen species (ROS) production. In light of the inflammatory roles of Lp-PLA_2 and the association between localized inflammatory processes and diabetic retinopathy, it is postulated that Lp-PLA_2 can be used to treat diabetic eye disease.

Glaucoma and age-related macular degeneration (AMD) are retina neurodegenerative diseases. Studies suggested that inflammation, including TNF-alpha signaling, may play an important role in the pathogenesis of glaucoma and AMD (*See* e.g., Buschini et al., *Progress in Neurobiology*, 95, 14–25 (2011); Tezel, *Progress in Brain Research*, vol. 173, ISSN0079-6123, Chapter 28). Thus, considering Lp-PLA_2 inhibitors' function of blocking inflammatory cytokine release (*See* e.g., Shi, et al. *Atherosclerosis*, 191, 54–62 (2007)), it is believed that Lp-PLA_2 inhibitors can provide a potential therapeutic application for both glaucoma and AMD.

In view of the number of pathological responses that are mediated by Lp-PLA_2, attempts have been made to prepare compounds that inhibit its activity. Though a number of such compounds have been disclosed in the art, there remains a continuing need for inhibitors of Lp-PLA_2 which can be used in the treatment of a variety of conditions.

SUMMARY OF THE INVENTION

In a first aspect, this invention relates to compounds of Formula (I) or pharmaceutically acceptable salts thereof,



Formula (I)

wherein:

R^1 is H or CH_3;

R^2 is H or C_{1-3}alkyl;

R^3 is halo, CN or H;

R^a is H or D;

R^4 is H, F or CN;

R^5 is selected from the group consisting of halo, H, CN, and –O-R^8,

wherein R^8 is selected from the group consisting of C_{1-3}alkyl, C_{4-6}cycloalkyl, phenyl, pyridinyl, and pyrimidinyl, wherein phenyl, pyridinyl or pyrimidinyl is optionally substituted with one or more substituents independently selected from halo or CF_3; and

R^6 and R^7 are each independently H or F.

This invention also relates to a pharmaceutical composition comprising compounds of this invention and one or more pharmaceutically acceptable excipients.

The invention also relates to methods of treating or preventing a disease associated with the activity of Lp-PLA_2, which comprises administering to a subject in need thereof with a therapeutically effective amount of a compound of the invention described herein. The disease may be associated with the increased involvement of monocytes, macrophages or lymphocytes; with the formation of lysophosphatidylcholine and oxidized free fatty acids; with lipid oxidation in conjunction with Lp-PLA_2 activity; or with endothelial dysfunction.

This invention also provides methods of treating or preventing a disease by inhibiting Lp-PLA_2 activity. Exemplary diseases include, but are not limited to, neurodegeneration disease (e.g., Alzheimer's disease, vascular dementia), atherosclerosis, stroke, metabolic bone disorder (e.g., bone marrow abnormalities), dyslipidemia, Paget's diseases, type II diabetes, metabolic syndrome, insulin resistance, and hyperparathyroidism, diabetic ocular disorder (e.g., macular edema, diabetic retinopathy, and posterior uveitis), macular edema, wound healing, rheumatoid arthritis, chronic obstructive pulmonary disease (COPD), psoriasis, and multiple sclerosis.

The methods comprise administering a therapeutically effective amount of a compound of this invention to a subject in need thereof. It is not intended that the present invention is limited to any particular stage of the disease (e.g. early or advanced).

This invention also provides methods of treating or preventing Alzheimer's disease. The methods comprise administering to a subject in need thereof a therapeutically effective amount of a compound of this invention.

This invention also provides methods of treating or preventing atherosclerosis. The methods comprise administering to a subject in need thereof a therapeutically effective amount of a compound of this invention.

This invention also provides methods of decreasing beta amyloid (also referred to as "Aβ") accumulation in the brain of a subject. The methods comprise administering to a subject in need thereof a therapeutically effective amount of a compound of the present invention. In certain embodiment, the beta amyloid is Abeta-42.

This invention also provides methods for treating or preventing ocular diseases by administering a compound of this invention. In certain embodiment, this invention provides methods of treating macular edema, which comprises administering to the subject a therapeutically effective amount of a compound of this invention. In certain embodiment, the macular edema is associated with diabetic ocular disease, for example, diabetic macular edema or diabetic retinopathy. In one embodiment, the macular edema is associated with posterior uveitis.

This invention also provides a use of compounds of this invention in the manufacture of a medicament for treating or preventing diseases described herein.

This invention also provides compounds of this invention for use in the treatment or prevention described herein.

DETAILED DESCRIPTION OF THE INVENTION

As used in the description of the embodiments of the invention and the appended claims, the singular forms "a", "an" and "the" are intended to include the plural forms as well, unless the context clearly indicates otherwise. Also, as used herein, "and/or" refers to encompasses any and all possible combinations of one or more of the associated listed items. It will be further understood that the terms "comprises" and/or "comprising" when used in this specification, specify the presence of stated features, integers, steps, operations, elements, and/or components, but do not preclude the presence or addition of one or more other features, integers, steps, operations, elements, components, and/or groups thereof.

Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, biology described herein are those well known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. In the event that there is a plurality of definitions for a term used herein, those in this section prevail unless stated otherwise.

All patents, patent applications and publications referred to herein are incorporated by reference in their entirety. In case of a conflict in terminology, the present specification is controlling.

A. Definitions

As used herein, the term "disease" refers to any alteration in state of the body or of some of the organs, interrupting or disturbing the performance of the functions and/or causing symptoms such as discomfort, dysfunction, distress, or even death to the person afflicted or those in contact

with a person. A disease can also include a distemper, ailing, ailment, malady, disorder, sickness, illness, complain, interdisposition and/or affectation.

The term "neurodegeneration disease" as used herein refers to a varied assortment of central nervous system disorder characterized by gradual and progressive loss of neural tissue and/or neural tissue function. A neurodegeneration disease is a class of neurological disease where the neurological disease is characterized by a gradual and progressive loss of neural tissue, and/or altered neurological function, typically reduced neurological function as a result of a gradual and progressive loss of neural tissue. In certain embodiments, the neurodegeneration diseases described herein include neurodegeneration diseases where there is a defective blood brain barrier, for example a permeable blood brain barrier. Examples of neurodegeneration diseases where there is a defective blood brain barrier include, but are not limited to, Alzheimer's disease, Huntington's disease, Parkinson's disease, vascular dementia and the like.

The term "vascular dementia" is also referred to as "multi-infarct dementia", which refers to a group of syndromes caused by different mechanisms, which all result in vascular lesions in the brain. The main subtypes of vascular dementia are, for example, vascular mild cognitive impairment, multi-infarct dementia, vascular dementia due to a strategic single infarct, (affecting the thalamus, the anterior cerebral artery, the parietal lobes or the cingulated gyrus), vascular dementia due to hemorrhagic lesions, small vessel disease (including, e.g. vascular dementia due to lacunar lesions and Binswanger disease), and mixed dementia.

The phrase "blood-brain barrier" or "BBB" are used interchangeably herein, and are used to refer to the permeable barrier that exists in blood vessels as they travel through the brain tissue that severely restricts and closely regulates what is exchanged between the blood and the brain tissue. The blood brain barrier components include the endothelial cells that form the innermost lining of all blood vessels, the tight junctions between adjacent endothelial cells that are structural correlate of the BBB, the basement membrane of endothelial cells and the expanded foot process of nearby astrocytes which cover nearly all of the exposed outer surface of the blood vessel.

The phrase "metabolic bone disease" as used herein refers to a varied assortment of bone diseases and disorders characterized by gradual and progressive loss of bone tissue. Metabolic bone diseases described herein are metabolic bone diseases whereby there is a condition of diffusely decreased bone density and/or diminished bone strength. Such diseases are characterized by histological appearance. Exemplary metabolic bone diseases include, but are not limited to, osteoporosis which is characterized by decreased mineral and bone matrix, and osteomalacia which is characterized by decreased mineral but intact bone matrix.

The term "osteopenic diseases" or "osteopenia" are used interchangeably herein, and refer to conditions with decreased calcification and/or bone density, and is a descriptive term used to refer to all skeletal systems in which decreased calcification and/or bone density is observed. Osteopenia also refers to a reduced bone mass due to inadequate osteiod synthesis.

The term “osteoporosis” refers to conditions in which mineral and/or bone matrix are decreased and/or bone mass is reduced.

“Alkyl” refers to a monovalent, saturated hydrocarbon chain having a specified number of carbon atoms. For example, C_1-C_3 alkyl refers to an alkyl group having from 1 to 3 carbon atoms. Alkyl groups may be straight or branched. In some embodiments, branched alkyl groups may have one, two, or three branches. Exemplary alkyl groups include, but are not limited to, methyl, methylethyl, ethyl, propyl (n-propyl and isopropyl), butyl (n-butyl, isobutyl, and t-butyl).

“Cycloalkyl” refers to a saturated monocyclic hydrocarbon ring of 3 to 10 carbon atoms. In some embodiments, the cycloalkyl has 4 to 6 carbon atoms. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

"Halogen" refers to fluorine (F), chlorine (Cl), bromine (Br), or iodine (I). “Halo” refers to the halogen radicals: fluoro (-F), chloro (-Cl), bromo (-Br), or iodo (-I).

"Optionally substituted" indicates that a group, such as phenyl, pyridinyl or pyrimidinyl may be unsubstituted, or the group may be substituted with one or more substituent as defined.

As used herein, “substituted” in reference to a group indicates that one or more hydrogen atom attached to a member atom (e.g., carbon atom) within the group is replaced with a substituent selected from the group of defined substituents. It should be understood that the term "substituted" includes the implicit provision that such substitution be in accordance with the permitted valence of the substituted atom and the substituent and that the substitution results in a stable compound (i.e. one that does not spontaneously undergo transformation such as by rearrangement, cyclization, or elimination and that is sufficiently robust to survive isolation from a reaction mixture). When it is stated that a group may contain one or more substituent, one or more (as appropriate) member atom within the group may be substituted. In addition, a single member atom within the group may be substituted with more than one substituent as long as such substitution is in accordance with the permitted valence of the atom. Exemplary substituents include, but are not limited to, halo (e.g., Cl, F), haloalkyl (e.g., CF_3). Suitable substituents are defined herein for each substituted or optionally substituted group.

As used herein, “treat”, “treating” or “treatment” in reference to a disease means: (1) to ameliorate the disease or one or more of the biological manifestations of the disease, (2) to interfere with (a) one or more points in the biological cascade that leads to or is responsible for the disease or (b) one or more of the biological manifestations of the disease, (3) to alleviate one or more of the symptoms or effects associated with the disease, (4) to slow the progression of the disease or one or more of the biological manifestations of the disease, and/or (5) to diminish the likelihood of severity of a disease or biological manifestations of the disease.

As used herein, “prevent”, “preventing” or “prevention” means the prophylactic administration of a drug to diminish the likelihood of the onset of or to delay the onset of a disease or biological manifestation thereof.

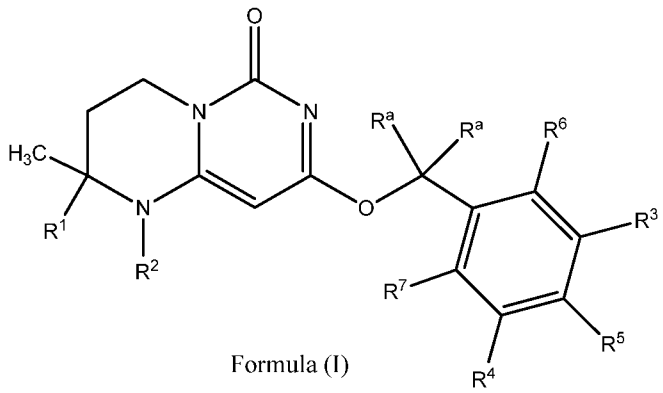
As used herein, "subject" means a mammalian subject (*e.g.*, dog, cat, horse, cow, sheep, goat, monkey, etc.), and particularly human subjects including both male and female subjects, and including neonatal, infant, juvenile, adolescent, adult and geriatric subjects, and further including various races and ethnicities including, but not limited to, white, black, Asian, American Indian and Hispanic.

As used herein, "pharmaceutically-acceptable salts" refers to salts that retain the desired biological activity of the subject compound and exhibit minimal undesired toxicological effects. These pharmaceutically-acceptable salts may be prepared *in situ* during the final isolation and purification of the compound, or by separately reacting the purified compound in its free acid or free base form with a suitable base or acid, respectively.

As used herein, the term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in treating or preventing a disease, but low enough to avoid serious side effects (at a reasonable benefit/risk ratio) within the scope of sound medical judgment. A therapeutically effective amount of a compound will vary with the particular compound chosen (e.g. consider the potency, efficacy, and half-life of the compound); the route of administration chosen; the disease being treated; the severity of the disease being treated; the age, size, weight, and physical condition of the patient being treated; the medical history of the patient to be treated; the duration of the treatment; the nature of concurrent therapy; the desired therapeutic effect; and like factors, but can nevertheless be routinely determined by the skilled artisan.

B. Compounds

This invention provides, in a first aspect, compounds of Formula I and pharmaceutically acceptable salts thereof:



Formula (I)

wherein:

R^1 is H or CH_3;

R^2 is H or C_{1-3}alkyl;

R^3 is halo, CN or H;

R^a is H or D;

R^4 is H, F or CN;

R^5 is selected from the group consisting of halo, H, CN, and –O-R^8,

wherein R^8 is selected from the group consisting of C_{1-3}alkyl, C_{4-6}cycloalkyl, phenyl, pyridinyl, and pyrimidinyl, wherein phenyl, pyridinyl or pyrimidinyl is optionally substituted with one or more substituents independently selected from halo or CF_3; and

R^6 and R^7 are each independently H or F.

In one embodiment, this invention relates to compounds of Formula (I), wherein R^1 is H, or pharmaceutically acceptable salts thereof. In one embodiment, this invention relates to compounds of Formula (I), wherein R^1 is CH_3, or pharmaceutically acceptable salts thereof.

In another embodiment, this invention relates to compounds of Formula (I) and any of the above applicable embodiments, wherein R^2 is H or pharmaceutically acceptable salts thereof. In another embodiment, this invention relates to compounds of Formula (I) and any of the above applicable embodiments, wherein R^2 is CH_3 or C_2H_5 or pharmaceutically acceptable salts thereof.

In one embodiment, this invention relates to compounds of Formula (I) and any of the above applicable embodiments, wherein R^3 is H or pharmaceutically acceptable salts thereof. In one embodiment, this invention also relates to compounds of Formula (I) and any of the above applicable embodiments, wherein R^3 is F or pharmaceutically acceptable salts thereof. Yet, in one embodiment, this invention also relates to compounds of Formula (I) and any of the above applicable embodiments, wherein R^3 is CN or pharmaceutically acceptable salts thereof.

In one embodiment, this invention relates to compounds of Formula (I) and any of the above applicable embodiments, wherein R^a is H.

In one embodiment, this invention relates to compounds of Formula (I) and any of the above applicable embodiments, wherein R^4 is H or pharmaceutically acceptable salts thereof. In one embodiment, this invention also relates to compounds of Formula (I) and any of the above applicable embodiments, wherein R^4 is F or pharmaceutically acceptable salts thereof. Yet, in one embodiment, this invention also relates to compounds of Formula (I) and any of the above applicable embodiments, wherein R^4 is CN or pharmaceutically acceptable salts thereof.

In one embodiment, the invention relates to compounds of Formula (I) and any of the above applicable embodiments, wherein R^3 and R^4 are independently selected from H, F or CN. In other embodiment, the invention relates to compounds of Formula (I) and any of the above applicable embodiments, at least one of R^3 or R^4 is F, or pharmaceutically acceptable salts thereof.

In one embodiment, this invention relates to compounds of Formula (I) and any of the above applicable embodiments, wherein R^5 is H or F or pharmaceutically acceptable salts thereof. Yet, in one embodiment, this invention also relates to compounds of Formula (I) and any of the

above applicable embodiments, wherein R^5 is –O-R^8, wherein R^8 is phenyl, substituted with one or two substituents independently selected from F or CF_3, or pharmaceutically acceptable salts thereof. In another embodiment, this invention also relates to compounds of Formula (I) and any of the above applicable embodiments, wherein R^5 is –O-R^8, wherein R^8 is cyclopentyl or cyclohexyl or pharmaceutically acceptable salts thereof. In one embodiment, this invention also relates to compounds of Formula (I) and any of the above applicable embodiments, wherein R^5 is –O-R^8, wherein R^8 is pyrimidinyl or pyridinyl substituted with one or two substituents independently selected from F or CF_3, or pharmaceutically acceptable salts thereof.

In one embodiment, this invention relates to compounds of Formula (I) and any of the above applicable embodiments, wherein R^6 is H or pharmaceutically acceptable salts thereof. In one embodiment, this invention also relates to compounds of Formula (I) and any of the above applicable embodiments, wherein R^6 is F or pharmaceutically acceptable salts thereof.

In one embodiment, this invention relates to compounds of Formula (I) and any of the above applicable embodiments, wherein R^7 is H or pharmaceutically acceptable salts thereof. In one embodiment, this invention also relates to compounds of Formula (I) and any of the above applicable embodiments, wherein R^7 is F or pharmaceutically acceptable salts thereof.

In one embodiment, this invention relates to compounds of Formula (I), wherein R^1 is H or CH_3; R^2 is CH_3 or C_2H_5; R^3 and R^4 are independently F or H; R^5 is F or H and R^6 and R^7 are each independently H or F; or pharmaceutically acceptable salts thereof.

In one embodiment, this invention relates to compounds of Formula (I), wherein R^1 is H; R^2 is CH_3; at least of one of R^3 and R^4 is F; R^5 is –O- phenyl, wherein phenyl is substituted with one or more F; and R^6 and R^7 are H; or pharmaceutically acceptable salts thereof.

In one embodiment, this invention relates to compounds of Formula (I), wherein R^1 is H; R^2 is CH_3; at least of one of R^3 and R^4 is F; R^5 is –O-R^8, wherein R^8 is pyrimidinyl or pyridinyl, substituted with one substituent of CF_3; and R^6 and R^7 are H; or pharmaceutically acceptable salts thereof.

In one embodiment, the compound of Formula (I) is a compound of any one of Examples 1 to 153, a free base form, a free acid form, or a salt (e.g., a pharmaceutically acceptable salt) thereof.

The compounds of Formula (I), salts (e.g., pharmaceutically acceptable salts) thereof may exist in stereoisomeric forms (e.g., it contains one or more asymmetric carbon atoms). The individual stereoisomers (enantiomers and diastereomers) and mixtures of these are included within the scope of the present invention. The invention also covers the individual isomers of the compounds of Formula (I), salts (e.g., pharmaceutically acceptable salts) thereof as mixtures with isomers thereof in which one or more chiral centers are inverted. Likewise, it is understood that the compounds of Formula (I), salts (e.g., pharmaceutically acceptable salts) thereof may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention. It is to be understood that the present invention includes all combinations

and subsets of the particular groups defined hereinabove. The scope of the present invention includes mixtures of stereoisomers as well as purified enantiomers or enantiomerically/diastereomerically enriched mixtures. Also included within the scope of the invention are individual isomers of the compounds of Formula (I), salts (e.g., pharmaceutically acceptable salts) thereof, as well as any wholly or partially equilibrated mixtures thereof. The present invention also includes the individual isomers of the compounds of Formula (I), salts (e.g., pharmaceutically acceptable salts) thereof as well as mixtures with isomers thereof in which one or more chiral centers are inverted. It is to be understood that the present invention includes all combinations and subsets of the particular groups defined hereinabove. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

The invention also includes various deuterated forms of compounds of Formula (I), salts (e.g., pharmaceutically acceptable salts) thereof. Each available hydrogen atom attached to a carbon atom may be independently replaced with a deuterium atom. A person of ordinary skill in the art will know how to synthesize deuterated forms of compounds of Formula (I), salts (e.g., pharmaceutically acceptable salts) thereof. Commercially available deuterated starting materials may be employed in the preparation of deuterated forms of compounds of Formula (I), salts (e.g., pharmaceutically acceptable salts) thereof, or they may be synthesized using conventional techniques employing deuterated reagents (e.g. lithium aluminum deuteride).

In addition to the free base or free acid form of the compounds described herein, the salt form of the compounds is also within the scope of the present invention. The salts or pharmaceutically-acceptable salts of the compounds described herein may be prepared *in situ* during the final isolation and purification of the compound, or by separately reacting the purified compound in its free acid or free base form with a suitable base or acid, respectively. For reviews on suitable pharmaceutical salts see Berge *et al*, J. Pharm, Sci., 66, 1-19, 1977; P L Gould, International Journal of Pharmaceutics, 33 (1986), 201-217; and Bighley *et al*, Encyclopedia of Pharmaceutical Technology, Marcel Dekker Inc, New York 1996, Volume 13, page 453-497.

In certain embodiments, compounds of the present invention may contain an acidic functional group, which is acidic enough to form salts. Representative salts include pharmaceutically-acceptable metal salts such as sodium, potassium, lithium, calcium, magnesium, aluminum, and zinc salts; carbonates and bicarbonates of a pharmaceutically-acceptable metal cation such as sodium, potassium, lithium, calcium, magnesium, aluminum, and zinc; pharmaceutically-acceptable organic primary, secondary, and tertiary amines including aliphatic amines, aromatic amines, aliphatic diamines, and hydroxy alkylamines such as methylamine, ethylamine, diethylamine, triethylamine, ethylenediamine, ethanolamine, diethanolamine, and cyclohexylamine.

In certain embodiments, compounds of the present invention may contain a basic group and are therefore capable of forming pharmaceutically-acceptable acid addition salts by treatment with a suitable acid. Suitable acids include pharmaceutically-acceptable inorganic acids and pharmaceutically-acceptable organic acids. These salts may be crystalline or amophorus. Exemplary pharmaceutically-acceptable acid addition salts include hydrochloride, hydrobromide, nitrate, methylnitrate, sulfate, bisulfate, sulfamate, phosphate, acetate, hydroxyacetate, phenylacetate, propionate, butyrate, isobutyrate, valerate, maleate, hydroxymaleate, acrylate, fumarate, malate, tartrate, citrate, salicylate, *p*-aminosalicyclate, glycollate, lactate, heptanoate, phthalate, oxalate, succinate, benzoate, *o*-acetoxybenzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, mandelate, tannate, formate, stearate, ascorbate, palmitate, oleate, pyruvate, pamoate, malonate, laurate, glutarate, glutamate, estolate, methanesulfonate (mesylate), ethanesulfonate (esylate), 2-hydroxyethanesulfonate, benzenesulfonate (besylate), *p*-aminobenzenesulfonate, *p*-toluenesulfonate (tosylate), and napthalene-2-sulfonate. In some embodiments, the pharmaceutically acceptable salts include the L-tartrate, ethanedisulfonate (edisylate), sulfate, phosphate, p-toluenesulfonate (tosylate), hydrochloride salt, methanesulfonate, citrate, fumarate, benzenesulfonate, maleate, hydrobromate, L-lactate, malonate, and S-camphor-10-sulfonate. Some of these salts form solvates, some are crystalline.

The compounds described herein, their salts (e.g., pharmaceutically acceptable salts), deuterated form, solvates or hydrates thereof, may exist in one or more polymorphic form. Therefore, in a further aspect, the invention provides a polymorph of a compound defined herein, their salts (e.g., pharmaceutically acceptable salts), or a polymorph of a solvate or hydrate of a compound described herein or a salt (e.g., pharmaceutically acceptable salt) thereof.

The compounds of Formula (I) and salts (including pharmaceutically acceptable salts) thereof may be in the form of a solvate. For solvates of the compounds of Formula (I), including solvates of salts of the compounds of Formula (I), that are in crystalline form, the skilled artisan will appreciate that pharmaceutically acceptable solvates may be formed wherein solvent molecules are incorporated into the crystalline lattice during crystallization. Solvates may involve nonaqueous solvents such as ethanol, isopropanol, dimethylsulfoxide, acetic acid, ethanolamine, and ethyl acetate, or they may involve water as the solvent that is incorporated into the crystalline lattice. Solvates wherein water is the solvent that is incorporated into the crystalline lattice are typically referred to as "hydrates." Solvates include stoichiometric solvates as well as compositions containing variable amounts of the incorporated solvent(s), e.g. a hydrate includes stoichiometic hydrates and compositions containing variable amounts of water.

The invention also includes isotopically-labeled compounds and salts, which are identical to compounds of Formula (I) or salts thereof, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number

most commonly found in nature. Examples of isotopes that can be incorporated into compounds of Formula (I) or salts thereof isotopes of hydrogen, carbon, nitrogen, fluorine, such as ^{3}H, ^{11}C, ^{14}C and ^{18}F. Such isotopically-labeled compound of Formula (I) or salts thereof are useful in drug and/or substrate tissue distribution assays. For example, ^{11}C and ^{18}F isotopes are useful in PET (positron emission tomography). PET is useful in brain imaging. Isotopically-labeled compounds of Formula (I) and salts thereof can generally be prepared by carrying out the procedures disclosed below, by substituting a readily available isotopically-labeled reagent for a non-isotopically labeled reagent. In one embodiment, compounds of Formula (I) or salts thereof are not isotopically labeled.

As used herein, the terms "compound(s) of the invention" or "compound(s) of the present invention" mean a compound of Formula (I), as defined herein, in any form, i.e., any salt or non-salt form (e.g., as a free acid or base form, or as a salt, for example, a pharmaceutically acceptable salt thereof), deuterated form and any physical form thereof (e.g., including non-solid forms (e.g., liquid or semi-solid forms), and solid forms (e.g., amorphous or crystalline forms, specific polymorphic forms, solvate forms, including hydrate forms (e.g., mono-, di- and hemi- hydrates)), and mixtures of various forms.

Accordingly, a compound of the invention includes a compound of Formula (I), or a salt thereof, for example a pharmaceutically acceptable salt thereof. Representative compounds of this invention include the specific compounds described.

C. Synthesis of Compounds

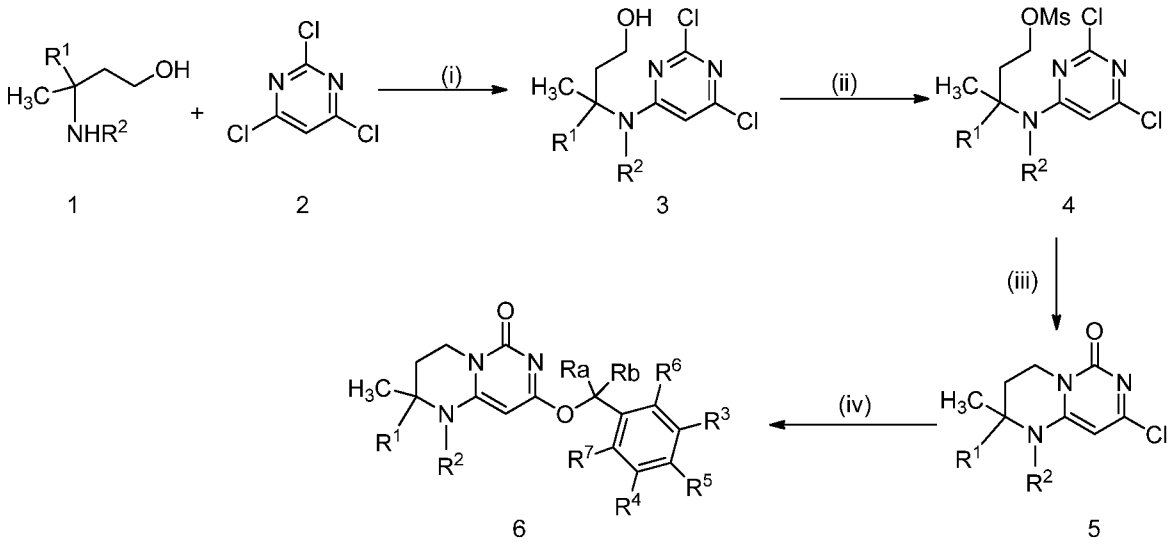
The process to be utilized in the preparation of the compounds described herein depends upon the desired compounds. Such factors as the selection of the specific substituent and various possible locations of the specific substituent all play a role in the path to be followed in the preparation of the specific compounds of this invention. Those factors are readily recognized by one of ordinary skill in the art.

In general, the compounds of the present invention may be prepared by standard techniques known in the art and by known processes analogous thereto. General methods for preparing compounds of the present invention are set forth below. All starting material and reagents described in the below general experimental schemes are commercially available.

The skilled artisan will appreciate that if a substituent described herein is not compatible with the synthetic methods described herein, the substituent may be protected with a suitable protecting group that is stable to the reaction conditions. The protecting group may be removed at a suitable point in the reaction sequence to provide a desired intermediate or target compound. Suitable protecting groups and the methods for protecting and de-protecting different substituents using such suitable protecting groups are well known to those skilled in the art; examples of which may be found in T. Greene and P. Wuts, Protecting Groups in Chemical Synthesis (3rd ed.), John Wiley & Sons, NY (1999). In some instances, a substituent may be specifically selected to be reactive under the reaction conditions used. Under these circumstances, the reaction conditions

convert the selected substituent into another substituent that is either useful as an intermediate compound or is a desired substituent in a target compound.

General Experimental Scheme 1



General Experimental Scheme 1 provides an exemplary synthesis for compound 6. Step (i) may be carried out by reacting amine 1 with 2,4,6-trichloropyrimidine using an appropriate base such as triethylamine (TEA) in an appropriate solvent such as acetonitrile under an suitable temperature such as a room temperature to provide compound 3. Step (ii) may be taken place using an appropriate reagent such as MsCl and an appropriate base such as TEA in a suitable solvent such as THF at suitable temperature such as room temperature to afford compound 4. Step (iii) may be carried out by hydrolysis of compound 4 with a suitable base such as K_2CO_3 under a suitable solvent such as 1,4-dioxane and water at an appropriate temperature such as 70°C to obtain bicyclic compound 5. Step (iv) may be carried out by reacting compound 5 with an appropriate starting material in the presence of a suitable base such as NaH in a suitable solvent such as dimethylformamide (DMF) at suitable temperature such as 0 °C to provide compound 6, wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^a and R^b are as defined in Formula (I).

All temperatures are reported in degrees Celsius. All other abbreviations are as described in the ACS Style Guide (American Chemical Society, Washington, DC, 1986).

LCMS Conditions:

1) Acidic conditions:

Mobile phase: water containing 0.05 % TFA / 0.05% acetonitrile

Column: Agilent SB-C18 4.6 x 30 mm-1.8 microns

Detection: MS and photodiode array detector (PDA)

2) Basic conditions:

Mobile phase: water containing 10 mmol NH_4HCO_3 / acetonitrile

Column: XBridgeTM C18 4.6 x 50 mm-3.5 microns

Detection: MS and photodiode array detector (PDA)

Mass directed autoprep purification (MDAP) Conditions:

1) Acidic conditions:

Instrument: Waters instrument

Column: Sunfire Prep C18 column (5 um, 19 x 50 mm)

Mobile phase: water containing 0.05% TFA / acetonitrile.

2) Basic conditions:

Instrument: Waters instrument

Column: Xbridge Prep C18 column (5 um, 19 x 50 mm)

Mobile phase: water containing 0.04% ammonia/ acetonitrile.

Abbreviations and Resource Sources

The following abbreviations and resources are used herein below:

ISCO system – Teledyne ISCO (http://www.isco.com/html/seFlashChromatography.html)

r.t/rt/RT – room temperature;

ACN – acetonitrile;

AcCl– Acetic chloride

Aq. – aqueous

$(BOC)_2O$ – di-tert-butyl dicarbonate

CV – Column volumes

DABCO –1,4-diazabicyclo[2.2.2]octane

DAST – diethylaminosulfur trifluoride

DBU– 1,8-diazabicyclo[5.4.0]undec-7-ene

DCM – dichloromethane;

DIAD – diisopropyl azodiformate

DIPEA –N, N-diisopropylethylamine

DMA – *N, N*-dimethylacetamide;

DMAP–4-dimethylaminopyridine

DME – 1, 2-dimethoxyethane;

DMF – dimethylformamide ;

DMSO – dimethyl sulfoxide

EA – ethyl acetate;

EDC – 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride

FC– flash chromatography

HATU–2-(1H-7-Azabenzotriazol-1-yl)--1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium

NBS – N-bromosuccinamide;

NIS – N-iodosuccinimide

NMP – *N*-methyl-2-pyrrolidone;

TEA – triethylamine;

TFA – trifluoro acetic acid

THF – tetrahydrofuran;

PE – petroleum ether;

DIBAL-H – diisobutylaluminum hydride;

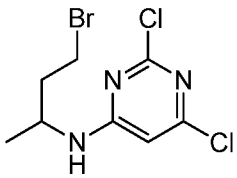
9-BBN – 9-borabicyclo[3,3,1]nonane;

Examples

The following synthetic processes and examples are provided to more specifically illustrate the invention. These examples are not intended to limit the scope of the invention, but rather to provide guidance to the skilled artisan to prepare and use the compounds, compositions, and methods of the invention. While particular embodiments of the invention are described, the skilled artisan will appreciate that various changes and modifications can be made without departing from the spirit and scope of the invention.

D1

N-(4-bromobutan-2-yl)-2,6-dichloropyrimidin-4-amine

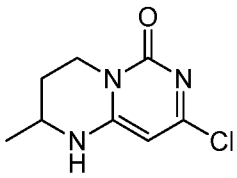


To a mixture of 4-bromobutan-2-amine (24.70 g, 162 mmol) and TEA (67.9 mL, 487 mmol) in acetonitrile (500 mL) was added 2,4,6-trichloropyrimidine (29.8 g, 162 mmol) at 0 °C, and stirred for 12 h at rt. The reaction mixture was concentrated, washed by water, extracted by ethyl acetate. Purification via ISCO (PE: ethyl acetate = 10:1) afforded the title compound (3.6 g).

LC-MS (ESI): m/z 299 $[M + 1]^+$; 1.11 min (ret time).

D2

8-chloro-2-methyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

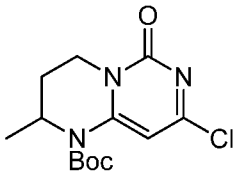


To a solution of N-(4-bromobutan-2-yl)-2,6-dichloropyrimidin-4-amine (3.5 g, 11.71 mmol) in 1,4-dioxane (20 mL) and water (20 mL) was added K_2CO_3 (2.427 g, 17.56 mmol), and stirred for 30 min at 70 °C. The reaction mixture was concentrated, washed by water, extracted by ethyl acetate, and concentrated to afford the title compound (2.1 g) as a crude product.

LC-MS (ESI): m/z 200 $[M + 1]^+$; 0.37 min (ret time).

D3

tert-butyl 8-chloro-2-methyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidine-1-carboxylate

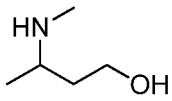


To a solution of 8-chloro-2-methyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one (500 mg, 2.50 mmol) in tetrahydrofuran (THF) (10 mL) were added triethylamine (253 mg, 2.50 mmol) and N,N-dimethylpyridin-4-amine (30.6 mg, 0.25 mmol), then di-tert-butyl dicarbonate (1.09 g, 5.01 mmol), and stirred for 12 h at 25 °C. The reaction mixture was concentrated, washed by PE:EA 20:1(20 mL), filtered to afford the title compound (275 mg).

LC-MS (ESI): m/z 300 $[M + 1]^+$; 1.02 min (ret time).

D4

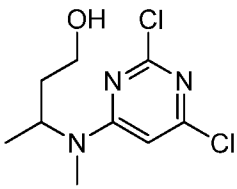
3-(methylamino)butan-1-ol



To a solution of 4-hydroxybutan-2-one (5 ml, 57.9 mmol) in ethanol (100 mL) were added methanamine (8.65 ml, 69.5 mmol, 33% in ethanol) and Pd/C (3.08 g, 2.89 mmol, 10%), and stirred at r.t overnight under hydrogen gas. The reaction mixture was filtered and the filtrate was concentrated to afford the title compound (5.8 g) as a crude product.

D5

3-((2,6-dichloropyrimidin-4-yl)(methyl)amino)butan-1-ol

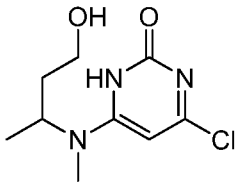


The title compound was prepared by a procedure similar to that described for D1 starting from 3-(methylamino)butan-1-ol and 2,4,6-trichloropyrimidine.

LC-MS (ESI): m/z 250 $[M + 1]^+$; 2.49 min (ret time).

D6

4-chloro-6-((4-hydroxybutan-2-yl)(methyl)amino)pyrimidin-2-ol

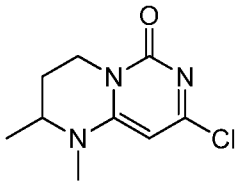


To a solution of 3-((2,6-dichloropyrimidin-4-yl)(methyl)amino)butan-1-ol (1.3 g, 5.20 mmol) in tetrahydrofuran (THF) (10 mL) and water (10.00 mL) were added LiOH (0.498 g, 20.79 mmol) and H_2O_2 (0.319 mL, 10.39 mmol, 33% in water), stirred for 2 h at 50 °C. The reaction mixture was cooled to r.t. and quenched by sodium sulfite solution, concentrated. Purification via ISCO afforded the title compound (600 mg) as a white solid.

LC-MS (ESI): m/z 232 $[M + 1]^+$; 1.40 min (ret time).

D7

8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

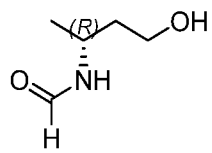


To a solution of 4-chloro-6-((4-hydroxybutan-2-yl)(methyl)amino)pyrimidin-2-ol (600 mg, 2.59 mmol) and triethylamine (1.083 mL, 7.77 mmol) in tetrahydrofuran (THF) (10 mL), was added dropwise MsCl (0.202 mL, 2.59 mmol) in THF (2 mL) at r.t., stirred for 1h. The reaction mixture was concentrated to afford the title compound as a crude product.

LC-MS (ESI): m/z 214 $[M + 1]^+$; 1.66 min (ret time).

D8

(R)-3-formamidobutanoic acid

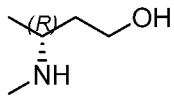


To a solution of (R)-3-aminobutanoic acid (10.8 g, 105 mmol) in 115 mL of 80% formic acid was added dropwise 70 mL of acetic anhydride at 0 °C, stirred for 10 min, then stirred for 4 h at r.t. The

reaction mixture was quenched with water (70 mL), concentrated. The residue was recrystallized from water to afford the title compound (13.6 g).

D9

(R)-3-(methylamino)butan-1-ol

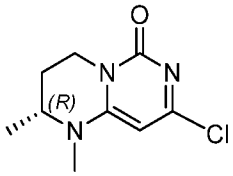


To a suspension of $LiAlH_4$ (15.05 g, 397 mmol) in dry THF (80 mL) was added dropwise (R)-3-formamidobutanoic acid (13 g, 99 mmol) in THF (120 mL) at 0 °C, stirred for 30 min at 0 °C, 3 h at rt, then refluxed for 9 h. The mixture was cooled at 0 °C and 25 mL of 15% NaOH was slowly added, stirred for 2 h at r.t. The reaction mixture was filtered, dried over Na_2SO_4, concentrated to afford the title compound.

^1H NMR (400 MHz, $CDCl_3$): δ: 3.84 (m, 2H), 3.14 (m,1H), 2.42 (s, 3H), 1.65 (m, 1H), 1.53 (m, 1H), 1.14 (m, 3H).

D10

(R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

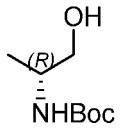


The title compound was prepared by a procedure similar to that described for D2 starting from (R)-3-(methylamino)butan-1-ol and 2,4,6-trichloropyrimidine.

LC-MS (ESI): m/z 214 $[M + 1]^+$; 0.72 min (ret time).

D11

(R)-tert-butyl (1-hydroxypropan-2-yl)carbamate

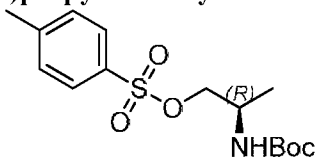


To a solution of (R)-2-aminopropan-1-ol (15 g, 200 mmol), triethylamine (60.6 g, 599 mmol) in tetrahydrofuran (THF) (300 mL) was added di-tert-butyl dicarbonate (87 g, 399 mmol), stirred at stirred at 25 °C overnight. The organic phase was washed with saturated brine, dried over sodium sulphate, concentrated to afford the title compound (20.3 g) as yellow oil.

LC-MS (ESI): m/z 121 $[M + 1]^+$; 1.01 min (ret time).

D12

(R)-2-((tert-butoxycarbonyl)amino)propyl 4-methylbenzenesulfonate

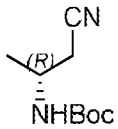


To a solution of (R)-tert-butyl (1-hydroxypropan-2-yl)carbamate (19.0 g, 108 mmol), triethylamine (32.9 g, 325 mmol) and N,N-dimethylpyridin-4-amine (1.325 g, 10.84 mmol) in dichloromethane (500 mL) was added 4-methylbenzene-1-sulfonyl chloride (31.0 g, 163 mmol), stirred for 1 h at 25 °C. The organic phase was separated, washed with brine, dried over Na_2SO_4, and concentrated. Purification via ISCO afforded the title compound (21.5 g).

LC-MS (ESI): m/z 230 $[M + 1]^+$; 0.81 min (ret time).

D13

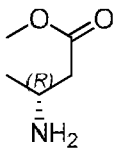
(R)-tert-butyl (1-cyanopropan-2-yl)carbamate



To a solution of (R)-2-((tert-butoxycarbonyl)amino)propyl 4-methylbenzenesulfonate (21.5 g, 65.3 mmol) in N,N-dimethylformamide (DMF) (300 mL) was added cyanosodium (4.80 g, 98 mmol), stirred at 120 °C overnight, and diluted with EtOAc. The organic phase was washed with water, saturated aq. sodium bicarbonate and brine, dried over sodium sulphate, concentrated. Purification via ISCO afforded the title compound (4.0 g) as a yellow solid.

D14

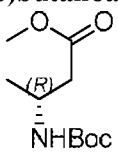
(R)-methyl 3-aminobutanoate



A solution of (R)-tert-butyl (1-cyanopropan-2-yl)carbamate (2.6 g, 14.11 mmol) in concentrated HCl was heated to reflux overnight, and concentrated. The residue was dissolved in methanol (100 mL), added dropwise $SOCl_2$ (3.09 ml, 42.3 mmol) at r.t. The reaction mixture was stirred at 90 °C overnight, and concentrated to afford the title compound (1.4g) as a crude product.

D15

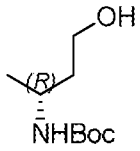
Methyl (R)-3-((tert-butoxycarbonyl)amino)butanoate



To a solution of (R)-methyl 3-aminobutanoate (1.3 g, 11.10 mmol), TEA (4.64 mL, 33.3 mmol) and N,N-dimethylpyridin-4-amine (0.136 g, 1.110 mmol) in tetrahydrofuran (THF) (40 mL) was added di-tert-butyl dicarbonate (3.63 g, 16.65 mmol), stirred at stirred at 25 °C for overnight under nitrogen. The organic phase was washed with brine, dried over sodium sulphate to afford the title compound (3.0 g).

D16

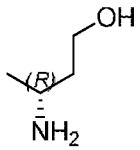
(R)-tert-butyl(4-hydroxybutan-2-yl) carbamate



To a solution of methyl (R)-3-((tert-butoxycarbonyl)amino)butanoate (3.0 g, 14.76 mmol) in tetrahydrofuran (THF) (50 mL) was added aluminum(III) lithium hydride (0.728 g, 19.19 mmol), stirred at -78 °C for 1 h under nitrogen. The reaction mixture was warmed to 0°C, quenched by addition of H_2O (0.7 mL) and aq. 15% NaOH (0.7 mL), stirred for 1 h at r.t., filtered through celite, dried over Na_2SO4, concentrated to afford the title compound (1.3 g).

D17

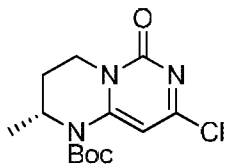
(R)-3-aminobutan-1-ol



To a solution of (R)-tert-butyl(4-hydroxybutan-2-yl) carbamate (1.3 g, 6.87 mmol) in methanol (30 mL) was added HCl (30 mL, 4M in MeOH), stirred at 25°C overnight, concentrated to afford the title compound (0.5 g).

D18

(R)-tert-butyl 8-chloro -2-methyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidine- 1-carboxylate

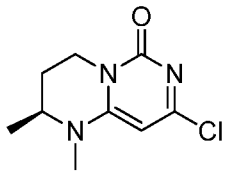


The title compound was prepared by a procedure similar to that described for **D3** starting from 3-(ethylamino)propan-1-ol and 2,4,6-trichloropyrimidine.

LC-MS (ESI): m/z 239 $[M+1]^+$; 0.74 min (ret time).

D19

(S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

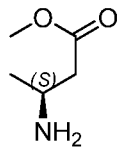


The title compound was prepared by a procedure similar to that described for D2 starting from (S)-3-(methylamino)butan-1-ol and 2,4,6-trichloropyrimidine.

LC-MS (ESI): m/z 214 [M + 1] +: 1.58 min (ret time).

D20

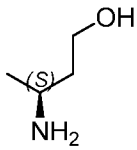
(S)-methyl 3-aminobutanoate



To a solution of (S)-3-aminobutanoic acid (6 g, 58.2 mmol) in methanol (100 mL) stirred under nitrogen at 0 °C was added $SOCl_2$ (13.84 g, 116 mmol) dropwise during 5 min. Then the reaction mixture was stirred for 16 h at 90 °C, concentrated to afford the title compound (6.6g) as a crude product.

D21

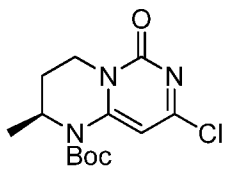
(S)-3-aminobutan-1-ol



The title compound was prepared by a procedure similar to that described for D17 starting from (S)-methyl 3-aminobutanoate.

D22

(S)-tert-butyl 8-chloro-2-methyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidine -1-carboxylate

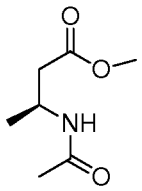


The title compound was prepared by a procedure similar to that described for D3 starting from (S)-3-aminobutan-1-ol and 2,4,6-trichloropyrimidine.

LC-MS (ESI): m/z 300 $[M+1]^+$; 1.06 min (ret time).

D23

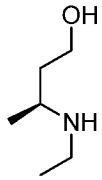
(S)-methyl 3-acetamidobutanoate



To a solution of (S)-methyl 3-aminobutanoate hydrochloride (5.5 g, 35.8 mmol) and DIEA (25.01 mL, 143 mmol) in dichloromethane (DCM) (100 mL) was added acetyl chloride (4.22 g, 53.7 mmol) under nitrogen at 0 °C, stirred at 25 °C overnight. The reaction mixture was quenched by addition of water (2 mL), then the organic phase was washed with brine, dried over Na_2SO_4, and concentrated to afford the title compound (4.0g) as a yellow oil.

D24

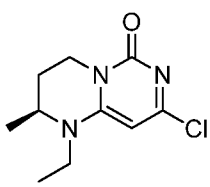
(S)-3-(ethylamino)butan-1-ol



To a solution of (S)-methyl 3-acetamidobutanoate (3.8 g, 23.87 mmol) in tetrahydrofuran (THF) (20 mL) was added $LiAlH_4$ (2.72 g, 71.6 mmol) portionwise under nitrogen at 0°C, and stirred at 90 °C overnight. The reaction mixture was cooled, quenched by addition of water (2.7 mL) followed by aq. 15% NaOH (2.7 mL) and water (5 mL). Then the mixture was stirred at r.t. for 2 h, filtered, and concentrated to afford the title compound as yellow oil.

D25

(S)-8-chloro-1-ethyl-2-methyl-3,4-dihydro-1H-pyrimido[1,6-a] pyrimidin-6(2H)-one

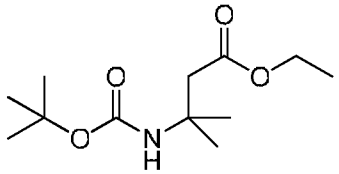


The title compound was prepared by a procedure similar to that described for D2 starting from (S)-3-(ethylamino)butan-1-ol and 2,4,6-trichloropyrimidine.

LC-MS (ESI): m/z 228 $[M+1]^+$; 0.97 min (ret time).

D26

ethyl 3-((tert-butoxycarbonyl)amino)-3-methylbutanoate

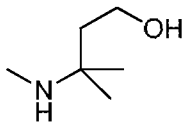


To a solution of ethyl 3-amino-3-methylbutanoate hydrochloride (10 g, 55.0 mmol), Boc_2O (14.06 mL, 60.6 mmol) in the mixed solvents of dichloromethane (DCM) (100 mL) and water (100 mL) was added potassium carbonate (15.22 g, 110 mmol), and stirred overnight. Then the organic phase was washed with water, brine and dried over Na_2SO_4, and concentrated to afford the title compound.

LC-MS (ESI): m/z 246 $[M+1]^+$; 3.20 min (ret time).

D27

3-methyl-3-(methylamino)butan-1-ol

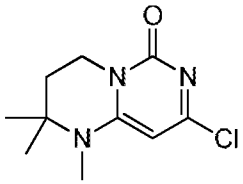


To a solution of ethyl 3-((tert-butoxycarbonyl) amino)-3-methylbutanoate (13.5 g, 55.0 mmol) in THF (100 mL) was added $LiAlH_4$ solution (2.0 M, 83 mL) dropwise at 0 °C. Then the reaction mixture was refluxed overnight, cooled to r.t., quenched by addition of water (4.5 mL), filtrated, and concentrated to afford the title compound (6.45 g).

LC-MS (ESI): m/z 118 $[M+1]^+$; 0.35 min (ret time).

D28

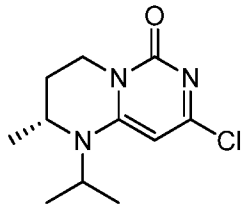
8-chloro-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one



The title compound was prepared by a procedure similar to that described for **D2** starting from **3-methyl-3-(methylamino)butan-1-ol** and 2,4,6-trichloropyrimidine.

D29

(R)-8-chloro-1-isopropyl-2-methyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

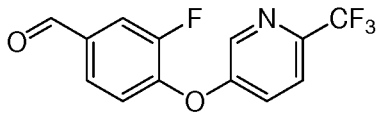


To a solution of 2-iodopropane (2299 mg, 13.52 mmol) and (R)-8-chloro-2-methyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one (0.957 mL, 4.51 mmol) in N,N-dimethylformamide (DMF) (15 mL) was added Cs_2CO_3 (2938 mg, 9.02 mmol). The reaction vessel was sealed and stirred for 2 h at 120 °C, and cooled. Purification via ISCO afforded the title compound (120 mg).

LC-MS (ESI): m/z 242 $[M+1]^+$; 0.65 min (ret time).

D30

3-fluoro-4-((6-(trifluoromethyl)-3-pyridinyl)oxy)benzaldehyde

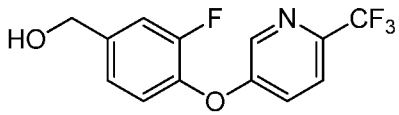


To a solution of 3,4-difluorobenzaldehyde (3.49 g, 24.53 mmol) and 6-(trifluoromethyl)pyridin-3-ol (4 g, 24.53 mmol) in DMF (50 mL) was added potassium carbonate (3.73 g, 27.0 mmol). The reaction mixture was stirred at 110 °C for 2h. The resultant mixture was extracted with EtOAc, washed with water, and concentrated to afford the title compound (6.9 g).

LC-MS (ESI): m/z 286$[M + 1]^+$, 1.10 min (ret time).

D31

(3-fluoro-4-((6-(trifluoromethyl)-3-pyridinyl)oxy)phenyl)methanol

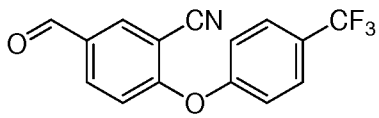


To a solution of 3-fluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)benzaldehyde (6.9 g, 24.19 mmol) in methanol (100 mL) was added $NaBH_4$ (1.098 g, 29.0 mmol), and stirred at rt for 2h. The reaction mixture was quenched by acetone and concentrated. The residue was purified via ISCO (DCM: MeOH =20:1) to afford the title compound (6 g).

LC-MS (ESI): m/z 288$[M + 1]^+$, 1.0 min (ret time).

D32

5-formyl-2-(4-(trifluoromethyl)phenoxy)benzonitrile

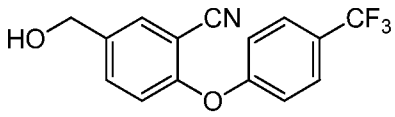


The title compound was prepared by a procedure similar to that described for D30 starting from 4-(trifluoromethyl)phenol and 2-fluoro-5-formylbenzonitrile.

LC-MS (ESI): m/z 292 $[M + 1]^+$; 0.99 min (ret time).

D33

5-(hydroxymethyl)-2-(4-(trifluoromethyl)phenoxy)benzonitrile

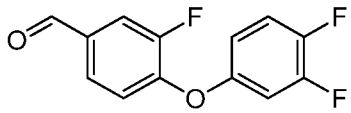


The title compound was prepared by a procedure similar to that described for D31 starting from 5-formyl-2-(4-(trifluoromethyl)phenoxy)benzonitrile.

LC-MS (ESI): m/z 294 $[M + 1]^+$; 1.11 min (ret time).

D34

4-(3, 4-fluorophenoxy)-3-fluoro-benzaldehyde

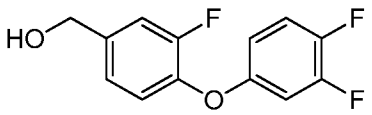


The title compound was prepared by a procedure similar to that described for D30 starting from 3,4-difluorophenol and 3,4-difluorobenzaldehyde.

LC-MS (ESI): m/z 253 $[M + 1]^+$; 1.24 min (ret time).

D35

(4-(3,4-fluorophenoxy)-3-fluorophenyl)methanol

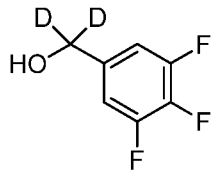


The title compound was prepared by a procedure similar to that described for D31 starting from 4-(3,4-difluorophenoxy)-3-fluorobenzaldehyde.

LC-MS (ESI): m/z 237 $[M -17]^+$; 1.01 min (ret time).

D36

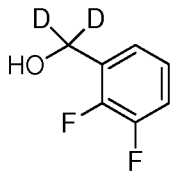
Dideutero(3,4,5-trifluorophenyl)methanol



To a solution of 3,4,5-trifluorobenzoic acid (500 mg, 2.84 mmol) in tetrahydrofuran (10 mL) was added $LiAlD_4$ (119 mg, 2.84 mmol) at 0 °C, stirred for 5 min at r.t. The resulted mixture was quenched, and concentrated. Purification via FC afforded the title compound (400 mg) as clear oil.
LC-MS (ESI): m/z 147 $[M-17]^+$; 2.81 (ret time).

D37

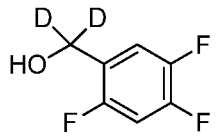
Dideutero(2,4,-difluorophenyl)methanol



The title compound was prepared by a procedure similar to that described for D36 starting from 2,3-difluorobenzoic acid.
LC-MS (ESI): m/z 129 $[M-17]^+$; 1.29 min (ret time).

D38

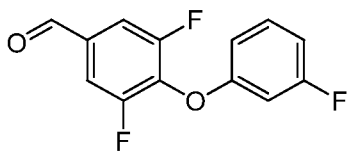
Dideutero(2,4,5-trifluorophenyl)methanol



The title compound was prepared by a procedure similar to that described for D36 starting from 2,4,5-trifluorobenzoic acid.
LC-MS (ESI): m/z 147 $[M-17]^+$; 2.15 min (ret time).

D39

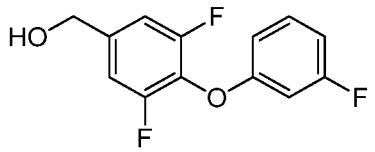
3,5-difluoro-4-(3-fluorophenoxy)benzaldehyde



The title compound was prepared by a procedure similar to that described for D30 starting from 3-fluorophenol and 3,4,5-trifluorobenzaldehyde.
LC-MS (ESI): m/z 253 $[M+1]^+$; 1.15 min (ret time).

D40

(3,5-difluoro-4-(3-fluorophenoxy)phenyl)methanol

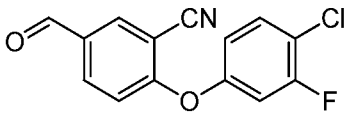


The title compound was prepared by a procedure similar to that described for D31 starting from 3,5-difluoro-4-(3-fluorophenoxy)benzaldehyde.

LC-MS (ESI): m/z 237 $[M -17]^+$; 1.06 min (ret time).

D41

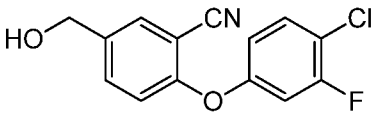
2-(4-chloro-3-fluorophenoxy)-5-(hydroxymethyl)benzonitrile



The title compound was prepared by a procedure similar to that described for D30 starting from 3-fluoro -4- chloro phenol and 2-fluoro-5-formylbenzonitrile.

LC-MS (ESI): m/z 276 $[M + 1]^+$; 1.12 min (ret time).

D42

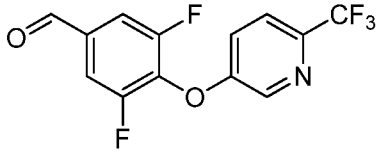


The title compound was prepared by a procedure similar to that described for D31 starting from 2-(4-chloro-3-fluorophenoxy)-5-formylbenzonitrile.

LC-MS (ESI): m/z 278 $[M + 1]^+$; 1.05 min (ret time).

D43

3,5-difluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)benzaldehyde



The title compound was prepared by a procedure similar to that described for D30 starting from 6-(trifluoromethyl)pyridin-3-ol and 3,4,5-trifluorobenzaldehyde.

LC-MS (ESI): m/z 304 $[M + 1]^+$; 0.80 min (ret time).

D44

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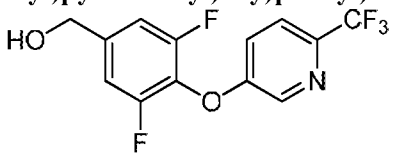
(3,5-difluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)phenyl)methanol

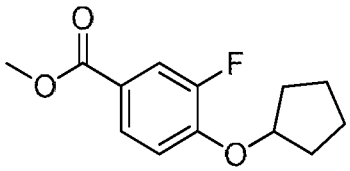


The title compound was prepared by a procedure similar to that described for **D31** starting from 3,5-difluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)benzaldehyde.

LC-MS (ESI): m/z 306 $[M + 1]^+$; 0.76 min (ret time).

D45

Methyl 4-(cyclopentyloxy)-3-fluorobenzoate

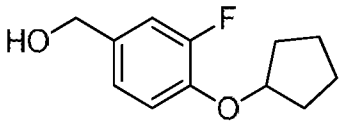


To a solution of methyl 3-fluoro-4-hydroxybenzoate (1 g, 5.88 mmol), cyclopentanol (1.60 mL, 17.63 mmol) and triphenylphosphine (4.62 g, 17.63 mmol) in tetrahydrofuran (THF) (20 mL) was added DIAD (2.86 mL, 14.69 mmol) at 0 °C. The reaction mixture was stirred at r.t. for 16 h, diluted with EtOAc (20 mL), washed with 1 N HCl (10 mL), brine (10 mL), dried over Na_2SO_4, and concentrated. Purification via FC afforded the title compound (700 mg).

^{1}HNMR ($CDCl_3$, 400 MHz) ppm: 7.82~7.68 (m, 2H), 6.96 (t, 1H, J = 8 Hz), 4.90~4.82 (m, 1H), 3.88 (s, 3H).

D46

4-(cyclopentyloxy)-3-fluorophenyl)methanol



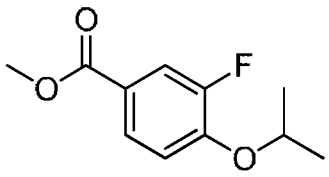
To a solution of methyl 4-(cyclopentyloxy)-3-fluorobenzoate (700 mg, 2.94 mmol) in tetrahydrofuran (THF) (10 mL) was added $LiAlH_4$ (112 mg, 2.94 mmol) at 0 °C, and stirred at 0 °C for 1 h. The reaction mixture was quenched by addition of water (0.24 mL), 0.12 mL of aq. 30% NaOH (0.12 mL), stirred at r.t. for 10 min., then was added 2 g of $MgSO_4$, filtered, and concentrated to afford the title compound (500 mg) as a yellow oil.

LC-MS (ESI): m/z 193 $[M-17]^+$; 1.12 (ret time).

D47

Methyl 4-(isopropyloxy)-3-fluorobenzoate

2014210260 06 Jul 2016

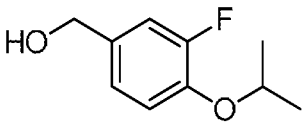


The title compound was prepared by a procedure similar to that described for **D45** starting from methyl 3-fluoro-4-hydroxybenzoate and isopropanol.

LC-MS (ESI): m/z 213 $[M + 1]^+$; 1.22 min (ret time).

D48

4-(isopropyloxy)-3-fluorophenyl)methanol

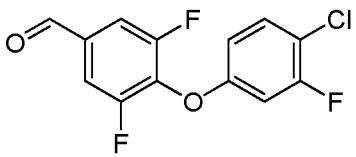


The title compound was prepared by a procedure similar to that described for **D46** starting from methyl 4-(isopropyloxy)-3-fluorobenzoate.

LC-MS (ESI): m/z 167 $[M - 17]^+$; 1.16 min (ret time).

D49

4-(4-chloro-3-fluorophenoxy)-3,5-difluorobenzaldehyde

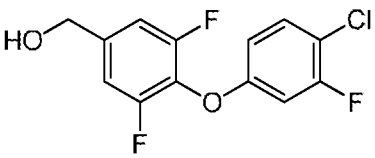


The title compound was prepared by a procedure similar to that described for **D30** starting from 4-chloro-3-fluorophenol and 3,4,5-trifluorobenzaldehyde.

LC-MS (ESI): m/z 287 $[M + 1]^+$; 1.31 min (ret time).

D50

(4-(4-chloro-3-fluorophenoxy)-3,5-difluorophenyl)methanol

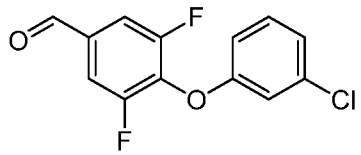


The title compound was prepared by a procedure similar to that described for **D31** starting from 4-(4-chloro-3-fluorophenoxy)-3,5-difluorobenzaldehyde.

LC-MS (ESI): m/z 271 $[M - 17]^+$; 1.19 min (ret time).

D51

4-(3-chlorophenoxy)-3,5-difluorobenzaldehyde

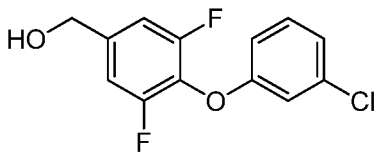


The title compound was prepared by a procedure similar to that described for D30 starting from 3-chlorophenol and 3,4,5-trifluorobenzaldehyde.

LC-MS (ESI): m/z 269 $[M + 1]^+$; 1.20 min (ret time).

D52

(4-(3-chlorophenoxy)-3,5-difluorophenyl)methanol

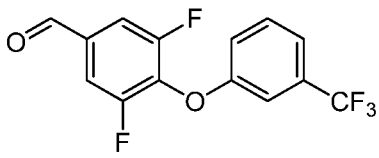


The title compound was prepared by a procedure similar to that described for D31 starting from 4-(3-chlorophenoxy)-3,5-difluorobenzaldehyde.

LC-MS (ESI): m/z 253 $[M - 17]^+$; 1.26 min (ret time).

D53

3,5-difluoro-4-(3-(trifluoromethyl)phenoxy)benzaldehyde

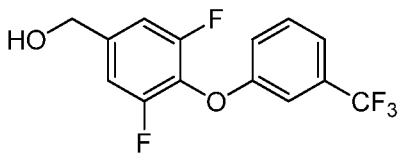


The title compound was prepared by a procedure similar to that described for D30 starting from 3-(trifluoromethyl)phenol and 3,4,5-trifluorobenzaldehyde.

LC-MS (ESI): m/z 303 $[M + 1]^+$; 1.28 min (ret time).

D54

(3,5-difluoro-4-(3-(trifluoromethyl)phenoxy)phenyl)methanol

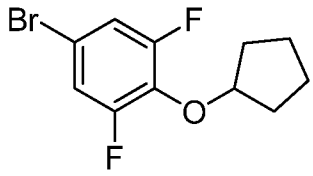


The title compound was prepared by a procedure similar to that described for D31 starting from 3,5-difluoro-4-(3-(trifluoromethyl)phenoxy)benzaldehyde.

^{1}HNMR ($CDCl_3$, 400 MHz): 7.43-7.31 (m, 2H), 7.16-7.03 (m, 4H), 4.71 (s, 2H).

D55

5-bromo-2-(cyclopentyloxy)-1,3-difluorobenzene

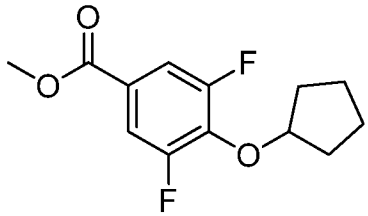


To a solution of 4-bromo-2,6-difluorophenol (5 g, 23.92 mmol), cyclopentanol (6.51 mL, 71.8 mmol) and triphenylphosphine (18.83 g, 71.8 mmol) in tetrahydrofuran (THF) (100 mL) was added DIAD (11.63 mL, 59.8 mmol) at 0 °C. The reaction mixture was stirred at r.t. for 16 h, diluted with EtOAc (100 mL), washed with 1 N HCl (50 mL), brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. Purification via FC afforded the title compound (4.55 g).

^{1}HNMR ($CDCl_3$, 400 MHz) ppm: 7.07 (td, 2H, J = 7.8 Hz, 5.6 Hz), 4.84~4.79 (m, 1H), 1.95~1.80 (m, 4H), 1.79~1.57 (m, 4H).

D56

methyl 4-(cyclopentyloxy)-3,5-difluorobenzoate

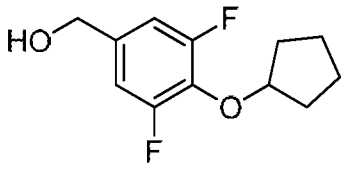


To a 1L autoclave was charged with 5-bromo-2-(cyclopentyloxy)-1,3-difluorobenzene (4.55 g, 16.42 mmol), MeOH (6.64 mL, 164 mmol), TEA (6.87 mL, 49.3 mmol), PdCl2(dppf) (1.20 g, 1.64 mmol) and N,N-dimethylformamide (DMF) (100 mL). The autoclave was sealed, evacuated, flushed with Ar three times, charged with CO to 1.2 MPa, and stirred at 90 °C for 16 h. The reaction mixture was concentrated in vacuo to remove DMF, diluted with EtOAc (50 mL), washed with water (20 mL×3), brine (20 mL), dried over Na_2SO_4, filtered and concentrated. Purification via FC afforded the title compound (300 mg) as colorless oil.

LC-MS (ESI): m/z 257 $[M + 1]^+$; 1.40 min (ret time).

D57

(4-(cyclopentyloxy)-3,5-difluorophenyl)methanol

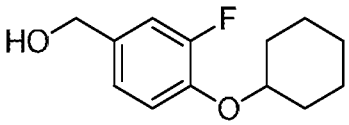


The title compound was prepared by a procedure similar to that described for **D46** starting from methyl 4-(cyclopentyloxy)-3,5-difluorobenzoate.

LC-MS (ESI): m/z 211 $[M - 17]^+$; 1.18 min (ret time).

D58

4-(cyclohexyloxy)-3-fluorophenyl)methanol

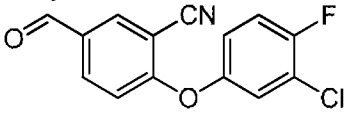


The title compound was prepared by a procedure similar to that described for **D46** starting from 3-fluoro-4-hydroxybenzoate and cyclohexanol.

LC-MS (ESI): m/z 225 $[M + 1]^+$; 1.18 min (ret time).

D59

2-(3-chloro-4-fluorophenoxy)-5-formylbenzonitrile

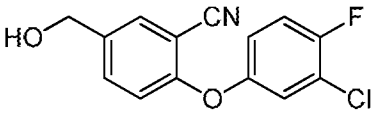


The title compound was prepared by a procedure similar to that described for **D30** starting from 3-chloro-4-fluorophenol and 2-fluoro-5-formylbenzonitrile.

LC-MS (ESI): m/z 276 $[M + 1]^+$; 3.31 min (ret time).

D60

2-(3-chloro-4-fluorophenoxy)-5-(hydroxymethyl)benzonitrile

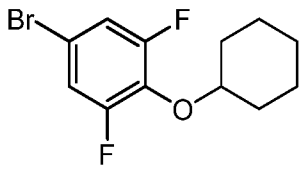


The title compound was prepared by a procedure similar to that described for **D31** starting from 2-(3-chloro-4-fluorophenoxy)-5-formylbenzonitrile.

LC-MS (ESI): m/z 278 $[M + 1]^+$; 3.02min (ret time).

D61

5-bromo-2-(cyclohexyloxy)-1,3-difluorobenzene

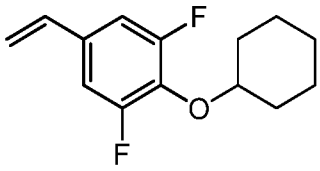


The title compound was prepared by a procedure similar to that described for D55 starting from 4-bromo-2,6-difluorophenol and cyclohexanol.

^{1}HNMR ($CDCl_3$, 400 MHz) ppm: 7.06 (dd, 2H, J = 6.8Hz, 0.8Hz), 2.00~1.92 (m, 2H), 1.89~1.76 (m, 2H), 1.68~1.50 (m, 3H), 1.40~1.25 (m, 3H).

D62

2-(cyclohexyloxy)-1,3-difluoro-5-vinylbenzene

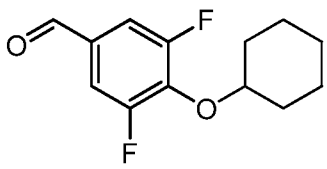


To a solution of 5-bromo-2-(cyclohexyloxy)-1,3-difluorobenzene (1 g, 3.43 mmol) and 2,4,6-trivinyl-1,3,5,2,4,6-trioxatriborinane (0.555 g, 3.43 mmol) in 1,4-dioxane (15 mL) were added sodium carbonate (0.728 g, 6.87 mmol) in water (3.75 mL) and $Pd(Ph_3P)_4$ (0.397 g, 0.343 mmol) under N_2. The reaction mixture was stirred at 100 °C for 16 h under N_2 atmosphere, cooled to r.t., diluted with EtOAc (50 mL), washed with water (20 mL×2), brine (30 mL), dried over Na_2SO_4, and concentrated. Purification via FC afforded the title compound (560 mg) as colorless oil.

^{1}HNMR ($CDCl_3$, 400 MHz) ppm: 6.93 (d, 2H, J = 9.2Hz), 6.56 (dd, 1H, J = 10.8Hz, 2.7Hz), 5.65 (d, 1H, J = 8.8Hz), 5.28 (d, 1H, J = 8.8Hz), 4.18~4.09 (m, 1H), 2.00~1.92 (m, 2H), 1.89~1.76 (m, 2H), 1.68~1.50 (m, 3H), 1.40~1.25 (m, 3H).

D63

4-(cyclohexyloxy)-3,5-difluorobenzaldehyde

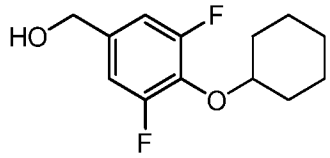


A solution of 2-(cyclohexyloxy)-1,3-difluoro-5-vinylbenzene (560 mg, 2.35 mmol) in dichloromethane (DCM) (15 mL) was cooled to -78 °C. O_3 was bubbled into the solution for 5 min, and stirred at -78 °C for 10 min. Then, the reaction mixture was bubbled with N_2, quenched with dimethylsulfane (9 g, 145 mmol), concentrated. The residue was diluted with EtOAc (10 mL), washed with water (5 mL×3), brine (5 mL), dried over Na_2SO_4, filtered and concentrated to afford the title compound (380 mg) as a colorless gum.

^{1}HNMR ($CDCl_3$, 400 MHz) ppm: 9.84 (s, 1H), 7.44 (d, 2H, J = 8.0 Hz), 4.44~4.36 (m, 1H), 2.00~1.92 (m, 2H), 1.89~1.76 (m, 2H), 1.68~1.50 (m, 3H), 1.40~1.25 (m, 3H).

D64

(4-(cyclohexyloxy)-3,5-difluorophenyl)methanol

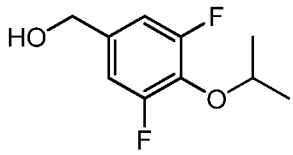


To a solution of 4-(cyclohexyloxy)-3,5-difluorobenzaldehyde (380 mg, 1.58 mmol) in tetrahydrofuran (THF) (20 mL) was added $LiAlH_4$ (60.0 mg, 1.58 mmol) at 0 °C, and stirred at 0 °C for 1 h. The reaction mixture was quenched by addition of water (0.2 mL), 0.1 mL of aq. 30% NaOH (0.1 mL), stirred at r.t. for 10 min, then was added 5 g of $MgSO_4$, filtered, and concentrated to afford the title compound (350 mg) as a pale yellow oil.

^{1}HNMR ($CDCl_3$, 400 MHz) ppm: 6.90 (td, 2H, J = 8.8 Hz, 5.6 Hz), 4.61 (s, 2H), 4.16~4.08 (m, 1H), 2.00~1.92 (m, 2H), 1.89~1.76 (m, 2H), 1.63~1.50 (m, 3H), 1.36~1.25 (m, 3H).

D65

(3,5-difluoro-4-isopropoxyphenyl)methanol

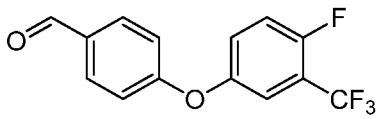


The title compound was prepared by a procedure similar to that described for D64 starting from 4-bromo-2,6-difluorophenol and propan-2-ol.

^{1}HNMR ($CDCl_3$, 400 MHz) ppm: 6.91 (d, 2H, J = 8.0Hz), 4.62 (d, 2H, J = 6.0Hz), 4.46~4.38 (m, 1H), 1.84 (t, 1H, J =10Hz), 1.34 (d, 6H, J = 6.2Hz).

D66

4-(4-fluoro-3-(trifluoromethyl)phenoxy)benzaldehyde

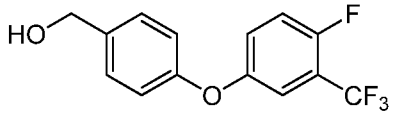


The title compound was prepared by a procedure similar to that described for D30 starting from 4-fluoro-3-(trifluoromethyl)phenol and 4-fluorobenzaldehyde.

LC-MS (ESI): m/z 285 $[M + 1]^+$; 0.80 min (ret time).

D67

(4-(4-fluoro-3-(trifluoromethyl)phenoxy)phenyl)methanol

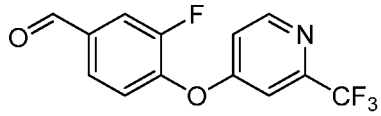


The title compound was prepared by a procedure similar to that described for D31 starting from 4-(4-fluoro-3-(trifluoromethyl)phenoxy)benzaldehyde.

LC-MS (ESI): m/z 269 $[M -17]^+$; 1.20 min (ret time).

D68

3-fluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)benzaldehyde

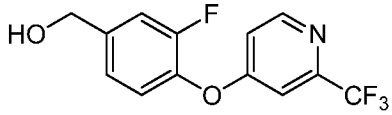


The title compound was prepared by a procedure similar to that described for D30 starting from 2-(trifluoromethyl)pyridin-4-ol and 3,4-difluorobenzaldehyde.

LC-MS (ESI): m/z 286 $[M + 1]^+$; 1.17 min (ret time).

D69

(3-fluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)phenyl)methanol

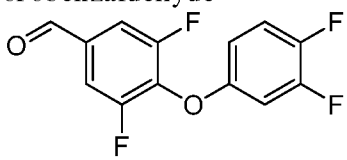


The title compound was prepared by a procedure similar to that described for D31 starting from 3-fluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)benzaldehyde.

LC-MS (ESI): m/z 288 $[M -17]^+$; 1.10 min (ret time).

D70

4-(3,4-difluorophenoxy)-3,5-difluorobenzaldehyde

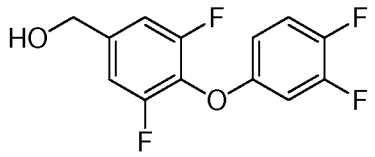


The title compound was prepared by a procedure similar to that described for D30 starting from 3,4-difluorophenol and 3,4,5-trifluorobenzaldehyde.

LC-MS (ESI): m/z 271 $[M + 1]^+$; 1.28 min (ret time).

D71

(4-(3,4-difluorophenoxy)-3,5-difluorophenyl)methanol

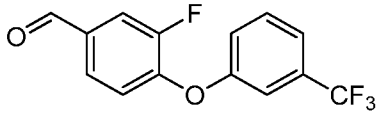


The title compound was prepared by a procedure similar to that described for D31 starting from 4-(3,4-difluorophenoxy)-3,5-difluorobenzaldehyde.

LC-MS (ESI): m/z 255 $[M -17]^+$; 0.78 min (ret time).

D72

3-fluoro-4-(3-(trifluoromethyl)phenoxy)benzaldehyde

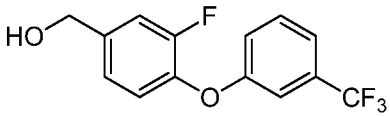


The title compound was prepared by a procedure similar to that described for D30 starting from 3-(trifluoromethyl)phenol and 3,4-difluorobenzaldehyde.

LC-MS (ESI): m/z 285 $[M + 1]^+$; 1.31 min (ret time).

D73

(3-fluoro-4-(3-(trifluoromethyl)phenoxy)phenyl)methanol

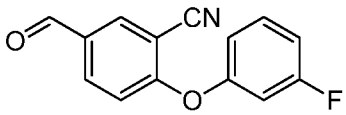


The title compound was prepared by a procedure similar to that described for D31 starting from 3-fluoro-4-(3-(trifluoromethyl)phenoxy)benzaldehyde.

LC-MS (ESI): m/z 269 $[M -17]^+$; 0.80 min (ret time).

D74

2-(3-fluorophenoxy)-5-formylbenzonitrile

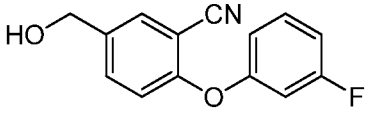


The title compound was prepared by a procedure similar to that described for D30 starting from 3-fluorophenol and 2-fluoro-5-formylbenzonitrile.

LC-MS (ESI): m/z 242 $[M + 1]^+$; 0.74 min (ret time).

D75

2-(3-fluorophenoxy)-5-(hydroxymethyl)benzonitrile

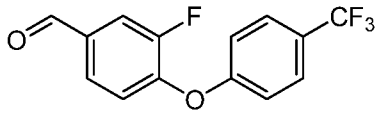


The title compound was prepared by a procedure similar to that described for D31 starting from 2-(3-fluorophenoxy)-5-formylbenzonitrile.

LC-MS (ESI): m/z 244 $[M+1]^+$; 0.70 min (ret time).

D76

3-fluoro-4-(4-(trifluoromethyl)phenoxy)benzaldehyde

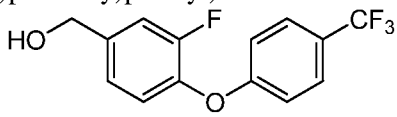


The title compound was prepared by a procedure similar to that described for D30 starting from 4-(trifluoromethyl)phenol and 3,4-difluorobenzaldehyde.

LC-MS (ESI): m/z 285 $[M+1]^+$; 1.26 min (ret time).

D77

(3-fluoro-4-(3-(trifluoromethyl)phenoxy)phenyl)methanol

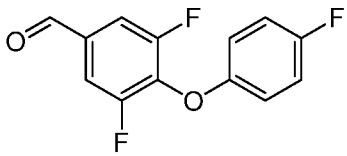


The title compound was prepared by a procedure similar to that described for D31 starting from 3-fluoro-4-(3-(trifluoromethyl)phenoxy)benzaldehyde.

LC-MS (ESI): m/z 287 $[M+1]^+$; 1.18 min (ret time).

D78

3,5-difluoro-4-(4-fluorophenoxy)benzaldehyde

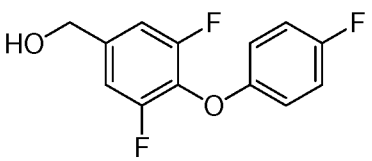


The title compound was prepared by a procedure similar to that described for D30 starting from 4-fluorophenol and 3,4,5-trifluorobenzaldehyde.

LC-MS (ESI): m/z 253 $[M+1]^+$; 1.19 min (ret time).

D79

(3,5-difluoro-4-(4-fluorophenoxy)phenyl)methanol

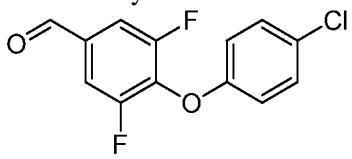


The title compound was prepared by a procedure similar to that described for D31 starting from 3,5-difluoro-4-(4-fluorophenoxy)benzaldehyde.

LC-MS (ESI): m/z 237 $[M -17]^+$; 1.06 min (ret time).

D80

4-(4-chlorophenoxy)-3,5-difluorobenzaldehyde

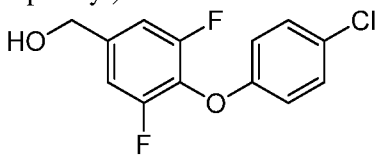


The title compound was prepared by a procedure similar to that described for D30 starting from 4-chlorophenol and 3,4,5-trifluorobenzaldehyde.

LC-MS (ESI): m/z 269 $[M + 1]^+$; 1.31 min (ret time).

D81

(4-(4-chlorophenoxy)-3,5-difluorophenyl)methanol

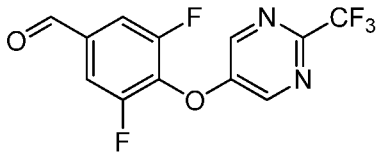


The title compound was prepared by a procedure similar to that described for D31 starting from 4-(4-chlorophenoxy)-3,5-difluorobenzaldehyde.

LC-MS (ESI): m/z 253 $[M -17]^+$; 1.22 min (ret time).

D82

3,5-difluoro-4-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)benzaldehyde

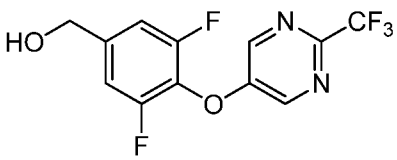


The title compound was prepared by a procedure similar to that described for D30 starting from 2-(trifluoromethyl)pyrimidin-5-ol and 3,4,5-trifluorobenzaldehyde.

LC-MS (ESI): m/z 305 $[M + 1]^+$; 0.78 min (ret time).

D83

(3,5-difluoro-4-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)phenyl)methanol

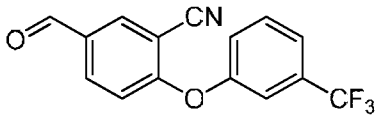


The title compound was prepared by a procedure similar to that described for **D31** starting from 3,5-difluoro-4-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)benzaldehyde.

LC-MS (ESI): m/z 307 $[M + 1]^+$; 0.78 min (ret time).

D84

5-formyl-2-(3-(trifluoromethyl)phenoxy)benzonitrile

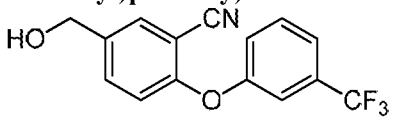


The title compound was prepared by a procedure similar to that described for **D30** starting from 3-(trifluoromethyl)phenol and 2-fluoro-5-formylbenzonitrile.

LC-MS (ESI): m/z 292 $[M + 1]^+$; 1.24 min (ret time).

D85

5-(hydroxymethyl)-2-(3-(trifluoromethyl)phenoxy)benzonitrile

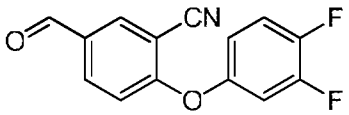


The title compound was prepared by a procedure similar to that described for **D31** starting from 5-formyl-2-(3-(trifluoromethyl)phenoxy)benzonitrile.

LC-MS (ESI): m/z 276 $[M -17]^+$; 1.18 min (ret time).

D86

2-(3,4-difluorophenoxy)-5-formylbenzonitrile

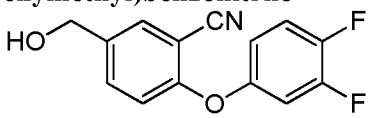


The title compound was prepared by a procedure similar to that described for **D30** starting from 3,4-difluorophenol and 2-fluoro-5-formylbenzonitrile.

LC-MS (ESI): m/z 260 $[M + 1]^+$; 1.18 min (ret time).

D87

2-(3,4-difluorophenoxy)-5-(hydroxymethyl)benzonitrile



The title compound was prepared by a procedure similar to that described for **D31** starting from 2-(3,4-difluorophenoxy)-5-formylbenzonitrile.

LC-MS (ESI): m/z 262 $[M +1]^+$; 1.11 min (ret time).

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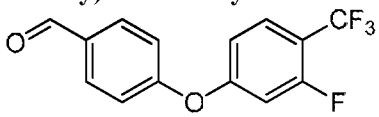
D88

4-(3-fluoro-4-(trifluoromethyl)phenoxy)benzaldehyde

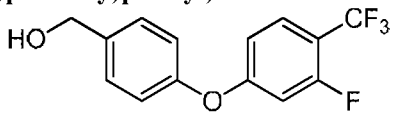


The title compound was prepared by a procedure similar to that described for **D30** starting from 3-fluoro-4-(trifluoromethyl)phenol and 4-fluorobenzaldehyde.

LC-MS (ESI): m/z 285 $[M + 1]^+$; 1.31 min (ret time).

D89

(4-(3-fluoro-4-(trifluoromethyl)phenoxy)phenyl)methanol

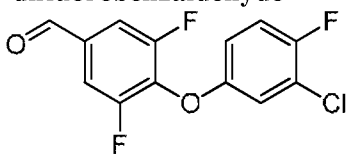


The title compound was prepared by a procedure similar to that described for **D31** starting from 4-(3-fluoro-4-(trifluoromethyl)phenoxy)benzaldehyde.

LC-MS (ESI): m/z 269 $[M -17]^+$; 1.25 min (ret time).

D90

4-(3-chloro-4-fluorophenoxy)-3,5-difluorobenzaldehyde

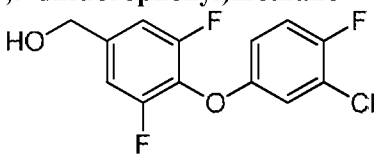


The title compound was prepared by a procedure similar to that described for **D30** starting from 3-chloro-4-fluorophenol and 3,4,5-trifluorobenzaldehyde.

LC-MS (ESI): m/z 287 $[M + 1]^+$; 1.32 min (ret time).

D91

(4-(3-chloro-4-fluorophenoxy)-3,5-difluorophenyl)methano



The title compound was prepared by a procedure similar to that described for **D31** starting from 4-(3-chloro-4-fluorophenoxy)-3,5-difluorobenzaldehyde.

LC-MS (ESI): m/z 271 $[M -17]^+$; 0.81 min (ret time).

D92

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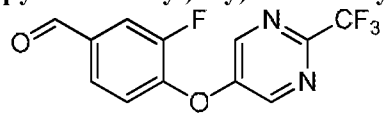
3-fluoro-4-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)benzaldehyde

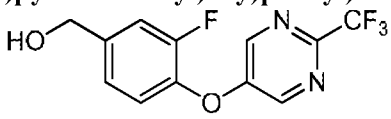


The title compound was prepared by a procedure similar to that described for **D30** starting from 2-(trifluoromethyl)pyrimidin-5-ol and 3,4-difluorobenzaldehyde.

LC-MS (ESI): m/z 287 $[M + 1]^+$; 1.16 min (ret time).

D93

(3-fluoro-4-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)phenyl)methanol

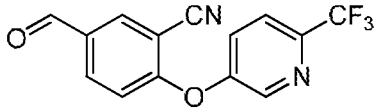


The title compound was prepared by a procedure similar to that described for **D31** starting from 3-fluoro-4-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)benzaldehyde.

LC-MS (ESI): m/z 289 $[M +1]^+$; 1.10 min (ret time).

D94

5-Formyl-2-[(6-(trifluoromethyl)3-pyridinyl)oxy]benzonitrile

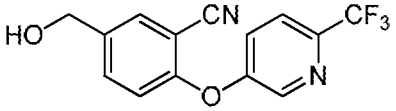


The title compound was prepared by a procedure similar to that described for **D30** starting from 2-fluoro-5-formylbenzonitrile and 6-(trifluoromethyl)-pyridin-3-ol.

LC-MS (ESI): m/z 293 $[M+1]^+$; 2.97 min (ret time).

D95

5-Hydroxymethyl-2-[(6-(trifluoromethyl)3-pyridinyl)oxy]benzonitrile

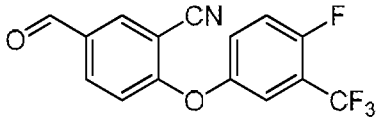


The title compound was prepared by a procedure similar to that described for **D31** starting from 5-Formyl-2-[(6-(trifluoromethyl)3-pyridinyl)oxy]benzonitrile .

LC-MS (ESI): m/z 295 $[M+1]^+$; 2.68 min (ret time).

D96

2-(4-fluoro-3-(trifluoromethyl)phenoxy)-5-formylbenzonitrile



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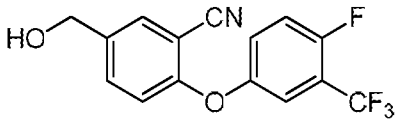
The title compound was prepared by a procedure similar to that described for **D30** starting from 2-fluoro-5-formylbenzonitrile and 4-fluoro-3-(trifluoromethyl)phenol.

LC-MS (ESI): m/z 310 $[M+1]^+$; 1.22 min (ret time).

D97

2-(4-fluoro-3-(trifluoromethyl)phenoxy)-5-(hydroxymethyl)benzonitrile

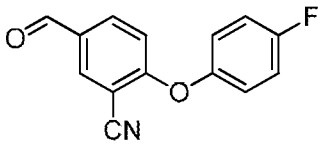


The title compound was prepared by a procedure similar to that described for **D31** starting from 2-(4-fluoro-3-(trifluoromethyl)phenoxy)-5-formylbenzonitrile.

LC-MS (ESI): m/z 312 $[M+1]^+$; 1.16 min (ret time).

D98

2-(4-fluorophenoxy)-5-formylbenzonitrile

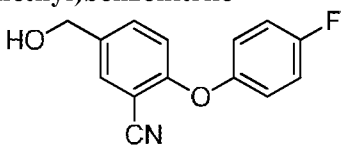


The title compound was prepared by a procedure similar to that described for **D30** starting from 2-fluoro-5-formylbenzonitrile and 4-fluorophenol.

LC-MS (ESI): m/z 242 $[M+1]^+$; 3.12 min (ret time).

D99

2-(4-fluorophenoxy)-5-(hydroxymethyl)benzonitrile

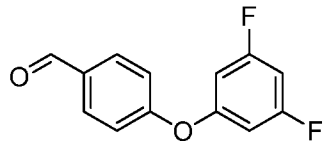


The title compound was prepared by a procedure similar to that described for **D31** starting from 2-(4-fluorophenoxy)-5-formylbenzonitrile.

LC-MS (ESI): m/z 244 $[M+1]^+$; 2.80 min (ret time).

D100

4-(3,5-difluorophenoxy)benzaldehyde

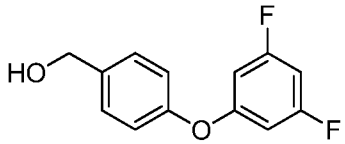


The title compound was prepared by a procedure similar to that described for D30 starting from 4-fluorobenzaldehyde and 3, 5-difluorophenol.

LC-MS (ESI): m/z 235 $[M+1]^+$; 1.13 min (ret time).

D101

(4-(3,5-difluorophenoxy)phenyl)methanol

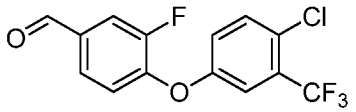


The title compound was prepared by a procedure similar to that described for D31 starting from 4-(3, 5-difluorophenoxy)benzaldehyde.

LC-MS (ESI): m/z 219 $[M-17]^+$; 1.08 min (ret time).

D102

4-(4-chloro-3-(trifluoromethyl)phenoxy)-3-fluorobenzaldehyde

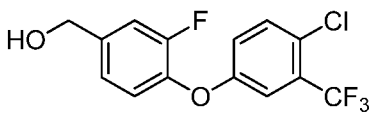


The title compound was prepared by a procedure similar to that described for D30 starting from 3, 4-difluorobenzaldehyde and 4-chloro-3-(trifluoromethyl)phenol.

LC-MS (ESI): m/z 319 $[M+1]^+$; 1.24 min (ret time).

D103

(4-(4-chloro-3-(trifluoromethyl)phenoxy)-3-fluorophenyl)methanol

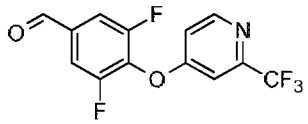


The title compound was prepared by a procedure similar to that described for D31 starting from 4-(4-chloro-3-(trifluoromethyl)phenoxy)-3-fluorobenzaldehyde.

LC-MS (ESI): m/z 303 $[M-17]^+$; 1.18 min (ret time).

D104

3,5-difluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)benzaldehyde

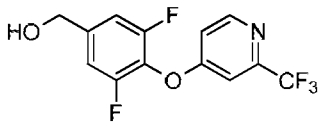


The title compound was prepared by a procedure similar to that described for **D30** starting from 2-(trifluoromethyl)pyridin-4-ol and 3,4,5-trifluorobenzaldehyde.

LC-MS (ESI): m/z 304 $[M + H]^+$; 1.17 min (ret time).

D105

(3,5-difluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)phenyl)methanol

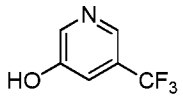


The title compound was prepared by a procedure similar to that described for **D31** starting from 3,5-difluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)benzaldehyde (D104).

LC-MS (ESI): m/z 306 $[M + H]^+$; 1.07 min (ret time).

D106

5-(trifluoromethyl)pyridin-3-ol

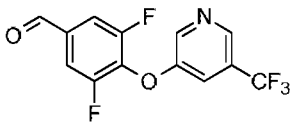


To a solution of 3-(benzyloxy)-5-(trifluoromethyl)pyridine (10 g, 39.5 mmol) in methanol (100 mL) was added Pd/C (0.500 g, 4.70 mmol). The reaction mixture was stirred at 50 °C under H_2 (55 psi) for 24 h, filtered and concentrated under reduce pressure to afford the crude product (2.5 g).

LC-MS (ESI): m/z 164 $[M + H]^+$; 0.51 min (ret time).

D107

3, 5-difluoro-4-((5-(trifluoromethyl)pyridin-3-yl)oxy)benzaldehyde

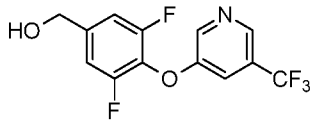


The title compound was prepared by a procedure similar to that described for **D30** starting from 5-(trifluoromethyl)pyridin-3-ol and 3,4,5-trifluorobenzaldehyde.

LC-MS (ESI): m/z 304 $[M + H]^+$; 0.83 min (ret time).

D108

(3, 5-difluoro-4-((5-(trifluoromethyl)pyridin-3-yl)oxy)phenyl)methanol

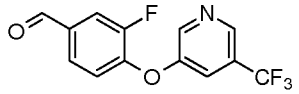


The title compound was prepared by a procedure similar to that described for D31 starting from 3, 5-difluoro-4-((5-(trifluoromethyl)pyridin-3-yl)oxy)benzaldehyde.

LC-MS (ESI): m/z 306 $[M + H]^+$; 0.79 min (ret time).

D109

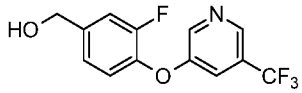
3-fluoro-4-((5-(trifluoromethyl)pyridin-3-yl)oxy)benzaldehyde



The title compound was prepared by a procedure similar to that described for D30 starting from 3,4-difluorobenzaldehyde and 5-(trifluoromethyl)pyridin-3-ol.

D110

(3-fluoro-4-((5-(trifluoromethyl)pyridin-3-yl)oxy)phenyl)methanol

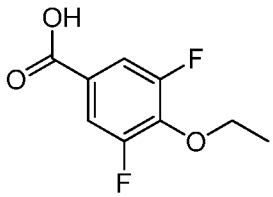


The title compound was prepared by a procedure similar to that described for D31 starting from 3-fluoro-4-((5-(trifluoromethyl)pyridin-3-yl)oxy)benzaldehyde.

LC-MS (ESI): m/z 288 $[M + H]^+$; 0.77 min (ret time).

D111

4-Ethoxy-3,5-difluorobenzoic acid

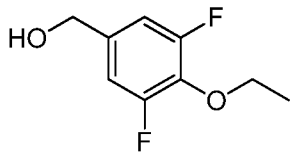


To a solution of 3,4,5-trifluorobenzoic acid (5.28 g, 3.0 mmol) and ethanol (1.38 g, 3 mmol) in DMF (50 mL) was added NaH (4.8 g, 12.0 mmol, 60% w/t in mineral oil) at 0 °C . Then, the reaction mixture was stirred for 1h, and then concentrated. The residue was dissolved in water and adjusted pH to lower than 7 with 1N HCl, and then extracted with EtOAc. The EtOAc solution was washed with brine, dried over sodium sulphate, and concentrated. The residue was purified by FC (PE/EtOAc =4:1) to afford the title compound (4.2 g, 69%) as a white solid.

^{1}H NMR (300MHz, CDCl3) δ: 7.67 (1H), 7.65 (1H), 4.37 (2H), 1.43 (3H).

D112

(4-Ethoxy-3,5-difluorophenyl)methanol

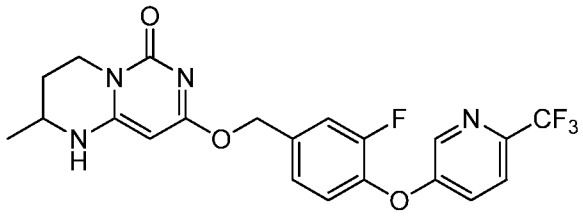


To a THF solution of BH_3 (1M) (20.0 mL, 20.0 mmol) was added 4-ethoxy-3,5-difluorobenzoic acid (2.02 g, 10.0 mmol) in THF (10 mL) dropwise at 0 °C. The reaction mixture was stirred under reflux for 3 h, quenched by methanol at 0 °C, and then concentrated. The residue was purified by prep HPLC to afford the title compound (1.1 g, 59%) as a colorless oil.

^{1}H NMR (300MHz, CDCl3) δ: 6.92 (1H), 6.90 (1H, s), 4.62 (2H, s), 4.19 (2H, q, J = 7.2 Hz), 1.38 (3H, t, J = 7.2Hz).

E1

8-((3-fluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)benzyl)oxy)-2-methyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

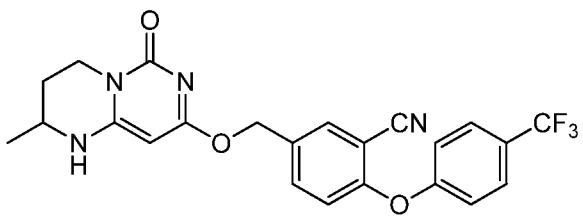


To a solution of (3-fluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)phenyl)methanol (96 mg, 0.33 mmol) in tetrahydrofuran (THF) (3 mL) was added sodium hydride (24.02 mg, 1.00 mmol) at -78 °C, stirred at 25 °C until there was no gas produced. Then tert-butyl 8-chloro-2-methyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidine-1-carboxylate (100 mg, 0.33 mmol) was charged at -78 °C, and stirred at 25 °C for 12 h. The reaction mixture was quenched by addition of water (1mL), and concentrated. Purification by pre-HPLC afforded the title compound (12 mg).

LC-MS (ESI): m/z 451 $[M+1]^+$; 0.95 (ret time).

E2

5-(((2-methyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidin-8-yl)oxy)methyl)-2-(4-(trifluoromethyl)phenoxy)benzonitrile

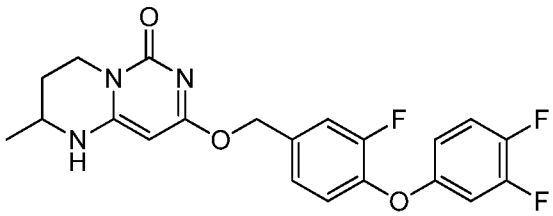


The title compound was prepared by a procedure similar to that described for E1 starting from 5-(hydroxymethyl)-2-(4-(trifluoromethyl)phenoxy)benzonitrile and tert-butyl 8-chloro-2-methyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidine-1-carboxylate.

LC-MS(ESI): m/z 457 $[M+1]^+$; 0.99 min (ret time).

E3

8-((4-(3,4-difluorophenoxy)-3-fluorobenzyl)oxy)-2-methyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

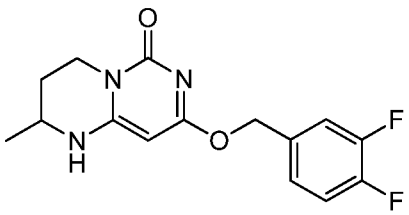


The title compound was prepared by a procedure similar to that described for E1 starting from (4-(3,4-fluorophenoxy)-3-fluorophenyl)methanol and tert-butyl 8-chloro-2-methyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidine-1-carboxylate.

LC-MS(ESI): m/z 386 $[M+1]^+$; 0.97 min (ret time).

E4

8-((3,4-difluorobenzyl)oxy)-2-methyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

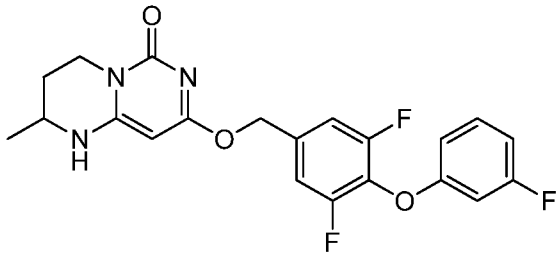


The title compound was prepared by a procedure similar to that described for E1 starting from (3,4-difluorophenyl)methanol and tert-butyl 8-chloro-2-methyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidine-1-carboxylate.

LC-MS(ESI): m/z 308 $[M+1]^+$; 0.72 min (ret time).

E5

8-((3,5-difluoro-4-(3-fluorophenoxy)benzyl)oxy)-2-methyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

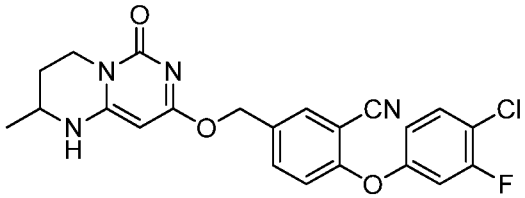


The title compound was prepared by a procedure similar to that described for E1 starting from (3,5-difluoro-4-(3-fluorophenoxy)phenyl)methanol and tert-butyl 8-chloro-2-methyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidine-1-carboxylate.

LC-MS(ESI): m/z 418 $[M+1]^+$; 0.97 min (ret time).

E6

2-(4-chloro-3-fluorophenoxy)-5-(((2-methyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidin-8-yl)oxy)methyl)benzonitrile

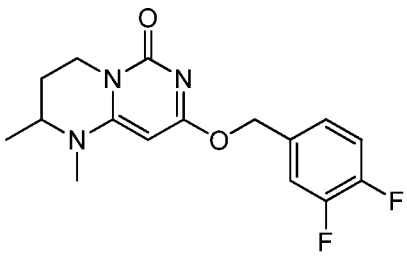


The title compound was prepared by a procedure similar to that described for E1 starting from 2-(4-chloro-3-fluorophenoxy)-5-(hydroxymethyl)benzonitrile and tert-butyl 8-chloro-2-methyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidine-1-carboxylate.

LC-MS(ESI): m/z 442 $[M+1]^+$; 1.13 min (ret time).

E7

8-((3,4-difluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

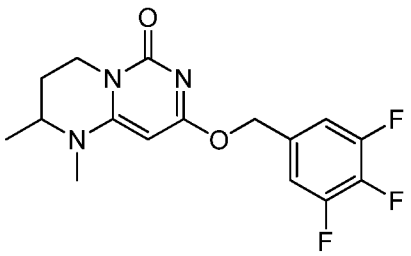


The title compound was prepared by a procedure similar to that described for E1 starting from 8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one and (3, 4-difluoro phenyl) methanol.

LC-MS (ESI): m/z 322 $[M+1]^+$: 3.30 min (ret time).

E8

1,2-dimethyl-8-((3,4,5-trifluorobenzyl)oxy)-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

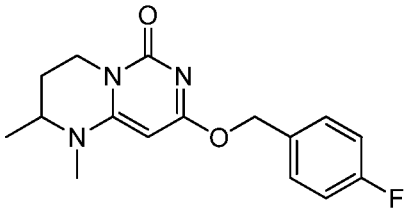


The title compound was prepared by a procedure similar to that described for E1 starting from 8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one and (3,4,5-trifluoro phenyl)methanol.

LC-MS (ESI): m/z 340 $[M+1]^+$: 2.21min (ret time).

E9

8-((4-fluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

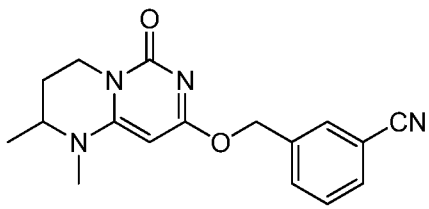


The title compound was prepared by a procedure similar to that described for E1 starting from 8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one and (3, 4, 5-trifluoro phenyl) methanol.

LC-MS (ESI): m/z 304 $[M+1]^+$: 2.00min (ret time).

E10

3-(((1,2-dimethyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidin-8-yl)oxy)methyl) benzonitrile

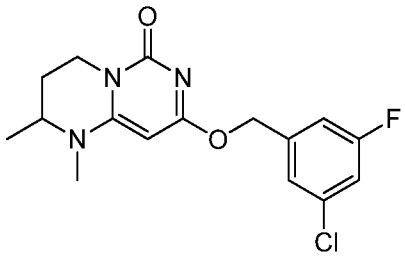


The title compound was prepared by a procedure similar to that described for E1 starting from 8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one and 3-(hydroxyl methyl)benzonitrile.

LC-MS (ESI): m/z 311 $[M+1]^+$: 2.99min (ret time).

E11

8-((3-chloro-5-fluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

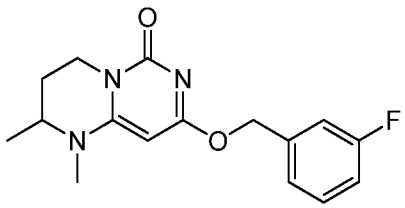


The title compound was prepared by a procedure similar to that described for E1 starting from 8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one and (3-chloro-5-fluoro phenyl)methanol.

LC-MS (ESI): m/z 338 $[M+1]^+$: 3.55min (ret time).

E12

8-((3-fluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

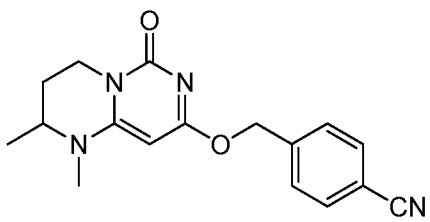


The title compound was prepared by a procedure similar to that described for E1 starting from 8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one and (3-fluorophenyl) methanol.

LC-MS (ESI): m/z 304 $[M+1]^+$: 3.22min (ret time).

E13

4-(((1,2-dimethyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidin-8-yl)oxy)methyl) benzonitrile

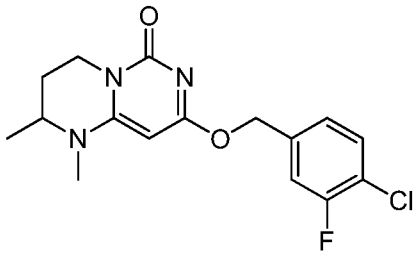


The title compound was prepared by a procedure similar to that described for E1 starting from 8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one and 4-(hydroxymethyl) benzonitrile.

LC-MS (ESI): m/z 311 $[M+1]^+$: 2.96 min (ret time).

E14

8-((4-chloro-3-fluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

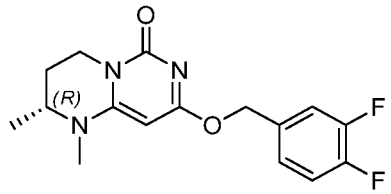


The title compound was prepared by a procedure similar to that described for E1 starting from 8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one and (4-chloro-3-fluoro phenyl)methanol.

LC-MS (ESI): m/z 311 $[M+1]^+$: 2.96 min (ret time).

E15

(R)-8-((3,4-difluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one



To a solution of (3,4-difluorophenyl)methanol (40.5 mg, 0.281 mmol) in tetrahydrofuran (THF) (3 mL) was added sodium hydride (33.7 mg, 0.842 mmol) dropwise at 0 °C, stirred for 30 min, and then was added (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one (60 mg, 0.28 mmol). The reaction mixture was stirred at r.t. for 1h, and concentrated. Purification via pre-TLC afforded the title compound (45 mg).

LC-MS (ESI): m/z 322 $[M+1]^+$; 0.84 (ret time).

E16

(R)-1,2-dimethyl-8-((3,4,5-trifluorobenzyl)oxy)-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

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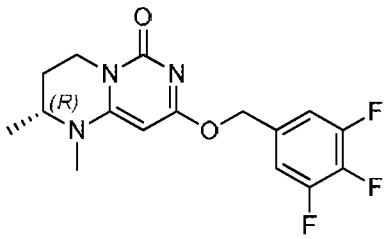
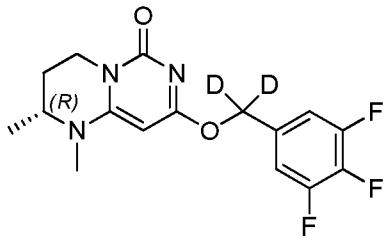


The title compound was prepared by a procedure similar to that described for **E15** starting from (3,4,5-trifluorophenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 340 $[M+1]^+$; 0.89 min (ret time).

E17

(R)-1,2-dimethyl-8-((3,4,5-trifluorophenyl)dideuteromethoxy)-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

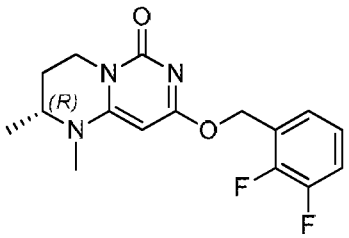


The title compound was prepared by a procedure similar to that described for **E15** starting from dideutero(3,4,5-trifluorophenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 342 $[M+1]^+$; 2.24 min (ret time).

E18

(R)-8-((2,3-difluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

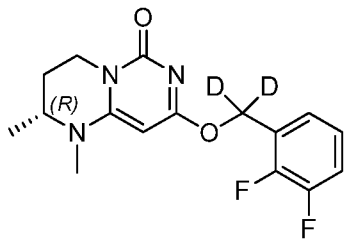


The title compound was prepared by a procedure similar to that described for **E15** starting from (2,3-difluorophenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 322 $[M+1]^+$; 0.83 min (ret time).

E19

(R)-8-((2,3-difluorophenyl)dideuteromethoxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

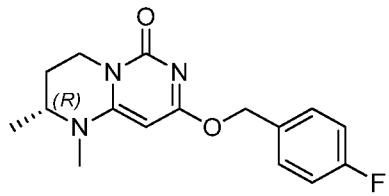


The title compound was prepared by a procedure similar to that described for E15 starting from (2, 3-difluoro phenyl)dideuteromethanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 324 $[M+1]^+$; 2.42 min (ret time).

E20

(R)-8-((4-fluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

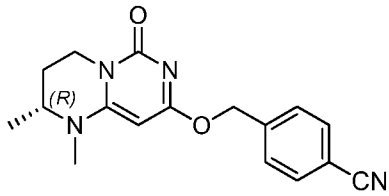


The title compound was prepared by a procedure similar to that described for E15 starting from (4-fluorophenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 304 $[M+1]^+$; 0.80 min (ret time).

E21

(R)-4-(((1,2-dimethyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidin-8-yl)oxy) methyl)benzonitrile

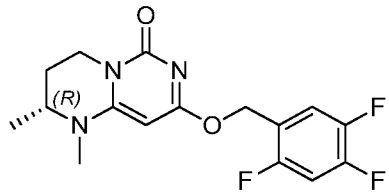


The title compound was prepared by a procedure similar to that described for E15 starting from 4-(hydroxymethyl)benzonitrile and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 311 $[M+1]^+$; 0.75 min (ret time).

E22

(R)-1,2-dimethyl-8-((2,4,5-trifluorobenzyl)oxy)-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

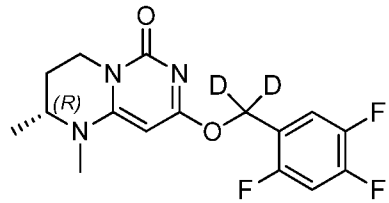


The title compound was prepared by a procedure similar to that described for E15 starting from (2,4,5-trifluorophenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 340 $[M+1]^+$; 0.86 min (ret time).

E23

(R)-8-(dideutero(2,4,5-trifluorophenyl)methoxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido [1,6-a]pyrimidin-6(2H)-one

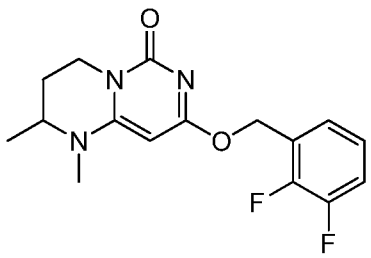


The title compound was prepared by a procedure similar to that described for E15 starting from dideutero(2,4,5-trifluorophenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 342 $[M+1]^+$; 2.2 min (ret time).

E24

8-((2,3-difluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

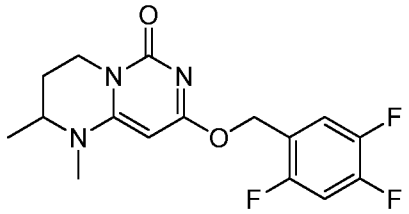


The title compound was prepared by a procedure similar to that described for E1 starting from 8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one and (2,3-difluorophenyl)methanol.

LC-MS (ESI): m/z 322 $[M+1]^+$: 3.29 min (ret time).

E25

1,2-dimethyl-8-((2,4,5-trifluorobenzyl)oxy)-3,4-dihydro-1H-pyrimido[1,6-a] pyrimidin-6(2H)-one

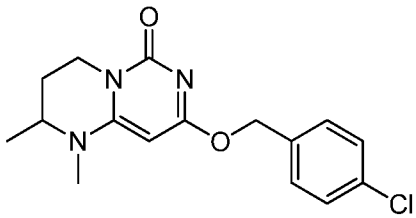


The title compound was prepared by a procedure similar to that described for E1 starting from 8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one and (2,4,5-trifluorophenyl)methanol.

LC-MS (ESI): m/z 340 $[M+1]^+$: 3.40 min (ret time).

E26

8-((4-chlorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

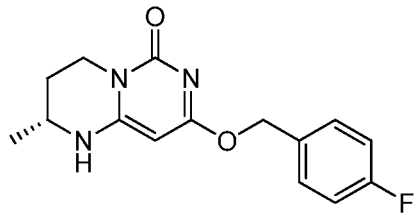


The title compound was prepared by a procedure similar to that described for E1 starting from 8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one and (4-chlorophenyl) methanol.

LC-MS (ESI): m/z 320 $[M+1]^+$: 3.45 min (ret time).

E27

(R)-8-((4-fluorobenzyl)oxy)-2-methyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

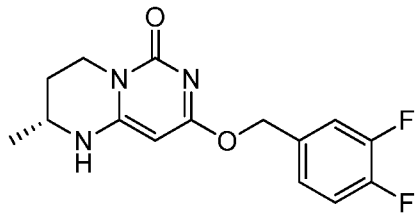


The title compound was prepared by a procedure similar to that described for E1 starting from (4-fluorophenyl)methanol and (R)-tert-butyl 8-chloro -2-methyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidine- 1-carboxylate.

LC-MS(ESI): m/z 290 $[M+1]^+$; 1.49 min (ret time).

E28

(R)-8-((3,4-difluorobenzyl)oxy)-2-methyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

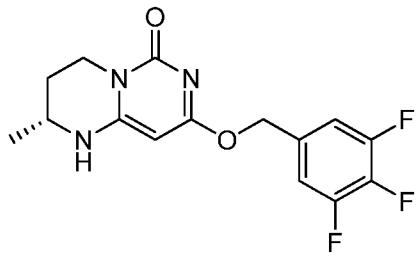


The title compound was prepared by a procedure similar to that described for E1 starting from (3,4-difluorophenyl)methanol and (R)-tert-butyl 8-chloro -2-methyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidine-1-carboxylate.

LC-MS(ESI): m/z 308 $[M+1]^+$; 1.58 min (ret time).

E29

(R)-2-methyl-8-((3,4,5-trifluorobenzyl)oxy)-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

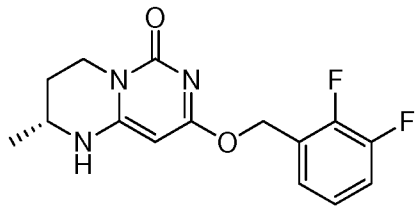


The title compound was prepared by a procedure similar to that described for E1 starting from (3,4,5-trifluorophenyl)methanol and (R)-tert-butyl 8-chloro -2-methyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidine- 1-carboxylate.

LC-MS(ESI): m/z 326 $[M+1]^+$; 1.66 min (ret time).

E30

(R)-8-((2,3-difluorobenzyl)oxy)-2-methyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

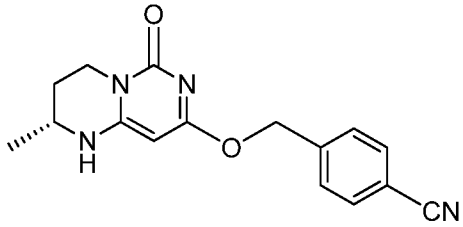


The title compound was prepared by a procedure similar to that described for E1 starting from (2,3-difluorophenyl)methanol and (R)-tert-butyl- 8-chloro -2-methyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidine- 1-carboxylate.

LC-MS(ESI): m/z 308 $[M+1]^+$; 1.55 min (ret time).

E31

(R)-4-(((2-methyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidin-8-yl)oxy)methyl)benzonitrile

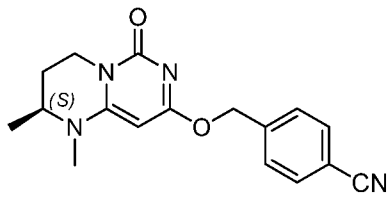


The title compound was prepared by a procedure similar to that described for E1 starting from 4-(hydroxymethyl)benzonitrile and (R)-tert-butyl 8-chloro -2-methyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidine- 1-carboxylate.

LC-MS(ESI): m/z 297 $[M+1]^+$; 1.41 min (ret time).

E32

(S)-4-(((1,2-dimethyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidin-8-yl)oxy) methyl)benzonitrile

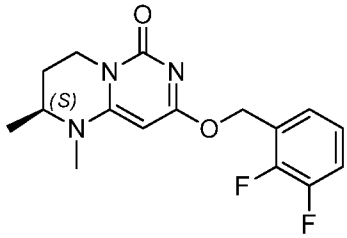


The title compound was prepared by a procedure similar to that described for E1 starting from 4-(hydroxymethyl)benzonitrile and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 311 $[M+1]^+$; 0.97 min (ret time).

E33

(S)-8-((2,3-difluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

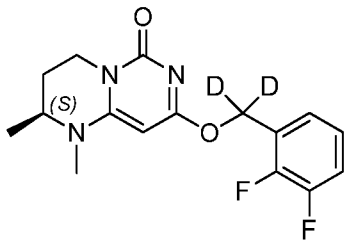


The title compound was prepared by a procedure similar to that described for E1 starting from (2,3-difluorophenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido [1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 322 $[M+1]^+$; 0.84 min (ret time).

E34

(S)-8-((2,3-difluorophenyl)dideuteromethoxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

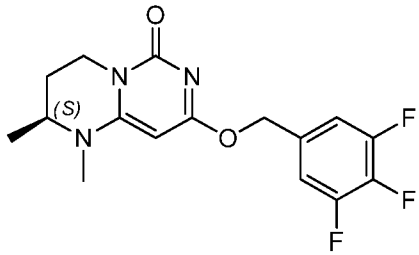


The title compound was prepared by a procedure similar to that described for E1 starting from (2,3-difluorophenyl)dideuteromethanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 324 $[M+1]^+$; 2.39 min (ret time).

E35

(S)-1,2-dimethyl-8-((3,4,5-trifluorobenzyl)oxy)-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

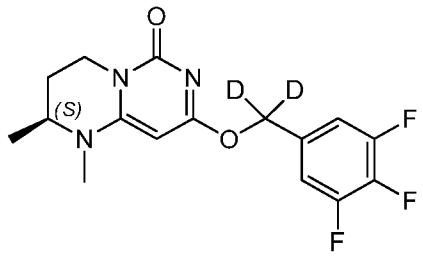


The title compound was prepared by a procedure similar to that described for E1 starting from (3,4,5-trifluorophenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 340 $[M+1]^+$; 0.90 min (ret time).

E36

(S)-8-(dideutero(3,4,5-trifluorophenyl)methoxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

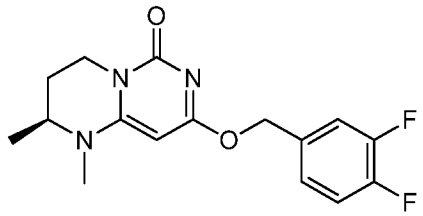


The title compound was prepared by a procedure similar to that described for E1 starting from dideutero(3,4,5-trifluorophenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 342 $[M+1]^+$; 2.26 min (ret time).

E37

(S)-8-((3,4-difluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

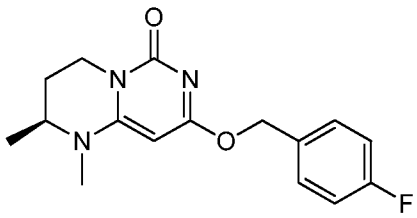


The title compound was prepared by a procedure similar to that described for E1 starting from (3,4-difluorophenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 322 $[M+1]^+$; 0.86 min (ret time).

E38

(S)-8-((4-fluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

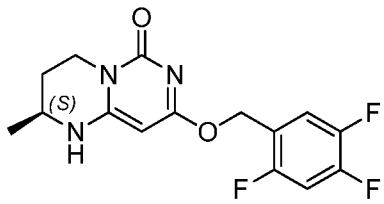


The title compound was prepared by a procedure similar to that described for E1 starting from (4-fluorophenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 304 $[M+1]^+$; 1.29 min (ret time).

E39

(S)-2-methyl-8-((2,4,5-trifluorobenzyl)oxy)-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

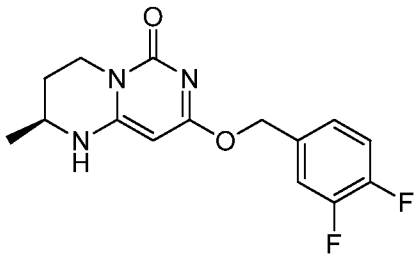


The title compound was prepared by a procedure similar to that described for E1 starting from (2,4,5-trifluorophenyl)methanol and (S)-tert-butyl 8-chloro-2-methyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidine-1-carboxylate.

LC-MS(ESI): m/z 326 $[M+1]^+$; 0.81 min (ret time).

E40

(S)-8-((3,4-difluorobenzyl)oxy)-2-methyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

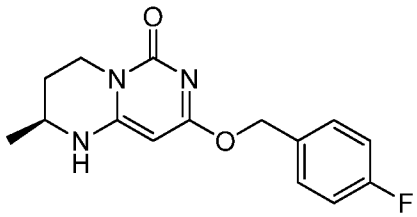


The title compound was prepared by a procedure similar to that described for E1 starting from (3,4-difluorophenyl)methanol and (S)-tert-butyl 8-chloro-2-methyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidine-1-carboxylate.

LC-MS(ESI): m/z 308 $[M+1]^+$; 1.58 min (ret time).

E41

(S)-8-((4-fluorobenzyl)oxy)-2-methyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

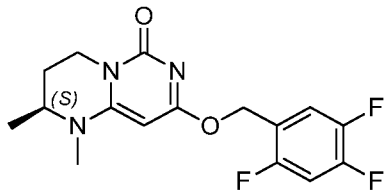


The title compound was prepared by a procedure similar to that described for E1 starting from (4-fluorophenyl)methanol and (S)-tert-butyl 8-chloro-2-methyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidine-1-carboxylate.

LC-MS(ESI): m/z 290 $[M+1]^+$; 0.77 min (ret time).

E42

(S)-1,2-dimethyl-8-((2,4,5-trifluorobenzyl)oxy)-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

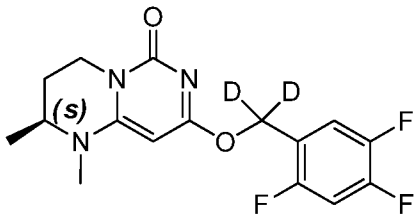


The title compound was prepared by a procedure similar to that described for E1 starting from (2,4,5-trifluorophenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 341 $[M+1]^+$; 0.86 min (ret time).

E43

(S)-8-(dideutero(2,4,5-trifluorophenyl)methoxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

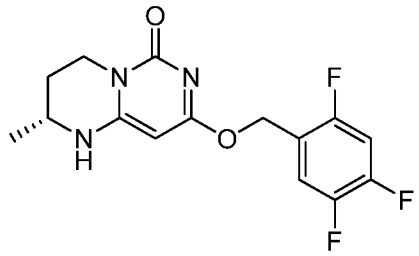


The title compound was prepared by a procedure similar to that described for E1 starting from dideutero(2,4,5-trifluorophenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 342 $[M+1]^+$; 2.16 min (ret time).

E44

(R)-2-methyl-8-((2,4,5-trifluorobenzyl)oxy)-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

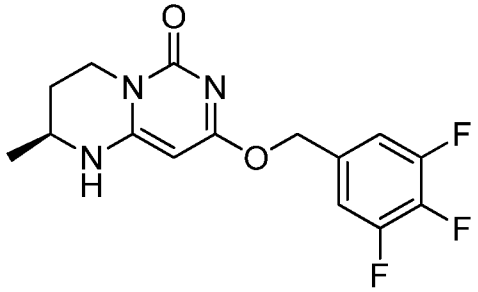


The title compound was prepared by a procedure similar to that described for E1 starting from (2,4,5-trifluorophenyl)methanol and (R)-tert-butyl 8-chloro-2-methyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidine-1-carboxylate.

LC-MS(ESI): m/z 326 $[M+1]^+$; 1.61 min (ret time).

E45

(S)-2-methyl-8-((3,4,5-trifluorobenzyl)oxy)-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

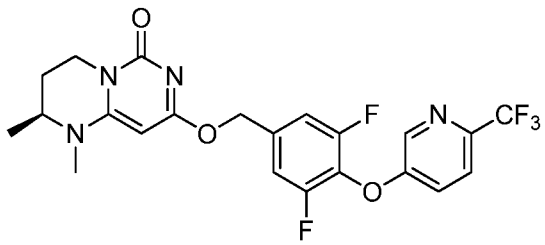


The title compound was prepared by a procedure similar to that described for E1 starting from (3,4,5-trifluorophenyl) methanol and (S)-tert-butyl 8-chloro-2-methyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidine-1-carboxylate.

LC-MS(ESI): m/z 326 $[M+1]^+$; 1.67 min (ret time).

E46

(S)-8-((3,5-difluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)benzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

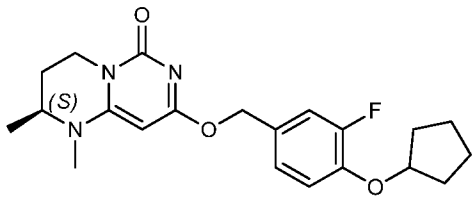


The title compound was prepared by a procedure similar to that described for E1 starting from (3,5-difluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)phenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 483 $[M+1]^+$; 2.82 min (ret time).

E47

(S)-8-((4-(cyclopentyloxy)-3-fluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

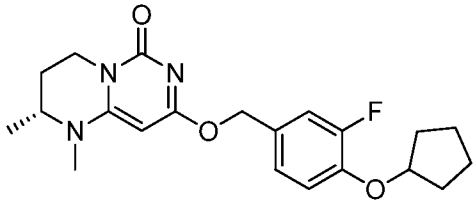


The title compound was prepared by a procedure similar to that described for E1 starting from (4-(cyclopentyloxy)-3-fluorophenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 388 $[M+1]^+$; 1.01 min (ret time).

E48

(R)-8-((4-(cyclopentyloxy)-3-fluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

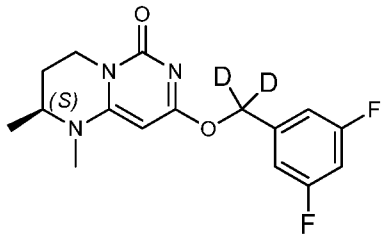


The title compound was prepared by a procedure similar to that described for E1 starting from (4-(cyclopentyloxy)-3-fluorophenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 388 $[M+1]^+$; 1.23 min (ret time).

E49

(S)-8-((3,5-difluorophenyl)dideuteromethoxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

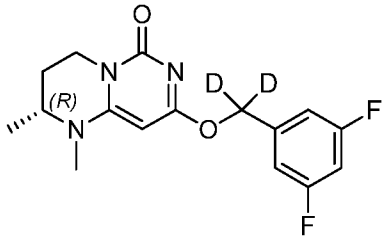


The title compound was prepared by a procedure similar to that described for E1 starting from (3,5-difluoro-phenyl)dideuteromethanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 324 $[M+1]^+$; 2.14 min (ret time).

E50

(R)-8-((3,5-difluorophenyl)dideuteromethoxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

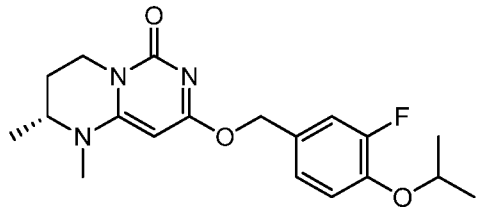


The title compound was prepared by a procedure similar to that described for E1 starting from (3,5-difluoro-phenyl)dideuteromethanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 324 $[M+1]^+$; 2.14 min (ret time).

E51

(R)-8-((3-fluoro-4-isopropoxybenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

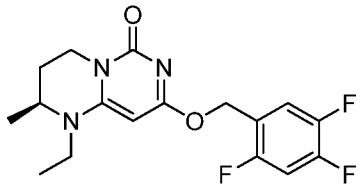


The title compound was prepared by a procedure similar to that described for E1 starting from (3-fluoro-4-isopropoxyphenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 362 $[M+1]^+$; 1.14 min (ret time).

E52

(S)-1-ethyl-2-methyl-8-((2,4,5-trifluorobenzyl)oxy)-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

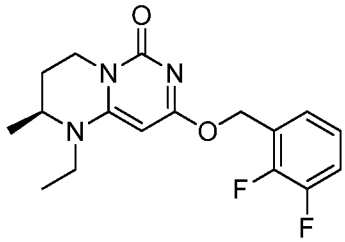


The title compound was prepared by a procedure similar to that described for E1 starting from (2,4,5-trifluorophenyl) methanol and (S)-8-chloro-1-ethyl-2-methyl-3,4-dihydro-1H-pyrimido[1,6-a] pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 354 $[M+1]^+$; 1.83 min (ret time).

E53

(S)-8-((2,3-difluorobenzyl)oxy)-1-ethyl-2-methyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

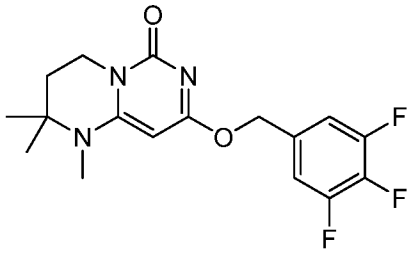


The title compound was prepared by a procedure similar to that described for E1 starting from (2,3-difluorophenyl)methanol and (S)-8-chloro-1-ethyl-2-methyl-3,4-dihydro-1H-pyrimido [1,6-a] pyrimidin-6(2H)- one.

LC-MS(ESI): m/z 336 $[M+1]^+$; 1.77 min (ret time).

E54

1,2,2-trimethyl-8-((3,4,5-trifluorobenzyl)oxy)-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

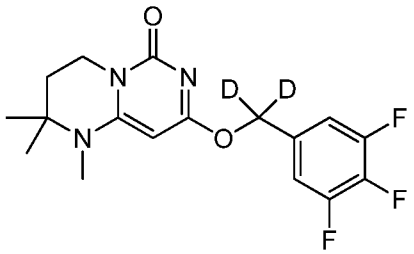


The title compound was prepared by a procedure similar to that described for E1 starting from (3,4,5-trifluoro-phenyl)methanol and 8-chloro-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido [1,6-a] pyrimidin-6(2H)-one and (3,4,5-trifluoro-phenyl)methanol.

LC-MS(ESI): m/z 354 $[M+1]^+$; 2.52 min (ret time).

E55

8-(dideutero(3,4,5-trifluorophenyl)methoxy)-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

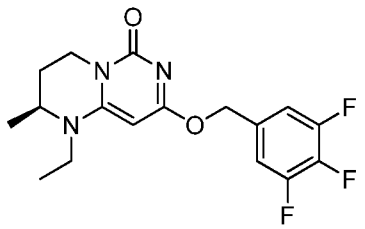


The title compound was prepared by a procedure similar to that described for E1 starting from dideutero(3,4,5-trifluorophenyl)methanol and 8-chloro-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one and (3,4,5-trifluoro-phenyl)methanol.

LC-MS(ESI): m/z 356 $[M+1]^+$; 2.48 min (ret time).

E56

(S)-1-ethyl-2-methyl-8-((3,4,5-trifluorobenzyl)oxy)-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

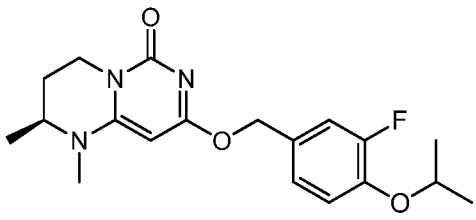


To a solution of (3,4,5-trifluorophenyl)methanol (214 mg, 1.32 mmol) in tetrahydrofuran(THF) (15 mL) was added sodium hydride (105 mg, 2.64 mmol) at 0°C, then (S)-8-chloro-1-ethyl-2-methyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)- one(300 mg, 1.32 mmol) was added, and stirred for 2 h at 25 °C. The reaction mixture was quenched by addition of water (2 mL), and diluted with EtOAc (15 mL). The organic phase was washed with brine, dried over sodium sulphate, and concentrated. Purification by PreTLC (DCM /MeOH =10/1 afforded the title compound (66 mg) as a white solid.

LC-MS(ESI): m/z 354 $[M+1]^+$; 1.87 min (ret time).

E57

(S)-8-((3-fluoro-4-isopropoxybenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

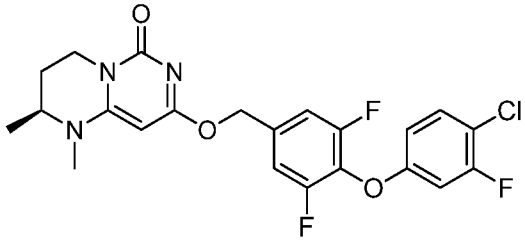


The title compound was prepared by a procedure similar to that described for E1 starting from (3-fluoro-4-isopropoxyphenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 362 $[M+1]^+$; 1.14 min (ret time).

E58

(S)-8-((4-(4-chloro-3-fluorophenoxy)-3,5-difluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

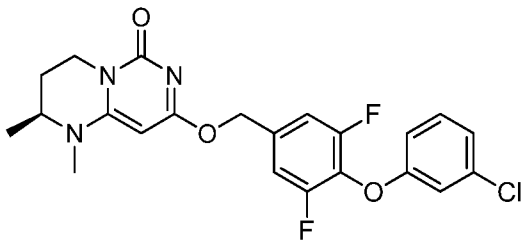


The title compound was prepared by a procedure similar to that described for E1 starting from (4-(4-chloro-3-fluorophenoxy)-3,5-difluorophenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 466 $[M+1]^+$; 1.10 min (ret time).

E59

(S)-8-((4-(3-chlorophenoxy)-3,5-difluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

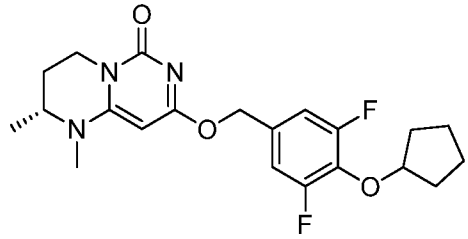


The title compound was prepared by a procedure similar to that described for E1 starting from (4-(3-chlorophenoxy)-3,5-difluorophenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 448 $[M+1]^+$; 1.08 min (ret time).

E60

(R)-8-((4-(cyclopentyloxy)-3,5-difluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

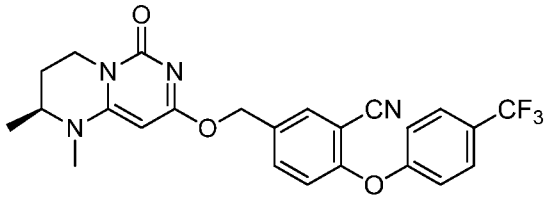


The title compound was prepared by a procedure similar to that described for E1 starting from (4-(cyclopentyloxy)-3,5-difluorophenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 406 $[M+1]^+$; 1.05 min (ret time).

E61

(S)-5-(((1,2-dimethyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidin-8-yl)oxy)methyl)-2-(4-(trifluoromethyl)phenoxy)benzonitrile

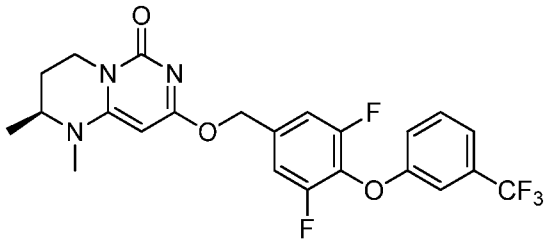


The title compound was prepared by a procedure similar to that described for E1 starting from 5-(hydroxymethyl)-2-(4-(trifluoromethyl)phenoxy)benzonitrile and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 471 $[M+1]^+$; 1.09 min (ret time).

E62

(S)-8-((3,5-difluoro-4-(3-(trifluoromethyl)phenoxy)benzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

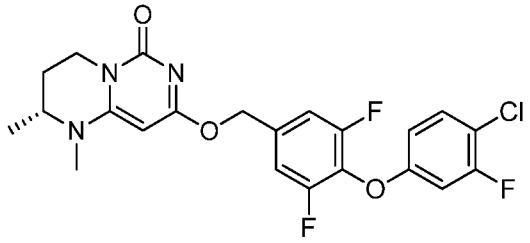


The title compound was prepared by a procedure similar to that described for E1 starting from (3,5-difluoro-4-(3-(trifluoromethyl)phenoxy)phenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 482 $[M+1]^+$; 1.13 min (ret time).

E63

(R)-8-((4-(4-chloro-3-fluorophenoxy)-3,5-difluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

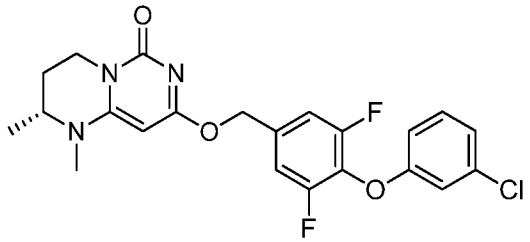


The title compound was prepared by a procedure similar to that described for E1 starting from (4-(4-chloro-3-fluorophenoxy)-3,5-difluorophenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 466 $[M+1]^+$; 1.10 min (ret time).

E64

(R)-8-((4-(3-chlorophenoxy)-3,5-difluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

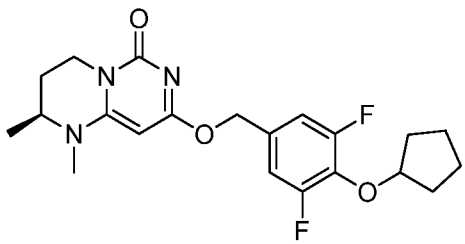


The title compound was prepared by a procedure similar to that described for E1 starting from (4-(3-chlorophenoxy)-3,5-difluorophenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 448 $[M+1]^+$; 1.09 min (ret time).

E65

(S)-8-((4-(cyclopentyloxy)-3,5-difluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

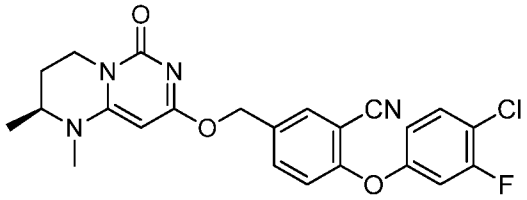


The title compound was prepared by a procedure similar to that described for E1 starting from (4-(cyclopentyloxy)-3,5-difluorophenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 406 $[M+1]^+$; 1.06 min (ret time).

E66

(S)-2-(4-chloro-3-fluorophenoxy)-5-(((1,2-dimethyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidin-8-yl)oxy)methyl)benzonitrile

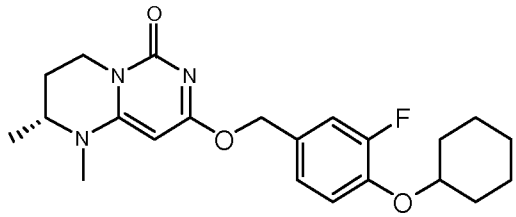


The title compound was prepared by a procedure similar to that described for E1 starting from 2-(4-chloro-3-fluorophenoxy)-5-(hydroxymethyl)benzonitrile and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 455 $[M+1]^+$; 1.06 min (ret time).

E67

(R)-8-((4-(cyclohexyloxy)-3-fluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

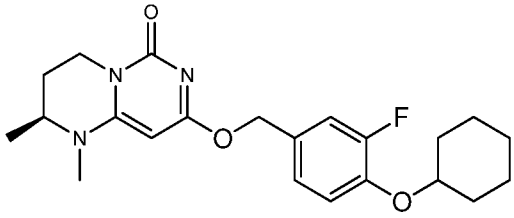


The title compound was prepared by a procedure similar to that described for E1 starting from (4-(cyclohexyloxy)-3-fluorophenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 402 $[M+1]^+$; 1.27 min (ret time).

E68

(S)-8-((4-(cyclohexyloxy)-3-fluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

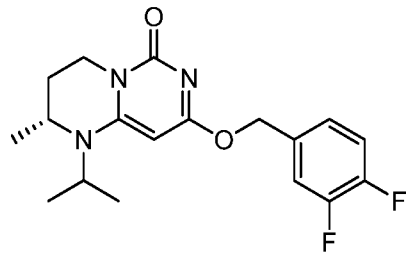


The title compound was prepared by a procedure similar to that described for E1 starting from (4-(cyclohexyloxy)-3-fluorophenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 402 $[M+1]^+$; 1.27 min (ret time).

E69

(R)-8-((3,4-difluorobenzyl)oxy)-1-isopropyl-2-methyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

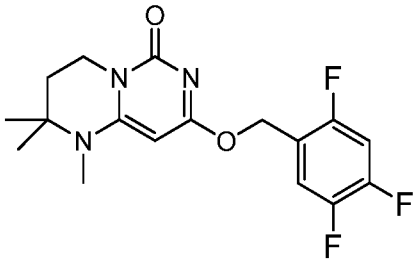


The title compound was prepared by a procedure similar to that described for E1 starting from (3,4-difluorophenyl)methanol and (R)-8-((3,4-difluorobenzyl)oxy)-1-isopropyl-2-methyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 350 $[M+1]^+$; 0.79 min (ret time).

E70

1,2,2-trimethyl-8-((2,4,5-trifluorobenzyl)oxy)-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

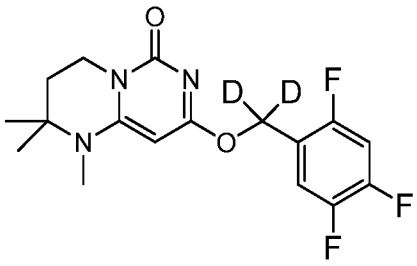


The title compound was prepared by a procedure similar to that described for E1 starting from (2,4,5-trifluoro-phenyl)methanol and 8-chloro-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 354 $[M+1]^+$; 2.51 min (ret time).

E71

8-(dideutero(2,4,5-trifluorophenyl)methoxy)-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

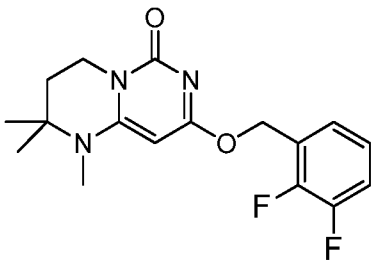


The title compound was prepared by a procedure similar to that described for E1 starting from dideutero(2,4,5-trifluorophenyl)methanol and 8-chloro-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 356 $[M+1]^+$; 2.52 min (ret time).

E72

8-((2,3-difluorobenzyl)oxy)-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

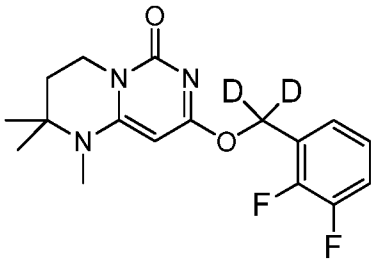


The title compound was prepared by a procedure similar to that described for E1 starting from (2,3-difluoro-phenyl)methanol and 8-chloro-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 336 $[M+1]^+$; 2.44 min (ret time).

E73

8-((2,3-difluorophenyl)dideuteromethoxy)-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

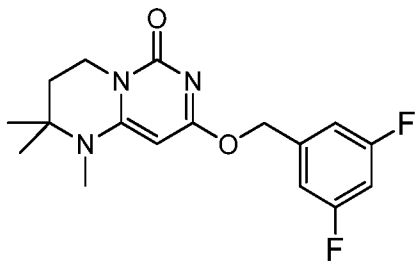


The title compound was prepared by a procedure similar to that described for E1 starting from dideutero(2,3-trifluorophenyl)methanol and 8-chloro-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 338 $[M+1]^+$; 2.46 min (ret time).

E74

8-((3,5-difluorobenzyl)oxy)-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

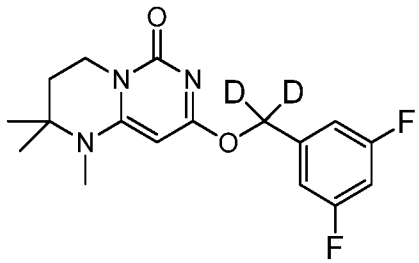


The title compound was prepared by a procedure similar to that described for E1 starting from (3,5-difluoro-phenyl)methanol and 8-chloro-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 336 $[M+1]^+$; 2.49 min (ret time).

E75

8-((3,5-difluorophenyl)dideuteromethoxy)-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

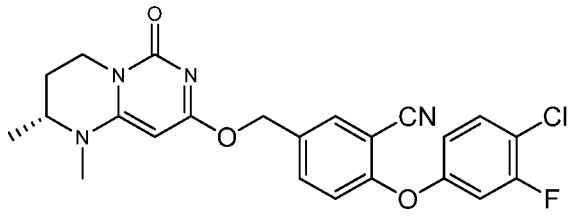


The title compound was prepared by a procedure similar to that described for E1 starting from dideutero(3,5-trifluorophenyl)methanol and 8-chloro-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 338 $[M+1]^+$; 2.49 min (ret time).

E76

(R)-2-(4-chloro-3-fluorophenoxy)-5-(((1,2-dimethyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidin-8-yl)oxy)methyl)benzonitrile

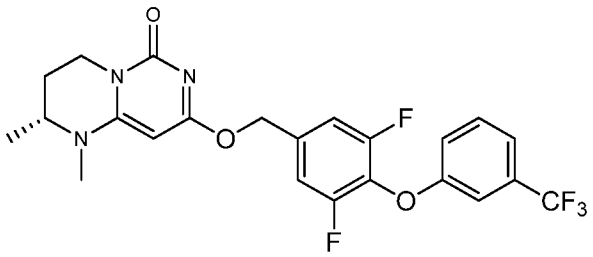


The title compound was prepared by a procedure similar to that described for E1 starting from 2-(4-chloro-3-fluorophenoxy)-5-(hydroxymethyl)benzonitrile and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 455 $[M+1]^+$; 1.06 min (ret time).

E77

(R)-8-((3,5-difluoro-4-(3-(trifluoromethyl)phenoxy)benzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

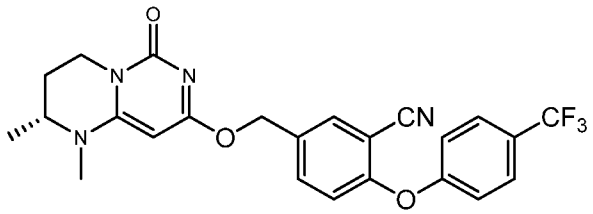


The title compound was prepared by a procedure similar to that described for E1 starting from (3,5-difluoro-4-(3-(trifluoromethyl)phenoxy)phenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 482 $[M+1]^+$; 1.07 min (ret time).

E78

(R)-5-(((1,2-dimethyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidin-8-yl)oxy)methyl)-2-(4-(trifluoromethyl)phenoxy)benzonitrile

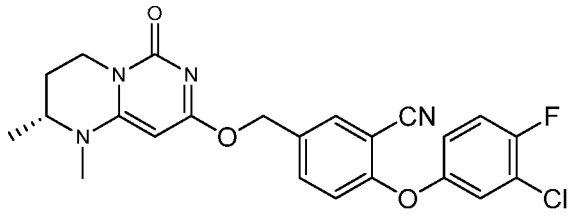


The title compound was prepared by a procedure similar to that described for E1 starting from 5-(hydroxymethyl)-2-(4-(trifluoromethyl)phenoxy)benzonitrile and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 471 $[M+1]^+$; 1.08 min (ret time).

E79

(R)-2-(3-chloro-4-fluorophenoxy)-5-(((1,2-dimethyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidin-8-yl)oxy)methyl)benzonitrile

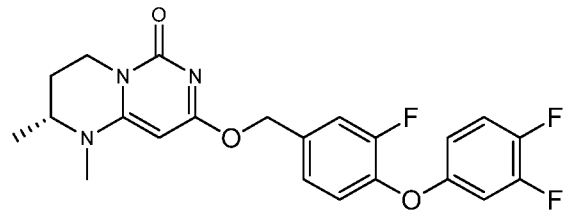


The title compound was prepared by a procedure similar to that described for E1 starting from 2-(3-chloro-4-fluorophenoxy)-5-(hydroxymethyl)benzonitrile and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 455 $[M+1]^+$; 1.05 min (ret time).

E80

(R)-8-((4-(3,4-difluorophenoxy)-3-fluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

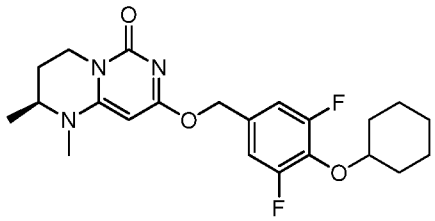


The title compound was prepared by a procedure similar to that described for E1 starting from (4-(3,4-difluorophenoxy)-3-fluorophenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 432 $[M+1]^+$; 1.05 min (ret time).

E81

(S)-8-((4-(cyclohexyloxy)-3,5-difluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one



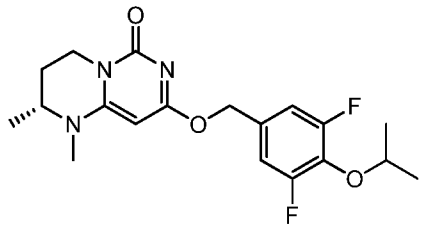
The title compound was prepared by a procedure similar to that described for E1 starting from (4-(cyclohexyloxy)-3,5-difluorophenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 420 $[M+1]^+$; 1.31 min (ret time).

E82

(R)-8-((3,5-difluoro-4-isopropoxybenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-

a]pyrimidin-6(2H)-one

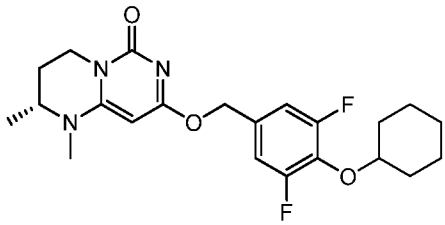


The title compound was prepared by a procedure similar to that described for E1 starting from (3,5-difluoro-4-isopropoxyphenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 380 $[M+1]^+$; 1.19 min (ret time).

E83

(R)-8-((4-(cyclohexyloxy)-3,5-difluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

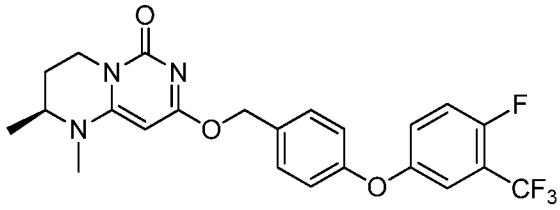


The title compound was prepared by a procedure similar to that described for E1 starting from (4-(cyclohexyloxy)-3,5-difluorophenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 420 $[M+1]^+$; 1.32 min (ret time).

E84

(S)-8-((4-(4-fluoro-3-(trifluoromethyl)phenoxy)benzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

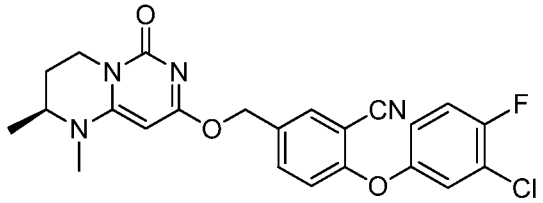


The title compound was prepared by a procedure similar to that described for E1 starting from (4-(4-fluoro-3-(trifluoromethyl)phenoxy)phenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 464 $[M+1]^+$; 1.10 min (ret time).

E85

(S)-2-(3-chloro-4-fluorophenoxy)-5-(((1,2-dimethyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidin-8-yl)oxy)methyl)benzonitrile

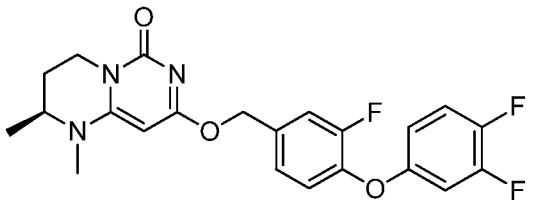


The title compound was prepared by a procedure similar to that described for E1 starting from 2-(3-chloro-4-fluorophenoxy)-5-(hydroxymethyl)benzonitrile and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 455 $[M+1]^+$; 1.06 min (ret time).

E86

(S)-8-((4-(3,4-difluorophenoxy)-3-fluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

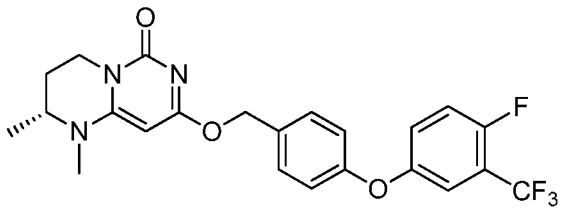


The title compound was prepared by a procedure similar to that described for E1 starting from (4-(3,4-difluorophenoxy)-3-fluorophenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 432 $[M+1]^+$; 1.04 min (ret time).

E87

(R)-8-((4-(4-fluoro-3-(trifluoromethyl)phenoxy)benzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

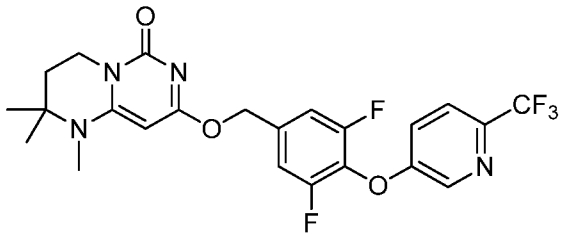


The title compound was prepared by a procedure similar to that described for E1 starting from (4-(4-fluoro-3-(trifluoromethyl)phenoxy)phenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 464 $[M+1]^+$; 1.10 min (ret time).

E88

8-((3,5-difluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)benzyl)oxy)-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

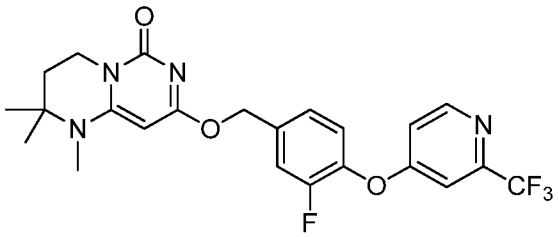


The title compound was prepared by a procedure similar to that described for E1 starting from (3,5-difluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)phenyl)methanol and 8-chloro-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 497 $[M+1]^+$; 2.89 min (ret time).

E89

8-((3-fluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)benzyl)oxy)-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

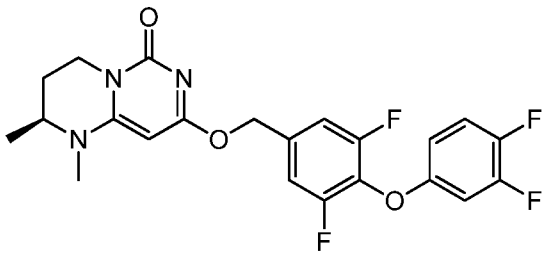


The title compound was prepared by a procedure similar to that described for E1 starting from (3-fluoro-4-((2-(trifluoromethyl)pyridin-4-yl)methyl)phenyl)methanol and 8-chloro-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 497 $[M+1]^+$; 2.75 min (ret time).

E90

(S)-8-((4-(3,4-difluorophenoxy)-3,5-difluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

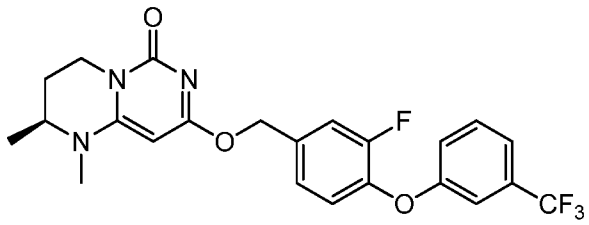


The title compound was prepared by a procedure similar to that described for E1 starting from (4-(3,4-difluorophenoxy)-3,5-difluorophenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 450 $[M+1]^+$; 0.73 min (ret time).

E91

(S)-8-((3-fluoro-4-(3-(trifluoromethyl)phenoxy)benzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

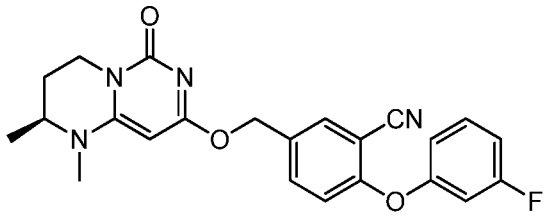


The title compound was prepared by a procedure similar to that described for E1 starting from (3-fluoro-4-(3-(trifluoromethyl)phenoxy)phenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 464 $[M+1]^+$; 0.74 min (ret time).

E92

(S)-5-(((1,2-dimethyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidin-8-yl)oxy)methyl)-2-(3-fluorophenoxy)benzonitrile

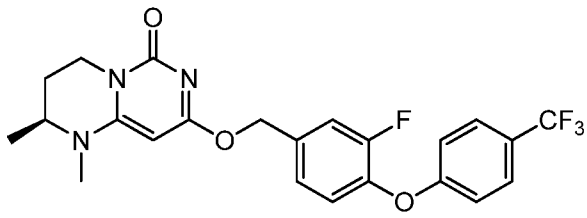


The title compound was prepared by a procedure similar to that described for E1 starting from 2-(3-fluorophenoxy)-5-(hydroxymethyl)benzonitrile and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 421 $[M+1]^+$; 0.68 min (ret time).

E93

(S)-8-((3-fluoro-4-(4-(trifluoromethyl)phenoxy)benzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

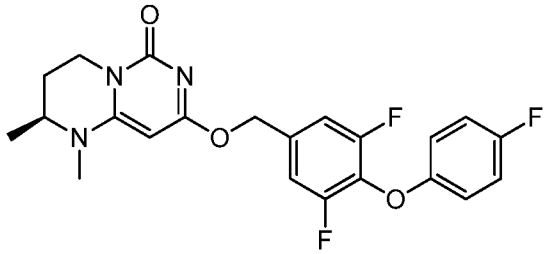


The title compound was prepared by a procedure similar to that described for E1 starting from (3-fluoro-4-(4-(trifluoromethyl)phenoxy)phenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 464 $[M+1]^+$; 0.77 min (ret time).

E94

(S)-8-((3,5-difluoro-4-(4-fluorophenoxy)benzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

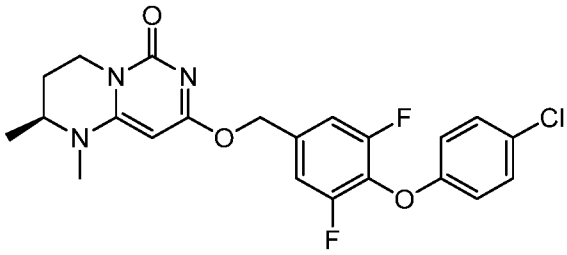


The title compound was prepared by a procedure similar to that described for E1 starting from (3,5-difluoro-4-(4-fluorophenoxy)phenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 432 $[M+1]^+$; 0.74 min (ret time).

E95

(S)-8-((4-(4-chlorophenoxy)-3,5-difluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

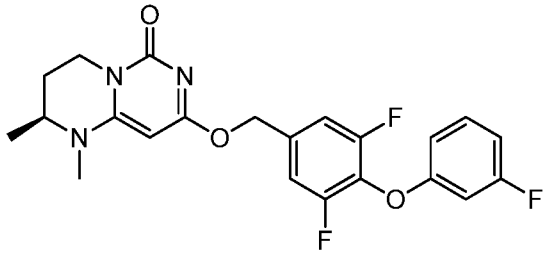


The title compound was prepared by a procedure similar to that described for E1 starting from (4-(4-chlorophenoxy)-3,5-difluorophenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 448 $[M+1]^+$; 0.76 min (ret time).

E96

(S)-8-((3,5-difluoro-4-(3-fluorophenoxy)benzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

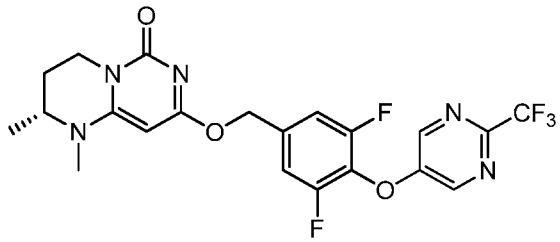


The title compound was prepared by a procedure similar to that described for E1 starting from (3,5-difluoro-4-(3-fluorophenoxy)phenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 432 $[M+1]^+$; 0.72 min (ret time).

E97

(R)-8-((3,5-difluoro-4-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)benzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

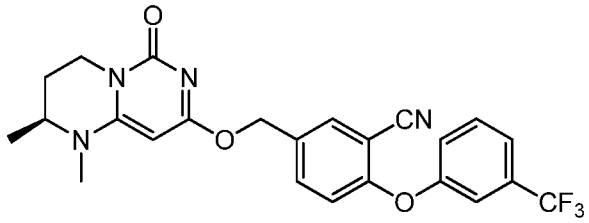


The title compound was prepared by a procedure similar to that described for E1 starting from (3,5-difluoro-4-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)phenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 484 $[M+1]^+$; 1.03 min (ret time).

E98

(S)-5-(((1,2-dimethyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidin-8-yl)oxy)methyl)-2-(3-(trifluoromethyl)phenoxy)benzonitrile

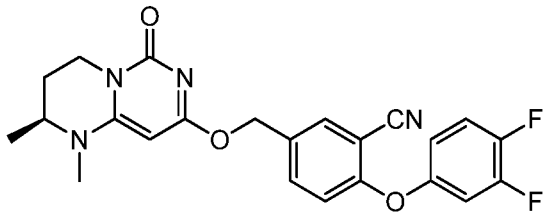


The title compound was prepared by a procedure similar to that described for E1 starting from 5-(hydroxymethyl)-2-(3-(trifluoromethyl)phenoxy)benzonitrile and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 471 $[M+1]^+$; 0.74 min (ret time).

E99

(S)-2-(3,4-difluorophenoxy)-5-(((1,2-dimethyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidin-8-yl)oxy)methyl)benzonitrile

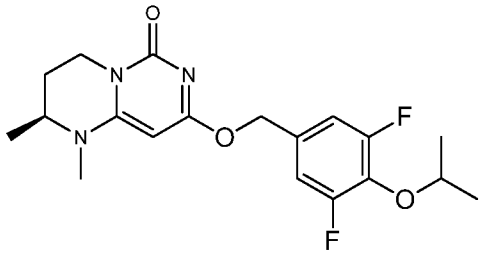


The title compound was prepared by a procedure similar to that described for E1 starting from 2-(3,4-difluorophenoxy)-5-(hydroxymethyl)benzonitrile and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 439 $[M+1]^+$; 0.72 min (ret time).

E100

(S)-8-((3,5-difluoro-4-isopropoxybenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

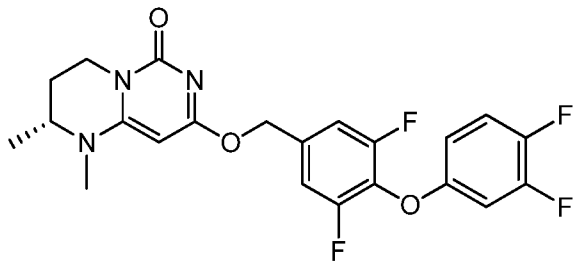


The title compound was prepared by a procedure similar to that described for E1 starting from (3,5-difluoro-4-isopropoxyphenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 480 $[M+H]^+$; 0.98 min (ret time).

E101

(R)-8-((4-(3,4-difluorophenoxy)-3,5-difluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

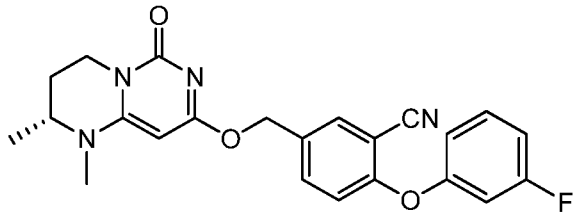


The title compound was prepared by a procedure similar to that described for E1 starting from (4-(3,4-difluorophenoxy)-3,5-difluorophenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 450 $[M+1]^+$; 1.07 min (ret time).

E102

(R)-5-(((1,2-dimethyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidin-8-yl)oxy)methyl)-2-(3-fluorophenoxy)benzonitrile

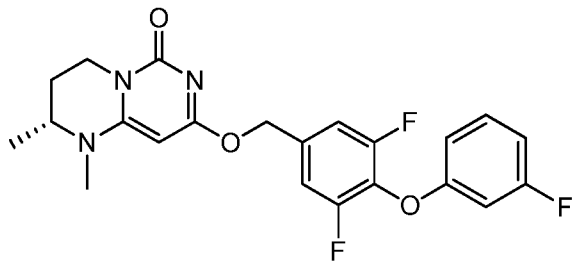


The title compound was prepared by a procedure similar to that described for E1 starting from 2-(3-fluorophenoxy)-5-(hydroxymethyl)benzonitrile and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 421 $[M+1]^+$; 1.00 min (ret time).

E103

(R)-8-((3,5-difluoro-4-(3-fluorophenoxy)benzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

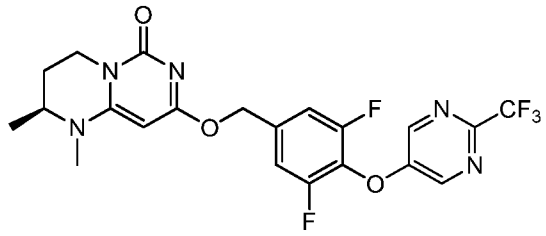


The title compound was prepared by a procedure similar to that described for E1 starting from (3,5-difluoro-4-(3-fluorophenoxy)phenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 432 $[M+1]^+$; 1.05 min (ret time).

E104

(S)-8-((3,5-difluoro-4-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)benzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

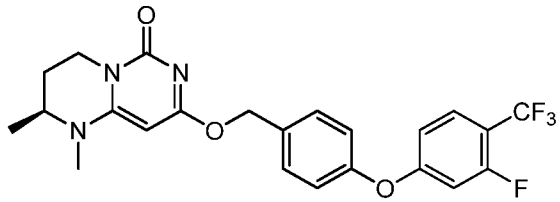


The title compound was prepared by a procedure similar to that described for E1 starting from (3,5-difluoro-4-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)phenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 484 $[M+1]^+$; 1.03 min (ret time).

E105

(S)-8-((4-(3-fluoro-4-(trifluoromethyl)phenoxy)benzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

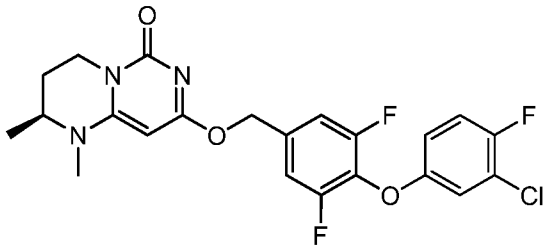


The title compound was prepared by a procedure similar to that described for E1 starting from (4-(3-fluoro-4-(trifluoromethyl)phenoxy)phenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 464 $[M+1]^+$; 1.11 min (ret time).

E106

(S)-8-((4-(3-chloro-4-fluorophenoxy)-3,5-difluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

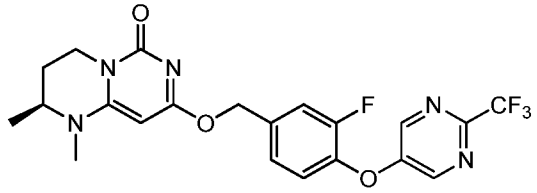


The title compound was prepared by a procedure similar to that described for E1 starting from (4-(3-chloro-4-fluorophenoxy)-3,5-difluorophenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 466 $[M+1]^+$; 1.10 min (ret time).

E107

(S)-8-((3-fluoro-4-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)benzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

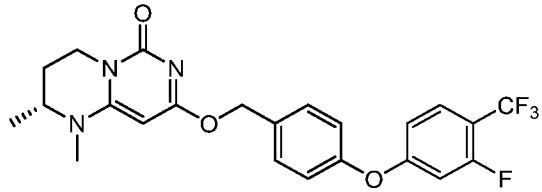


The title compound was prepared by a procedure similar to that described for E1 starting from (3-fluoro-4-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)phenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 466 $[M+1]^+$; 0.99 min (ret time).

E108

(R)-8-((4-(3-fluoro-4-(trifluoromethyl)phenoxy)benzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

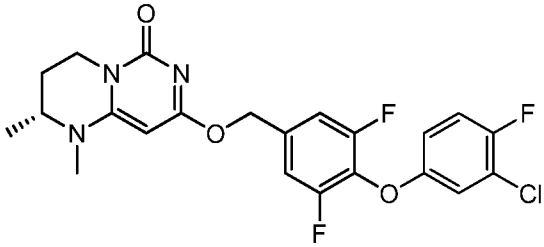


The title compound was prepared by a procedure similar to that described for E1 starting from (4-(3-fluoro-4-(trifluoromethyl)phenoxy)phenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 464 $[M+1]^+$; 1.11 min (ret time).

E109

(R)-8-((4-(3-chloro-4-fluorophenoxy)-3,5-difluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

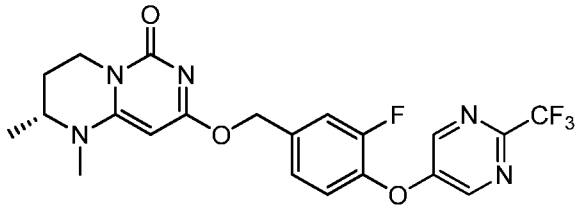


The title compound was prepared by a procedure similar to that described for E1 starting from (4-(3-chloro-4-fluorophenoxy)-3,5-difluorophenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 466 $[M+1]^+$; 1.10 min (ret time).

E110

(R)-8-((3-fluoro-4-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)benzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

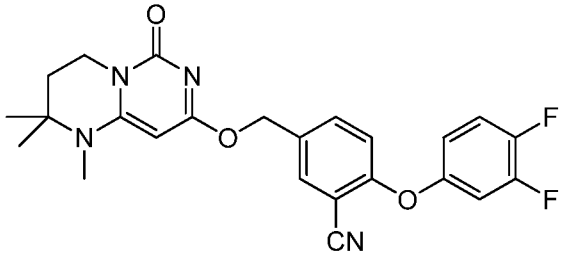


The title compound was prepared by a procedure similar to that described for E1 starting from (3-fluoro-4-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)phenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 466 $[M+1]^+$; 1.00 min (ret time).

E111

2-(3,4-difluorophenoxy)-5-(((1,2,2-trimethyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidin-8-yl)oxy)methyl)benzonitrile

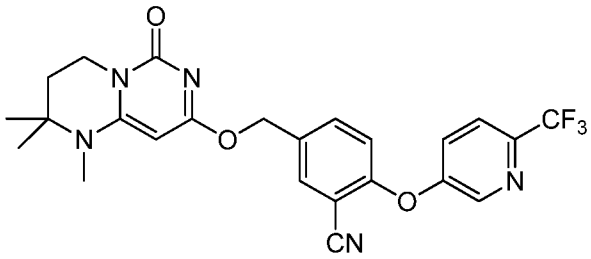


The title compound was prepared by a procedure similar to that described for E1 starting from 2-(3,4-difluoro phenoxy)-5-(hydroxymethyl)benzonitrile and 8-chloro-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 453 $[M+1]^+$; 2.84 min (ret time).

E112

2-((6-(trifluoromethyl)pyridin-3-yl)oxy)-5-(((1,2,2-trimethyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidin-8-yl)oxy)methyl)benzonitrile

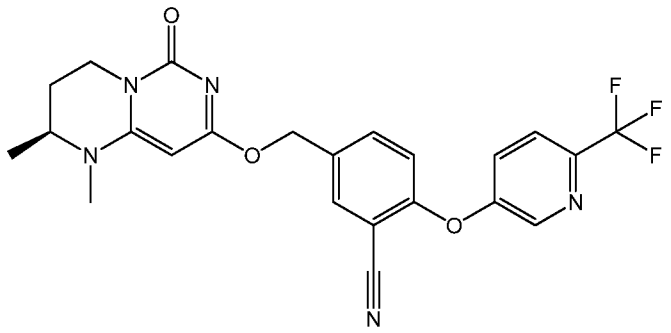


The title compound was prepared by a procedure similar to that described for E1 starting from 5-(hydroxyl methyl)-2-((6-(trifluoromethyl)pyridin-3-yl)oxy)benzonitrile and 8-chloro-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 486 $[M+1]^+$; 2.73 min (ret time).

E113

(S)-5-(((1,2-dimethyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidin-8-yl)oxy)methyl)-2-((6-(trifluoromethyl)pyridin-3-yl)oxy)benzonitrile

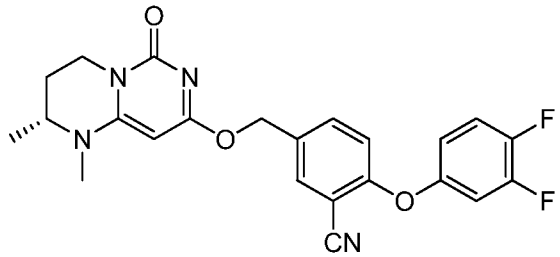


The title compound was prepared by a procedure similar to that described for E1 starting from 5-(hydroxymethyl)-2-((6-(trifluoromethyl)pyridin-3-yl)oxy)benzonitrile and (S)-8-chloro-1,2-dimethyl- 3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 472 $[M+1]^+$; 3.44 min (ret time).

E114

(R)-2-(3,4-difluorophenoxy)-5-(((1,2-dimethyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidin-8-yl)oxy)methyl)benzonitrile

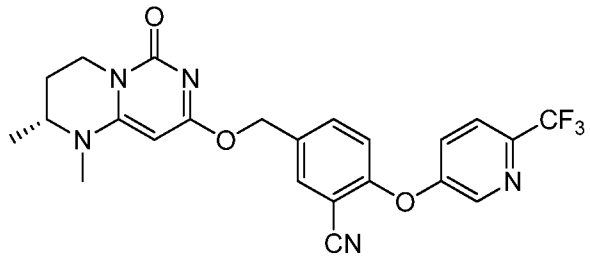


The title compound was prepared by a procedure similar to that described for E1 starting from 2-(3,4-difluoro phenoxy)-5-(hydroxymethyl)benzonitrile and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 439 $[M+1]^+$; 3.56 min (ret time).

E115

(R)-5-(((1,2-dimethyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidin-8-yl)oxy)methyl)-2-((6-(trifluoromethyl)pyridin-3-yl)oxy)benzonitrile

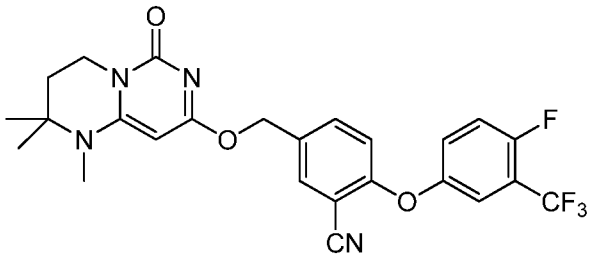


The title compound was prepared by a procedure similar to that described for E1 starting from 5-(hydroxyl methyl)-2-((6-(trifluoromethyl)pyridin-3-yl)oxy)benzonitrile and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 472 $[M+1]^+$; 3.56 min (ret time).

E116

2-(4-fluoro-3-(trifluoromethyl)phenoxy)-5-(((1,2,2-trimethyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidin-8-yl)oxy)methyl)benzonitrile

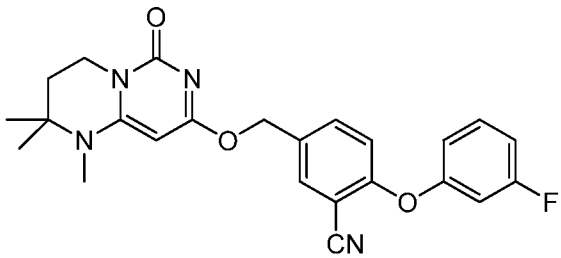


The title compound was prepared by a procedure similar to that described for E1 starting from 2-(4-fluoro-3-(trifluoromethyl)phenoxy)-5-(hydroxymethyl)benzonitrile and 8-chloro-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS (ESI): m/z 503 $[M+1]^+$: 3.99 min (ret time).

E117

2-(3-fluorophenoxy)-5-(((1,2,2-trimethyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a] pyrimidin-8-yl)oxy)methyl)benzonitrile

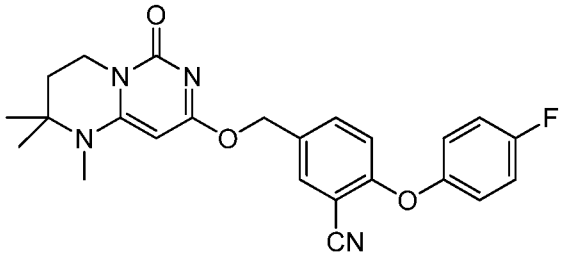


The title compound was prepared by a procedure similar to that described for E1 starting from 2-(3-fluoro phenoxy)-5-(hydroxymethyl)benzonitrile and 8-chloro-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS (ESI): m/z 435 $[M+1]^+$: 2.67 min (ret time).

E118

2-(4-fluorophenoxy)-5-(((1,2,2-trimethyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidin-8-yl)oxy)methyl)benzonitrile

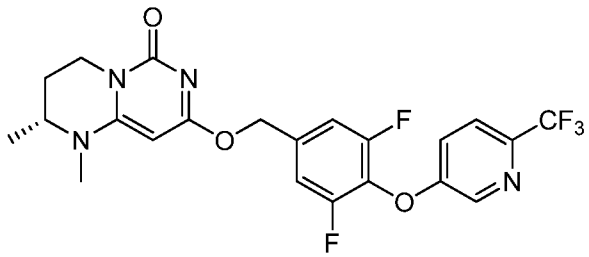


The title compound was prepared by a procedure similar to that described for E1 starting from 2-(4-fluoro phenoxy)-5-(hydroxymethyl)benzonitrile and 8-chloro-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS (ESI): m/z 435 $[M+1]^+$: 2.74 min (ret time).

E119

(R)-8-((3,5-difluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)benzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

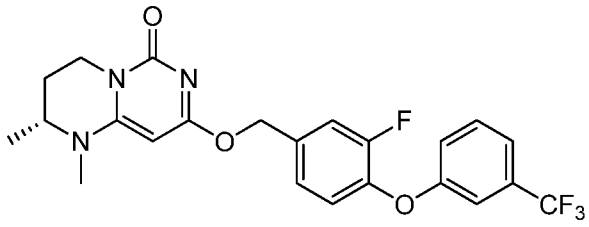


The title compound was prepared by a procedure similar to that described for E1 starting from (3,5-difluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)phenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 483 $[M+1]^+$; 1.04 min (ret time).

E120

(R)-8-((3-fluoro-4-(3-(trifluoromethyl)phenoxy)benzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

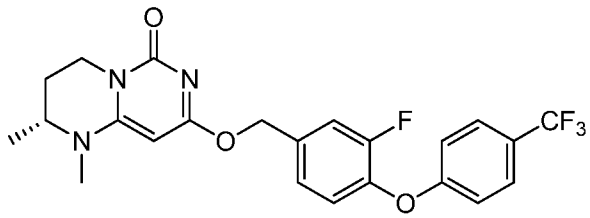


The title compound was prepared by a procedure similar to that described for E1 starting from (3-fluoro-4-(3-(trifluoromethyl)phenoxy)phenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 464 $[M+1]^+$; 1.10 min (ret time).

E121

(R)-8-((3-fluoro-4-(4-(trifluoromethyl)phenoxy)benzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

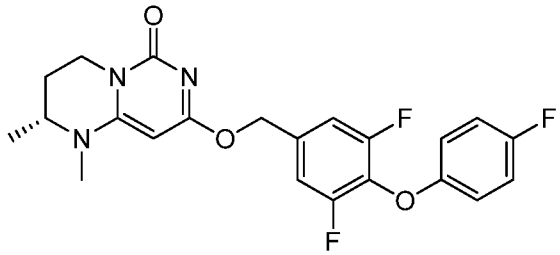


The title compound was prepared by a procedure similar to that described for E1 starting from (3-fluoro-4-(4-(trifluoromethyl)phenoxy)phenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 464 $[M+1]^+$; 1.10 min (ret time).

E122

(R)-8-((3,5-difluoro-4-(4-fluorophenoxy)benzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

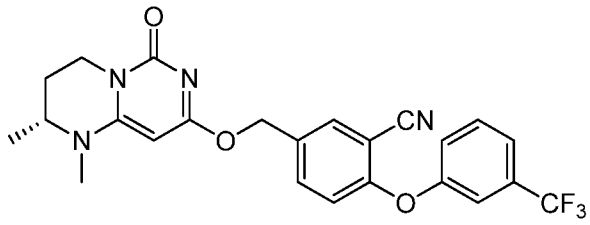


The title compound was prepared by a procedure similar to that described for E1 starting from (3,5-difluoro-4-(4-fluorophenoxy)phenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 432 $[M+1]^+$; 1.06 min (ret time).

E123

(R)-5-(((1,2-dimethyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidin-8-yl)oxy)methyl)-2-(3-(trifluoromethyl)phenoxy)benzonitrile

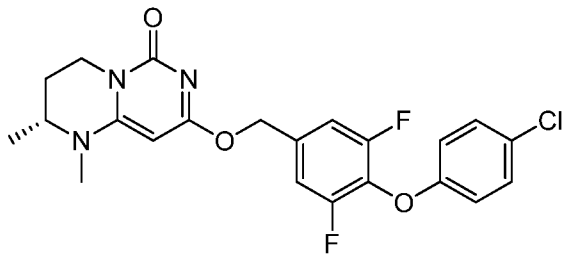


The title compound was prepared by a procedure similar to that described for E1 starting from 5-(hydroxymethyl)-2-(3-(trifluoromethyl)phenoxy)benzonitrile and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 471 $[M+1]^+$; 1.09 min (ret time).

E124

(R)-8-((4-(4-chlorophenoxy)-3,5-difluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

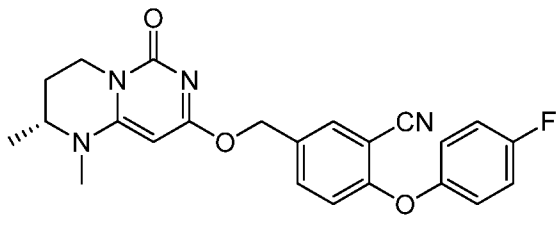


The title compound was prepared by a procedure similar to that described for E1 starting from (4-(4-chlorophenoxy)-3,5-difluorophenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 448 $[M+1]^+$; 1.12 min (ret time).

E125

(R)-5-(((1,2-dimethyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidin-8-yl)oxy)methyl)-2-(4-fluorophenoxy)benzonitrile

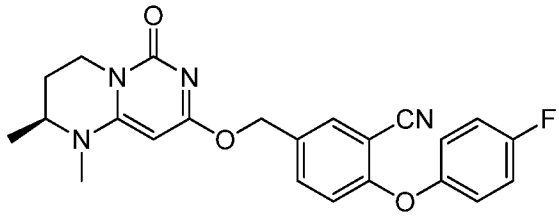


The title compound was prepared by a procedure similar to that described for E1 starting 2-(4-fluorophenoxy)-5-(hydroxymethyl)benzonitrile and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 421 $[M+1]^+$; 2.62 min (ret time).

E126

(S)-5-(((1,2-dimethyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidin-8-yl)oxy)methyl)-2-(4-fluorophenoxy)benzonitrile

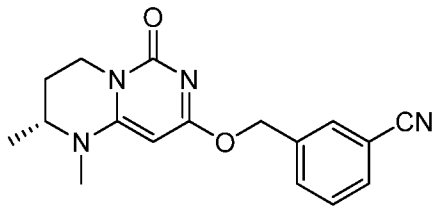


The title compound was prepared by a procedure similar to that described for E1 starting 2-(4-fluorophenoxy)-5-(hydroxymethyl)benzonitrile and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 421 $[M+1]^+$; 2.62 min (ret time).

E127

(R)-3-(((1,2-dimethyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidin-8-yl)oxy)methyl)benzonitrile

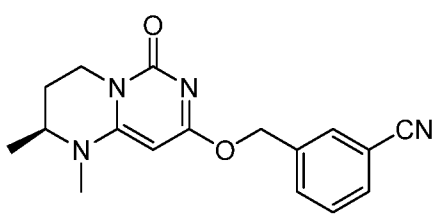


The title compound was prepared by a procedure similar to that described for E1 starting 3-(hydroxymethyl)benzonitrile and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 311 $[M+1]^+$; 1.88 min (ret time).

E128

(S)-3-(((1,2-dimethyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidin-8-yl)oxy)methyl)benzonitrile

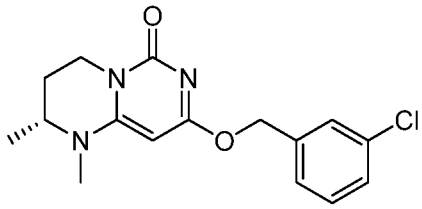


The title compound was prepared by a procedure similar to that described for E1 starting 3-(hydroxymethyl)benzonitrile and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 311 $[M+1]^+$; 1.88 min (ret time).

E129

(R)-8-((3-chlorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

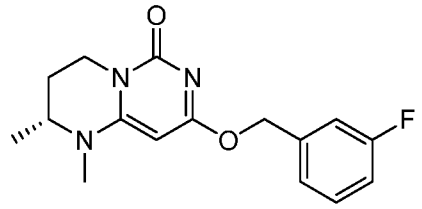


The title compound was prepared by a procedure similar to that described for E1 starting from (3-chlorophenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 320 $[M+1]^+$; 2.53 min (ret time).

E130

(R)-8-((3-fluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

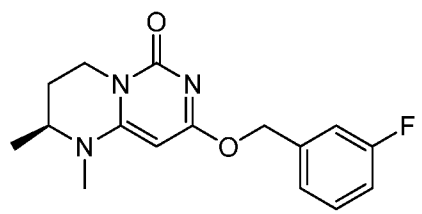


The title compound was prepared by a procedure similar to that described for E1 starting from (3-fluorophenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 304 $[M+1]^+$; 2.00 min (ret time).

E131

(S)-8-((3-fluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

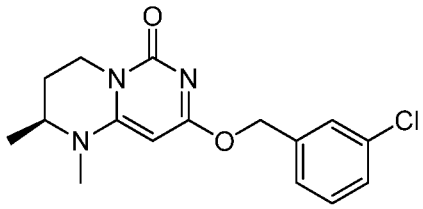


The title compound was prepared by a procedure similar to that described for E1 starting from (3-fluorophenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 304 $[M+1]^+$; 2.02 min (ret time).

E132

(S)-8-((3-chlorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

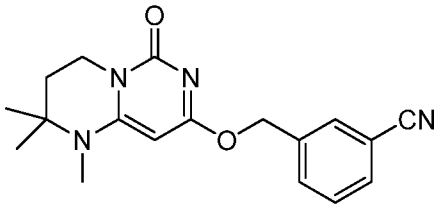


The title compound was prepared by a procedure similar to that described for E1 starting from (3-chlorophenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 320 $[M+1]^+$; 2.53 min (ret time).

E133

3-(((1,2,2-trimethyl-6-oxo-2,3,4,6-tetrahydro-1H-pyrimido[1,6-a]pyrimidin-8-yl)oxy)methyl)benzonitrile

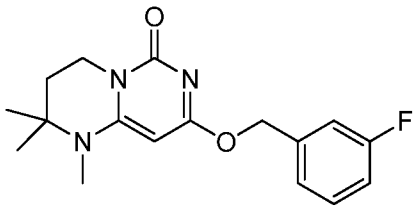


The title compound was prepared by a procedure similar to that described for E1 starting from 3-(hydroxymethyl)benzonitrile and 8-chloro-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 325 $[M+1]^+$; 2.03 min (ret time).

E134

8-((3-fluorobenzyl)oxy)-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

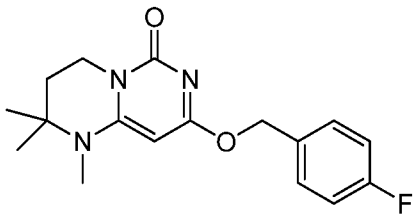


The title compound was prepared by a procedure similar to that described for E1 starting from (3-fluorophenyl)methanol and 8-chloro-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 318 $[M+1]^+$; 2.18 min (ret time).

E135

8-((4-fluorobenzyl)oxy)-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

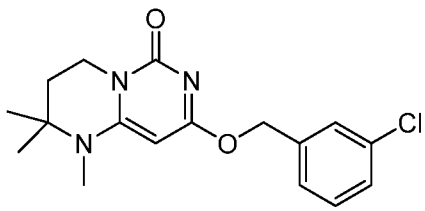


The title compound was prepared by a procedure similar to that described for E1 starting from (4-fluorophenyl)methanol and 8-chloro-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 318 $[M+1]^+$; 2.17 min (ret time).

E136

8-((3-chlorobenzyl)oxy)-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

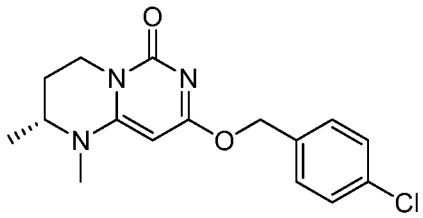


The title compound was prepared by a procedure similar to that described for E1 starting from (3-chlorophenyl)methanol and 8-chloro-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 334 $[M+1]^+$; 2.37 min (ret time).

E137

(R)-8-((4-chlorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

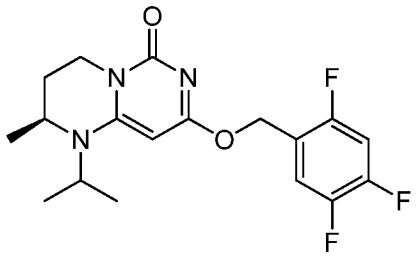


The title compound was prepared by a procedure similar to that described for E1 starting from (4-chlorophenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 320 $[M+1]^+$; 3.17 min (ret time).

E138

(S)-1-isopropyl-2-methyl-8-((2,4,5-trifluorobenzyl)oxy)-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

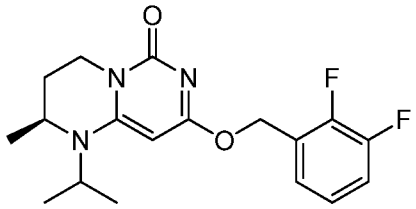


The title compound was prepared by a procedure similar to that described for E1 starting from (2,4,5-trifluorophenyl)methanoland (S)-8-chloro-1-isopropyl-2-methyl-3,4-dihydro-1Hpyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 368 $[M+1]^+$; 1.41 min (ret time).

E139

(S)-8-((2,3-difluorobenzyl)oxy)-1-isopropyl-2-methyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

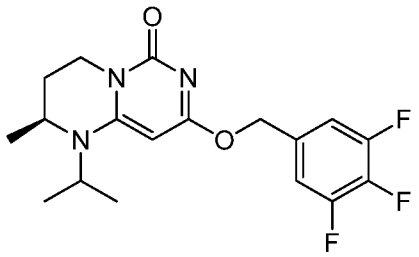


The title compound was prepared by a procedure similar to that described for E1 starting from (2,3-difluorophenyl)methanol and (S)-8-chloro-1-isopropyl-2-methyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 350 $[M+1]^+$; 1.37 min (ret time).

E140

(S)-1-isopropyl-2-methyl-8-((3,4,5-trifluorobenzyl)oxy)-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

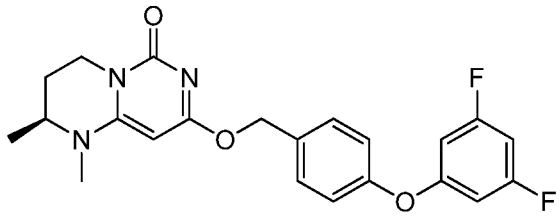


The title compound was prepared by a procedure similar to that described for E1 starting from (3,4,5-trifluorophenyl)methanol and (S)-8-chloro-1-isopropyl-2-methyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 368 $[M+1]^+$; 1.42 min (ret time).

E141

(S)-8-((4-(3,5-difluorophenoxy)benzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

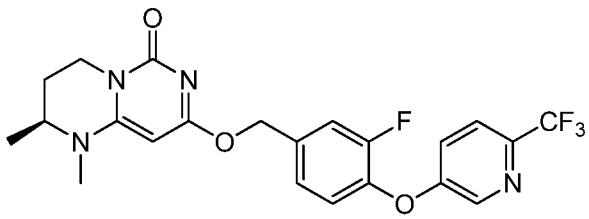


The title compound was prepared by a procedure similar to that described for E1 starting from (4-(3,5-difluorophenoxy)phenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 414 $[M+1]^+$; 2.76 min (ret time).

E142

(S)-8-((3-fluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)benzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

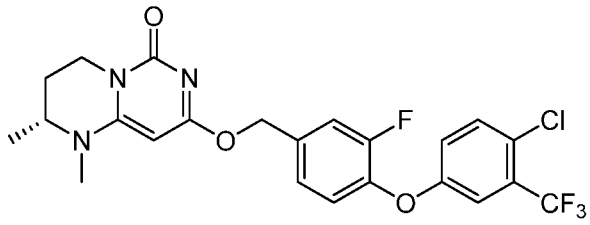


The title compound was prepared by a procedure similar to that described for E1 starting from (3-fluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)phenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 465 $[M+1]^+$; 2.46 min (ret time).

E143

(R)-8-((4-(4-chloro-3-(trifluoromethyl)phenoxy)-3-fluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

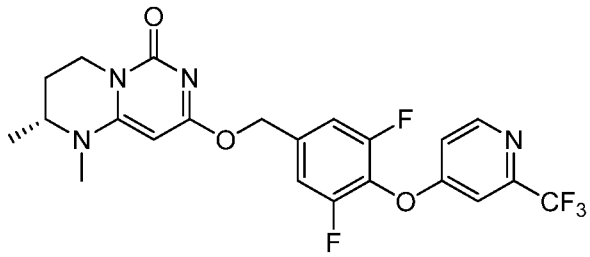


The title compound was prepared by a procedure similar to that described for E1 starting from (4-(4-chloro-3-(trifluoromethyl)phenoxy)-3-fluorophenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 498 $[M+1]^+$; 2.85 min (ret time).

E144

(R)-8-((3,5-difluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)benzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

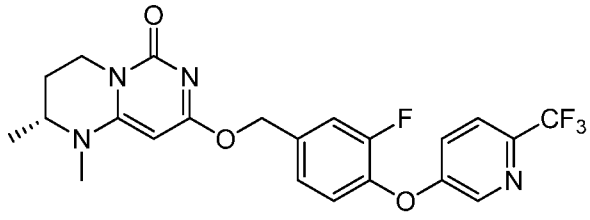


The title compound was prepared by a procedure similar to that described for E1 starting from (4-(3,5-difluorophenoxy)cyclohexyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 483 $[M+1]^+$; 4.14 min (ret time).

E145

(R)-8-((3-fluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)benzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

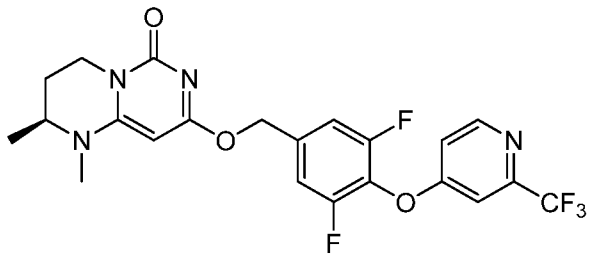


The title compound was prepared by a procedure similar to that described for E1 starting (3-fluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)phenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 465 $[M+1]^+$; 2.43 min (ret time).

E146

(S)-8-((3,5-difluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)benzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

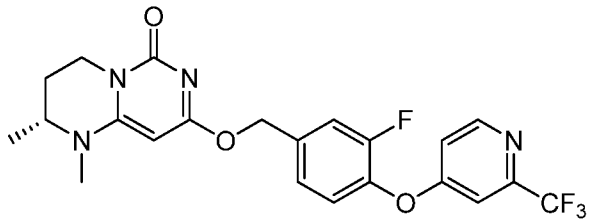


The title compound was prepared by a procedure similar to that described for E1 starting from (3,5-difluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)phenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 483 $[M+1]^+$; 2.89 min (ret time).

E147

(R)-8-((3-fluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)benzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

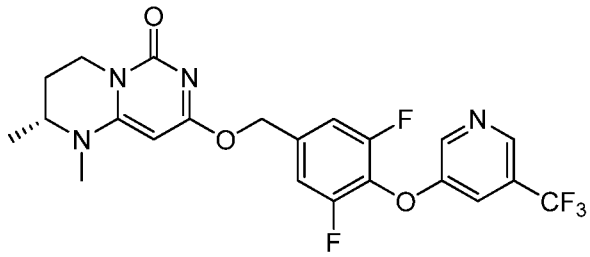


The title compound was prepared by a procedure similar to that described for E1 starting from (3-fluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)phenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 465 $[M+1]^+$; 2.80 min (ret time).

E148

(R)-8-((3,5-difluoro-4-((5-(trifluoromethyl)pyridin-3-yl)oxy)benzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

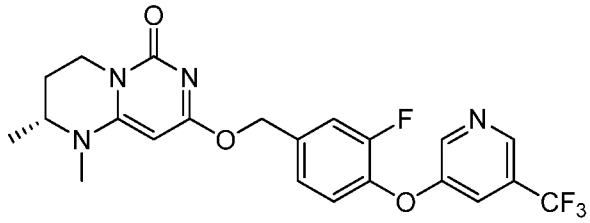


The title compound was prepared by a procedure similar to that described for E1 starting from (3,5-difluoro-4-((5-(trifluoromethyl)pyridin-3-yl)oxy)phenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 483 $[M+1]^+$; 2.89 min (ret time).

E149

(R)-8-((3-fluoro-4-((5-(trifluoromethyl)pyridin-3-yl)oxy)benzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

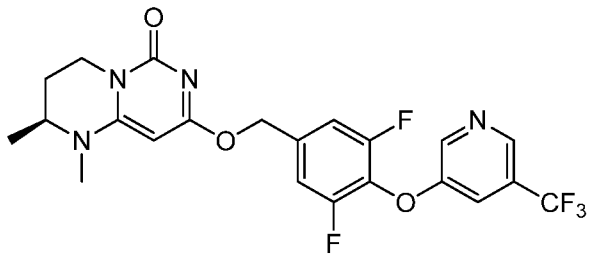


The title compound was prepared by a procedure similar to that described for E1 starting from (3-fluoro-4-((5-(trifluoromethyl)pyridin-3-yl)oxy)phenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 465 $[M+1]^+$; 2.60 min (ret time).

E150

(S)-8-((3,5-difluoro-4-((5-(trifluoromethyl)pyridin-3-yl)oxy)benzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

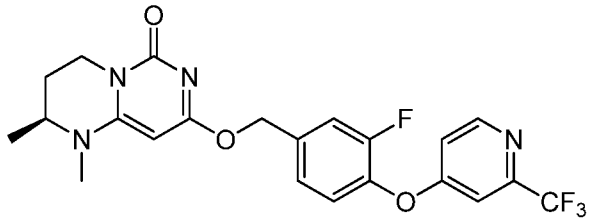


The title compound was prepared by a procedure similar to that described for E1 starting from (3,5-difluoro-4-((5-(trifluoromethyl)pyridin-3-yl)oxy)phenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 483 $[M+1]^+$; 2.71 min (ret time).

E151

(S)-8-((3-fluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)benzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

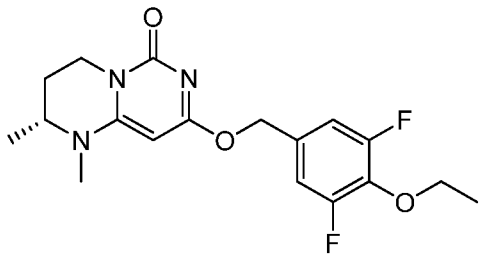


The title compound was prepared by a procedure similar to that described for E1 starting from (3-fluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)phenyl)methanol and (S)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 465 $[M+1]^+$; 2.61 min (ret time).

E152

(R)-8-((4-ethoxy-3,5-difluorobenzyl)oxy)-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one

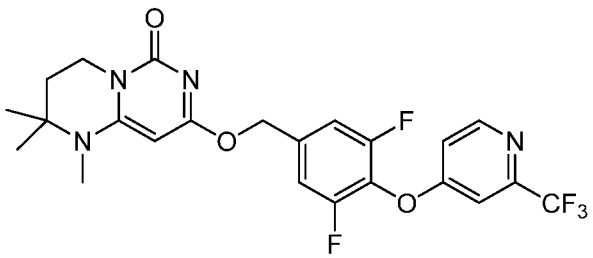


The title compound was prepared by a procedure similar to that described for E1 starting from (4-ethoxy-3,5-difluorophenyl)methanol and (R)-8-chloro-1,2-dimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.

LC-MS(ESI): m/z 366 $[M+1]^+$; 2.40 min (ret time).

E153

8-((3,5-difluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)benzyl)oxy)-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one



The title compound was prepared by a procedure similar to that described for E1 starting from (3,5-difluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)phenyl)methanol and 8-chloro-1,2,2-trimethyl-3,4-dihydro-1H-pyrimido[1,6-a]pyrimidin-6(2H)-one.
LC-MS(ESI): m/z 497 $[M+1]^+$; 2.81 min (ret time).

D. Biological assays and data

The compounds of present invention are Lp-PLA_2 inhibitors, and are useful in the treatment of diseases mediated by Lp-PLA_2. The biological activities of the compounds of present invention can be determined by using any suitable assay for determining the activity of a compound as a Lp-PLA_2 inhibitor, as well as tissue and in vivo models.

The biological activity data for each compound was either reported in at least one experiment or the average of multiple experiments. It is understood that the data described herein may have reasonable variations depending on the specific conditions and procedures used by the person conducting the experiments.

Lipoprotein-associated phospholipase A2 (Lp-PLA_2) biochemical assay

(1) Recombinant human Lp-PLA_2 assay (rhLp-PLA_2) (also referred to as "PED6" assay)

N-((6-(2,4-dinitrophenyl)amino)-hexanoyl)-2-(4,4-difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-*s*-indacene-3-pentanoyl)-1-hexadecanoyl-*sn*-glycero-3-phosphoethanolamine, triethylammonium salt (PED6) is a commercially available fluorescently-labeled phospholipid, which is commercially available from Invitrogene and Molecular Probes. There is a quenching para-nitro phenyl (PNP) group in the sn3 position and a Bodipy fluorescein (FL) group in the sn2 position. Upon cleavage with Lp-PLA_2, the Bodipy FL group is liberated and then may result in an increase in fluorescence. Inhibitors of Lp-PLA_2 therefore prevent this cleavage and no fluorescent increase is observed.

The PED6 assay was run as an unquenched 10 μL assay. The source plate containing the compounds to be tested was prepared by making 1:3 (by volume) serial dilution of the compounds within DMSO on 384-well microplate. Then, 0.01 μL of the compounds on compound source plate were transferred into 384 well Greiner 784076 (black) plates using ECHO liquid dispenser. 5μL of recombinant human Lp-PLA_2 enzyme (4 nM (or 110 pM) rhLp-PLA_2 in assay buffer of 50 mM HEPES, pH 7.4, 150 mM NaCl, 1 mM CHAPS) was added to each well of the plate. Plates were centrifuged for 10 sec at 500 rpm. After 30 minutes preincubation, 5 μL of substrate (4 μM (or 5 μM) PED6 [from 5 mM DMSO stock] in assay buffer of 50 mM HEPES, pH 7.4, 150 mM NaCl, 1 mM CHAPS) was added to 384 well Greiner 784076 (black) plates. Plates were centrifuged for 10 sec at 500 rpm. The plate was covered to protect it from light and incubated for 20 min at room temperature. The plates were read for fluorescence intensity at ex: 480 / em: 540

using ViewLux microplate imager for Envision spectrofluroimeters. pIC50 data, curve and QC analysis was conducted by using XL fit module in Excel.

All compounds of Examples E1-E153 of the present invention were tested according to the recombinant human Lp-PLA_2 assay described above and were found to demonstrate inhibition activity to Lp-PLA_2. The pIC_{50} value for each compound was either reported in at least one experiment or the average of multiple experiments.

The pIC_{50} values in the recombinant human Lp-PLA_2 assay for compounds of Examples E1-E153 were at least 7.0.

The pIC_{50} values in the recombinant human Lp-PLA_2 assay for Examples E1-E3, E5-E8, E15, E17, E28, E35, E37, E46, E54, E56, E69, E71, E73, E75-E126, E133, E135, E140-E151, and E153 were at least 9.0.

For example, the pIC50 values of recombinant human Lp-PLA_2 assay for following examples are:

Example No.	rhLp-PLA_2 (PED6 assay) (pIC50)
E2	9.9
E4	8.5
E5	9.4
E8	9.4
E17	9.0
E23	7.9
E29	8.9
E46	9.9
E48	8.1
E51	7.3
E56	9.4
E62	8.4
E67	8.3
E82	9.9
E97	10.0
E107	9.4
E110	9.2
E144	10.6
E146	10.8

(2) PLA2 VIIB assay

PLA2 VIIB (also known as Novel Serine Dependent Lipase, NSDL) is a serine hydrolase with 40% amino acid identity with human Lp-PLA_2. Sequence comparisons indicate that the PLA VIIB active site catalytic triad positions are similar to those of Lp-PLA_2. Similar to Lp-PLA_2, it is capable of hydrolyzing oxidatively modified phospholipids and may be assayed using known Lp-PLA_2 substrates.

Upon cleavage by a phopholipase, PLA2 VIIB liberates a fluorescent Bodipy group. Recombinant human PLA2 VIIB is used as the phospholipase source in this assay, and compounds are screened to test their degree of inhibition in this assay. The assay is used to determine the degree of selectivity of the testing compounds between PLA2 VIIB and Lp-PLA_2.

The PLA2 VIIB assay was applied as an unquenched 10 μL assay. The source plate containing the compounds is prepared by making 1:3 (by volume) serial dilution of the compounds with pure DMSO on 384-well microplate. 0.01 μL of compounds on the compound source plate were transferred into 384 well Greiner 784076 (black) plates by ECHO liquid dispenser. 5 μL of Novel Serine Dependent Lipase (NSDL) enzyme (5 nM NSDL in assay buffer of 50 mM HEPES, pH 7.4, 150 mM NaCl, 1 mM CHAPS) was added to each well. Alternatively, in some instances, this step was carried out by adding 10 μL of recombinant human PLA2 VIIB (200 pM rhPLA_2 VIIB in assay buffer of 50 mM HEPES, pH 7.4, 150 mM NaCl, 1 mM CHAPS) to each well. Plates were centrifuged for 10 sec at 500 rpm. After 30 minutes preincubation, 5 μL of substrate (5 μM PED6 [from 5 mM DMSO stock] in assay buffer of 50mM HEPES, pH 7.4, 150 mM NaCl, 1 mM CHAPS) was added to 384 well Greiner 784076 (black) low-volume plates. Plates were kinetic read by starting read immediately after PED6 addition at ex: 480 / em: 540 using ViewLux microplate reader or Envision spectrofluorimeters. IC 50 data (which may be converted to pIC50 data), curve and QC analysis was conducted using XLfit module in Excel.

The compounds of Examples E1-E153 of the present invention were tested in PLA2 VIIB assay as described above. All tested compounds except Example E39, E61-E64, E132 and E137, had over 100 fold selectivity between human recombinant Lp-PLA_2 and PLA2 VIIB.

(3) Lipoprotein-associated phospholipase A2 (Lp-PLA_2) Human Plasma assay (also referred to as "Thio-PAF assay")

The human plasma assay utilizes a thioester analog of PAF (phosphatidylcholine), where hydrolysis yields to the formation of a phospholipid containing a free thiol group. The amount of thiol is quantitated continuously by reacting with CPM (7-diethylamino-3-(4'-maleimidylphenyl)-4-methylcoumarin), a maleimide which increases in fluoresence after Michael addition of thiols. This assay may detect the activity of Lp-PLA_2 in human plasma, as determined by specific inhibition by Lp-PLA_2 inhibitors.

The thio-PAF assay was run as a quenched 15 μL assay. Compounds source plate was prepared by making 1:3 (by volume) serial dilution of the compounds into pure DMSO on 384-well microplate. 0.01 μL of compounds on compound source plate were transferred to 384 well

Greiner 784076 (black) low-volume plates by ECHO liquid dispenser. 8 μL pooled human plasma, which was previously aliquoted and frozen, was added. Plates were centrifuged for 10 sec at 500 rpm. After 30 minutes preincubation, 2 μL of substrate solution comprising 2.5mM 2-thio-PAF [from ethanol stock], 32 μM CPM [from a DMSO stock] and 3.2 mM NEM (N-ethylmaleimide) [made fresh daily in DMSO] in assay buffer of 50mM HEPES, pH 7.4, 150 mM NaCl, 1 mM CHAPS was added to 384 well Greiner 784076 (black) low-volume plates by BRAVO liquid handling station. After 2 mins, reaction was quenched with 5 μL of 5% aqueous trifluoroacetic acid (TFA). Plates were covered to protect from light and incubated for 40 min at room temperature. Plates were read at ex: 380 / em: 485 using-Envision microplate reader. pIC50 data, curve and QC analysis was conducted by using XLFit module in Excel.

The compounds of Examples E1-E153 of the present invention were tested in thio-PAF assay as described above.

The pIC_{50} values in the thio-PAF assay for Examples E1-E153 were at least 5.0.

The pIC_{50} values in the thio-PAF assay for Examples E1-E4, E6-E10, E12, E15-E20, E27-E29, E35-E37, E40, E42, E45, E46, E49, E50, E52-E56, E58, E59, E61-E64, E66, E71-E80, E84-E99, E101-E128, E130, E133-E135, E139, E140, E142-E151, and E153 were at least 7.0.

The pIC_{50} values in the thio-PAF assay for Examples E45, E46, E56, E58, E61-E64, E66, E77, E84, E85, E87, E89-E93, E97-E99, E101, E102, E109, E111, E112, E114-E116, E123, E133, E135, E142-E151, and E153 were at least 8.0.

E. Methods of use

The compounds of the invention are inhibitors of Lp-PLA_2. Therefore, these compounds may be used in therapy, for example, in the treatment or prevention of diseases associated with the activity of Lp-PLA_2, which comprises treating a subject in need thereof with a therapeutically effective amount of an inhibitor of Lp-PLA_2. Accordingly, one aspect of the invention is directed to methods of treating or preventing diseases associated with the activity of Lp-PLA_2. As will be appreciated by those skilled in the art, a particular disease or its treatment may involve one or more underlying mechanisms associated with Lp-PLA_2 activity, including one or more of the mechanisms described herein.

In some embodiments, an inhibitor of Lp-PLA_2 according to the invention may be used in treating or preventing any of diseases disclosed in the following published patent applications: WO96/13484, WO96/19451, WO97/02242, WO97/12963, WO97/21675, WO97/21676, WO 97/41098, WO97/41099, WO99/24420, WO00/10980, WO00/66566, WO00/66567, WO00/68208, WO01/60805, WO02/30904, WO02/30911, WO03/015786, WO03/016287, WO03/041712, WO03/042179, WO03/042206, WO03/042218, WO03/086400, WO03/87088, WO08/048867, US 2008/0103156, US 2008/0090851, US 2008/0090852, WO08/048866, WO05/003118 CA

2530816A1), WO06/063811, WO06/063813, WO 2008/141176, JP 200188847, US 2008/0279846 A1, US 2010/0239565 A1, and US 2008/0280829 A1.

In certain embodiments, the compounds of the present invention may be used to treat or prevent any diseases that involve endothelial dysfunction, for example, atherosclerosis, (e.g. peripheral vascular atherosclerosis and cerebrovascular atherosclerosis), diabetes, hypertension, angina pectoris and after ischaemia and reperfusion.

In certain embodiments, the compounds of the present invention may be used to treat or prevent any disease that involves lipid oxidation in conjunction with enzyme activity, for example, in addition to conditions such as atherosclerosis and diabetes, other conditions such as rheumatoid arthritis, stroke, inflammatory conditions of the brain such as Alzheimer's Disease, various neuropsychiatric disorders such as schizophrenia, myocardial infarction, ischaemia, reperfusion injury, sepsis, and acute and chronic inflammation.

In certain embodiments, the compounds of the present invention may be used to lower the chances of having a cardiovascular event (such as a heart attack, myocardial infarction or stroke) in a patient with coronary heart disease.

In certain embodiments, the compounds of the present invention may be used to treat or prevent diseases that involve activated monocytes, macrophages or lymphocytes, as all of these cell types express Lp-PLA_2 including diseases involving activated macrophages such as M1, dendritic and/or other macrophages which generate oxidative stress. Exemplary diseases include, but are not limited to, psoriasis, rheumatoid arthritis, wound healing, chronic obstructive pulmonary disease (COPD), liver cirrhosis, atopic dermatitis, pulmonary emphysema, chronic pancreatitis, chronic gastritis, aortic aneurysm, atherosclerosis, multiple sclerosis, Alzheimer's disease, and autoimmune diseases such as lupus.

In other embodiments, the compounds of the invention may be used for the primary or secondary prevention of acute coronary events, e.g. caused by atherosclerosis; adjunctive therapy in the prevention of restenosis; or delaying the progression of diabetic or hypertensive renal insufficiency. Prevention includes treating a subject at risk of having such conditions.

In certain embodiments, the present invention provides methods of treating or preventing a neurological disease associated with an abnormal blood brain barrier (BBB) function, inflammation, and/or microglia activation in a subject in need thereof. In some embodiments, the present invention provides methods of treating a neurological disease associated with an abnormal blood brain barrier (BBB) function, inflammation, and/or microglia activation in a subject in need thereof. The methods comprise administering to the subject a therapeutically effective amount of a compound of the present invention. In a further embodiment, the abnormal BBB is a permeable BBB. In yet a further embodiment, the disease is a neurodegeneration disease. Such neurodegeneration diseases are, for example, but are not limited to, vascular dementia, Alzheimer's disease, Parkinson's disease and Huntington's disease. In one embodiment, the present invention

provides methods of treating or preventing disease associated with a subject with blood brain barrier (BBB) leakage. In some embodiment, the present invention provides methods of treating disease associated with a subject with blood brain barrier (BBB) leakage. Exemplary diseases include, but are not limited to, brain hemorrhage, cerebral amyloid angiopathy. In one embodiment, the neurodegeneration disease is Alzheimer's disease. In a certain embodiment, the neurodegeneration disease is vascular dementia. In one embodiment, the neurodegeneration disease is multiple sclerosis (MS).

In one embodiment, the compounds of the present invention may be used to treat a neurodegeneration disease in a subject. In one embodiment, the compounds of the present invention may be used to prevent a neurodegeneration disease in a subject. The methods comprise administering to a subject in need thereof a compound of the invention, e.g., as a pharmaceutical composition comprising a compound of the invention. In one embodiment, the compounds of the present invention may be used to treat a neurodegeneration disease in a subject. Exemplary neurodegeneration diseases include, but are not limited to, Alzheimer's disease, vascular dementia, Parkinson's disease and Huntington's disease. In a certain embodiment, the neurodegeneration disease described herein is associated with an abnormal blood brain barrier. In one embodiment, the subject which is administered an agent that inhibits the activity of Lp-PLA_2 is a human.

In one embodiment, the present invention provides methods of treating or preventing a subject with or at risk of vascular dementia. The methods comprise administering to the subject a compound of the invention, e.g., as a pharmaceutical composition comprising a therapeutically effective amount of a compound of the present invention. In one embodiment, the present invention provides methods of treating a subject with or at risk of vascular dementia. In a certain embodiment, the vascular dementia is associated with Alzheimer's disease.

In certain embodiments, the present invention provides methods of decreasing beta amyloid, referred to as "Aβ" accumulation in the brain of a subject. The methods comprise administering to a subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of a compound of the present invention. In a further embodiment, the beta amyloid is Abeta-42.

In certain embodiments, when a subject is administered a therapeutically effective amount of a compound of the present invention, the methods may further comprise administering to the subject another therapeutic agent that may be useful in treating the neurodegenerative disease for which the subject is being treated, or that may be a co-morbidity. In one embodiment, the present invention provides methods of slowing or delaying the progression of cognitive and function decline in patients with mild Alzheimer's disease. In certain embodiment, the compounds of the present invention described herein may be used as an adjunct to an agent that used to provide symptomatic treatment to patients with Alzheimer's disease. For example, when the neurodegenerative disease is or is similar to Alzheimer's disease, the subject may be treated with

other agents targeting Alzheimer's disease such as ARICEPT® or donepezil, COGNEX® or tacrine, EXELON® or rivastigmine, REMINYL® or galantamine, anti-amyloid vaccine, Abeta-lowering therapies, mental exercise or stimulation. In certain embodiments, the present invention provides methods of slowing or delaying the progression of cognitive or function decline in a patient with mild or moderate Alzheimer's disease and/ or cerebrovascular disease (CVD) comprise administering a therapeutically effective amount of a compound of the present invention to the patient who has been administered an agent used to provide symptomatic treatment to Alzheimer's disease (e.g., ARICEPT® or memantine) for 6 months or longer.

In certain embodiments, the present invention relates to methods of treating or preventing metabolic bone diseases by administering to the subject in need thereof a therapeutically effective amount of a compound of the present invention. In some embodiments, the present invention relates to methods of treating metabolic bone diseases by administering to the subject in need thereof a therapeutically effective amount of a compound of the present invention. Exemplary metabolic bone diseases include, diseases associated with loss of bone mass and density including, but are not limited to, osteoporosis and osteopenic related diseases. Exemplary osteoporosis and osteopenic related diseases include, but are not limited to, bone marrow abnormalities, dyslipidemia, Paget's diseases, type II diabetes, metabolic syndrome, insulin resistance, hyperparathyroidism and related diseases. In a further embodiment, the subject in need thereof is a human.

It is believed that methods of preventing osteoporosis and/or osteopenic diseases described herein may be affected by inhibiting the expression of Lp-PLA_2 and/or inhibiting the protein activity of Lp-PLA_2. Accordingly, some embodiments of the present invention provide methods for inhibiting Lp-PLA_2 by blocking enzyme activity. In a further embodiment, methods for inhibiting Lp-PLA_2 by reducing and/or down-regulating the expression of Lp-PLA_2 RNA are provided. In a further embodiment, preventing and/or reducing loss of bone mass and/or loss of bone density leads to preventing or reducing symptoms associated with metabolic bone diseases such as osteoporosis and/or osteopenic diseases.

In certain embodiments, the methods further comprise administering to a subject in need thereof additional therapeutic agents used in the treatment of metabolic bone diseases. For example, when the metabolic bone disease is osteoporosis additional therapeutic agents such as bisphosphates (e.g., alendronate, ibandromate, risedronate, calcitonin, raloxifene), a selective estrogen modulator (SERM), estrogen therapy, hormone replacement therapy (ET/HRT) and teriparatide may be used.

One aspect of the present invention provides methods for treating or preventing ocular diseases by administering a therapeutically effective amount of a compound of the present invention. In some embodiments, the present invention provides methods for treating ocular diseases by administering a therapeutically effective amount of a compound of the present

invention. Ocular diseases applicable in the present invention may be associated with the breakdown of the inner blood-retinal barrier (iBRB). Exemplary ocular diseases relate to diabetic ocular, which include macular edema, diabetic retinopathy, posterior uveitis, retinal vein occlusion and the like. Further, in one embodiment, the present invention relates to methods for treating ocular diseases by administering a compound of the present invention to inhibit Lp-PLA_2. Exemplary ocular diseases include, but are not limited to, central retinal vein occlusion, branched retinal vein occlusion, Irvine-Gass syndrome (post cataract and post-surgical), retinitis pigmentosa, pars planitis, birdshot retinochoroidopathy, epiretinal membrane, choroidal tumors, cystic macular edema, parafoveal telengiectasis, tractional maculopathies, vitreomacular traction syndromes, retinal detachment, neuroretinitis, idiopathic macular edema, and the like. More details of using Lp-PLA_2 inhibitor to treat eye diseases are provided in WO2012/080497, which is incorporated by reference herein.

Further, some embodiments of the present invention provide methods for treating or preventing diabetic macular edema in a subject. In some embodiments, the present invention provides methods for treating diabetic macular edema in a subject. The method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of the present invention.

In certain embodiments, the present invention provides methods of treating or preventing a subject with or at risk of macular edema. In some embodiments, the present invention provides methods of treating a subject with or at risk of macular edema. The methods comprise administering to the subject a therapeutically effective amount of a compound of the present invention. In a further embodiment, the macular edema is associated with diabetic ocular disease, for example, diabetic macular edema or diabetic retinopathy. In yet a further embodiment, the macular edema is associated with posterior uveitis.

In certain embodiments, the present invention provides methods of treating or preventing glaucoma or macular degeneration. In some embodiments, the present invention provides methods of treating glaucoma or macular degeneration. The methods comprise administering to the subject a therapeutically effective amount of a compound of the present invention.

In one embodiment, the present invention provides methods of treating or preventing a disease associated with the breakdown of the inner blood-retinal barrier in a subject in need thereof. In one embodiment, the present invention provides methods of treating a disease associated with the breakdown of the inner blood-retinal barrier in a subject in need thereof. The methods comprise administering to the subject a therapeutically effective amount of a compound of the present invention.

In one embodiment, systemic inflammatory diseases such as, juvenile rheumatoid arthritis, inflammatory bowel disease, Kawasaki disease, multiple sclerosis, sarcoidosis, polyarteritis, psoriatic arthritis, reactive arthritis, systemic lupus erythematosus, Vogt-Koyanagi-Harada

syndrome, Lyme disease, Bechet's disease, ankylosing sponsylitis, chronic granulomatous disease, enthesitis, may be the underlying cause of posterior uveitis affecting the retina, and which can result in macula edema. The present invention relates to methods for treating or preventing posterior uveitis or any of these systemic inflammatory diseases by administering a therapeutically effective amount of a compound of the present invention. In one embodiment, the present invention provides methods for treating posterior uveitis or any of these systemic inflammatory diseases by administering a therapeutically effective amount of a compound of the present invention.

It is believed that Lp-PLA_2 inhibitors may have beneficial effects on diseases associated with M1/M2 macrophage polarization. The belief is based on the following studies. A study was carried out by GSK to investigate the relationship between M1/M2 macrophage polarization and different diseases. 94 human markers described in Martinez FO et al., which distinguished M1 and M2 phenotypes was used against a GSK subscribed GeneLogic database. (*See* Martinez FO et al. (2006) J Immunol 177, 7303-7311.) The Connectivity Map methodology described in Lamb J et al. was used to identify the fraction of samples in each disease state having expression characteristics consistent with a M1-favoring or M2-favoring macrophage population. (*See* Lamb J et al. (2006) Science 313, 1929-1935) (PMID 17008526)). The study showed that liver cirrhosis, skin psoriasis, atopic dermatitis, pulmonary emphysema, chronic pancreatitis, chronic gastritis, and aortic aneurysm have M1/M2 imbalance.

A further study was carried out to study the impact of Lp-PLA_2 inhibitors on modulating M1/M2 imbalance. In this study, rats were induced to develop experimental autoimmune encephalomyelitis (EAE) by immunization with myelin basic protein (MBP) antigen and treated with a known Lp-PLA_2 inhibitor: 5-((9-Methoxy-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-2-yl)oxy)-2-(3-(trifluoromethyl)phenoxy)benzonitrile (*See* PCT application no. PCT/CN2011/001597). In this preventive treatment model, the compound was administered at day 0 (day of immunization) and continued to administer until day 22. The study lasted for 25 days. Rats were subsequently monitored for symptoms of EAE. Rats were immunized with MBP to develop EAE and symptoms were monitored daily. Plasma Lp-PLA_2 activity, OxLDL, and LysoPC concentration were determined at different time points through the course of EAE. The results showed that plasma Lp-PLA_2 activity, OxLDL, and LysoPC concentrations increased as the clinical EAE disease progressed in the model, which indicates that they played a role in the pathology development. Lp-PLA_2 inhibitor treatment led to reduction in clinical disease associated with decreased Lp-PLA_2 activity and LysoPC levels in rat EAE plasma. Hence, inhibition of Lp-PLA_2 activity is beneficial in ameliorating disease in the rat EAE model.

Ex vivo analysis of proinflammatory (M1) and anti-inflammatory (M2) markers in control and compound treated EAE rats. Splenic macrophages were harvested at day 13 post MBP-immunization and assayed for expression of a variety of markers by realtime PCR. CNS

infiltrating cells were harvested and macrophages were analyzed for expression of M1 and M2 markers by realtime PCR. Treatment with compound resulted in the decrease in M1 markers and increase in M2 markers, which potentially indicated the possibility of anti-inflammation and tissue repair.

Therefore, in certain embodiments, the present invention provides methods of treating or preventing disease associated with macrophage polarization, for example, M1/M2 macrophage polarization. In some embodiments, the present invention provides methods of treating disease associated with macrophage polarization, for example, M1/M2 macrophage polarization. Exemplary diseases associated with macrophage polarization include, but are not limited to, liver cirrhosis, skin psoriasis, atopic dermatitis, pulmonary emphysema, chronic pancreatitis, chronic gastritis, aortic aneurysm, atherosclerosis, multiple sclerosis, amyotrophic lateral sclerosis (ALS) and other autoimmune diseases that are associated with macrophage polarization.

Treatment and or prevention of a disease associated with Lp-PLA_2 activity may be achieved using a compound of this invention as a monotherapy, or in dual or multiple combination therapy. For example, the compounds of the present invention may be used to treat or prevent the disease described herein in combination with an anti-hyperlipidaemic, anti-atherosclerotic, anti-diabetic, anti-anginal, anti-inflammatory, or anti-hypertension agent or an agent for lowering Lipoprotein (a) (Lp(a)). Examples of the above include, but are not limited to, cholesterol synthesis inhibitors such as statins, anti-oxidants such as probucol, insulin sensitizers, calcium channel antagonists, and anti-inflammatory drugs such as non-steroidal anti-inflammatory Drugs (NSAIDs). Examples of agents for lowering Lp(a) include the aminophosphonates described in WO 97/02037, WO 98/28310, WO 98/28311 and WO 98/28312. In one embodiment, the compounds of the present invention may be used with one or more statins. The statins are a well-known class of cholesterol lowering agents and include atorvastatin, simvarstatin, pravastatin, cerivastatin, fluvastatin, lovastatin and rosuvastatin. In a certain embodiment, the compounds of the present invention may be used with an anti-diabetic agent or an insulin sensitizer. In one embodiment, a compound of the present invention may be used with PPAR gamma activators, for instance GI262570 (GlaxoSmithKline) and the glitazone class of compounds such as rosiglitazone, troglitazone and pioglitazone. Such agents may be administered in therapeutically effective amounts, e.g., as is known in the art, or lesser or greater amounts than known in the art provided that the amount administered is therapeutically effective.

Combination therapy includes administration of the therapeutic agents in separate dosage forms or together in a single dosage form. Combination therapy may involve simultaneous administration or separate administration of the therapeutic agents, which may be substantially simultaneous or substantially separate administration. Typically, combination therapy will involve administration of each agent such that therapeutically effective amounts of each agent are present in the subject's body in at least an overlapping period.

One aspect of the present invention provides the use of a compound of the present invention for the preparation of a medicament for carrying out a method described herein. Another aspect of the present invention provides a compound of the present invention for use in carrying out methods of treatment or prevention described herein. A further aspect of the present invention provides a compound described herein or a pharmaceutically acceptable salt thereof, for use in therapy.

F. Composition

The compounds of the present invention may be formulated into pharmaceutical compositions prior to administration to a subject. Accordingly, one aspect of the invention is directed to pharmaceutical compositions comprising a compound of the invention and one or more pharmaceutically-acceptable excipients. In accordance with another aspect of the invention, a process is provided for the preparation of a pharmaceutical composition including admixing a compound of the Formula (I) or salts thereof, solvates etc thereof, with one or more pharmaceutically acceptable excipient.

Pharmaceutical compositions may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain, for example, 0.1 mg, 0.5 mg, or 1 mg to 50 mg, 100 mg, 200 mg, 250 mg, 500 mg, 750 mg or 1g of a compound of the present invention, depending on the condition being treated, the route of administration and the age, weight and condition of the subject, or pharmaceutical compositions may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. In other embodiments, the unit dosage compositions are those containing a daily dose or sub-dose as described herein, or an appropriate fraction thereof, of an active ingredient. Furthermore, such pharmaceutical compositions may be prepared by any of the methods well-known to one skilled in the art.

A therapeutically effective amount of a compound of the present invention will depend upon a number of factors including, for example, the age and weight of the intended recipient, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration, and will ultimately be at the discretion of the attendant prescribing the medication. However, a therapeutically effective amount of a compound of present invention for the treatment of the disease described herein will generally be in the range of 0.1 to 100 mg/kg body weight of recipient per day and more usually in the range of 1 to 10 mg/kg body weight per day. Thus, for example, for a 70kg adult mammal, the actual amount per day would usually be from 70 to 700 mg and this amount may be given in a single dose per day or in a number of sub-doses per day as such as two, three, four, five or six doses per day. Or the dosing can be done intermittently, such as once every other day, once a week or once a month. It is envisaged that similar dosages would be appropriate for treatment of the other conditions referred to above.

The pharmaceutical compositions of the invention may contain one or more compounds of the invention. In some embodiments, the pharmaceutical compositions may contain more than one compound of the invention. For example, in some embodiments, the pharmaceutical compositions may contain two or more compounds of the invention. In addition, the pharmaceutical compositions may optionally further comprise one or more additional pharmaceutically active compounds.

As used herein, "pharmaceutically-acceptable excipient" means a pharmaceutically acceptable material, composition or vehicle involved in giving form or consistency to the pharmaceutical composition. Each excipient may be compatible with the other ingredients of the pharmaceutical composition when commingled such that interactions which would substantially reduce the efficacy of the compound of the invention when administered to a subject and interactions which would result in pharmaceutical compositions that are not pharmaceutically acceptable are avoided.

The compounds of the invention and the pharmaceutically-acceptable excipient or excipients may be formulated into a dosage form adapted for administration to the subject by the desired route of administration. For example, dosage forms include those adapted for (1) oral administration (including buccal or sublingual) such as tablets, capsules, caplets, pills, troches, powders, syrups, elixers, suspensions, solutions, emulsions, sachets, and cachets; (2) parenteral administration (including subcutaneous, intramuscular, intravenous or intradermal) such as sterile solutions, suspensions, and powders for reconstitution; (3) transdermal administration such as transdermal patches; (4) rectal administration such as suppositories; (5) nasal inhalation such as dry powders, aerosols, suspensions, and solutions; and (6) topical administration (including buccal, sublingual or transdermal) such as creams, ointments, lotions, solutions, pastes, sprays, foams, and gels. Such compositions may be prepared by any methods known in the art of pharmacy, for example by bringing into association a compound of Formula (I) with the carrier(s) or excipient(s).

Pharmaceutical compositions adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

Suitable pharmaceutically-acceptable excipients may vary depending upon the particular dosage form chosen. In addition, suitable pharmaceutically-acceptable excipients may be chosen for a particular function that they may serve in the composition. For example, certain pharmaceutically-acceptable excipients may be chosen for their ability to facilitate the production of uniform dosage forms. Certain pharmaceutically-acceptable excipients may be chosen for their ability to facilitate the production of stable dosage forms. Certain pharmaceutically-acceptable excipients may be chosen for their ability to facilitate carrying or transporting the compound or compounds of the invention once administered to the subject from an organ, or a portion of the

body, to another organ, or a portion of the body. Certain pharmaceutically-acceptable excipients may be chosen for their ability to enhance patient compliance.

Suitable pharmaceutically-acceptable excipients include the following types of excipients: diluents, fillers, binders, disintegrants, lubricants, glidants, granulating agents, coating agents, wetting agents, solvents, co-solvents, suspending agents, emulsifiers, sweeteners, flavoring agents, flavor masking agents, coloring agents, anticaking agents, hemectants, chelating agents, plasticizers, viscosity increasing agents, antioxidants, preservatives, stabilizers, surfactants, and buffering agents. The skilled artisan will appreciate that certain pharmaceutically-acceptable excipients may serve more than one function and may serve alternative functions depending on how much the excipient is present in the formulation and what other ingredients are present in the formulation.

Skilled artisans possess the knowledge and skill in the art to enable them to select suitable pharmaceutically-acceptable excipients in appropriate amounts for use in the invention. In addition, there are a number of resources that are available to the skilled artisan which describe pharmaceutically-acceptable excipients and may be useful in selecting suitable pharmaceutically-acceptable excipients. Examples include Remington's Pharmaceutical Sciences (Mack Publishing Company), The Handbook of Pharmaceutical Additives (Gower Publishing Limited), and The Handbook of Pharmaceutical Excipients (the American Pharmaceutical Association and the Pharmaceutical Press).

The pharmaceutical compositions of the invention are prepared using techniques and methods known to those skilled in the art. Some of the methods commonly used in the art are described in Remington's Pharmaceutical Sciences (Mack Publishing Company).

In one aspect, the invention is directed to a solid oral dosage form such as a tablet or capsule comprising a therapeutically effective amount of a compound of the invention and a diluent or filler. Suitable diluents and fillers include lactose, sucrose, dextrose, mannitol, sorbitol, starch (e.g. corn starch, potato starch, and pre-gelatinized starch), cellulose and its derivatives (e.g. microcrystalline cellulose), calcium sulfate, and dibasic calcium phosphate. The oral solid dosage form may further comprise a binder. Suitable binders include starch (e.g. corn starch, potato starch, and pre-gelatinized starch), gelatin, acacia, sodium alginate, alginic acid, tragacanth, guar gum, povidone, and cellulose and its derivatives (e.g. microcrystalline cellulose). The oral solid dosage form may further comprise a disintegrant. Suitable disintegrants include crospovidone, sodium starch glycolate, croscarmelose, alginic acid, and sodium carboxymethyl cellulose. The oral solid dosage form may further comprise a lubricant. Suitable lubricants include stearic acid, magnesium stearate, calcium stearate, and talc.

In certain embodiment, the present invention is directed to a pharmaceutical composition comprising 0.01 to 1000 mg of one or more compounds of Formula (I) described herein or a

pharmaceutically acceptable salt thereof and 0.01 to 5 g of one or more pharmaceutically acceptable excipients.

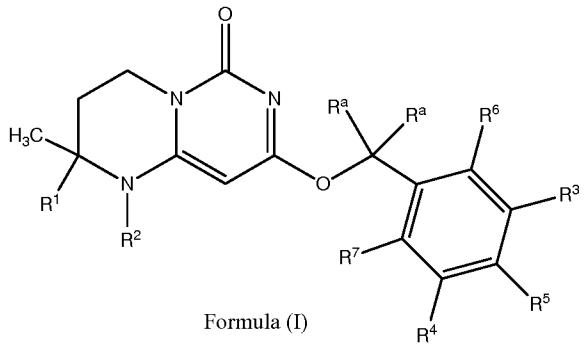
In another embodiment, the present invention is directed to a pharmaceutical composition for the treatment of neurodegeneration disease comprising a compound described herein or a pharmaceutically acceptable salt thereof.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

WHAT IS CLAIMED IS:

1. A compound of Formula (I) or a pharmaceutically acceptable salt thereof,



Formula (I)

wherein:

R^1 is H or CH_3;

R^2 is H or C_{1-3}alkyl;

R^3 is halo, CN or H;

R^a is H or D;

R^4 is H, F or CN;

R^5 is selected from the group consisting of halo, H, CN, and –O-R^8,

wherein R^8 is selected from the group consisting of C_{1-3}alkyl, C_{4-6}cycloalkyl, phenyl, pyridinyl, and pyrimidinyl, wherein phenyl, pyridinyl or pyrimidinyl is optionally substituted with one or more substituents independently selected from halo or CF_3; and

R^6 and R^7 are each independently H or F.

2. The compound of Formula (I) or a pharmaceutically acceptable salt thereof according to claim 1, wherein R^1 is H.

3. The compound of Formula (I) or a pharmaceutically acceptable salt thereof according to claim 1 or claim 2, wherein R^2 is CH_3 or C_2H_5.

4. The compound of Formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 3, wherein R^a is H.

5. The compound of Formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 4, wherein R^3 is F.

6. The compound of Formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 5, wherein R^4 is F.

7. The compound of Formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 6, wherein R^5 is F or H.

8. The compound of Formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 7, wherein R^5 is –O-R^8, wherein R^8 is pyrimidinyl or pyridinyl substituted with one or two substituents independently selected from F or CF_3.

9. The compound of Formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 7, wherein R^5 is –O-R^8, wherein R^8 is phenyl substituted with one or two substituents independently selected from F or CF_3.

10. The compound of Formula (I) according to claim 1, which is a compound of any one of Examples 1 to 153, a free base form, a free acid form or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1-10, and one or more pharmaceutically acceptable excipients.

12. A method for treating neurodegeneration disease in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1-10.

13. The method according to claim 12, wherein the neurodegeneration disease is Alzheimer's disease.

14. A method for treating atherosclerosis in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1-10.

15. The method according to any one of claims 12-14, wherein the subject is human.

16. A use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 10, in the manufacture of a medicament for treating a disease according to any one of claims 12 to 15.

17. A compound of Formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 10 for use in the treatment according to any one of claims 12 to 15.

18. A compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 10 for use in therapy.