Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2899091 A1 2014/07/31

(21) 2 899 091

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2014/01/23
(87) Date publication PCT/PCT Publication Date: 2014/07/31
(85) Entrée phase nationale/National Entry: 2015/07/23
(86) N° demande PCT/PCT Application No.: EP 2014/051286
(87) N° publication PCT/PCT Publication No.: 2014/114694
(30) Priorités/Priorities: 2013/01/25 (CNPCT/CN2013/070976); 2013/12/12 (CNPCT/CN2013/001556)

(51) Cl.Int./Int.Cl. *C07D 487/04* (2006.01), *A61K 31/519* (2006.01), *A61P 25/28* (2006.01)

(71) Demandeur/Applicant:
GLAXOSMITHKLINE INTELLECTUAL PROPERTY DEVELOPMENT LIMITED, GB

(72) Inventeurs/Inventors:
SANG, YINGXIA, CN;
WAN, ZEHONG, CN;
ZHANG, QING, CN

(74) Agent: GOWLING LAFLEUR HENDERSON LLP

(54) Titre : INHIBITEURS DE LA PHOSPHOLIPASE ASSOCIEE AUX LIPOPROTEINES A2 (LP-PLA$_2$) A BASE DE 2,3-DIHYDRO-IMIDAZOL[1,2-C]PYRIMIDIN-5(1 H)-ONE

(54) Title: 2,3-DIHYDROIMIDAZOL[1,2-C]PYRIMIDIN-5(1H)-ONE BASED LIPOPROTEIN-ASSOCIATED PHOSPHOLIPASE A2 (LP-PLA$_2$) INHIBITORS

(57) Abrégé/Abstract:
The present invention relates to novel 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.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
31 July 2014 (31.07.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/114694 A1

(51) **International Patent Classification**:
C07D 487/04 (2006.01) ***A61P 25/28*** (2006.01)
A61K 31/519 (2006.01)

(21) **International Application Number**:
PCT/EP2014/051286

(22) **International Filing Date**:
23 January 2014 (23.01.2014)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
PCT/CN2013/070976
25 January 2013 (25.01.2013) CN
PCT/CN2013/001556
12 December 2013 (12.12.2013) CN

(71) **Applicant**: **GLAXOSMITHKLINE INTELLECTUAL PROPERTY DEVELOPMENT LIMITED** [GB/GB]; 980 Great West Road, Brentford Middlesex TW8 9GS (GB).

(72) **Inventors**: **SANG, Yingxia**; GlaxoSmithKline (China) R&D Co Ltd, Building 3, 898 Halei Road, Zhangjiang Hi-Tech Park, Shanghai, 201203 (CN). **WAN, Zehong**; GlaxoSmithKline (China) R&D Co Ltd, Building 3, 898 Halei Road, Zhangjiang Hi-Tech Park, Shanghai, 201203 (CN). **ZHANG, Qing**; GlaxoSmithKline (China) R&D Co Ltd, Building 3, 898 Halei Road, Zhangjiang Hi-Tech Park, Shanghai, 201203 (CN).

(74) **Agents**: **KONDO, Rie** et al.; GlaxoSmithKline, Global Patents CN925.1, 980 Great West Road, Brentford Middlesex TW8 9GS (GB).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

WO 2014/114694 A1

(54) **Title**: 2,3-DIHYDROIMIDAZOL[1,2-C]PYRIMIDIN-5(1H)-ONE BASED LIPOPROTEIN-ASSOCIATED PHOSPHOLIPASE A2 ($LP\text{-}PLA_2$) INHIBITORS

(57) **Abstract**: The present invention relates to novel compounds that inhibit $Lp\text{-}PLA_2$ activity, processes for their preparation, to compositions containing them and to their use in the treatment of diseases associated with the activity of $Lp\text{-}PLA_2$, for example atherosclerosis, Alzheimer's disease.

2,3-DIHYDROIMIDAZOL[1 ,2-C]PYRIMIDIN-5(1 H)-ONE BASED LIPOPROTEIN-ASSOCIATED PHOSPHOLIPASE A2 (LP-PLA2) INHIBITORS

RELATED APPLICATION

The present application claims priority from PCT International Application No. PCT/CN2013/070976 filed on January 25, 2013 and PCT/CN2013/001556 filed on December 12, 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 bicyclic [5,6] imidazo pyrimidone compounds, processes for their preparation, intermediates useful in their preparation, pharmaceutical compositions containing them, and their use in therapy for the treatment of diseases 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 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 disease 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 studies indicate 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 levels of oxidized LDL have 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, studies show 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, these studies provide 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, use of an Lp-PLA_2 inhibitor in a diabetic and hypercholesterolemia swine model demonstrated that blood-brain-barrier leakage and 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.

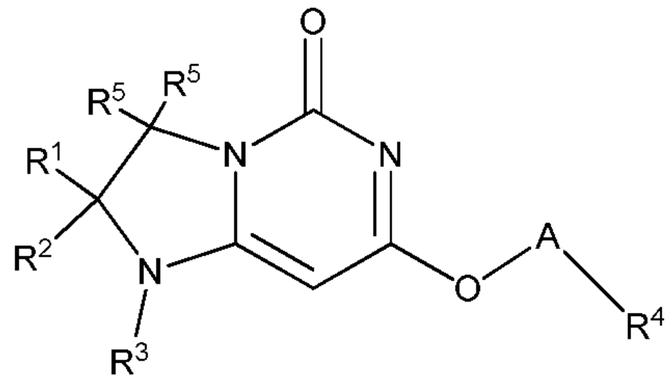
In addition to the inflammatory effect, LysoPC has been implicated in leukocyte activation, induction of apoptosis and mediation of endothelial dysfunction (*See*, e.g., Wilensky et al., *Current Opinion in Lipidology*, 20, 415–420 (2009)). Therefore, it is believed that Lp-PLA_2 inhibitors can be used 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 ocular disease.

Glaucoma and age-related macular degeneration (AMD) are retina neurodegenerative diseases. Studies suggest 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) and pharmaceutically acceptable salts thereof,



Formula (I)

wherein

R^1 and R^2 are independently CH_3 or H;

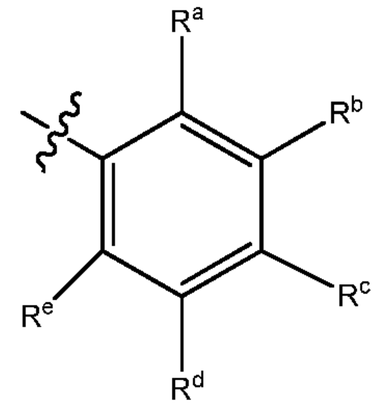
R^3 is H, C_{1-3}alkyl, cyclopropyl, or CD_3,

with the proviso that when R^3 is H, CD_3, or C_{1-3}alkyl, at least one of R^1 or R^2 is CH_3;

each R^5 is H or D;

A is $(CH_2)_n$ or $(CD_2)_n$, wherein each occurrence of n is 1 or 2; and

R^4 is cyclopentyl or thiophenyl optionally substituted with one or more Cl, or R^4 is



wherein

R^a is H or F,

R^b is H, CN, or halo,

R^c is H, halo, or -O-Y wherein Y is phenyl, pyridinyl, or pyrimidinyl, wherein phenyl, pyridinyl, or pyrimidinyl is optionally substituted with one or two substituents independently selected from the group consisting of CN, CF_3 and halo;

R^d is selected from the group consisting of F, H, CN and CF_3, and

R^e is 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 characterized by gradual and progressive loss of bone tissue. Metabolic bone diseases described herein are metabolic bone diseases where 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_{1-3} 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).

"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 cyclopentyl, thiophenyl, phenyl, pyridinyl, or pyrimidinyl may be unsubstituted, or the group may be substituted with one or more substituent as defined herein.

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), CN, 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.

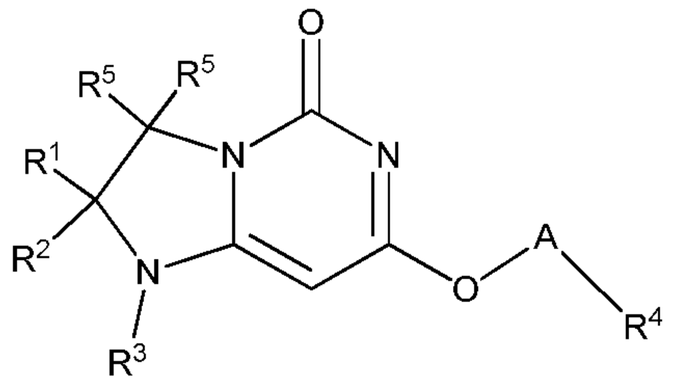
As used herein, "subject" means a mammalian subject (*e.g.,* dog, cat, horse, cow, sheep, goat, monkey, etc.), and particularly human subjects including both male and female subjects, and including neonatal, infant, juvenile, adolescent, adult and geriatric subjects, and further including various races 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 and R^2 are independently CH_3 or H;

R^3 is H, C_{1-3}alkyl, cyclopropyl, or CD_3,

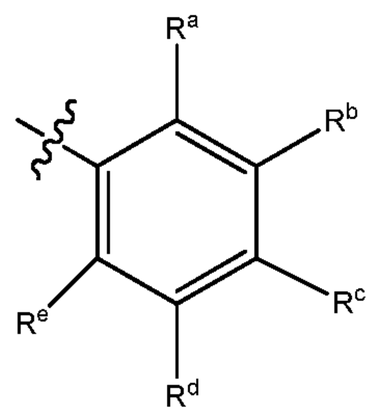
with the proviso that when R^3 is H, CD_3, or C_{1-3}alkyl, at least one of R^1 or R^2 is CH_3;

each R^5 is H or D;

A is $(CH_2)_n$ or $(CD_2)_n$, wherein each occurrence of n is 1 or 2; and

R^4 is cyclopentyl or thiophenyl optionally substituted with one or more Cl,

or R^4 is



wherein

R^a is H or F,

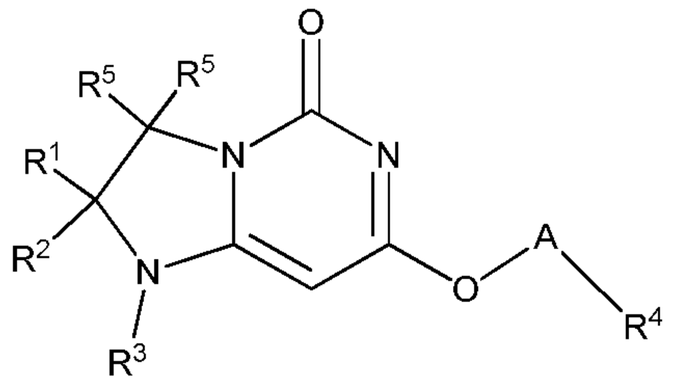
R^b is H, CN, or halo,

R^c is H, halo, or -O-Y wherein Y is phenyl, pyridinyl, or pyrimidinyl, wherein phenyl, pyridinyl, or pyrimidinyl is optionally substituted with one or two substituents independently selected from the group consisting of CN, CF_3 and halo;

R^d is selected from the group consisting of F, H, CN and CF_3, and

R^e is H or F.

In some embodiments, the present invention provides compounds of Formula I and pharmaceutically acceptable salts thereof



Formula (I)

wherein

R^1 and R^2 are independently CH_3 or H;

R^3 is H, C_{1-3}alkyl, cyclopropyl, or CD_3,

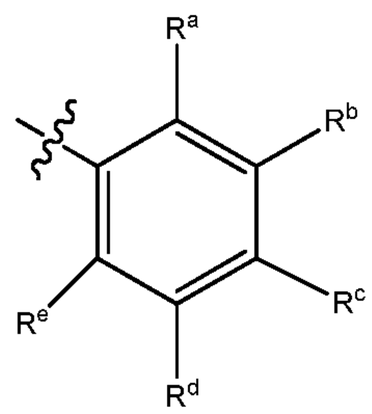
with the proviso that when R^3 is H, CD_3, or C_{1-3}alkyl, at least one of R^1 or R^2 is CH_3;

each R^5 is H or D;

A is $(CH_2)_n$ or $(CD_2)_n$, wherein each occurrence of n is 1 or 2; and

R^4 is cyclopentyl or thiophenyl optionally substituted with one or more Cl,

or R^4 is



wherein

R^a is H or F,

R^b is H, CN, or F,

R^c is H, halo, or -O-Y wherein Y is phenyl, pyridinyl, or pyrimidinyl, wherein phenyl, pyridinyl, or pyrimidinyl is optionally substituted with one or two substituents independently selected from the group consisting of CN, CF_3 and halo;

R^d is H, CN or F, and

R^e is H or F.

In one embodiment, this invention relates to compounds of Formula (I), wherein R^1 or R^2 is CH_3, or pharmaceutically acceptable salts thereof. In the other embodiment, this invention relates to compounds of Formula (I), wherein R^1 and R^2 are CH_3, or pharmaceutically acceptable salts thereof.

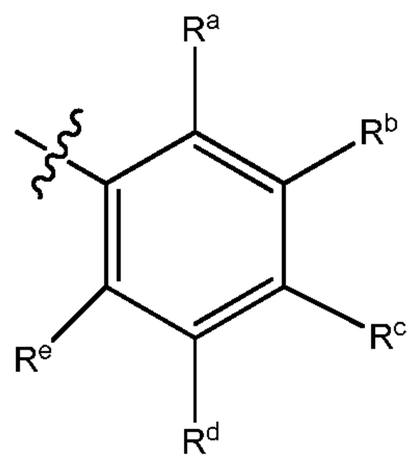
In one embodiment, this invention relates to compounds of Formula (I) and any of the above applicable embodiments, wherein R^3 is CH_3 or pharmaceutically acceptable salts thereof. Yet, in one embodiment, this invention also relates to compounds of Formula (I) and any of the

above applicable embodiments, wherein R^3 is isopropyl or pharmaceutically acceptable salts thereof.

In one embodiment, this invention relates to compounds of Formula (I) and any of the above applicable embodiments, wherein A is CH_2 and n is 1 or pharmaceutically acceptable salts thereof. In one embodiment, this invention relates to compounds of Formula (I) and any of the above applicable embodiments, wherein A is CD_2 and n is 1 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 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



wherein

R^a is H or F,

R^b is H, CN, or halo,

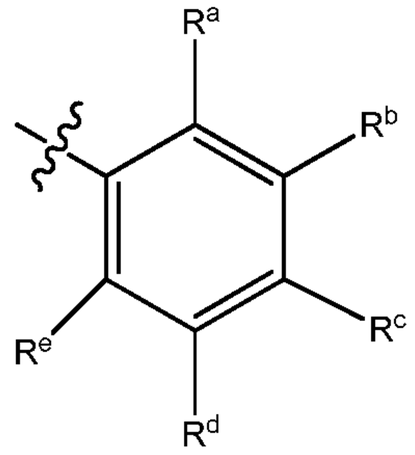
R^c is H, halo, or -O-Y wherein Y is phenyl, pyridinyl, or pyrimidinyl, wherein phenyl, pyridinyl, or pyrimidinyl is optionally substituted with one or two substituents independently selected from the group consisting of CN, CF_3 and halo;

R^d is selected from the group consisting of F, H, CN and CF_3, and

R^e 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^4 is



wherein

R^a is H,

R^b is H or F,

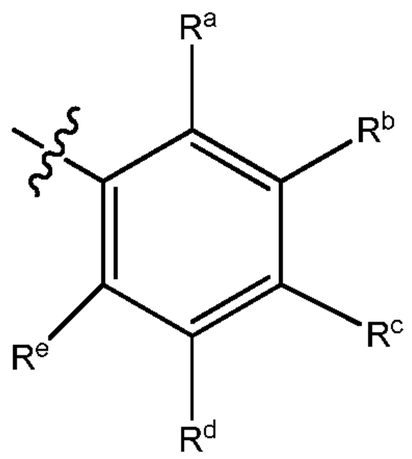
R^c is -O-Y wherein Y is pyridinyl or pyrimidinyl substituted with one substituent selected from the group consisting of F, Cl and CF_3,

R^d is H or F, and

R^e 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



wherein

R^a is H or F,

R^b is H, CN or F,

R^c is F or H,

R^d is H, CN or F, and

R^e is H or F,

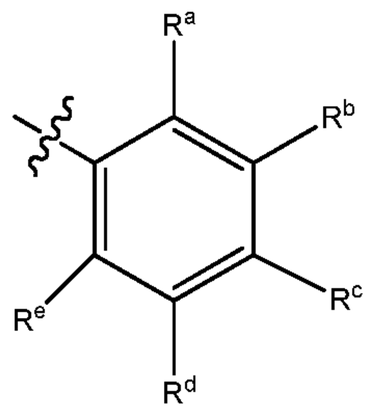
or pharmaceutically acceptable salts thereof.

In one embodiment, the invention relates to compounds of Formula (I) and any of the above applicable embodiments, wherein R^4 is cyclopentyl or thiophenyl optionally substituted with one or two Cl.

In one embodiment, this invention relates to compounds of Formula (I) and any of the above applicable embodiments, wherein R^1, R^2 and R^3 are CH_3 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^1 or R^2 is CH_3, and R^3 is isopropyl 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^1 or R^2 is CH_3, and R^3 is CH_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^1 and R^2 are CH_3, R^3 is CH_3 or isopropyl, and R^4 is cyclopentyl or thiophenyl optionally substituted with one or more Cl, 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^1 and R^2 are CH_3, R^3 is CH_3 or isopropyl, and R^4 is



wherein

R^a is H or F,

R^b is H, CN, or halo,

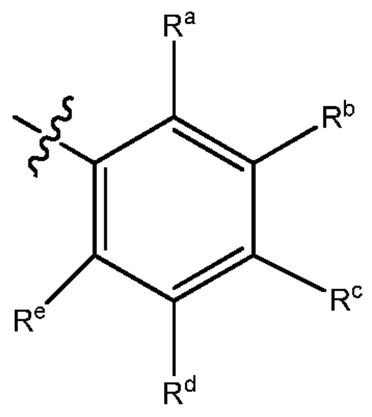
R^c is H or halo,

R^d is selected from the group consisting of F, H, CN and CF_3, and

R^e is H or 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^1 and R^2 are CH_3, R^3 is CH_3 or isopropyl, and R^4 is



wherein

R^a is H or F,

R^b is H, CN, or halo,

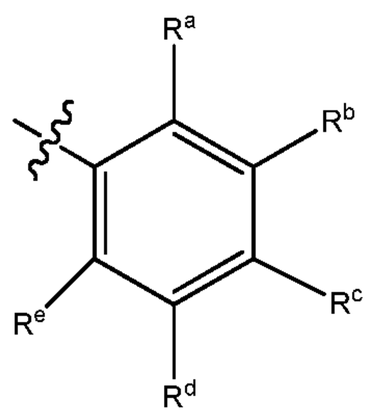
R^c is -O-Y wherein Y is pyridinyl or pyrimidinyl substituted with one substituent selected from the group consisting of F, Cl and CF_3,

R^d is H, CN or F, and

R^e is H or 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^1 or R^2 is CH_3, R^3 is CH_3, and R^4 is



wherein

R^a is H or F,

R^b is H, CN, or halo,

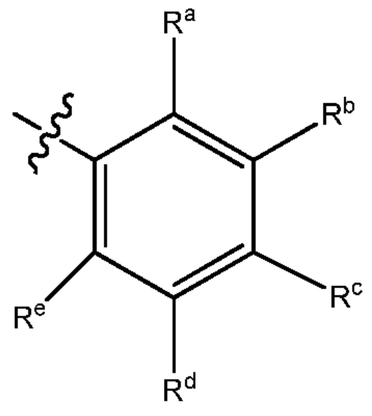
R^c is -O-Y wherein Y is pyridinyl substituted with one substituent selected from the group consisting of F, Cl and CF_3,

R^d is H, CN or F, and

R^e is H or 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^1 and R^2 are CH_3, R^3 is CH_3, and R^4 is



wherein

R^a is H or F,

R^b is H, CN, or halo,

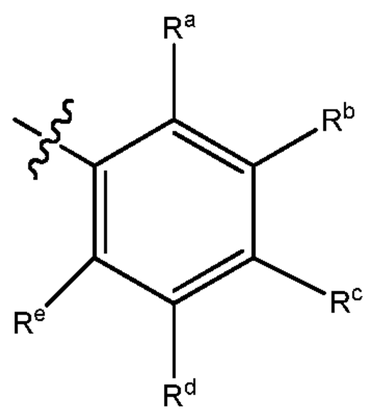
R^c is -O-Y wherein Y is pyridinyl substituted with one substituent selected from the group consisting of F, Cl and CF_3,

R^d is H, CN or F, and

R^e is H or 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^1 or R^2 is CH_3, R^3 is H, and R^4 is



wherein

R^a is H or F,

R^b is H, CN, or halo,

R^c is -O-Y wherein Y is pyridinyl substituted with one substituent selected from the group consisting of F, Cl and CF_3,

R^d is H, CN or F, and

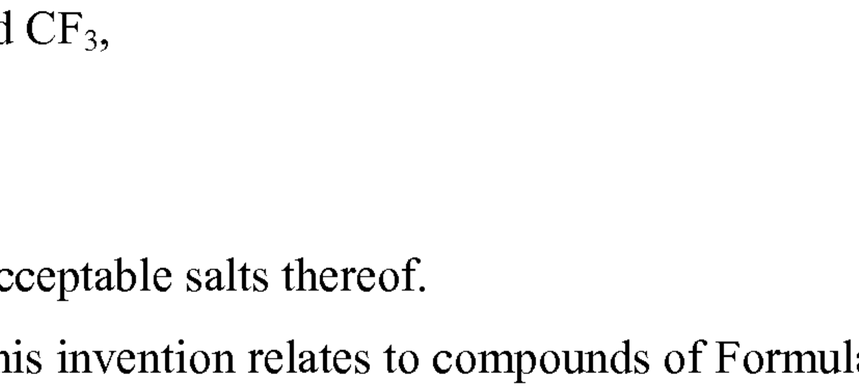
R^e is H or F,

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^1 and R^2 are CH_3, R^3 is CH_3 or isopropyl, n is 1, and R^4 is phenyl substituted with two F and R^5 is H, or pharmaceutically acceptable salts thereof.

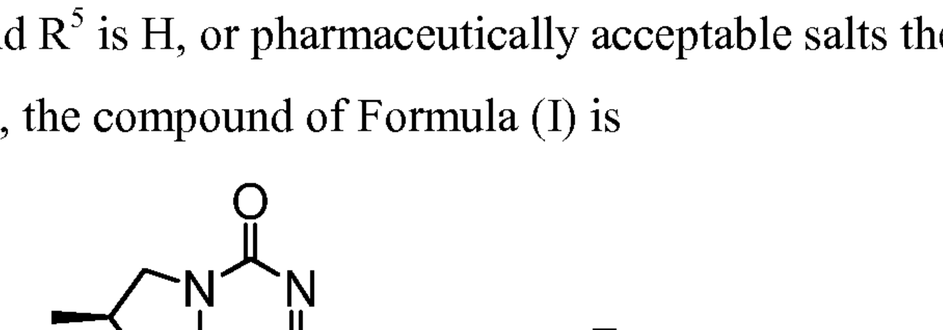
In one embodiment, this invention relates to compounds of Formula (I) and any of the above applicable embodiments, wherein R^1 and R^2 are CH_3, R^3 is isopropyl, n is 1, and R^4 is phenyl substituted with two F and R^5 is H, or pharmaceutically acceptable salts thereof.

In one embodiment, the compound of Formula (I) is



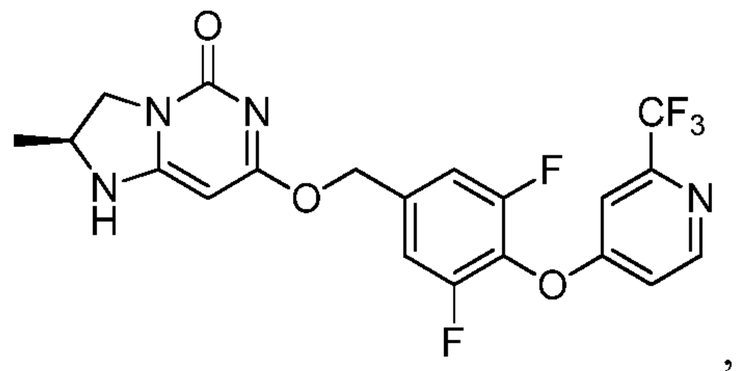
or pharmaceutically acceptable salts thereof.

In one embodiment, the compound of Formula (I) is



or pharmaceutically acceptable salts thereof.

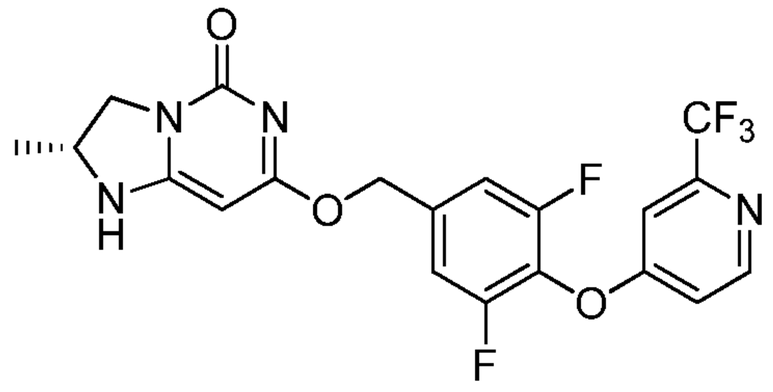
In one embodiment, the compound of Formula (I) is



,

or pharmaceutically acceptable salts thereof.

In one embodiment, the compound of Formula (I) is



,

or pharmaceutically acceptable salts thereof.

In one embodiment, the compound of Formula (I) is a compound of any one of Examples 1 to 138, a free base, free acid, 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.

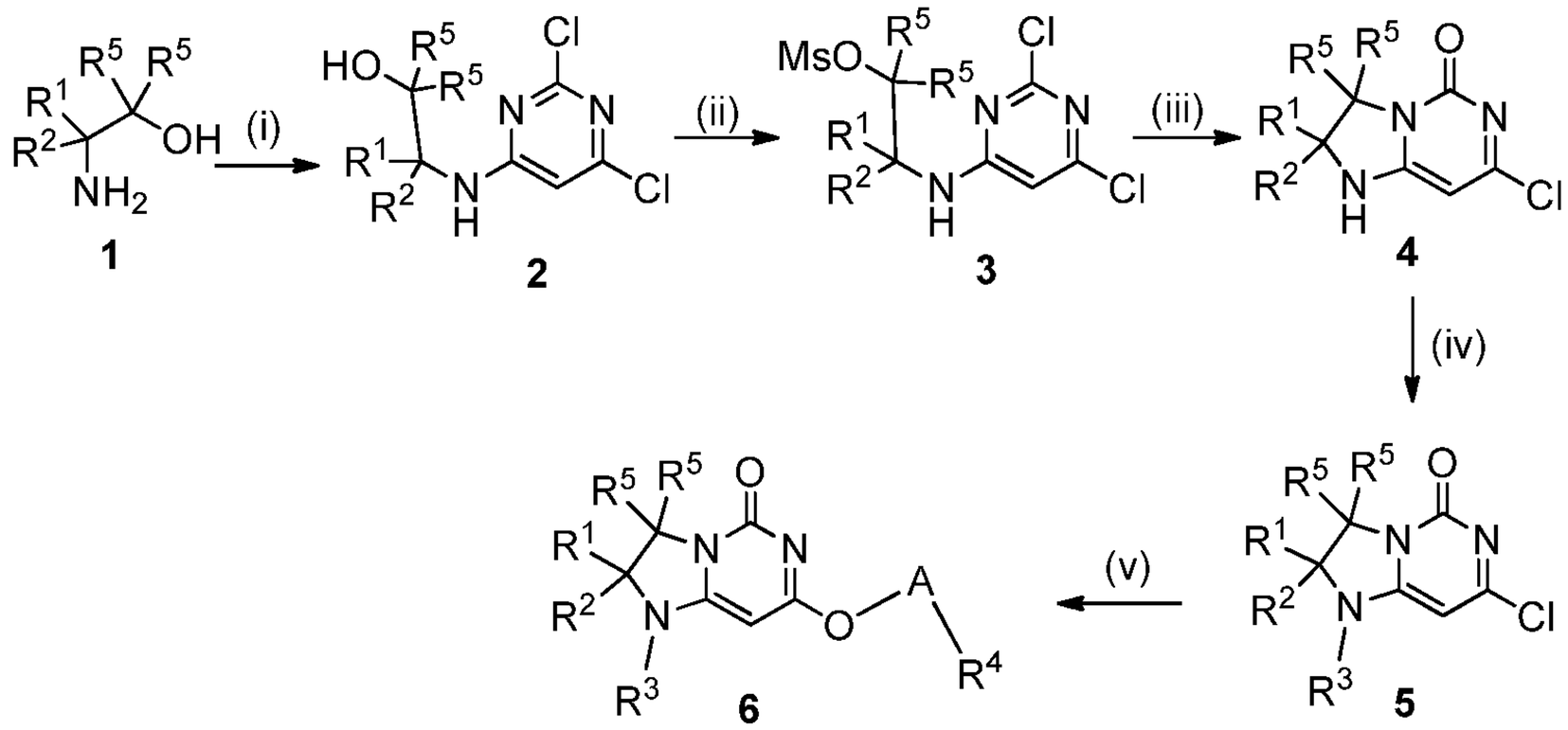
C. Synthesis of Compounds

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 Synthetic Scheme 1



R^1, R^2, R^3, R^4, R^5 and A are as defined in Formula (I).

General Synthetic Scheme 1 provides an exemplary synthesis for compound 6. The starting material or reagents for Scheme 1 are commercially available (for example TCI Shanghai Fine Chemicals) or are made from commercially available starting materials using methods known to those skilled in the art.

Step (i) may be carried out by reacting $H_2NC(R^1)(R^2)$ $C(R^5)_2OH$ with trichloropyrimidine using appropriate reagents such as triethylamine in an appropriate solvent such as acetonitrile under a suitable temperature such as room temperature to provide compound 2.

Step (ii) may use appropriate reagents such as methanesulfonyl chloride (MsCl) and triethylamine (NEt_3) in a suitable solvent such as dichloromethane (DCM) at a suitable temperature such as room temperature.

Step (iii) may be taken place by reacting compound 3 with a suitable reagent such as potassium carbonate (K_2CO_3) at an appropriate temperature such as 80 °C.

Step (iv) may be carried out by reacting compound 4 with alkylating reagents such as R_3-X (wherein X is halo) in the presence of a suitable base such as potassium carbonate (K_2CO_3) under suitable solvent such as acetonitrile at suitable temperature 90 °C to provide compound 5.

Step (v) may be carried out by reacting compound 5 with R_4-A-OH in the presence of suitable base such as sodium hydride (NaH) in a suitable solvent such as N,N-dimethyformamide (DMF) at suitable temperature such as room temperature to provide compound 6.

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

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

Aq. – aqueous

Brine-saturated NaCl aqueous solution

CDI –1,1'-carbonyldiimidazole

CV – Column volumes

DCM – dichloromethane

DMAP–4-dimethylaminopyridine

DMF – dimethylformamide

DMSO – dimethyl sulfoxide

EA – ethyl acetate

FC– flash chromatography (usually conducted on silica gel column)

MTBE –methyl tertiary butyl ether

TFA – trifluoro acetic acid

THF – tetrahydrofuran

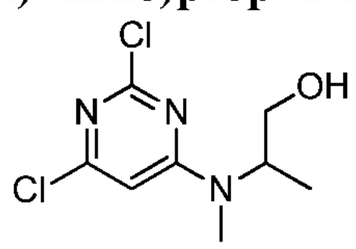
PE – petroleum ether

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

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

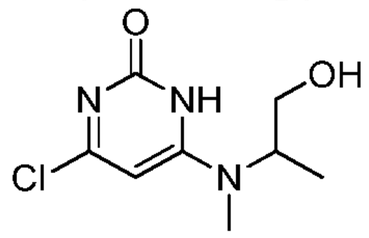


To a mixture of 2,4,6-trichloropyrimidine (5.0 g, 27 mmol) and triethylamine (11 mL, 82 mmol) in acetonitrile (20 mL) was slowly added a solution of 2-(methylamino)propan-1-ol (2.9 g, 33 mmol) in N,N-dimethylformamide (DMF) (2 mL) at 0 °C. The reaction mixture was stirred at same temperature for 1h, then filtered through a thin pad of celite and concentrated. Purification via silica gel flash chromatography (petroleum ether/ethyl acetate = 4/1~1/1) afforded the title product as an oil.

LC-MS (ESI): m/z 236$[M + H]^+$; 1.09 min (ret time).

D2

4-chloro-6-((1-hydroxypropan-2-yl)(methyl)amino)pyrimidin-2(1H)-one

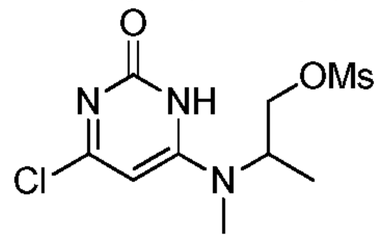


To a mixture of 2-((2,6-dichloropyrimidin-4-yl)(methyl)amino)propan-1-ol (3.0 g, 13 mmol) and LiOH one hydrate (1.60 g, 38 mmol) in water (2 mL) was added H_2O_2 (0.78 mL, 25 mmol). The reaction mixture was stirred at 45 °C for 3 h, then quenched with $Na_2S_3O_3$ solution (2 mL) and concentrated. Purification via Biotage Spla HPFC system (C18, mobile phase: 0.01% NH_4HCO_3 in H_2O/CH_3CN, 10~95%, 9.5 min, 30 mL/min) afforded the title product as a white solid.

LC-MS (ESI): m/z 218 $[M + H]^+$; 0.73 min (ret time).

D3

2-((6-chloro-2-oxo-2,3-dihydropyrimidin-4-yl)(methyl)amino)propyl methanesulfonate

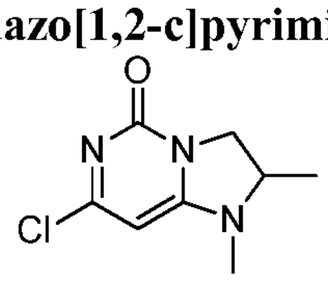


To a mixture of 4-chloro-6-((1-hydroxypropan-2-yl)(methyl)amino)pyrimidin-2(1H)-one (1.0 g, 4.6 mmol) and triethylamine (1.9 mL, 14 mmol) in tetrahydrofuran (THF) (15 mL) was added MsCl (0.72 mL, 9.2 mmol) at 0~5°C. The reaction mixture was stirred at room temperature overnight, and then quenched with 1 M $NaHCO_3$ solution, diluted with water and extracted with ethyl acetate. Combined organic parts were dried over anhydrous Na_2SO_4, filtered and concentrated to give the residue as yellow oil. The crude was used into next step without further purification.

LC-MS (ESI): m/z 296$[M + H]^+$; 1.04 min (ret time).

D4

7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

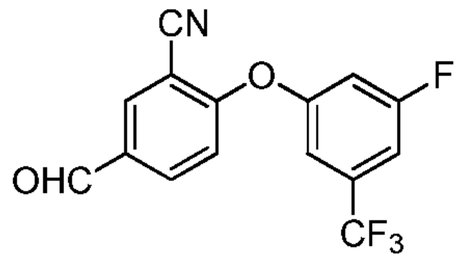


A mixture of 2-((6-chloro-2-oxo-2,3-dihydropyrimidin-4-yl)(methyl)amino)propyl methanesulfonate (800 mg, 2.71 mmol) and K_2CO_3 (748 mg, 5.41 mmol) in acetonitrile (6 mL) was stirred at 80°C for 3h, cooled to room temperature and concentrated. Purification via Biotage Spla HPFC system (C18, mobile phase: 0.01% NH_4HCO_3/H_2O, 10~95% CH_3CN, 9.5 min, 30mL/min) afforded the title product as an orange solid.

LC-MS (ESI): m/z 200 $[M + H]^+$; 0.77 min (ret time).

D5

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

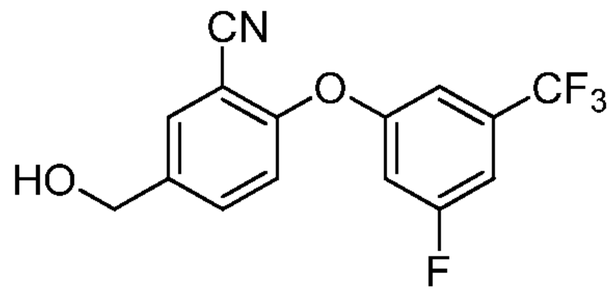


The title compound was prepared by a procedure similar to that described for **D30** starting from 3-fluoro-5-(trifluoromethyl)phenol and 2-fluoro-5-formylbenzonitrile.

LC-MS (ESI): m/z 308 $[M - H]^-$; 1.78 min (ret time).

D6

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

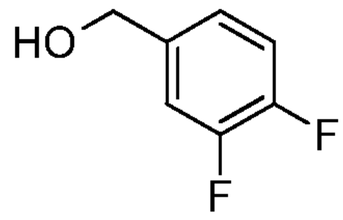


The title compound was prepared by a procedure similar to that described for **D31** starting from 2-(3-fluoro-5-(trifluoromethyl)phenoxy)-5-formylbenzonitrile.

LC-MS (ESI): m/z 294 $[M - H_2O + H]^+$; 1.71 min (ret time).

D7

(3,4-difluorophenyl)methanol

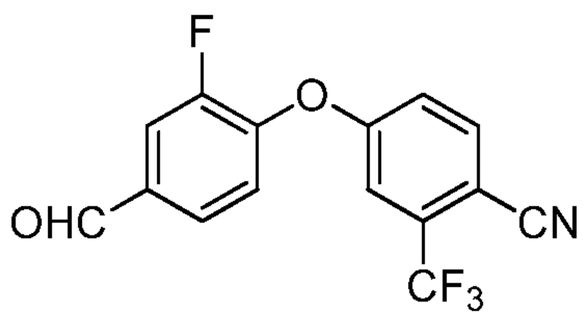


To a solution of 3,4-difluorobenzaldehyde (200 mg, 1.41 mmol) in methanol (4 mL) was added $NaBH_4$ (80 mg, 2.1 mmol). The reaction mixture was stirred at rt for 10 min., then diluted with water and extracted with ethyl acetate. The organic part was separated, washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude was used into next step without further purification.

LCMS (ESI): m/z 308 $[M + H]^+$; 2.03min (ret time)

D8

4-(2-fluoro-4-formylphenoxy)-2-(trifluoromethyl)benzonitrile

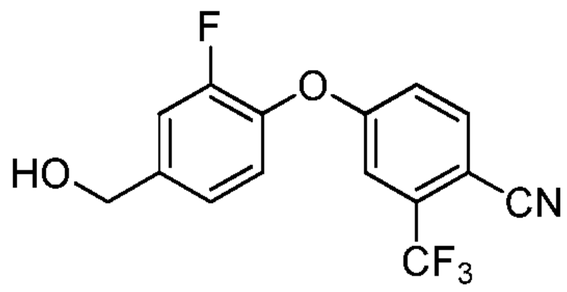


The title compound was prepared by a procedure similar to that described for **D30** starting from 3,4-difluorobenzaldehyde and 4-hydroxy-2-(trifluoromethyl)–benzonitrile.

LC-MS (ESI): m/z 308 $[M - H]^-$; 1.40 min (ret time).

D9

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

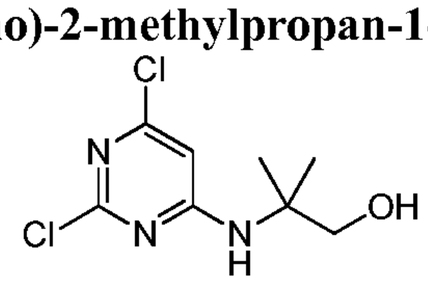


The title compound was prepared by a procedure similar to that described for **D31** starting from 4-(2-fluoro-4-formylphenoxy)-2-(trifluoromethyl)benzonitrile.

LC-MS (ESI): m/z 310 $[M - H]^-$; 1.30 min (ret time).

D10

2-((2,6-dichloropyrimidin-4-yl)amino)-2-methylpropan-1-ol

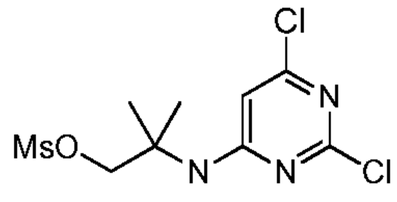


To a solution of 2,4,6-trichloropyrimidine (20.0 g, 109 mmol) in acetonitrile (500 mL) was added triethylamine (11.03 g, 109 mmol) at 0°C. After 5 min at room temperature, 2-amino-2-methylpropan-1-ol (9.72 g, 109 mmol) was added portionwise. The reaction mixture was stirred for another 1 h at room temperature, filtered and concentrated. Purification via silica gel column (ethyl acetate/petroleum ether = 1/10 to 1/1) afforded the title product.

LC-MS (ESI): m/z 236 $[M + H]^+$; 1.11 min (ret time)

D11

2-((2,6-dichloropyrimidin-4-yl)amino)-2-methylpropyl methanesulfonate

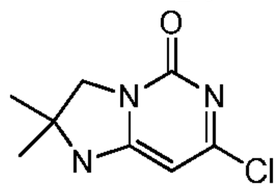


To a solution of 2-((2,6-dichloropyrimidin-4-yl)amino)-2-methylpropan-1-ol (6.67 g, 28.3 mmol) and triethylamine (11.59 mL, 85 mmol) in dichloromethane (DCM) (100 mL) was added dropwise MsCl (4.40 mL, 56.5 mmol) at 0 °C. The reaction mixture was stirred at rt for 2 h, diluted with DCM (100 mL), washed with water (50 mL×3) then brine (50 mL×2), dried over Na_2SO_4, filtered and concentrated to give the residue as a yellow solid, which was used for the next step without further purification.

LC-MS (ESI): m/z 314 $[M + H]^+$; 1.04 min (ret time)

D12

7-chloro-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one



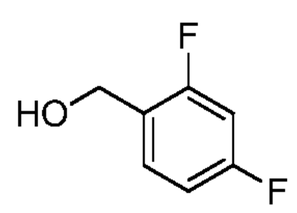
To a solution of 2-((2,6-dichloropyrimidin-4-yl)amino)-2-methylpropyl methanesulfonate (3.00 g, 9.55 mmol) in 1,4-dioxane (15 mL) and water (15 mL) was added potassium carbonate (4.62 g, 33.4 mmol). The reaction mixture was stirred at 80 °C for 2 h, filtered, extracted with ethyl acetate

(5 mL×2), dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product, which was used into next step without further purification.

LC-MS (ESI): m/z 200 $[M + H]^+$; 0.73 min (ret time)

D13

(2,4-difluorophenyl)methanol

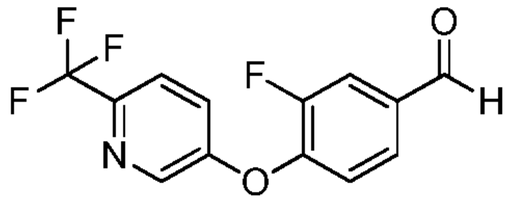


The title compound was prepared by a procedure similar to that described for **D31** starting from 2,4-difluorobenzaldehyde.

LC-MS (ESI): m/z 127 $[M - H_2O + H]^+$; 1.93 min (ret time).

D14

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

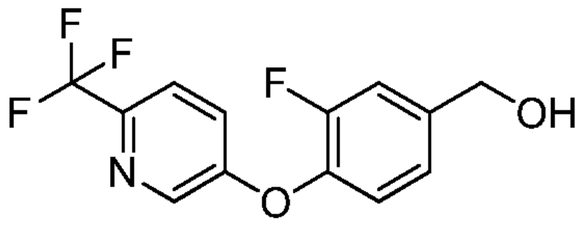


The title compound was prepared by a procedure similar to that described for **D30** starting from 6-(trifluoromethyl)3-pyridinol and 3,4-difluorobenzaldehyde.

LC-MS (ESI): m/z 286$[M + H]^+$, 3.20 min (ret time).

D15

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

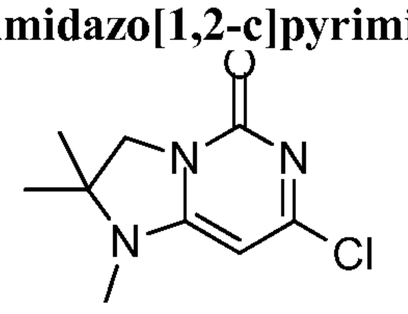


The title compound was prepared by a procedure similar to that described for **D31** starting from 3-fluoro-4-((6-(trifluoromethyl)-3-pyridinyl)oxy)benzaldehyde.

LC-MS (ESI): m/z 288$[M + H]^+$, 2.88 min (ret time).

D16

7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one



To a solution of 7-chloro-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one (500 mg, 2.505 mmol) and dimethyl carbonate (0.422 ml, 5.01 mmol) in N,N-dimethylf-ormamide (DMF) (16 ml) was added K_2CO_3 (346 mg, 2.51 mmol). The reaction mixture was sealed in a microwave and irradiated with a microwave using initial normal to 140 °C for 1h. Purification via reverse phase chromarography (water/acetonitrile, 0.05% TFA in water) afforded the title product as a brown solid.

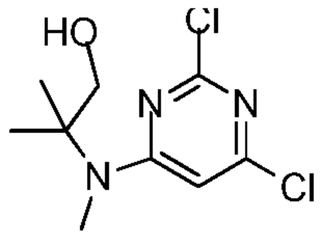
LC-MS (ESI): m/z 214 $[M + H]^+$; 1.25 min (ret time)

An alternative synthetic process is provided below: methanesulfonyl chloride (11.91 g, 104 mmol) was added dropwise to a solution of 2-((2,6-dichloropyrimidin-4-yl)(methyl)amino)-2-methylpropan-1-ol (13 g, 52 mmol) and triethylamine (15.78 g, 156 mmol) in tetrahydrofuran (THF) (100 mL) at 0 ^{0}C with stirring. The reaction mixture was stirred at 25 ^{0}C overnight, and then concentrated. The residue was purified by silica gel column (DCM/MeOH 10/1) to afford the title compound (9.8 g, 88%) as a yellow solid.

LC-MS (ESI): m/z 214 $[M + H]^+$; 0.85 min (ret time).

D16(a)

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

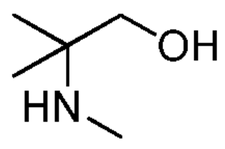


2-methyl-2-(methylamino)propan-1-ol (6.5 g, 63.0 mmol) in acetonitrile (50 mL) was added dropwise to solution of 2,4,6-trichloropyrimidine (11.56 g, 63.0 mmol) and triethylamine (8.78 mL, 63.0 mmol) in acetonitrile (100 mL) at 0 ^{0}C with stirring. The reaction mixture was stirred at 25 ^{0}C for 6 h, and then concentrated. EtOAc (20 mL) was then added. The organic phase was washed with water, brine, dried over sodium sulphate, and concentrated in vacuo. The residue was purified by silica gel column (PE/EA 5/1 to 3/1) to afford the title compound (2.5 g, 15.9%) as a yellow solid.

LC-MS (ESI): m/z 250 $[M + H]^+$; 0.95 min (ret time).

D16 (b)

2-methyl-2-(methylamino)propan-1-ol



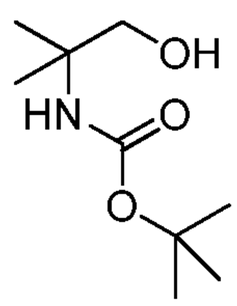
27

A solution of tert-butyl(1-hydroxy-2-methylpropan-2-yl)carbamate (67 g, 354 mmol) in tetrahydrofuran (THF) (150 mL) was added dropwise to a stirred solution of $LiAlH_4$ (40.3 g, 1062 mmol) in tetrahydrofuran (THF) (400 mL) under nitrogen at 0 ^{0}C with stirring. The reaction mixture was stirred at 90 ^{0}C overnight, cooled, and then quenched by adding water (40.5 mL) at 0 ^{0}C. Then aqueous NaOH (15%, 40.5 mL) was added dropwise followed by adding water (40.5 mL). The mixture was stirred for 1 h, and then filtered through ceilite. The organic layer was dried over sodium sulphate, and then concentrated in vacuo to afford the title compound (28 g, 77%) without further purification.

LC-MS (ESI): m/z 104 $[M + H]^+$; 0.24 min (ret time).

D16(c)

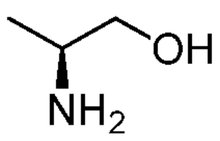
tert-butyl (1-hydroxy-2-methylpropan-2-yl)carbamate



Di-tert-butyl dicarbonate (118 g, 539 mmol) was added slowly to a solution of 2-amino-2-methylpropan-1ol (40 g, 449 mmol), sodium bicarbonate (0.82 g, 9.76 mmol) and sodium carbonate (0.82 g, 7.74 mmol) in 1,4-dioxane(120 mL)/water (40 mL) at 0 ^{0}C with stirring. Then, the reaction mixture was stirred at 25 ^{0}C for 6 h, concentrated, and then EtOAc (1000 mL) was added. The organic phase was washed with water and saturated brine, dried over sodium sulphate, and concentrated in vacuo to afford the title compound (94 g, 111%) as a white solid.

D17

(S)-2-aminopropan-1-ol

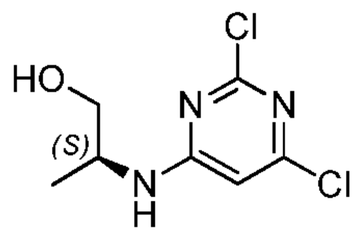


To a suspension of $LiAlH_4$ (20.5 g, 539 mmol) in dry THF (80 mL) was added dropwise a solution of (S)-2-aminopropanoic acid (12.0 g, 135 mmol) in THF (120 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, then room temperature for 3 h and refluxed for 9 h. The reaction mixture was cooled to 0 °C, then diluted with 15% NaOH solution (25 mL), stirred at room temperature for 2 h and filtered. The filtrate was dried over anhydrous Na_2SO_4, filtered and concentrated. The crude was used into next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ: 3.49(m, 1H), 3.19 (m, 1H), 2.95 (m, 1H), 2.42 (s, 3H), 0.99 (d, *J* =6.4 Hz, 3H).

D18

(S)-2-((2,6-dichloropyrimidin-4-yl)amino)propan-1-ol

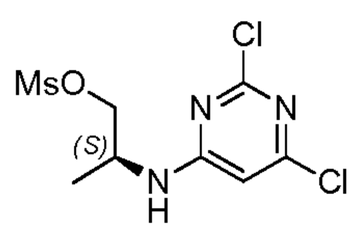


To a solution of 2,4,6-trichloropyrimidine (4.70 g, 25.6 mmol) and triethylamine (7.78 g, 77.0 mmol) in acetonitrile (150 mL) was added a solution of (S)-2-aminopropan-1-ol (2.31 g, 30.7 mmol) in acetonitrile (150 mL) at 0 °C. The reaction mixture was allowed to room temperature and stirred for 12 h, then filtered and concentrated. Purification via column chromatography (elutriant: petroleum ether/ethyl acetate = 4/1) afforded the title product.

LC-MS (ESI): m/z 222 $[M + H]^+$; 0.86 min (ret time).

D19

(S)-2-((2,6-dichloropyrimidin-4-yl)amino)propyl methanesulfonate

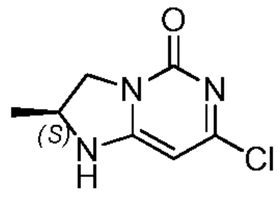


To a solution of (S)-2-((2,6-dichloropyrimidin-4-yl)amino)propan-1-ol (2.10 g, 9.46 mmol), MsCl (1.19 g, 10.4 mmol) and triethylamine (2.87 g, 28.4 mmol) in tetrahydrofuran (THF) (60 mL) was added dropwise methanesulfonyl chloride (1.19 g, 10.4 mmol) at 0°C. The reaction mixture was stirred at room temperature for 16 h, then filtered and concentrated. The crude was used into next step without further purification.

LC-MS (ESI): m/z 300 $[M + H]^+$;1.029 (ret time).

D20

(S)-7-chloro-2-methyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

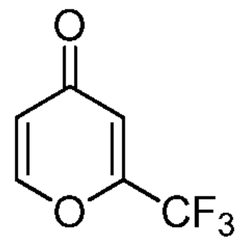


A mixture of (S)-2-((2,6-dichloropyrimidin-4-yl)amino)propyl methanesulfonate (1.86 g, 6.20 mmol) and potassium carbonate (2.57 g, 18.6 mmol) in 1,4-dioxane (100 mL) and water (20 mL) was stirred at 100 °C for 2 h, then concentrated to remove solvent, diluted with water (20 mL), stirred at room temperature for 10 min and filtered. The filter cake was recrystallized with DCM (30 mL) to give the title product.

LC-MS (ESI): m/z 186 $[M + H]^+$; 0.41 min (ret time).

D21

2-(trifluoromethyl)-4H-pyran-4-one

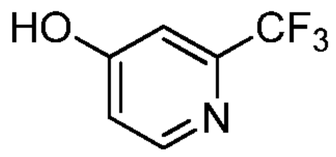


To a mixture of KO^{t}Bu (729 mg, 6.49 mmol) in diethyl ether (10 mL) at 5 °C were added methyl 2,2,2-trifluoroacetate (767 mg, 5.99 mmol) and (*E*)-4-methoxybut-3-en-2-one (500 mg, 4.99 mmol). The reaction mixture was stirred at rt for 3h, then quenched with water and extracted with ether. Combined organic parts were dried over Na_2SO_4, filtered and concentrated. The residue was dissolved in isopropanol (150 mL) and 35% solution of hydrochloric acid (0.5 mL) and refluxed for 45 min. Then the solution was concentrated to remove alcohol and fractionated at reduced pressure to get the title product as yellow oil.

LC-MS (ESI): m/z 165 $[M + H]^+$; 1.30 min (ret time).

D22

2-(trifluoromethyl)pyridin-4-ol

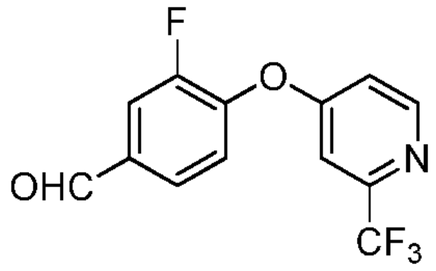


To a solution of 2-(trifluoromethyl)-4H-pyran-4-one (350 mg, 2.13 mmol) in MeOH (15 mL) was added ammonium hydroxide (14.8 mL, 107 mmol) at 25 °C. The reaction mixture was stirred at 90 °C for 10 h, then concentrated, diluted with water and extracted with ethyl acetate. Combined organic parts were dried over Na_2SO_4, filtered and con. Purification via Biotage Spla HPFC system (C18, mobile phase: 0.01% NH_4HCO_3, CH_3CN/water, 10~95%, 9.5 min, 30 mL/min) afforded the title product (280 mg) as a yellow solid.

LC-MS (ESI): m/z 164 $[M + H]^+$; 1.30 min (ret time).

D23

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 3,4-difluorobenzaldehyde and 2-(trifluoromethyl)pyridin-4-ol.

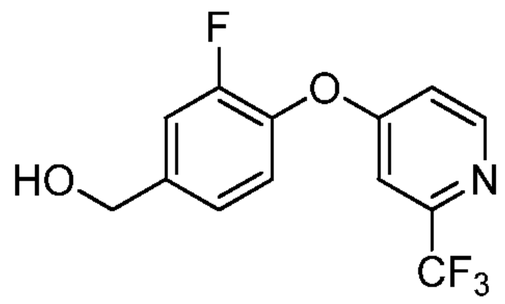
LC-MS (ESI): m/z 286 $[M + H]^+$; 1.65 min (ret time).

An alternative synthetic process is provided: A mixture of 2-(trifluoromethyl)pyridin-4-ol (5 g, 30.7 mmol), 3,4-difluorobenzaldehyde (4.36 g, 30.7 mmol) and potassium carbonate (8.47 g, 61.3 mmol) in N,N-dimethylformamide (DMF) (30 mL) was sealed and heated under microwave at 110 °C for 3 h. Then the reaction mixture was cooled, and concentrated in vacuo. The concentrate was purified via Biotage column (Hexane/EtOAc 100% to 3/1) to afford the title compound (6.4 g, 37.6%) as a white solid.

LCMS (ESI): m/z 286 $[M + H]^+$; 1.35 min (ret time)

D24

(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.

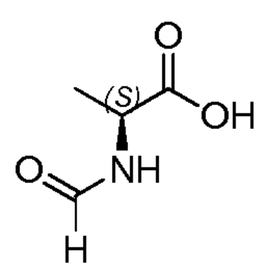
LC-MS (ESI): m/z 288 $[M + H]^+$; 1.62 min (ret time).

An alternative synthetic process is provided: $NaBH_4$ (0.849 g, 22.44 mmol) was added to a solution of 3-fluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)benzaldehyde (6.4 g, 22.44 mmol) in methanol (40 mL) at 0 ^{0}C. The reaction mixture was stirred at rt for 2 h, quenched with water (2 mL), filtered and then washed with EtOAc (50 mL). The filtrate was concentrated in vacuo, and the residue was purified by chromatography on silica gel (200-300 mesh, PE/EtOAc 2/1) to afford the title compound (3.7 g, 48%) as a colorless oil.

LCMS (ESI): m/z 288 $[M + H]^+$; 1.23 min (ret time)

D25

(S)-2-formamidopropanoic acid



To a solution of (S)-2-aminopropanoic acid (27 g, 303 mmol) in formic acid (80 %, 115 mL) was added dropwise acetic anhydride (70 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min, then room temperature for 4 h, diluted with water (70 mL) and concentrated to remove solvent. Recrystallization with water afforded the title product.

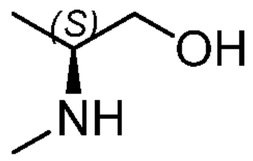
^{1}H NMR (400 MHz, DMSO-d6) δ: 8.34 (br, 1H), 7.96 (s, 1H), 4.24 (m, 1H), 1.25 (d, J = 4.4 Hz, 3H)

An alternative synthetic process is provided: acetic anhydride (51.9 mL, 549 mmol) was added dropwise to a solution of (S)-2-aminopropanoic acid (20 g, 224 mmol) in formic acid (69.6 mL, 1845 mmol) at 0 °C with stirring. The reaction mixture was stirred at 0 °C for 10 min, then was stirred at rt for 4 h, treated with water (52 mL) and concentrated in vacuo. The residue was re-crystallized from water to afford the title compound (7.1 g, 27.0% yield).

LC-MS (ESI): m/z 118 $[M + H]^+$; 0.28 min (ret time).

D26

(S)-2-(methylamino)propan-1-ol



To a suspension of $LiAlH_4$ (2.59 g, 68.3 mmol) in dry THF (80 mL) was added dropwise a solution of (S)-2-formamidopropanoic acid (2.00 g, 17.1 mmol) in THF (120 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min then rt for 3 h and reflux for 9 h. The mixture was cooled at 0 °C and 15% NaOH solution (5 mL) was slowly added. The reaction mixture was stirred at rt for 2 h, filtered, dried over Na_2SO_4, and concentrated. The crude product was used into next step without further purification.

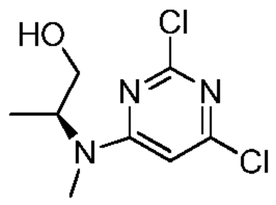
^{1}H NMR (400 MHz, $CDCl_3$): δ: 3.61(m, 1H), 3.27 (m, 1H), 2.67 (m, 1H), 2.42 (s, 3H), 1.04 (d, J = 7.6 Hz, 3H).

An alternative synthetic process is provided: a solution of (S)-2-formamidopropanoic acid (D25) (5.3 g, 45.3 mmol) in THF (100 mL) was added dropwise to a suspension of $LiAlH_4$ (6.87 g, 181 mmol) in THF (200 mL) at 0 °C with stirring. The reaction mixture was stirred at 0 °C for 30 min, and then stirred at rt for 3 h and then was refluxxed for 9 h. The reaction mixture was cooled to 0 °C and 15% NaOH aqueous solution (6.9 mL) was added dropwise and then followed by addition of water (6.9 mL). The reaction mixture was stirred at rt for 2 h, filtered, and the solids dried over Na_2SO_4, and concentrated to afford the title compound without further purification (3.7 g, 92%).

LC-MS (ESI): m/z 90.3 $[M + H]^+$; 0.25 min (ret time).

D27

(S)-2-((2,6-dichloropyrimidin-4-yl)(methyl)amino)propan-1-ol



To a solution of 2,4,6-trichloropyrimidine (5.42 mL, 47.1 mmol) and triethylamine (19.7 mL, 141 mmol) in acetonitrile (40 mL) was slowly added (S)-2-(methylamino)propan-1-ol (6.30 g, 70.7 mmol) in N,N-dimethylformamide (DMF) (3.00 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1h, filtered, dried over anhydrous Na_2SO_4, and concentrated. Purification via flash chromatography column (petroleum ether/ethyl acetate = 10/1) afforded the title product.

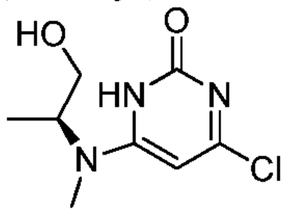
^1H NMR (400 MHz, $CDCl_3$): δ: 6.37 (br, 1H), 3.71(m, 2H), 2.93 (br, 3H), 2.03 (br, 1H), 1.18 (d, *J* = 6.8 Hz, 3H).

An alternative synthetic process is provided: (S)-2-(methylamino)propan-1-ol (D26) (3.72 g, 41.7 mmol) in acetonitrile was added dropwise to a solution of 2,4,6-trichloropyrimidine (7.65 g, 41.7 mmol) and triethylamine (5.82 mL, 41.7 mmol) in acetonitrile (200 mL) at 0 °C with stirring. The reaction mixture was stirred at 30 °C overnight, and then concentrated. Then, EtOAc (20 mL) was added to the concentrated portion, and the organic phase was washed with water, saturated brine, and dried over sodium sulphate, and then concentrated. The concentrated portion was purified via flash chromatography column (silica gel) (PE/EA = 5/1 to 3/1) to afford the title compound (4.5 g, 45.7%) as a yellow solid.

LC-MS (ESI): m/z 236 $[M + H]^+$; 0.88 min (ret time).

<u>D28</u>

(S)-4-chloro-6-((1-hydroxypropan-2-yl)(methyl)amino)pyrimidin-2(1H)-one

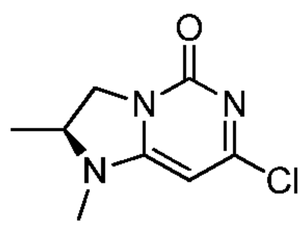


To a mixture of (S)-2-((2,6-dichloropyrimidin-4-yl)(methyl)amino)propan-1-ol (3.80 g, 16.1 mmol) and lithium hydroxide one hydrate (2.03 g, 48.3 mmol) in water (5 mL) was added hydrogen peroxide (3.29 mL, 32.2 mmol). The reaction mixture was stirred at 45 °C for 3h, diluted with water (30 mL) and extracted with ethyl acetate (20 mL×3). Combined organic parts were dried over Na_2SO_4, filtered and concentrated. The crude was used into next step without purification.

LC-MS (ESI): m/z 218 $[M + H]^+$; 0.63 min (ret time).

<u>D29</u>

(S)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one



To a solution of (S)-4-chloro-6-((1-hydroxypropan-2-yl)(methyl)amino)pyrimidin-2(1H)-one (700 mg, 3.22 mmol) and triethylamine (1.35 mL, 9.65 mmol) in tetrahydrofuran (THF) (20 mL) was added methanesulfonyl chloride (0.508 mL, 6.43 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 h and concentrated. Purification via Prep-HPLC (column: YMC -Actus Triart C18 150×30mm; 2 M NH_3 in methanol) afforded the title product.

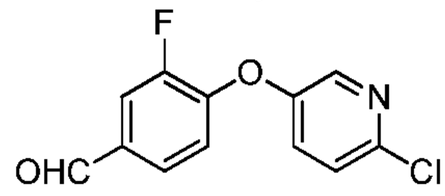
LC-MS (ESI): m/z 200 $[M + H]^+$; 0.34 min (ret time).

An alternative synthetic process is provided: methanesulfonyl chloride (4.27 g, 37.3 mmol) was added dropwise to a solution of (S)-2-((2,6-dichloropyrimidin-4-yl)(methyl)amino)propan-1-ol (4.4 g, 18.64 mmol) and triethylamine (7.79 mL, 55.9 mmol) in tetrahydrofuran (THF) (100 mL) at 0 °C with stirring. Then, the reaction mixture was stirred at 25 ^{0}C overnight, and then concentrated. The concentrated reaction mixture was purified via silica gel column (DCM/MeOH 10/1) to afford the title compound (3.2 g, 86%) as a yellow solid.

LC-MS (ESI): m/z 200 $[M + H]^+$; 0.63 min (ret time).

D30

4-((6-chloropyridin-3-yl)oxy)-3-fluorobenzaldehyde

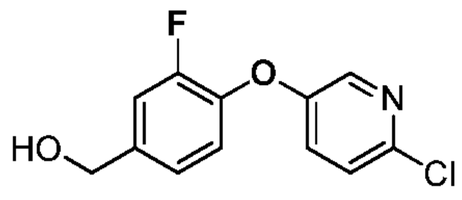


A mixture of 3,4-difluorobenzaldehyde (2.00 g, 14.8 mmol),6-chloropyridin-3-ol (1.82 g, 14.1 mmol) and potassium carbonate (2.14 g, 15.5 mmol) in N,N-dimethylformamide (DMF) (25 mL) was stirred at 110 °C for 12 h, diluted with ethyl acetate (50 mL), washed with water (50 mL×2). The organic part was separated, dried over anhydrous Na_2SO_4, filtered and concentrated. Purification via silica gel (3 % ethyl acetate in petroleum ether) afforded the title product (2.8 g)

LCMS (ESI): m/z 252 $[M + H]^+$; 0.80 min (ret time)

D31

(4-((6-chloropyridin-3-yl)oxy)-3-fluorophenyl)methanol

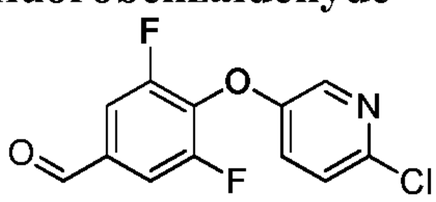


To a solution of 4-((6-chloropyridin-3-yl)oxy)-3-fluorobenzaldehyde (2.80 g, 11.1 mmol) in methanol (25 mL) was added portionwise solid $NaBH_4$ (0.842 g, 22.3 mmol) at room temperature. The reaction mixture was stirred at 25 °C for 2 h, concentrated to remove solvent, dissolved in water (50 mL) and extracted with ethyl acetate (50 mL×2). Combined organic parts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude was used into next step without purification (2.8 g).

LCMS (ESI): m/z 254 $[M + H]^+$; 0.74 min (ret time)

D32

4-((6-chloropyridin-3-yl)oxy)-3,5-difluorobenzaldehyde

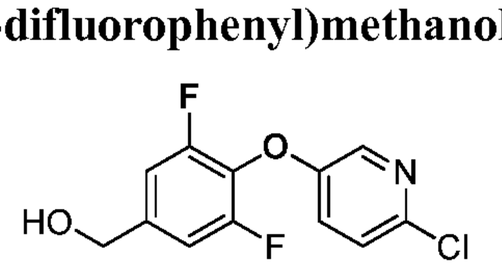


The title compound was prepared by a procedure similar to that described for **D30** starting from 3,4,5-trifluorobenzaldehyde and 6-chloropyridin-3-ol.

LCMS (ESI): m/z 252 $[M + H]^+$; 0.80 min (ret time)

D33

(4-((6-chloropyridin-3-yl)oxy)-3,5-difluorophenyl)methanol

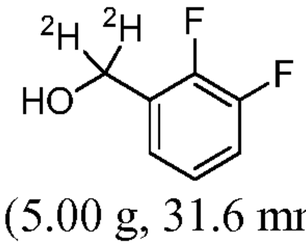


The title compound was prepared by a procedure similar to that described for **D31** starting from 4-((6-chloropyridin-3-yl)oxy)-3,5-difluorobenzaldehyde.

LCMS (ESI): m/z 272 $[M + H]^+$; 0.75 min (ret time)

D34

(2,3-difluorophenyl)dideuteromethanol

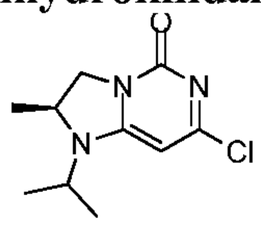


To a solution of 2,3-difluorobenzoic acid (5.00 g, 31.6 mmol) in tetrahydrofuran (THF) (80 mL) in ice bath was added lithium aluminium deuteride (1.00 g, 23.8 mmol). The reaction mixture was gradually allowed to rt and stirred for two days, then diluted with ethyl acetate (150 mL) and water (5 mL), mixed with anhydrous Na_2SO_4, filtered and concentrated. Purification via ISCO system (ethyl acetate/petroleum ether) afforded the title product as colorless oil.

LCMS (ESI): m/z 129 $[M - H_2O + H]^+$; 2.07 min (ret time).

D35

(S)-7-chloro-1-isopropyl-2-methyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

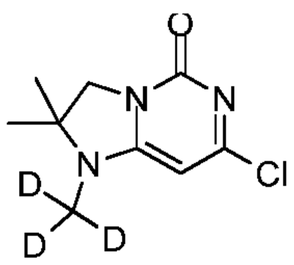


To a mixture of (S)-7-chloro-2-methyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one (50 mg, 0.27 mmol) and 2-iodopropane (68.7 mg, 0.404 mmol) in acetonitrile (1 mL) was added Cs_2CO_3 (176 mg, 0.539 mmol). The reaction mixture was stirred at 90 °C for 1h, then cooled to room temperature, filtered and concentrated to give the residue as a brown solid. The crude was used into next step without purification.

LCMS (ESI): m/z 228 $[M + H]^+$; 1.58 min (ret time)

D36

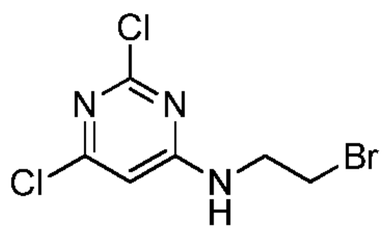
7-chloro-1-trideuteromethyl-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one



To a mixture of 7-chloro-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one (50 mg, 0.25 mmol) and $TsOCD_3$ (114 mg, 0.301 mmol) in acetonitrile (2 mL) was added Cs_2CO_3 (163 mg, 0.501 mmol). The reaction mixture was stirred at rt for 1 h, filtered and concentrated to give the residue as a brown solid. The crude was used into next step without purification.

D37

N-(2-bromoethyl)-2,6-dichloropyrimidin-4-amine

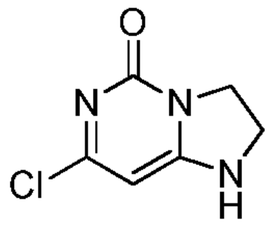


To a solution of 2,4,6-trichloropyrimidine (10 g, 54.5 mmol) and triethylamine (11.0 g, 109 mmol) in acetonitrile (15 ml) was added dropwise triethylamine (0.552 g, 5.45 mmol). The mixture was stirred for 3 h, diluted with water (40 mL) and extracted with ethyl acetate (20 mL×2). Combined organic parts were washed with brine (30 mL×2), dried over Na_2SO_4 and concentrated. The crude product (10 g) was directly used into next step without further purification.

LC-MS (ESI): m/z 270 $[M + H]^+$; 1.44 min (ret time)

D38

7-chloro-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

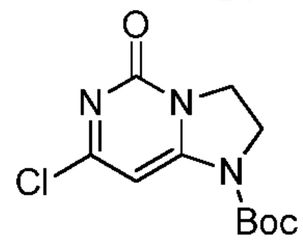


To a mixture of N-(2-bromoethyl)-2,6-dichloropyrimidin-4-amine (10 g, 18 mmol) in 1,4-dioxane (30 mL) and water (30.0 mL) was added K_2CO_3 (4.85 g, 35.1 mmol). The reaction mixture was stirred at 70 °C for 4 h, then directly used into next step without workup and purification.

LC-MS (ESI): m/z 172 $[M + H]^+$; 0.51 min (ret time)

D39

tert-butyl-7-chloro-5-oxo-2,3-dihydroimidazo[1,2-c]pyrimidine-1(5H)-carboxylate

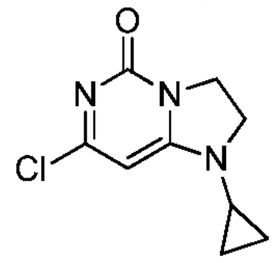


To the above mixture was added Boc_2O (1.999 g, 11.65 mmol) and DMAP (0.142 g, 1.17 mmol). The reaction mixture was stirred at rt for 3 h, diluted with brine (30 mL) and extracted with ethyl acetate (20 mL×2). Combined organic parts were washed with brine (20 mL×2), dried over anhydrous Na_2SO_4 and concentrated. Purification via column on silica gel (eluent: ethylacetate) afforded the title product (1.5 g) as a white solid.

LC-MS (ESI): m/z 272 $[M + H]^+$;1.24 min (ret time)

D40

7-chloro-1-cyclopropyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

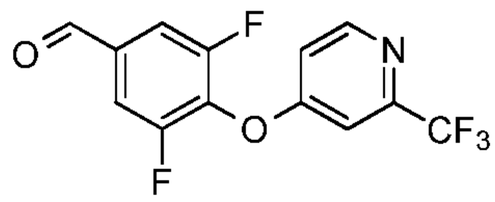


A mixtrue of 7-chloro-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one (300 mg, 1.75 mmol), cyclopropylboronic acid (300 mg, 3.50 mmol), 4,4'-bipyridine (273 mg, 1.75 mmol), copper (I) acetate (214 mg, 1.75 mmol) and Na_2CO_3 (371 mg, 3.50 mmol) in 1,2-dichloroethane (DCE) (20 mL) was stirred at 70 °C for 3 h and concentrated to remove solvent under vacuo. Purification via Biotage system with inverse phase column (water and acetonitrile as eluent) afforded the title product (200 mg).

LC-MS (ESI): m/z 212 $[M + H]^+$; 1.20 min (ret time)

D41

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.

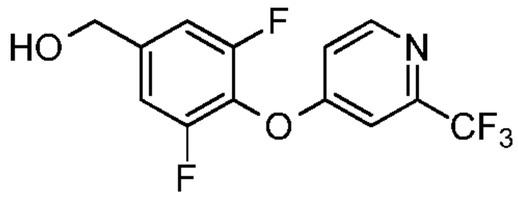
LC-MS (ESI): m/z 304 $[M + H]^+$; 1.17 min (ret time).

An alternative synthetic procedure is provided: 3,4,5-trifluorobenzaldehyde (1.08 g, 6.74 mmol) was added to a solution of 2-trifluoromethyl)pyridin-4-ol (1 g, 6.13 mmol) and potassium carbonate (1.017 g, 7.36 mmol) in N,N-dimethylformamide (DMF) (10 mL) under nitrogen with stirring. The reaction mixture was stirred at 100 °C for 16 h, cooled to rt, and then diluted with EtOAc (30 mL) and water (30 mL). The organic phase was washed three times with water (30 mL), dried over sodium sulphate, and then concentrated in vacuo to afford the title compound (1.8 g, 97%).

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

<u>D42</u>

(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 (D41).

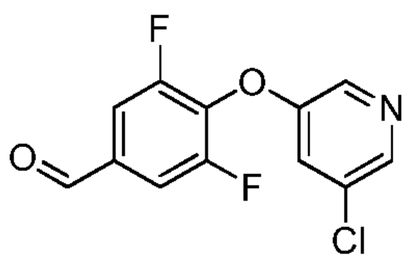
LC-MS (ESI): m/z 306 $[M + H]^+$; 1.07 min (ret time).

An alternative synthetic process is provided: $NaBH_4$ (0.449 g, 11.87 mmol) was added portionwise to a solution of 3,5-difluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)benzaldehyde (1.8 g, 5.94 mmol) in methanol (20 mL) at 0 ^{0}C. The reaction mixture was stirred at 20 ^{0}C for 1 h, and then quenched with saturated aqueous NH_4Cl, extracted with EtOAc (40 mL×3). The combined extracts were then washed with brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo to afford the title compound (1.8 g, 99%).

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

<u>D43</u>

4-((5-chloropyridin-3-yl)oxy)-3,5-difluorobenzaldehyde

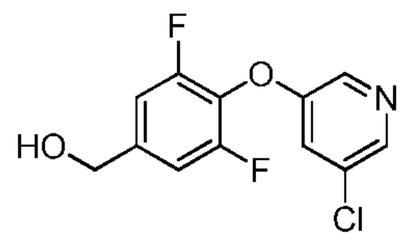


The title compound was prepared by a procedure similar to that described for **D30** starting from 3,4,5-trifluorobenzaldehyde and 5-chloropyridin-3-ol.

LCMS (ESI): m/z 270 $[M + H]^+$; 0.78 min (ret time).

D44

(4-((5-chloropyridin-3-yl)oxy)-3,5-difluorophenyl)methanol

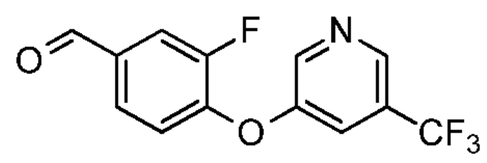


The title compound was prepared by a procedure similar to that described for **D31** starting from 4-((5-chloropyridin-3-yl)oxy)-3,5-difluorobenzaldehyde.

LCMS (ESI): m/z 272 $[M + H]^+$; 0.72 min (ret time)

D45

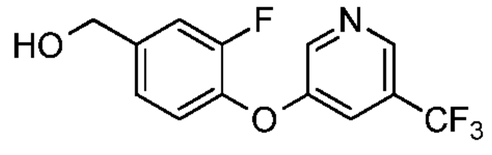
3-fluoro-4-((5-(trifluoromethyl)pyridin-3-yl)oxy)benzaldehyde



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.

D46

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

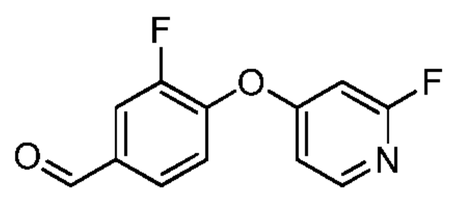


The title compound was prepared by a procedure similar to that described for **D31** starting from 3-fluoro-4-((5-(trifluoromethyl)pyridin-3-yl)oxy)benzaldehyde.

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

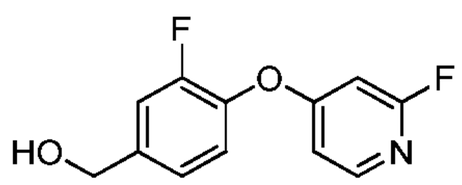
D47

3-fluoro-4-((6-fluoropyridin-3-yl)oxy)benzaldehyde



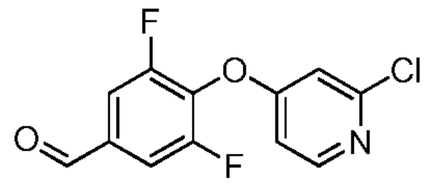
The title compound was prepared by a procedure similar to that described for **D30** starting from 2-fluoropyridin-4-ol and 3,4-difluorobenzaldehyde.
LC-MS (ESI): m/z 236 $[M + H]^+$; 0.74 min (ret time).

D48
(3-fluoro-4-((6-fluoropyridin-3-yl)oxy)phenyl)methanol



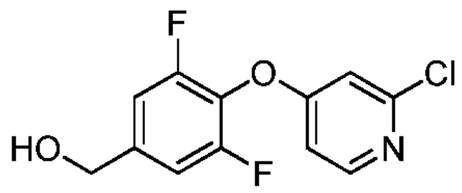
The title compound was prepared by a procedure similar to that described for **D31** starting from 3-fluoro-4-((2-fluoropyridin-4-yl)oxy)benzaldehyde.
LC-MS (ESI): m/z 272 $[M + H]^+$; 1.08 min (ret time).

D49
4-((2-chloropyridin-4-yl)oxy)-3,5-difluorobenzaldehyde



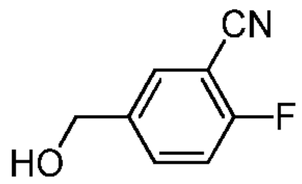
The title compound was prepared by a procedure similar to that described for **D30** starting from 3,4,5-trifluorobenzaldehyde and 2-chloropyridin-4-ol.
LC-MS (ESI): m/z 270 $[M + H]^+$; 0.79 min (ret time).

D50
(4-((2-chloropyridin-4-yl)oxy)-3,5-difluorophenyl)methanol



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

D51
2-fluoro-5-(hydroxymethyl)benzonitrile



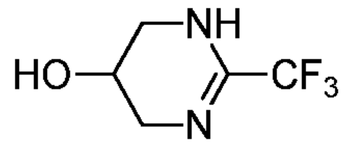
To a solution of 3-cyano-4-fluorobenzoic acid (1.00 g, 6.06 mmol) in tetrahydrofuran (THF) (20 mL) was added dropwise CDI (1.47 g, 9.08 mmol) at 0 °C. After the reaction mixture was left at room temperature for 30 min, sodium borohydride (0.687 g, 18.2 mmol) was added dropwise at 0

°C. The reaction mixture was stirred at room temperature for 16 h, quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The organic part was separated, dried over Na_2SO_4, filtered and concentrated. Purification via flash column (petroleum ether/ethyl acetate = 10/1) afforded the title product (350 mg).

LC-MS (ESI): m/z 152 $[M + H]^+$; 0.52 min (ret time).

D52

2-(trifluoromethyl)-1,4,5,6-tetrahydropyrimidin-5-ol



A solution of 1,3-diaminopropan-2-ol (10.0 g, 111 mmol) and ethyl 2,2,2-trifluoroacetate (15.8 g, 111 mmol) in p-xylene (150 mL) was stirred at 160 °C for 4 h, then concentrated to remove solvent under reduced pressure to afford the crude product as an oil, which was used into next step without purification.

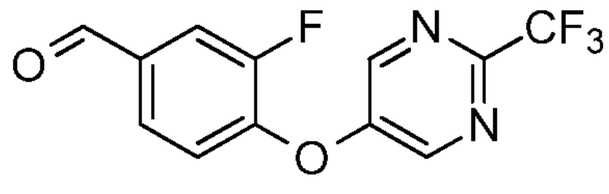
LC-MS (ESI): m/z 169 $[M + H]^+$; 0.85 min (ret time).

An alternative synthetic process is also provided: A mixture of ethyl 2,2,2-trifluoroacetate (158 g, 1110 mmol) and 1,3-diaminopropan-2-ol (100 g, 1110 mmol) was heated to 160 °C for 2 hr (open to air to remove EtOH). p-Xylene (625 mL) was added and heated to reflux while removing water. After the reaction is completed, the reaction mixture was concentrated to provide 2-(trifluoromethyl)-1,4,5,6-tetrahydropyrimidin-5-ol (125 g, 701 mmol, 63.2 % yield) as pale yellow solid.

LC-MS (ESI): m/z 168 $[M + H]^+$; 0.38 min (ret time).

D53

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

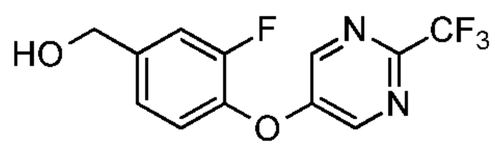


The title compound was prepared by a procedure similar to that described for **D30** starting from 3,4-difluorobenzaldehyde and 2-(trifluoromethyl)pyrimidin-5-ol.

LC-MS (ESI): m/z 287 $[M + H]^+$; 3.72 min (ret time).

D54

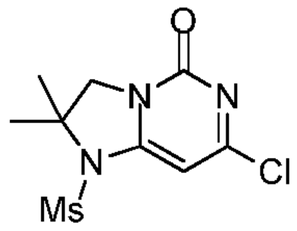
(3-fluoro-4-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)phenyl)methanol



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 $[M + H]^+$; 3.21 min (ret time).

D55

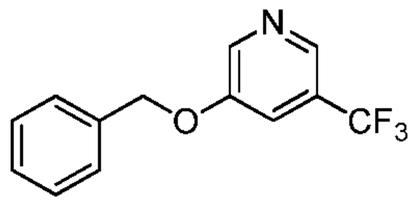
7-chloro-2,2-dimethyl-1-(methylsulfonyl)-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one



To a solution of 2-((2,6-dichloropyrimidin-4-yl)amino)-2-methylpropan-1-ol (3.40 g, 14.4 mmol) and triethylamine (11.8 mL, 86.4 mmol) in dichloromethane (DCM) (40 mL) was added dropwise MsCl (4.48 mL, 57.6 mmol) at 0 °C. The reaction mixture was stirred at rt for 2 h, then diluted with DCM (40 mL), washed with water (30 mL×3) then brine (30 mL×2), dried over Na_2SO_4, filtered and concentrated. Purification via MDAP (column: Luna 250×50 mm×10 um; MeCN, 0.2% water, 0.2% Formic acid) afforded the title product (850 mg) as a yellow solid.
LC-MS (ESI): m/z 278 $[M + H]^+$; 0.71 min (ret time).

D56

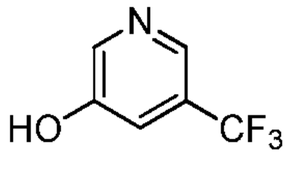
3-(benzyloxy)-5-(trifluoromethyl)pyridine



To a solution of 3-chloro-5-(trifluoromethyl)pyridine (10.0 g, 55.1 mmol) in N,N-dimethylformamide (DMF) (150 mL) was added dropwise phenylmethanol (5.96 g, 55.1 mmol) under nitrogen at rt. The reaction mixture was stirred at 40 °C for 2 h, diluted with water (300 mL) and extracted with ethyl acetate (300 mL×3). Combined organic parts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product (100 g) was used into next step without further purification.
LC-MS (ESI): m/z 254 $[M + H]^+$; 0.86 min (ret time).

D57

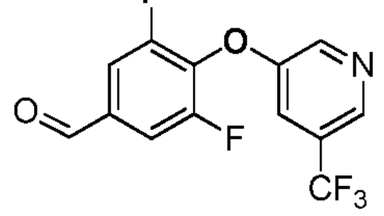
5-(trifluoromethyl)pyridin-3-ol



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).

D58

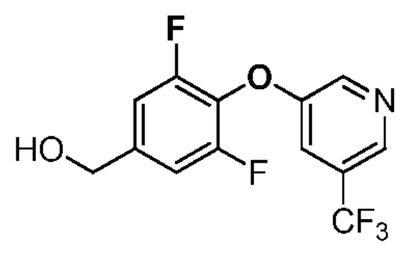
3, 5-difluoro-4-((5-(trifluoromethyl)pyridin-3-yl)oxy)benzaldehyde



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).

D59

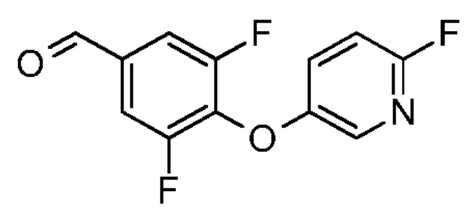
(3, 5-difluoro-4-((5-(trifluoromethyl)pyridin-3-yl)oxy)phenyl)methanol



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).

D60

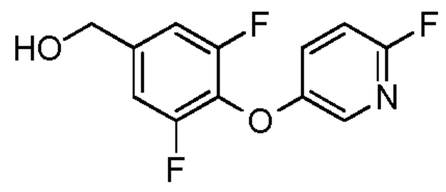
3, 5-difluoro-4-((6-fluoropyridin-3-yl)oxy)benzaldehyde



The title compound was prepared by a procedure similar to that described for **D30** starting from 3,4,5-trifluorobenzaldehyde and 6-fluoropyridin-3-ol.
LC-MS (ESI): m/z 254 $[M + H]^+$; 1.13 min (ret time).

D61

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

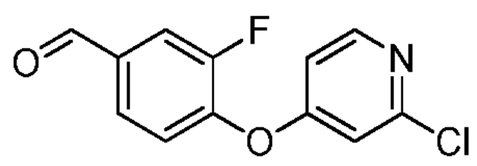


The title compound was prepared by a procedure similar to that described for **D31** starting from 3,5-difluoro-4-((6-fluoropyridin-3-yl)oxy)benzaldehyde.

LC-MS (ESI): m/z 256 $[M + H]^+$; 1.04 min (ret time).

D62

4-((2-chloropyridin-4-yl)oxy)-3-fluorobenzaldehyde

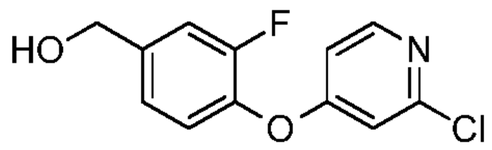


The title compound was prepared by a procedure similar to that described for **D30** starting from 3,4-difluorobenzaldehyde and 2-chloropyridin-4-ol.

LC-MS (ESI): m/z 252 $[M + H]^+$; 0.76 min (ret time).

D63

(4-((2-chloropyridin-4-yl)oxy)-3-fluorophenyl)methanol

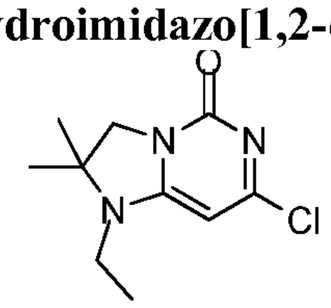


The title compound was prepared by a procedure similar to that described for **D31** starting from 4-((2-chloropyridin-4-yl)oxy)-3-fluorobenzaldehyde.

LC-MS (ESI): m/z 254 $[M + H]^+$; 1.04 min (ret time).

D64

7-chloro-1-ethyl-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

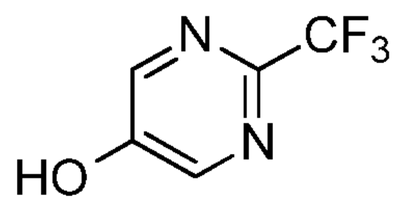


To a solution of 7-chloro-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one (100 mg, 0.501 mmol) and iodoethane (94.0 mg, 0.601 mmol) in acetonitrile (4 mL) was added Cs_2CO_3 (326 mg, 1.00 mmol). The reaction mixture was stirred at 90 °C for 1h, filtered and concentrated to afford the crude product (110 mg) as a brown solid.

LCMS (ESI): 228 $[M + H]^+$; 1.52 min (ret time)

D65

2-(trifluoromethyl)pyrimidin-5-ol

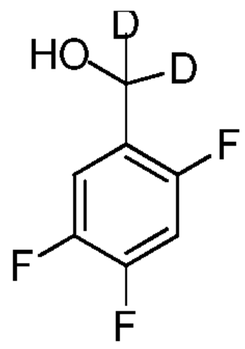


A solution of sodium methoxide (24.10 g, 446 mmol) in methanol (150 mL) was added dropwise to a stirred solution of 2-(trifluoromethyl)-1,4,5,6-tetrahydropyrimidin-5-ol (25 g, 149 mmol) in nitrobenzene (153 mL, 1487 mmol) at 120 °C. The MeOH in the reaction mixture was removed by distillation. Then, the resulting reaction mixture was diluted with p-xylene (80 mL), and was heated to reflux for 5 hrs. After the reaction is completed, the reaction mixture was cooled to rt. Then, the residue was diluted with petroleum ether (800 mL) and water (800 mL). An aqueous layer was separated and was acidified to PH=2 by adding 12 M HCL solution at 0 °C. Then, the reaction mixture was extracted with ethyl acetate (1000 ml × 2). The combined organic layer was dried over sodium sulphate, concentrated under vacuum to obtain the raw product. The raw product was purified by silica gel (100-200 mesh) column chromatography (eluting 30% ethylacetate in pet ether) to afford 2-(trifluoromethyl)pyrimidin-5-ol (6 g, 36.0 mmol, 24.22 % yield) as brown solid.

LC-MS (ESI): m/z 165 $[M + H]^+$; 1.52 min (ret time).

D66

Dideutero(2,4,5-trifluorophenyl)methanol

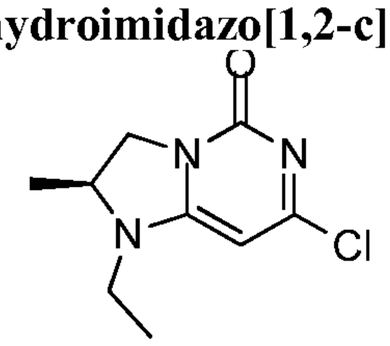


The title compound was prepared by a procedure similar to that described for **D34** starting from 2,4,5-trifluorobenzoic acid.

LC-MS (ESI): m/z 147 $[M + H]^+$; 2.15 min (ret time).

D67

(S)-7-chloro-1-ethyl-2-methyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

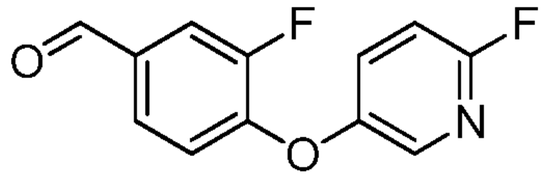


To a solution of (S)-7-chloro-2-methyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one (50.0 mg, 0.269 mmol) and iodoethane (63.0 mg, 0.404 mmol) in acetonitrile (1ml) was added Cs_2CO_3 (176

mg, 0.539 mmol). The reaction mixture was stirred at 90 °C for 1h, filtered and concentrated to give crude product (80 mg) as a brown solid.
LCMS (ESI): m/z 214[M + H]$^+$;1.38 min (ret time)

D68

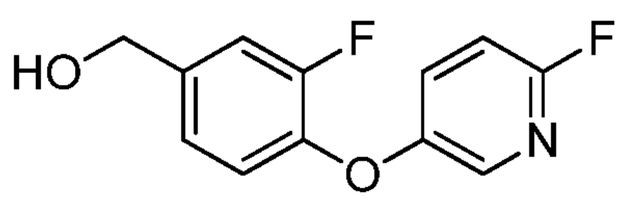
3-fluoro-4-((6-fluoropyridin-3-yl)oxy)benzaldehyde



The title compound was prepared by a procedure similar to that described for **D30** starting from 3,4-difluorobenzaldehyde and 6-fluoropyridin-3-ol.
LCMS (ESI): m/z 236 [M + H]$^+$; 1.09 min (ret time)

D69

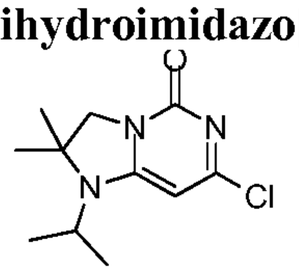
(3-fluoro-4-((6-fluoropyridin-3-yl)oxy)phenyl)methanol



The title compound was prepared by a procedure similar to that described for **D31** starting from 3-fluoro-4-((6-fluoropyridin-3-yl)oxy)benzaldehyde.
LCMS (ESI): m/z 238 [M + H]$^+$; 1.02 min (ret time)

D70

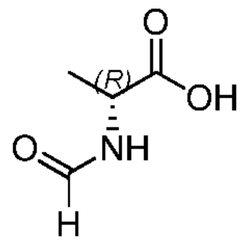
7-chloro-1-isopropyl-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one



To a solution of 7-chloro-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one (400 mg, 2.00 mmol) and 2-iodopropane (375 mg, 2.20 mmol) in acetonitrile (7 mL) was added Cs_2CO_3 (1.31 g, 4.01 mmol). The reaction mixture was stirred at 90 °C for 2 h, filtered and concentrated. Purification via MDAP afforded the title product (40 mg) as a white solid.
LCMS (ESI): m/z 242 [M + H]$^+$; 1.77 min (ret time).

D71

(R)-2-formamidopropanoic acid

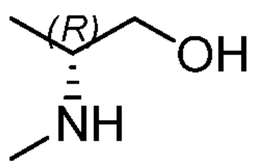


The title compound was prepared by a procedure similar to that described for **D25** starting from (R)-2-aminopropanoic acid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.62 (s, 1H), 8.11 (br, 1H), 5.05 (m, 1H), 1.92 (m, 3H).

D72

(R)-2-(methylamino)propan-1-ol

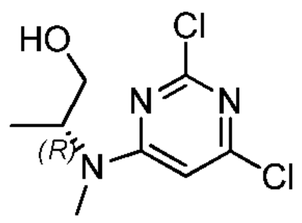


The title compound was prepared by a procedure similar to that described for **D26** starting from (R)-2-formamidopropanoic acid.

^{1}H NMR (400 MHz, $CDCl_3$): δ: 3.60(m, 1H), 3.28 (m, 1H), 2.65 (m, 1H), 2.42 (s, 3H), 1.05 (d, J = 7.2 Hz, 3H).

D73

(R)-2-((2,6-dichloropyrimidin-4-yl)(methyl)amino)propan-1-ol

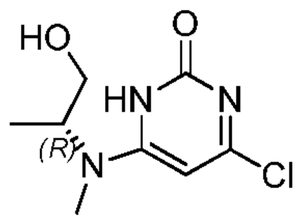


The title compound was prepared by a procedure similar to that described for **D27** starting from 2,4,6-trichloropyrimidine and (S)-2-(methylamino)propan-1-ol.

LC-MS (ESI): m/z 236 $[M + H]^+$; 0.85 min (ret time).

D74

(R)-4-chloro-6-((1-hydroxypropan-2-yl)(methyl)amino)pyrimidin-2(1H)-one

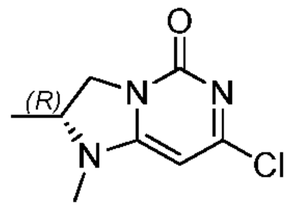


The title compound was prepared by a procedure similar to that described for **D28** starting from (R)-2-((2,6-dichloropyrimidin-4-yl)(methyl)amino)propan-1-ol.

LC-MS (ESI): m/z 218 $[M + H]^+$; 0.65 min (ret time).

D75

(R)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

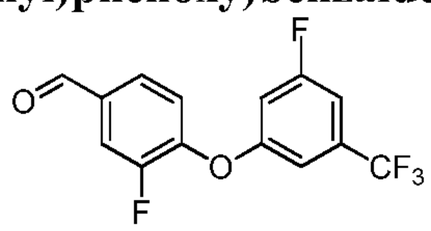


The title compound was prepared by a procedure similar to that described for **D29** starting from (R)-4-chloro-6-((1-hydroxypropan-2-yl)(methyl)amino)pyrimidin-2(1H)-one.

LC-MS (ESI): m/z 200 $[M + H]^+$; 0.61 min (ret time).

D76

3-fluoro-4-(3-fluoro-5-(trifluoromethyl)phenoxy)benzaldehyde

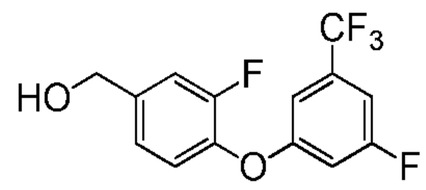


The title compound was prepared by a procedure similar to that described for **D30** starting from 3,4-difluorobenzaldehyde and 3-fluoro-5-(trifluoromethyl)phenol.

LCMS (ESI):m/z 303 $[M + H]^+$; 3.72 min (ret time).

D77

7-((3-fluoro-4-(3-fluoro-5-(trifluoromethyl)phenoxy)benzyl)oxy)-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

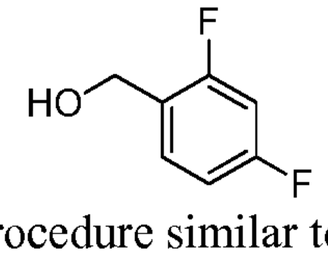


The title compound was prepared by a procedure similar to that described for **D31** starting from 3,4-fluorobenzaldehyde and 3-fluoro-5-(trifluoromethyl)phenol.

LC-MS (ESI): m/z 287 $[M - H_2O + H]^+$; 1.25 min (ret time).

D78

(2,4-difluorophenyl)methanol

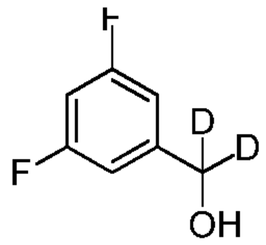


The title compound was prepared by a procedure similar to that described for **D31** starting from 2,4-difluorobenzaldehyde.

LCMS (ESI): m/z 127 $[M - H_2O + H]^+$; 1.93 min (ret time).

D79

Dideutero(3,5-difluorophenyl)methanol

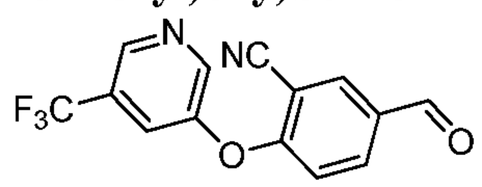


The title compound was prepared by a procedure similar to that described for **D34** starting from methyl 3,5-difluorobenzoate.

LCMS (ESI): m/z 129 $[M - H_2O + H]^+$; 2.06 min (ret time)

D80

5-formyl-2-((5-(trifluoromethyl)pyridin-3-yl)oxy)benzonitrile

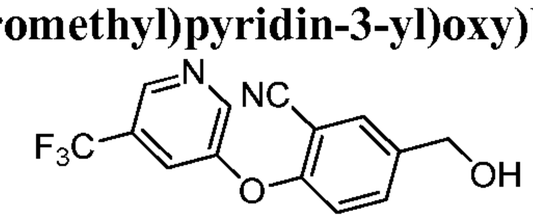


The title compound was prepared by a procedure similar to that described for **D30** starting from 5-(trifluoromethyl)pyridin-3-ol and 2-fluoro-5-formylbenzonitrile.

LC-MS (ESI): m/z 293 $[M + H]^+$; 1.64 min (ret time).

D81

5-(hydroxymethyl)-2-((5-(trifluoromethyl)pyridin-3-yl)oxy)benzonitrile

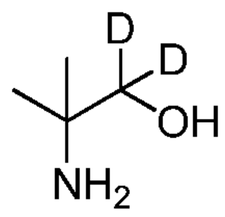


The title compound was prepared by a procedure similar to that described for **D31** starting from 5-formyl-2-((5-(trifluoromethyl)pyridin-3-yl)oxy)benzonitrile.

LC-MS (ESI): m/z 293 $[M - H]^-$; 1.23 min (ret time).

D82

1,1-dideutero2-amino-2-methylpropan-1-ol

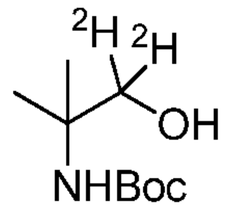


The title compound was prepared by a procedure similar to that described for **D25** starting from 2-amino-2-methylpropanoic acid and $LiAlD_4$.

^1H NMR (400 MHz, $CDCl_3$): δ: 1.98 (s, 2 H), 1.28 (s, 3H), 1.10 (s, 3H).

D83

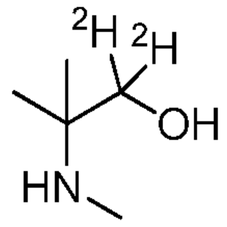
tert-butyl (1,1-dideutero1-hydroxy-2-methylpropan-2-yl)carbamate



The title compound was prepared by a procedure similar to that described for **D16(c)** starting from 2-amino-1,1-dideutero-2-methylpropan-1-ol and Boc_2O.

D84

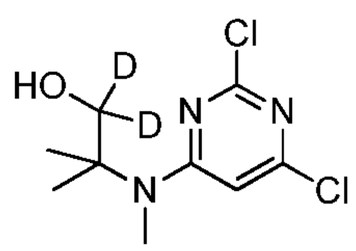
1,1-dideutero-2-methyl-2-(methylamino)propan-1-ol



The title compound was prepared by a procedure similar to that described for **D26** starting from $LiAlH_4$ and tert-butyl (1,1-dideutero-1-hydroxy-2-methylpropan-2-yl)carbamate.

D85

1,1-dideutero-2-((2,6-dichloropyrimidin-4-yl)(methyl)amino)-2-methylpropan-1-ol

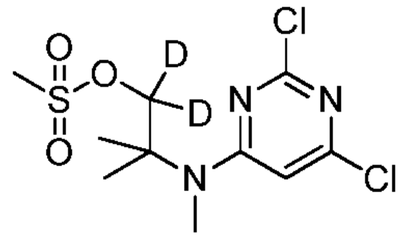


The title compound was prepared by a procedure similar to that described for **D27** starting from 2,4,6-trichloropyrimidine and 1,1-dideutero-2-methyl-2-(methylamino)propan-1-ol.

LC-MS (ESI): m/z 252 $[M + H]^+$; 1.08 min (ret time).

D86

1,1-dideutero-2-((2,6-dichloropyrimidin-4-yl)(methyl)amino)-2-methylpropyl methanesulfonate



The title compound was prepared by a procedure similar to that described for **D29** starting from 1,1-dideutero-2-methyl-2-(methylamino)propan-1-ol, triethylamine and methanesulfonyl chloride.

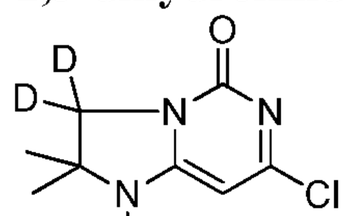
LC-MS (ESI): m/z 216 $[M + H]^+$; 0.81 min (ret time).

An alternative synthesis is provided: methanesulfonyl chloride (0.752 mL, 9.52 mmol) was dropwise added to a solution of 1,1-dideutero-2-methyl-2-(methylamino)propan-1-ol (2 g, 7.93 mmol) and triethylamine (2.211 mL, 15.86 mmol) in tetrahydrofuran (THF) (20 mL) at 0 °C. Then,

the reaction mixture was filtered and concentrated to give the crude product, which was used in the next step without further purification.

D87

7-chloro-1,2,2-trimethyl-3,3-dideutero-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

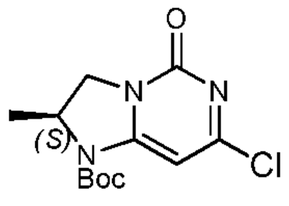


The title compound was prepared by a procedure similar to that described for **D30** starting 1,1-dideutero-2-((2,6-dichloropyrimidin-4-yl)(methyl)amino)-2-methylpropyl methanesulfonate.
LC-MS (ESI): m/z 216 $[M + H]^+$; 0.83 min (ret time).

An alternative synthesis is provided: Potassium carbonate (2.080 g, 15.05 mmol) was added to a solution of 1,1-dideutero-2-((2,6-dichloropyrimidin-4-yl)(methyl)amino)-2-methylpropylmethanesulfonate (2.5 g, 7.52 mmol) in a mixture of 1,4-dioxane (30 mL) and water (10.00 mL). Then, the reaction mixture was stirred at 100 °C for 1.5 h, and then concentrated to give the crude product. The residue was dissolved in DCM (100 mL), which was stirred at rt for 15 min. filtered, concentrated and then purified by pre-TLC eluting with EtOAc to provide 3,3,7-dideutero-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one (153 mg, 0.702 mmol, 9.33 % yield)
LC-MS (ESI): m/z 216 $[M + H]^+$; 0.83 min (ret time).

D88

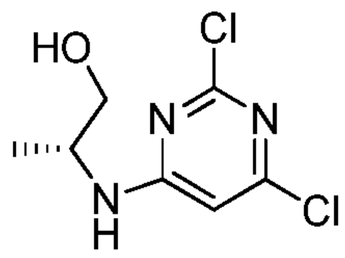
(S)-tert-butyl 7-chloro-2-methyl-5-oxo-2, 3-dihydroimidazo[1,2-c]pyrimidine-1(5H)-carboxylate



To a solution of (S)-7-chloro-2-methyl-2,3-dihydroimidazol[1,2-c]pyrimidin-5(1H)-one (500 mg, 2.69 mmol) in DCM (50 mL) were added di-tert-butyl dicarbonate (705 mg, 3.23 mmol), DMAP (32.9 mg, 0.269 mmol) and TEA (1.126 mL, 8.08 mmol). The reaction mixture was stirred at rt for 2h, concentrated. The residue was diluted with DCM (100 mL), washed with water (50 mL × 2), dried over Na_2SO_4, filtered and concentrated to afford the title compound (1g, 53.1% yield) as a red solid.
LC-MS (ESI): m/z 286 $[M + H]^+$; 1.54 min (ret time).

D89

***(R)*-2-((2,6-dichloropyrimidin-4-yl)amino)propan-1-ol**



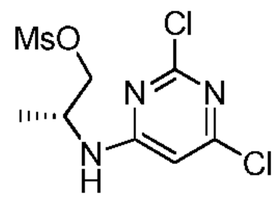
To a suspension of *(R)*-2-aminopropan-1-ol (100 g, 1331 mmol)(AK Scientific) and K_2CO_3 (736 g, 5326 mmol) in N,N-dimethylformamide (DMF) (1000 mL) was added a solution of 2,4,6-trichloropyrimidine (244 g, 1331 mmol) in N,N-dimethylformamide (DMF) (100 mL) at 0° C dropwise over 30 min and stirred at rt for 18 h. The reaction mixture was partitioned between ethyl acetate (1000 mL) and water (1000 mL). The organic layer was washed with brine and dried over Na_2SO_4, concentrated to afford crude thick gummy material (300 g). The crude material was dissolved in ethyl acetate (500 mL) and stirred for 1h. The precipitated solid was filtered to afford 40 g of pure product and repeat above procedure on filtrate to afford additional 60 g of *(R)*-2-((2,6-dichloropyrimidin-4-yl)amino)propan-1-ol (100 g, 30.0 % yield).

^{1}H NMR (400MHz, DMSO-d_6) δ: 8.06-8.04 (1H, d, *J* = 7.6 Hz), 6.51 (1H, s), 4.83-4.82 (1H, t, *J* = 6.4Hz), 4.05-4.00 (1H, m), 3.44-3.34 (2H, m), 1.11-1.10 (3H, d, *J* = 6.4Hz).

LC-MS (ESI): m/z 222 $[M + H]^+$; 1.54 min (ret time).

D90

***(R)*-2-((2,6-dichloropyrimidin-4-yl)amino)propyl methanesulfonate**



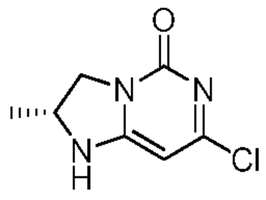
To a solution of *(R)*-2-((2,6-dichloropyrimidin-4-yl)amino)propan-1-ol (50 g, 225 mmol) in tetrahydrofuran (THF) (500 mL) was added TEA (94 mL, 675 mmol). The reaction mixture was stirred at 0°C for 5 mins, then MsCl (26.3 mL, 338 mmol) was added at 0°C, and stirred at rt for 2 h. The reaction mixture was filtered through celite bed and filtrate was evaporated completely to afford the title compound (60 g, 64.8 % yield) as a pale yellow gummy liquid.

^{1}H NMR (400MHz, $CDCl_3$) δ: 6.4 (1H, s), 5.8 (1H, s), 4.23-4.22(1H, m), 3.18-3.11 (2H, m), 3.06 (3H, s), 1.41-1.34 (3H, m).

LC-MS (ESI): m/z 300 $[M + H]^+$; 3.17min (ret time).

D91

***(R)*-7-chloro-2-methyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one**



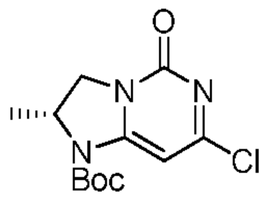
A solution of *(R)*-2-((2,6-dichloropyrimidin-4-yl)amino)propyl methanesulfonate (60 g, 200 mmol) and TEA (84 mL, 600 mmol) in water (500 mL) was heated at 100 °C for 5 hr. The reaction was cooled to rt, then the precipitated solid was filtered to afford the title compound (30 g, 74.0 % yield) as an off white solid

^{1}H NMR (400MHz, DMSO-d_6) δ: 8.75 (1H, s), 5.62 (1H, s), 4.22-4.17 (1H, m), 4.12-4.07 (1H, t, *J* = 9.6Hz), 3.56-3.51 (1H, m), 1.26-1.24 (3H, d, *J* = 6.4Hz).

LC-MS (ESI): m/z 186 $[M + H]^+$; 0.84 min (ret time).

D92

***(R)*-tert-butyl 7-chloro-2-methyl-5-oxo-2,3-dihydroimidazo[1,2-c]pyrimidine-1 (5H)-carboxylate**



To a solution of *(R)*-7-chloro-2-methyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one (30 g, 162 mmol) in tetrahydrofuran (THF) (600 mL) was added TEA (56.3 mL, 404 mmol) and 4-DMAP (0.987 g, 8.08 mmol). The reaction mixture was stirred at 0°C for 10 mins, then Boc-anhydride (37.5 mL, 162 mmol) was added at 0 °C and stirred at rt for 3 h. The reaction mixture was diluted with ethyl acetate (100 mL×2) and water (150 mL). The organic layer was separated, dried over Na_2SO_4, concentrated to afford the title compound (22 g, 47.6 % yield) as an off white solid.

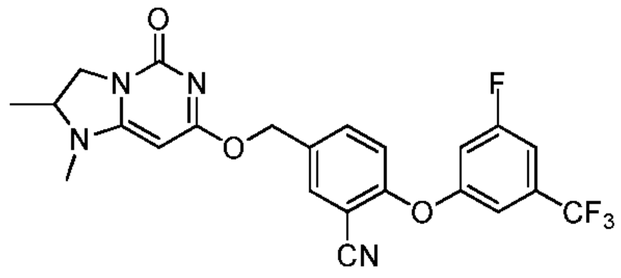
^{1}H NMR (400MHz, DMSO-d_6) δ: 6.51 (1H, s), 4.57-4.52 (1H, m), 4.15-4.10 (1H, t, *J* = 9.6Hz), 3.70-3.66 (1H, m), 1.52 (9H, s), 1.39-1.37 (3H, d, *J* = 6.4Hz).

LC-MS (ESI): m/z 286 $[M + H]^+$; 1.94 min (ret time).

Examples

E1

5-(((1,2-dimethyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-c]pyrimidin-7-yl)oxy)methyl)-2-(3-fluoro-5-(trifluoromethyl)phenoxy)benzonitrile

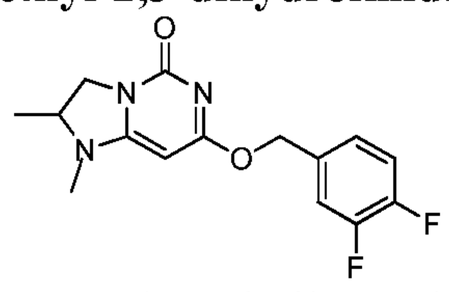


To a solution of 7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one (30 mg, 0.15 mmol) and 2-(3-fluoro-5-(trifluoromethyl)phenoxy)-5-(hydroxymethyl)be-nzonitrile (47 mg, 0.15 mmol) in N,N-dimethylformamide (DMF) (1 mL) was added NaH (12 mg, 0.30 mmol). The

reaction mixture was stirred at rt for 30 min, then quenched with water. Purification via mass-directed autopreparation afforded the title product with trifluoroacetic acid salt as a white solid.
LCMS (ESI): 475 $[M + H]^+$; 2.83 min (ret time)

E2

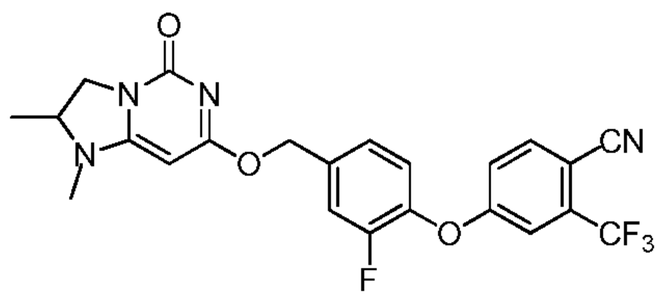
7-((3,4-difluorobenzyl)oxy)-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one



The title compound was prepared by a procedure similar to that described for **E1** starting from 7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and (3,4-difluorophenyl)methanol.
LCMS (ESI): m/z 308 $[M + H]^+$; 2.03 min (ret time)

E3

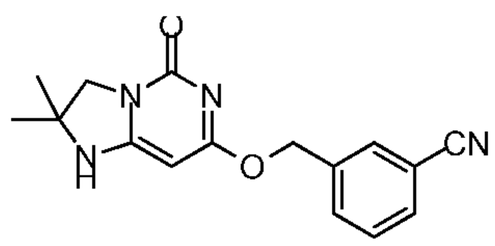
4-(4-(((1,2-dimethyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-c]pyrimidin-7-yl)oxy)methyl)-2-fluorophenoxy)-2-(trifluoromethyl)benzonitrile



The title compound was prepared by a procedure similar to that described for **E1** starting from 7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and 4-(2-fluoro-4-(hydroxymethyl)phenoxy)-2-(trifluoromethyl)benzonitrile.
LCMS (ESI): m/z 475 $[M + H]^+$; 2.78 min (ret time)

E4

3-(((2,2-dimethyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-c]pyrimidin-7-yl)oxy)methyl)benzonitrile



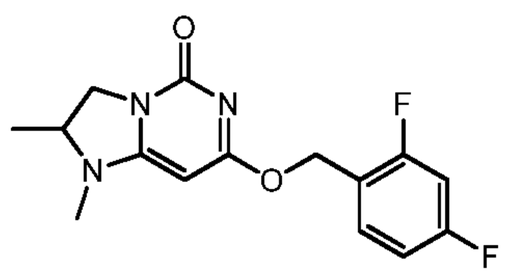
To a solution of 7-chloro-2,2-dimethyl-1-(methylsulfonyl)-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one (200 mg, 0.720 mmol) and 3-(hydroxymethyl)benzonitrile (288 mg, 2.16 mmol) in N,N-dimethylformamide (DMF) (3.5 mL) was added K_2CO_3 (299 mg, 2.16 mmol). The reaction mixture was sealed in a microwave vial and irradiated with a microwave using initial normal to 100

°C for 1 h. Purification via mass-directed auto-preparation afforded the title product as a white solid.

LCMS (ESI): m/z 297 $[M + H]^+$; 2.24 min (ret time)

E5

7-((2,4-difluorobenzyl)oxy)-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

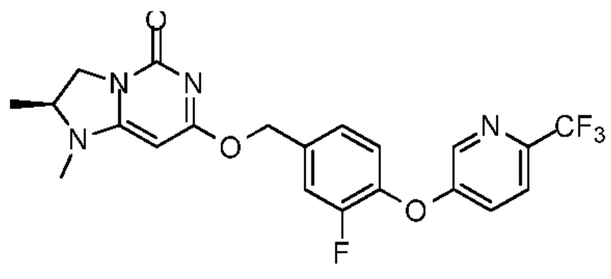


The title compound was prepared by a procedure similar to that described for **E9** starting from (2,4-difluorophenyl)methanol and 7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 308 $[M + H]^+$; 0.99 min (ret time).

E6

(S)-7-((3-fluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)benzyl)oxy)-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

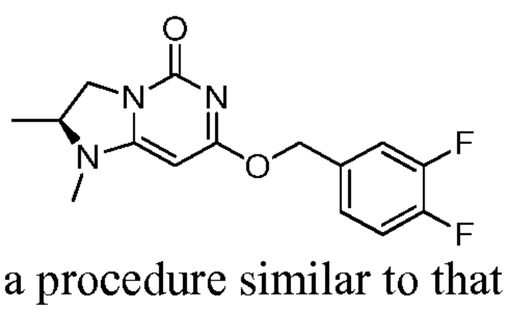


The title compound was prepared by a procedure similar to that described for **E1** starting from (*s*)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and (3-fluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)phenyl)methanol.

LCMS (ESI): m/z 451$[M + H]^+$; 2.71 min (ret time).

E7

(S)-7-((3,4-difluorobenzyl)oxy)-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

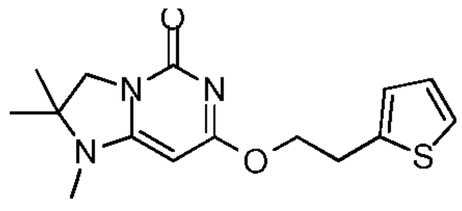


The title compound was prepared by a procedure similar to that described for **E9** starting from (3,4-difluorophenyl)methanol and (S)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo [1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 308 $[M + H]^+$; 0.96 min (ret time).

E8

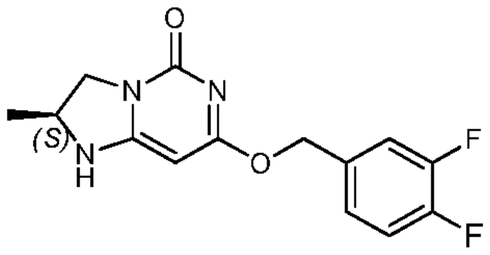
1,2,2-trimethyl-7-(2-(thiophen-2-yl)ethoxy)-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one



The title compound was prepared by a procedure similar to that described for **E1** starting from 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and 2-(thiophen-2-yl)ethanol.

LCMS (ESI): m/z 306 $[M + H]^+$; 2.36 min (ret time)

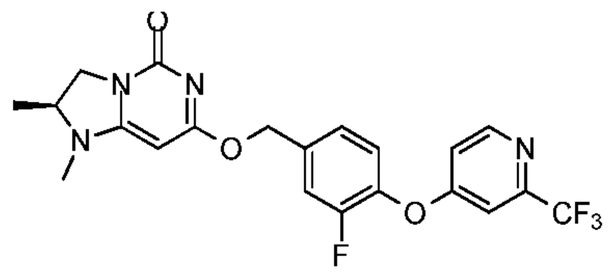
E9
(S)-7-((3,4-difluorobenzyl)oxy)-2-methyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one



To a solution of (3,4-difluorophenyl)methanol (45.4 mg, 0.315 mmol) in tetrahydrofuran (THF) (3 mL) was added dropwise sodium hydride (37.8 mg, 0.945 mmol) at 0 °C. After 30 min, (S)-tert-butyl-7-chloro-2-methyl-5-oxo-2,3-dihydroimidazo[1,2-c]pyrimidine-1(5H)-carboxylate (D88) (90 mg, 0.32 mmol) was added. The reaction mixture was stirred at room temperature for 16 h, then concentrated. Purification via pre-TLC (ethyl acetate) afforded the title product.

LC-MS (ESI): m/z 294 $[M + H]^+$; 1.26 min (ret time).

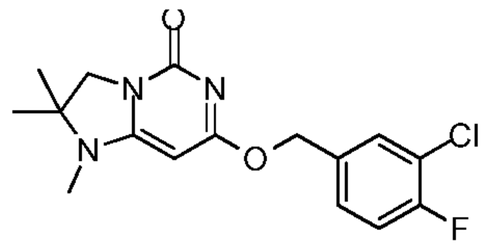
E10
(S)-7-((3-fluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)benzyl)oxy)-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one



The title compound was prepared by a procedure similar to that described for **E1** starting from (S)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and (3-fluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)phenyl)methanol.

LCMS (ESI): m/z 451$[M + H]^+$; 3.03 min (ret time).

E11
7-((3-chloro-4-fluorobenzyl)oxy)-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

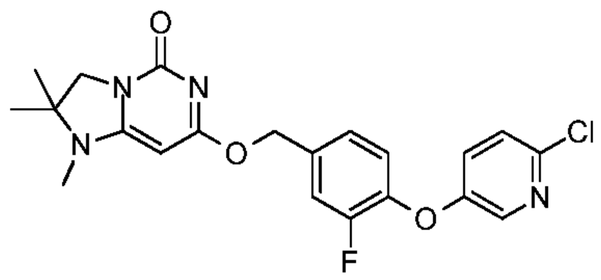


The title compound was prepared by a procedure similar to that described for **E1** starting from 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and (3-chloro-4-fluorophenyl)methanol.

LCMS (ESI): m/z 338 $[M + H]^+$; 2.36 min (ret time)

E12

7-((4-((6-chloropyridin-3-yl)oxy)-3-fluorobenzyl)oxy)-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

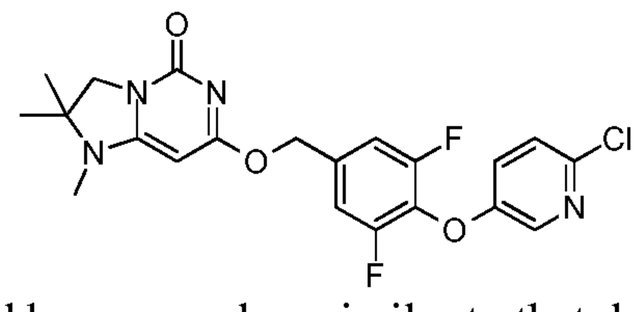


The title compound was prepared by a procedure similar to that described for **E9** starting from (4-((6-chloropyridin-3-yl)oxy)-3-fluorophenyl)methanol and 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LCMS (ESI): m/z 431 $[M + H]^+$; 1.01 min (ret time)

E13

7-((4-((6-chloropyridin-3-yl)oxy)-3,5-difluorobenzyl)oxy)-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

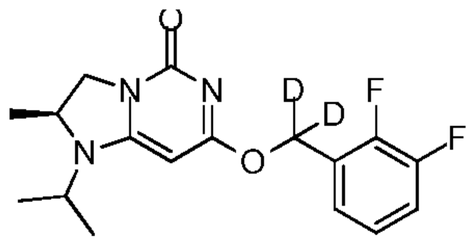


The title compound was prepared by a procedure similar to that described for **E9** starting from (4-((6-chloropyridin-3-yl)oxy)-3,5-difluorophenyl)methanol and 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LCMS (ESI): m/z 449 $[M + H]^+$; 1.04 min (ret time)

E14

(S)-7-(dideutero(2,3-difluorobenzyl)oxy)-1-isopropyl-2-methyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

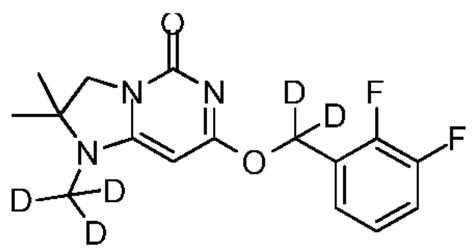


The title compound was prepared by a procedure similar to that described for **E1** starting from (S)-7-chloro-1-isopropyl-2-methyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and (2,3-difluorophenyl)dideuteromethanol.

LCMS (ESI): m/z 338 $[M + H]^+$; 2.37min (ret time)

E15

7-(dideutero(2,3-difluorobenzyl)oxy)-1-trideuteromethyl-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

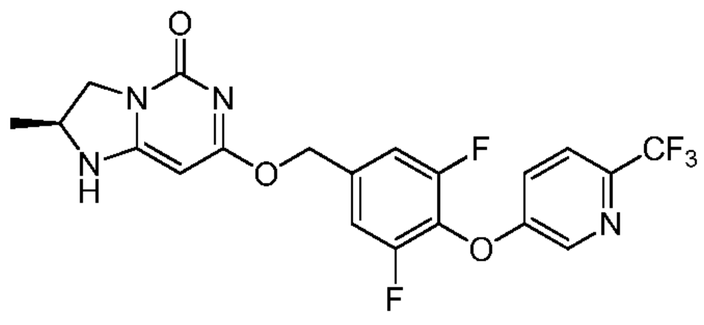


The title compound was prepared by a procedure similar to that described for **E1** starting from 7-chloro-2,2-dimethyl-1-(trideuteromethyl)-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and (2,3-difluorophenyl)dideuteromethanol.

LCMS (ESI): m/z 327 $[M + H]^+$; 2.16 min (ret time)

E16

(S)-7-((3,5-difluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)benzyl)oxy)-2-methyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

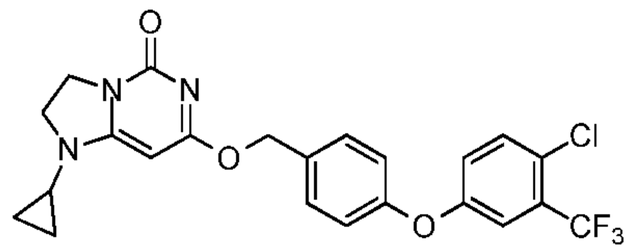


The title compound was prepared by a procedure similar to that described for **E9** starting from (3,5-difluoro-4-((6-(trifluoromethyl)pyri din-3-yl)oxy)phenyl)methanol and (S)-tert-butyl,7-chloro-2 -methyl-5-oxo-2,3-dihydroimidazo[1,2-c]pyrimidine-1(5H)-carboxylate.

LC-MS (ESI): m/z 455 $[M+1]^+$; 1.91 min (ret time).

E17

7-((4-(4-chloro-3-(trifluoromethyl)phenoxy)benzyl)oxy)-1-cyclopropyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one



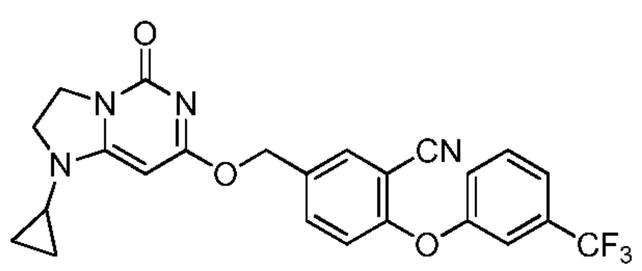
The title compound was prepared by a procedure similar to that described for **E9** starting from (4-(4-chloro-3-(trifluoromethyl)phenoxy)phenyl)methanol and 7-chloro-1-cyclopropyl-2,3-dihydroimi-dazo[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 478 $[M + H]^+$; 1.82 min (ret time).

^{1}H NMR (400 MHz, MeOD) δ 7.59 (d, *J* = 8.8 Hz, 1H), 7.52 (d, *J* = 8.6 Hz, 2H), 7.36 (d, *J* = 2.9 Hz, 1H), 7.21 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.08 (d, *J* = 8.6 Hz, 2H), 5.41 (s, 1H), 5.35 (s, 2H), 4.02 (t, *J* = 8.7 Hz, 2H), 3.76 (t, *J* = 8.7 Hz, 2H), 2.65 – 2.53 (m, 1H), 0.88 – 0.75 (m, 4H).

E18

5-(((1-cyclopropyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-c]pyrimidin-7-yl)oxy)methyl)-2-(3-(trifluoromethyl)phenoxy)benzonitrile



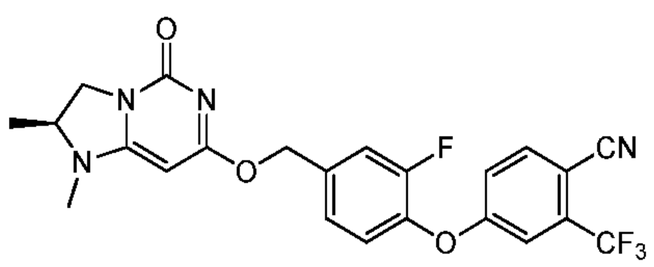
The title compound was prepared by a procedure similar to that described for **E9** starting from 5-(hydroxymethyl)-2-(3-(trifluoromethyl)phenoxy)benzonitrile and 7-chloro-1-cyclopropyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 469 $[M + H]^-$; 1.92 min (ret time)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 2.0 Hz, 1H), 7.61 – 7.44 (m, 3H), 7.33 (s, 1H), 7.27 (s, 1H), 6.90 (d, *J* = 8.6 Hz, 1H), 5.39 (s, 2H), 5.30 (s, 1H), 4.07 (t, *J* = 8.6 Hz, 2H), 3.68 (dd, *J* = 10.3, 6.9 Hz, 2H), 2.56 – 2.42 (m, 1H), 0.90 – 0.72 (m, 4H).

E19

(S)-4-(4-(((1,2-dimethyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-c]pyrimidin-7-yl)ox-y)methyl)-2-fluorophenoxy)-2-(trifluoromethyl)benzonitrile

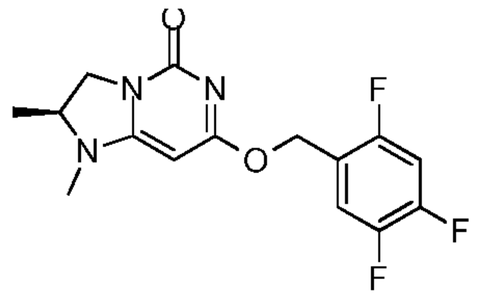


The title compound was prepared by a procedure similar to that described for **E9** starting from 4-(2-fluoro-4-(hydroxymethyl)phenoxy)-2-(trifluoromethyl)benzonitrile and (S)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo [1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 475 $[M + H]^+$; 1.06 min (ret time).

E20

(S)-1,2-dimethyl-7-((2,4,5-trifluorobenzyl)oxy)-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

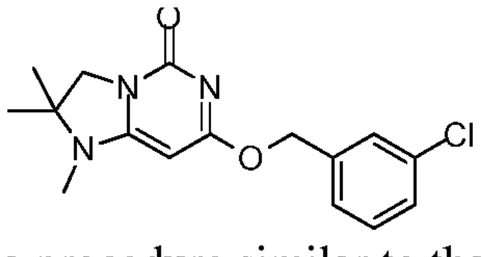


The title compound was prepared by a procedure similar to that described for **E1** starting from (S)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and (2,4,5-trifluorophenyl)methanol.

LCMS (ESI): m/z 326 $[M + H]^+$; 2.62 min (ret time)

E21

7-((3-chlorobenzyl)oxy)-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

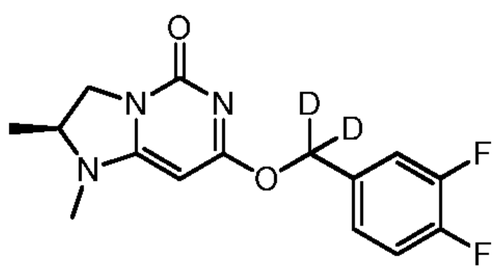


The title compound was prepared by a procedure similar to that described for **E1** starting from 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and (3-chlorophenyl)methanol.

LCMS (ESI): m/z 320 $[M + H]^+$; 2.29 min (ret time).

E22

(S)-7-(dideutero(3,4-difluorophenyl)methoxy)-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

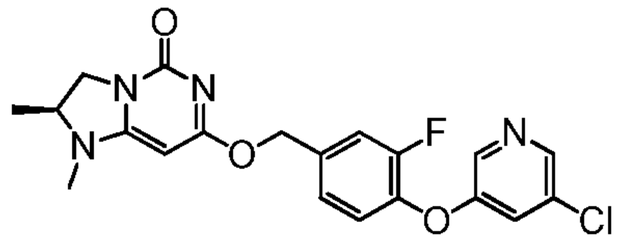


The title compound was prepared by a procedure similar to that described for **E9** starting from dideutero (3,4-difluorophenyl)methanol and (S)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 310 $[M + H]^+$; 1.03 min (ret time).

E23

(S)-7-((4-((5-chloropyridin-3-yl)oxy)-3-fluorobenzyl)oxy)-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

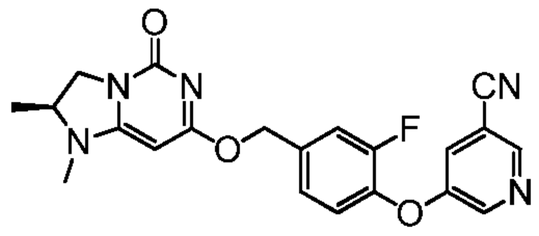


The title compound was prepared by a procedure similar to that described for **E9** starting from (4-((5-chloropyridin-3-yl)oxy)-3-fluorophenyl)methanol and (S)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin -5(1H)-one.

LC-MS (ESI): m/z 209 $[M + H]^+$; 0.96 min (ret time).

E24

(S)-5-(4-(((1,2-dimethyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-c]pyrimidin-7-yl)ox-y)methyl)-2-fluorophenoxy)nicotinonitrile

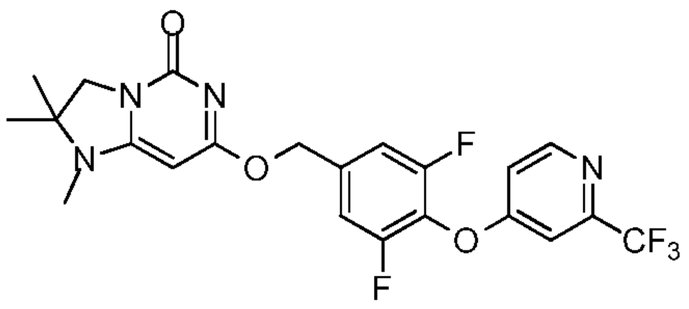


The title compound was prepared by a procedure similar to that described for **E9** starting from 5-(2-fluoro-4-(hydroxymethyl)phenoxy)nicotinonitrile and (S)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5 (1H)-one.

LC-MS (ESI): m/z 408 $[M + H]^+$; 0.88 min (ret time).

E25

7-((3,5-difluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)benzyl)oxy)-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

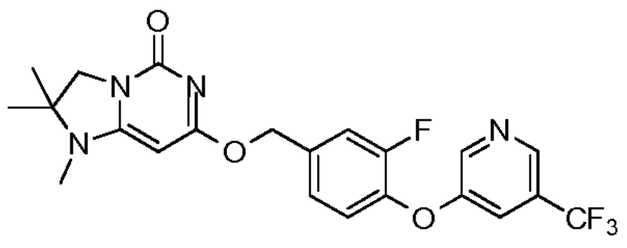


The title compound was prepared by a procedure similar to that described for **E9** starting from (3,5-difluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)phenyl)methanol and 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 400 $[M + H]^+$; 1.99 min (ret time).

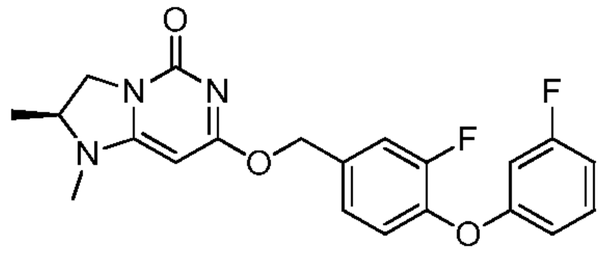
E26

7-((3-fluoro-4-((5-(trifluoromethyl)pyridin-3-yl)oxy)benzyl)oxy)-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one



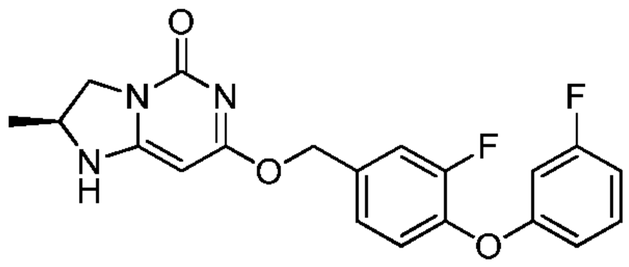
The title compound was prepared by a procedure similar to that described for **E9** starting from (3-fluoro-4-((5-(trifluoromethyl)pyridin-3-yl)oxy)phenyl)methanol and 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.
LC-MS (ESI): m/z 465 $[M + H]^+$; 1.03 min (ret time).

E27
(S)-7-((3-fluoro-4-(3-fluorophenoxy)benzyl)oxy)-1,2-dimethyl-2,3-dihydroimidazo-[1,2-c]pyrimidin-5(1H)-one



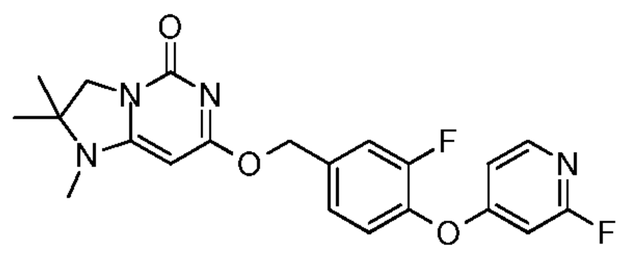
The title compound was prepared by a procedure similar to that described for **E9** starting from (3-fluoro-4-(3-fluorophenoxy)phenyl)methanol and (S)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo [1,2-c]pyrimidin-5(1H)-one.
LC-MS (ESI): m/z 400 $[M + H]^+$; 1.99 min (ret time).

E28
(S)-7-((3-fluoro-4-(3-fluorophenoxy)benzyl)oxy)-2-methyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one



The title compound was prepared by a procedure similar to that described for **E9** starting from (3-fluoro-4-(3-fluorophenoxy)phenyl)methanol and (S)-tert-butyl-7-chloro-2-methyl-5-oxo-2,3–dihydroimi dazo[1,2-c]pyrimidine-1(5H)-carboxylate.
LC-MS (ESI): m/z 386 $[M + H]^+$; 1.91 min (ret time).

E29
7-((3-fluoro-4-((2-fluoropyridin-4-yl)oxy)benzyl)oxy)-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

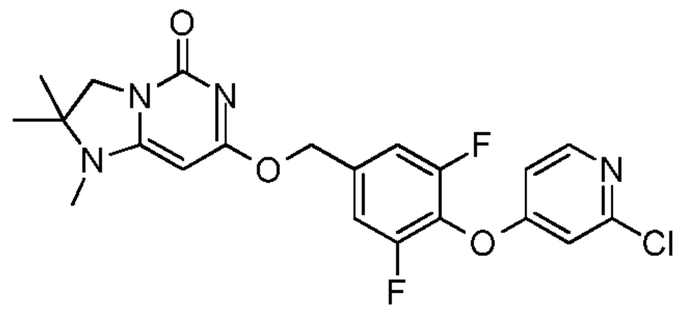


The title compound was prepared by a procedure similar to that described for **E9** starting from (3-fluoro-4-((2-fluoropyridin-4-yl)oxy)phenyl)methanol and 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 415 $[M + H]^+$; 0.96 min (ret time).

E30

7-((4-((2-chloropyridin-4-yl)oxy)-3,5-difluorobenzyl)oxy)-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

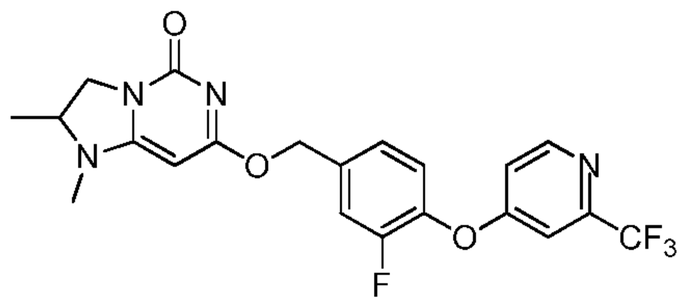


The title compound was prepared by a procedure similar to that described for **E9** starting from (4-((2-chloropyridin-4-yl)oxy)-3,5-difluorophenyl)methanol and 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 449 $[M + H]^+$; 1.02 min (ret time).

E31

7-((3-fluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)benzyl)oxy)-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

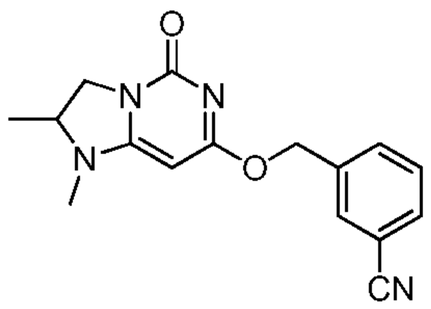


The title compound was prepared by a procedure similar to that described for **E1** starting from 7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and (3-fluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)phenyl).

LC-MS (ESI): m/z 451 $[M + H]^+$; 2.53 min (ret time).

E32

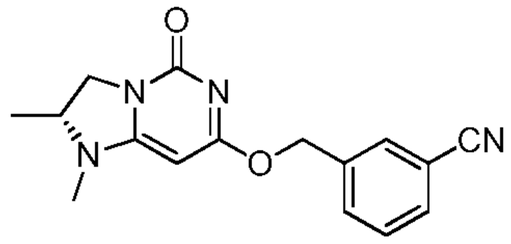
3-(((1,2-dimethyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-c]pyrimidin-7-yl)oxy)methyl)benzonitrile



The title compound was prepared by a procedure similar to that described for **E1** starting from 7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and 3-(hydroxylmethyl)benzonitrile.

LCMS (ESI): m/z 297 $[M + H]^+$; 1.79 min (ret time)

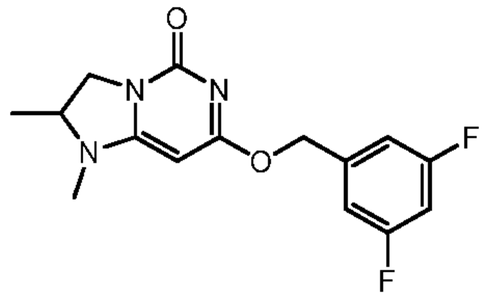
E33
(R)-3-(((1,2-dimethyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-c]pyrimidin-7-yl)oxy)methyl)benzonitrile



The title compound was prepared by a procedure similar to that described for **E9** starting from 3-(hydroxymethyl)benzonitrile and (R)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 297 $[M + H]^+$; 1.09 min (ret time).

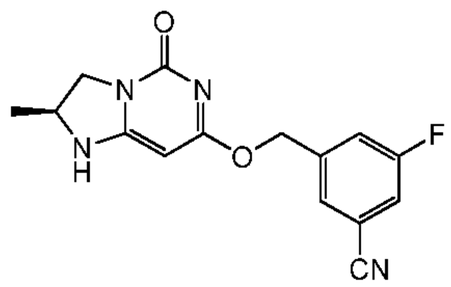
E34
7-((3,5-difluorobenzyl)oxy)-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one



The title compound was prepared by a procedure similar to that described for **E9** starting from (3,5-difluorophenyl)methanol and 7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 308 $[M + H]^+$; 1.01 min (ret time).

E35
(S)-3-fluoro-5-(((2-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-c]pyrimidin-7-yl)oxy)methyl)benzonitrile

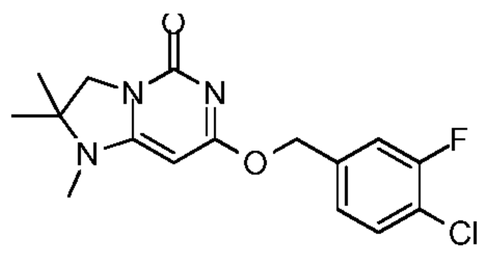


The title compound was prepared by a procedure similar to that described for **E1** starting from 3-fluoro-5-(hydroxymethyl)benzonitrile and (S)-tert-butyl 7-chloro-2-methyl-5-oxo-2,3-dihydroimidazo[1,2-c] pyrimidine-1(5H)-carboxylate.

LC-MS (ESI): m/z 301 $[M + H]^+$; 1.17 min (ret time).

E36

7-((4-chloro-3-fluorobenzyl)oxy)-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

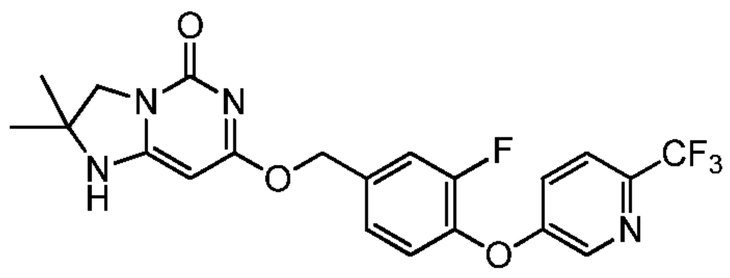


The title compound was prepared by a procedure similar to that described for **E1** starting from 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and (4-chloro-3-fluorophenyl)methanol.

LCMS (ESI): m/z 338 $[M + H]^+$; 2.34 min (ret time)

E37

7-((3-fluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)benzyl)oxy)-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

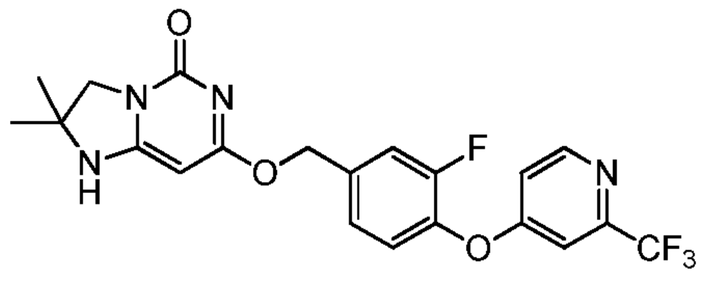


The title compound was prepared by a procedure similar to that described for **E9** starting from (3-fluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)phenyl)methanol and tert-butyl- 7-chloro-2,2-dimethyl-5-oxo-2,3-dihydroimidazo[1,2-c]pyrimidine-1(5H)-carboxylate.

LC-MS (ESI): m/z 451 $[M + H]^+$; 0.99 min (ret time).

E38

7-((3-fluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)benzyl)oxy)-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

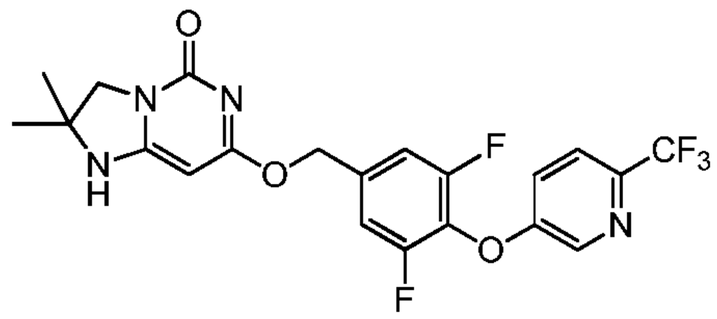


The title compound was prepared by a procedure similar to that described for **E9** starting from (3-fluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)phenyl)methanol and tert-butyl-7-chloro-2,2-dimethyl-5-oxo-2,3-dihydroimidazo[1,2-c]pyrimidine-1(5H)-carboxylate.

LC-MS (ESI): m/z 451 $[M + H]^+$; 0.98 min (ret time).

E39

7-((3,5-difluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)benzyl)oxy)-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

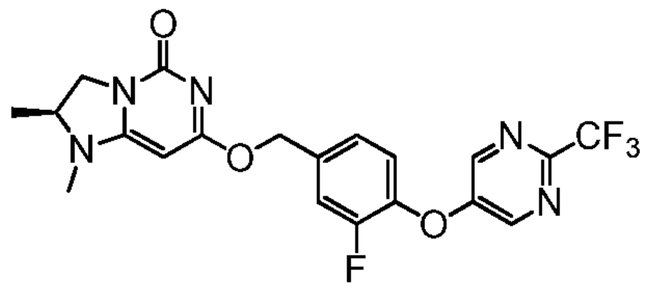


To a solution of tert-butyl 7-((3,5-difluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)benzyl) oxy)-2,2-dimethyl-5-oxo-2,3-dihydroimidazo[1,2-c]pyrimidine-1(5H)-carboxylate (95 mg, 0.167 mmol) in tetrahydrofuran (THF) (2 mL) stirred at 0 °C was added NaH (20.05 mg, 0.501 mmol). The reaction mixture was stirred for 18 h at 20 °C, quenched with water and concentrated in vacuo. Purification via preparative TLC with ethyl acetate afforded the title product.

LC-MS (ESI): m/z 469 $[M + H]^+$; 1.03 min (ret time).

E40

(S)-7-((3-fluoro-4-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)benzyl)oxy)-1,2-dimethyl 2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

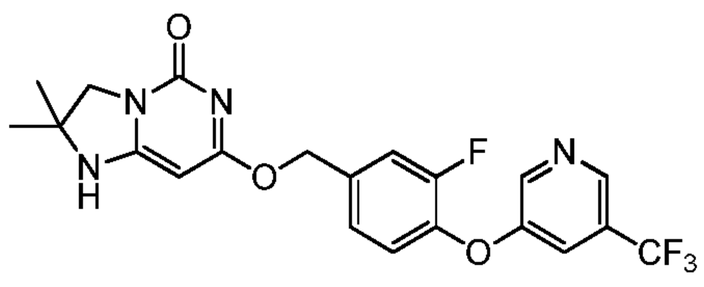


The title compound was prepared by a procedure similar to that described for **E9** starting from (3-fluoro-4-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)phenyl)methanol and (S)-7-chloro-1,2-dimethyl -2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 452 $[M + H]^+$; 1.20 min (ret time).

E41

7-((3-fluoro-4-((5-(trifluoromethyl)pyridin-3-yl)oxy)benzyl)oxy)-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

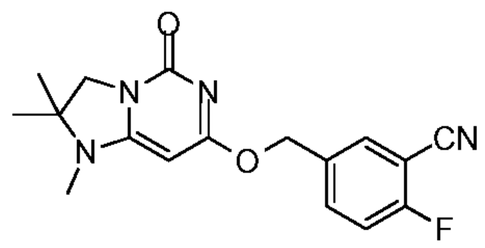


The title compound was prepared by a procedure similar to that described for **E9** starting from (3-fluoro-4-((5-(trifluoromethyl)pyridin-3-yl)oxy)phenyl)methanol and tert-butyl-7-chloro-2,2-dimethyl-5-oxo-2,3-dihydroimidazo[1,2-c]pyrimidine-1(5H)-carboxylate.

LC-MS (ESI): m/z 451 $[M + H]^+$; 0.98 min (ret time).

E42

2-fluoro-5-(((1,2,2-trimethyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-c]pyrimidin-7-yl)oxy)methyl)benzonitrile

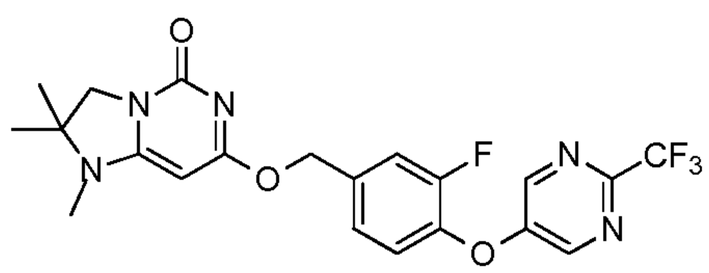


The title compound was prepared by a procedure similar to that described for **E9** starting from 2-fluoro-5-(hydroxymethyl)benzonitrile and 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 329 $[M + H]^+$; 1.06 min (ret time).

E43

7-((3-fluoro-4-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)benzyl)oxy)-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

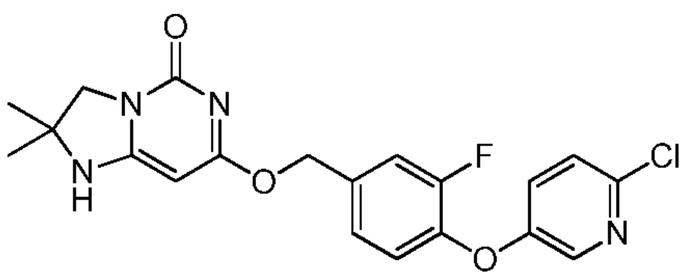


The title compound was prepared by a procedure similar to that described for **E9** starting from (3-fluoro-4-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)phenyl)methanol and 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 466 $[M + H]^+$; 1.03 min (ret time).

E44

7-((4-((6-chloropyridin-3-yl)oxy)-3-fluorobenzyl)oxy)-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

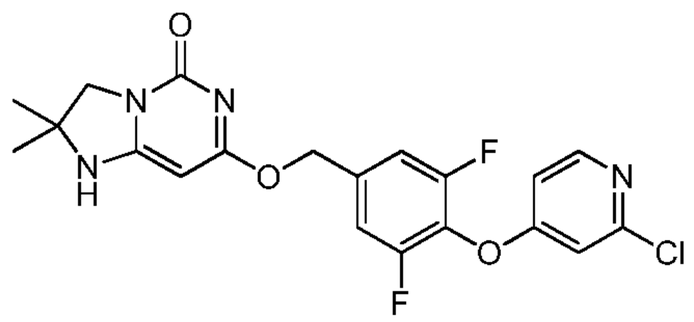


The title compound was prepared by a procedure similar to that described for **E9** starting from (4-((6-chloropyridin-3-yl)oxy)-3-fluorophenyl)methanol and tert-butyl 7-chloro-2,2-dimethyl-5-oxo-2,3-dihydroimidazo[1,2-c]pyrimidine-1(5H)-carboxylate.

LC-MS (ESI): m/z 417 $[M + H]^+$; 1.81 min (ret time).

E45

7-((4-((2-chloropyridin-4-yl)oxy)-3,5-difluorobenzyl)oxy)-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

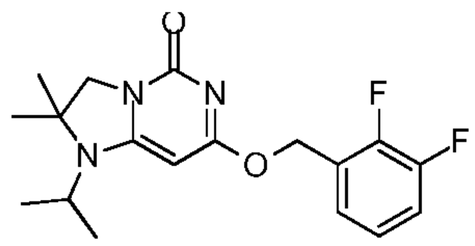


The title compound was prepared by a procedure similar to that described for **E9** starting from (4-((2-chloropyridin-4-yl)oxy)-3,5-difluorophenyl)methanol and tert-butyl-7-chloro-2,2-dimethyl-5-oxo-2,3-dihydroimidazo[1,2-c]pyrimidine-1(5H)-carboxylate.

LC-MS (ESI): m/z 435 $[M + H]^+$; 1.81 min (ret time).

E46

7-((2,3-difluorobenzyl)oxy)-1-isopropyl-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin5(1H)-one

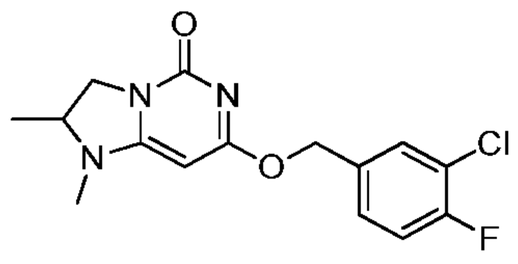


The title compound was prepared by a procedure similar to that described for **E1** starting from 7-chloro-1-isopropyl-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and (2,3-difluorophenyl)methanol.

LCMS (ESI): m/z 350 $[M + H]^+$; 2.55 min (ret time).

E47

7-((3-chloro-4-fluorobenzyl)oxy)-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

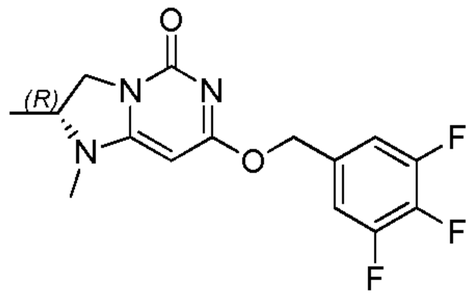


The title compound was prepared by a procedure similar to that described for **E1** starting from (3-chloro-4-fluorophenyl)methanol and 7-chloro-1,2-dimethyl-2,3-dihydro imidazo[1,2-c]pyrimidin5(1H)-one.

LC-MS (ESI): m/z 324 $[M + H]^+$; 1.50 min (ret time).

E48

(R)-1,2-dimethyl-7-((3,4,5-trifluorobenzyl)oxy)-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

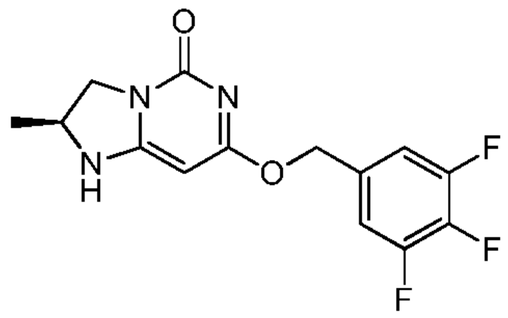


The title compound was prepared by a procedure similar to that described for **E1** starting from (3,4,5-trifluorophenyl)methanol and (R)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo [1,2-c]pyrimidin-5(1H)-one

LC-MS (ESI): m/z 326 $[M + H]^+$; 0.77 min (ret time).

E49

(S)-2-methyl-7-((3,4,5-trifluorobenzyl)oxy)-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

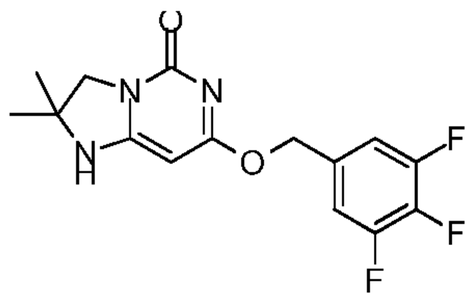


The title compound was prepared by a procedure similar to that described for **E1** starting from (3,4,5-trifluorophenyl)methanol and (S)-tert-butyl-7-chloro-2-methyl-5-oxo-2,3-dihydroimidazo[1,2-c]pyrimidine-1(5H) –carboxylate.

LC-MS (ESI): m/z 312 $[M + H]^+$; 1.03 min (ret time).

E50

2,2-dimethyl-7-((3,4,5-trifluorobenzyl)oxy)-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

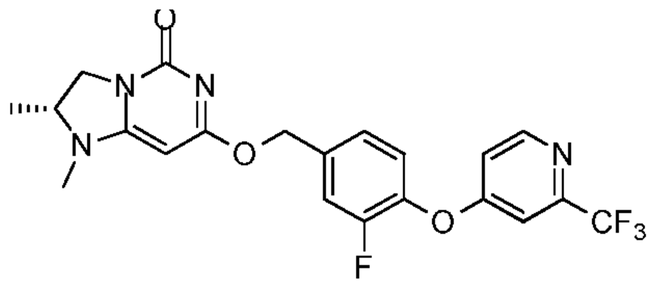


To a solution of 7-chloro-2,2-dimethyl-1-(methylsulfonyl)-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one (180 mg, 0.648 mmol) and (3,4,5-trifluorophenyl)methanol (210 mg, 1.30 mmol) in N,N-dimethylformamide (DMF) (3.5 mL) was added K_2CO_3 (269 mg, 1.94 mmol). The reaction mixture was sealed in a microwave vial and irradiated with a microwave using initial normal to 100 °C for 1h. Purification via MDAP afforded the title product as a white solid.

LCMS (ESI): m/z 326 $[M + H]^+$; 3.39 min (ret time).

E51

(R)-7-((3-fluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)benzyl)oxy)-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

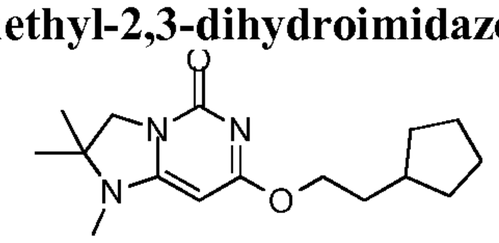


The title compound was prepared by a procedure similar to that described for **E1** starting from (R)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and (3-fluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)phenyl)methanol.

LCMS (ESI): m/z 451 $[M + H]^+$; 3.23 min (ret time).

E52

7-(2-cyclopentylethoxy)-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

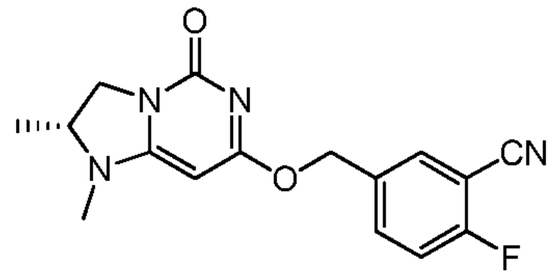


The title compound was prepared by a procedure similar to that described for **E1** starting from 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and 2-cyclopentylethanol.

LCMS (ESI): m/z 292 $[M + H^+$; 2.42 min (ret time).

E53

(R)-5-(((1,2-dimethyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-c]pyrimidin-7-yl)oxy)methyl)-2-fluorobenzonitrile

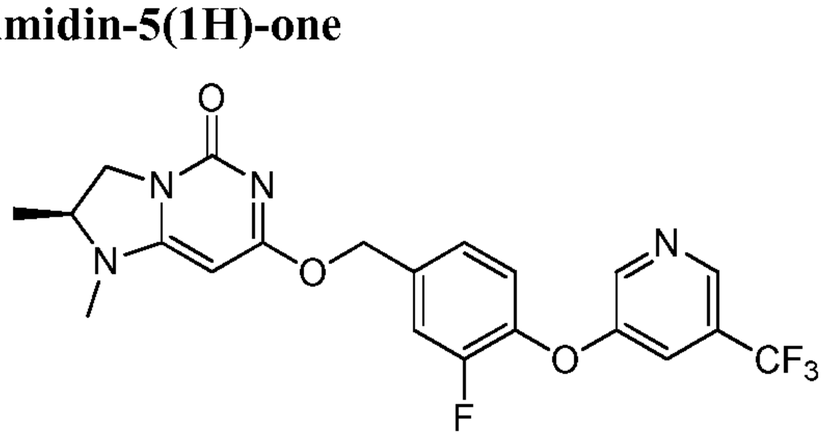


The title compound was prepared by a procedure similar to that described for **E9** starting from (R)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and 2-fluoro-5-(hydroxymethyl)benzonitrile.

LC-MS (ESI): m/z 315 $[M + H]^+$; 1.00 min (ret time).

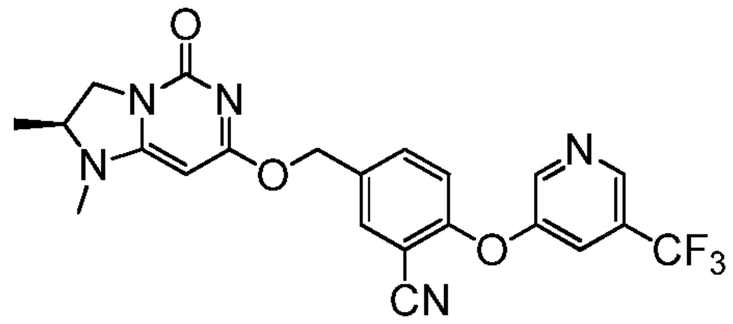
E54

(S)-7-((3-fluoro-4-((5-(trifluoromethyl)pyridin-3-yl)oxy)benzyl)oxy)-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one



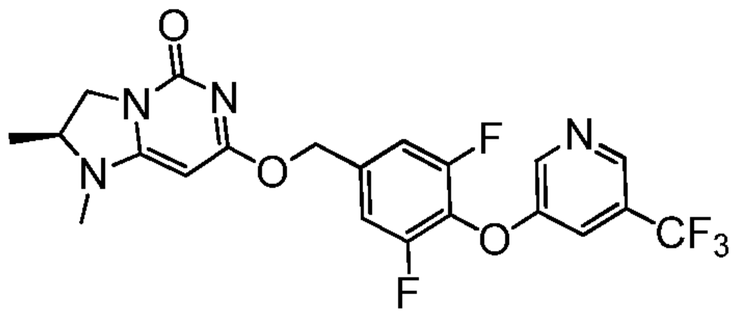
The title compound was prepared by a procedure similar to that described for **E9** starting from (3-fluoro-4-((5-(trifluoromethyl)pyridin-3-yl)oxy)phenyl)methanol and (S)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c] pyrimidin-5(1H)-one.
LC-MS (ESI): m/z 226 $[M + H]^+$; 1.20 min (ret time).

E55
(S)-5-(((1,2-dimethyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-c]pyrimidin-7-yl)oxy)methyl)-2-((5-(trifluoromethyl)pyridin-3-yl)oxy)benzonitrile



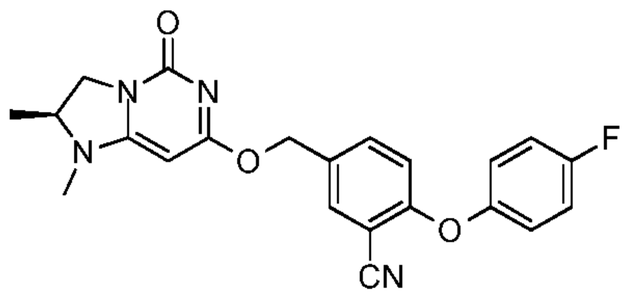
The title compound was prepared by a procedure similar to that described for **E9** starting from 5-(hydroxymethyl)-2-((5-(trifluoromethyl)pyridin-3-yl)oxy)benzonitrile and (S)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo [1,2-c]pyrimidin-5(1H)-one.
LC-MS (ESI): m/z 458 $[M + H]^+$; 1.17 min (ret time).

E56
(S)-7-((3,5-difluoro-4-((5-(trifluoromethyl)pyridin-3-yl)oxy)benzyl)oxy)-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one



The title compound was prepared by a procedure similar to that described for **E9** starting from (3,5-difluoro-4-((5-(trifluoromethyl)pyridin-3-yl)oxy)phenyl)methanol and (S)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo [1,2-c] pyrimidin-5(1H)-one.
LC-MS (ESI): m/z 469 $[M + H]^+$; 1.24 min (ret time).

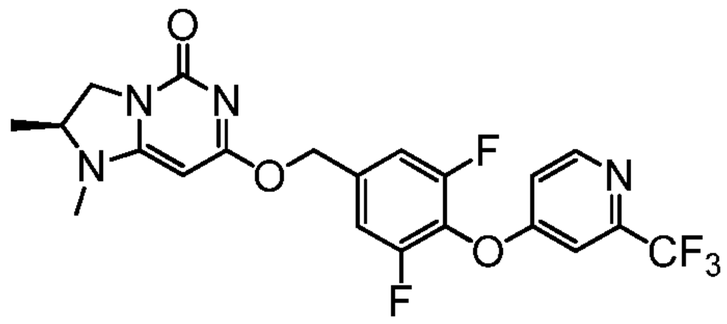
E57
(S)-5-(((1,2-dimethyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-c]pyrimidin-7-yl)oxy)methyl)-2-(4-fluorophenoxy)benzonitrile



The title compound was prepared by a procedure similar to that described for **E9** starting from 2-(4-fluorophenoxy)-5-(hydroxymethyl)benzonitrile and (S)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.
LC-MS (ESI): m/z 407 $[M + H]^+$; 1.03 min (ret time).

E58

(S)-7-((3,5-difluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)benzyl)oxy)-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

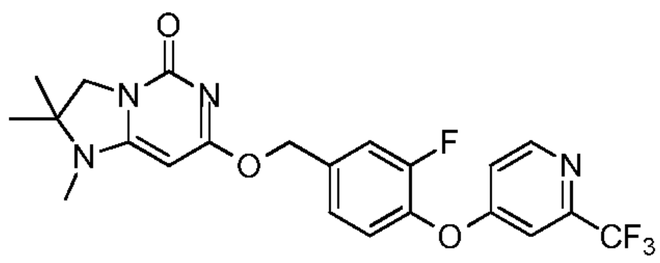


The title compound was prepared by a procedure similar to that described for **E9** starting from (3,5-difluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)phenyl)methanol and (S)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo [1,2-c]pyrimidin-5(1H)-one.
LC-MS (ESI): m/z 470 $[M + H]^+$; 1.02 min (ret time).

An alternative synthetic process is provided: NaH (0.52 g, 13.0 mmol) was added to a mixture of (3,5-difluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)phenyl)methanol (3g, 9.83 mmol) in N,N-dimethylformamide (DMF) (40 mL) at 0 ^{0}C with stirring. The reaction mixture was stirred at 0 ^{0}C for 30 mins. Then, a solution of (S)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo [1,2-c]pyrimidin-5(1H)-one (2.06 g, 10.32 mmol) in N,N-dimethylformamide (DMF) (40 mL) was added dropwise into the reaction mixture. The reaction mixture was stirred at 0 ^{0}C for 3 hours. Then, the reaction mixture was left overnight with stirring to warm up to rt. After the reaction is completed, the reaction mixture was quenched by adding water, and then was stirred for 30 mins, partitioned with DCM and water. The DCM layer was separated and the aqueous layer was extracted with DCM, then the combined DCM solution was washed with water twice followed by brine, and then concentrated in vacuo. The residue was dissolved in 1N HCl and extracted with MTBE. The MTBE layer was removed and the aqueous layer was then acidified to pH=7 and extracted with MTBE. The aqueous solution was discarded and the MTBE layer was combined with the prior MTBE layer. The combined MTBE solution was evaporated in vacuum to afford crude product, which was recrystallized with MTBE to provide the title compound (569 mg, 12.1% yield).
^{1}H NMR (400MHz, DMSO-d_6) δ: 8.69 (1H, d, J = 5.62Hz), 7.68 (1H, d, J = 2.2Hz), 7.45 (2H, d, J = 9.05Hz), 7.32 (1H, dd, J = 5.50, 2.32Hz), 5.33 (2H, s), 5.28 (1H, s), 4.04-4.18 (1H, m), 3.86-4.04 (1H, m), 3.48 (1H, dd, J = 11.25, 7.34Hz), 2.83 (3H, s), 1.28 (3H, d, J = 6.36Hz).
LC-MS (ESI): m/z 469 $[M + H]^+$; 2.90 min (ret time).

E59

7-((3-fluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)benzyl)oxy)-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one



The title compound was prepared by a procedure similar to that described for **E9** starting from (3-fluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)phenyl)methanol and 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 465 $[M + H]^+$; 1.02 min (ret time).

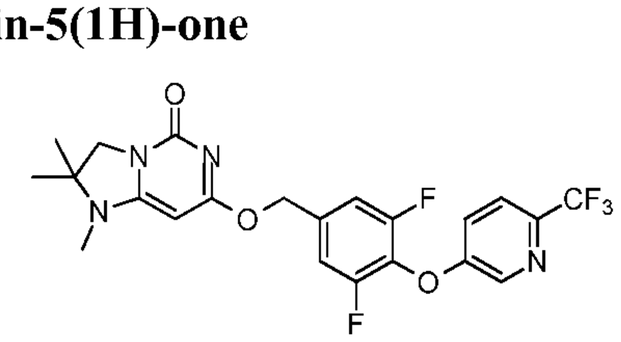
An alternative synthetic process is provided: NaH (0.439 g, 10.97 mmol) was added to a solution of (3-fluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)phenyl)methanol (1.05g, 3.66 mmol) in tetrahydrofuran (20 mL) at 0 ^{0}C under N_2. The reaction mixture was stirred at 0 ^{0}C for 30 mins. Then, 7-chloro-1, 2, 2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one (0.781g, 3.66 mmol) was added to the reaction mixture. The reaction mixture was stirred at 0 ^{0}C for 1h, quenched by addition of water (2 mL), and then concentrated in vacuo. Then, the residue was diluted with DCM (50 mL), washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The concentrated portion was purified by FC purification (DCM/MeOH 50:1) to afford the crude product as a light yellow solid, which was further purified by prep-HPLC to obtain the title compound (1.02 g, 60% yield) as a white solid.

^{1}H NMR (400MHz, MeOD) δ: 8.58 (1H, d, *J* = 2.0Hz), 7.47 (1H, dd, *J* = 1.6, 11.2Hz), 7.34-7.38 (3H, m), 7.11 (1H, dd, *J* = 2.4, 5.6Hz), 5.39 (2H, s), 5.26 (1H, s), 3.86 (2H, s), 2.87 (3H, s), 1.41 (6H, s).

LC-MS (ESI): m/z 465 $[M + H]^+$; 1.36 min (ret time).

E60

7-((3,5-difluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)benzyl)oxy)-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

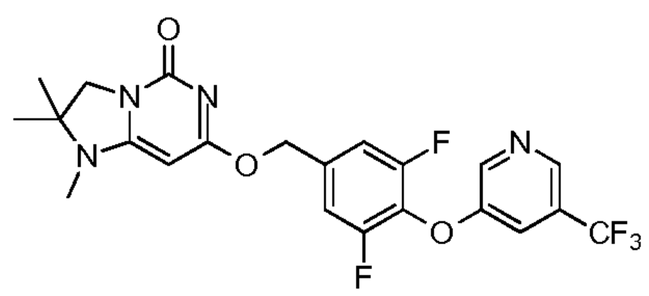


The title compound was prepared by a procedure similar to that described for **E9** starting from (3,5-difluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)phenyl)methanol and 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 483 $[M + H]^+$; 1.07 min (ret time).

E61

7-((3,5-difluoro-4-((5-(trifluoromethyl)pyridin-3-yl)oxy)benzyl)oxy)-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

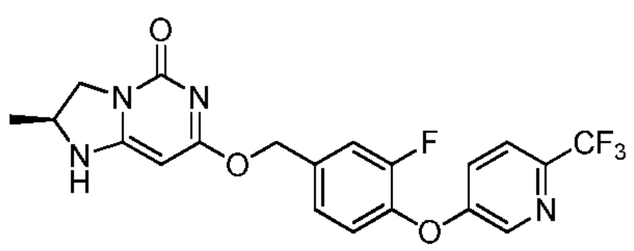


The title compound was prepared by a procedure similar to that described for **E9** starting from (3,5-difluoro-4-((5-(trifluoromethyl)pyridin-3-yl)oxy)phenyl)methanol and 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 483 $[M + H]^+$; 1.05 min (ret time).

E62

(S)-7-((3-fluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)benzyl)oxy)-2-methyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

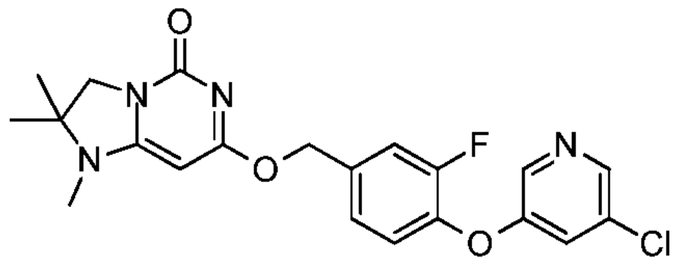


The title compound was prepared by a procedure similar to that described for **E9** starting from (3-fluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)phenyl)methanol and (S)-tert-butyl-7-chloro-2–methyl-5-oxo-2,3-dihydroimidazo[1,2-c]pyrimidine-1(5H)-carboxylate.

LC-MS (ESI): m/z 437 $[M + H]^+$; 1.85 min (ret time).

E63

7-((4-((5-chloropyridin-3-yl)oxy)-3-fluorobenzyl)oxy)-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

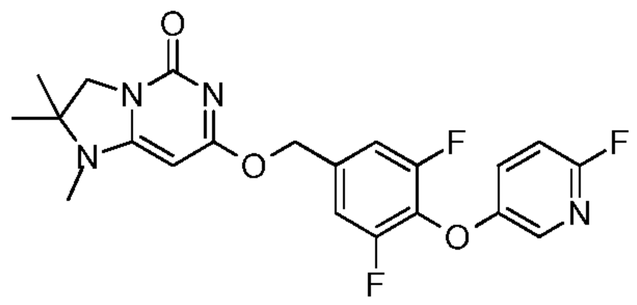


The title compound was prepared by a procedure similar to that described for **E9** starting from (4-((5-chloropyridin-3-yl)oxy)-3-fluorophenyl)methanol and 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 431 $[M + H]^+$; 1.01 min (ret time).

E64

7-((3,5-difluoro-4-((6-fluoropyridin-3-yl)oxy)benzyl)oxy)-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

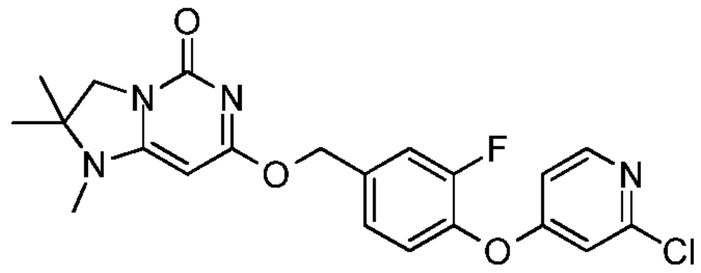


The title compound was prepared by a procedure similar to that described for **E9** starting from (3,5-difluoro-4-((6-fluoropyridin-3-yl)oxy)phenyl)methanol and 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 433 $[M + H]^+$; 1.00 min (ret time).

E65

7-((4-((2-chloropyridin-4-yl)oxy)-3-fluorobenzyl)oxy)-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

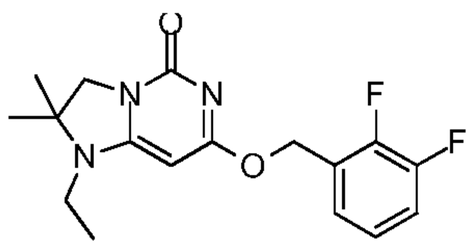


The title compound was prepared by a procedure similar to that described for **E9** starting from (4-((2-chloropyridin-4-yl)oxy)-3-fluorophenyl) and 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 431 $[M + H]^+$; 0.97 min (ret time).

E66

7-((2,3-difluorobenzyl)oxy)-1-ethyl-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

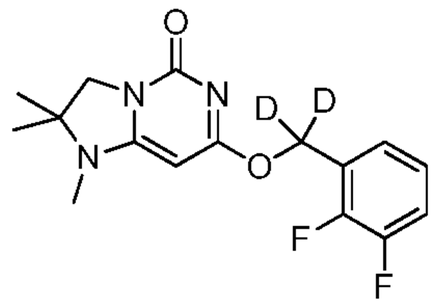


The title compound was prepared by a procedure similar to that described for **E1** starting from 7-chloro-1-ethyl-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and (2,3-difluorophenyl)methanol.

LCMS (ESI): m/z 336 $[M + H]^+$; 2.33 min (ret time).

E67

7-(dideutero(2,3-difluorobenzyl)oxy)-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

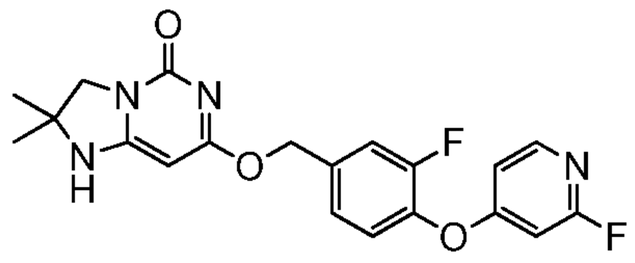


The title compound was prepared by a procedure similar to that described for **E9** starting from (2,3-difluorophenyl)dideuteromethanol and 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LCMS (ESI): 324 $[M + H]^+$; 2.14 min (ret time)

E68

7-((3-fluoro-4-((2-fluoropyridin-4-yl)oxy)benzyl)oxy)-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

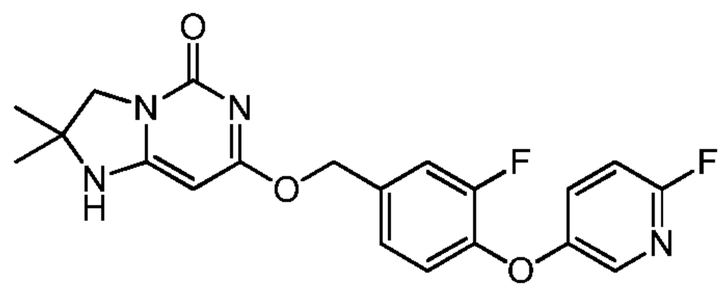


The title compound was prepared by a procedure similar to that described for **E9** starting from (3-fluoro-4-((2-fluoropyridin-4-yl)oxy)phenyl)methanol and tert-butyl-7-chloro-2,2-dimethyl-5-oxo -2,3-dihydroimidazo[1,2-c]pyrimidine-1(5H)-carboxylate.

LC-MS (ESI): m/z 401 $[M + H]^+$; 1.70 min (ret time).

E69

7-((3-fluoro-4-((6-fluoropyridin-3-yl)oxy)benzyl)oxy)-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

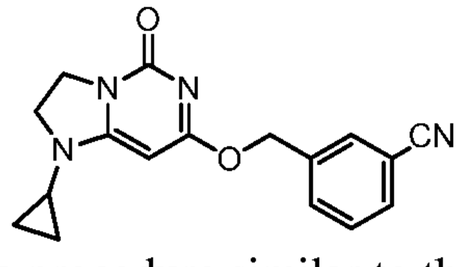


To a solution of tert-butyl-7-((3-fluoro-4-((6-fluoropyridin-3-yl)oxy)benzyl)oxy)-2,2–dimethyl-5-oxo-2,3-dihydroimidazo[1,2-c]pyrimidine-1(5H)-carboxylate (130 mg, 0.260 mmol) in dichloromethane (DCM) (4 mL) was added TFA (1.00 mL, 13.0 mmol) at 25°C. The reaction mixture was stirred at 25 °C overnight, concentrated and diluted with ethyl acetate/saturated sodium bicarbonate solution. Organic layer was separated, washed with water then saturated brine, dried over sodium sulphate. Purification via preparative TLC (DCM/MeOH = 10/1) afforded the desired product as a white solid.

LC-MS (ESI): m/z 401 $[M + H]^+$; 1.73 min (ret time).

E70

3-(((1-cyclopropyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-c]pyrimidin-7-yl)oxy)methyl)benzonitrile

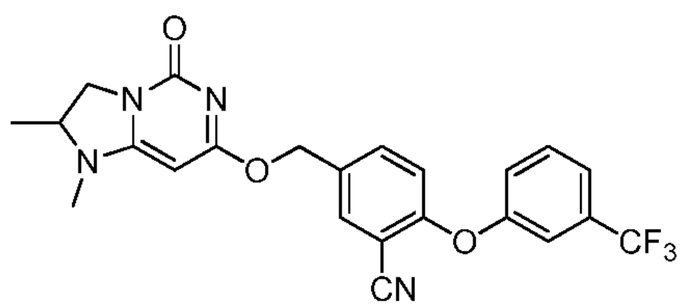


The title compound was prepared by a procedure similar to that described for **E9** starting from 3-(hydroxymethyl)benzonitrile and 7-chloro-1-cyclopropyl-2,3-dihydroimidazo-[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 309 $[M + H]^+$; 1.52 min (ret time)

E71

5-(((1,2-dimethyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-c]pyrimidin-7-yl)oxy)methyl)-2-(3-(trifluoromethyl)phenoxy)benzonitrile

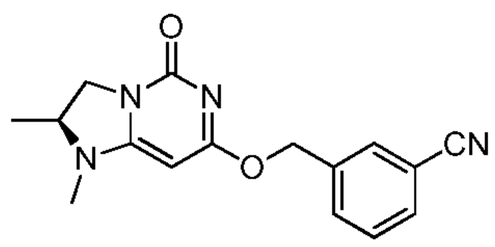


The title compound was prepared by a procedure similar to that described for **E1** starting from 7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and 5-(hydroxymethyl)-2-(3-(trifluoromethyl)phenoxy)benzonitrile.

LC-MS (ESI): m/z 457 $[M + H]^+$; 2.75 min (ret time).

E72

(S)-3-(((1,2-dimethyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-c]pyrimidin-7-yl)oxy)methyl) benzonitrile

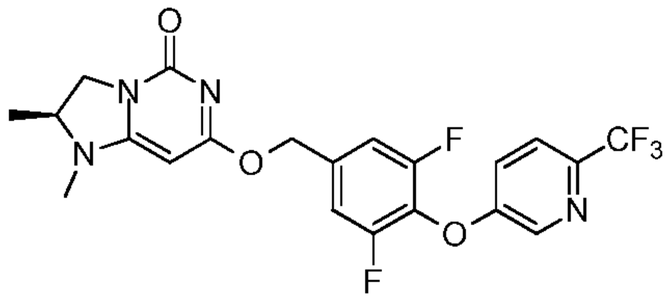


The title compound was prepared by a procedure similar to that described for **E9** starting from 3-(hydroxymethyl)benzonitrile and (S)-7-chloro-1,2-dimethyl-2,3-dihydroimidaz-o[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 297 $[M + H]^+$; 1.09 min (ret time).

E73

(S)-7-((3,5-difluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)benzyl)oxy)-1,2-dimethy-l-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

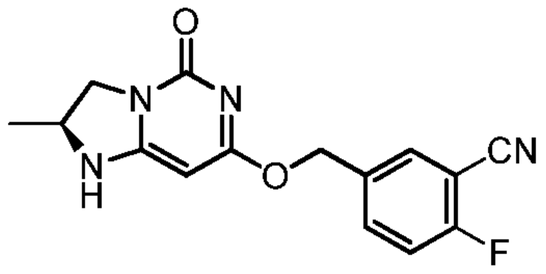


The title compound was prepared by a procedure similar to that described for **E9** starting from (3,5-difluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)phenyl)methanol and (S)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 469 $[M + H]^+$; 3.73 min (ret time).

E74

(S)-2-fluoro-5-(((2-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-c]pyrimidin-7-yl)oxy)methyl)benzonitrile

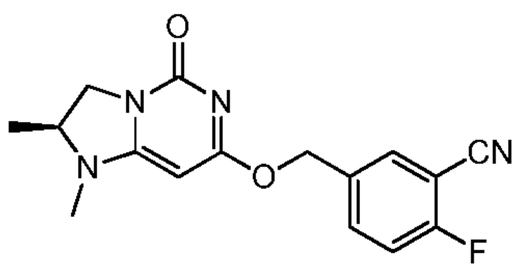


The title compound was prepared by a procedure similar to that described for **E9** starting from 2-fluoro-5-(hydroxymethyl)benzonitrile and (S)-tert-butyl-7-chloro-2-methyl-5-oxo-2,3-dihydroimidazo[1,2-c]pyrimidine-1(5H)-carboxylate.

LC-MS (ESI): m/z 301 $[M + H]^+$; 0.99 min (ret time).

E75

(S)-5-(((1,2-dimethyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-c]pyrimidin-7-yl)oxy)methyl)-2-fluorobenzonitrile

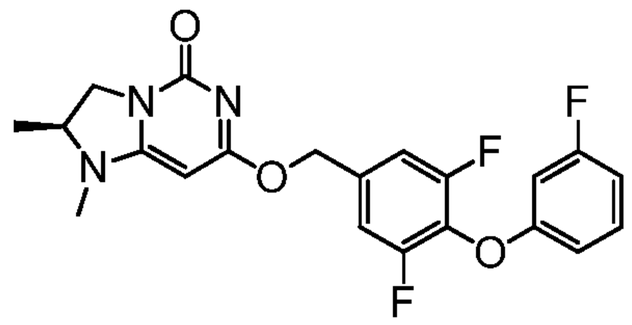


The title compound was prepared by a procedure similar to that described for **E9** starting from 2-fluoro-5-(hydroxymethyl)benzonitrile and (S)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 315 $[M + H]^+$; 1.00 min (ret time).

E76

(S)-7-((3,5-difluoro-4-(3-fluorophenoxy)benzyl)oxy)-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

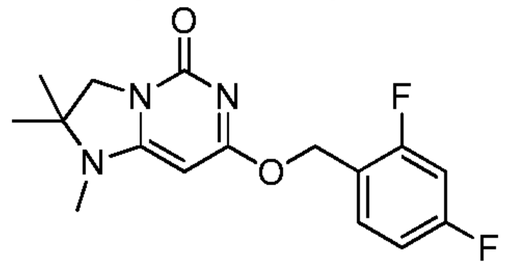


The title compound was prepared by a procedure similar to that described for **E9** starting from (3,5-difluoro-4-(3-fluorophenoxy)phenyl)methanol and (S)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 419 $[M + H]^+$; 1.04 min (ret time).

E77

7-((2,4-difluorobenzyl)oxy)-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

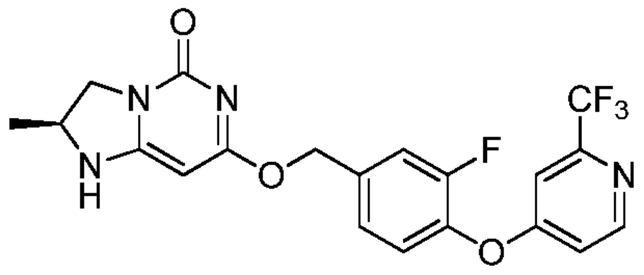


The title compound was prepared by a procedure similar to that described for **E9** starting from (2,4-difluorophenyl) and 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

LC-MS (ESI): m/z 322 $[M + H]^+$; 2.32 min (ret time).

E78

(S)-7-((3-fluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)benzyl)oxy)-2-methyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

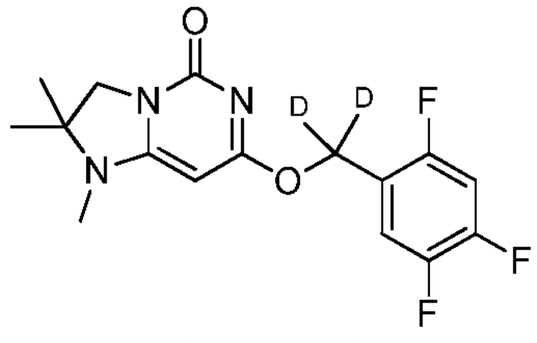


The title compound was prepared by a procedure similar to that described for **E9** starting from (3-fluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)phenyl)methanol and (S)-tert-butyl-7-chloro-2-methyl-5-oxo-2,3-dihydroimidazo[1,2-c]pyrimidine-1(5H)-carboxylate.

LC-MS (ESI): m/z 437 $[M + H]^+$; 1.79 min (ret time).

E79

1,2,2-trimethyl-7-(dideutero(2,4,5-trifluorobenzyl)oxy)-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

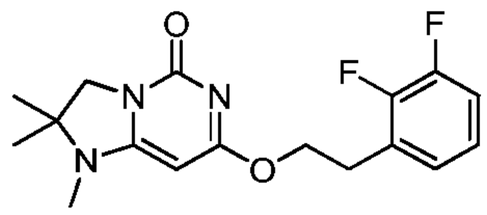


The title compound was prepared by a procedure similar to that described for **E9** starting from (2,4,5-trifluorophenyl)dideuteromethanol and 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 342 $[M + H]^+$; 2.14 min (ret time).

E80

7-(2,3-difluorophenethoxy)-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

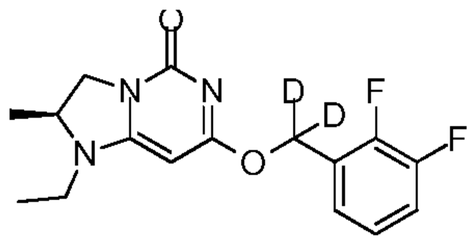


The title compound was prepared by a procedure similar to that described for **E9** starting from 2-(2,3-difluorophenyl)ethanol and 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 336 $[M + H]^+$; 0.89 min (ret time).

E 81

(S)-7-(dideutero(2,3-difluorobenzyl)oxy)-1-ethyl-2-methyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

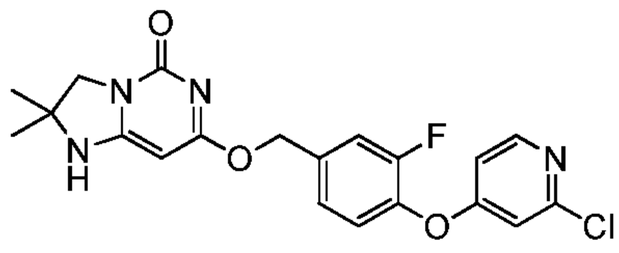


The title compound was prepared by a procedure similar to that described for **E9** starting from (S)-7-chloro-1-ethyl-2-methyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and (2,3-difluorophenyl)dideuteromethanol.

LCMS (ESI): m/z 324 $[M + H]^+$; 2.21min (ret time).

E82

7-((4-((2-chloropyridin-4-yl)oxy)-3-fluorobenzyl)oxy)-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

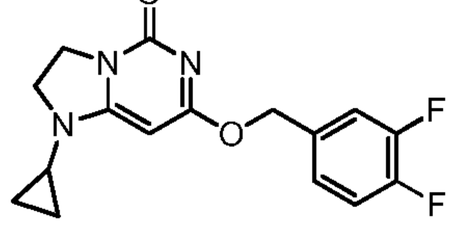


The title compound was prepared by a procedure similar to that described for **E9** starting from (4-((2-chloropyridin-4-yl)oxy)-3-fluorophenyl)methanol and tert-butyl-7-chloro-2,2-dimethyl-5-oxo-2,3-dihydroimidazo[1,2-c]pyrimidine-1(5H)-carboxylate.

LC-MS (ESI): m/z 417 $[M + H]^+$; 1.76 min (ret time).

E83

1-cyclopropyl-7-((3,4-difluorobenzyl)oxy)-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

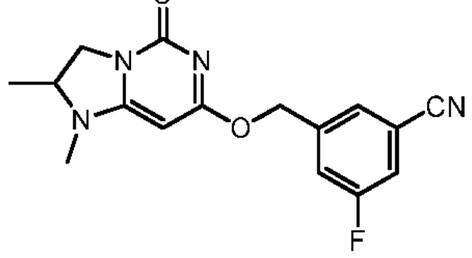


The title compound was prepared by a procedure similar to that described for **E9** starting from (3,4-difluorophenyl)methanol and 7-chloro-1-cyclopropyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 320 $[M + H]^+$; 1.61 min (ret time)

E84

3-(((1,2-dimethyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-c]pyrimidin-7-yl)oxy)methyl)-5-fluorobenzonitrile

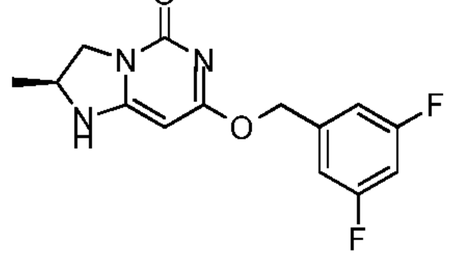


The title compound was prepared by a procedure similar to that described for **E9** starting from 3-fluoro-5-(hydroxymethyl)benzonitrile and 7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H) –one.

LC-MS (ESI): m/z 316 $[M + H]^+$; 1.28 min (ret time).

E85

(S)-7-((3,5-difluorobenzyl)oxy)-2-methyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

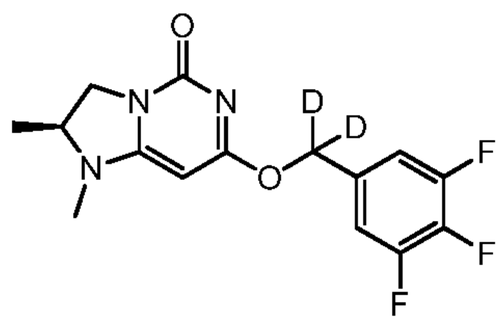


The title compound was prepared by a procedure similar to that described for **E9** starting from (3,5-difluorophenyl)methanol and (S)-tert-butyl-7-chloro-2-methyl-5-oxo-2,3-dihydroimidazo[1,2-c]pyrimidine-1(5H)-carboxylate.

LC-MS (ESI): m/z 294 $[M + H]^+$; 0.79 min (ret time).

E86

(S)-7-(dideutero(3,4,5-trifluorophenyl)methoxy)-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

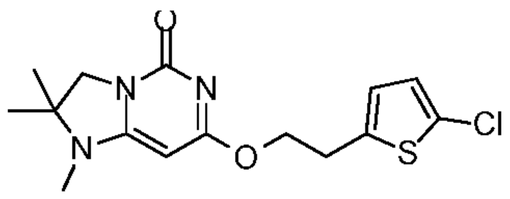


The title compound was prepared by a procedure similar to that described for **E9** starting from dideutero (3,4,5-trifluorophenyl)methanol and (S)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 328 $[M + H]^+$; 1.08 min (ret time).

E87

7-(2-(5-chlorothiophen-2-yl)ethoxy)-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

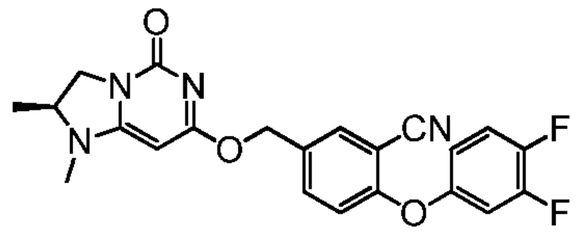


To a solution of 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one (90.0 mg, 0.421 mmol) and 2-(5-chlorothiophen-2-yl)ethanol (68.5 mg, 0.421 mmol) in N,N-dimethylformamide (DMF) (3 mL) was added Cs_2CO_3 (274 mg, 0.842 mmol). The reaction mixture was stirred at 130 °C for 5 h, quenched with water. Purification via MDAP afforded the title product as a white solid.

LCMS (ESI): m/z 340 $[M + H]^+$; 2.37 min (ret time).

E88

(S)-2-(3,4-difluorophenoxy)-5-(((1,2-dimethyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-c]pyrimidin-7-yl)oxy)methyl)benzonitrile

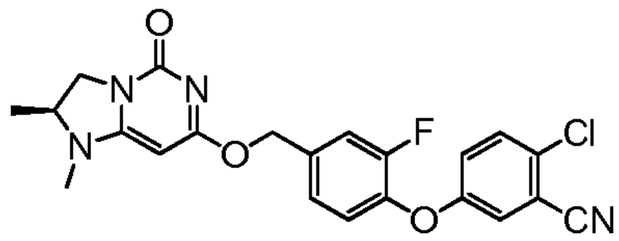


The title compound was prepared by a procedure similar to that described for **E9** starting from 2-(3,4-difluorophenoxy)-5-(hydroxymethyl)benzonitrile and (S)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c] pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 425 $[M + H]^+$; 1.00 min (ret time).

E89

(S)-2-chloro-5-(4-(((1,2-dimethyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-c]pyrimidin-7-yl)oxy)methyl)-2-fluorophenoxy)benzonitrile

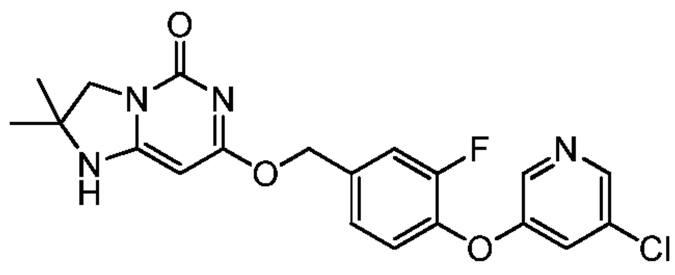


The title compound was prepared by a procedure similar to that described for **E9** starting from 2-chloro-5-(2-fluoro-4-(hydroxymethyl)phenoxy)benzonitrile and (S)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 441 $[M + H]^+$; 1.03 min (ret time).

E90

7-((4-((5-chloropyridin-3-yl)oxy)-3-fluorobenzyl)oxy)-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

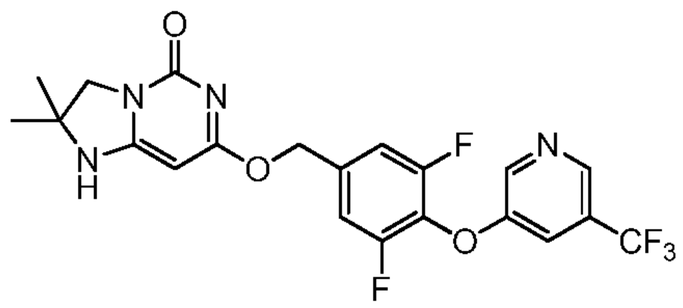


The title compound was prepared by a procedure similar to that described for **E9** starting from (4-((5-chloropyridin-3-yl)oxy)-3-fluorophenyl)methanol and tert-butyl-7-chloro-2,2-dimethyl-5-oxo-2,3-dihydroimidazo[1,2-c]pyrimidine-1(5H)-carboxylate.

LC-MS (ESI): m/z 417 $[M + H]^+$; 0.94 min (ret time).

E91

7-((3,5-difluoro-4-((5-(trifluoromethyl)pyridin-3-yl)oxy)benzyl)oxy)-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

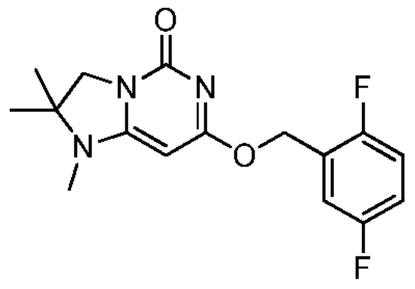


The title compound was prepared by a procedure similar to that described for **E9** starting from (3,5-difluoro-4-((5-(trifluoromethyl)pyridin-3-yl)oxy)phenyl)methanol and tert-butyl-7-chloro-2,2-dimethyl-5-oxo-2,3-dihydroimidazo[1,2-c]pyramidine-1(5H)-carboxylate.

LC-MS (ESI): m/z 469 $[M + H]^+$; 1.01 min (ret time).

E92

7-((2,5-difluorobenzyl)oxy)-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

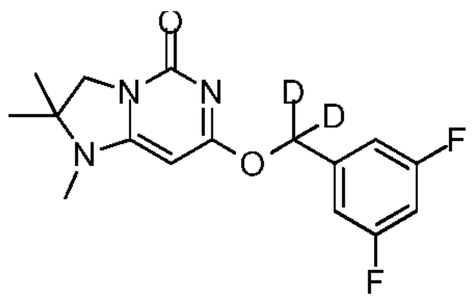


The title compound was prepared by a procedure similar to that described for **E9** starting from (2,5-difluorophenyl)methanol and 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 322 $[M + H]^+$; 2.31 min (ret time).

E93

7-(dideutero(3,5-difluorobenzyl)oxy)-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

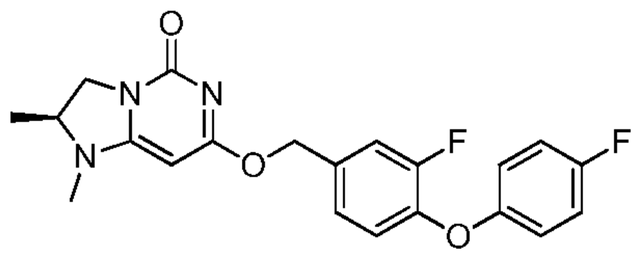


The title compound was prepared by a procedure similar to that described for **E9** starting from of 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and (3,5-difluorophenyl) dideuteromethanol.

LCMS(ESI): m/z 324 $[M + H]^+$; 2.22 min (ret time).

E94

(S)-7-((3-fluoro-4-(4-fluorophenoxy)benzyl)oxy)-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

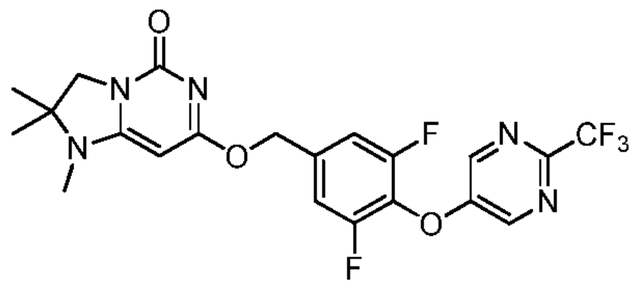


The title compound was prepared by a procedure similar to that described for **E9** starting from (3-fluoro-4-(4-fluorophenoxy)phenyl)methanol and (S)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c] pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 400 $[M + H]^+$; 1.98 min (ret time).

E95

7-((3,5-difluoro-4-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)benzyl)oxy)-1,2,2-trimet-hyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

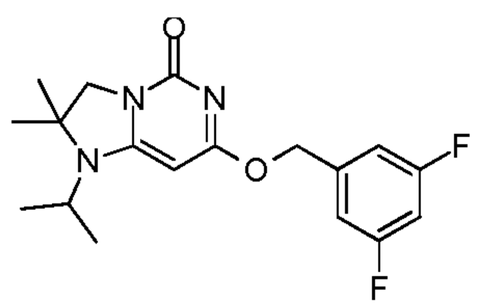


The title compound was prepared by a procedure similar to that described for **E9** starting from (3,5-difluoro-4-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)phenyl)methanol and 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one at -78 °C then rt.

LC-MS (ESI): m/z 484 $[M + H]^+$; 1.05 min (ret time).

E96

7-((3,5-difluorobenzyl)oxy)-1-isopropyl-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

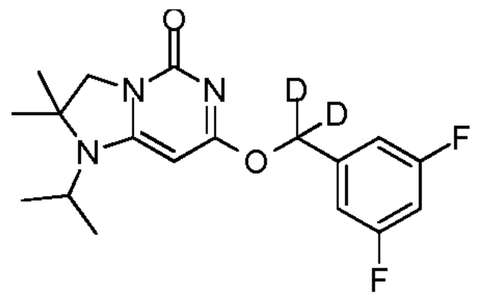


The title compound was prepared by a procedure similar to that described for **E9** starting from 7-chloro-1-isopropyl-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and (3,5-difluorophenyl)methanol.

LCMS (ESI): m/z 350 $[M + H]^+$; 2.53 min (ret time).

E97

7-(dideutero(3,5-difluorobenzyl)oxy)-1-isopropyl-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

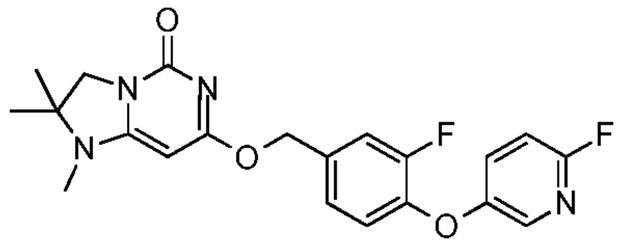


The title compound was prepared by a procedure similar to that described for **E9** starting from 7-chloro-1-isopropyl-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and (3,5-difluorophenyl)dideuteromethanol.

LCMS (ESI): m/z 352 $[M + H]^+$; 2.53 min (ret time)

E98

7-((3-fluoro-4-((6-fluoropyridin-3-yl)oxy)benzyl)oxy)-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

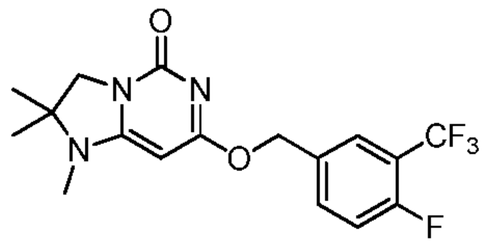


The title compound was prepared by a procedure similar to that described for **E9** starting from (3-fluoro-4-((6-fluoropyridin-3-yl)oxy)phenyl) and 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LCMS (ESI): m/z 415 $[M + H]^+$; 0.97 min (ret time)

E99

7-((4-fluoro-3-(trifluoromethyl)benzyl)oxy)-1,2,2-trimethyl-2,3-dihydroimidazo-[1,2c]pyrimidin-5(1H)-one

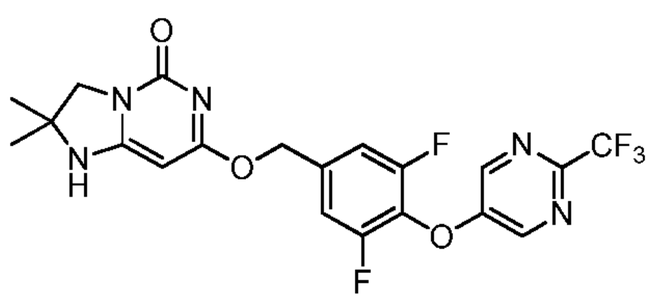


The title compound was prepared by a procedure similar to that described for **E9** starting from (4-fluoro-3-(trifluoromethyl)phenyl)methanol, NaH and 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one from -78 °C to rt.

LC-MS (ESI): m/z 372 $[M + H]^+$; 0.97 min (ret time).

E100

7-((3,5-difluoro-4-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)benzyl)oxy)-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

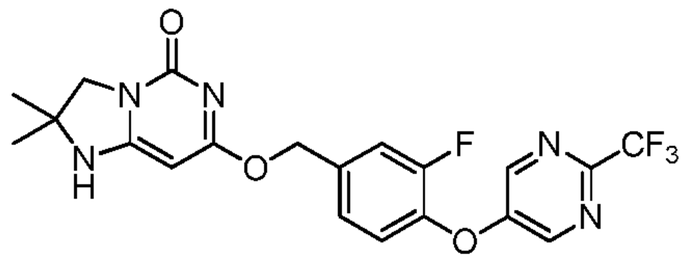


The title compound was prepared by a procedure similar to that described for **E9** starting from (3,5-difluoro-4-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)phenyl)methanol and tert-butyl-7-chloro-2,2-dimethyl-5-oxo-2,3-dihydroimidazo[1,2-c]pyrimidine-1(5H)-carboxylate.

LC-MS (ESI): m/z 470 $[M + H]^+$; 1.02 min (ret time).

E101

7-((3-fluoro-4-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)benzyl)oxy)-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

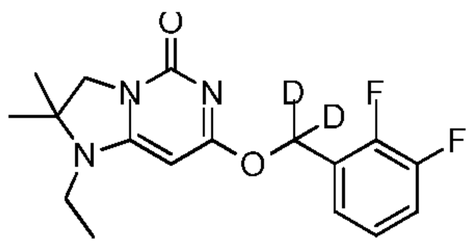


The title compound was prepared by a procedure similar to that described for **E9** starting from (3-fluoro-4-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)phenyl)methanol and tert-buty-7-chloro-2,2-dimethyl-5-oxo-2,3-dihydroimidazo[1,2-c]pyrimidine-1(5H)-carboxylate.

LC-MS (ESI): m/z 452 $[M + H]^+$; 0.99 min (ret time).

E102

7-(dideutero(2,3-difluorobenzyl)oxy)-1-ethyl-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

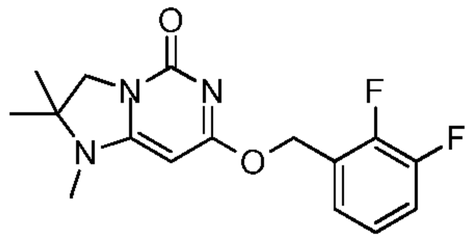


The title compound was prepared by a procedure similar to that described for **E1** starting from 7-chloro-1-ethyl-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and (2,3-difluorophenyl)dideuteromethanol.

LCMS (ESI): m/z 338 $[M + H]^+$; 2.33 min (ret time).

E103

7-((2,3-difluorobenzyl)oxy)-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

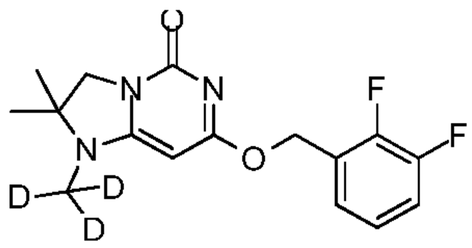


The title compound was prepared by a procedure similar to that described for **E1** starting from 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and (2,3-difluorophenyl)methanol.

LCMS (ESI): m/z 322 $[M + H]^+$; 2.19 min (ret time).

E104

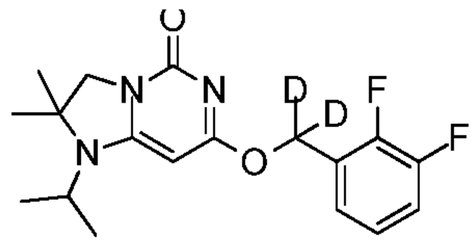
7-((2,3-difluorobenzyl)oxy)-1-trideuteromethyl-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one



The title compound was prepared by a procedure similar to that described for **E1** starting from 7-chloro-2,2-dimethyl-1-(trideuteromethyl)-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and (2,3-difluorophenyl)methanol.
LCMS (ESI): m/z 325 $[M + H]^+$; 2.18 min (ret time).

E105

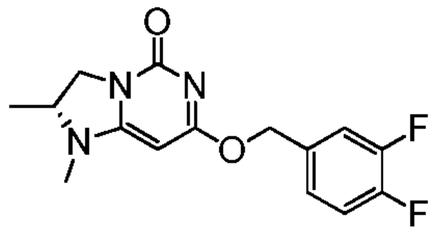
7-(dideutero(2,3-difluorobenzyl)oxy)-1-isopropyl-2,2-dimethyl-2,3-dihydroimidazo-[1,2-c]pyrimidin-5(1H)-one



The title compound was prepared by a procedure similar to that described for **E1** starting from 7-chloro-1-isopropyl-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and (2,3-difluorophenyl)dideuteromethanol.
LCMS (ESI): m/z 352 $[M + H]^+$; 2.50 min (ret time).

E106

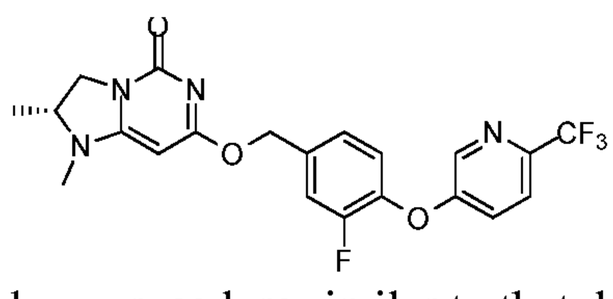
(R)-7-((3,4-difluorobenzyl)oxy)-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one



The title compound was prepared by a procedure similar to that described for **E9** starting from (3,4-difluorophenyl)methanol and (R)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo-[1,2-c]pyrimidin-5(1H)-one.
LC-MS (ESI): m/z 308 $[M + H]^+$; 0.97 min (ret time).

E107

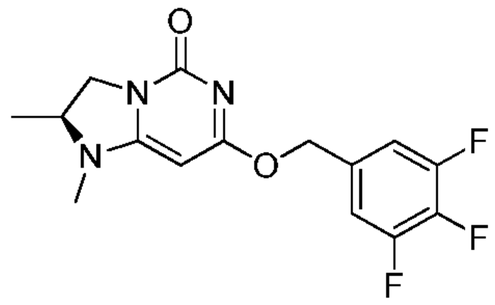
(R)-7-((3-fluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)benzyl)oxy)-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one



The title compound was prepared by a procedure similar to that described for **E1**starting from (R)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and (3-fluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)phenyl)methanol.
LCMS (ESI): m/z 451 $[M + H]^+$; 2.70 min (ret time)

E108

(S)-1,2-dimethyl-7-((3,4,5-trifluorobenzyl)oxy)-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

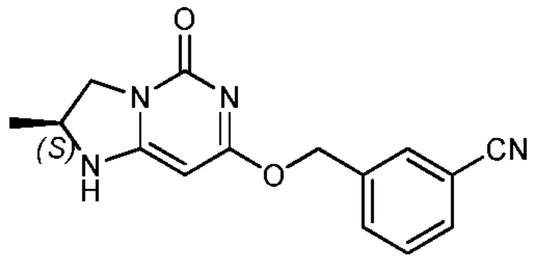


The title compound was prepared by a procedure similar to that described for **E9** starting from (3,4,5-trifluorophenyl)methanol and (S)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo-[1,2-c]pyrimidin-5(1H)-one.

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

E109

(S)-3-(((2-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-c]pyrimidin-7-yl)oxy)methyl)benzonitrile

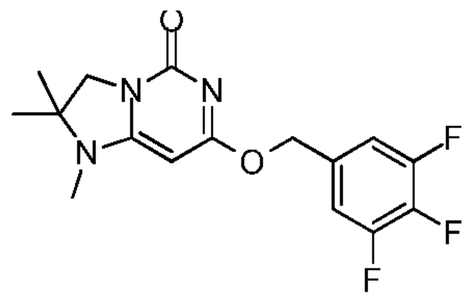


The title compound was prepared by a procedure similar to that described for **E9** starting from 3-(hydroxymethyl)benzonitrile and (S)-tert-butyl-7-chloro-2-methyl-5-oxo-2,3-dihydroimidazo[1,2-c]pyrimidine-1(5H)-carboxylate.

LC-MS (ESI): m/z 283 $[M + H]^+$; 0.92 min (ret time).

E110

1,2,2-trimethyl-7-((3,4,5-trifluorobenzyl)oxy)-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

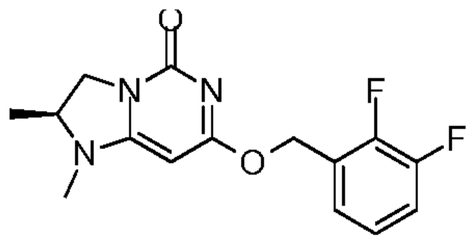


The title compound was prepared by a procedure similar to that described for **E1**starting from 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and (3,4,5-trifluorophenyl)methanol.

LCMS (ESI): m/z 340 $[M + H]^+$; 2.64 min (ret time).

E111

(S)-7-((2,3-difluorobenzyl)oxy)-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

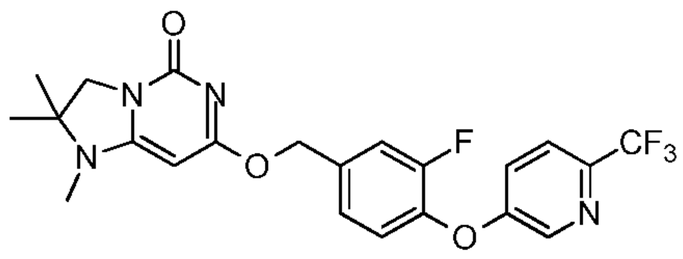


The title compound was prepared by a procedure similar to that described for **E1** starting from (S)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and (2,3-difluorophenyl)methanol.

LCMS (ESI): m/z 308 $[M + H]^+$; 2.44 min (ret time).

E112

7-((3-fluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)benzyl)oxy)-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

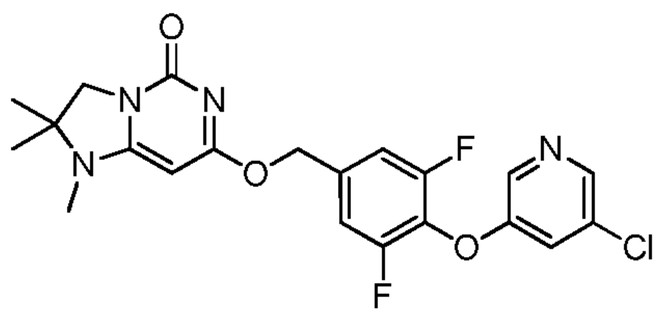


The title compound was prepared by a procedure similar to that described for **E1** starting from (3-fluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)phenyl)methanol and 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LCMS (ESI): m/z 465 $[M + H]^+$; 1.06 min (ret time)

E113

7-((4-((5-chloropyridin-3-yl)oxy)-3,5-difluorobenzyl)oxy)-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

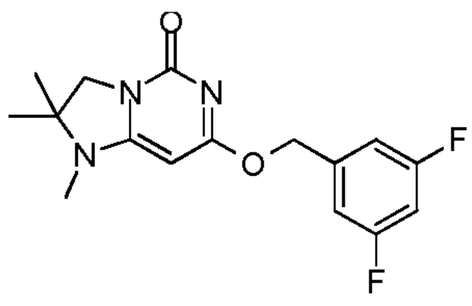


The title compound was prepared by a procedure similar to that described for **E9** starting from (4-((5-chloropyridin-3-yl)oxy)-3,5-difluorophenyl)methanol and 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LCMS (ESI): m/z 449 $[M + H]^+$; 1.03 min (ret time)

E114

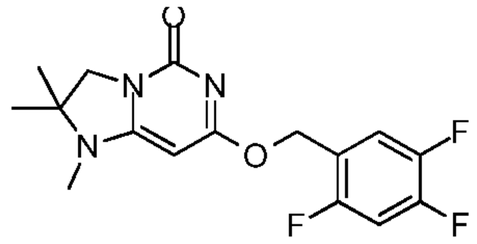
7-((3,5-difluorobenzyl)oxy)-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one



The title compound was prepared by a procedure similar to that described for **E1** starting from 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and (3,5-difluorophenyl)methanol.
LCMS (ESI): m/z 322 $[M + H]^+$; 2.87 min (ret time).

E115

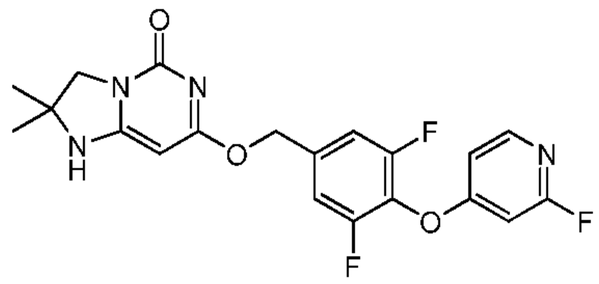
1,2,2-trimethyl-7-((2,4,5-trifluorobenzyl)oxy)-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one



The title compound was prepared by a procedure similar to that described for **E1** starting from 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and (2,4,5-trifluorophenyl)methanol.
LCMS (ESI): m/z 340 $[M + H]^+$; 3.04 min (ret time)

E116

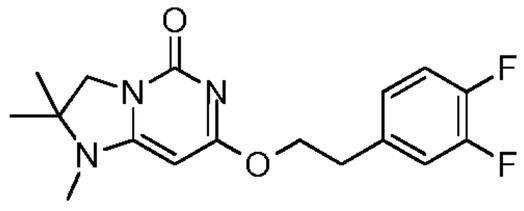
7-((3,5-difluoro-4-((2-fluoropyridin-4-yl)oxy)benzyl)oxy)-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one



The title compound was prepared by a procedure similar to that described for **E9** starting from (3,5-difluoro-4-((2-fluoropyridin-4-yl)oxy)phenyl)methanol and tert-butyl-7-chloro-2,2-dimethyl-5- oxo-2,3-dihydroimidazo[1,2-c]pyrimidine-1(5H)-carboxylate.
LC-MS (ESI): m/z 419 $[M + H]^+$; 1.76 min (ret time).

E117

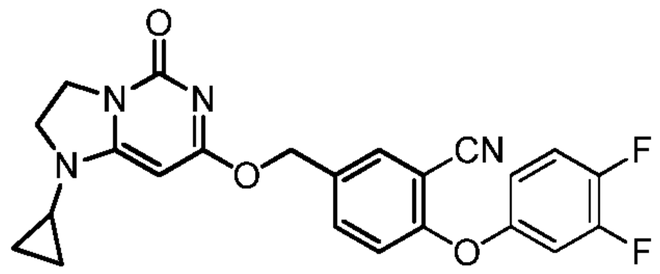
7-(3,4-difluorophenethoxy)-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one



The title compound was prepared by a procedure similar to that described for **E9** starting from 2-(3,4-difluorophenyl)ethanol and 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.
LC-MS (ESI): m/z 336 $[M + H]^+$; 1.11 min (ret time).

E118

5-(((1-cyclopropyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-c]pyrimidin-7-yl)oxy)methyl)-2-(3,4-difluorophenoxy)benzonitrile

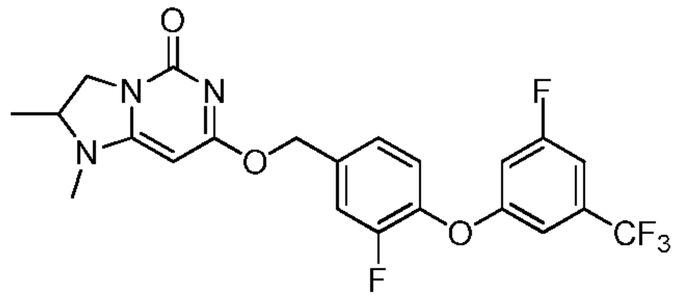


The title compound was prepared by a procedure similar to that described for **E9** starting from 2-(3,4-difluorophenoxy)-5-(hydroxymethyl)benzonitrile and 7-chloro-1-cyclopropyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 437 $[M + H]^+$; 1.65 min (ret time)

E119

7-((3-fluoro-4-(3-fluoro-5-(trifluoromethyl)phenoxy)benzyl)oxy)-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

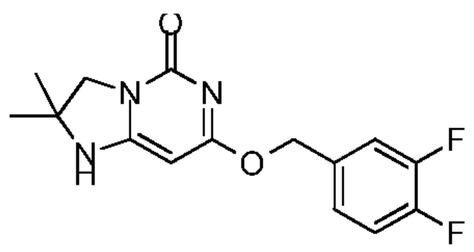


The title compound was prepared by a procedure similar to that described for **E9** starting from 7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and (3-fluoro-4-(3-fluoro-5-(trifluoromethyl)phenoxy)phenyl)methanol.

LCMS (ESI): m/z 468 $[M + H]^+$; 3.02 min (ret time).

E120

7-((3,4-difluorobenzyl)oxy)-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

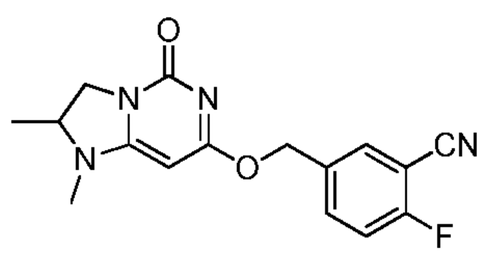


To a solution of 7-chloro-2,2-dimethyl-1-(methylsulfonyl)-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one (200 mg, 0.720 mmol) and (3,4-difluorophenyl)methanol (311 mg, 2.160 mmol) in N,N-dimethylformamide (DMF) (3.5ml) was added K_2CO_3 (299 mg, 2.160 mmol). The reaction mixture was sealed in a microwave vial and irradiated with a microwave using initial normal to 100 °C for 1 h. Purification via MDAP afforded the title product with trifluoroacetic acid salt (16 mg) as a white solid.

LCMS (ESI): m/z 308 $[M + H]^+$; 2.71 min (ret time).

E121

5-(((1,2-dimethyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-c]pyrimidin-7-yl)oxy)methyl)-2-fluorobenzonitrile

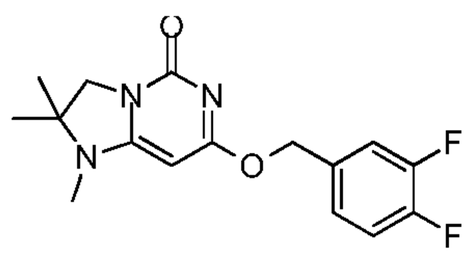


The title compound was prepared by a procedure similar to that described for **E9** starting from 2-fluoro-5-(hydroxymethyl)benzonitrile and 7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 315 $[M + H]^+$; 2.20 min (ret time).

E122

7-((3,4-difluorobenzyl)oxy)-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

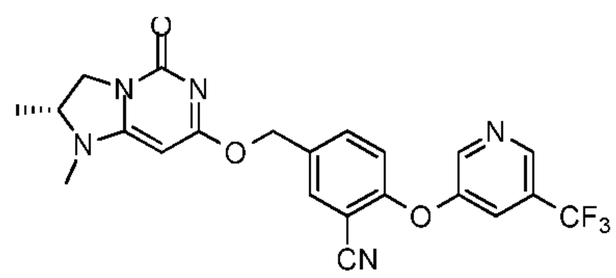


The title compound was prepared by a procedure similar to that described for **E9** starting from 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and (3,4-difluorophenyl)methanol.

LCMS (ESI): m/z 322 $[M + H]^+$; 2.26 min (ret time).

E123

(R)-5-(((1,2-dimethyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-c]pyrimidin-7-yl)oxy)methyl)-2-((5-(trifluoromethyl)pyridin-3-yl)oxy)benzonitrile

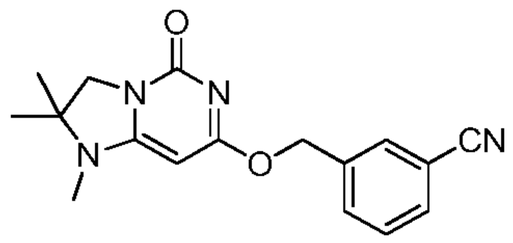


The title compound was prepared by a procedure similar to that described for **E1** starting from (R)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and 5-(hydroxymethyl)-2-((5-(trifluoromethyl)pyridin-3-yl)oxy)benzonitrile.

LCMS (ESI): m/z 458 $[M + H]^+$; 2.42 min (ret time).

E124

3-(((1,2,2-trimethyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-c]pyrimidin-7-yl)oxy)methyl)benzonitrile

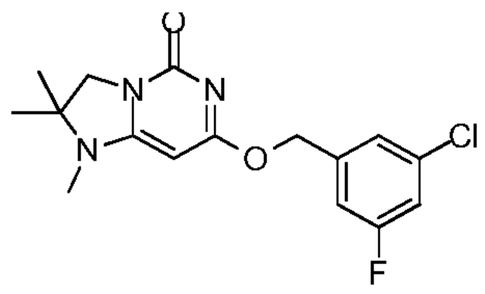


The title compound was prepared by a procedure similar to that described for **E9** starting from 3-(hydroxymethyl)benzonitrile and 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo-[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 311 $[M + H]^+$; 1.92 min (ret time).

E125

7-((3-chloro-5-fluorobenzyl)oxy)-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

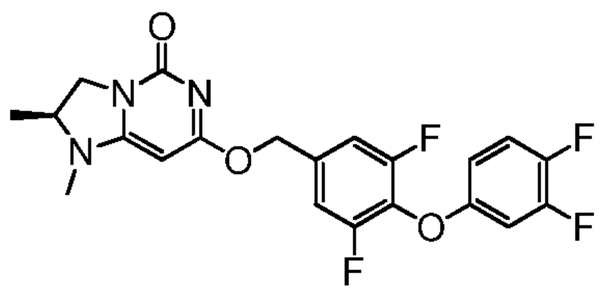


The title compound was prepared by a procedure similar to that described for **E9** starting from 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and (3-chloro-5-fluorophenyl)methanol.

LCMS (ESI): m/z 338 $[M + H]^+$; 2.39 min (ret time).

E126

(S)-7-((4-(3,4-difluorophenoxy)-3,5-difluorobenzyl)oxy)-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

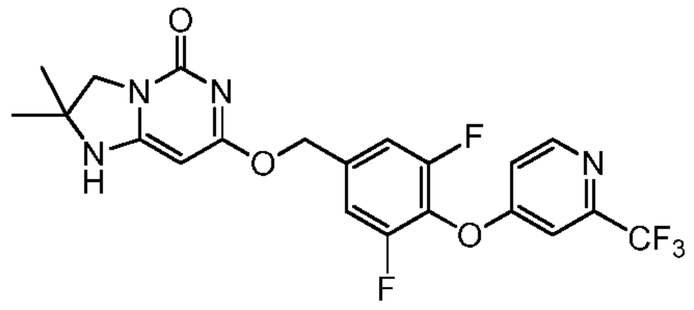


The title compound was prepared by a procedure similar to that described for **E9** starting from (4-(3,4-difluorophenoxy)-3,5-difluorophenyl)methanol and (S)-7-chloro-1,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 437 $[M + H]^+$; 1.06 min (ret time).

E127

7-((3,5-difluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)benzyl)oxy)-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

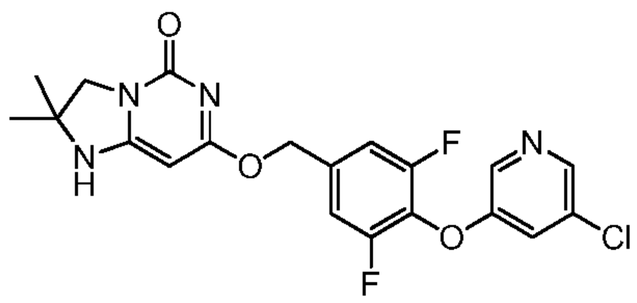


The title compound was prepared by a procedure similar to that described for **E9** starting from (3,5-difluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)phenyl)methanol and tert-butyl-7-chloro-2,2-dimethyl-5-oxo-2,3-dihydroimidazo[1,2-c]pyrimidine-1(5H)-carboxylate.

LC-MS (ESI): m/z 469 $[M + H]^+$; 1.01 min (ret time).

E128

7-((4-((5-chloropyridin-3-yl)oxy)-3,5-difluorobenzyl)oxy)-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

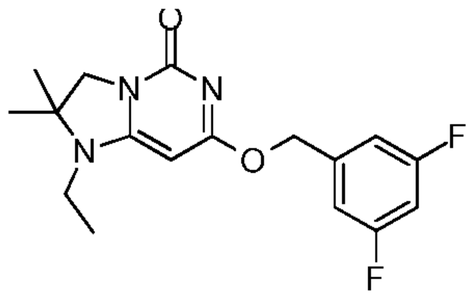


The title compound was prepared by a procedure similar to that described for **E39** starting from tert-butyl-7-((4-((5-chloropyridin-3-yl)oxy)-3,5-difluorobenzyl)oxy)-2,2-dimethyl-5-oxo-2,3-dihydroimidazo[1,2-c]pyrimidine-1(5H)-carboxylate.

LC-MS (ESI): m/z 435 $[M + H]^+$; 0.97 min (ret time).

E129

7-((3,5-difluorobenzyl)oxy)-1-ethyl-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

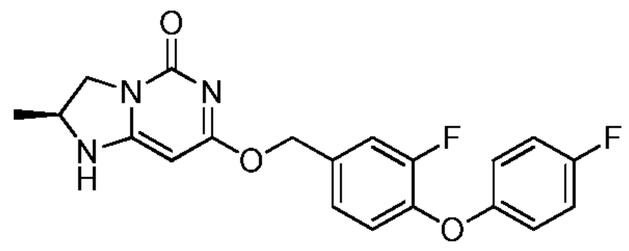


The title compound was prepared by a procedure similar to that described for **E1** starting from 7-chloro-1-ethyl-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and (3,5-difluorophenyl)methanol.

LCMS (ESI): m/z 336 $[M + H]^+$; 3.65 min (ret time).

E130

(S)-7-((3-fluoro-4-(4-fluorophenoxy)benzyl)oxy)-2-methyl-2,3-dihydroimidazo[1,2 c]pyrimidin-5(1H)-one

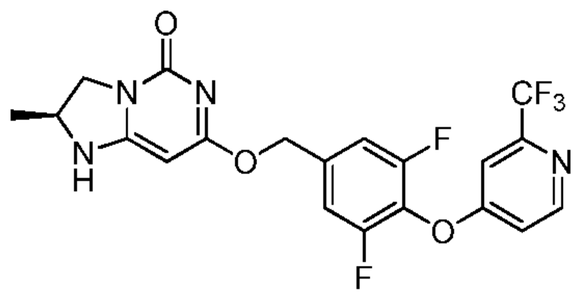


The title compound was prepared by a procedure similar to that described for **E9** starting from (3-fluoro-4-(4-fluorophenoxy)phenyl)methanol and (S)-tert-butyl-7-chloro-2-methyl-5-oxo-2,3-dihydroimidazo[1,2-c]pyrimidine-1(5H)-carboxylate.

LC-MS (ESI): m/z 386 $[M + H]^+$; 1.90 min (ret time).

E131

(S)-7-((3,5-difluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)benzyl)oxy)-2-methyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one



The title compound was prepared by a procedure similar to that described for **E9** starting from (3,5-difluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)phenyl)methanol and (S)-tert-butyl-7-chloro-2-methyl-5-oxo-2,3-dihydroimidazo[1,2-c]pyrimidine-1(5H)-carboxylate.

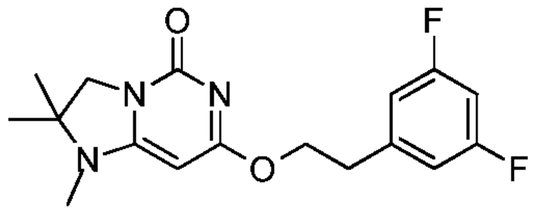
LC-MS (ESI): m/z 455 $[M + H]^+$; 1.85 min (ret time).

An alternative synthetic process is provided: To a solution of (3,5-difluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)phenyl)methanol (660 mg, 2.163 mmol) in THF (80 mL) was added NaH (259 mg, 6.49 mmol) at 0 ^{0}C under N_2. The reaction mixture was stirred at 0 ^{0}C for 30 mins, and then (S)-tert-butyl-7-chloro-2-methyl-5-oxo-2, 3-dihydroimidazo[1,2-c]pyrimidine-1(5H)-carboxylate (400 mg, 1.4 mmol) was added in one portion. The reaction was stirred at 0 ^{0}C for 1 h, quenched by addition of water (2 mL), and concentrated. The residue was diluted with DCM (50 mL), washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated to afford (S)-tert-butyl-7-((3,5-difluoro-4-((2- (trifluoromethyl)pyridin-4-yl)oxy)benzyl)oxy)2-methyl-5-oxo-2,3-dihydroimidazo[1,2-c]pyrimidine-1(5H)-carboxylate (1.4g, 70.1% yield) as a yellow solid. Then, 600 mg (1.082 mmol) of the yellow solid was dissolved in DCM (50 mL), TFA (0.541 mL, 7.02 mmol) was added. The reaction mixture was stirred at rt for 1h. FC (DCM/MeOH 50:1) purification afforded the crude product as a light yellow solid, which was further purified by prep-HPLC to obtain the title compound (200 mg, 40.6% yield) as a white solid.

LC-MS (ESI): m/z 455 $[M + H]^+$; 1.55 min (ret time).

E132

7-(3,5-difluorophenethoxy)-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

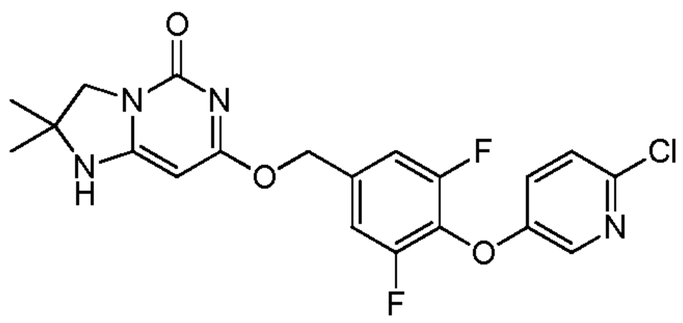


The title compound was prepared by a procedure similar to that described for **E9** starting from 2-(3,5-difluorophenyl)ethanol and 7-chloro-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one.

LC-MS (ESI): m/z 336 $[M + H]^+$; 0.67 min (ret time).

E133

7-((4-((6-chloropyridin-3-yl)oxy)-3,5-difluorobenzyl)oxy)-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

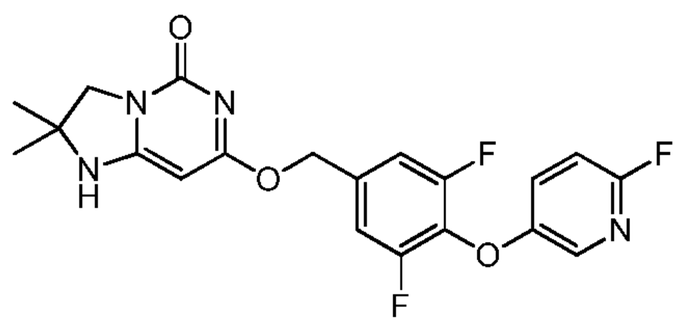


The title compound was prepared by a procedure similar to that described for **E69** starting from tert-butyl-7-((4-((6-chloropyridin-3-yl)oxy)-3,5-difluorobenzyl)oxy)-2,2-dimethyl-5-oxo-2,3-dihydroimidazo[1,2-c]pyrimidine-1(5H)-carboxylate.

LC-MS (ESI): m/z 435 $[M + H]^+$; 1.86 min (ret time).

E134

7-((3,5-difluoro-4-((6-fluoropyridin-3-yl)oxy)benzyl)oxy)-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

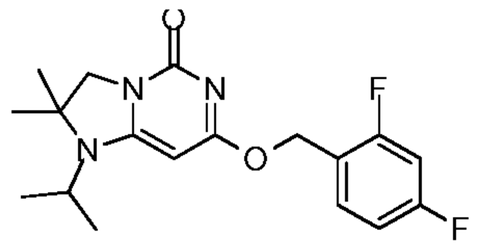


The title compound was prepared by a procedure similar to that described for **E69** starting from tert-butyl 7-((3,5-difluoro-4-((6-fluoropyridin-3-yl)oxy)benzyl)oxy)-2,2-dimethyl-5-oxo-2,3-dihydroimidazo[1,2-c]pyrimidine-1(5H)-carboxylate.

LC-MS (ESI): m/z 419 $[M + H]^+$; 1.78 min (ret time).

E135

7-((2,4-difluorobenzyl)oxy)-1-isopropyl-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin5(1H)-one

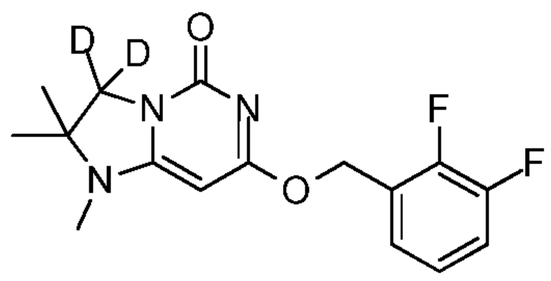


The title compound was prepared by a procedure similar to that described for **E1** starting from 7-chloro-1-isopropyl-2,2-dimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one and (2,4-difluorophenyl)methanol.

LCMS (ESI): m/z 350 $[M + H]^+$; 2.48 min (ret time).

E136

7-((2,3-difluorobenzyl)oxy)-1,2,2-trimethyl-3,3-dideutero-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

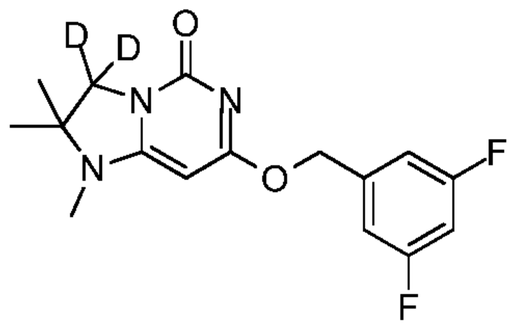


The title compound was prepared by a procedure similar to that described for **E1** starting from 7-chloro-3,3-dideutero-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one, (2,3-difluorophenyl)methanol and sodium hydride.

LCMS (ESI): m/z 324 $[M + H]^+$; 2.09 min (ret time)

E137

7-((3,5-difluorobenzyl)oxy)-1,2,2-trimethyl-3,3-dideutero-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one

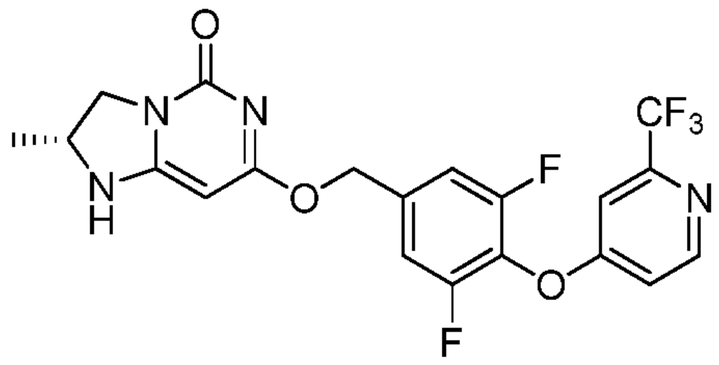


The title compound was prepared by a procedure similar to that described for **E1** starting from 7-chloro-3,3-dideutero-1,2,2-trimethyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one, (2,3-difluorophenyl)methanol and sodium hydride.

LCMS (ESI): m/z 324 $[M + H]^+$; 2.13 min (ret time)

E138

(R)-7-((3,5-difluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)benzyl)oxy)-2-methyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one



A solution of (3,5-difluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)phenyl)methanol (32.0 g, 105 mmol) in tetrahydrofuran (THF) (200 mL) was added to a suspension of NaH (7.64 g, 175 mmol) in tetrahydrofuran (THF) (500 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 mins, then a solution of *(R)*-tert-butyl-7-chloro-2-methyl-5-oxo-2,3-dihydroimidazo[1,2-c]pyrimidine-1(5H)-carboxylate (20 g, 70.0 mmol) in tetrahydrofuran (THF) (200 mL) was added and stirred at 0 °C for 3 h. The reaction was quenched with ice water (200 mL), extracted with ethyl acetate (250 mL), washed with brine (250 mL), dried over Na_2SO_4, and concentrated to afford the crude product (20 g), which was stirred with diethyl ether and the solid was filtered to afford 17 g of product. The product was washed with ethyl acetate, which was subsequently dissolved in methanol (25 V) at heated condition and cooled to rt for 2 h. Then crystalline solid was filtered to afford 8.5 g of raw product with 98.5% LCMS purity. Then, the compound was dissolved in 10% methanol in DCM and concentrated under reduced pressure to afford *(R)*-7-((3,5-difluoro-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)benzyl)oxy)-2-methyl-2,3-dihydroimidazo[1,2-c]pyrimidin-5(1H)-one (5.5 g) as a white solid.

^{1}H NMR (400MHz, DMSO-d_6) δ: 8.69-8.68 (1H, d, *J* = 5.6Hz), 8.21 (1H, s), 7.66-7.65 (1H, d, *J* = 2.4Hz), 7.41-7.43 (2H, m), 7.32-7.30 (1H, m), 5.32 (2H, s), 5.08 (1H, s), 4.16-4.03 (2H, m), 3.50-3.45 (1H, m), 1.24-1.22 (3H, d, *J* = 6.0Hz).

LC-MS (ESI): m/z 455 $[M + H]^+$; 3.75 min (ret time).

D. Biological assays and data

The compounds of present invention are Lp-PLA_2 inhibitors, and are useful in the treatment and prevention 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)

(1a) 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.

(1b) hrThioPAF assay

1-O-hexadecyl-2-deoxy-2-thio-S-acetyl-sn-glyceryl-3-phosphorylcholine (2-thio-PAF) is a substrate for PAF-hydrolases (PAF-AH) commercially available from Cayman Chemical. Upon cleavage with PAF-AH, the free thiol is released at the *sn*-2 position and can then react with 7-diethylamino-3-(4'-maleimidylphenyl)-4-methylcoumarin (CPM) a thiol-reactive coumarin. This reaction (Michael addition) results in an increase in fluorescence. Inhibitors of Lp-PLA_2 therefore prevent this cleavage and no fluorescent increase is observed.

The Thio-PAF assay was run as an unquenched 20 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, 5 μL of the compounds on compound source plate were transferred into 384 well Greiner 784076 (black) plates using STAR+ (Hamilton) liquid dispenser. 10μL of recombinant human Lp-PLA_2 enzyme (20 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. 5 μL of substrate comprising 40 μM 2-thio-PAF [from ethanol stock], 40 μM CPM [from a DMSO

stock] and 400 μM NEM (N-ethylmaleimide) [made fresh daily in DMSO] in assay buffer (50 mM HEPES, pH 7.4, 150 mM NaCl, 1 mM CHAPS) was added to 384 well Greiner 784076 black plates. Plates were vortexed for 10 sec. The plate was covered to protect it from light and incubated for 20 min at 25 °C. The plates were read for fluorescence intensity at ex: 380nm / em: 485nm using Envision plate reader (Perkin Elmer). Raw data are transferred to Excel software and pIC50 data, curve and QC analysis was conducted by using XL fit module in Excel.

The compounds of Examples 1-137 were tested in the PED6 assay and Example 138 was tested in hrThioPAF assay. All exemplified compounds were found to demonstrate inhibition activity to Lp-PLA_2. The pIC_{50} value for all exemplified compounds 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 all exemplified compounds were at least 6.0.

The pIC_{50} values in the recombinant human Lp-PLA_2 assay for examples 1-3, 6-13, 15-19, 21-31, 36-46, 48-51, 53-69, 71, 73-78, 82, 86, 88-98, 100-108, 110, 112-114, 116, 118, 119, 121-131, 133, 134 , 136, 137 and 138 were at least 8.0.

The pIC_{50} values in the recombinant human Lp-PLA_2 assay for examples 1, 3, 6, 10-13, 16, 18, 19, 23, 25, 26, 29-31, 37-39, 41-45, 50, 51, 54-65, 68, 69, 71, 73, 76, 78, 82, 88, 89-91, 95-98, 100, 101, 105, 107, 112-114, 116, 119, 122-124, 126-128, 131, 133, 134 and 138 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 (pIC50)
E12	10.5
E13	10.3
E23	9.8
E25	10.1
E26	10.8
E29	9.7
E42	9.5
E43	10.3
E46	8.4
E54	9.9
E56	10.0
E58	10.2
E59	10.4

E60	10.4
E61	9.9
E63	10.0
E64	10.1
E95	10.1
E96	9.5
E97	9.2
E105	9.2
E114	9.1
E131	9.6
E138	9.1

(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.

All exemplified compounds of the present invention were tested in PLA2 VIIB assay described above. All tested examples except examples 5, 35, 99, 111 and 120 had at least 100 fold selectivity between human recombinant Lp-PLA_2 and PLA2 VIIB.

(3) Lipoprotein-associated phospholipase A2 (Lp-PLA_2) Human Plasma assay

(3a) 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 were conducted by using XLFit module in Excel.

(3b) Alternative Thio-PAF assay

The human plasma assay utilizes the same thioester analog of PAF as described in (1b) "hr ThioPAF" assay. 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 20 µL assay. Compounds source plate was prepared by making 1:3 (by volume) serial dilution of the compounds into pure DMSO on 96-well microplate. 5 µL of compounds on compound source plate were transferred to 96-well Corning 3686 (black) low-volume plates by STAR+ (Hamilton) liquid dispenser. 10 µL pooled human plasma, which was previously aliquoted and frozen, was added. Plates were centrifuged for 30 sec at 1000 rpm. After 15 minutes preincubation at room temperature, 5 µL of substrate solution

comprising 2 mM 2-thio-PAF [from ethanol stock], 52 μM CPM [from a DMSO stock] and 2.5 mM NEM (N-ethylmaleimide) [made fresh daily in DMSO] in assay buffer (50mM HEPES, pH 7.4, 150 mM NaCl, 1 mM CHAPS) was added to 96-well Corning 3686 (black) low-volume plates. After 3 mins, reaction was quenched with 10 μL of 5% aqueous trifluoroacetic acid (TFA). Plates were centrifuged 30 sec at 1000 rpm, covered to protect from light and incubated for 10 min at room temperature. Plates were read at ex: 380nm / em: 485nm using Envision plate reader (Perkin Elmer). Raw data are transferred to Excel software and pIC50 data, curve and QC analysis was conducted by using XL fit module in Excel.

The compounds of Examples 1-137 were tested in the Thio-PAF assay described in (3a) and Example 138 was tested in the alternative Thio-PAF assay described in (3b). The pIC_{50} value for all exemplified compounds was either reported in at least one experiment or the average of multiple experiments.

The pIC_{50} values in the Lp-PLA_2 human plasma assay for all compounds except examples 111 and 120 were at least 5.0.

The pIC_{50} values in the Lp-PLA_2 human plasma assay for examples 1-3, 7, 8, 10-13, 15, 16, 18, 19, 23, 25, 26, 29-31, 33, 37-46, 48-56, 58-61, 63-69, 71-75, 77, 78, 82, 85, 88-91, 93, 95-98, 100-110, 112-117, 119, 121-124, 127-129, 131, 133, 134, 136, 137 and 138 were at least 7.0.

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, WO97/41098, 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 embodiments, 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 or 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 and/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 a pharmaceutical composition for the treatment of neurodegeneration disease comprising a compound described herein or a pharmaceutically acceptable salt thereof.

What is claimed is:

1. A compound of Formula (I) or a pharmaceutically acceptable salt thereof,

Formula (I)

wherein:

R^1 and R^2 are independently CH_3 or H;

R^3 is H, C_{1-3}alkyl, cyclopropyl, or CD_3,

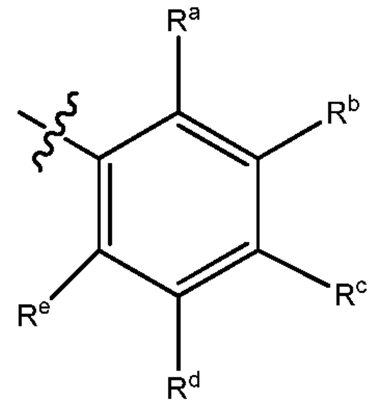
with the proviso that when R^3 is H, CD_3, or C_{1-3}alkyl, at least one of R^1 or R^2 is CH_3;

each R^5 is H or D;

A is $(CH_2)_n$ or $(CD_2)_n$, wherein each occurrence of n is 1 or 2; and

R^4 is cyclopentyl or thiophenyl optionally substituted with one or more Cl,

or R^4 is



wherein

R^a is H or F,

R^b is H, CN, or halo,

R^c is H, halo, or -O-Y wherein Y is phenyl, pyridinyl, or pyrimidinyl, wherein phenyl, pyridinyl, or pyrimidinyl is optionally substituted with one or two substituents independently selected from the group consisting of CN, CF_3 and halo;

R^d is selected from the group consisting of F, H, CN and CF_3, and

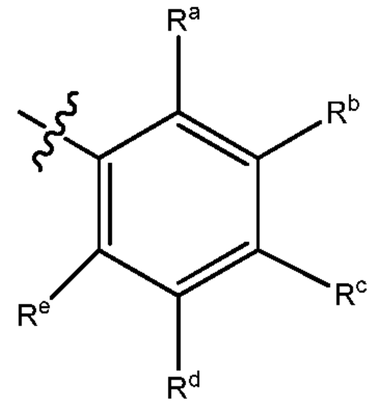
R^e is H or F.

2. The compound of Formula (I) or a pharmaceutically acceptable salt thereof according to claim 1, wherein R^1 or R^2 is CH_3.

3. The compound of Formula (I) or a pharmaceutically acceptable salt thereof according to claim 1, wherein R^1 and R^2 are CH_3.

4. The compound of Formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 3, wherein R^3 is CH_3 or isopropyl.

5. The compound of Formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 4, wherein R^4 is



wherein

R^a is H or F,

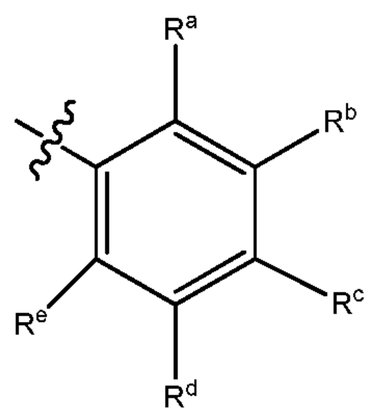
R^b is H, CN, or halo,

R^c is H, halo, or -O-Y wherein Y is phenyl, pyridinyl, or pyrimidinyl, wherein phenyl, pyridinyl, or pyrimidinyl is optionally substituted with one or two substituents independently selected from the group consisting of CN, CF_3 and halo;

R^d is selected from the group consisting of F, H, CN and CF_3, and

R^e is H or F.

6. The compound of Formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 5, wherein R^1 or R^2 is CH_3, R^3 is CH_3, and R^4 is



wherein

R^a is H or F,

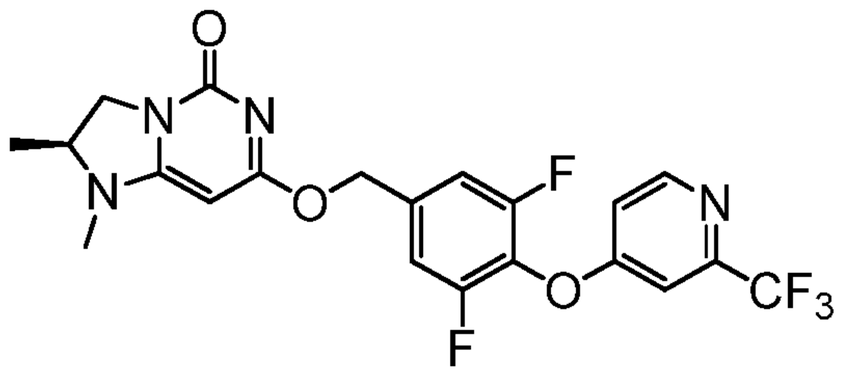
R^b is H, CN, or halo,

R^c is -O-Y wherein Y is pyridinyl substituted with one substituent selected from the group consisting of F, Cl and CF_3,

R^d is H, CN or F, and

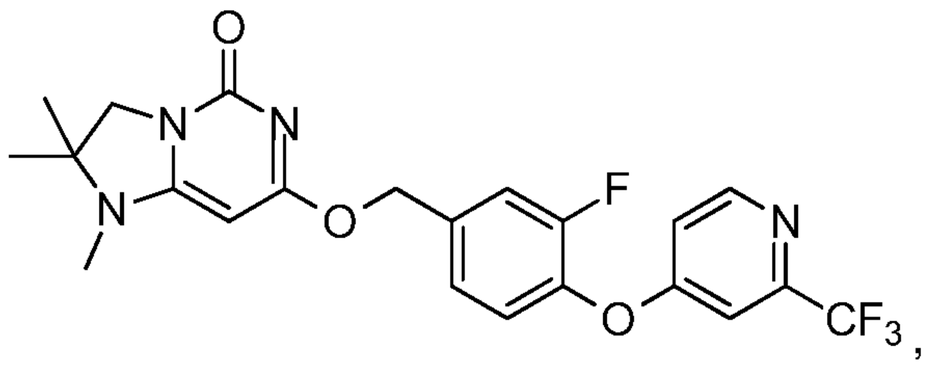
R^e is H or F.

7. The compound of Formula (I) according to claim 1, wherein the compound is



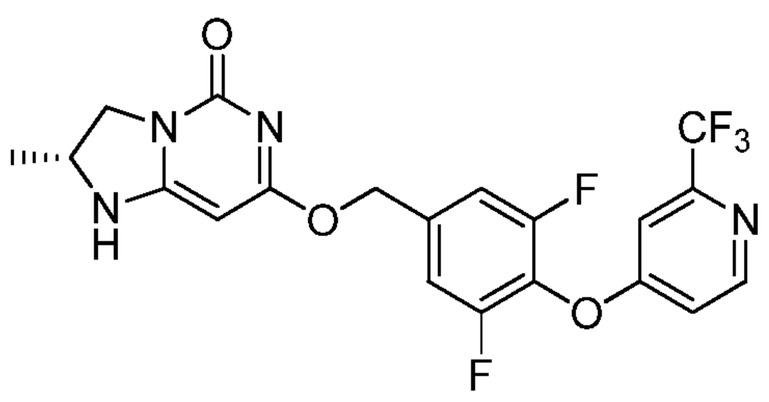
or a pharmaceutically acceptable salt thereof.

8. The compound of Formula (I) according to claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

9. The compound of Formula (I) according to claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

10. The compound of Formula (I) according claim 1, wherein the compound is a compound of any one of Example 1 to 138, 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) 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 of Formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 10 for use in therapy.