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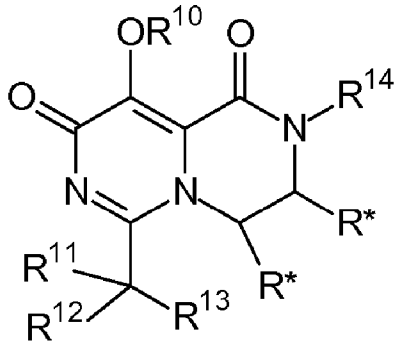
(54) Title: PYRIMIDONE DERIVATIVES AND THEIR USE IN THE TREATMENT, AMELIORATION OR PREVENTION OF A VIRAL DISEASE



(I)

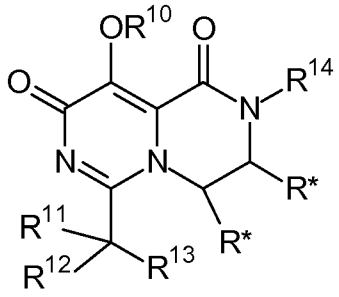
(57) Abstract: The present invention relates to a compound having the general formula (I), optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph,codrug, cocrystal,prodrug, tautomer, racemate, enantiomer, or diastereomer or mixture thereof, which are useful in treating, ameloriating or preventing a viral disease. Furthermore, specific combination therapies are disclosed.

WO 2014/108406 A1

Pyrimidone derivatives
and their use in the treatment, amelioration or prevention of a viral disease

Field of the invention

The present invention relates to a compound having the general formula (I), optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, codrug, cocrystal, prodrug, tautomer, racemate, enantiomer, or diastereomer or mixture thereof,



(I)

which is useful in treating, ameloriating or preventing a viral disease. Furthermore, specific combination therapies are disclosed.

Background of the invention

In recent years the serious threat posed by influenza virus infection to worldwide public health has been highlighted by, firstly, the ongoing level transmission to humans of the highly pathogenic avian influenza A virus H5N1 strain (63% mortality in infected humans, http://www.who.int/csr/disease/avian_influenza/en/) and secondly, the unexpected emergence in 2009 of a novel pandemic influenza virus strain A/H1N1 that has rapidly spread around the entire world (http://www.who.int/csr/disease/swineflu/en/). Whilst the new virus strain is highly

contagious but currently generally results in relatively mild illness, the future evolution of this virus is unpredictable. In a much more serious, but highly plausible scenario, H5N1 and related highly pathogenic avian influenza viruses could acquire mutations rendering them more easily transmissible between humans or the new A/H1N1 could become more virulent and only a single point mutation would be enough to confer resistance to oseltamivir (Neumann et al., Nature, 2009 (18; 459(7249) 931-939)); as many seasonal H1N1 strains have recently done (Dharan et al., The Journal of the American Medical Association, 2009 Mar 11; 301 (10), 1034-1041; Moscona et al., The New England Journal of Medicine, 2009 (Mar 5;360(10) pp 953-956)). In this case, the delay in generating and deploying a vaccine (~6 months in the relatively favourable case of A/H1N1 and still not a solved problem for H5N1) could have been catastrophically costly in human lives and societal disruption.

It is widely accepted that to bridge the period before a new vaccine is available and to treat severe cases, as well as to counter the problem of viral resistance, a wider choice of anti-influenza drugs is required. Development of new anti-influenza drugs has therefore again become high priority, having been largely abandoned by the major pharmaceutical companies once the neuraminidase inhibitors became available.

An excellent starting point for the development of antiviral medication is structural data of essential viral proteins. Thus, the crystal structure determination of e.g. the influenza virus surface antigen neuraminidase (Von Itzstein, M. et al., (1993), Nature, 363, pp. 418-423) led directly to the development of neuraminidase inhibitors with antiviral activity preventing the release of virus from the cells, however, not the virus production itself. These and their derivatives have subsequently developed into the anti-influenza drugs, zanamivir (Glaxo) and oseltamivir (Roche), which are currently being stockpiled by many countries as a first line of defence against a possible pandemic. However, these medicaments only provide a reduction in the duration of the clinical disease. Alternatively, adamantanes, the other class of licenced anti-influenza drugs (e.g.amantadine and rimantadine) target the viral M2 ion channel protein, which is located in the viral membrane interfering with the uncoating of the virus particle inside the cell. However, they have not been extensively used due to their side effects and the rapid development of resistant virus mutants (Magden, J. et al., (2005), Appl. Microbiol. Biotechnol., 66, pp. 612-621). In addition, more unspecific viral drugs, such as ribavirin, have been shown to work for treatment of influenza and other virus infections (Eriksson, B. et al., (1977), Antimicrob. Agents Chemother., 11, pp. 946-951). However, ribavirin is only approved in a few countries, probably due to severe side effects (Furuta et al., ANTIMICROBIAL AGENTS AND

CHEMOTHERAPY, 2005, p. 981–986). Clearly, new antiviral compounds are needed, preferably directed against different targets.

Influenza virus as well as Thogotovirus and isavirus belong to the family of Orthomyxoviridae which, as well as the family of the Bunyaviridae, including the Hantavirus, Nairovirus, Orthobunyavirus, and Phlebovirus, are, amongst others, negative stranded RNA viruses. Their genome is segmented and comes in ribonucleoprotein particles that include the RNA dependent RNA polymerase which carries out (i) the initial copying of the single-stranded negative-sense viral RNA (vRNA) into viral mRNAs (i.e. transcription) and (ii) the vRNA replication. This enzyme, a trimeric complex composed of subunits PA, PB1 and PB2, is central to the life cycle of the virus since it is responsible for the replication and transcription of viral RNA. In previous work the atomic structure of two key domains of the polymerase, the mRNA cap-binding domain in the PB2 subunit (Guilligay et al., Nature Structural & Molecular Biology 2008; May;15(5): 500-506) and the endonuclease-active site residing within the PA subunit (Dias et al., Nature 2009, 458, 914-918) have been identified and and their molecular architecture has been characterized. These two sites are critical for the unique “cap-snatching” mode used to initiate mRNA transcription that is used by the influenza virus and certain other virus families of this genus to generate viral mRNAs. A 5' cap is a modified guanine nucleotide that has been added to the 5' end of a messenger RNA. The 5' cap (also termed an RNA cap or RNA m7G cap) consists of a terminal 7-methylguanosine residue which is linked through a 5'-5'-triphosphate bond to the first transcribed nucleotide. The viral polymerase binds to the 5’ RNA cap of cellular mRNA molecules and cleaves the RNA cap together with a stretch of 10 to 15 nucleotides. The capped RNA fragments then serve as primers for the synthesis of viral mRNA (Plotch, S. J. et al., (1981), Cell, 23, pp. 847-858; Kukkonen, S. K. et al (2005), Arch. Virol., 150, pp. 533-556; Leahy, M. B. et al., (2005), J. Virol., 71, pp. 8347-8351; Noah, D. L. et al., (2005), Adv. Virus Res., 65, pp. 121-145).

The polymerase complex seems to be an appropriate antiviral drug target since it is essential for synthesis of viral mRNA and viral replication and contains several functional active sites likely to be significantly different from those found in host cell proteins (Magden, J. et al., (2005), Appl. Microbiol. Biotechnol., 66, pp. 612-621). Thus, for example, there have been attempts to interfere with the assembly of polymerase subunits by a 25-amino-acid peptide resembling the PA-binding domain within PB1 (Ghanem, A. et al., (2007), J. Virol., 81, pp. 7801-7804). Furthermore, the endonuclease activity of the polymerase has been targeted and a series of 4-substituted 2,4-dioxobutanoic acid compounds has been identified as selective

inhibitors of this activity in influenza viruses (Tomassini, J. et al., (1994), Antimicrob. Agents Chemother., 38, pp. 2827-2837). In addition, flutimide, a substituted 2,6-diketopiperazine, identified in extracts of Delitschia confertaspora, a fungal species, has been shown to inhibit the endonuclease of influenza virus (Tomassini, J. et al., (1996), Antimicrob. Agents Chemother., 40, pp. 1189-1193). Moreover, there have been attempts to interfere with viral transcription by nucleoside analogs, such as 2'-deoxy-2'-fluoroguanosine (Tisdale, M. et al., (1995), Antimicrob. Agents Chemother., 39, pp. 2454-2458).

WO 2005/087766 discloses certain pyridopyrazine- and pyrimidopyrazine-dione compounds which are stated to be inhibitors of HIV integrase and inhibitors of HIV replication. The compounds are described as being useful in the prevention and treatment of infection by HIV and in the prevention, delay in the onset, and treatment of AIDS.

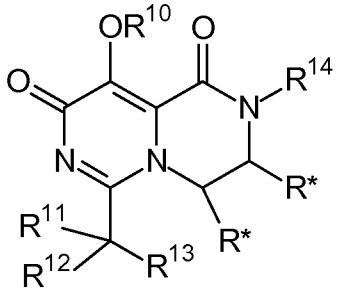
WO 2012/039414 describes compounds which are described as having antiviral effects, particularly having growth inhibitory activity on influenza viruses.

EP-A-2 444 400 also discloses compounds which allegedly have antiviral activities, especially inhibiting activity for influenza viruses.

It is an object of the present invention to identify further compounds which are effective against viral diseases and which have improved pharmacological properties.

Summary of the invention

Accordingly, in a first embodiment, the present invention provides a compound having the general formula (I).



It is understood that throughout the present specification the term "a compound having the general formula (I)" encompasses pharmaceutically acceptable salts, solvates, polymorphs, prodrugs, codrugs, cocrystals, tautomers, racemates, enantiomers, or diastereomers or mixtures thereof unless mentioned otherwise.

A further embodiment of the present invention relates to a pharmaceutical composition comprising a compound having the general formula (I) and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

The compounds having the general formula (I) are useful for treating, ameliorating or preventing viral diseases.

It has been surprisingly found that the compounds according to the present invention which have the bulky group on the left hand ring have improved properties compared to the compounds disclosed in EP-A-2 444 400. In particular, the interaction with protein could be optimized resulting in better binding properties. Furthermore, shifting of the bulky group should avoid problems due to a chiral center and due to the planarization through shift from sp3 to sp2. In addition, the crucial vector for additional hydrophobic interactions may be stabilized and improved.

Detailed description of the invention

Before the present invention is described in detail below, it is to be understood that this invention is not limited to the particular methodology, protocols and reagents described herein as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art.

Preferably, the terms used herein are defined as described in "A multilingual glossary of biotechnological terms: (IUPAC Recommendations)", Leuenberger, H.G.W, Nagel, B. and Kölbl, H. eds. (1995), Helvetica Chimica Acta, CH-4010 Basel, Switzerland.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps. In the following passages different aspects of the invention are defined in more detail. Each aspect so defined may be combined with any other aspect or aspects unless clearly indicated to the contrary. In particular, any feature indicated as being preferred or advantageous may be combined with any other feature or features indicated as being preferred or advantageous.

Several documents are cited throughout the text of this specification. Each of the documents cited herein (including all patents, patent applications, scientific publications, manufacturer's specifications, instructions, etc.), whether supra or infra, are hereby incorporated by reference in their entirety. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

Definitions

The term “alkyl” refers to a saturated straight or branched carbon chain.

The term "cycloalkyl" represents a cyclic version of "alkyl". The term "cycloalkyl" is also meant to include bicyclic, tricyclic and polycyclic versions thereof. Unless specified otherwise, the cycloalkyl group can have 3 to 12 carbon atoms.

"Hal" or "halogen" represents F, Cl, Br and I.

"3- to 7-membered carbo- or heterocyclic ring" refers to a three-, four-, five-, six- or seven-membered ring wherein none, one or more of the carbon atoms in the ring have been replaced by 1 or 2 (for the three-membered ring), 1, 2 or 3 (for the four-membered ring), 1, 2, 3, or 4 (for the five-membered ring) or 1, 2, 3, 4, or 5 (for the six-membered ring) and 1, 2, 3, 4, 5 or 6 (for the seven-membered ring) of the same or different heteroatoms, whereby the heteroatoms are selected from O, N and S.

The term “aryl” preferably refers to an aromatic monocyclic ring containing 6 carbon atoms, an aromatic bicyclic ring system containing 10 carbon atoms or an aromatic tricyclic ring system containing 14 carbon atoms. Examples are phenyl, naphthyl or anthracenyl, preferably phenyl.

The term “heteroaryl” preferably refers to a five-or six-membered aromatic ring wherein one or more of the carbon atoms in the ring have been replaced by 1, 2, 3, or 4 (for the five-membered ring) or 1, 2, 3, 4, or 5 (for the six-membered ring) of the same or different heteroatoms, whereby the heteroatoms are selected from O, N and S. Examples of the heteroaryl group include pyrrole, pyrrolidine, oxolane, furan, imidazolidine, imidazole, pyrazole, oxazolidine, oxazole, thiazole, piperidine, pyridine, morpholine, piperazine, and dioxolane.

The term "hydrocarbon group which contains from 5 to 20 carbon atoms and optionally 1 to 4 heteroatoms selected from O, N and S and which contains at least one ring" refers to any group having 5 to 20 carbon atoms and optionally 1 to 4 heteroatoms selected from O, N and 2 as long as the group contains at least one ring. The term is also meant to include bicyclic, tricyclic and polycyclic versions thereof. If more than one ring is present, they can be separate from each other or be annelated. The ring(s) can be either carbocyclic or heterocyclic and can be saturated, unsaturated or aromatic. The carbon atoms and heteroatoms can either all be present in the one or more rings or some of the carbon atoms and/or heteroatoms can be present outside of the ring, e.g., in a linker group (such as $–(CH_2)_p-$ with p = 1 to 6). Examples of these groups include –(optionally substituted $C_{3–7}$ cycloalkyl), –(optionally substituted aryl) wherein the aryl group can be, for example, phenyl, -(optionally substituted biphenyl), adamantyl, -(C_{3-7} cycloalkyl)-aryl as well as the corresponding compounds with a linker.

If a compound or moiety is referred to as being “optionally substituted”, it can in each instance include 1 or more of the indicated substituents, whereby the substituents can be the same or different.

The term "pharmaceutically acceptable salt" refers to a salt of a compound of the present invention. Suitable pharmaceutically acceptable salts include acid addition salts which may, for example, be formed by mixing a solution of compounds of the present invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compound carries an acidic moiety, suitable

pharmaceutically acceptable salts thereof may include alkali metal salts (e.g., sodium or potassium salts); alkaline earth metal salts (e.g., calcium or magnesium salts); and salts formed with suitable organic ligands (e.g., ammonium, quaternary ammonium and amine cations formed using counteranions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl sulfonate and aryl sulfonate). Illustrative examples of pharmaceutically acceptable salts include, but are not limited to, acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, calcium edetate, camphorate, camphorsulfonate, camsylate, carbonate, chloride, citrate, clavulanate, cyclopentanepropionate, digluconate, dihydrochloride, dodecylsulfate, edetate, edisylate, estolate, esylate, ethanesulfonate, formate, fumarate, gluceptate, glucoheptonate, gluconate, glutamate, glycerophosphate, glycolylarsanilate, hemisulfate, heptanoate, hexanoate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, lauryl sulfate, malate, maleate, malonate, mandelate, mesylate, methanesulfonate, methylsulfate, mucate, 2-naphthalenesulfonate, napsylate, nicotinate, nitrate, N-methylglucamine ammonium salt, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, pectinate, persulfate, 3-phenylpropionate, phosphate/diphosphate, picrate, pivalate, polygalacturonate, propionate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, undecanoate, valerate, and the like (see, for example, S. M. Berge et al., "Pharmaceutical Salts", J. Pharm. Sci., 66, pp. 1-19 (1977)).

When the compounds of the present invention are provided in crystalline form, the structure can contain solvent molecules. The solvents are typically pharmaceutically acceptable solvents and include, among others, water (hydrates) or organic solvents. Examples of possible solvates include ethanolates and iso-propanolates.

The term "codrug" refers to two or more therapeutic compounds bonded via a covalent chemical bond. A detailed definition can be found, e.g., in N. Das et al., European Journal of Pharmaceutical Sciences, 41, 2010, 571–588.

The term "cocrystal" refers to a multiple component crystal in which all components are solid under ambient conditions when in their pure form. These components co-exist as a stoichiometric or non-stoichometric ratio of a target molecule or ion (i.e., compound of the present invention) and one or more neutral molecular cocrystal formers. A detailed discussion

can be found, for example, in Ning Shan et al., Drug Discovery Today, 13(9/10), 2008, 440-446 and in D. J. Good et al., Cryst. Growth Des., 9(5), 2009, 2252–2264.

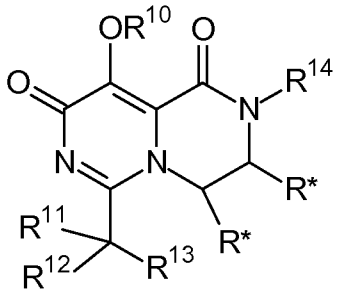
The compounds of the present invention can also be provided in the form of a prodrug, namely a compound which is metabolized *in vivo* to the active metabolite. Suitable prodrugs are, for instance, esters. Specific examples of suitable groups are given, among others, in US 2007/0072831 in paragraphs [0082] to [0118] under the headings prodrugs and protecting groups. Preferred examples of the prodrug include compounds in which R^{10} is replaced by $P(O)(O)OR^{19}$; $C(O)OR^{19}$; $C(O)R^{19}$; or $C–R^{19}$;

wherein R^{19} is selected from $C_{5–10}$aryl, C_{1-6}alkyl–$C_{5–10}$aryl, $C_{1–6}$alkyl, $C_{1–6}$alkyl$(–O–C_{1–6}alkyl)_n$ (with n = 1 to 30), $C_{1–6}$alkyl–C(O)OR, and $C_{5–10}$aryl–C(O)OR.

The group R is H or $C_{1–6}$ alkyl.

Compounds having the general formula (I)

The present invention provides a compound having the general formula (I).



(I)

In the appended claims certain provisos are recited. It is understood that any of the compounds which are included in any of the provisos can be excluded, either individually or in combination with other compounds, from one or more of the independent claims having a different category even if it is not currently disclaimed in the independent claim of this category. It is also understood that the disclaimer covers the compounds in the form of their pharmaceutically acceptable salts, solvates, polymorphs, tautomers, racemates, enantiomers, and diastereomers.

The present invention provides a compound having the general formula (I) in which the following definitions apply.

X^{10} is NR^{15}, $N(R^{15})C(O)$, $C(O)NR^{15}$, O, C(O), C(O)O, OC(O); $N(R^{15})SO_2$, $SO_2N(R^{15})$, S, SO, or SO_2; preferably X^{10} is $N(R^{15})$ or $N(R^{15})SO_2$; more preferably X^{10} is $N(R^{15})SO_2$.

R^{10} is –H, a $–C_{1–6}$ alkyl group or a $–C(O)–C_{1–6}$ alkyl group. In a preferred embodiment R^{10} is –H, or –(optionally substituted $C_{1–6}$ alkyl); more preferably –H.

R^{11} is –H, a $–C_{1–6}$ alkyl group, or a $–C_{1–6}$ alkyl group which is substituted by one or more halogen atoms; preferably R^{11} is –H.

R^{12} is –H, a $–C_{1–6}$ alkyl group, or a $–C_{1–6}$ alkyl group which is substituted by one or more halogen atoms; preferably R^{12} is –H.

In one embodiment R^{11} and R^{12} can be joined together to form a 3- to 7-membered carbo- or heterocyclic ring.

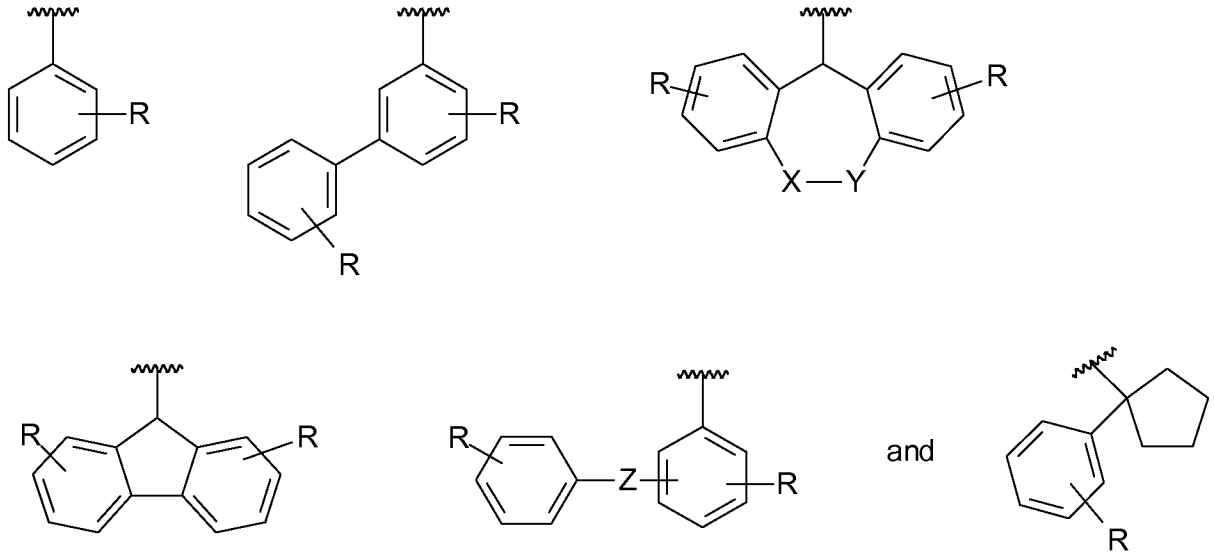
R^{13} is $–R^{16}$, or $–X^{10}–R^{16}$. In one embodiment R^{13} is $–R^{16}$. In an alternative embodiment, R^{13} is $–X^{10}–R^{16}$.

R^{14} is –H, –(optionally substituted $C_{1–6}$ alkyl), –(optionally substituted $C_{3–7}$ cycloalkyl), –(optionally substituted aryl), $–C_{1–4}$ alkyl–(optionally substituted $C_{3–7}$ cycloalkyl), or $–C_{1–4}$ alkyl–(optionally substituted aryl); preferably R^{14} is –H, –(optionally substituted $C_{1–6}$ alkyl), or –(optionally substituted aryl).

R^{15} is –H, –(optionally substituted $C_{1–6}$ alkyl), –(optionally substituted $C_{3–7}$ cycloalkyl), –(optionally substituted aryl), $–C_{1–4}$ alkyl–(optionally substituted $C_{3–7}$ cycloalkyl), or $–C_{1–4}$ alkyl–(optionally substituted aryl). In a preferred embodiment R^{15} is –H or –(optionally substituted $C_{1–6}$ alkyl).

R^{16} is –(optionally substituted hydrocarbon group which contains from 5 to 20 carbon atoms and optionally 1 to 4 heteroatoms selected from O, N and S and which contains at least one ring). Preferably, the at least one ring is aromatic such as an aryl or heteroaryl ring.

More preferably, R^{16} is a hydrocarbon group which contains from 5 to 20 carbon atoms and optionally 1 to 4 heteroatoms and which contains at least two rings, wherein the hydrocarbon group can be optionally substituted. Even more preferably, at least one of the at least two rings is aromatic such as an aryl or heteroaryl ring. Preferred examples of R^{16} can be selected from the group consisting of



X is absent, CH_2, NH, C(O)NH, S or O. Furthermore,

Y is CH_2.

In an alternative embodiment, X and Y can be joined together to form an annulated, carbo- or heterocylic 3- to 8-membered ring which can be saturated or unsaturated. Specific examples of X-Y include -CH_2-, -CH_2-CH_2-, -O-, and -NH-.

Z is O or S.

R is independently selected from –H, –C_{1-6} alkyl, –CF_3, –halogen, –CN, –OH, and –O–C_{1-6} alkyl.

R^{17} is –H, –C_{1-6} alkyl, or –$(CH_2CH_2O)_rH$; preferably R^{17} is –H, or –C_{1-6} alkyl.

R^{18} is –H, or –C_{1-6} alkyl.

R is independently selected from $-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkyl, –Hal, $-CF_3$, –CN, $-COOR^{17}$, $-OR^{17}$, $-(CH_2)_qNR^{17}R^{18}$, $-C(O)-NR^{17}R^{18}$, and $-NR^{17}-C(O)-C_{1-6}$ alkyl. Preferably R is –Hal, $-CF_3$, or –CN; more preferably –Hal, or $-CF_3$.

R* is independently selected from –H, $-C_{1-6}$ alkyl, and $-C_{3-7}$ cycloalkyl.

q is 0 to 4.

r is 1 to 3.

The optional substituent of the alkyl group, aryl group, hydrocarbon group and/or cycloalkyl group is selected from the group consisting of one or more substituents R, which includes $-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkyl, –Hal, $-CF_3$, –CN, $-COOR^{17}$, $-OR^{17}$, $-(CH_2)_qNR^{17}R^{18}$, $-C(O)-NR^{17}R^{18}$, and $-NR^{17}-C(O)-C_{1-6}$ alkyl. Preferably, the optional substituent of the aryl group, hydrocarbon group and/or cycloalkyl group is -halogen (preferably F), $-OCH_3$ or -CN. Preferably, the optional substituent of the alkyl group is selected from the group consisting of halogen, –CN, $-NR^{18}R^{18}$ (wherein each R^{18} is chosen independently of each other), –OH, and $-O-C_{1-6}$ alkyl. Preferably the substituent of the alkyl group is –halogen, more preferably F.

The present inventors have surprisingly found that the compounds of the present invention which have a bulky moiety R^{13} have improved pharmacological properties compared to corresponding compounds which have a smaller moiety R^{13}. Without wishing to be bound by theory it is assumed that the viral polymerase protein has a pocket for binding and that the bulky moiety R^{13} of the compounds of the present invention fills this pocket to a larger extent. It is further assumed that the larger moiety R^{13} is able to provide more hydrophobic interaction with the pocket than smaller moieties such as methyl.

The compounds of the present invention can be administered to a patient in the form of a pharmaceutical composition which can optionally comprise one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

The compounds of the present invention can be administered by various well known routes, including oral, rectal, intragastrical, intracranial and parenteral administration, e.g. intravenous, intramuscular, intranasal, intradermal, subcutaneous, and similar administration routes. Oral, intranasal and parenteral administration are particularly preferred. Depending on the route of

administration different pharmaceutical formulations are required and some of those may require that protective coatings are applied to the drug formulation to prevent degradation of a compound of the invention in, for example, the digestive tract.

Thus, preferably, a compound of the invention is formulated as a syrup, an infusion or injection solution, a spray, a tablet, a capsule, a capslet, lozenge, a liposome, a suppository, a plaster, a band-aid, a retard capsule, a powder, or a slow release formulation. Preferably, the diluent is water, a buffer, a buffered salt solution or a salt solution and the carrier preferably is selected from the group consisting of cocoa butter and vitebesole.

Particular preferred pharmaceutical forms for the administration of a compound of the invention are forms suitable for injectionable use and include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the final solution or dispersion form must be sterile and fluid. Typically, such a solution or dispersion will include a solvent or dispersion medium, containing, for example, water-buffered aqueous solutions, e.g. biocompatible buffers, ethanol, polyol, such as glycerol, propylene glycol, polyethylene glycol, suitable mixtures thereof, surfactants or vegetable oils. A compound of the invention can also be formulated into liposomes, in particular for parenteral administration. Liposomes provide the advantage of increased half life in the circulation, if compared to the free drug and a prolonged more even release of the enclosed drug.

Sterilization of infusion or injection solutions can be accomplished by any number of art recognized techniques including but not limited to addition of preservatives like anti-bacterial or anti-fungal agents, e.g. parabene, chlorobutanol, phenol, sorbic acid or thimersal. Further, isotonic agents, such as sugars or salts, in particular sodium chloride, may be incorporated in infusion or injection solutions.

Production of sterile injectable solutions containing one or several of the compounds of the invention is accomplished by incorporating the respective compound in the required amount in the appropriate solvent with various ingredients enumerated above as required followed by sterilization. To obtain a sterile powder the above solutions are vacuum-dried or freeze-dried as necessary. Preferred diluents of the present invention are water, physiological acceptable buffers, physiological acceptable buffer salt solutions or salt solutions. Preferred carriers are

cocoa butter and vitebesole. Excipients which can be used with the various pharmaceutical forms of a compound of the invention can be chosen from the following non-limiting list:

a) binders such as lactose, mannitol, crystalline sorbitol, dibasic phosphates, calcium phosphates, sugars, microcrystalline cellulose, carboxymethyl cellulose, hydroxyethyl cellulose, polyvinyl pyrrolidone and the like;
b) lubricants such as magnesium stearate, talc, calcium stearate, zinc stearate, stearic acid, hydrogenated vegetable oil, leucine, glycerids and sodium stearyl fumarates,
c) disintegrants such as starches, croscarmellose, sodium methyl cellulose, agar, bentonite, alginic acid, carboxymethyl cellulose, polyvinyl pyrrolidone and the like.

In one embodiment the formulation is for oral administration and the formulation comprises one or more or all of the following ingredients: pregelatinized starch, talc, povidone K 30, croscarmellose sodium, sodium stearyl fumarate, gelatin, titanium dioxide, sorbitol, monosodium citrate, xanthan gum, titanium dioxide, flavoring, sodium benzoate and saccharin sodium.

If a compound of the invention is administered intranasally in a preferred embodiment, it may be administered in the form of a dry powder inhaler or an aerosol spray from a pressurized container, pump, spray or nebulizer with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoro-alkane such as 1,1,1,2-tetrafluoroethane (HFA 134A^{TM}) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA^{TM}), carbon dioxide, or another suitable gas. The pressurized container, pump, spray or nebulizer may contain a solution or suspension of the compound of the invention, e.g., using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e.g., sorbitan trioleate.

Other suitable excipients can be found in the Handbook of Pharmaceutical Excipients, published by the American Pharmaceutical Association, which is herein incorporated by reference.

It is to be understood that depending on the severity of the disorder and the particular type which is treatable with one of the compounds of the invention, as well as on the respective patient to be treated, e.g. the general health status of the patient, etc., different doses of the respective compound are required to elicit a therapeutic or prophylactic effect. The

determination of the appropriate dose lies within the discretion of the attending physician. It is contemplated that the dosage of a compound of the invention in the therapeutic or prophylactic use of the invention should be in the range of about 0.1 mg to about 1 g of the active ingredient (i.e. compound of the invention) per kg body weight. However, in a preferred use of the present invention a compound of the invention is administered to a subject in need thereof in an amount ranging from 1.0 to 500 mg/kg body weight, preferably ranging from 1 to 200 mg/kg body weight. The duration of therapy with a compound of the invention will vary, depending on the severity of the disease being treated and the condition and idiosyncratic response of each individual patient. In one preferred embodiment of a prophylactic or therapeutic use, from 10 mg to 200 mg of the compound are orally administered to an adult per day, depending on the severity of the disease and/or the degree of exposure to disease carriers.

As is known in the art, the pharmaceutically effective amount of a given composition will also depend on the administration route. In general, the required amount will be higher if the administration is through the gastrointestinal tract, e.g., by suppository, rectal, or by an intragastric probe, and lower if the route of administration is parenteral, e.g., intravenous. Typically, a compound of the invention will be administered in ranges of 50 mg to 1 g/kg body weight, preferably 10 mg to 500 mg/kg body weight, if rectal or intragastric administration is used and in ranges of 1 to 100 mg/kg body weight if parenteral administration is used. For intranasal administration, 1 to 100 mg/kg body weight are envisaged.

If a person is known to be at risk of developing a disease treatable with a compound of the invention, prophylactic administration of the biologically active blood serum or the pharmaceutical composition according to the invention may be possible. In these cases the respective compound of the invention is preferably administered in above outlined preferred and particular preferred doses on a daily basis. Preferably, from 0.1 mg to 1 g/kg body weight once a day, preferably 10 to 200 mg/kg body weight. This administration can be continued until the risk of developing the respective viral disorder has lessened. In most instances, however, a compound of the invention will be administered once a disease/disorder has been diagnosed. In these cases it is preferred that a first dose of a compound of the invention is administered one, two, three or four times daily.

The compounds of the present invention are particularly useful for treating, ameliorating, or preventing viral diseases. The type of viral disease is not particularly limited. Examples of possible viral diseases include, but are not limited to, viral diseases which are caused by Poxviridae, Herpesviridae, Adenoviridae, Papillomaviridae, Polyomaviridae, Parvoviridae, Hepadnaviridae, Reoviridae, Filoviridae, Paramyxoviridae, Rhabdoviridae, Orthomyxoviridae, Bunyaviridae, Arenaviridae, Coronaviridae, Picornaviridae, Hepeviridae, Caliciviridae, Astroviridae, Togaviridae, Flaviviridae, Deltavirus, Bornaviridae, and prions. Preferably viral diseases which are caused by Herpesviridae, Filoviridae, Paramyxoviridae, Rhabdoviridae, Orthomyxoviridae, Bunyaviridae, Arenaviridae, Coronaviridae, Picornaviridae, Togaviridae, Flaviviridae, more preferably viral diseases which are caused by orthomyxoviridae.

Examples of the various viruses are given in the following table.

Family	**Virus (preferred examples)**
Poxviridae	Smallpox virus Molluscum contagiosum virus
Herpesviridae	Herpes simplex virus Varicella zoster virus Cytomegalovirus Epstein Barr virus Kaposi's sarcoma-associated herpesvirus
Adenoviridae	Human adenovirus A-F
Papillomaviridae	Papillomavirus
Polyomaviridae	BK-virus JC-Virsu
Parvoviridae	B19 virus Adeno associated virus 2/3/5
Hepadnaviridae	Hepatitis B virus
Reoviridae	Reovirus 1/2/3 Rotavirus A/B/C Colorado tick fever virus
Filoviridae	Ebola virus Marburg virus
Paramyxoviridae	Parainfluenza virus 1-4 Mumps virus Measles virus Respiratory syncytial virus Hendravirus

Family	Virus (preferred examples)
Rhabdoviridae	Vesicular stomatitis virus Rabies virus Mokola virus European bat virus Duvenhage virus
Orthomyxoviridae	Influenza virus types A-C
Bunyaviridae	California encephalitis virus La Crosse virus Hantaan virus Puumala virus Sin Nombre virus Seoul virus Crimean- Congo hemorrhagic fever virus Sakhalin virus Rift valley virus Sandfly fever virus Uukuniemi virus
Arenaviridae	Lassa virus Lymphocytic choriomeningitis virus Guanarito virus Junin virus, Machupo virus Sabia virus
Coronaviridae	Human coronavirus
Picornaviridae	Human enterovirus types A-D (Poliovirus, Echovirus, Coxsackie virus A/B) Rhinovirus types A/B/C Hepatitis A virus Parechovirus Food and mouth disease virus
Hepeviridae	Hepatitis E virus
Caliciviridae	Norwalk virus Sapporo virus
Astroviridae	Human astrovirus 1
Togaviridae	Ross River virus Chikungunya virus O'nyong-nyong virus Rubella virus

Family	Virus (preferred examples)
Flaviviridae	Tick-borne encephalitis virus Dengue virus Yellow Fever virus Japanese encephalitis virus Murray Valley virus St. Louis encephalitis virus West Nile virus Hepatitis C virus Hepatitis G virus Hepatitis GB virus
Deltavirus	Hepatitis deltavirus
Bornaviridae	Bornavirus
Prions	

Preferably, the compounds of the present invention are employed to treat influenza. The present invention covers all virus genera belonging to the family of orthomyxoviridae, specifically influenza virus type A, B, and C, isavirus, and thogotovirus. Within the present invention, the term "influenza" includes influenza caused by any influenza virus such as influenza virus type A, B, and C including their various stains and isolates, and also covers influenza A virus strains commonly referred to as bird flu and swine flu. The subject to be treated is not particularly restricted and can be any vvertebrate, such as birds and mammals (including humans).

Without wishing to be bound by theory it is assumed that the compounds of the present invention are capable of inhibiting endonuclease activity, particularly that of influenza virus. More specifically it is assumed that they directly interfere with the N-terminal part of the influenza virus PA protein, which harbors endonuclease activity and is essential for influenza virus replication. Influenza virus replication takes place inside the cell within the nucleus. Thus, compounds designed to inhibit PA endonuclease activity need to cross both the cellular and the nuclear membrane, a property which strongly depends on designed-in physico-chemical properties of the compounds. The present invention shows that the claimed compounds have *in vitro* endonuclease inhibitory activity and have antiviral activity *in vitro* in cell-based assays.

A possible measure of the *in vitro* endonuclease inhibitory activity of the compounds having the formula (I) is the FRET (fluorescence-resonance energy transfer)–based endonuclease activity assay disclosed herein. Preferably, the compounds exhibit a % reduction of at least

about 50 % at 25 µM in the FRET assay. In this context, the % reduction is the % reduction of the initial reaction velocity (v0) measured as fluorescence increase of a dual-labelled RNA substrate cleaved by the influenza virus endonuclease subunit (PA-Nter) upon compound treatment compared to untreated samples. Preferably, the compounds exhibit an IC_{50} of less than about 40 µM, more preferably less than about 20 µM, in this assay. The half maximal inhibitory concentration (IC_{50}) is a measure of the effectiveness of a compound in inhibiting biological or biochemical function and was calculated from the initial reaction velocities (v0) in a given concentration series ranging from maximum 100 µM to at least 2 nM.

The compounds having the general formula (I) can be used in combination with one or more other medicaments. The type of the other medicaments is not particularly limited and will depend on the disorder to be treated. Preferably, the other medicament will be a further medicament which is useful in treating, ameliorating or preventing a viral disease, more preferably a further medicament which is useful in treating, ameliorating or preventing influenza that has been caused by influenza virus infection and conditions associated with this viral infection such as viral pneumonia or secondary bacterial pneumonia and medicaments to treat symptoms such as chills, fever, sore throat, muscle pains, severe headache, coughing, weakness and fatigue. Furthermore, the compounds having the general formula (I) can be used in combination with anti-inflammatories.

The following combinations of medicaments are envisaged as being particularly suitable:

(i) The combination of endonuclease and cap-binding inhibitors (particularly targeting influenza). The endonuclease inhibitors are not particularly limited and can be any endonuclease inhibitor, particularly any viral endonuclease inhibitor. Preferred endonuclease inhibitors are those as defined in the US applications with the serial numbers 61/550,045 (filed on October 21, 2011), 61/650,713 (filed on May 23, 2012), 61/650,725 (filed on May 23, 2012) and 61/679,968 (filed on August 6, 2012). The complete disclosure of these applications is incorporated herein by reference. In particular, all descriptions with respect to the general formula of the compounds according to these US applications, the preferred embodiments of the various substituents as well as the medical utility and advantages of the compounds are incorporated herein by reference.

Further preferred endonuclease inhibitors are the compounds having the general formula (II) as defined in the copending application with attorney's docket number U2798 US, and the compounds having the general formula (V) as defined in the copending application with attorney's docket number U2799 US, which were filed on even date herewith, the complete disclosure of which is incorporated by reference. In particular, all descriptions with respect to the general formula of these compounds, the preferred embodiments of the various substituents as well as the medical utility and advantages of the compounds are incorporated herein by reference. These compounds can be optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, codrug, cocrystal, prodrug, tautomer, racemate, enantiomer, or diastereomer or mixture thereof.

The cap-binding inhibitors are not particularly limited either and can be any cap-binding inhibitor, particularly any viral cap-binding inhibitor. Preferred cap-binding inhibitors are those having the general formula (II) as defined in US application 61/550,057 (filed on October 21, 2011) and/or the compounds disclosed in WO2011/000566, the complete disclosure of which is incorporated by reference. In particular, all descriptions with respect to the general formula of the compounds according to US 61/550,057 or WO2011/000566, the preferred embodiments of the various substituents as well as the medical utility and advantages of the compounds are incorporated herein by reference.

Widespread resistance to both classes of licensed influenza antivirals (M2 ion channel inhibitors (adamantanes) and neuraminidase inhibitors (e.g. oseltamivir)) occurs in both pandemic and seasonal emerging influenza strains, rendering these drugs to be of marginal utility in the treatment modality. For M2 ion channel inhibitors, the frequency of viral resistance has been increasing since 2003 and for seasonal influenza A/H3N2, adamantanes are now regarded as ineffective. Virtually all 2009 H1N1 and seasonal H3N2 strains are resistant to adamantanes (rimantadine and amantadine), and for oseltamivir, the most widely prescribed neuraminidase inhibitor (NAI), the WHO reported on significant emergence of influenza A/H1N1 resistance starting in the influenza season 2007/2008; and for the second and third quarters of 2008 in the southern hemisphere. Even more serious numbers were published for the fourth quarter of 2008 (northern hemisphere) where 95% of all tested isolates revealed no oseltamivir-susceptibility. Considering the fact that now most national governments have been stockpiling NAIs as part of their influenza pandemic preparedness plan, it is obvious that

the demand for new, effective drugs is growing significantly. To address the need for more effective therapy, preliminary studies using double or even triple combinations of antiviral drugs with different mechanisms of action have been undertaken. Adamantanes and neuraminidase inhibitors in combination were analysed *in vitro* and *in vivo* and were found to act highly synergistically. However, it is known that for both types of antivirals resistant viruses emerge rather rapidly and this issue is not tackled by combining these established antiviral drugs.

Influenza virus polymerase inhibitors are novel drugs targeting the transcription activity of the polymerase. Selective inhibitors against the cap-binding and endonuclease active sites of the viral polymerase severely attenuate virus infection by stopping the viral reproductive cycle. These two targets are located within distinct subunits of the polymerase complex and thus represent unique drug targets. Due to the fact that both functions are required for the so-called “cap-snatching” mechanism which is essential for viral transcription, concurrent inhibition of both functions is expected to act highly synergistically. This highly efficient drug combination would result in lower substance concentrations and hence improved dose-response-relationships and better side effect profiles.

Both active sites are highly conserved among all influenza A strains (e.g., avian and human) and even influenza B viruses, and hence this high degree of sequence conservation underpins the perception that these targets are not likely to trigger rapid resistant virus generation. Additionally, close interaction with host proteins render these viral proteins less prone to mutations. Thus, endonuclease and cap-binding inhibitors individually and in combination are ideal drug candidates to combat both seasonal and pandemic influenza, irrespectively of the virus strain.

The combination of an endonuclease inhibitor and a cap-binding inhibitor or a dual specific polymerase inhibitor targeting both the endonuclease active site and the cap-binding domain would be effective against virus strains resistant against adamantanes and neuraminidase inhibitors and moreover combine the advantage of low susceptibility to resistance generation with activity against a broad range of virus strains.

(ii) The combination of inhibitors of different antiviral targets (particularly targeting influenza virus) focusing on the combination with (preferably influenza virus) polymerase inhibitors as dual or multiple combination therapy. Influenza virus polymerase inhibitors are novel drugs targeting the transcription and replication activity of the polymerase. Selective inhibitors against the viral polymerase severely attenuate virus infection by stopping the viral reproductive cycle. The combination of a polymerase inhibitor specifically addressing a viral intracellular target with an inhibitor of a different antiviral target is expected to act highly synergistically. This is based on the fact that these different types of antiviral drugs exhibit completely different mechanisms of action requiring different pharmacokinetics properties which act advantageously and synergistically on the antiviral efficacy of the combination.

This highly efficient drug combination would result in lower substance concentrations and hence improved dose-response-relationships and better side effect profiles. Moreover, advantages described above for polymerase inhibitors would prevail for combinations of inhibitors of different antiviral targets with polymerase inhibitors.

Typically, at least one compound selected from the first group of polymerase inhibitors (e.g., cap-binding and endonuclease inhibitors) is combined with at least one compound selected from the second group of polymerase inhibitors.

The first group of polymerase inhibitors which can be used in this type of combination therapy includes, but is not limited to, the compounds having the formula (I).

The second group of polymerase inhibitors which can be used in this type of combination therapy includes, but is not limited to, the compounds having the general formula (I) as defined in the US application with the serial number 61/550,045 filed on October 21, 2011, the compounds having the general formula (II) as defined in US application 61/550,057 filed on October 21, 2011, the compounds disclosed in WO 2011/000566, WO 2010/110231, WO 2010/110409, WO 2006/030807 or US 5,475,109 as well as flutimide and analogues, favipiravir and analogues, epigallocatechin gallate and analogues, as well as nucleoside analogs such as ribavirine.

(iii) The combination of polymerase inhibitors with neuraminidase inhibitors

Influenza virus polymerase inhibitors are novel drugs targeting the transcription and replication activity of the polymerase. The combination of a polymerase inhibitor specifically addressing a viral intracellular target with an inhibitor of a different extracellular antiviral target, especially the (e.g., viral) neuraminidase is expected to act highly synergistically. This is based on the fact that these different types of antiviral drugs exhibit completely different mechanisms of action requiring different pharmacokinetic properties which act advantageously and synergistically on the antiviral efficacy of the combination.

This highly efficient drug combination would result in lower substance concentrations and hence improved dose-response-relationships and better side effect profiles. Moreover, advantages described above for polymerase inhibitors would prevail for combinations of inhibitors of different antiviral targets with polymerase inhibitors.

Typically, at least one compound selected from the above mentioned first group of polymerase inhibitors is combined with at least one neuraminidase inhibitor.

The neuraminidase inhibitor (particularly influenza neuramidase inhibitor) is not specifically limited. Examples include zanamivir, oseltamivir, peramivir, KDN DANA, FANA, and cyclopentane derivatives.

(iv) The combination of polymerase inhibitors with M2 channel inhibitors

Influenza virus polymerase inhibitors are novel drugs targeting the transcription and replication activity of the polymerase. The combination of a polymerase inhibitor specifically addressing a viral intracellular target with an inhibitor of a different extracellular and cytoplasmic antiviral target, especially the viral M2 ion channel, is expected to act highly synergistically. This is based on the fact that these different types of antiviral drugs exhibit completely different mechanisms of action requiring different pharmacokinetic properties which act advantageously and synergistically on the antiviral efficacy of the combination.

This highly efficient drug combination would result in lower substance concentrations and hence improved dose-response-relationships and better side effect profiles. Moreover, advantages described above for polymerase inhibitors would prevail for combinations of inhibitors of different antiviral targets with polymerase inhibitors.

Typically, at least one compound selected from the above mentioned first group of polymerase inhibitors is combined with at least one M2 channel inhibitor.

The M2 channel inhibitor (particularly influenza M2 channel inhibitor) is not specifically limited. Examples include amantadine and rimantadine.

(v) The combination of polymerase inhibitors with alpha glucosidase inhibitors

Influenza virus polymerase inhibitors are novel drugs targeting the transcription and replication activity of the polymerase. The combination of a polymerase inhibitor specifically addressing a viral intracellular target, with an inhibitor of a different host-cell target, especially alpha glucosidase, is expected to act highly synergistically. This is based on the fact that these different types of antiviral drugs exhibit completely different mechanisms of action requiring different pharmacokinetic properties which act advantageously and synergistically on the antiviral efficacy of the combination.

This highly efficient drug combination would result in lower substance concentrations and hence improved dose-response-relationships and better side effect profiles. Moreover, advantages described above for polymerase inhibitors would prevail for combinations of inhibitors of cellular targets interacting with viral replication with polymerase inhibitors.

Typically, at least one compound selected from the above-mentioned first group of polymerase inhibitors is combined with at least one alpha glucosidase inhibitor.

The alpha glucosidase inhibitor is not specifically limited. Examples include the compounds described in Chang et al., Antiviral Research 2011, 89, 26-34.

(vi) The combination of polymerase inhibitors with ligands of other influenza targets

Influenza virus polymerase inhibitors are novel drugs targeting the transcription and replication activity of the polymerase. The combination of a polymerase inhibitor specifically addressing a viral intracellular target with an inhibitor of different extracellular, cytoplasmic or nucleic antiviral targets is expected to act highly synergistically. This is based on the fact that these different types of antiviral drugs exhibit completely different mechanisms of action requiring different pharmacokinetic properties which act advantageously and synergistically on the antiviral efficacy of the combination.

This highly efficient drug combination would result in lower substance concentrations and hence improved dose-response-relationships and better side effect profiles. Moreover, advantages described above for polymerase inhibitors would prevail for combinations of inhibitors of different antiviral targets with polymerase inhibitors.

Typically at least one compound selected from the above mentioned first group of polymerase inhibitors is combined with at least one ligand of another influenza target.

The ligand of another influenza target is not specifically limited. Examples include compounds acting on the sialidase fusion protein (e.g., Fludase (DAS181), siRNAs and phosphorothioate oligonucleotides), signal transduction inhibitors (e.g., ErbB tyrosine kinase, Abl kinase family, MAP kinases, PKCa-mediated activation of ERK signalling) as well as interferon (inducers).

(vii) The combination of (preferably influenza) polymerase inhibitors with a compound used as an adjuvant to minimize the symptoms of the disease (antibiotics, anti-inflammatory agents like COX inhibitors (e.g., COX-1/COX-2 inhibitors, selective COX-2 inhibitors), lipoxygenase inhibitors, EP ligands (particularly EP4 ligands), bradykinin ligands, and/or cannabinoid ligands (e.g., CB2 agonists)). Influenza virus polymerase inhibitors are novel drugs targeting the transcription and replication activity of the polymerase.. The combination of a polymerase inhibitor specifically addressing a viral intracellular target with a compound used as an adjuvance to minimize the symptoms of the disease address the causative and symptomatic pathological consequences of viral infection.

This combination is expected to act synergistically because these different types of drugs exhibit completely different mechanisms of action requiring different pharmacokinetic properties which act advantageously and synergistically on the antiviral efficacy of the combination.

This highly efficient drug combination would result in lower substance concentrations and hence improved dose-response-relationships and better side effect profiles. Moreover, advantages described above for polymerase inhibitors would prevail for combinations of inhibitors of different antiviral targets with polymerase inhibitors.

Various modifications and variations of the invention will be apparent to those skilled in the art without departing from the scope of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in the relevant fields are intended to be covered by the present invention.

The following examples are merely illustrative of the present invention and should not be construed to limit the scope of the invention as indicated by the appended claims in any way.

EXAMPLES

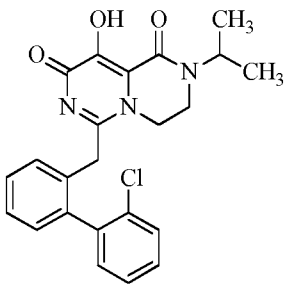
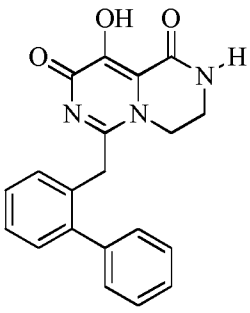
FRET endonuclease activity assay

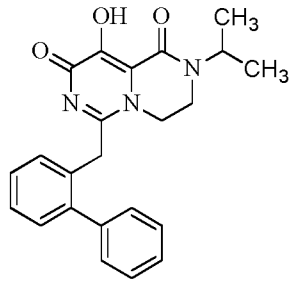
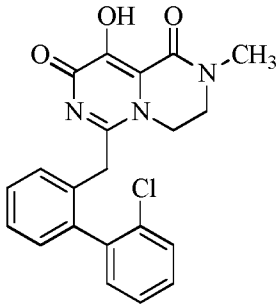
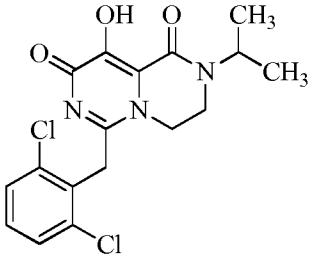
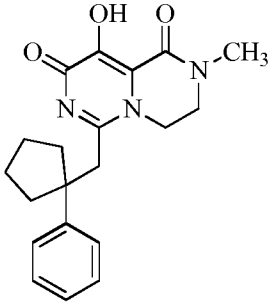
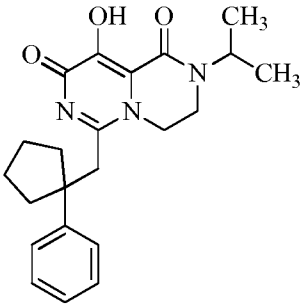
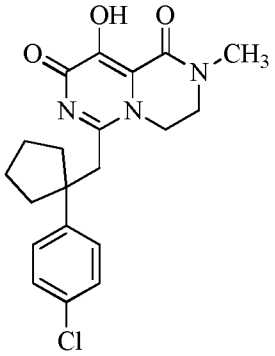
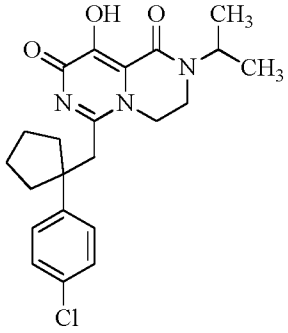
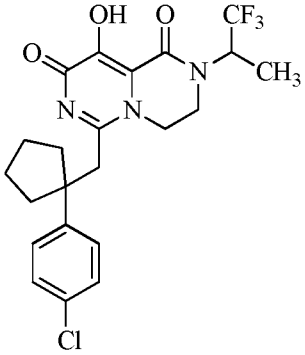
The influenza A virus (IAV) PA-Nter fragment (amino acids 1 – 209) harboring the influenza endonuclease activity was generated and purified as described in Dias et al., Nature 2009; Apr 16; 458(7240), 914-918. The protein was dissolved in buffer containing 20mM Tris pH 8.0, 100mM NaCl and 10mM β-mercaptoethanol and aliquots were stored at –20 °C.

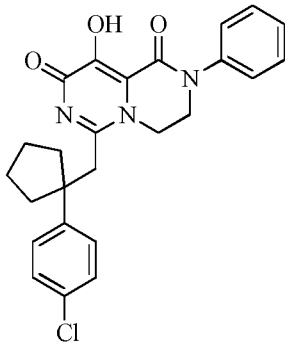
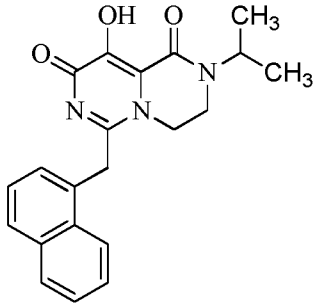
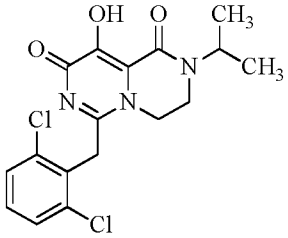
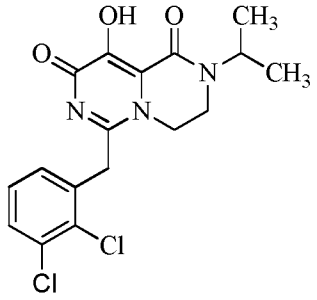
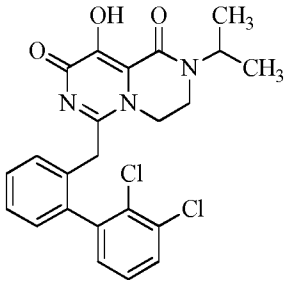
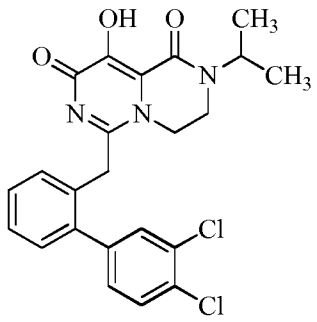
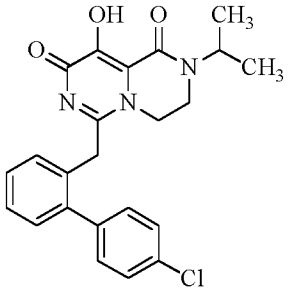
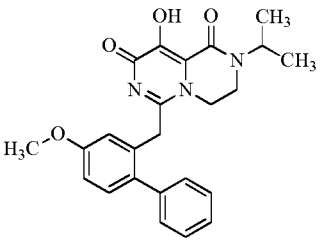
A 20 bases dual-labelled RNA oligo with 5´-FAM fluorophore and 3´-BHQ1 quencher was used as a substrate to be cleaved by the endonuclease activity of the PA-Nter. Cleavage of the RNA substrate frees the fluorophore from the quencher resulting in an increase of the fluorescent signal.

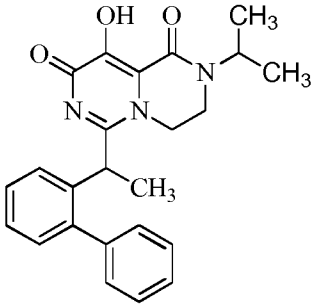
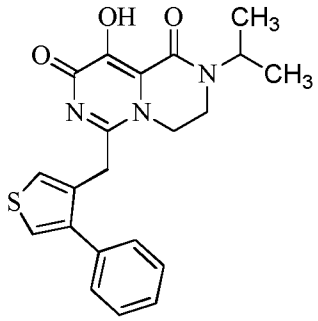
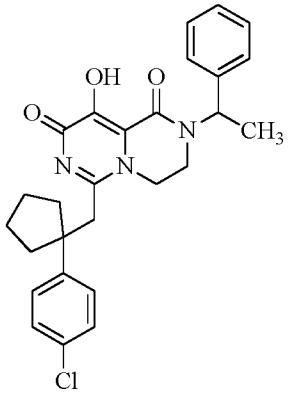
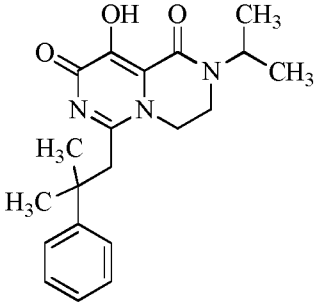
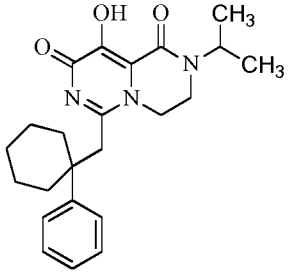
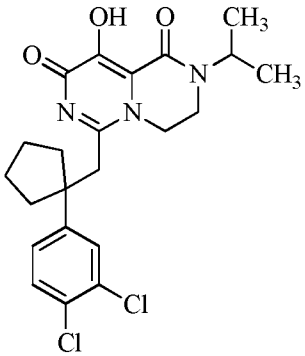
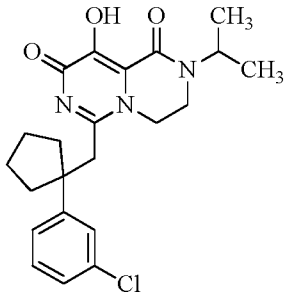
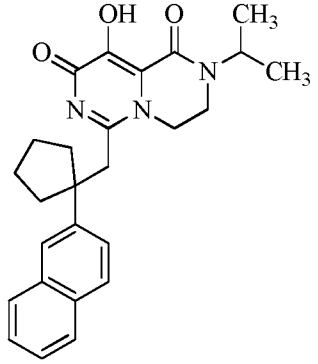
All assay components were diluted in assay buffer containing 20mM Tris-HCl pH 8.0, 100mM NaCl, 1mM $MnCl_2$, 10mM $MgCl_2$ and 10mM β-mercaptoethanol. The final concentration of PA-Nter was 0.5µM and 1.6µM RNA substrate. The test compounds were dissolved in DMSO and generally tested at two concentrations or a concentration series resulting in a final plate well DMSO concentration of 0.5 %. In those cases where the compounds were not soluble at that concentration, they were tested at the highest soluble concentration.

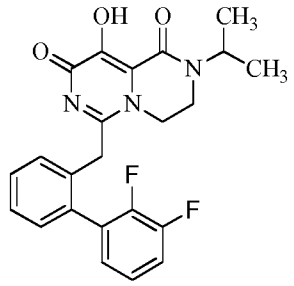
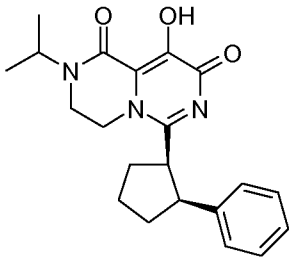
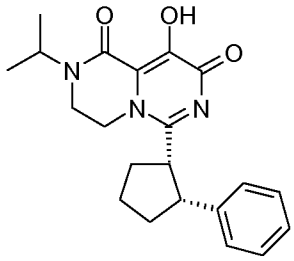
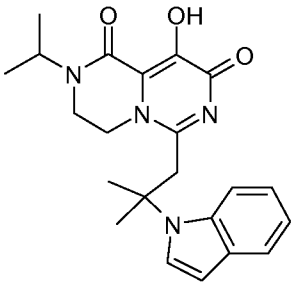
5µl of each compound dilution was provided in the wells of white 384-well microtiter plates (PerkinElmer) in eight replicates. After addition of PA-Nter dilution, the plates were sealed and incubated for 30min at room temperature prior to the addition of 1.6µM RNA substrate diluted in assay buffer. Subsequently, the increasing fluorescence signal of cleaved RNA was measured in a microplate reader (Synergy HT, Biotek) at 485nm excitation and 535nm emission wavelength. The kinetic read interval was 35sec at a sensitivity of 35. Fluorescence signal data over a period of 20min were used to calculate the initial velocity (v0) of substrate cleavage. Final readout was the % reduction of v0 of compound-treated samples compared to untreated. The half maximal inhibitory concentration (IC_{50}) is a measure of the effectiveness of a compound in inhibiting biological or biochemical function and was calculated from the initial reaction velocities (v0) in a given concentration series ranging from maximum 100 µM to at least 2 nM.

Formula no.	FRET	Formula no.	FRET
 **(12-04)**	IC_{50}=0.657 µM		IC_{50}=0.06 µM

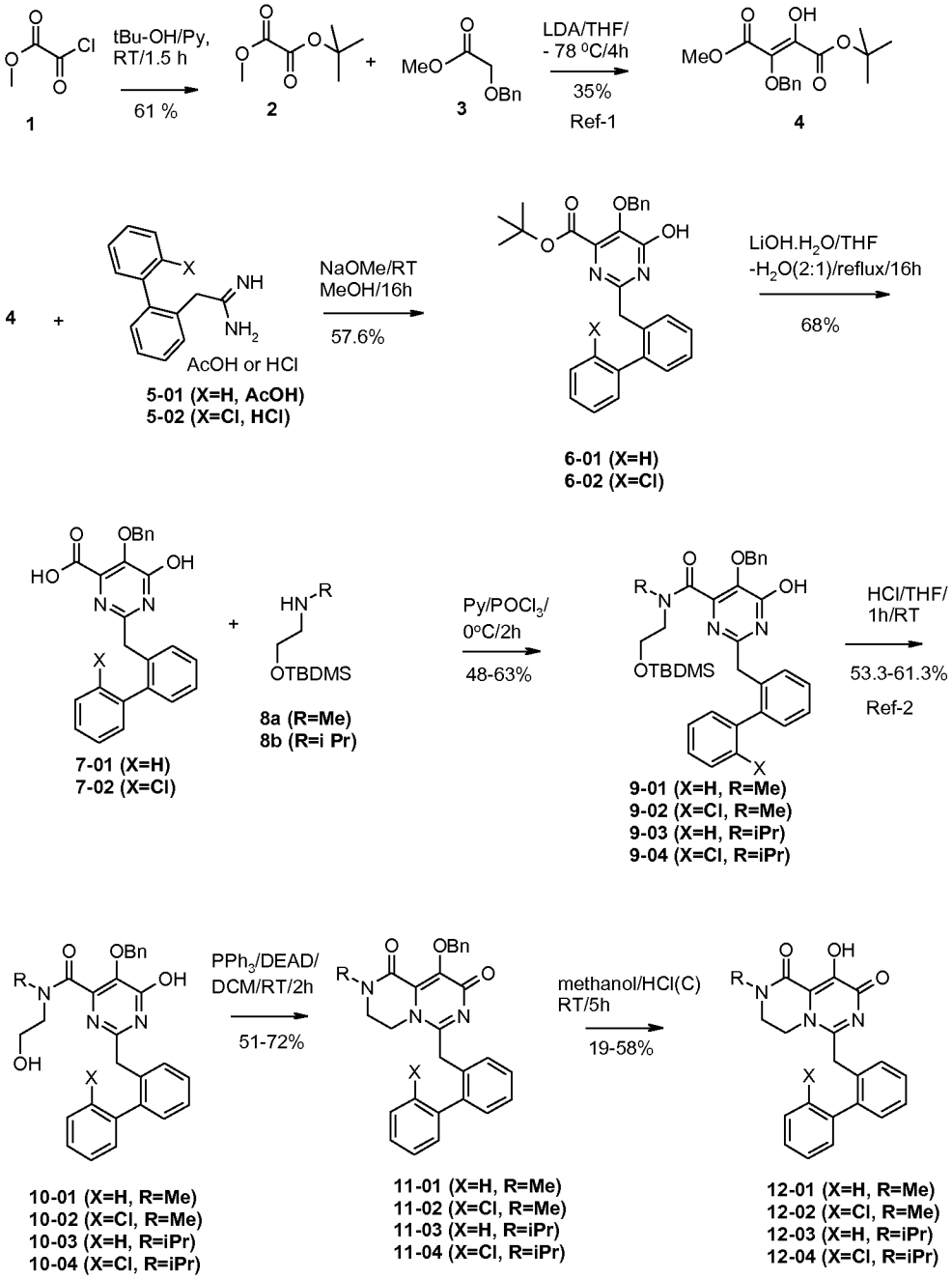
 **(12-03)**	IC_{50}=0.196 μM	 **(12-02)**	IC_{50}=0.175 μM
 **(66)**	IC_{50}=0.392 μM	 **(32-01)**	IC_{50}=0.116 μM
 **(32-04)**	IC_{50}=0.093 μM	 **(32-02)**	IC_{50}=0.16 μM
 **(32-03)**	IC_{50}=0.252 μM	 **(45)**	IC_{50}=0.296 μM

 **(50)**	IC_{50}=1.18 μM	 **(81)**	IC_{50}=1.81 μM
 **(66)**	IC_{50}=0.39 μM		IC_{50}=0.35 μM
 **(74)**	IC_{50}=0.37 μM	 **(72)**	IC_{50}=2.51 μM
 **(73)**	IC_{50}=1.37 μM		IC_{50}=0.43 μM

 (89)	IC_{50}=1.70 μM	 (100)	IC_{50}=1.39 μM
 (38)	IC_{50}=1.13 μM	 (60)	IC_{50}=0.25 μM
	IC_{50}=0.12 μM		IC_{50}=0.61 μM
	IC_{50}=0.32 μM		IC_{50}=0.11 μM

 **(108)**	IC_{50}=0.2 μM	 **(118)**	IC_{50}=0.5 μM
 **(119)**	IC_{50}=0.23 μM	 **(127)**	IC_{50}=0.24 μM

Scheme 1



1

2

3

4

5-01 (X=H, AcOH)
5-02 (X=Cl, HCl)

6-01 (X=H)
6-02 (X=Cl)

7-01 (X=H)
7-02 (X=Cl)

8a (R=Me)
8b (R=i Pr)

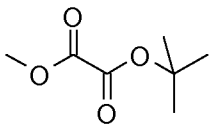
9-01 (X=H, R=Me)
9-02 (X=Cl, R=Me)
9-03 (X=H, R=iPr)
9-04 (X=Cl, R=iPr)

10-01 (X=H, R=Me)
10-02 (X=Cl, R=Me)
10-03 (X=H, R=iPr)
10-04 (X=Cl, R=iPr)

11-01 (X=H, R=Me)
11-02 (X=Cl, R=Me)
11-03 (X=H, R=iPr)
11-04 (X=Cl, R=iPr)

12-01 (X=H, R=Me)
12-02 (X=Cl, R=Me)
12-03 (X=H, R=iPr)
12-04 (X=Cl, R=iPr)

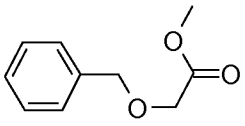
Preparation of (2):



Oxalic acid tert-butyl ester methylester

To a stirred solution of methyl oxalyl chloride **(1)** (5g, 40.98 mmol) in ether (80mL) a mixture of pyridine (5.1mL, 63.93mmol) and t-butanol (6.07mL, 63.9mmol) was added dropwise and the reaction mixture was stirred for 1.5h at room temperature. After completion of the reaction, the reaction mixture was washed with water (60mL) and saturated sodium carbonate, aqueous solution (100mL) and water. The separated organic part was dried over sodium sulfate and concentrated under reduced pressure to get oxalic acid tert-butyl ester methyl ester **(2)** (4g, 60.94%) as a colourless oil.

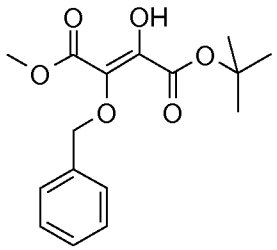
Preparation of (3):



Benzyloxy-acetic acid methyl ester

To a stirred solution of benzyloxy-acetic acid (5g, 30.12mmol) in methanol (100mL) was added $SOCl_2$ (2.66mL, 35.8mmol) at 0 °C. The mixture was stirred for 30min at 0 °C, finally at room temperature for 2.5 h. After completion of the reaction, the solvent was evaporated and the reaction mixture was diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate solution. The separated organic part was dried over sodium sulfate and concentrated under reduced pressure to get benzyloxy-acetic acid methyl ester **(3)** as a crude colorless oil (4.98g).

Preparation of (4):

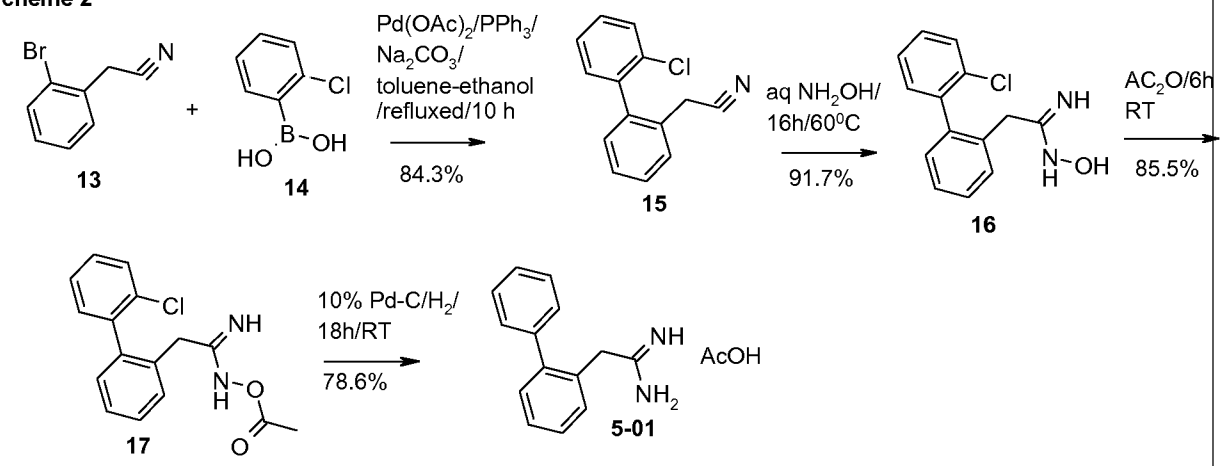


(E)-2-Benzyloxy-3-hydroxy-but-2-enedioic acid 4-tert-butyl ester 1-methyl ester

Lithium diisopropylamide was generated by addition of n-butyl lithium (17mL, 1.9M in hexane, 33.33 mmol), di-isopropyl amine (4.66mL, 33.33mmol) in tetrahydrofuran (15mL) at 0 °C and stirred for 10 min. In a separate flask, a mixture of benzyloxy-acetic acid methyl ester **(3)** (4g, 22.22mmol) and oxalic acid tert-butyl ester methyl ester **(2)** (5.33g, 33.33 mmol) in tetrahydrofuran (50mL) was cooled to –78 °C and then lithium diisopropylamide was added at –78°C. The mixture was stirred at –78°C for 1h. After 1h, the reaction mixture was allowed to warm to room temperature and stirred at room temperature for another 1h. After completion of the reaction, the reaction was quenched with 1N HCl, and extracted with ethyl acetate. The separated organic part was dried over sodium sulfate and concentrated under reduced pressure, passed over a normal silica column using 25% ethyl acetate in hexane to get (E)-2-benzyloxy-3-hydroxy-but-2-enedioic acid 4-tert-butyl ester 1-methyl ester **(4)** (2.4g, 35%) as keto enol tautomers and ketone hydrate as a thick light yellow coloured oil. These were immediately used for next step.

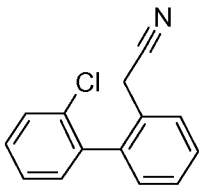
Synthesis of 5-01:

Scheme 2



Experimental:

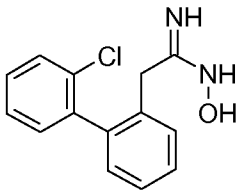
Preparation of (15):



(2'-Chloro-biphenyl-2-yl)-acetonitrile

To a stirred solution of (2-bromo-phenyl)-acetonitrile **(13)** (5g, 25.51mmol) in a mixture of toluene and ethanol (1:1, 150mL) was added 2-chloro phenyl boronic acid **(14)** (6g, 38.2mmol) and Na_2CO_3 (8.1g, 76.53mmol) at room temperature. Purging was conducting for 30 min with nitrogen. Then triphenyl phosphine (2.6 g, 10.2 mmol) was added followed by $Pd(OAc)_2$ (0.287g, 1.27mmol) and further degassing was conducted for another 10 min. The reaction mixture was heated to reflux for 10h. After completion of the reaction, the mixture was concentrated under reduced pressure to get a crude product which was purified using a silica column using 2% ethyl acetate in hexane to get (2'-chloro-biphenyl-2-yl)-acetonitrile **(15)** (4.9g, 84.36%) as a yellow liquid.

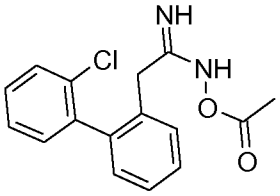
Preparation of (16):



2-(2'-Chloro-biphenyl-2-yl)-N-hydroxy-acetamidine

To a stirred solution of (2'-chloro-biphenyl-2-yl)-acetonitrile **(15)** (2g, 8.78mmol) in ethanol (20 mL) was added aqueous hydroxyl amine (50%) (1.16g, 17.8). The mixture was heated to 60 °C for 16h. After completion of the reaction, the reaction mixture was evaporated, extracted with ethyl acetate and concentrated to get 2-(2'-chloro-biphenyl-2-yl)-N-hydroxy-acetamidine **(16)** (2.1g, 91.7%) as an off-white solid which was directly used in the next step.

Preparation of (17):

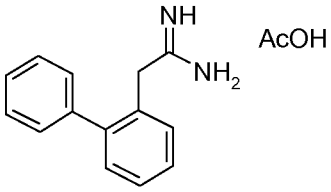


2-(2'-Chloro-biphenyl-2-yl)-N-acetyl-acetamidine

To 10 mL acetic anhydride was added 2-(2'-chloro-biphenyl-2-yl)-N-hydroxy-acetamidine **(16)** (2g, 7.692mmol). The mixture was stirred for 6h at room temperature. After completion of the reaction, water was added, the mixture was extracted with ethyl acetate, evaporated, dried and purified using a CombiFlash column using 25% ethyl acetate in hexane to get 2-(2'-chloro-biphenyl-2-yl)-N-acetyl-acetamidine **(17)** (2g, 85.88%) as an off-white solid.

LCMS: 302.8 (M+H).

Preparation of (5-01):



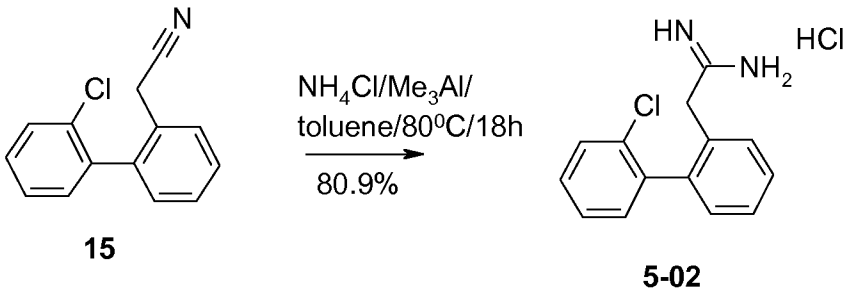
2-Biphenyl-2-yl-acetamidine acetate salt

To the solution of 2-(2'-chloro-biphenyl-2-yl)-N-acetyl-acetamidine **(17)** (2g, 6.623mmol) in methanol (10mL) was added 200mg 10% Pd-C. The mixture was hydrogenated by balloon pressure at room temperature for 18h. After completion of the reaction, the mixture was filtered and evaporated to afford 2-biphenyl-2-yl-acetamidine acetic acid salt **(5-01)** (1.4g, 78.4%) as a white solid.

LCMS: 211 (M+H).

Synthesis of 5-02:

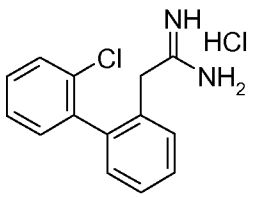
Scheme 3



15 **5-02**

Experimental:

Preparation of (5-02):

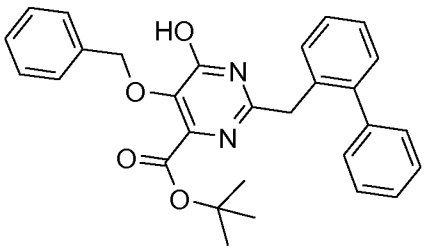


2-(2'-Chloro-biphenyl-2-yl)-acetamidine hydrochloride salt.

To a stirred suspension of NH_4Cl (1.4g, 26.43mmol) in dry toluene (40mL) was added tri-methyl aluminium (2M in toluene, 13.2mL, 26.43mmol) at 5 °C. The reaction mixture was then warmed to room temperature and stirred for 2h. A solution of (2'-chloro-biphenyl-2-yl)-acetonitrile **(15)** (2g, 8.8mmol) in toluene (10mL) was added to the reaction mixture, which was then stirred for 14h at 80 °C. After completion of the reaction, it was quenched with a suspension of silica gel in chloroform and the reaction mixture was stirred for half an hour at room temperature and then filtered through a sintered funnel. The silica gel was washed with methanol and the combined filtrates were concentrated under reduced pressure to get 2-(2'-chloro-biphenyl-2-yl)-acetamidine hydrochloride salt as a crude product **(5-02)** (2g, 80.97%) as a white solid.

LCMS: 245 (M+H).

Preparation of (6-01):

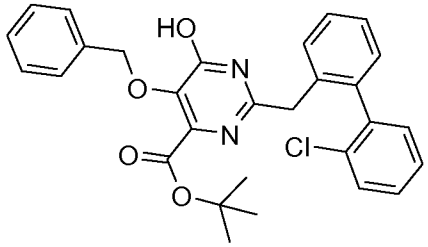


5-Benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester

To a stirred solution of 2-biphenyl-2-yl-acetamidine acetate salt **(5-01)** (2.5g, 9.2mmol) and (E)-2-benzyloxy-3-hydroxy-but-2-enedioic acid 4-tert-butyl ester 1-methyl ester **(4)** (4.2g, 13.88mmol) in methanol (60mL) was added sodium methoxide (1.5g, 27.77mmol) at 0 °C, then the reaction mixture was allowed to warm to room temperature and was stirred for 16h. After completion of the reaction, it was quenched with 1N HCl, evaporated and water was added. The mixture was extracted with ethyl acetate and the separated organic part was dried over sodium sulfate and concentrated under reduced pressure to get a crude product, which was purified using a normal silica column using 30% ethyl acetate in hexane to get 5-benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester **(6-01)** (2.5g, 57.63%) as a white solid.

LCMS: 469.2 (M+H).

Preparation of (6-02):

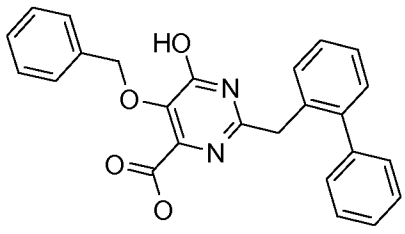


5-Benzyloxy-2-(2'-chloro-biphenyl-2-ylmethyl)-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester

5-Benzyloxy-2-(2'-chloro-biphenyl-2-ylmethyl)-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester **(6-02)** (5g, 55.8%) was synthesized as a brown solid from 2-(2'-chloro-biphenyl-2-yl)-acetamidine hydrochloride salt **(5-02)** (5g, 17.82mmol) and (E)-2-benzyloxy-3-hydroxy-but-2-enedioic acid 4-tert-butyl ester 1-methyl ester **(4)** (9.4g, 30.73mmol) following the procedure as described for 5-benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester **(6-01)**.

LCMS: 503.4(M+H).

Preparation of (7-01):



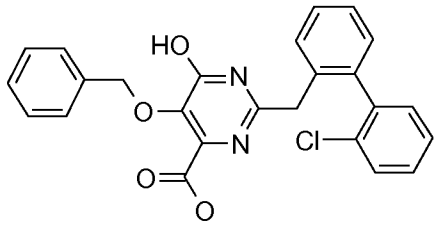
5-Benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid

To a stirred solution of 5-benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester **(6-01)** (5g, 10.68mmol) in a mixture of tetrahydrofuran and water (2:1, 90mL) was added lithium hydroxide, monohydrate (2.2g, 53.4mml). The mixture was refluxed for 18h. After completion of the reaction, the volume was reduced by evaporation as much as

possible, water was added and the mixture was washed with ethyl acetate to remove non-acidic impurities. The separated aqueous part was acidified with 1(N) HCl to bring the pH to about 5 to 6. The acidified aqueous part was extracted with dichloromethane to get 5-benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid **(7-01)** (3g, 68%) as a white solid.

LCMS: 413.2(M+H).

Preparation of (7-02):



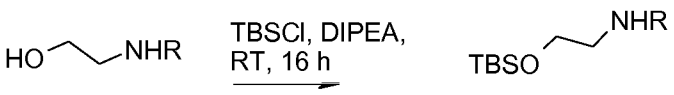
5-Benzyloxy-2-(2'-chloro-biphenyl-2-ylmethyl)-6-hydroxy-pyrimidine-4-carboxylic acid

5-Benzyloxy-2-(2'-chloro-biphenyl-2-ylmethyl)-6-hydroxy-pyrimidine-4-carboxylic acid **(7-02)** (3g, 67.53%) was synthesized as a white solid from 5-benzyloxy-2-(2'-chloro-biphenyl-2-ylmethyl)-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester **(6-02)** (5g, 9.94mmol) following the procedure as described for 5-benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid **(7-01)**.

LCMS: 447 (M+H).

Synthesis of 8:

Scheme 4

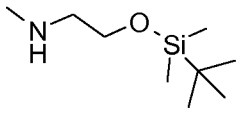


18-a (R=Me)
18-b (R=iPr)

8-a (R=Me)
8-b (R=iPr)

Experimental:

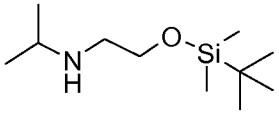
Preparation of (8-a):



[2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-methyl-amine

To a stirred solution of 2-methylamino-ethanol **(18-a)** (10g, 133.13mmol) in dichloromethane (200mL) were added diisopropylethylamine (30.8 ml, 186.39mmol) and tert-butyl-chloro-dimethyl-silane (20.06g, 133.13mmol) at room temperature. The mixture was stirred for 16h. After completion of the reaction, water was added and the mixture was extracted with dichloromethane. The separated organic part was washed with water and was dried over sodium sulfate and concentrated under reduced pressure to get [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amine **(8-a)** (18g, 71.39%) as a yellow liquid.

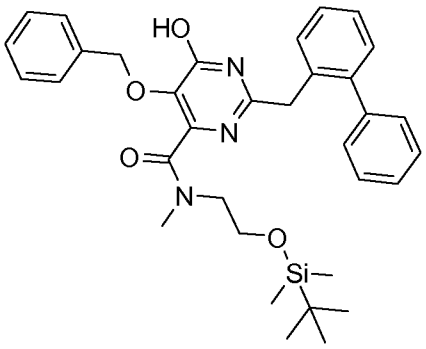
Preparation of (8-b):



[2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amine

[2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amine **(8-b)** (20gm, 37.4%) was synthesized as a yellow liquid from 2-isopropylamino-ethanol **(18-b)** (25g, 242.31mmol) and tert-butyl-chloro-dimethyl-silane (25.5g, 242.31mmol) following the procedure as described for [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amine **(8-a)**.

Preparation of (9-01):

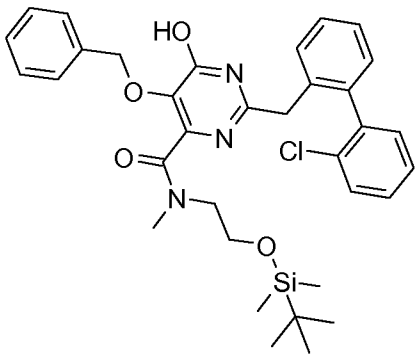


5-Benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide

To a stirred solution of 5-benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid **(7-01)** (3g, 7.28mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amine **(8-a)** (1.51g, 8.01mmol) in pyridine (40mL) was added $POCl_3$ (2ml, 21.84 mol) at –10 °C. The mixture was stirred at 0 °C for 2h. After completion of the reaction, ice cooled-water (30mL) was added to the reaction mxiture at 0 °C. The mixture was extracted with ethyl acetate (4x200mL). The separated organic part was washed with saturated aqueous solution of $NaHCO_3$, dried and concentrated to get a crude product which was purified by normal silica column using 40% ethyl acetate in hexane to get 5-benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(9-01)** (2.1g, 49.4%) as a yellow sticky mass.

LCMS: 584.2 (M+H).

Preparation of (9-02):

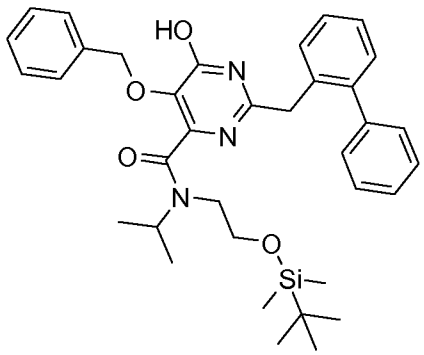


5-Benzyloxy-2-(2'-chloro-biphenyl-2-ylmethyl)-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide

5-Benzyloxy-2-(2'-chloro-biphenyl-2-ylmethyl)-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(9-02)** (2g, 48.09%) was synthesized as a yellow liquid from 5-benzyloxy-2-(2'-chloro-biphenyl-2-ylmethyl)-6-hydroxy-pyrimidine-4-carboxylic acid **(7-02)** (3g, 6.72 mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amine **(8-a)** (1.39g, 7.399mmol) following the procedure as described for 5-benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(9-01)**.

LCMS: 618.2 (M+H).

Preparation of (9-03):

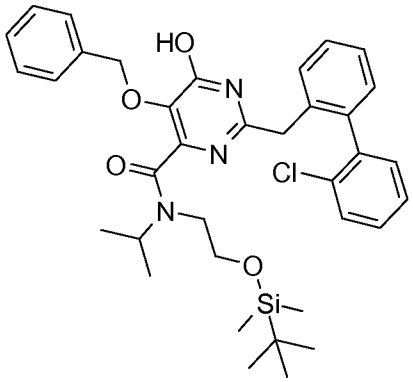


5-Benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide

5-Benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide (**9-03**) (1.7g, 38.16%) was synthesized as a dark liquid from 5-benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid **(7-01)** (3g, 7.28mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl amine **(8-b)** (1.73g, 8.01mmol) following the procedure as described for 5-benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(9-01)**.

LCMS: 611.9 (M+H).

Preparation of (9-04):

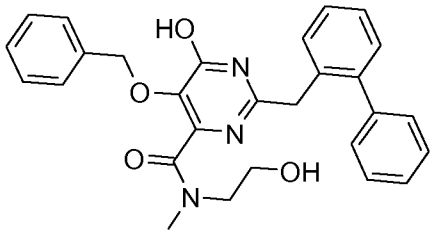


5-Benzyloxy-2-(2'-chloro-biphenyl-2-ylmethyl)-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide

5-Benzyloxy-2-(2'-chloro-biphenyl-2-ylmethyl)-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(9-04)** (2.74g, 63.03%) was synthesized as a dark liquid from 5-benzyloxy-2-(2'-chloro-biphenyl-2-ylmethyl)-6-hydroxy-pyrimidine-4-carboxylic acid **(7-02)** (3 g, 6.72 mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl amine **(8-b)** (1.6g, 7.399mmol) following the procedure as described for 5-benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(9-01)**.

LCMS: 646.3 (M+H).

Preparation of (10-01):



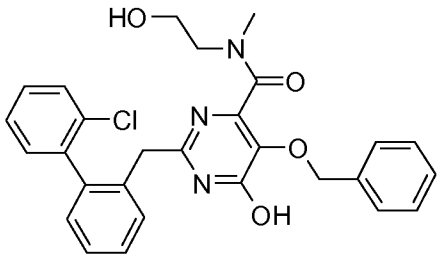
5-Benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide

To a stirred solution of 5-benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(9-01)** (2.1g, 3.602mmol) in

tetrahydrofuran (30mL) was added 1N HCl (5.4ml, 5.4mmol) at room temperature. The mixture was stirred for 60 min at room temperature. After completion of the reaction, the mixture was neutralized with 1N sodium hydroxide aqueous solution, extracted with ethyl acetate, dried over sodium sulfate and concentrated under reduced pressure to get a crude product which was purified using a normal silica column using 60% ethyl acetate in hexane to get 5-benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide **(10-01)** (900mg, 53.33%) as a floppy light yellow solid.

LCMS: 470 (M+H).

Preparation of (10-02):

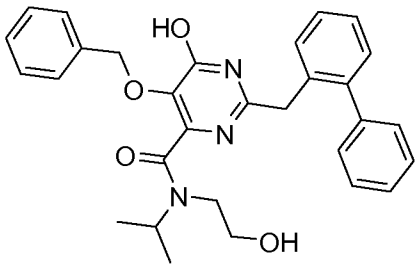


5-Benzyloxy-2-(2'-chloro-biphenyl-2-ylmethyl)-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide

5-Benzyloxy-2-(2'-chloro-biphenyl-2-ylmethyl)-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide **(10-02)** (1g, 61.34%) was synthesized as a yellow liquid from 5-benzyloxy-2-(2'-chloro-biphenyl-2-ylmethyl)-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(9-02)** (2g, 3.23mmol) following the procedure as described for 5-benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide **(10-01)**.

LCMS: 504.1(M+H).

Preparation of (10-03):

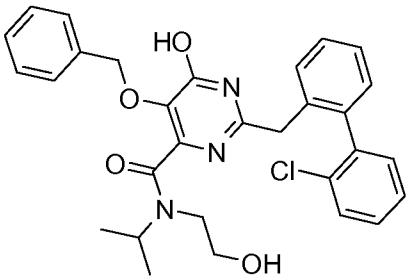


5-Benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide

5-Benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(10-03)** (650mg, 47%) was synthesized as a yellow liquid from 5-benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(9-03)** (1.7g, 38.16mmol) following the procedure as described for 5-benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide **(10-01)**.

LCMS: 498.2(M+H).

Preparation of (10-04):



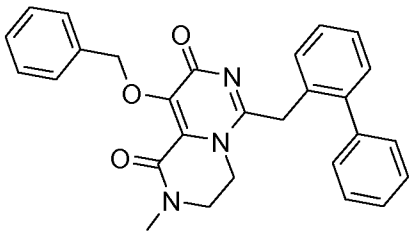
5-Benzyloxy-2-(2'-chloro-biphenyl-2-ylmethyl)-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide

5-Benzyloxy-2-(2'-chloro-biphenyl-2-ylmethyl)-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(10-04)** (1.2g, 53.97%) was synthesized as a yellow liquid from 5-benzyloxy-2-(2'-chloro-biphenyl-2-ylmethyl)-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(9-04)** (2.7g, 4.18mmol) following the

procedure as described for 5-benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide **(10-01)**.

LCMS: 532.2(M+H).

Preparation of (11-01):

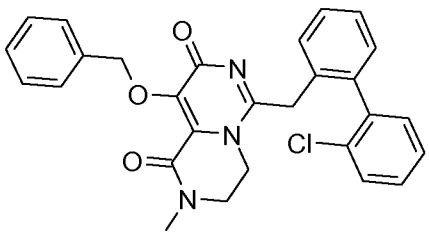


9-Benzyloxy-6-biphenyl-2-ylmethyl-2-methyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a stirred solution of 5-benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide **(10-01)** (400mg, 0.853mmol) in dichloromethane (10mL) was added triphenyl phosphine (336.46mg, 1.27mmol) at room temperature. The mixture was stirred for 10 min. Then DIAD (diisopropylazodicarboxylate) (258.4mg, 1.27mmol) was added at room temperature and the resultant mixture was stirred for another 2h. After completion of the reaction, the mixture was concentrated under reduced pressure to get a crude product, which was purified using normal silica column using 2% methanol in dichloromethane to afford 9-benzyloxy-6-biphenyl-2-ylmethyl-2-methyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(11-01)** (200mg, 51.94%) as a white solid.

LCMS: 452.2 (M+H).

Preparation of (11-02):

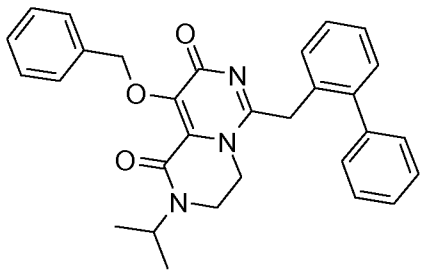


9-Benzyloxy-6-(2'-chloro-biphenyl-2-ylmethyl)-2-methyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

9-Benzyloxy-6-(2'-chloro-biphenyl-2-ylmethyl)-2-methyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(11-02)** (201mg, 52.5%) was synthesized as a white solid from 5-benzyloxy-2-(2'-chloro-biphenyl-2-ylmethyl)-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide **(10-02)** (400mg, 0.795mmol) following the procedure as described for 9-benzyloxy-6-biphenyl-2-ylmethyl-2-methyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(11-01)**.

LCMS:486.2 (M+H).

Preparation of (11-03):

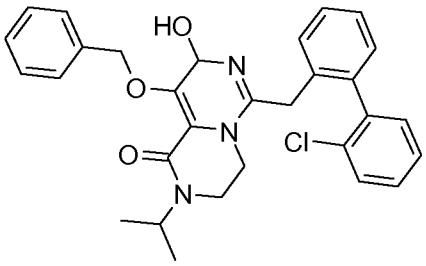


9-Benzyloxy-6-biphenyl-2-ylmethyl-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

9-Benzyloxy-6-biphenyl-2-ylmethyl-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(11-03)** (110mg, 17.54%) was synthesized as a white solid from 5-benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(10-03)** (650mg, 1.3mmol) following the procedure as described for 9-benzyloxy-6-biphenyl-2-ylmethyl-2-methyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(11-01)**.

LCMS: 480.2 (M+H).

Preparation of (11-04):

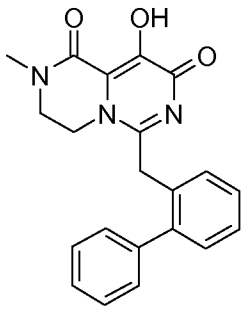


9-Benzyloxy-6-(2'-chloro-biphenyl-2-ylmethyl)-8-hydroxy-2-isopropyl-3,4-dihydro-2H,8H-pyrazino[1,2-c]pyrimidin-1-one

9-Benzyloxy-6-(2'-chloro-biphenyl-2-ylmethyl)-8-hydroxy-2-isopropyl-3,4-dihydro-2H,8H-pyrazino[1,2-c]pyrimidin-1-one **(11-04)** (350mg, 72.4%) was synthesized as a white solid from 5-benzyloxy-2-(2'-chloro-biphenyl-2-ylmethyl)-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(10-04)** (500mg, 0.94mmol) following the procedure as described for 9-benzyloxy-6-biphenyl-2-ylmethyl-2-methyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(11-01)**.

LCMS: 514 (M+H).

Preparation of (12-01):



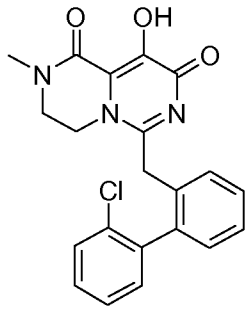
6-Biphenyl-2-ylmethyl-9-hydroxy-2-methyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a stirred solution of 9-benzyloxy-6-biphenyl-2-ylmethyl-2-methyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(11-01)** (350mg, 0.776mmol) in methanol (6mL) was added concentrated HCl (3mL) and the reaction mixture was stirred for 5 h at room temperature. After completion of the reaction, the volume of the reaction mixture was reduced by evaporation and the resultant mixture was basified with saturated aqueous $NaHCO_3$ solution. The mixture was extracted with 10% methanol in dichloromethane, the separated

organic part was dried over sodium sulfate and concentrated to get a crude product, which was purified by prep-HPLC (ammonium acetate-methanol) to afford 6-biphenyl-2-ylmethyl-9-hydroxy-2-methyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(12-01)** (68mg, 24.25%) as an off-white solid.

LCMS: 362.2 (M+H).

Preparation of (12-02):

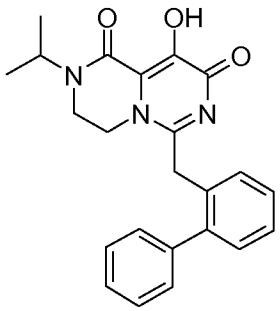


6-(2'-Chloro-biphenyl-2-ylmethyl)-9-hydroxy-2-methyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

6-(2'-Chloro-biphenyl-2-ylmethyl)-9-hydroxy-2-methyl-3,4-dihydro-2H-pyrazino [1,2-c] pyrimidine-1,8-dione (**12-02)** (215mg, 58.54%) was synthesized as an off-white solid from 9-benzyloxy-6-(2'-chloro-biphenyl-2-ylmethyl)-2-methyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(11-02)** (400mg, 0.887mmol) following the procedure as described for 6-biphenyl-2-ylmethyl-9-hydroxy-2-methyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione**(12-01)**.

LCMS: 396 (M+H).

Preparation of (12-03):

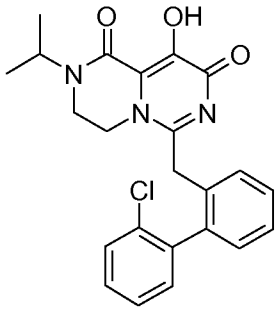


6-Biphenyl-2-ylmethyl-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

6-Biphenyl-2-ylmethyl-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(12-03)** (17mg, 19%) was synthesized as an off-white solid from 9-benzyloxy-6-biphenyl-2-ylmethyl-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(11-03)** (110mg, 0.229mmol) following the procedure as described for 6-biphenyl-2-ylmethyl-9-hydroxy-2-methyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(12-01)**.

LCMS:390.2 (M+H).

Preparation of (12-04):



6-(2'-Chloro-biphenyl-2-ylmethyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

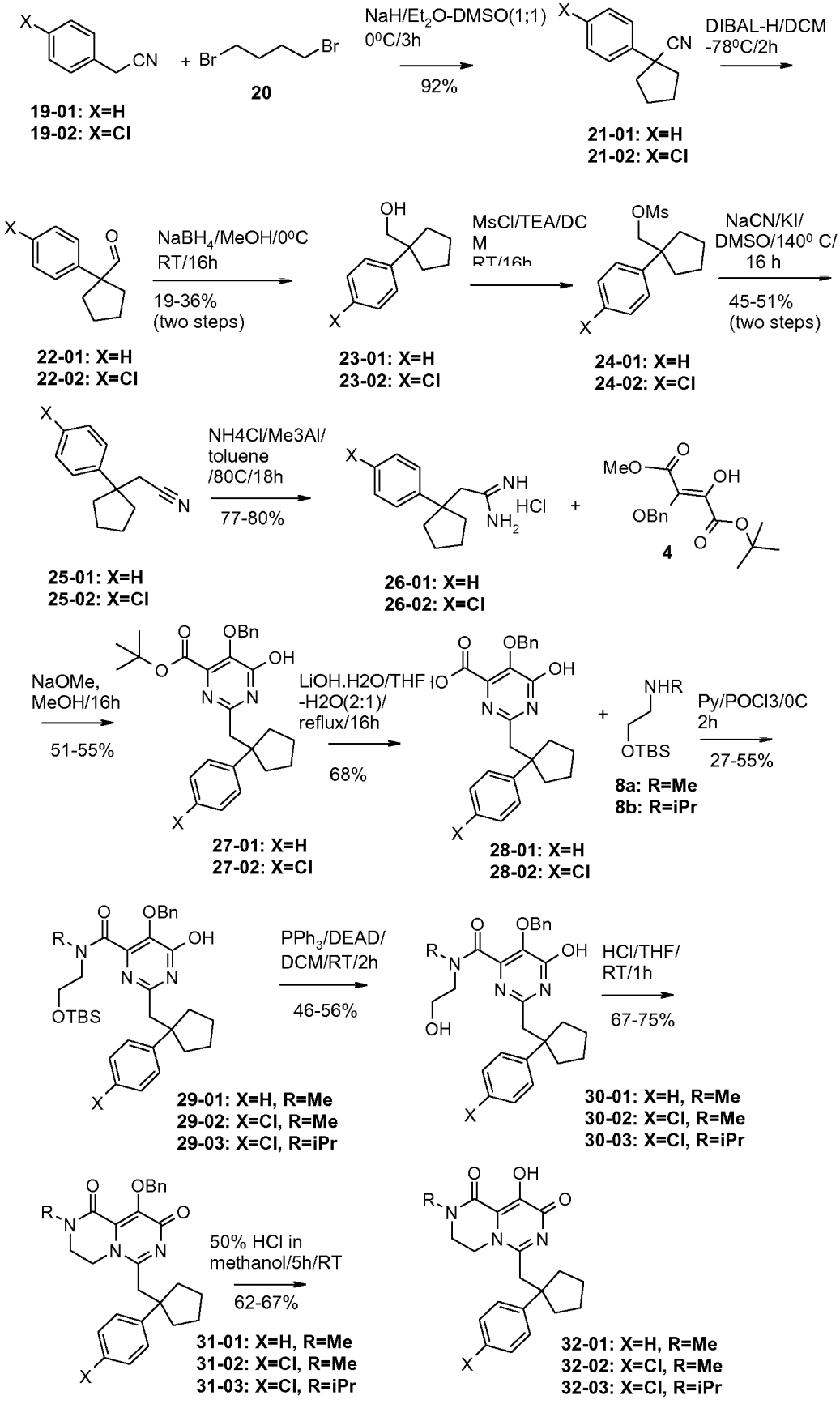
6-(2'-Chloro-biphenyl-2-ylmethyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(12-04)** (107mg, 37.07%) was synthesized as an off-white solid from 9-benzyloxy-6-(2'-chloro-biphenyl-2-ylmethyl)-8-hydroxy-2-isopropyl-3,4-dihydro-2H,8H-pyrazino[1,2-c]pyrimidin-1-one **(11-04)** (350mg, 0.682mmol) following the procedure as

described for 6-biphenyl-2-ylmethyl-9-hydroxy-2-methyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(12-01)**.

LCMS: 423.9 (M+H).

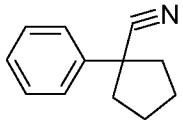
Synthesis of 32-01, 32-02 and 32-03:

Scheme 5


NaH/Et2O-DMSO(1;1)
0°C/3h
92%
DIBAL-H/DCM
-78°C/2h
19-01: X=H
19-02: X=Cl
20
21-01: X=H
21-02: X=Cl
NaBH4/MeOH/0°C
RT/16h
19-36%
(two steps)
MsCl/TEA/DC
M
NaCN/KI/
DMSO/140° C/
16 h
45-51%
(two steps)
22-01: X=H
22-02: X=Cl
23-01: X=H
23-02: X=Cl
24-01: X=H
24-02: X=Cl
NH4Cl/Me3Al/
toluene
/80C/18h
77-80%
25-01: X=H
25-02: X=Cl
26-01: X=H
26-02: X=Cl
4
NaOMe,
MeOH/16h
51-55%
LiOH.H2O/THF
-H2O(2:1)/
reflux/16h
68%
Py/POCl3/0C
2h
27-55%
8a: R=Me
8b: R=iPr
27-01: X=H
27-02: X=Cl
28-01: X=H
28-02: X=Cl
PPh3/DEAD/
DCM/RT/2h
46-56%
HCl/THF/
RT/1h
67-75%
29-01: X=H, R=Me
29-02: X=Cl, R=Me
29-03: X=Cl, R=iPr
30-01: X=H, R=Me
30-02: X=Cl, R=Me
30-03: X=Cl, R=iPr
50% HCl in
methanol/5h/RT
62-67%
31-01: X=H, R=Me
31-02: X=Cl, R=Me
31-03: X=Cl, R=iPr
32-01: X=H, R=Me
32-02: X=Cl, R=Me
32-03: X=Cl, R=iPr

Experimental:

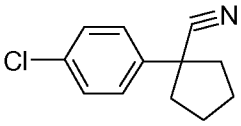
Preparation of (21-01):



1-Phenyl-cyclopentanecarbonitrile

To a suspension of sodium hydride (60%, 18.8 g, 470.08mmol) in dimethyl sulfoxide (125 mL) was added dropwise a mixture of phenyl acetonitrile **(19-01)** (25 g, 213.6mmol) and 1,4-dibromo-butane **(20)** (25.5 mL, 213.67mmol) dissolved in dimethyl sulfoxide : ether (300mL, 1:1). The mixture was stirred at room temperature for 3 h. After completion of the reaction, it was quenched with 1 N HCl. The mixture was extracted with ethyl acetate, the separated organic part was dried and concentrated to get a crude product which was purified using normal silica column using 3% ethyl acetate in hexane to afford 1-phenyl-cyclopentanecarbonitrile **(21-01)** (34g, 92.92%) as a yellow liquid.

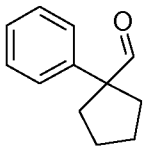
Preparation of (21-02):



1-(4-Chloro-phenyl)-cyclopentanecarbonitrile

1-(4-Chloro-phenyl)-cyclopentanecarbonitrile **(21-02)** (32.01g, 94%) was synthesized as a yellow liquid from (4-chloro-phenyl)-acetonitrile **(19-02)** (25 g, 165.56mmol) and 1,4-dibromo-butane **(20)** (19.7mL, 165.56mmol) following the procedure as described for 1-phenyl-cyclopentanecarbonitrile **(21-01)**.

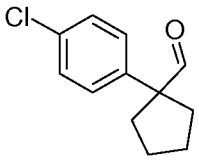
Preparation of (22-01):



1-Phenyl-cyclopentanecarbaldehyde

To a stirred solution of 1-phenyl-cyclopentanecarbonitrile **(21-01)** (23 gm, 134.50 mmol) in dichloromethane (270 mL), was added diisobutylaluminium hydride (25% in toluene, 190.9mL, 336.25mmol) at –78 °C. The mixture was stirred for 2h .After completion of the reaction, it was quenched with potassium sodium tartrate. The mixture was stirred for 16 h at room temperature, extracted with dichloromethane, washed with water and brine and the separated organic part was dried and evaporated to get 1-phenyl-cyclopentanecarbaldehyde **(22-01)** (23g) as a white solid as a crude product. This was directly used for next step.

Preparation of (22-02):

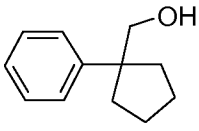


1-(4-Chloro-phenyl)-cyclopentanecarbaldehyde

1-(4-Chloro-phenyl)-cyclopentanecarbaldehyde (**22-02)** (66g, 98.23%) was synthesized from (4-chloro-phenyl)-acetonitrile **(21-02)** (66g, 321.95mmol) as a white solid as a crude product following the procedure as described for 1-phenyl-cyclopentanecarbaldehyde **(22-01)**.

GCMS:208(M).

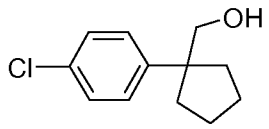
Preparation of (23-01):



(1-Phenyl-cyclopentyl)-methanol

To a stirred solution of 1-phenyl-cyclopentanecarbaldehyde **22-01** (23g, 132.18mmol) in methanol (300 mL) was added $NaBH_4$ (10.04g, 264.36mmol) at 0 °C. The mixture was stirred at room temperature for 16 h. After completion of the reaction, it was quenched with aqueous ammonium chloride solution. The mixture was concentrated as much as possible, then diluted with water, extracted with ethyl acetate and the separated organic part was dried over sodium sulfate and concentrated under reduced pressure to get a crude product which was purified using a normal silica column using 5% ethyl acetate in hexane to afford (1-phenyl-cyclopentyl)-methanol **(23-01)** (4.5g, 19.35%) as a yellow liquid.

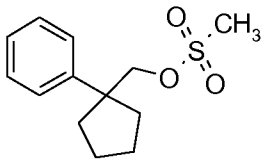
Preparation of (23-02):



[1-(4-Chloro-phenyl)-cyclopentyl]-methanol

[1-(4-Chloro-phenyl)-cyclopentyl]-methanol **(23-02)** (25g, 37.52%) was synthesized from 1-(4-chloro-phenyl)-cyclopentanecarbaldehyde **(22-02)** (66g, 317.3mmol) as a colourless liquid following the procedure as described for (1-phenyl-cyclopentyl)-methanol **(23-01)**.

Preparation of (24-01):

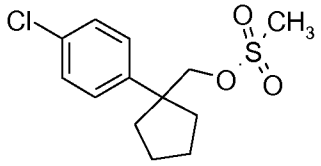


Methanesulfonic acid 1-phenyl-cyclopentylmethyl ester

To a stirred solution of 1-phenyl-cyclopentyl)-methanol **(23-01)** (9.1gm, 51.70mmol) in dichloromethane (100mL) was added triethyl amine (14.4mL, 104.96mmol) followed by methanesulfonyl chloride (5.09ml, 62.045 m mol) at cooling condition, it was stirred at room temperature for 16h. After completion of the reaction, the mixture was diluted with dichloromethane, washed with water, sodium bicarbonate solution and brine. The separated

organic part was dried over sodium sulfate and evaporated under reduced pressure to get methanesulfonic acid 1-phenyl-cyclopentylmethyl ester **(24-01)** (13g) as a crude product.

Preparation of (24-02):

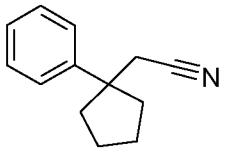


Methanesulfonic acid 1-(4-chloro-phenyl)-cyclopentylmethyl ester

Methanesulfonic acid 1-(4-chloro-phenyl)-cyclopentylmethyl ester **(24-02)** (32g, 93.08%) was synthesized from [1-(4-chloro-phenyl)-cyclopentyl]-methanol **(23-02)** (25g, 119.04mmol) as a crude product as a yellow liquid following the procedure as described for methanesulfonic acid 1-phenyl-cyclopentylmethyl ester **(24-01).**

GC-MS: 185(M).

Preparation of (25-01):

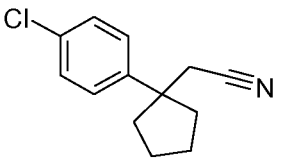


(1-Phenyl-cyclopentyl)-acetonitrile

To a stirred solution of methanesulfonic acid 1-phenyl-cyclopentylmethyl ester **(24-01)** (6g, 23.59mmol) in dimethyl sulfoxide (18mL) were added potassium iodide (392mg, 2.59mmol) and sodium cyanide (1.734g, 35.384mmol). The mixture was stirred for 140 °C for 16h. After completion of the reaction, water was added and the mixture was filtered through celite. The filtrate was extracted with ethyl acetate, dried and evaporated to get a crude product which was purified using a normal silica column using 15% ethyl acetate in hexane to afford (1-phenyl-cyclopentyl)-acetonitrile **(25-01)** (2.25g, 51.4%) as a yellow liquid.

GCMS:185(M).

Preparation of (25-02):

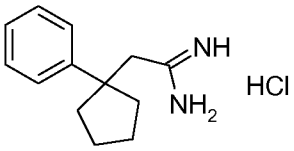


[1-(4-Chloro-phenyl)-cyclopentyl]-acetonitrile

[1-(4-Chloro-phenyl)-cyclopentyl]-acetonitrile **(25-02)** (12g, 49.16%) was synthesized from methanesulfonic acid 1-(4-chloro-phenyl)-cyclopentylmethyl ester **(24-02)** (32g, 111.11mmol) as a colourless liquid following the procedure as described for 1-phenyl-cyclopentyl)-acetonitrile **(25-01)**.

GCMS:219(M).

Preparation of (26-01):

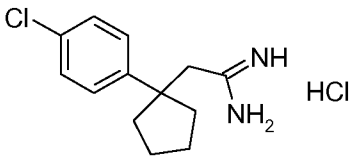


2-(1-Phenyl-cyclopentyl)-acetamidine HCl salt

2-(1-Phenyl-cyclopentyl)-acetamidine HCl salt **(26-01)** (4.2g, 77.7%) was synthesized from (1-phenyl-cyclopentyl)-acetonitrile **(25-01)** (4.2g, 22.703mmol) as a white gummy solid as a crude product following the procedure as described for 2-(2'-chloro-biphenyl-2-yl)-acetamidine hydrochloride salt **(5-02)**.

LCMS: 203(M+H).

Preparation of (26-02):

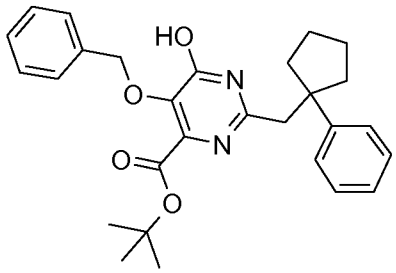


2-[1-(4-Chloro-phenyl)-cyclopentyl]-acetamidine HCl salt

2-[1-(4-Chloro-phenyl)-cyclopentyl]-acetamidine HCl salt **(26-02)** (6g, 80.21%) was synthesized from [1-(4-chloro-phenyl)-cyclopentyl]-acetonitrile **(25-02)** (6g, 27.39mmol) as a white gummy solid as a crude product following the procedure as described for 2-(2'-chloro-biphenyl-2-yl)-acetamidine hydrochloride salt **(5-02)**.

LCMS: 236.8(M+H).

Preparation of (27-01):

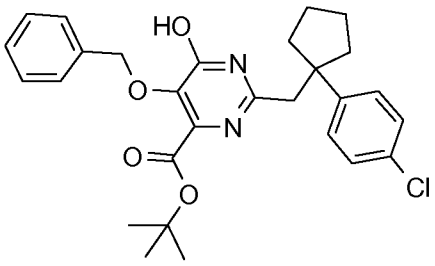


5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid tert-butyl ester

5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid tert-butyl ester **(27-01)** (4.5g, 51.8%) was synthesized from 2-(1-phenyl-cyclopentyl)-acetamidine HCl salt **(26-01)** (4.5g, 18.86mmol) and (E)-2-benzyloxy-3-hydroxy-but-2-enedioic acid 4-tert-butyl ester 1-methyl ester **(4)** (10.2g, 33.41mmol) as a yellow solid following the procedure as described for 5-benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester **(6-01)**.

LCMS: 461(M+H).

Preparation of (27-02):

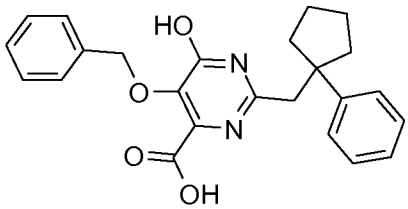


5-Benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester

5-Benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester **(27-02)** (12g, 55%) was synthesized from [1-(4-chloro-phenyl)-cyclopentyl]-acetonitrile **(26-02)** (12g, 44.03mmol) and (E)-2-benzyloxy-3-hydroxy-but-2-enedioic acid 4-tert-butyl ester 1-methyl ester **(4)** (23.49g, 76.27mmol) as a yellow solid following the procedure as described for 5-benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester **(6-01).**

LCMS: 495.2(M+H).

Preparation of (28-01):

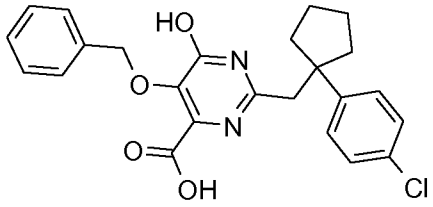


5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid

5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(28-01)** (2.7g, 68.33%) was synthesized from 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid tert-butyl ester **(27-01)** (4.5g, 9.77mmol) as a yellow solid following the procedure as described for 5-benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid **(7-01)**.

LCMS:405.2(M+H).

Preparation of (28-02):

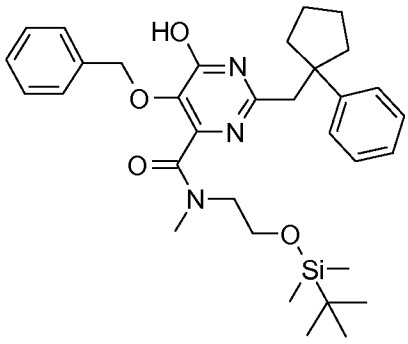


5-Benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid

5-Benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid **(28-02)** (7.3g, 68.6%) was synthesized from 5-benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester **(27-02)** (12g, 34.24mmol) as a white solid following the procedure as described for 5-benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid **(7-01)**.

LCMS:439.2(M+H).

Preparation of (29-01):



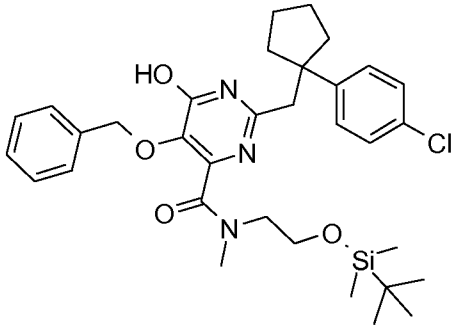
5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide

5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(29-01)** (1.05g, 27.29%) was synthesized from 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(28-01)** (2.7g, 6.683mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amine **(8-a)** (1.38g, 7.35mmol) as a yellow gummy liquid following the procedure as described for 5-benzyloxy-2-

biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(9-01).**

LCMS: 576.2 (M+H).

Preparation of (29-02):

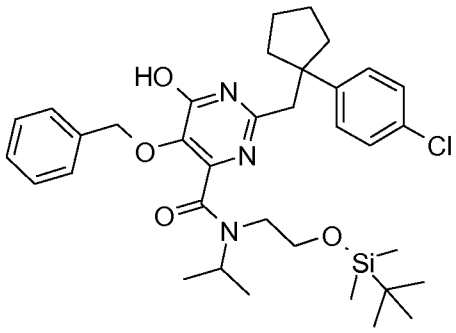


5-Benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide

5-Benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(29-02)** (2g, 47.85%) was synthesized from 5-benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid **(28-02)** (3g, 6.84mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amine **(8-a)** as a gummy solid (1.4g, 7.53mmol) following the procedure as described for 5-benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(9-01).**

LCMS: 610.4 (M+H).

Preparation of (29-03):

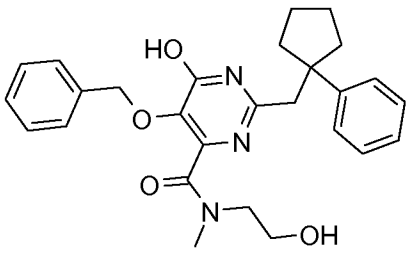


5-Benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide

5-Benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(29-03)** (3.5g, 55.85%) was synthesized from 5-benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid **(28-02)** (4.3g, 9.817mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amine **(8-b)** (2.34g, 10.79mmol) as a colourless gummy solid following the procedure as described for 5-benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(9-01).**

LCMS: 638.2 (M+H).

Preparation of (30-01):



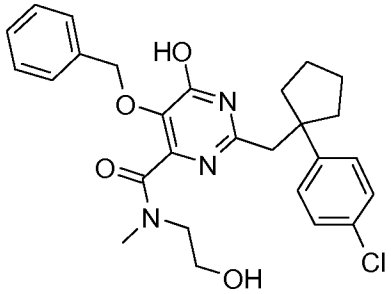
5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide

5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide **(30-01)** (600mg, 74.75%) was synthesized from 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(29-01)** (1.0g, 1.739mmol) as a yellow solid following the

procedure as described for 5-benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide **(10-01)**.

LCMS: 462.2(M+H).

Preparation of (30-02):

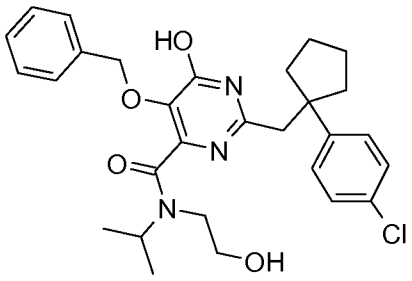


5-Benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide

5-Benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide **(30-02)** (1.1g, 67.53%) was synthesized from 5-benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(29-02)** (2g, 3.28 mmol) as an off-white solid following the procedure as described for 5-benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide **(10-01)**.

LCMS: 496.2(M+H).

Preparation of (30-03):

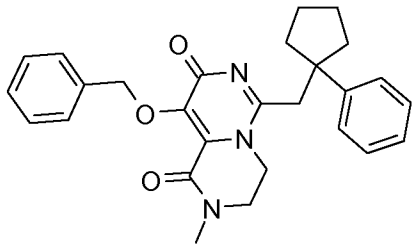


5-Benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide

5-Benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(30-03)** (2g, 69.57%) was synthesized from 5-benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide (**29-03)** (3.5g, 5.4mmol) as an off-white solid following the procedure as described for 5-benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide **(10-01)**.

LCMS: 524.4(M+H).

Preparation of (31-01):

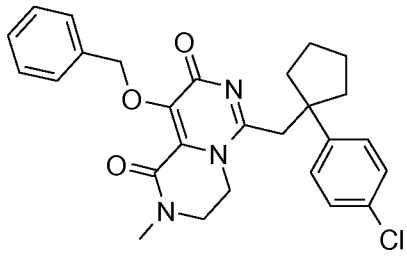


9-Benzyloxy-2-methyl-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

9-Benzyloxy-2-methyl-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(31-01)** (300mg, 56.69%) was synthesized from 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide **(30-01)** (550mg, 1.193mmol) as a white solid following the procedure as described for 9-benzyloxy-6-biphenyl-2-ylmethyl-2-methyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(11-01)**.

LCMS: 444.2(M+H).

Preparation of (31-02):

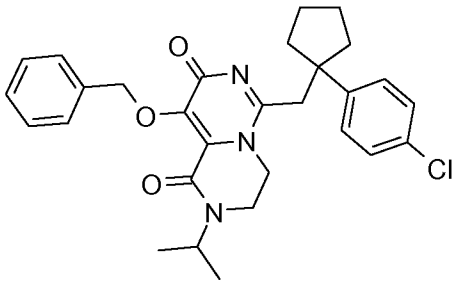


9-Benzyloxy-6-[1-(4-chloro-phenyl)-cyclopentylmethyl]-2-methyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

9-Benzyloxy-6-[1-(4-chloro-phenyl)-cyclopentylmethyl]-2-methyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(31-02)** (500mg, 51.88%) was synthesized from 5-benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide **(30-02)** (1g, 2.016mmol) as an off-white solid following the procedure as described for 9-benzyloxy-6-biphenyl-2-ylmethyl-2-methyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(11-01)**.

LCMS: 478.2 (M+H).

Preparation of (31-03):

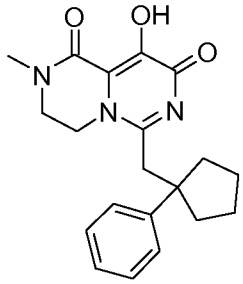


9-Benzyloxy-6-[1-(4-chloro-phenyl)-cyclopentylmethyl]-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

9-Benzyloxy-6-[1-(4-chloro-phenyl)-cyclopentylmethyl]-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **31-03** (900mg, 46.51%) was synthesized from 5-benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(30-03)** (2g, 3.824mmol) as a white solid following the procedure as described for 9-benzyloxy-6-biphenyl-2-ylmethyl-2-methyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(11-01)**.

LCMS: 506.2 (M+H).

Preparation of (32-01):

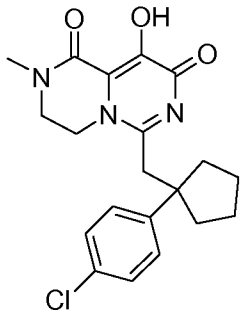


9-Hydroxy-2-methyl-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

9-Hydroxy-2-methyl-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(32-01)** (164mg, 69%) was synthesized from 9-benzyloxy-2-methyl-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(31-01)** (300mg, 0.67 mmol) as an off-white solid following the procedure as described for 6-biphenyl-2-ylmethyl-9-hydroxy-2-methyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(12-01)**.

LCMS: 354 (M+H).

Preparation of (32-02):



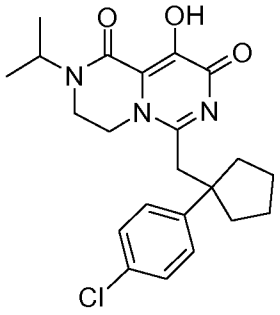
6-[1-(4-Chloro-phenyl)-cyclopentylmethyl]-9-hydroxy-2-methyl-3,4-dihydro-2H-pyrazino[1,2-c] pyrimidine-1,8-dione

6-[1-(4-Chloro-phenyl)-cyclopentylmethyl]-9-hydroxy-2-methyl-3,4-dihydro-2H-pyrazino[1,2-c] pyrimidine-1,8-dione **(32-02)** (296mg, 66.3%) was synthesized from 9-benzyloxy-6-[1-(4-

chloro-phenyl)-cyclopentylmethyl]-2-methyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(31-02)** (500mg, 1.151mmol) as an off-white solid following the procedure as described for 6-biphenyl-2-ylmethyl-9-hydroxy-2-methyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(12-01)**.

LCMS: 388.2 (M+H).

Preparation of (32-03):



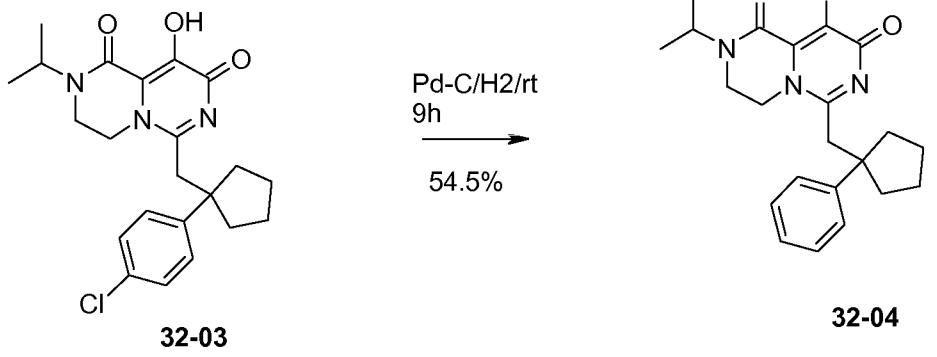
6-[1-(4-Chloro-phenyl)-cyclopentylmethyl]-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino [1,2-c] pyrimidine-1,8-dione

6-[1-(4-Chloro-phenyl)-cyclopentylmethyl]-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c] pyrimidine-1,8-dione **(32-03)** (465mg, 62.8%) was synthesized from 9-benzyloxy-6-[1-(4-chloro-phenyl)-cyclopentylmethyl]-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(31-03)** (900mg, 1.779mmol) as an off-white solid following the procedure as described for 6-biphenyl-2-ylmethyl-9-hydroxy-2-methyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(12-01)**.

LCMS: 416 (M+H).

Synthesis of 32-04:

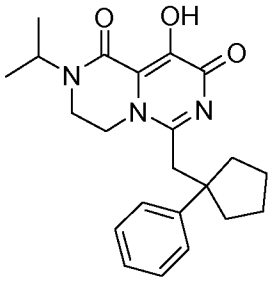
Scheme 6



32-03 **32-04**

Experimental:

Preparation of (32-04):



9-Hydroxy-2-isopropyl-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a stirred solution of 6-[1-(4-chloro-phenyl)-cyclopentylmethyl]-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(32-03)** (350mg, 0.842mmol) was added 35mg 10% Pd-C. Hydrogenation was conducted by balloon pressure at room temperature for 9h. After completion of the reaction, the mixture was filtered over a celite bed, which was washed with methanol, followed by 10% methanol in dichloromethane. The filtrate was concentrated to a pasty mass, which was washed with ether, followed by pentane to get 9-hydroxy-2-isopropyl-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(32-04)** (175mg, 54.5%) as a yellow solid.

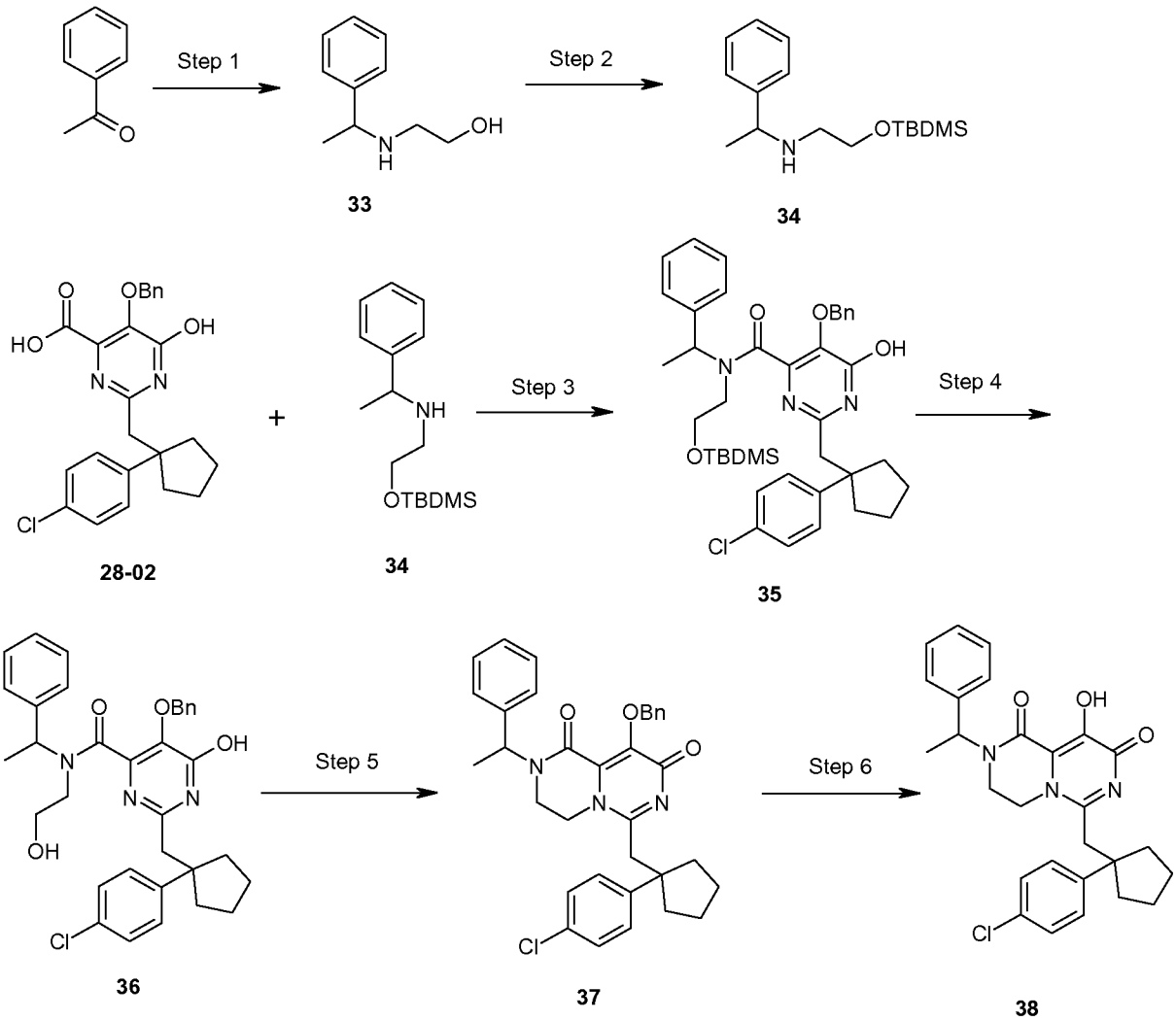
LCMS: 382(M+H).

Preparation of (38):

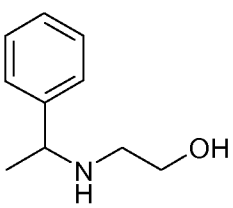
6-((1-(4-Chlorophenyl)cyclopentyl)methyl)-9-hydroxy-2-(1-phenylethyl)-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione **(38)**

The synthetic procedure used in this preparation is outlined in Scheme 7

Scheme 7



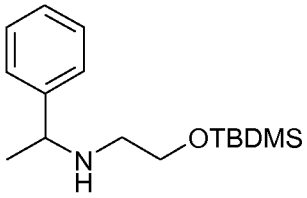
Preparation of (33):



Step 1: 2-(1-phenylethylamino)ethanol

A mixture of acetophenone (2.00g, 16.6 mmol, Eq: 1.00), 2-aminoethanol (3.05 g, 49.9 mmol, Eq: 3.00) and titanium(IV) isopropoxide (6.15 g, 6.41 ml, 21.6 mmol, Eq: 1.3) in absolute methanol (25 ml) was stirred under nitrogen at room temperature for 48 hrs. Sodium borohydride (630 mg, 16.6 mmol, Eq: 1.00) was then added at 0 °C and the resulting mixture was stirred for an additional 2 hr. The reaction was then quenched by adding water (1 ml). Stirring was continued at room temperature for 20 min., then the reaction mixture was acidified with 1N HCl. After filtration over a pad of Celite, washing with ethyl acetate, any drying over magnesium sulfate, the mixture was concentrated to obtain 2-(1-phenylethylamino)ethanol (oil, 2.71 g, 16.4 mmol, 98.5 % yield).

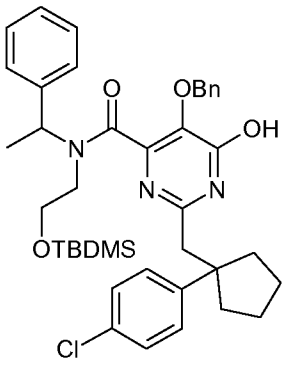
Preparation of (34):



Step 2: 2-(tert-Butyldimethylsilyloxy)-N-(1-phenylethyl)ethanamine

To a strirred solution of 2-(1-phenylethylamino)ethanol **(33)** (2.71 g, 16.4 mmol, Eq: 1.00) in dichloromethane (60 ml) were added diisopropylethylamine (2.97 g, 4.01 ml, 23.0 mmol, Eq: 1.4) followed by tert-butyldimethylsilyl chloride (2.72 g, 18.0 mmol, Eq: 1.1) at room temperature under nitrogen atmosphere. The resulting solution was stirred for 16 hrs and then it was poured into water (200 ml). The organic layer was separated, washed with brine, and dried with $MgSO_4$, concentrated, and chromatographed (silica gel, gradient 0 to 10% ethyl acetate-hexane) to obtain 2-(tert-butyldimethylsilyloxy)-N-(1-phenylethyl)ethanamine **(34)** (oil, 3.75 g, 13.4 mmol, 81.8 % yield).

Preparation of (35):

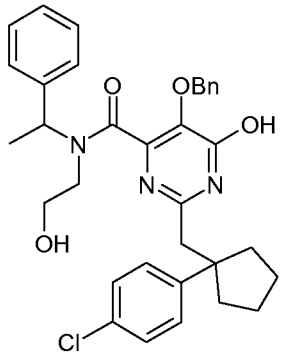


Step 3: 5-(Benzyloxy)-N-(2-(tert-butyldimethylsilyloxy)ethyl)-2-((1-(4-chlorophenyl)cyclopentyl)-methyl)-6-hydroxy-N-(1-phenylethyl)pyrimidine-4-carboxamide

To a solution of 5-(benzyloxy)-2-((1-(4-chlorophenyl)cyclopentyl)methyl)-6-hydroxypyrimidine-4-carboxylic acid **(28-02)** (170 mg, 387 µmol, Eq: 1.00) and 2-(tert-butyldimethylsilyloxy)-N-(1-phenylethyl)ethanamine **(34)** (108 mg, 387 µmol, Eq: 1.00) in pyridine (2.00 ml) was added $POCl_3$ (178 mg, 108 µl, 1.16 mmol, Eq: 3.00) at –10 °C (ethylene glycol-dry-ice bath), then the reaction mixture was stirred at 0 °C for 2 hr. The reaction mixture was quenched with ice cooled-water (0.5 ml), concentrated, and chromatographed (silica gel, gradient 5 to 30% ethyl acetate-hexane) to obtain 5-(benzyloxy)-N-(2-(tert-butyldimethylsilyloxy)ethyl)-2-((1-(4-chlorophenyl)cyclopentyl)methyl)-6-hydroxy-N-(1-phenylethyl)pyrimidine-4-carboxamide **(35)** (220 mg, 314 µmol, 81.1 % yield).

LC/MS: $(M+H)^+$ = 701.

Preparation of (36):

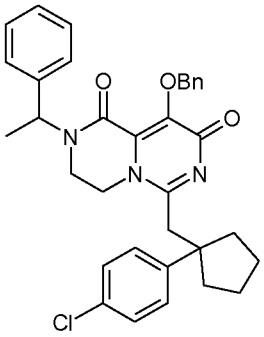


Step 4: 5-(Benzyloxy)-2-((1-(4-chlorophenyl)cyclopentyl)methyl)-6-hydroxy-N-(2-hydroxyethyl)-N-(1-phenylethyl)pyrimidine-4-carboxamide

To a stirred solution of 5-(benzyloxy)-N-(2-(tert-butyldimethylsilyloxy)ethyl)-2-((1-(4-chlorophenyl)cyclopentyl)methyl)-6-hydroxy-N-(1-phenylethyl)pyrimidine-4-carboxamide **(35)** (220 mg, 314 µmol, Eq: 1.00) in tetrahydrofuran (5 ml) was added HCl (1N) (471 µl, 471 µmol, Eq: 1.5) at room temperature. The reaction mixture was stirred for 6 hrs, neutralized with 1N NaOH aq. solution, extracted with ethyl acetate, dried ($MgSO_4$), concentrated and chromatographed (silica gel, gradient, 0 to 5% methanol-dichloromethane) to obtain 5-(benzyloxy)-2-((1-(4-chlorophenyl)cyclopentyl)methyl)-6-hydroxy-N-(2-hydroxyethyl)-N-(1-phenylethyl)pyrimidine-4-carboxamide **(36)** (white foam, 161.2 mg, 275 µmol, 87.6 % yield).

LC/MS: $(M+H)^+$ = 587

Preparation of (37):

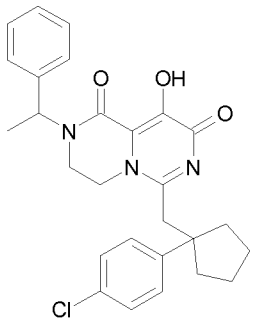


Step 5: 9-(Benzyloxy)-6-((1-(4-chlorophenyl)cyclopentyl)methyl)-2-(1-phenylethyl)-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione

To a stirred solution of 5-(benzyloxy)-2-((1-(4-chlorophenyl)cyclopentyl)methyl)-6-hydroxy-N-(2-hydroxyethyl)-N-(1-phenylethyl)pyrimidine-4-carboxamide **(36)** (158 mg, 270 µmol, Eq: 1.00) in dichloromethane (15 ml) at room temperature was added triphenylphosphine (106 mg, 404 µmol, Eq: 1.5). The reaction mixture was stirred for 10 min. Then DIAD (81.8 mg, 78.6 µl, 404 µmol, Eq: 1.5) was added. The reaction mixture was stirred for 18 hrs, concentrated, and chromatographed (silica gel, gradient 0 to 5% methanol-dichloromethane) to obtain 9-(benzyloxy)-6-((1-(4-chlorophenyl)cyclopentyl)methyl)-2-(1-phenylethyl)-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione **(37)** (colorless oil, 120 mg, 211 µmol, 78.4 % yield).

LC/MS: $(M+H)^+$ = 569.

Preparation of (38):



Step 6: 6-((1-(4-Chlorophenyl)cyclopentyl)methyl)-9-hydroxy-2-(1-phenylethyl)-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione

To a stirred solution of 9-(benzyloxy)-6-((1-(4-chlorophenyl)cyclopentyl)methyl)-2-(1-phenylethyl)-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione **(37)** (76 mg, 134 µmol, Eq: 1.00) in methanol (5 ml) was added HCl (conc) (195 mg, 163 µl, 5.35 mmol, Eq: 40) and heated at 70 °C for 48 hrs. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$ solution, extracted with dichloromethane, dried ($MgSO_4$), concentrated, and chromatographed (silica gel, gradient 0 to 5% methanol-dichloromethane) to obtain an off-white solid. The solid was triturated with diethyl ether, filtered, and dried to obtain 6-((1-(4-chlorophenyl)cyclopentyl)methyl)-9-hydroxy-2-(1-phenylethyl)-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione **(38)** (off-white powder, 51 mg, 107 µmol, 79.8 % yield).

LC/MS: $(M+H)^+$ = 478

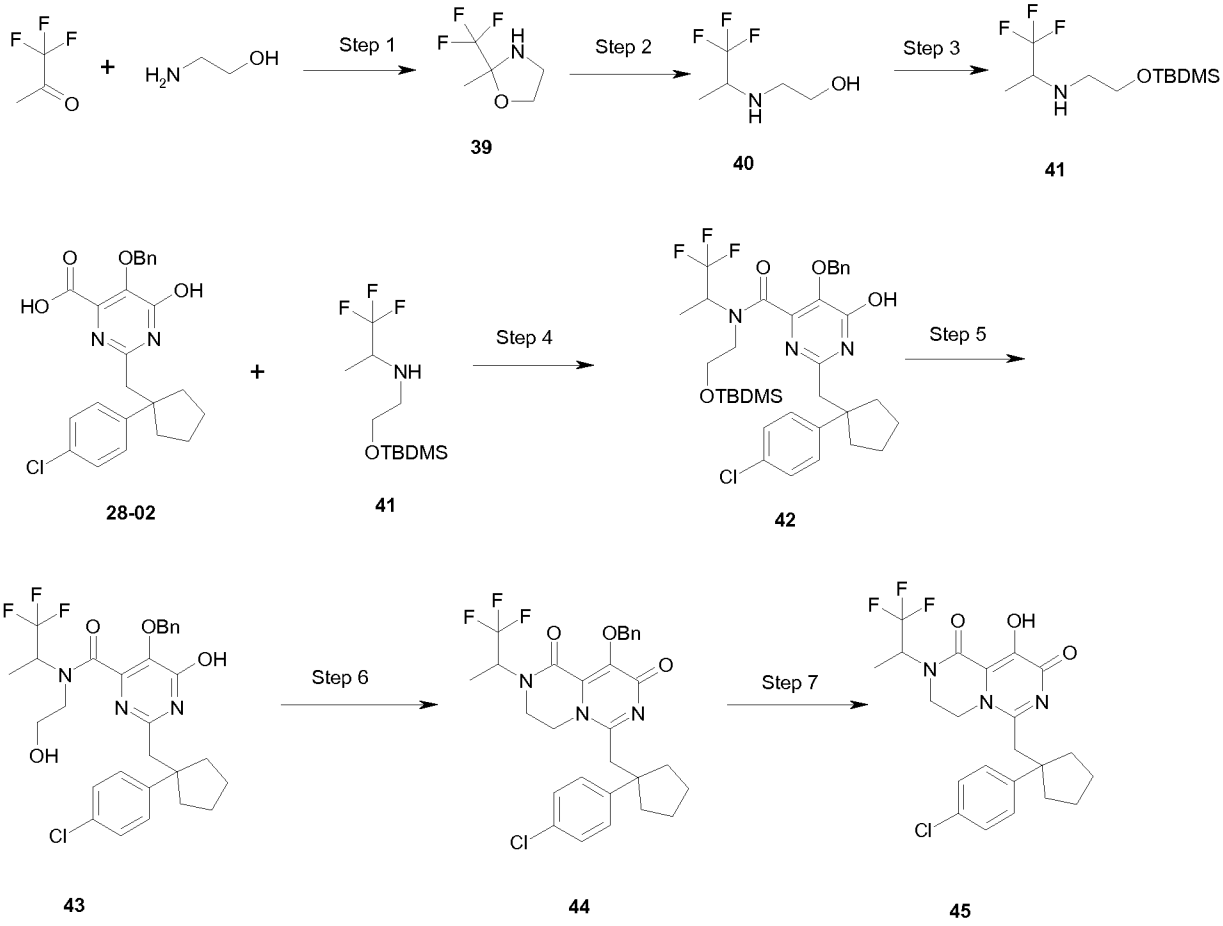
^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.47 (d, *J*=6.22 Hz, 4 H) 1.59 (br. s., 3 H) 1.78 (br. s., 4 H) 1.98 (s, 1 H) 2.26 (br. s., 3 H) 2.67 (br. s., 1 H) 2.85 (br. s., 2 H) 2.99 (d, *J*=11.87 Hz, 1 H) 3.19 (br. s., 1 H) 3.59 (br. s., 1 H) 5.70 (d, *J*=6.40 Hz, 1 H) 7.08 – 7.54 (m, 9 H) 12.19 (br. s., 1 H).

Preparation of (45):

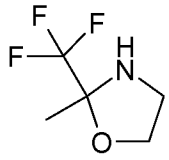
6-((1-(4-Chlorophenyl)cyclopentyl)methyl)-9-hydroxy-2-(1,1,1-trifluoropropan-2-yl)-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione **(45)**

The synthetic procedure used in this preparation is outlined in Scheme 8

Scheme 8



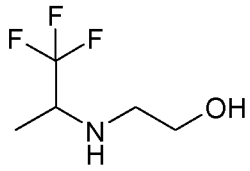
Preparation of (39):



Step 1: 2-Methyl-2-(trifluoromethyl)oxazolidine

A solution of 2-aminoethanol (10.15 g, 10.0 ml, 166 mmol, Eq: 1.00) in dichloromethane (250 ml) was cooled to –30 °C and stirred while 1,1,1-trifluoropropan-2-one (20.1 g, 16.1 ml, 179 mmol, Eq: 1.08), followed by molecular sieves (4Å, powder < 5 micron, activated; 20.0 g, 166 mmol, Eq: 1.00) were added. The mixture was stirred at –30 °C for 3 h and then allowed to warm to room temperature and left stirring for overnight. The mixture was filtered, washed with dichloromethane, and concentrated to obtain 2-methyl-2-(trifluoromethyl)oxazolidine **(39)** (oil,15.60 g, 101 mmol, 60.5 % yield).

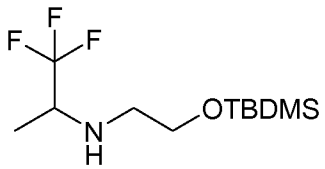
Preparation of (40):



Step 2: 2-(1,1,1-Trifluoropropan-2-ylamino)ethanol

To a solution of 2-methyl-2-(trifluoromethyl)oxazolidine **(39)** (5.58 g, 36.0 mmol, Eq: 1.00) in tetrahydrofuran (30 ml) at 0 °C was added lithium aluminum hydride (2M solution in tetrahydrofuran) (18.0 ml, 36.0 mmol, Eq: 1.00) and the reaction mixture was stirred at room temperature for 1 hr, quenched slowly with 1 ml of cold water, stirred for 20 min. Then 1 ml of 1N NaOH aq. solution was added and the reaction mixture was stirred for 10 min. 3 ml of water were added and the reaction mixture was stirred for 1 hr. Granular salt was formed. The white solid was filtered off, washed with diethyl ether (100 ml). The mixture was concentrated to obtain a crude product 2-(1,1,1-trifluoropropan-2-ylamino)ethanol **(40)** (oil, 5.50 g, 35.0 mmol, 97.3 % yield) which was used as such in the next step.

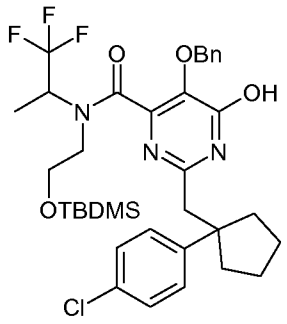
Preparation of (41):



Step 3: N-(2-(tert-Butyldimethylsilyloxy)ethyl)-1,1,1-trifluoropropan-2-amine

To a strirred solution of 2-(1,1,1-trifluoropropan-2-ylamino)ethanol **(40)** (5.50 g, 35.0 mmol, Eq: 1.00) in dichloromethane (100 ml) were added diisopropylethylamine (6.33 g, 8.56 ml, 49.0 mmol, Eq: 1.4) followed by *tert*-butyldimethylsilyl chloride (5.8 g, 38.5 mmol, Eq: 1.1) at room temperature under a nitrogen atmosphere. The resulting solution was stirred for 16 hrs and then it was poured into water (100 ml) and the organic layer was separated, washed with brine, dried ($MgSO_4$), concentrated, and chromatographed (silica gel, gradient 0 to 10% ethyl acetate-hexane) to obtain N-(2-(tert-butyldimethylsilyloxy)ethyl)-1,1,1-trifluoropropan-2-amine **(41)** (oil, 3.52 g, 13.0 mmol, 37.1 % yield).

Preparation of (42):

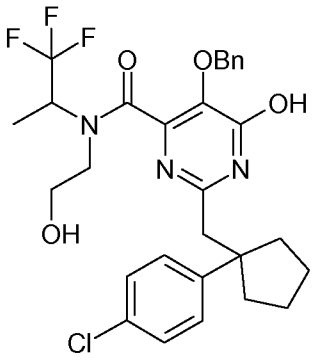


Step 4: 5-(Benzyloxy)-N-(2-(tert-butyldimethylsilyloxy)ethyl)-2-((1-(4-chlorophenyl)cyclopentyl)-methyl)-6-hydroxy-N-(1,1,1-trifluoropropan-2-yl)pyrimidine-4-carboxamide

To a solution of 5-(benzyloxy)-2-((1-(4-chlorophenyl)cyclopentyl)methyl)-6-hydroxypyrimidine-4-carboxylic acid **(28-02)** (150 mg, 342 µmol, Eq: 1.00) and N-(2-(tert-butyldimethylsilyloxy)ethyl)-1,1,1-trifluoropropan-2-amine **(41)** (102 mg, 376 µmol, Eq: 1.1) in pyridine (1.5 ml) was added $POCl_3$ (157 mg, 95.6 µl, 1.03 mmol, Eq: 3.00) at –10 °C (ethylene glycol-dry-ice bath), then the reaction mixture was stirred at 0 °C for 2 hr. Ice cooled-water was slowly added to the reaction mixture at 0 °C, which was extracted with ethyl acetate. The organic layer was washed with aqueous saturated $NaHCO_3$ solution, dried ($MgSO_4$), concentrated, and chromatographed (silica gel, gradient 5 to 50% ethyl acetate-hexane) to obtain 5-(benzyloxy)-N-(2-(tert-butyldimethylsilyloxy)ethyl)-2-((1-(4-chlorophenyl)cyclopentyl)methyl)-6-hydroxy-N-(1,1,1-trifluoropropan-2-yl)pyrimidine-4-carboxamide **(42)** (oil, 138 mg, 199 µmol, 58.3 % yield).

LC/MS: $(M+H)^+$ = 693.

Preparation of (43):

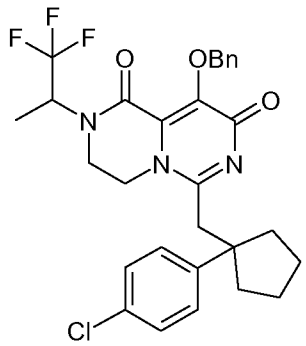


Step 5: 5-(Benzyloxy)-2-((1-(4-chlorophenyl)cyclopentyl)methyl)-6-hydroxy-N-(2-hydroxyethyl)-N-(1,1,1-trifluoropropan-2-yl)pyrimidine-4-carboxamide

To a stirred solution of 5-(benzyloxy)-N-(2-(tert-butyldimethylsilyloxy)ethyl)-2-((1-(4-chlorophenyl)cyclopentyl)methyl)-6-hydroxy-N-(1,1,1-trifluoropropan-2-yl)pyrimidine-4-carboxamide **(42)** (138 mg, 199 µmol, Eq: 1.00) in tetrahydrofuran (5 ml) was added HCl (1N) (299 µl, 299 µmol, Eq: 1.5) at room temperature and the reaction mixture was stirred for 4 hrs, neutralized with aqueous 1N NaoH solution, extracted with ethyl acetate, dried ($MgSO_4$), concentrated, and chromatographed (silica gel, gradient, 0 to 5% methanol-dichloromethane) to obtain 5-(benzyloxy)-2-((1-(4-chlorophenyl)cyclopentyl)methyl)-6-hydroxy-N-(2-hydroxyethyl)-N-(1,1,1-trifluoropropan-2-yl)pyrimidine-4-carboxamide **(43)** (white foam, 102 mg, 176 µmol, 88.5 % yield).

LC/MS: $(M+H)^+$ = 579

Preparation of (44):



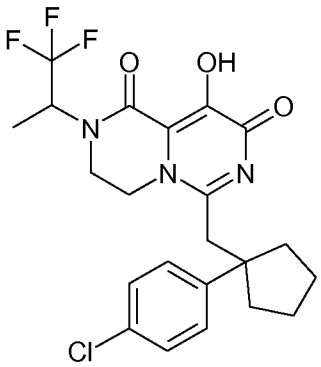
Step 6: 9-(Benzyloxy)-6-((1-(4-chlorophenyl)cyclopentyl)methyl)-2-(1,1,1-trifluoropropan-2-yl)-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione

To a stirred solution of 5-(benzyloxy)-2-((1-(4-chlorophenyl)cyclopentyl)methyl)-6-hydroxy-N-(2-hydroxyethyl)-N-(1,1,1-trifluoropropan-2-yl)pyrimidine-4-carboxamide **(43)** (102 mg, 176 µmol, Eq: 1.00) in dichloromethane (5 ml) was added triphenylphosphine (69.4 mg, 265 µmol, Eq: 1.5) at room temperature and the reaction mixture was stirred for 10 min. Then DIAD (53.5 mg, 51.5 µl, 265 µmol, Eq: 1.5) was added and the reaction mixture was stirred for 18 hrs at room temperature, concentrated, and chromatographed (silica gel, gradient, 0 to 5% methanol-dichloromethane) to obtain 9-(benzyloxy)-6-((1-(4-chlorophenyl)cyclopentyl)methyl)-

2-(1,1,1-trifluoropropan-2-yl)-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione **(44)** (white foam, 90.8 mg, 162 µmol, 91.9 % yield).

LC/MS: $(M+H)^+$ = 561

Preparation of (45):



Step 7: 6-((1-(4-Chlorophenyl)cyclopentyl)methyl)-9-hydroxy-2-(1,1,1-trifluoropropan-2-yl)-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione

To a stirred solution of 9-(benzyloxy)-6-((1-(4-chlorophenyl)cyclopentyl)methyl)-2-(1,1,1-trifluoropropan-2-yl)-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione **(44)** (90.8 mg, 162 µmol, Eq: 1.00) in methanol (5 ml) was added HCl (conc) (240 mg, 0.2 ml, 6.58 mmol, Eq: 40.6) and heated at 70 °C for 18 hrs. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$ solution, extracted with dichloromethane, dried ($MgSO_4$), concentrated, triturated with diethyl ether, filtered, and dried to obtain 6-((1-(4-chlorophenyl)cyclopentyl)methyl)-9-hydroxy-2-(1,1,1-trifluoropropan-2-yl)-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione **(45)** (pink powder, 40.1 mg, 85.3 µmol, 52.6 % yield).

LC/MS: $(M+H)^+$ = 470.

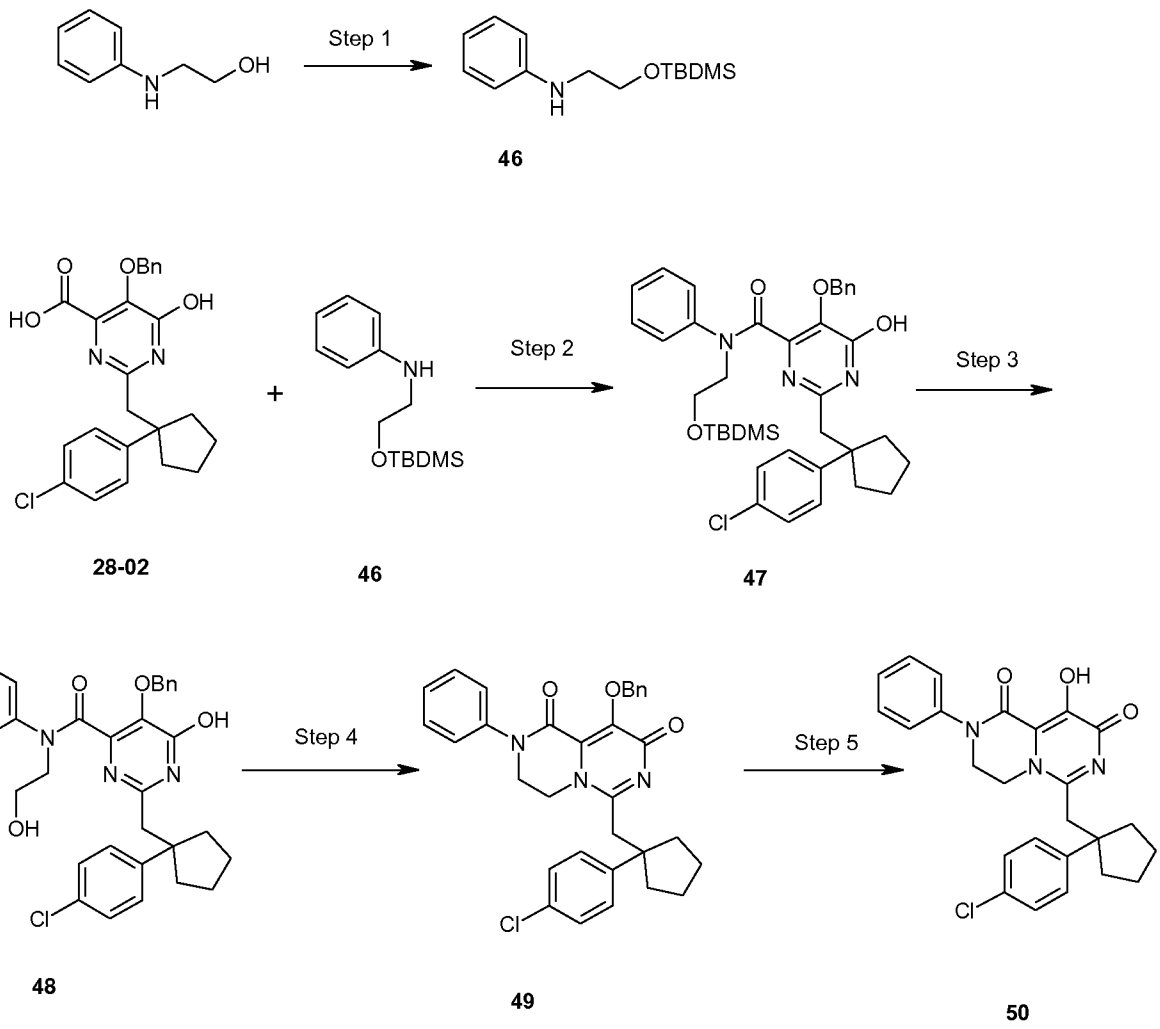
^{1}H NMR (400 MHz, DMSO-d_6) ppm 1.36 (d, *J*=7.03 Hz, 3 H) 1.62 (br. s., 2 H) 1.74 – 1.97 (m, 4 H) 2.19 – 2.39 (m, 2 H) 2.83 – 3.03 (m, 3 H) 3.19 – 3.29 (m, 1 H) 3.65 – 3.77 (m, 1 H) 5.24 (dt, *J*=15.25, 7.56 Hz, 1 H) 7.13 – 7.42 (m, 4 H) 11.53 (br. s., 1 H).

Preparation of (50):

6-((1-(4-Chlorophenyl)cyclopentyl)methyl)-9-hydroxy-2-phenyl-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione **(50)**

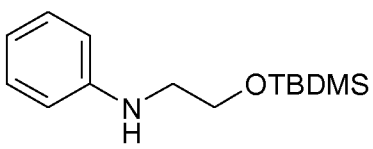
The synthetic procedure used in this preparation is outlined in Scheme 9

Scheme 9



Scheme 9

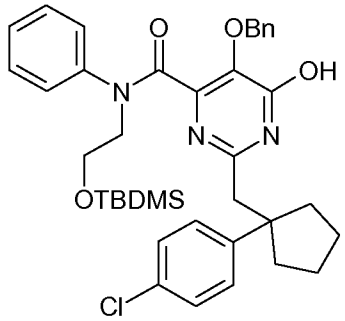
Preparation of (46):



Step 1 N-(2-(tert-Butyldimethylsilyloxy)ethyl)aniline

To a strirred solution of 2-(phenylamino)ethanol (10 g, 72.9 mmol, Eq: 1.00) in dichloromethane (200 ml) were added diisopropylethylamine (13.2 g, 17.8 ml, 102 mmol, Eq: 1.4) followed by *tert*-butyldimethylsilyl chloride (11.0 g, 72.9 mmol, Eq: 1.00) at room temperature under a nitrogen atmosphere. The resulting solution was stirred for 16 hrs and then it was poured into water (200 ml) and the organic layer was separated, washed with brine, dried ($MgSO_4$), concentrated, and chromatographed (silica gel, gradient 0 to 10% ethyl acetate-hexane) to obtain N-(2-(tert-butyldimethylsilyloxy)ethyl)aniline **(46)** (8.45 g, 33.6 mmol, 46.1 % yield).

Preparation of (47):

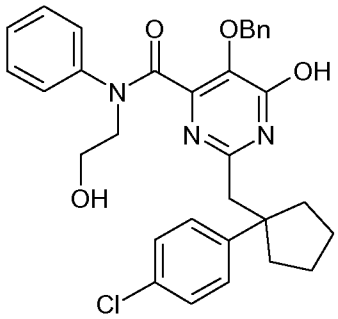


Step 2: 5-(Benzyloxy)-N-(2-(tert-butyldimethylsilyloxy)ethyl)-2-((1-(4-chlorophenyl)cyclopentyl)-methyl)-6-hydroxy-N-phenylpyrimidine-4-carboxamide

To a solution of 5-(benzyloxy)-2-((1-(4-chlorophenyl)cyclopentyl)methyl)-6-hydroxypyrimidine-4-carboxylic acid **(28-02)** (200 mg, 456 µmol, Eq: 1.00) and N-(2-(tert-butyldimethylsilyloxy)ethyl)aniline **(46)** (126 mg, 501 µmol, Eq: 1.1) in pyridine (2.00 ml) was added $POCl_3$ (210 mg, 127 µl, 1.37 mmol, Eq: 3.00) at –10 °C (ethylene glycol-dry-ice bath), then the reaction mixture was stirred at 0 °C for 2 hr. Ice cooled water was slowly added to the reaction mixture at 0 °C, the reaction mixture was extracted with ethyl acetate, the organic layer was washed with aqueous saturated $NaHCO_3$ solution, dried ($MgSO_4$), concentrated, and chromatographed (silica gel, gradient 5 to 30% ethyl acetate-hexane) to obtain 5-(benzyloxy)-N-(2-(tert-butyldimethylsilyloxy)ethyl)-2-((1-(4-chlorophenyl)cyclopentyl)methyl)-6-hydroxy-N-phenylpyrimidine-4-carboxamide **(47)** (colorless oil, 287 mg, 427 µmol, 93.7 % yield).

LC/MS: $(M+H)^+$ = 673.

Preparation of (48):

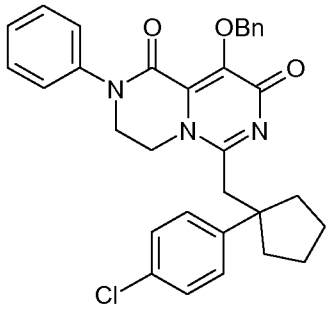


Step 3: 5-(Benzyloxy)-2-((1-(4-chlorophenyl)cyclopentyl)methyl)-6-hydroxy-N-(2-hydroxyethyl)-N-phenylpyrimidine-4-carboxamide

To a stirred solution of 5-(benzyloxy)-N-(2-(tert-butyldimethylsilyloxy)ethyl)-2-((1-(4-chlorophenyl)cyclopentyl)methyl)-6-hydroxy-N-phenylpyrimidine-4-carboxamide **(47)** (287 mg, 427 µmol, Eq: 1.00) in tetrahydrofuran (10 ml) was added HCl (1N) (640 µl, 640 µmol, Eq: 1.5) at room temperature and the reaction mixture was stirred for 6 hrs, neutralized with 1N NaOH aqueous solution, extracted with ethyl acetate, dried ($MgSO_4$), concentrated, and chromatographed (silica gel, gradient, 0 to 5% methanol-dichloromethane) to obtain 5-(benzyloxy)-2-((1-(4-chlorophenyl)cyclopentyl)methyl)-6-hydroxy-N-(2-hydroxyethyl)-N-phenylpyrimidine-4-carboxamide **(48)** (white foam, 179 mg, 321 µmol, 75.1 % yield).

LC/MS: $(M+H)^+$ = 559.

Preparation of (49):

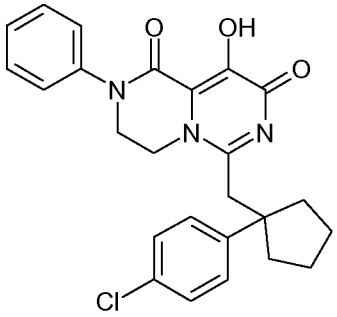


Step 4: 9-(Benzyloxy)-6-((1-(4-chlorophenyl)cyclopentyl)methyl)-2-phenyl-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione

To a stirred solution of 5-(benzyloxy)-2-((1-(4-chlorophenyl)cyclopentyl)methyl)-6-hydroxy-N-(2-hydroxyethyl)-N-phenylpyrimidine-4-carboxamide **(48)** (100.1 mg, 179 µmol, Eq: 1.00) in dichloromethane (5 ml) at room temperature was added triphenylphosphine (70.6 mg, 269 µmol, Eq: 1.5) and stirred for 10 min. Then DIAD (54.4 mg, 52.3 µl, 269 µmol, Eq: 1.5) was added and the reaction mixture was stirred for 18 hrs, concentrated, and chromatographed (silica gel, gradient 0 to 5% methanol-dichloromethane) to obtain 9-(benzyloxy)-6-((1-(4-chlorophenyl)cyclopentyl)methyl)-2-phenyl-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione **(49)** (white foam, 88.5 mg, 164 µmol, 91.4 % yield).

LC/MS: $(M+H)^+$ = 541

Preparation of (50):



Step 5: 6-((1-(4-Chlorophenyl)cyclopentyl)methyl)-9-hydroxy-2-phenyl-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione

To a stirred solution of 9-(benzyloxy)-6-((1-(4-chlorophenyl)cyclopentyl)methyl)-2-phenyl-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione **(49)** (88.5 mg, 164 µmol, Eq: 1.00) in methanol (5 ml) was added HCl (conc) (240 mg, 0.2 ml, 6.58 mmol, Eq: 40.2). The reaction mixture was heated at 70 °C for 18 hrs, neutralized with saturated aqueous $NaHCO_3$ solution, extracted with dichloromethane, dried ($MgSO_4$), concentrated, triturated with diethyl ether, filtered, and dried to obtain 6-((1-(4-chlorophenyl)cyclopentyl)methyl)-9-hydroxy-2-phenyl-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione **(50)** (pink powder, 48.2 mg, 107 µmol, 65.4 % yield).

LC/MS: $(M+H)^+$ = 450

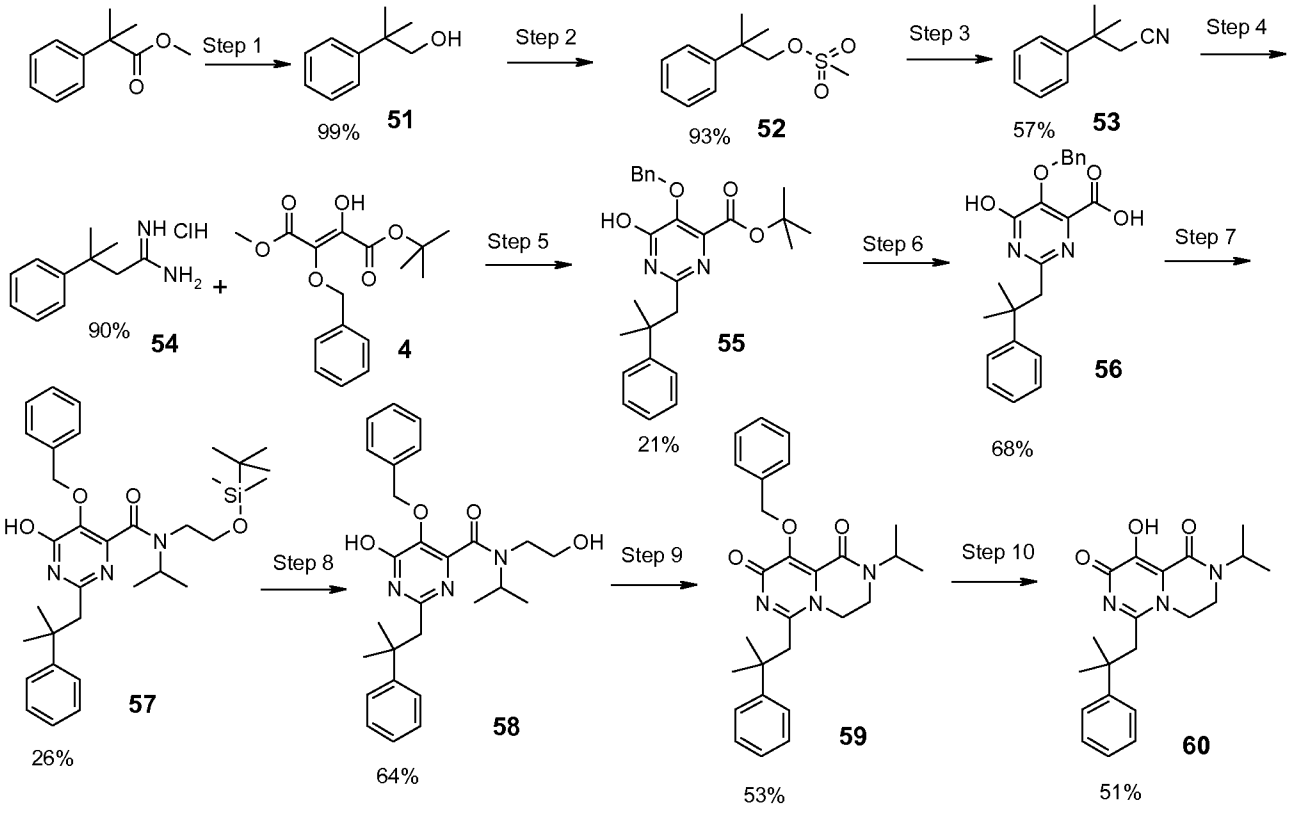
^{1}H NMR (400 MHz, DMSO–d_6) ppm 1.63 (br. s., 2 H) 1.75 – 1.99 (m, 4 H) 2.21 – 2.39 (m, 2 H) 2.98 (s, 2 H) 3.56 (br. s., 2 H) 3.78 (br. s., 2 H) 7.20 – 7.57 (m, 9 H) 12.95 – 13.74 (m, 1 H).

Preparation of (60):

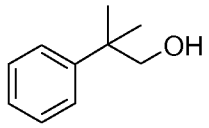
9-Hydroxy-2-isopropyl-6-(2-methyl-2-phenyl-propyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 10:

Scheme 10



Preparation of (51):

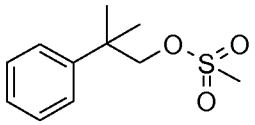


Step 1: 2-Methyl-2-phenyl-propan-1-ol

Methyl 2-methyl-2-phenylpropanoate (10.8 g, 60.6 mmol, Eq: 1.00) in tetrahydrofuran (193 ml) was cooled to 0 °C, lithium aluminium hydride was added (30.3 ml, 60.6 mmol, Eq: 1.00) via a syringe over 5 minutes. The mixture was stirred at 0 °C for 3 hours, and 2.3 ml water was added over 2 minutes. The mixture was stirred for 10 minutes, 2.3 ml 1N NaOH was added, the mixture was stirred for 5 minutes (a gel forms), 7 ml water was added, the mixture was stirred for 15 minutes, filtered through a pad of celite. The celite was washed with ether and the solvent was removed under vacuum to give methyl-2-phenyl-propan-1-ol **(51)** (9.0 g, 99%) as a clear oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.23 (s, 6 H) 3.43 (d, *J*=5.27 Hz, 2 H) 4.66 (t, *J*=5.27 Hz, 1 H) 7.06 – 7.51 (m, 5 H).

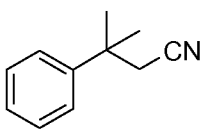
Preparation of (52):



Step 2: 2-Methyl-2-phenylpropyl methanesulfonate

2-Methyl-2-phenylpropan-1-ol **(51)** (8.5 g, 56.6 mmol, Eq: 1.00) was stirred in dichloromethane (90.4 ml) at 0 °C, triethylamine (6.87 g, 9.46 ml, 67.9 mmol, Eq: 1.2) and then methanesulfonyl chloride (7.13 g, 4.82 ml, 62.2 mmol, Eq: 1.1) were added over 3 minutes. The reaction mixture was stirred at 0 °C for 30 minutes, removed from the ice bath and allowed to warm to room temperature and stirred for 15 hours. The reaction mixture was diluted with dichloromethane, washed with water, saturated sodium bicarbonate, and brine, and dried with magnesium sulfate. The solvent was removed on a rotary evaporator to give 2-methyl-2-phenylpropyl methanesulfonate **(52)** as a clear oil, (12.0 g, 93%).

Preparation of (53):

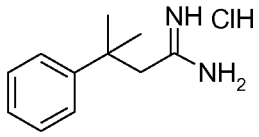


Step 3: 3-Methyl-3-phenylbutanenitrile

2-Methyl-2-phenylpropyl methanesulfonate **(52)** (12 g, 52.6 mmol) was stirred in dimethyl sulfoxide (106 ml), sodium cyanide (10.3 g, 210 mmol, Eq: 4) was added and the reaction mixture was heated to 110 °C for 20 hours. The reaction mixture was cooled, diluted with water, extracted three times with ether, washed with ether, water, and brine, and dried over magnesium sulfate. The solvent was removed on a rotary evaporator. Chromatography was conducted (2% to 15% over 20 min on a 40g silica gel column) to give 3-methyl-3-phenylbutanenitrile **(53)** as a clear oil (4.8 g, 57%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.41 (s, 6 H) 2.92 (s, 2 H) 7.11 - 7.53 (m, 5 H).

Preparation of (54):

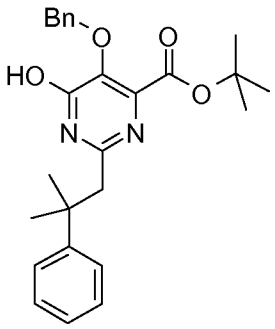


Step 4: 3-Methyl-3-phenylbutanimidamide

Ammonium chloride (2.52 g, 47.1 mmol, Eq: 3) as a suspension in toluene (56.8 ml) was cooled to 0 °C, trimethylaluminum (23.6 ml, 47.1 mmol, Eq: 3) was added via a syringe. The reaction mixture was stirred for 5 minutes, allowed to warm to room temperature and stirred at room temperature for 2.0 hours. Then 3-methyl-3-phenylbutanenitrile **(53)** (2.5 g, 15.7 mmol, Eq: 1.00) dissolved in toluene was added in two 5 ml aliquots. The reaction mixture was heated to 80 °C for 24 hours, and then cooled. About 10g silica gel in dichloromethane were added. The reaction mixture was stirred for 45 minutes, filtered through a sintered glass funnel and washed to a solid pad with a minimum amount of methanol: The solvent was removed on a rotary evaporator to give 325 mg white solid, which was not the product. The solid from the filter was placed in 1:1 dichloromethane/toluene = 50 ml. Then 50 grams silica gel were added and the reaction mixture was stirred at room temperature overnight. The mixture was filtered through a sintered glass funnel to give a milky solution, the filter was washed four times with methanol (total of about 80 ml). The solvents were removed from filtrate on a rotary evaporator and the residue was dried under high vacuum to give 3-methyl-3-phenylbutanimidamide hydrochloride **(54)** as a white solid (3.0 g, 90%).

LC/MS calcd. for $C_{11}H_{16}N_2$ (m/e) 176.26, obsd. 177.1 [M+H, ES^+].

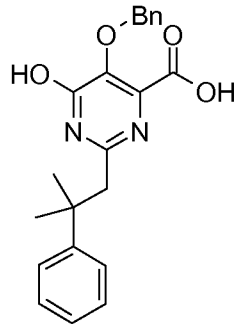
Preparation of (55):



Step 5: tert-Butyl 5-(benzyloxy)-6-hydroxy-2-(2-methyl-2-phenylpropyl)pyrimidine-4-carboxylate

4-tert-Butyl 1-methyl 2-(benzyloxy)-3-hydroxyfumarate **(4)** (652 mg, 2.12 mmol, Eq: 1.5,) and 3-methyl-3-phenylbutanimidamide hydrochloride **(54)** (300 mg, 1.41 mmol, Eq: 1.00) were stirred in methanol (7.2 ml). The reaction mixture was cooled to 0 °C and sodium methoxide (229 mg, 4.23 mmol, Eq: 3) (powdered, Aldrich) was added. The reaction mixture was stirred at room temperature. The reaction mixture is a suspension. It was stirred overnight. 5 ml 1 N aqueous HCl was added and the mixture was diluted with water, filtered through a sintered glass funnel. The solid was washed with water. The solid was placed under high vacuum to dry to give tert-butyl 5-(benzyloxy)-6-hydroxy-2-(2-methyl-2-phenylpropyl)pyrimidine-4-carboxylate as a yellow solid (260 mg, 21%) as a 1:1 mixture of tert-butyl 5-(benzyloxy)-6-hydroxy-2-(2-methyl-2-phenylpropyl)pyrimidine-4-carboxylate **(55)** and 3-methyl-3-phenylbutanimidamide. The product was used without further purification.

Preparation of (56):

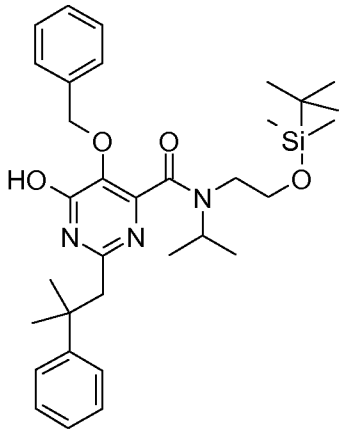


Step 6: 5-(Benzyloxy)-6-hydroxy-2-(2-methyl-2-phenylpropyl)pyrimidine-4-carboxylic acid

tert-Butyl 5-(benzyloxy)-6-hydroxy-2-(2-methyl-2-phenylpropyl)pyrimidine-4-carboxylate **(55)** (260 mg, 598 µmol, Eq: 1.00) was stirred in tetrahydrofuran/water. Lithium hydroxide monohydrate (126 mg, 2.99 mmol, Eq: 5) was added. The reaction mixture was heated at 85 °C for 7 hours, cooled, and stirred at room temperature for 16 hours. 1 N HCl was added until precipitate forms (about 10 ml). The mixture was diluted with water, extracted three times with ethyl acetate, washed with brine and dried over magnesium sulfate. The solvent was removed on a rotary evaporator to give 5-(benzyloxy)-6-hydroxy-2-(2-methyl-2-phenylpropyl)pyrimidine-4-carboxylic acid **(56)** as a white solid (155 mg, 68%).

LC/MS calcd. for $C_{22}H_{22}N_2O_4$ (m/e) 378.43, obsd. 379.3 [M+H, ES^+].

Preparation of (57):

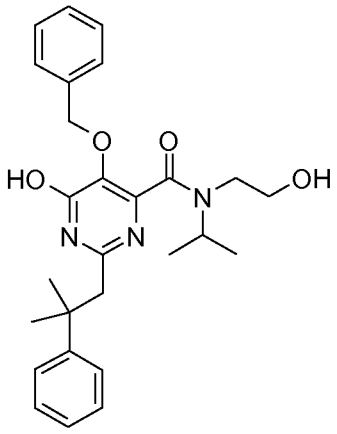


Step 7: 5-(Benzyloxy)-N-(2-(tert-butyldimethylsilyloxy)ethyl)-6-hydroxy-N-isopropyl-2-(2-methyl-2-phenylpropyl)pyrimidine-4-carboxamide

N-(2-(tert-Butyldimethylsilyloxy)ethyl)propan-2-amine **(8b)** (98.0 mg, 451 µmol, Eq: 1.1, prepared as previously described) was added to 5-(benzyloxy)-6-hydroxy-2-(2-methyl-2-phenylpropyl)pyrimidine-4-carboxylic acid **(56)** (155 mg, 410 µmol, Eq: 1.00), then pyridine (2.5 ml) was added, and the reaction mixture was cooled to –10 °C with stirring. $POCl_3$ (188 mg, 115 µl, 1.23 mmol, Eq: 3) was added dropwise, then the reaction mixture was stirred at –10 °C for 1 hour, allowed to warm to 0 °C and stirred for one hour. 10 drops of water were added at 0 °C, the reaction mixture was stirred for 5 min and the solvent was removed on a rotary evaporator to almost dryness. The mixture was placed on 12g silica gel column and eluted with 5% to 50% ethyl acetate/hexane over 20 min. to give 5-(benzyloxy)-N-(2-(tert-butyldimethylsilyloxy)ethyl)-6-hydroxy-N-isopropyl-2-(2-methyl-2-phenylpropyl)pyrimidine-4-carboxamide **(57)** (62 mg, 26%).

LC/MS calcd. for = $C_{33}H_{47}N_3O_4Si$ (m/e) 577.85 obsd. 578.5 [M+H, ES^+].

Preparation of (58):



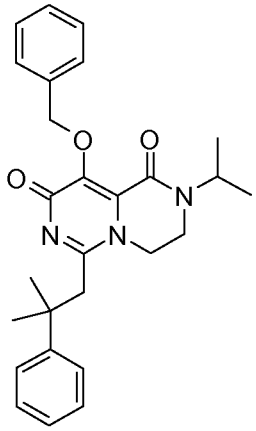
Step 8: 5-(Benzyloxy)-6-hydroxy-N-(2-hydroxyethyl)-N-isopropyl-2-(2-methyl-2-phenylpropyl)-pyrimidine-4-carboxamide

5-(Benzyloxy)-N-(2-(tert-butyldimethylsilyloxy)ethyl)-6-hydroxy-N-isopropyl-2-(2-methyl-2-phenylpropyl)pyrimidine-4-carboxamide **(57)** (62 mg, 107 µmol, Eq: 1.00) was stirred in tetrahydrofuran (2 ml), HCl (aqueous) (161 µl, 161 µmol, Eq: 1.5) was added. The reaction mixture was stirred at room temperature for 3.0 hours, 160 µl 1N NaOH was added and the

reaction mixture was diluted with water, extracted twice with ethyl acetate. The combined organic layers were washed with brine and dried over magnesium sulfate. Trituration in hexanes/ether was conducted to give 5-(benzyloxy)-6-hydroxy-N-(2-hydroxyethyl)-N-isopropyl-2-(2-methyl-2-phenylpropyl)pyrimidine-4-carboxamide **(58)** (32 mg, 64%).

LC/MS calcd. for $C_{27}H_{33}N_3O_4$ (m/e) = 463.58, obsd. 464.4 [M+H, ES^+], 486.4 [M+Na, ES^+].

Preparation of (59):

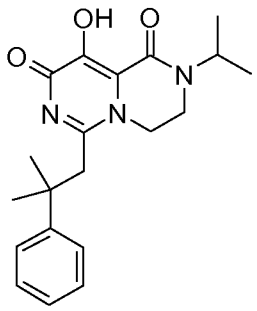


Step 9: 9-(Benzyloxy)-2-isopropyl-6-(2-methyl-2-phenylpropyl)-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione

To a stirred solution of 5-(benzyloxy)-6-hydroxy-N-(2-hydroxyethyl)-N-isopropyl-2-(2-methyl-2-phenylpropyl)pyrimidine-4-carboxamide **(58)** (35 mg, 75.5 µmol, Eq: 1.00) in dichloromethane (5.00 ml) was added triphenylphosphine (29.7 mg, 113 µmol, Eq: 1.5) at room temperature and the reaction mixture was stirred for 10 min. Then diisopropyl azodicarboxylate (22.9 mg, 22.0 µl, 113 µmol, Eq: 1.5) was added and the reaction mixture was stirred for 18 hrs at room temperature. The reaction mixture was concentrated on a rotary evaporator and chromatographed (silica gel, gradient, 2 to 5% methanol-dichloromethane) to obtain 9-(benzyloxy)-2-isopropyl-6-(2-methyl-2-phenylpropyl)-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione **(59)** (18 mg, 53.5 % yield).

LC/MS calcd. for Ia =$C_{27}H_{31}N_3O_3$ (m/e) 445.57, obsd. 446.4 [M+H, ES^+].

Preparation of (60):



Step 10: 9-Hydroxy-2-isopropyl-6-(2-methyl-2-phenyl-propyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a stirred solution of 9-(benzyloxy)-2-isopropyl-6-(2-methyl-2-phenylpropyl)-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione **(59)** (15 mg, 33.7 µmol, Eq: 1.00) in methanol (5.00 ml) was added HCl (conc) (49.1 mg, 40.9 µl, 1.35 mmol, Eq: 40); the mixture was heated at 70 °C for 48 hrs. The reaction mixture was cooled and stirred overnight at room temperature. The solvent was removed on a rotary evaporator, and saturated aqueous $NaHCO_3$ solution was added, this was extracted with dichloromethane, and the organic layers were combined and dried over magnesium sulfate. This was filtered, the solvents were removed on a rotary evaporator and the residue was triturated three times with diethyl ether. The resulting white solid was dried to obtain the title compound **(60)** (6.1 mg, 51%).

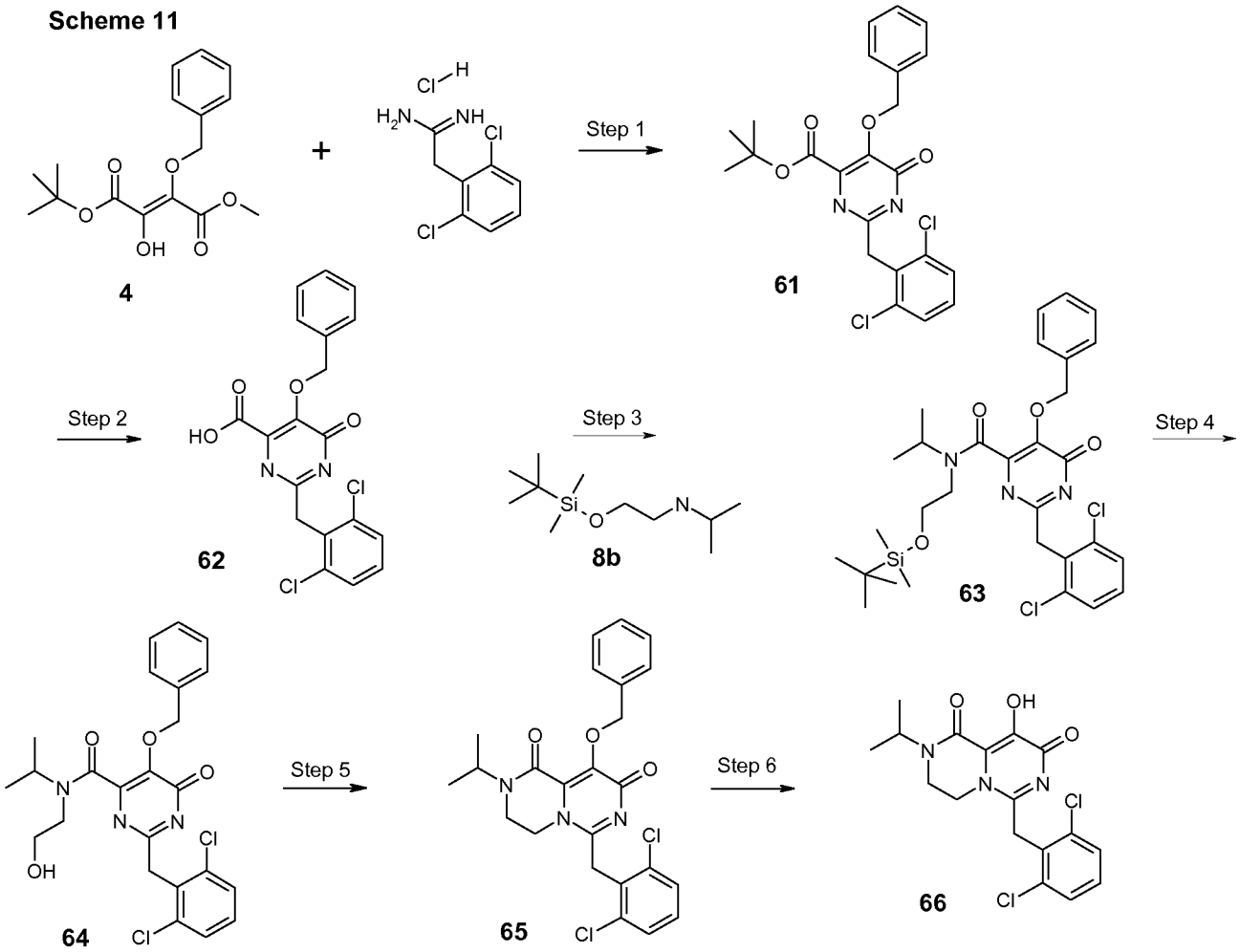
LC/MS calcd. for Ia = $C_{20}H_{25}N_3O_3$ (m/e) 355.44, obsd. 356.3 [M+H, ES^+].

Example 66

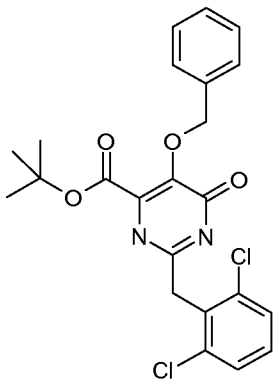
6-(2,6-Dichlorobenzyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(66)**

The synthetic procedure used in this preparation is outlined in Scheme 11.

Scheme 11



Preparation of (61):



5

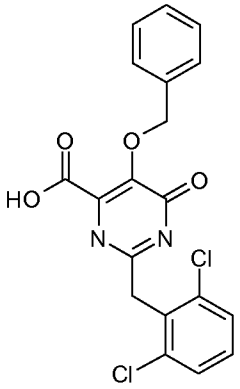
Step 1: 5-Benzyloxy-2-(2,6-dichlorobenzyl)-6-oxo-3,6-dihydro-pyrimidine-4-carboxylic acid tert-butyl ester

2-(2,6-Dichlorophenyl)acetimidamide hydrochloride (0.2 g, 835 µmol, Eq: 1.00) and 4-tert-butyl 1-methyl 2-(benzyloxy)-3-hydroxyfumarate **(4)** (386 mg, 1.25 mmol, Eq: 1.5) were dissolved in methanol (6.00 ml) and cooled to 0 °C. At that temperature, sodium methoxide (142 mg, 2.5 mmol, Eq: 3) was added. After another 15 minutes at this temperature, the resulting suspension was allowed to warm to room temperature overnight.

The mixture was diluted with 2ml of methanol and cooled to 0 °C. 1M HCl was added and a precipitate formed. After stirring for approx. 30 minutes the solid was collected by filtration, washed with little methanol/water 9/1 and dried to afford 5-(benzyloxy)-2-(2,6-dichlorobenzyl)-6-oxo-3,6-dihydro-pyrimidine-4-carboxylic acid tert-butyl ester **(61)** (0.245 g, 531 µmol, 63.6 % yield) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 13.25 (br. s., 1H), 7.51 (d, J = 8.0 Hz, 2H), 7.30 – 7.47 (m, 6H), 5.14 (s, 2H), 4.25 (s, 2H), 1.35 (s, 9H).

Preparation of (62):



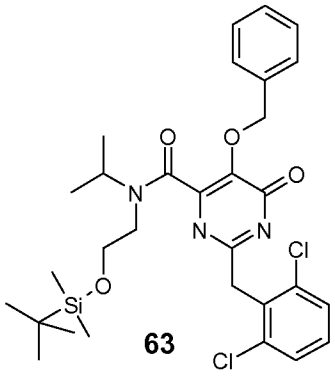
Step 2: 5-Benzyloxy-2-(2,6-dichlorobenzyl)-6-oxo-3,6-dihydro-pyrimidine-4-carboxylic acid

5-(Benzyloxy)-2-(2,6-dichlorobenzyl)-6-oxo-3,6-dihydro-pyrimidine-4-carboxylic acid tert-butyl ester **(61)** (0.24 g, 520 µmol, Eq: 1.00) and LiOH (62.3 mg, 2.6 mmol, Eq: 5) were stirred in tetrahydrofuran (2 ml)/water (1.00 ml) at reflux overnight. The solvent was mostly removed. The residue was taken up in water and was extracted once with ethyl acetate. The aqueous layer was acidified with HCl conc. The precipitate was collected by filtration, washed with

water and dried to afford 5-benzyloxy-2-(2,6-dichlorobenzyl)-6-oxo-3,6-dihydro-pyrimidine-4-carboxylic acid **(62)** (0.202 g, 498 µmol, 95.8 % yield) as a white solid.

^{1}H NMR (DMSO–d_6) δ: 13.49 (br. s., 1H), 13.24 (br. s., 1H), 7.50 (d, J = 8.0 Hz, 2H), 7.32 – 7.46 (m, 6H), 5.13 (s, 2H), 4.25 (s, 2H).

Preparation of (63):



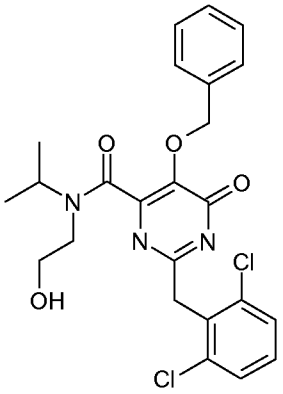
63

Step 3: 5-Benzyloxy-2-(2,6-dichlorobenzyl)-6-oxo-3,6-dihydro-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide

5-(Benzyloxy)-2-(2,6-dichlorobenzyl)-6-oxo-3,6-dihydro-pyrimidine-4-carboxylic acid **(62)** (0.2 g, 494 µmol, Eq: 1.00) and N-(2-(tert-butyldimethylsilyloxy)ethyl)propan-2-amine (118 mg, 543 µmol, Eq: 1.1) were dissolved in pyridine (3 ml) and cooled in an ice/NaCl bath. $POCl_3$ (227 mg, 138 µl, 1.48 mmol, Eq: 3) was added dropwise. After the addition was complete, sitrring of the reaction mixture was continued at 0 °C for approx. 40 minutes. The reaction mixture was quenched with ice and extracted twice with ethyl acetate. The organic layers were washed with $NaHCO_3$, were combined, dried over Na_2SO_4, filtered and concentrated. The remaining oil was purified by SiO_2 flash chromatography (24g SiO_2, hexanes/ethyl acetate 0-50% ethyl acetate). Product containing fractions were combined and concentrated. The remaining oil was treated with hexanes and concentrated again to afford 5-benzyloxy-2-(2,6-dichlorobenzyl)-6-oxo-3,6-dihydro-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(63)** (0.17 g, 281 µmol, 57.0 % yield) as a white solid.

LC/MS (M+H) = 604.

Preparation of (64):

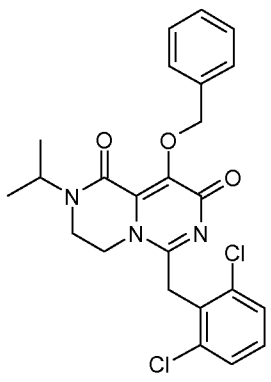


Step 4: 5-Benzyloxy-2-(2,6-dichlorobenzyl)-6-oxo-3,6-dihydro-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide

5-Benzyloxy-2-(2,6-dichlorobenzyl)-6-oxo-3,6-dihydro-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(63)** (0.17 g, 281 µmol, Eq: 1.00) was dissolved in tetrahydrofuran (1 ml). HCl (211 µl, 422 µmol, Eq: 1.5) was added and the resutlting mixture was stirred at room temperature for 30 minutes. The solvent was mostly removed. The residue was partitioned between ethyl acetate and 1M NaOH. The aqueous layer was washed with ethyl acetate, the organic layers were washed with brine, combined, dried over Na_2SO_4, filtered and concentrated. The remaining oil was triturated and concentrated several times with ether/hexanes to afford 5-benzyloxy-2-(2,6-dichlorobenzyl)-6-oxo-3,6-dihydro-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(64)** (0.113 g, 230 µmol, 82.0 % yield) as a white solid.

LC/MS (M+H) = 490.

Preparation of (65):

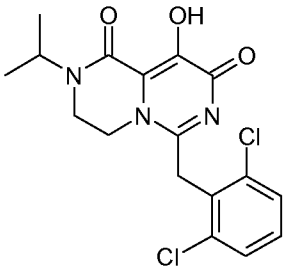


Step 5: 9-Benzyloxy-6-(2,6-dichlorobenzyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

5-Benzyloxy-2-(2,6-dichlorobenzyl)-6-oxo-3,6-dihydro-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(64)** (0.11 g, 224 µmol, Eq: 1.00) was dissolved in dichloromethane (1.5 ml) and Ph_3P (88.3 mg, 336 µmol, Eq: 1.5) was added. The clear colorless solution was stirred at room temperature for approx. 10min and then DIAD (diisopropylazodicarboxylate) (71.6 mg, 68.9 µl, 336 µmol, Eq: 1.5) was added. Stirring was continued at room temperature for 1h. The solvent was removed and the remaining oil was purified by SiO_2 flash chromatography (12g SiO_2, dichloromethane/methanol 0-3% methanol). SiO_2 flash chromatography was repeated (12g SiO_2, hexanes/ethyl acetate 7-50% ethyl acetate, then dichloromethane/methanol 0-3% methanol) to afford 9-benzyloxy-6-(2,6-dichlorobenzyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(65)** (0.045 g, 95.3 µmol, 42.5 % yield) as a white solid.

LC/MS (M+H) = 472.

Preparation of (66):



Step 6: 6-(2,6-Dichlorobenzyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

9-Benzyloxy-6-(2,6-dichlorobenzyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(65)** (0.04 g, 84.7 µmol, Eq: 1.00) was suspended in methanol (0.5 ml) and HCl conc (600 mg, 0.5 ml, 16.5 mmol, Eq: 194) was added. The resulting mixture was stirred at room temperature overnight. The organic solvent was mostly removed. Aqueous $NaHCO_3$ was added slowly. The water was removed under reduced pressure. The residue was taken up in ethanol and stirred at room temperature overnight. The suspension was filtered and the filtrate was concentrated to dryness. The remaining solid was purified by reverse phase flash chromatography (13g C18, water/acetonitrile 0-100% acetonitrile). Product containing

fractions were combined and lyophilized to afford 6-(2,6-dichlorobenzyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(66)** (0.01 g, 30.6 % yield) as a white solid.

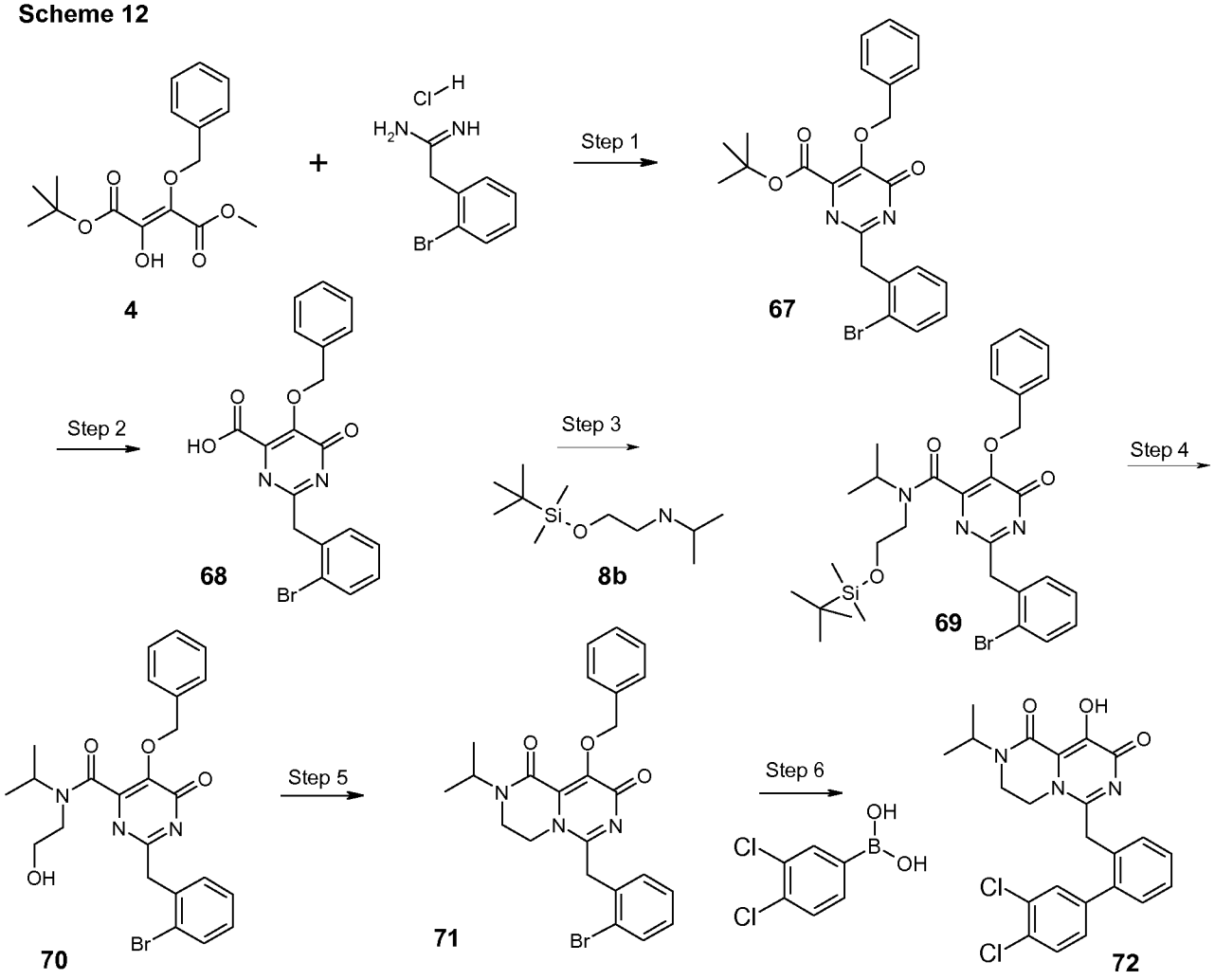
^{1}H NMR (methanol-d_4) δ: 7.28 – 7.34 (m, 1H), 7.15 – 7.21 (m, 1H), 4.34 – 4.41 (m, 4H), 3.64 – 3.70 (m, 2H), 1.18 (d, J = 6.8 Hz, 6H). LC/MS calcd. for C17H18Cl2N3O3 [(M+H)+] 382, obsd. 382.

Example 72

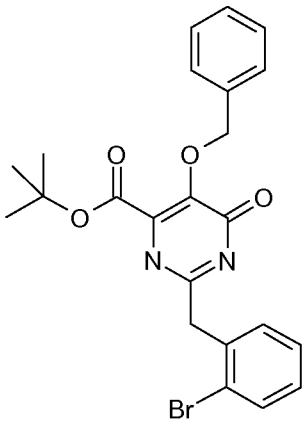
6-(3',4'-Dichloro-biphenyl-2-ylmethyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 12.

Scheme 12



Preparation of (67):



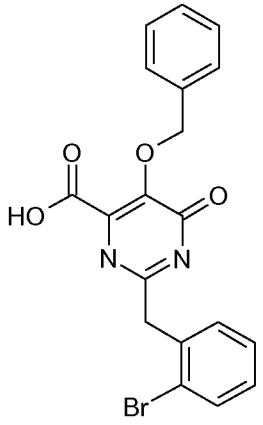
5

Step 1: 5-Benzyloxy-2-(2-bromobenzyl)-6-oxo-3,6-dihydro-pyrimidine-4-carboxylic acid tert-butyl ester

2-(2-Bromophenyl)acetimidamide hydrochloride (2 g, 8.01 mmol, Eq: 1.00) and 4-tert-butyl 1-methyl 2-(benzyloxy)-3-hydroxyfumarate **(4)** (3.44 g, 11.2 mmol, Eq: 1.39) were dissolved in methanol (40.0 ml) and cooled down to 0 °C. At that temperature sodium methoxide (1.37 g, 24.0 mmol, Eq: 3) was added. After another 15 minutes at this temperature, the resulting suspension was allowed to warm to room temperature overnight. A little methanol (~5ml) was added and the yellow suspension was cooled to 0 °C. 1M HCl (~50ml) was added and a precipitate formed. The suspension was stirred for ~20 minutes. The solid was collected by filtration, washed with water and a little methanol/water 9/1 and dried to afford 5-(benzyloxy)-2-(2-bromobenzyl)-6-oxo-3,6-dihydro-pyrimidine-4-carboxylic acid tert-butyl ester (2.69 g, 5.71 mmol, 71.2 % yield) **(67)** as an off-white solid.

^{1}H NMR (DMSO-d_6) δ: 13.18 (br. s., 1H), 7.62 – 7.67 (m, 1H), 7.33 – 7.46 (m, 6H), 7.21 – 7.30 (m, 2H), 5.16 (s, 2H), 4.04 (s, 2H), 1.39 (s, 9H).

Preparation of (68):



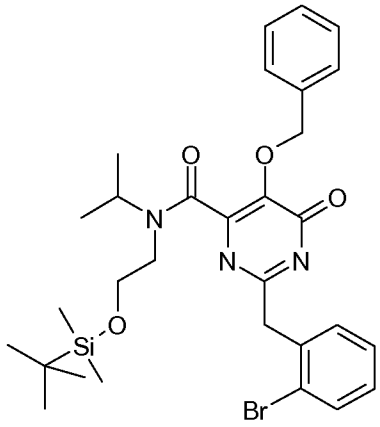
Step 2: 5-Benzyloxy-2-(2-bromobenzyl)-6-oxo-3,6-dihydro-pyrimidine-4-carboxylic acid

5-(Benzyloxy)-2-(2-bromobenzyl)-6-oxo-3,6-dihydro-pyrimidine-4-carboxylic acid tert-butyl ester **(67)** (2.69 g, 5.71 mmol, Eq: 1.00) and LiOH (683 mg, 28.5 mmol, Eq: 5) were stirred in tetrahydrofuran (18 ml)/water (9.00 ml) under reflux for 6h, at room temperature overnight and again to reflux for 3h. Then the solvent was mostly removed. The remaining oil was diluted with water and extracted with ethyl acetate. The aqueous layer was cooled in an ice bath and

was acidified with HCl conc. Precipitate formed, was collected by filtration, washed with water and dried to afford 5-(benzyloxy)-2-(2-bromobenzyl)-6-oxo-3,6-dihydro-pyrimidine-4-carboxylic acid **(68)** (2.14 g, 5.15 mmol, 90.3 % yield) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 13.48 (br. s., 1H), 13.16 (br. s., 1H), 7.60 – 7.67 (m, 1H), 7.29 – 7.47 (m, 7H), 7.21 – 7.28 (m, 1H), 5.14 (s, 2H), 4.05 (s, 2H).

Preparation of (69):

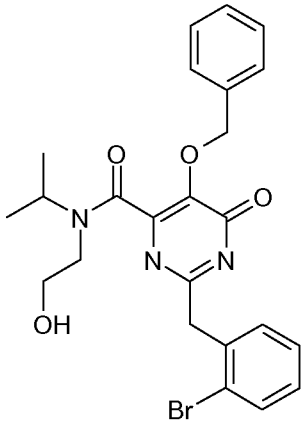


Step 3: 5-Benzyloxy-2-(2-bromobenzyl)-6-oxo-3,6-dihydro-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide

5-(Benzyloxy)-2-(2-bromobenzyl)-6-oxo-3,6-dihydro-pyrimidine-4-carboxylic acid **(68)** (1 g, 2.41 mmol, Eq: 1.00) was dissolved in pyridine (20 ml) and N-(2-(tert-butyldimethylsilyloxy)ethyl)propan-2-amine **(8b)** (576 mg, 2.65 mmol, Eq: 1.1) was added. Precipitate formed and gave a thick slurry. Additional 5ml of pyridine were added to ease stirring. The suspension was cooled in an ice/NaCl bath. $POCl_3$ (1.11 g, 673 µl, 7.22 mmol, Eq: 3) was added dropwise, keeping the inside temperature below 0 °C. After the addition was complete the mixture was stirred for 45 minutes at 0 °C. The reaction was quenched with ice and the organic solvent was mostly removed. The remaining aqueous layer was extracted three times with ethyl acetate. The organic layers were washed with brine, combined, dried over Na_2SO_4, filtered and concentrated. The remaining oil was taken up in a little dichloromethane, was filtered through Celite and then purified by SiO_2 flash chromatography (80g SiO_2, hexanes/ethyl acetate 0-50% ethyl acetate) to afford 5-benzyloxy-2-(2-bromobenzyl)-6-oxo-3,6-dihydro-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(69)** (0.758 g, 1.23 mmol, 51.2 % yield) as a light brown oil.

LC/MS (M+H) = 614/616.

Preparation of (70):

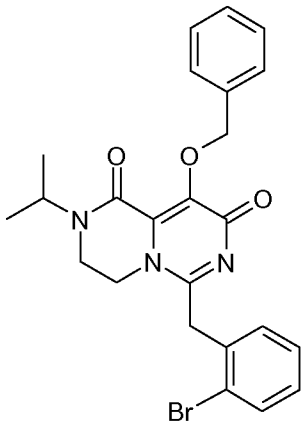


Step 4: 5-Benzyloxy-2-(2-bromobenzyl)-6-oxo-3,6-dihydro-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide

5-Benzyloxy-2-(2-bromobenzyl)-6-oxo-3,6-dihydro-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(69)** (0.75 g, 1.22 mmol, Eq: 1.00) was dissolved in tetrahydrofuran (10 ml). HCl (915 µl, 1.83 mmol, Eq: 1.5) was added and the resulting mixture was stirred at room temperature. After 30 minutes the solvent was mostly removed. The residue was partitioned between ethyl acetate and 1M NaOH. The aqueous layer was washed with ethyl acetate, the organic layers were washed with brine, combined, dried over Na_2SO_4, filtered and concentrated. The remaining brown oil was triturated in ethyl acetate/ether. The solid was collected by filtration, washed with a little ethyl acetate and dried to afford 5-benzyloxy-2-(2-bromobenzyl)-6-oxo-3,6-dihydro-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(70)** (0.21 g, 420 µmol, 34.4 % yield) as an off-white solid. The mother liquor also showed clean product (0.43g, 68 % yield) of brown solid.

LC/MS (M+H) = 500/502.

Preparation of (71):

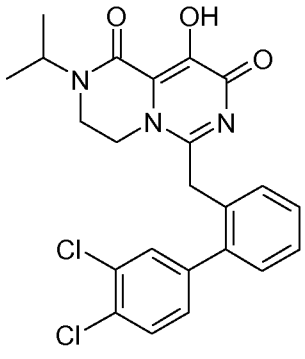


Step 5: 9-Benzyloxy-6-(2-bromobenzyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

5-Benzyloxy-2-(2-bromobenzyl)-6-oxo-3,6-dihydro-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(70)** (0.21 g, 420 µmol, Eq: 1.00) and Ph_3P (143 mg, 546 µmol, Eq: 1.3) were stirred in dichloromethane (5 ml) at room temperature for ~15min. Then DIAD (116 mg, 112 µl, 546 µmol, Eq: 1.3) was added and the resulting mixture was stirred at room temperature overnight. The solvent was removed. The remaining material was purified by SiO_2 flash chromatography (hexanes/ethyl acetate 5-50%, then dichloromethane/methanol 0-4% methanol). 300mg of 9-benzyloxy-6-(2-bromobenzyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(71)** (~40 % pure, ~60 % yield) as light yellow solid were isolated and used as obtained.

LC/MS (M+H) = 482/484.

Preparation of (72):



Step 6: 6-(3',4'-Dichloro-biphenyl-2-ylmethyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

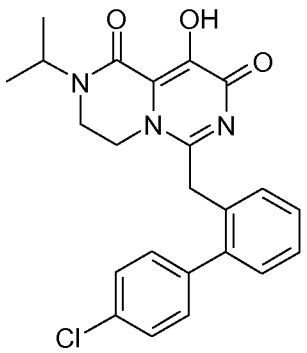
9-Benzyloxy-6-(2-bromobenzyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(71)** (0.1 g, 207 µmol, Eq: 1.00, ~40 % pure), 3,4-dichlorophenylboronic acid (47.5 mg, 249 µmol, Eq: 1.2), Na_2CO_3 (65.9 mg, 622 µmol, Eq: 3) and tetrakis(triphenylphosphine)palladium (0) (24.0 mg, 20.7 µmol, Eq: 0.1) were stirred in methanol (0.9 ml)/dichloromethane (300 µl) in the microwave at 115 °C for 30 minutes. The reaction mixture stood at room temperature overnight. The supernatant was pipetted off, concentrated and purified by SiO_2 flash chromatography (4g SiO_2, dichloromethane/methanol 0-5% methanol) to afford 6-(3',4'-dichloro-biphenyl-2-ylmethyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(72)** (0.016 g, 31.4 µmol, 15.2 % yield, 90 % pure) as a light yellow solid.

LC/MS (M+H) = 458.

^{1}H NMR (methanol-d_4) δ: 7.60 (d, J = 8.3 Hz, 1H), 7.52 (d, J = 2.0 Hz, 1H), 7.39 – 7.43 (m, 2H), 7.28 – 7.32 (m, 2H), 7.22 – 7.26 (m, 1H), 4.79 – 4.85 (m, 1H), 4.13 (s, 2H), 3.87 – 3.93 (m, 2H), 3.49 – 3.54 (m, 2H), 1.22 (d, J = 7.0 Hz, 6H).

Example 73

6-(4'-Chloro-biphenyl-2-ylmethyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

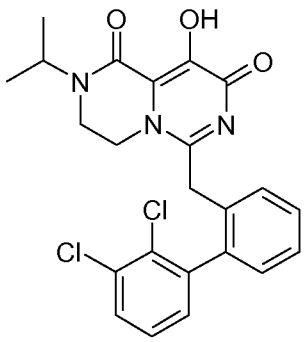


The title compound was prepared as example 2 using 4-chlorophenylboronic acid in step 6 to afford 6-(4'-chloro-biphenyl-2-ylmethyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(73)** (0.005 g, 10.6 µmol, 6.4 % yield) as a light yellow solid.

LC/MS (M+H) = 424.

Example 74

6-(2',3'-Dichloro-biphenyl-2-ylmethyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione



The title compound was prepared as example 2 using 2,3-dichlorophenylboronic acid in step 6 to afford 6-(2',3'-dichloro-biphenyl-2-ylmethyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(74)** (0.017 g, 33.4 µmol, 16.1 % yield) as a light yellow solid.

LC/MS (M+H) = 458.

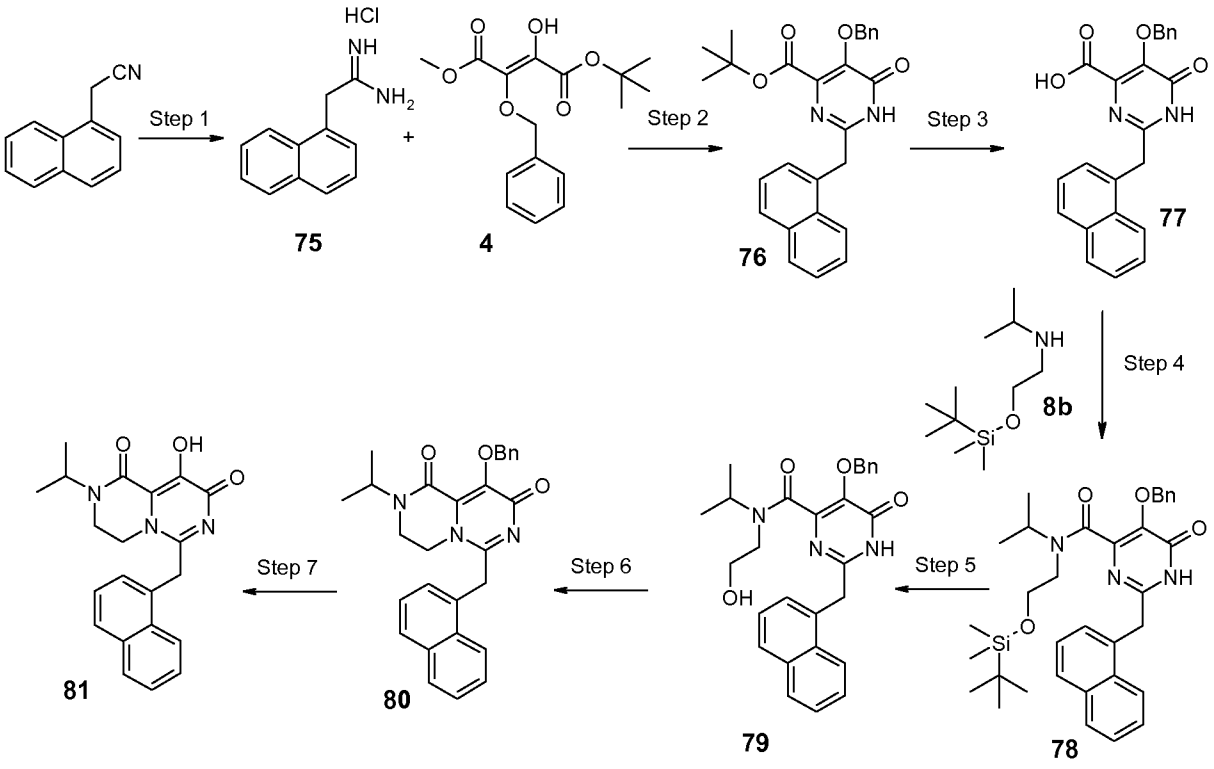
^{1}H NMR (methanol-d_4) δ: 7.58 (dd, J = 7.9, 1.4 Hz, 1H), 7.40 – 7.47 (m, 2H), 7.36 (t, J = 7.8 Hz, 1H), 7.23 – 7.31 (m, 3H), 4.78 – 4.86 (m, 1H), 3.90 – 4.12 (m, 3H), 3.81 – 3.89 (m, 1H), 3.51 (t, J = 5.6 Hz, 2H), 1.21 (dd, J = 6.8, 1.5 Hz, 6H).

Example 81

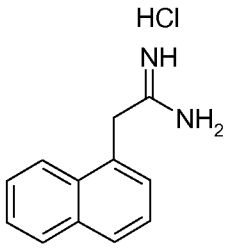
9-Hydroxy-2-isopropyl-6-naphthalen-1-ylmethyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 13.

Scheme 13



Preparation of (75):

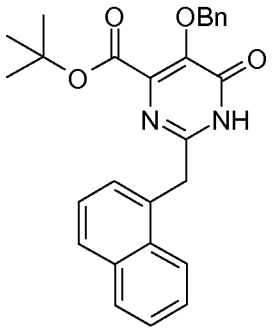


Step 1: 2-Naphthalen-1-yl-acetamidine hydrochloride

To a stirred suspension of NH_4Cl (1.6 g, 30 mmol) in anhydrous toluene (50 mL) was added trimethyl aluminium (2M in toluene, 15 mL, 30 mmol) at 0 °C. The mixture was then warmed to room temperature and stirred for 2 h. A solution of 2-(naphthalen-1-yl)acetonitrile (1.67 g, 10 mmol) in toluene (10 mL) was added to the above reaction mixture and the reaction mixture was stirred at 80 °C for 18 h. After completion of the reaction, the reaction mixture was quenched with a suspension of silica gel in chloroform. The mixture was stirred at room temperature for 0.5 h before being filtered through a sintered funnel. The silica gel was washed with methanol. The combined filtrate was concentrated under reduced pressure to give the crude product as an off-white solid (2 g, 91%), which was used directly without further purification.

MS (M+H) = 185.3.

Preparation of (76):



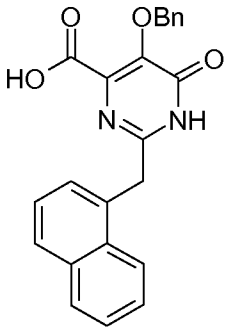
Step 2: 5-Benzyloxy-2-naphthalen-1-ylmethyl-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid tert-butyl ester

To a stirred solution of 2-naphthalen-1-yl-acetamidine hydrochloride **(75)** (0.9 g, 4.1 mmol) and (E)-2-benzyloxy-3-hydroxy-but-2-enedioic acid 4-tert-butyl ester 1-methyl ester **(4)** (1.3 g, 4.1 mmol) in anhydrous methanol (60 mL) at 0 °C was added a methanolic solution (Aldrich, 25%) of sodium methoxide (1.8 g, 8.2 mmol). The reaction mixture was slowly warmed to room temperature and stirred for 18 h. The reaction was quenched with aqueous HCl solution (1 N). The pH of the mixture was adjusted to 6-7, then the mixture was evaporated. The residue was partitioned between ethyl acetate and water. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extract was

washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (30-50% ethyl acetate in hexanes) to give the product **(76)** as a white solid (1 g, 55%).

MS (M+H) = 443.2.

Preparation of (77):

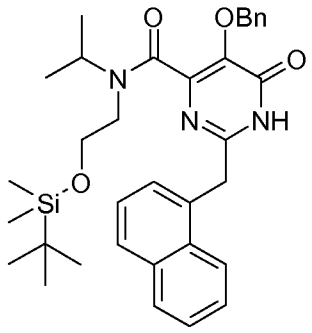


Step 3: 5-Benzyloxy-2-naphthalen-1-ylmethyl-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid

To a solution of 5-benzyloxy-2-naphthalen-1-ylmethyl-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid tert-butyl ester **(76)** (0.8 g, 1.8 mmol) in tetrahydrofuran (30 mL) and water (15 mL) was added LiOH (0.2 g, 9 mmol) . The reaction mixture was heated at 80 ^oC for 18 h. TLC analysis indicated the completion of reaction, and the mixture was concentrated to a small volume, then washed with ethyl acetate. The aqueous portion was acidified with aqueous HCl solution (1 N) to pH 3-4, then extracted with ethyl acetate and dichloromethane. The combined organic extract was washed with brine, dried over $MgSO_4$, and concentrated to give the crude product **(77)** as a white solid (0.69 g, 99%), which was used directly without further purification.

MS (M+H) = 387.2.

Preparation of (78):

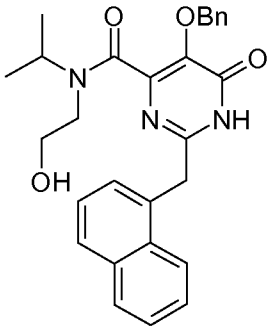


Step 4: 5-Benzyloxy-2-naphthalen-1-ylmethyl-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide

To a stirred solution of 5-benzyloxy-2-naphthalen-1-ylmethyl-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid **(77)** (0.6 g, 1.6 mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amine **(8b)** (0.5 g, 2.3 mmol) in pyridine (40 mL) was slowly added $POCl_3$ (0.43 mL, 4.7 mmol) at –10 °C. The reaction mixture was stirred at 0 °C for 2 h. The mixture was loaded into a pad of silica gel and directly purified by chromatography (40-60% ethyl acetate in hexanes) to give the product **(78)** as an off-white solid (0.45 g, 50%).

MS (M+H) = 586.3.

Preparation of (79):



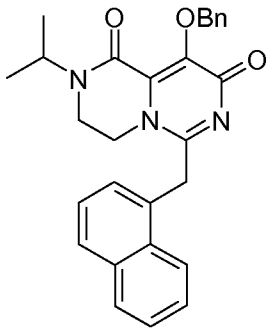
Step 5: 5-Benzyloxy-2-naphthalen-1-ylmethyl-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide

To a stirred solution of 5-benzyloxy-2-naphthalen-1-ylmethyl-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(78)** (0.45 g, 0.77

mmol) in tetrahydrofuran (30 mL) was added aqueous HCl (1 N, 1 mL, 1 mmol). The reaction mixture was stirred at room temperature for 1 h. The mixture was neutralized with aqueous saturated $NaHCO_3$ solution to pH 7, then extracted with ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extract was dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (50-80% ethyl acetate in hexanes) to give the product **(79)** as a white solid (0.36 g, 99%).

MS (M+H) = 472.2.

Preparation of (80):

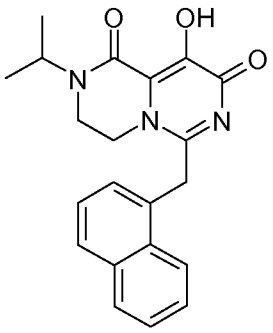


Step 6: 9-Benzyloxy-2-isopropyl-6-naphthalen-1-ylmethyl-2,3,4,7-tetrahydro-pyrazino[1,2-c]pyrimidine-1,8-dione

To a stirred solution of 5-benzyloxy-2-naphthalen-1-ylmethyl-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(79)** (0.36 g, 0.76 mmol) in dichloromethane (20 mL) was added triphenylphosphine (0.2 g, 0.76 mmol). The mixture was stirred at room temperature for 10 min. Then diisopropyl azodicarboxylate (DIAD) (0.15 mL, 0.76 mmol) was added. The reaction mixture was stirred at room temperature for 2 h. The mixture was concentrated, and the residue was purified by chromatography (0-10% methanol in ethyl acetate) to give the product **(80)** as a white solid (0.23 g, 66%).

MS (M+H) = 454.2.

Preparation of (81):



Step 7: 9-Hydroxy-2-isopropyl-6-naphthalen-1-ylmethyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a solution of 9-benzyloxy-2-isopropyl-6-naphthalen-1-ylmethyl-2,3,4,7-tetrahydro-pyrazino[1,2-c]pyrimidine-1,8-dione **(80)** (0.23 g, 0.51 mmol) in methanol (10 mL) was added concentrated HCl (aq 37%, 3 mL). The reaction mixture was stirred at room temperature for 24 h, then concentrated. To the residue was added aqueous saturated $NaHCO_3$ solution, extraction with 10% methanol in dichloromethane was conducted twice. The combined organic extract was concentrated. The residue was purified by chromatography (10-20% methanol in dichloromethane) to give the title compound **(81)** as a white solid (0.1 g, 54%).

MS (M+H) = 364.2.

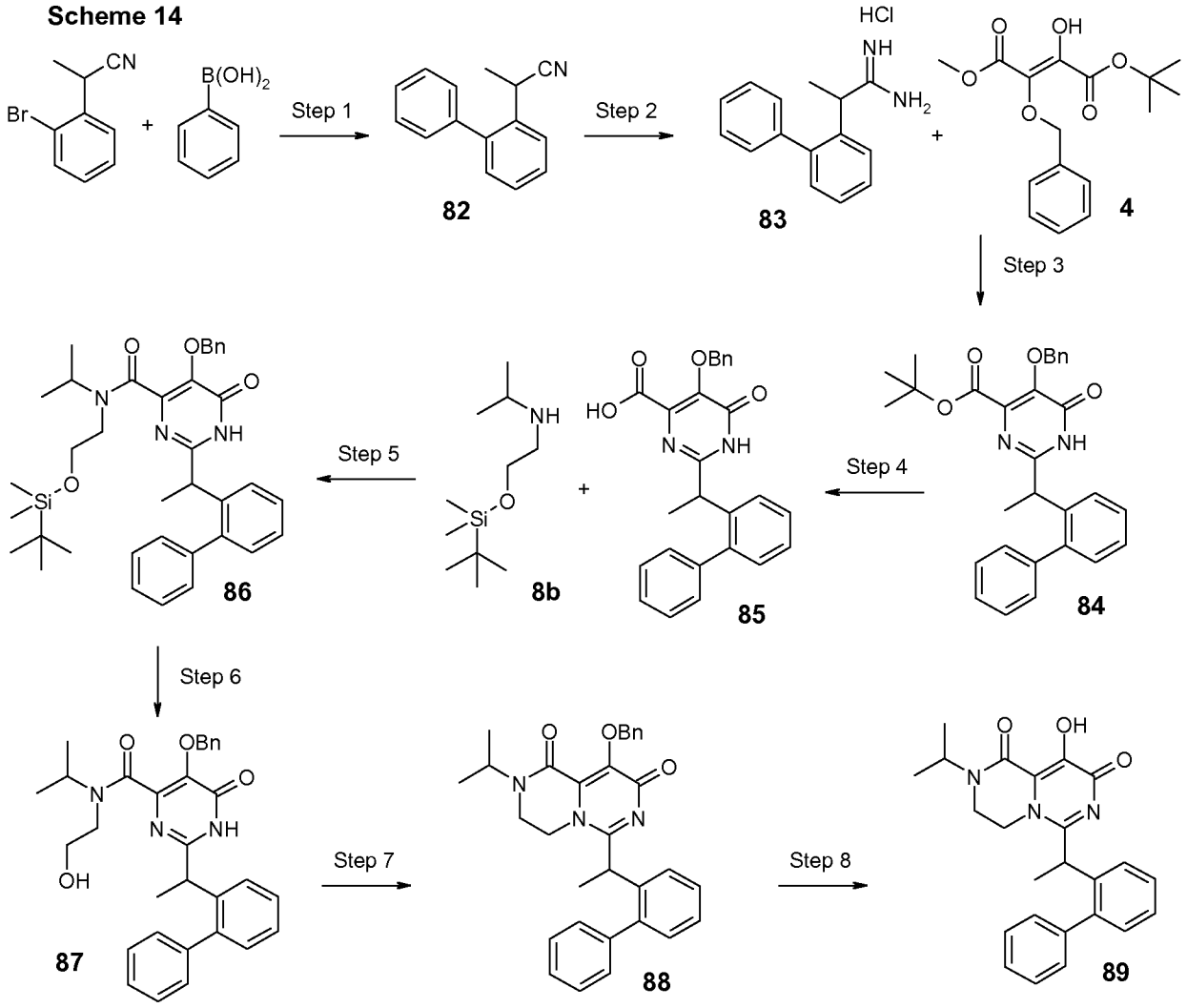
^{1}H NMR (DMSO-d_6) δ: 8.06 – 8.30 (m, 1H), 7.94 – 8.04 (m, 1H), 7.90 (d, J = 8.3 Hz, 1H), 7.54 – 7.65 (m, 2H), 7.49 (t, J = 7.7 Hz, 1H), 7.15 (d, J = 6.5 Hz, 1H), 4.80 – 4.96 (m, 1H), 4.54 – 4.72 (m, 2H), 4.00 – 4.27 (m, 2H), 3.63 (br. s., 1H), 3.52 (br. s., 1H), 1.06 – 1.29 (m, 6H)

Example 89

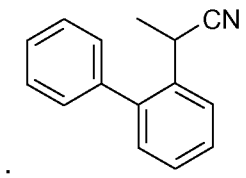
6-(1-Biphenyl-2-yl-ethyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 14.

Scheme 14



Preparation of (82):

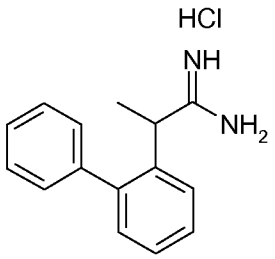


Step 1 2-Biphenyl-2-yl-propionitrile

To a suspension of 2-(2-bromo-phenyl)-propionitrile (2.1 g, 10 mmol) and phenylboronic acid (1.8 g, 15 mmol) in anhydrous methanol (10 mL) and toluene (20 mL) was added Cs_2CO_3 (9.8 g, 30 mmol). The mixture was degassed with nitrogen, followed by the addition of tetrakis(triphenylphosphine)palladium (0.58 g, 0.5 mmol). The reaction mixture was heated at

80 °C and stirred for 24 h. The mixture was cooled to room temperature and filtered through a short pad of silica gel. The silica gel was washed with ethyl acetate. The filtrate was concentrated. The residue was purified by chromatography (10-30% ethyl acetate in hexanes) to give the product **(82)** as a colorless oil (1.8 g, 87%).

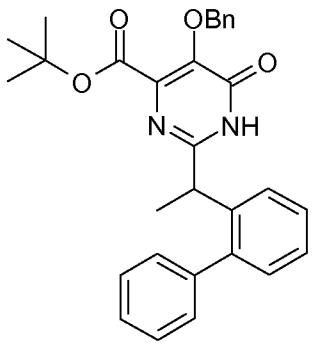
Preparation of (83):



Step 2: 2-Biphenyl-2-yl-propionamidine hydrochloride

To a stirred suspension of NH_4Cl (1.4 g, 26 mmol) in anhydrous toluene (40 mL) was added trimethylaluminum (2M in toluene, 13 mL, 26 mmol) at 0 °C. The mixture was then warmed to room temperature and stirred for 2 h. A solution of 2-biphenyl-2-yl-propionitrile **(82)** (1.8 g, 8.7 mmol) in toluene (10 mL) was added to the above reaction mixture and the reaction mixture was stirred at 80 °C for 18 h. After completion of the reaction, the mixture was quenched with a suspension of silica gel in chloroform. The mixture was stirred at room temperature for 0.5 h, then filtered through a sintered funnel. The silica gel was washed with methanol. The combined filtrate was concentrated under reduced pressure to give the crude product **(83)** as an off-white solid (2.3 g, 100%), which was used directly without further purification.

Preparation of (84)



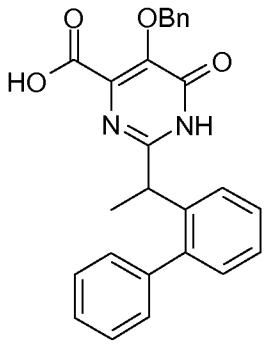
:

Step 3: 5-Benzyloxy-2-(1-biphenyl-2-yl-ethyl)-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid tert-butyl ester

To a stirred solution of 2-biphenyl-2-yl-propionamidine hydrochloride **(83)** (2.3 g, 8.7 mmol) and (E)-2-benzyloxy-3-hydroxy-but-2-enedioic acid 4-tert-butyl ester 1-methyl ester **(4)** (2.7 g, 8.7 mmol) in anhydrous methanol (40 mL) at 0 °C was added a methanolic solution (Aldrich, 25%) of sodium methoxide (5.6 g, 26 mmol). The reaction mixture was slowly warmed to room temperature and stirred for 18 h. The reaction was quenched with aqueous HCl solution (1 N). The pH of the mixture was adjusted to 6-7, then the mixture was evaporated. The residue was partitioned between ethyl acetate and water. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extract was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (30-50% ethyl acetate in hexanes) to give the product **(84)** as a white solid (2.4 g, 57%).

MS (M+H) = 483.6.

Preparation of (85):

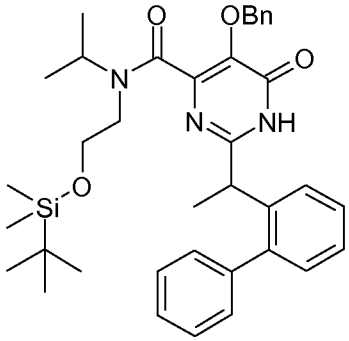


Step 4: 5-Benzyloxy-2-(1-biphenyl-2-yl-ethyl)-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid

To a solution of 5-benzyloxy-2-(1-biphenyl-2-yl-ethyl)-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid tert-butyl ester **(84)** (2.4 g, 4.9 mmol) in tetrahydrofuran (60 mL) and water (30 mL) was added LiOH (0.6 g, 30 mmol) . The reaction mixture was heated at 80 °C for 24 h. TLC analysis indicated the completion of reaction. The mixture was concentrated to a small volume, then extracted with ethyl acetate. The aqueous portion was acidified with aqueous HCl solution (1 N) to pH 3, then extracted with ethyl acetate and dichloromethane. The combined organic extract was washed with brine, dried over $MgSO_4$, and concentrated to give

the crude product **(85)** as a white foam (1.5 g, 71%), which was used directly without further purification.

Preparation of (86):

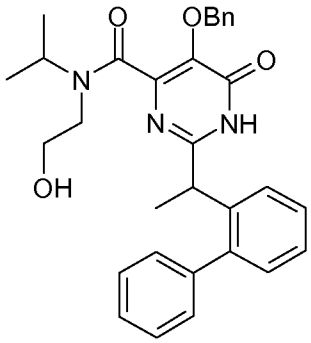


Step 5: 5-Benzyloxy-2-(1-biphenyl-2-yl-ethyl)-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide

To a stirred solution of 5-benzyloxy-2-(1-biphenyl-2-yl-ethyl)-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid **(85)** (1.5 g, 3.5 mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amine **(8b)** (1.2 g, 5.3 mmol) in pyridine (40 mL) was slowly added $POCl_3$ (0.49 g, 5.3 mmol) at –10 °C. The reaction mixture was stirred at 0 °C for 2 h. The mixture was loaded into a pad of silica gel and directly purified by chromatography (40-60% ethyl acetate in hexanes) to give the product **(86)** as a white foam (1.5 g, 68%).

MS (M+H) = 626.3.

Preparation of (87):

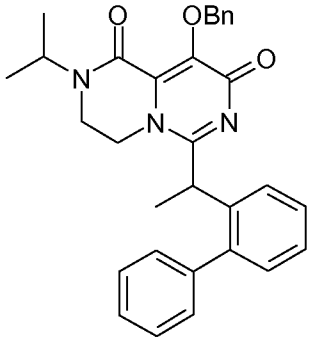


Step 6: 5-Benzyloxy-2-(1-biphenyl-2-yl-ethyl)-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide

To a stirred solution of 5-benzyloxy-2-(1-biphenyl-2-yl-ethyl)-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(86)** (1.5 g, 2.4 mmol) in tetrahydrofuran (20 mL) was added aqueous HCl (1 N, 2.4 mL, 2.4 mmol). The reaction mixture was stirred at room temperature for 1 h. The mixture was neutralized with aqueous saturated $NaHCO_3$ solution to pH 7, then extracted with ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extract was dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (50-80% ethyl acetate in hexanes) to give the product **(87)** as a white solid (0.9 g, 73%).

MS (M+H) = 512.2.

Preparation of (88):

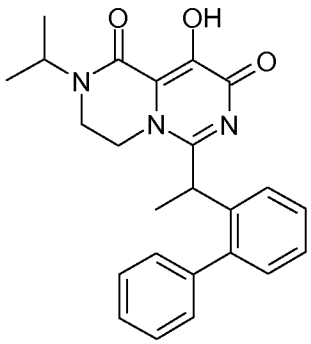


Step 7: 9-Benzyloxy-6-(1-biphenyl-2-yl-ethyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a stirred solution of 5-benzyloxy-2-(1-biphenyl-2-yl-ethyl)-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(87)** (0.9 g, 1.8 mmol) in dichloromethane (30 mL) was added triphenylphosphine (0.47 g, 1.8 mmol). The mixture was stirred at room temperature for 10 min. Then diisopropyl azodicarboxylate (DIAD) (0.35 mL, 1.8 mmol) was added. The reaction mixture was stirred at room temperature for 0.5 h. The mixture was concentrated, and the residue was purified by chromatography (50-100% ethyl acetate in hexanes) to give the product **(88)** as a white foam (0.22 g, 25%).

MS (M+H) = 494.2

Preparation of (89):



Step 8: 6-(1-Biphenyl-2-yl-ethyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a solution of 9-benzyloxy-6-(1-biphenyl-2-yl-ethyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(88)** (0.22 g, 0.45 mmol) in methanol (10 mL) was added concentrated HCl (aq 37%, 6 mL). The reaction mixture was stirred at 40 °C for 48 h, then concentrated to dryness. To the residue was added aqueous saturated $NaHCO_3$ solution, extraction with 10% methanol in dichloromethane was conducted twice. The combined organic extract was concentrated. The residue was purified by chromatography (10-20% methanol in dichloromethane) to give the title compound **(89)** as a white solid (45 mg, 25%).

MS (M+H) = 404.2.

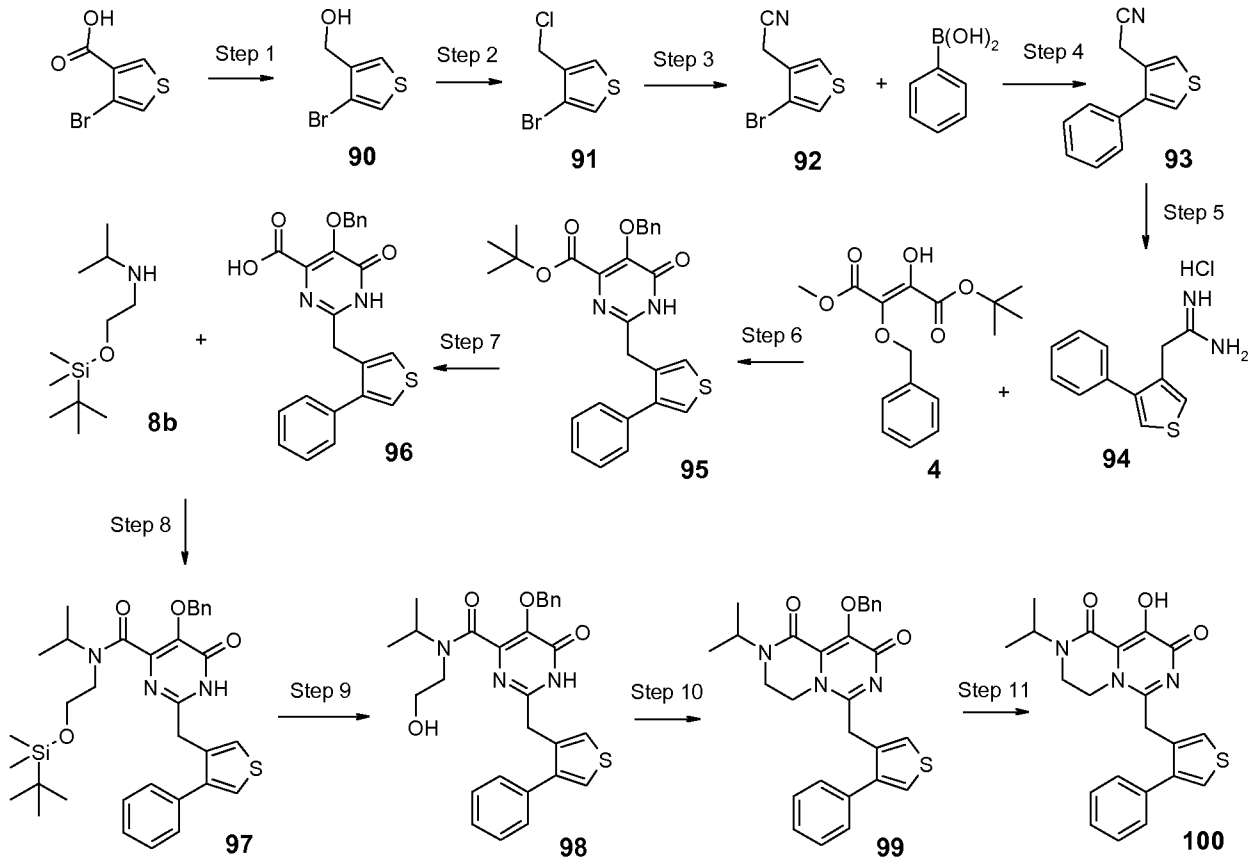
^{1}H NMR (DMSO-d_6) δ: 7.10 – 7.69 (m, 9H), 4.52 – 4.68 (m, 1H), 4.06 – 4.26 (m, 3H), 2.94 – 3.22 (m, 4H), 1.36 – 1.56 (m, 2H), 0.98 – 1.25 (m, 6H)

Example 100

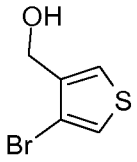
9-Hydroxy-2-isopropyl-6-(4-phenyl-thiophen-3-ylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 15

Scheme 15



Preparation of 90:

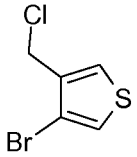


Step 1: (4-Bromo-thiophen-3-yl)-methanol

To a solution of 4-bromothiophene-3-carboxylic acid (3.6 g, 17 mmol) in anhydrous tetrahydrofuran at 0 °C was added a tetrahydrofuran solution (Aldrich, 1 M) of BH_3•tetrahydrofuran (243 mL, 0.24 mol). The reaction mixture was stirred at 0 °C for 0.5 h, then at room temperature for 2 h. The mixture was concentrated, and the residue was partitioned between ethyl acetate and aqueous dilute HCl solution. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extract was washed with saturated $NaHCO_3$ solution and brine, and then dried over $MgSO_4$,

and concentrated. The residue was purified by chromatography (10-50% ethyl acetate in hexanes) to give the product **(90)** as a colorless oil (2.6 g, 78%).

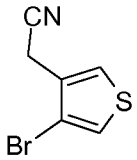
Preparation of (91):



Step 2: 3-Bromo-4-chloromethyl-thiophene

To a solution of (4-bromothiophen-3-yl)methanol **(90)** (2.6 g, 14 mmol) and triethylamine (5.6 mL, 40 mmol) in dichloromethane (20 mL) at 0 °C was added methanesulfonic chloride (1.6 mL, 20 mmol). The reaction mixture was stirred at 0 °C for 0.5 h, then warmed to room temperature for 2 h, and then quenched by aqueous HCl solution. The mixture was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate and chloroform. The combined organic extract was dried over $MgSO_4$, and concentrated. The residue was purified by chromatography (10-20% ethyl acetate in hexanes) to give the product **(91)** as a colorless oil (1 g, 35%).

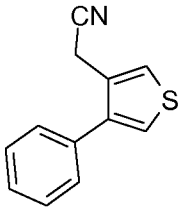
Preparation of (92):



Step 3: (4-Bromo-thiophen-3-yl)-acetonitrile

To a solution of 3-bromo-4-chloromethyl-thiophene **(91)** (1 g, 4.7 mmol) in anhydrous dimethyl sulfoxide at room temperature was added sodium cyanide. The reaction mixture was heated at 80 °C for 3 h, then cooled to room temperature. The mixture was partitioned between ethyl ether and water. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extract was washed with water and brine and then dried over $MgSO_4$, and concentrated. The residue was purified by chromatography (20-40% ethyl acetate in hexanes) to give the product **(92)** as a light yellow oil (0.7 g, 73%).

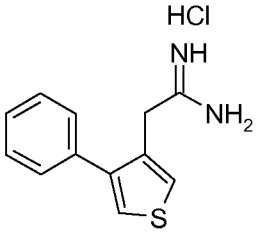
Preparation of (93):



Step 4: (4-Phenyl-thiophen-3-yl)-acetonitrile

To a suspension of (4-bromo-thiophen-3-yl)-acetonitrile **(92)** (0.7 g, 3.5 mmol) and phenylboronic acid (0.6 g, 5.2 mmol) in anhydrous methanol (10 mL) and toluene (20 mL) was added Cs_2CO_3 (3.4 g, 10 mmol). The mixture was degassed with nitrogen, followed by the addition of tetrakis(triphenylphosphine)palladium (0.4 g, 0.3 mmol). The reaction mixture was heated at 80 °C and stirred for 18 h. The mixture was cooled to room temperature and filtered through a short pad of silica gel. The silica gel was washed with ethyl acetate. The filtrate was concentrated. The residue was purified by chromatography (10-30% ethyl acetate in hexanes) to give the product **(93)** as a brown oil (0.7 g, 100%).

Preparation of (94):



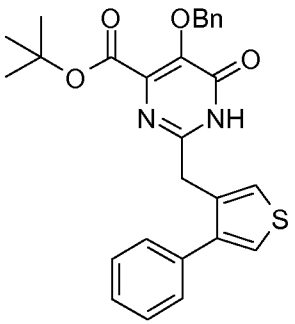
Step 5: 2-(4-Phenyl-thiophen-3-yl)-acetamidine hydrochloride

To a stirred suspension of NH_4Cl (0.55 g, 10 mmol) in anhydrous toluene (20 mL) was added trimethylaluminum (2 M in toluene, 5.2 mL, 10 mmol) at 0 °C. The mixture was then warmed to room temperature and stirred for 2 h. A solution of (4-phenyl-thiophen-3-yl)-acetonitrile **(93)** (0.7 g, 3.5 mmol) in toluene (10 mL) was added to the above reaction mixture and was stirred at 80 °C for 18 h. After completion of the reaction, the mixture was quenched with a suspension of silica gel in chloroform. The mixture was stirred at room temperature for 0.5 h, then filtered through a sintered funnel. The silica gel was washed with methanol. The

combined filtrate was concentrated under reduced pressure to give the crude product **(94)** as an off-white solid (0.9 g, 100%), which was used directly without further purification.

MS (M+H) = 217.1.

Preparation of (95):

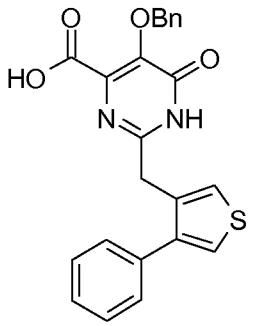


Step 6: 5-Benzyloxy-6-oxo-2-(4-phenyl-thiophen-3-ylmethyl)-1,6-dihydro-pyrimidine-4-carboxylic acid tert-butyl ester

To a stirred solution of 2-(4-phenyl-thiophen-3-yl)-acetamidine hydrochloride **(94)** (0.9 g, 3.5 mmol) and (E)-2-benzyloxy-3-hydroxy-but-2-enedioic acid 4-tert-butyl ester 1-methyl ester **(4)** (1.6 g, 5.2 mmol) in anhydrous methanol (40 mL) was added a methanolic solution (Aldrich, 25%) of sodium methoxide (2.3 g, 11 mmol) at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred for 18 h. The reaction was quenched with aqueous HCl solution (1 N). The pH of the mixture was adjusted to 6-7, then the mixture was evaporated. The residue was partitioned between ethyl acetate and water. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extract was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (30-50% ethyl acetate in hexanes) to give the product **(95)** as a white solid (0.9 g, 53%).

MS (M+H) = 475.1.

Preparation of (96):

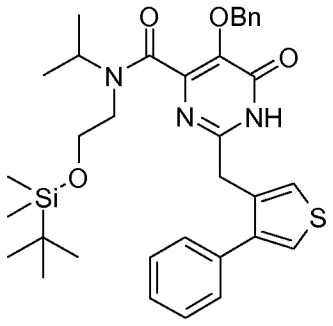


Step 7: 5-Benzyloxy-6-oxo-2-(4-phenyl-thiophen-3-ylmethyl)-1,6-dihydro-pyrimidine-4-carboxylic acid

To a solution of 5-benzyloxy-6-oxo-2-(4-phenyl-thiophen-3-ylmethyl)-1,6-dihydro-pyrimidine-4-carboxylic acid tert-butyl ester **(95)** (0.9 g, 1.9 mmol) in tetrahydrofuran (40 mL) and water (20 mL) was added LiOH (0.2 g, 9.5 mmol) . The reaction mixture was heated at 80 °C for 24 h. TLC analysis indicated the completion of reaction, and the mixture was concentrated to a small volume, then extracted with ethyl acetate. The aqueous potion was acidified with aqueous HCl solution (1 N) to pH 6-7, then extracted with ethyl acetate and dichloromethane. The combined organic extract was washed with brine, dried over $MgSO_4$, and concentrated to give the crude product **(96)** as a white foam (0.3 g, 38%), which was used directly without further purification.

MS (M+H) = 419.1.

Preparation of (97):

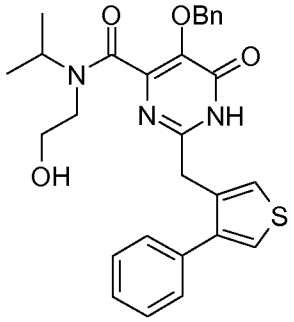


Step 9: 5-Benzyloxy-6-oxo-2-(4-phenyl-thiophen-3-ylmethyl)-1,6-dihydro-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide

To a stirred solution of 5-benzyloxy-6-oxo-2-(4-phenyl-thiophen-3-ylmethyl)-1,6-dihydro-pyrimidine-4-carboxylic acid **(96)** (0.3 g, 0.7 mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amine **(8b)** (0.2 g, 1.1 mmol) in pyridine (30 mL) was slowly added $POCl_3$ (0.2 g, 2.2 mmol) at –10 °C. The reaction mixture was stirred at 0 °C for 2 h. The mixture was loaded into a pad of silica gel and directly purified by chromatography (40-60% ethyl acetate in hexanes) to give the product **(97)** as a white solid (0.22 g, 50%).

MS (M+H) = 618.4.

Preparation of (98):

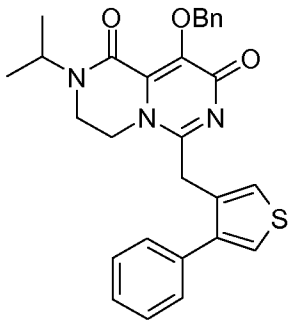


Step 10: 5-Benzyloxy-6-oxo-2-(4-phenyl-thiophen-3-ylmethyl)-1,6-dihydro-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide

To a stirred solution of 5-benzyloxy-6-oxo-2-(4-phenyl-thiophen-3-ylmethyl)-1,6-dihydro-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(97)** (0.22 g, 0.35 mmol) in tetrahydrofuran (10 mL) was added aqueous HCl (1 N, 1 mL, 1 mmol). The reaction mixture was stirred at room temperature for 1 h. The mixture was neutralized with aqueous saturated $NaHCO_3$ solution to pH 7, then extracted with ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extract was dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (50-80% ethyl acetate in hexanes) to give the product **(98)** as a white solid (0.12 g, 67%).

MS (M+H) = 504.2.

Preparation of (99):

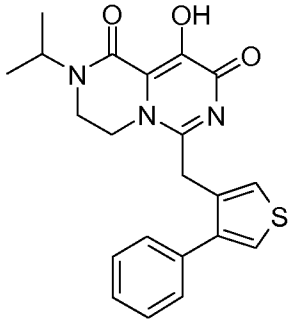


Step 11: 9-Benzyloxy-2-isopropyl-6-(4-phenyl-thiophen-3-ylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a stirred solution of 5-benzyloxy-6-oxo-2-(4-phenyl-thiophen-3-ylmethyl)-1,6-dihydro-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(98)** (0.12 g, 0.24 mmol) in dichloromethane (20 mL) was added triphenylphosphine (0.06 g, 0.24 mmol). The mixture was stirred at room temperature for 10 min. Then diisopropyl azodicarboxylate (DIAD) (0.046 mL, 0.24 mmol) was added. The reaction mixture was stirred at room temperature for 2 h. The mixture was concentrated, and the residue was purified by chromatography (0-10% methanol in ethyl acetate) to give the product **(99)** as a white foam (0.08 g, 69%).

MS (M+H) = 486.3.

Preparation of (100):



Step 12: 9-Hydroxy-2-isopropyl-6-(4-phenyl-thiophen-3-ylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a solution of 9-benzyloxy-2-isopropyl-6-(4-phenyl-thiophen-3-ylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(99)** (0.08 g, 0.17 mmol) in methanol (5 mL) was added

concentrated HCl (aq 37%, 5 mL). The reaction mixture was stirred at 40 °C for 48 h, then concentrated to dryness. To the residue was added aqueous saturated $NaHCO_3$ solution. The mixture was extracted with 10% methanol in dichloromethane twice. The combined organic extract was concentrated. The residue was purified by chromatography (10-20% methanol in dichloromethane) to give the title compound **(100)** as a white solid (35 mg, 54%).

MS (M+H) = 396.2.

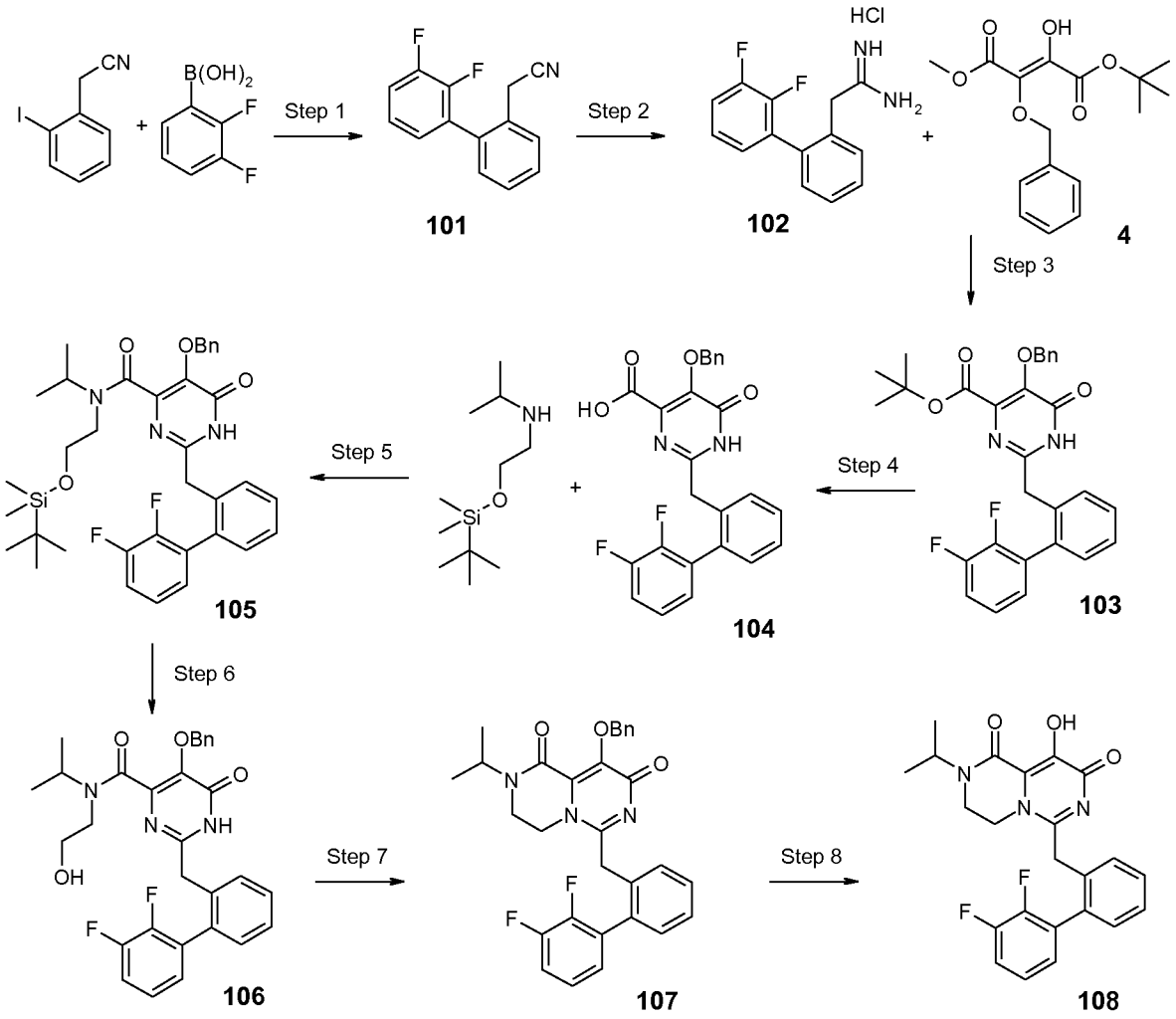
^{1}H NMR (DMSO-d_6) δ: 12.34 (s, 1H), 7.25 – 7.69 (m, 7H), 5.04 (s, 2H), 4.52 – 4.68 (m, 1H), 3.92 – 4.08 (m, 2H), 3.64 – 3.73 (m, 2H), 0.98 – 1.11 (m, 6H)

Example 108

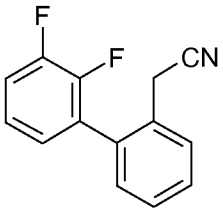
6-(2',3'-Difluoro-biphenyl-2-ylmethyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 16.

Scheme 16



Preparation of (101):

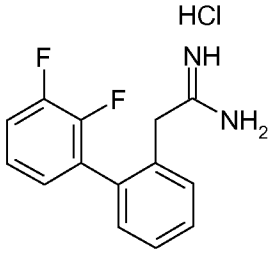


Step 1: (2',3'-Difluoro-biphenyl-2-yl)-acetonitrile

To a suspension of (2-iodo-phenyl)-acetonitrile (Aldrich, 2.4 g, 10 mmol) and 2,3-difluorophenylboronic acid (Aldrich, 2.4 g, 15 mmol) in anhydrous methanol (10 mL) and toluene (20 mL) was added Cs_2CO_3 (9.8 g, 30 mmol). The mixture was degassed with nitrogen, followed by the addition of tetrakis(triphenylphosphine)palladium (1.2 g, 1 mmol).

The reaction mixture was heated at 80 °C and stirred for 18 h. The mixture was cooled to room temperature and filtered through a short pad of silica gel. The silica gel was washed with ethyl acetate. The filtrate was concentrated. The residue was purified by chromatography (10-30% ethyl acetate in hexanes) to give the product **(101)** as a colorless oil (1.4 g, 62%)

Preparation of (102):

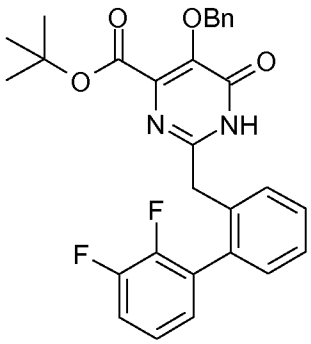


Step 2: 2-(2',3'-Difluoro-biphenyl-2-yl)-acetamidine hydrochloride

To a stirred suspension of NH_4Cl (0.62 g, 11.5 mmol) in anhydrous toluene (50 mL) was added trimethylaluminum (2M in toluene, 13 mL, 26 mmol) at 0 °C. The mixture was then warmed to room temperature and stirred for 2 h. A solution of (2',3'-difluoro-biphenyl-2-yl)-acetonitrile **(101)** (0.88 g, 3.9 mmol) in toluene (10 mL) was added to the above reaction mixture and stirred at 80 °C for 18 h. After completion of the reaction, the mixture was quenched with a suspension of silica gel in chloroform. The mixture was stirred at room temperature for 0.5 h, then filtered through a sintered funnel. The silica gel was washed with methanol. The combined filtrate was concentrated under reduced pressure to give the crude product **(102)** as an off-white solid (0.94 g, 100%), which was used directly without further purification.

MS (M+H) = 247.2.

Preparation of (103):

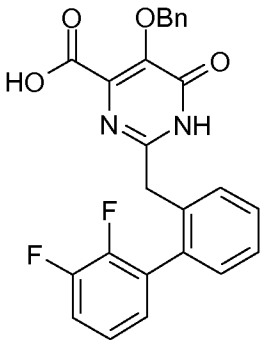


Step 3: 5-Benzyloxy-2-(2',3'-difluoro-biphenyl-2-ylmethyl)-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid tert-butyl ester

To a stirred solution of 2-(2',3'-difluoro-biphenyl-2-yl)-acetamidine hydrochloride **(102)** (0.94 g, 3.3 mmol) and (E)-2-benzyloxy-3-hydroxy-but-2-enedioic acid 4-tert-butyl ester 1-methyl ester **(4)** (1.0 g, 3.3 mmol) in anhydrous methanol (40 mL) at 0 °C was added a methanolic solution (Aldrich, 25%) of sodium methoxide (2.2 g, 10 mmol). The reaction mixture was slowly warmed to room temperature and stirred for 18 h. The reaction was quenched with aqueous HCl solution (1 N). The pH of the mixture was adjusted to 6-7, then the mixture was evaporated. The residue was partitioned between ethyl acetate and water. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extract was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (30-50% ethyl acetate in hexanes) to give the product **(103)** as a white solid (1.2 g, 72%).

MS (M+H) = 505.2.

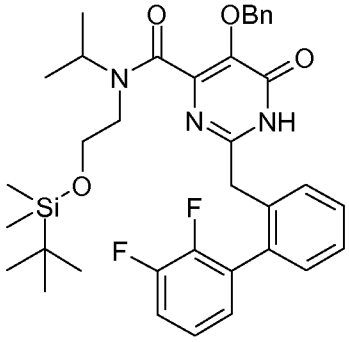
Preparation of (104):



Step 4: 5-Benzyloxy-2-(2',3'-difluoro-biphenyl-2-ylmethyl)-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid

To a solution of 5-benzyloxy-2-(2',3'-difluoro-biphenyl-2-ylmethyl)-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid tert-butyl ester **(103)** (1.2 g, 2.4 mmol) in tetrahydrofuran (40 mL) and water (20 mL) was added LiOH (0.29 g, 12 mmol) . The reaction mixture was heated at 80 °C for 24 h. TLC analysis indicated the completion of reaction, and the mixture was concentrated to a small volume, then extracted with ethyl acetate. The aqueous portion was acidified with aqueous HCl solution (1 N) to pH 3, then extracted with ethyl acetate and dichloromethane. The combined organic extract was washed with brine, dried over $MgSO_4$, and concentrated to give the crude product **(104)** as a white solid (0.85 g, 71%), which was used directly without further purification.

Preparation of (105):

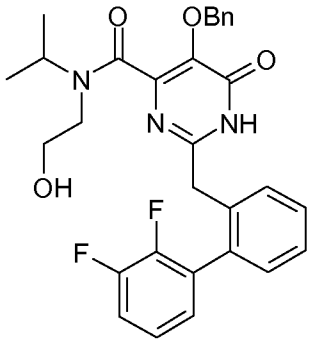


Step 5: 5-Benzyloxy-2-(2',3'-difluoro-biphenyl-2-ylmethyl)-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide

To a stirred solution of 5-benzyloxy-2-(2',3'-difluoro-biphenyl-2-ylmethyl)-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid **(104)** (0.85 g, 1.9 mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amine **(8b)** (0.62 g, 2.8 mmol) in pyridine (25 mL) was slowly added $POCl_3$ (0.27 g, 2.8 mmol) at –10 °C. The reaction mixture was stirred at 0 °C for 2 h. The mixture was loaded into a pad of silica gel and directly purified by chromatography (40-60% ethyl acetate in hexanes) to give the product (**105)** as a white foam (0.7 g, 57%).

MS (M+H) = 648.3.

Preparation of (106):

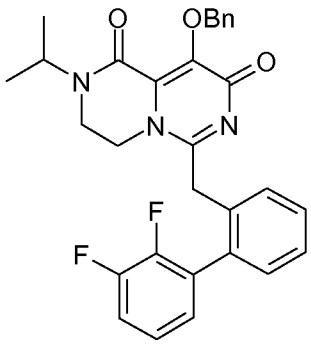


Step 6: 5-Benzyloxy-2-(2',3'-difluoro-biphenyl-2-ylmethyl)-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide

To a stirred solution of 5-benzyloxy-2-(2',3'-difluoro-biphenyl-2-ylmethyl)-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(105)** (0.7 g, 1.1 mmol) in tetrahydrofuran (20 mL) was added aqueous HCl (1 N, 2 mL, 6.6 mmol). The reaction mixture was stirred at room temperature for 1 h. The mixture was neutralized with aqueous saturated $NaHCO_3$ solution to pH 7, then extracted with ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extract was dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (50-80% ethyl acetate in hexanes) to give the product **(106)** as a white solid (0.57 g, 99%).

MS (M+H) = 534.2.

Preparation of (107):

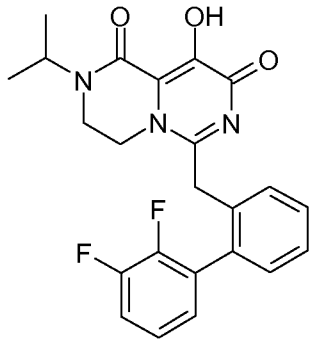


Step 7: 9-Benzyloxy-6-(2',3'-difluoro-biphenyl-2-ylmethyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a stirred solution of 5-benzyloxy-2-(2',3'-difluoro-biphenyl-2-ylmethyl)-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(106)** (0.57 g, 1.8 mmol) in dichloromethane (20 mL) was added triphenylphosphine (0.28 g, 1.1 mmol). The mixture was stirred at room temperature for 10 min. Then diisopropyl azodicarboxylate (DIAD) (0.21 mL, 1.1 mmol) was added. The reaction mixture was stirred at room temperature for 0.5 h. The mixture was concentrated, and the residue was purified by chromatography (50-100% ethyl acetate in hexanes) to give the product **(107)** as a white foam (0.34 g, 62%).

MS (M+H) = 516.2.

Preparation of (108):



Step 8: 6-(2',3'-Difluoro-biphenyl-2-ylmethyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a solution of 9-benzyloxy-6-(2',3'-difluoro-biphenyl-2-ylmethyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(107)** (0.3 g, 0.58 mmol) in methanol (10 mL) was added concentrated HCl (aq 37%, 5 mL). The reaction mixture was stirred at 50 °C for 24 h, then concentrated to dryness. To the residue was added aqueous saturated $NaHCO_3$ solution, the mixture was extracted with 10% methanol in dichloromethane twice. The combined organic extract was concentrated. The residue was purified by chromatography (10-20% methanol in dichloromethane) to give the title compound **(108)** as a white solid (150 mg, 62%).

MS (M+H) = 426.2.

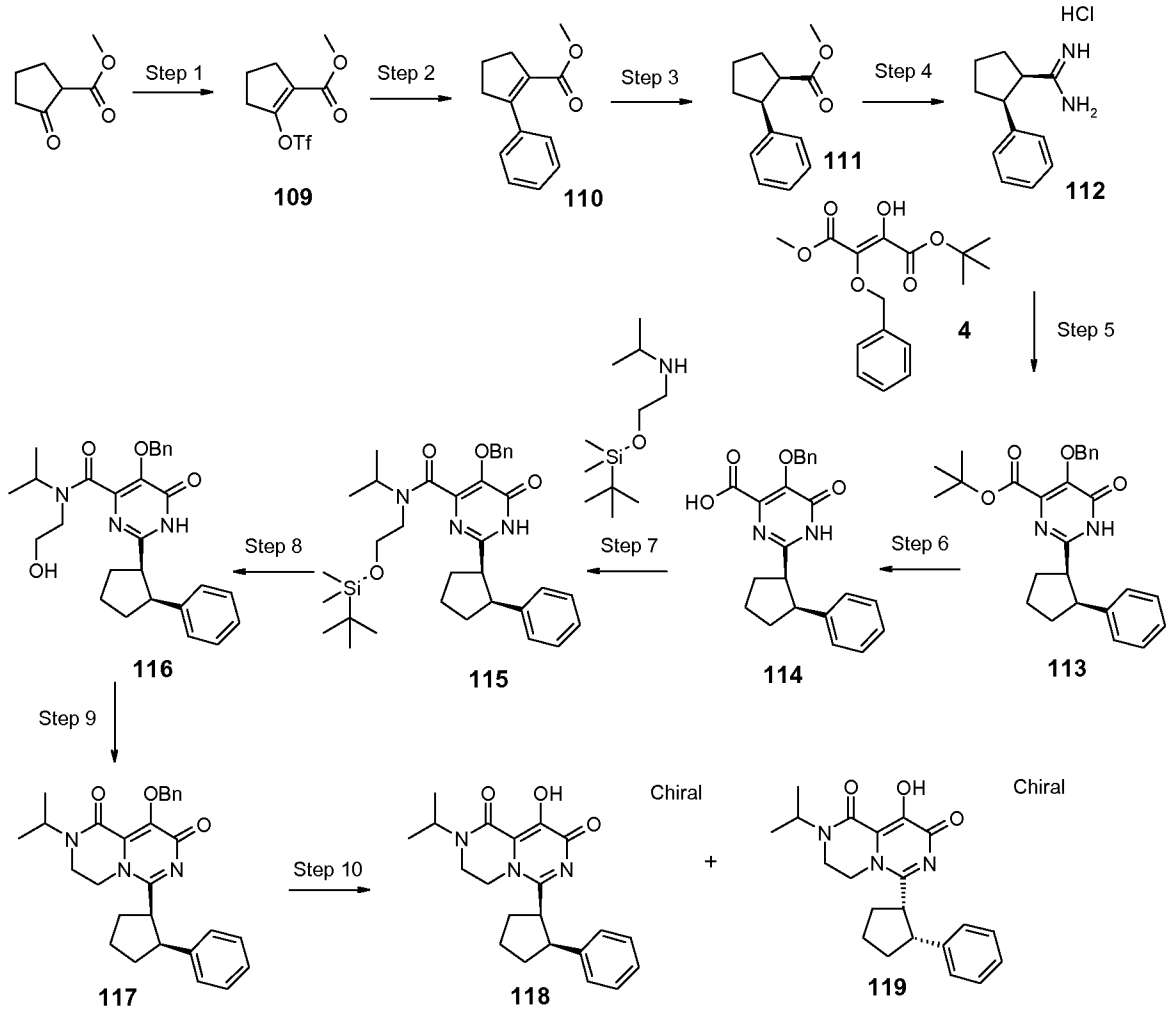
^{1}H NMR (DMSO-d_6) δ: 12.16 – 12.41 (m, 1H), 7.10 – 7.55 (m, 7H), 4.67 (quin, J = 6.8 Hz, 1H), 3.94 (br. s., 2H), 3.77 – 3.90 (m, 2H), 3.48 (t, J = 5.3 Hz, 2H), 1.13 (d, J = 6.8 Hz, 6H)

Examples 118 and 119:

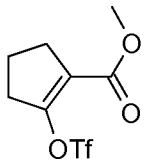
Chiral 9-hydroxy-2-isopropyl-6-((1R,2S)-2-phenyl-cyclopentyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione & chiral 9-hydroxy-2-isopropyl-6-((1S,2R)-2-phenyl-cyclopentyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 17.

Scheme 17



Preparation of (109):

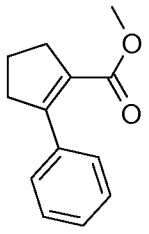


Step 1: 2-Trifluoromethanesulfonyloxy-cyclopent-1-enecarboxylic acid methyl ester

Follow the procedure described by Joel R. Calvin et al Org. Lett. 2012, Vol 14, No. 4, 1038-1041:

To a solution of methyl 2-oxocyclopentanecarboxylate (Aldrich, 7.5 g, 53 mmol) in anhydrous dichloromethane (100 mL) at –25 °C was added diisopropylethylamine (Aldrich, 14 mL, 79 mmol), followed by slow addition of trifluoromethanesulfonic anhydride (9.8 mL, 58 mmol). The reaction mixture was stirred at –25 °C for 1 h, then warmed to room temperature and stirred for 1 h. The mixture was poured into aqueous $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extract was washed with water and brine, and dried over $MgSO_4$, and concentrated. The residue was purified by chromatography (10-30% ethyl acetate in hexanes) to give the product **(109)** as a colorless oil (14 g, 97%).

Preparation of (110):



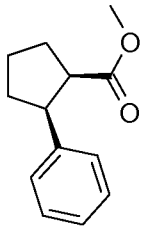
Step 2: 2-Phenyl-cyclopent-1-enecarboxylic acid methyl ester

To a suspension of 2-trifluoromethanesulfonyloxy-cyclopent-1-enecarboxylic acid methyl ester **(109)** (14 g, 51 mmol) and phenylboronic acid (9.3 g, 77 mmol) in anhydrous methanol (40 mL) and toluene (80 mL) was added Cs_2CO_3 (33 g, 102 mmol). The mixture was degassed with nitrogen, followed by the addition of tetrakis(triphenylphosphine)palladium (2.1 g, 1.8 mmol). The reaction mixture was heated at 80 °C and stirred for 18 h. The mixture was cooled

to room temperature and filtered through a short pad of silica gel. The silica gel was washed with ethyl acetate. The filtrate was concentrated. The residue was purified by chromatography (10-30% ethyl acetate in hexanes) to give the product **(110)** as a colorless oil (8.8 g, 85%).

MS (M+H) = 203.2.

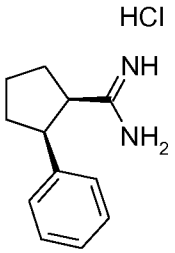
Preparation of (111):



Step 3: Racemic (1R,2S)-2-phenyl-cyclopentanecarboxylic acid methyl ester

To a solution of 2-phenyl-cyclopent-1-enecarboxylic acid methyl ester **(110)** (8.8 g, 43.5 mmol) in methanol (100 mL) under nitrogen was added Pd-C (Aldrich, 10%, 4.4 g). The mixture was vigorously shaken under a hydrogen atmosphere (55 psi) in a Parr for 4 h. The mixture was filtered through a short pad of celite. The filtrate was concentrated to give the crude product **(111)** as a colorless oil (8.4 g, 95%).

Preparation of (112):



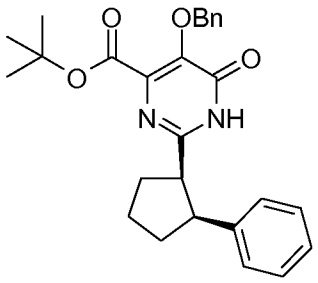
Step 4: Racemic (1R,2S)-2-phenyl-cyclopentanecarboxamidine hydrochloride

To a stirred suspension of NH_4Cl (6.6 g, 122 mmol) in anhydrous toluene (100 mL) was added trimethylaluminum (2 M in toluene, 61 mL, 122 mmol) at 0 °C. The mixture was then warmed to room temperature and stirred for 2 h. A solution of racemic (1R,2S)-2-phenyl-cyclopentanecarboxylic acid methyl ester **(111)** (5 g, 24.5 mmol) in toluene (10 mL) was

added to the above reaction mixture and the mixture was stirred at 80 °C for 18 h. After completion of the reaction, the mixture was quenched with a suspension of silica gel in chloroform. The mixture was stirred at room temperature for 0.5 h, then filtered through a sintered funnel. The silica gel was washed with methanol. The combined filtrate was concentrated under reduced pressure to give the crude product **(112)** as an off-white solid (5.4 g, 98%), which was used directly without further purification.

MS (M+H) = 189.3.

Preparation of (113):

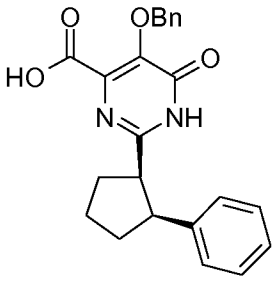


Step 5: Racemic 5-benzyloxy-6-oxo-2-((1R,2S)-2-phenyl-cyclopentyl)-1,6-dihydro-pyrimidine-4-carboxylic acid tert-butyl ester

To a stirred solution of racemic (1R,2S)-2-phenyl-cyclopentanecarboxamidine hydrochloride **(112)** (3.2 g, 14 mmol) and (E)-2-benzyloxy-3-hydroxy-but-2-enedioic acid 4-tert-butyl ester 1-methyl ester **(4)** (4.4 g, 14 mmol) in anhydrous methanol (100 mL) at 0 °C was added a methanolic solution (Aldrich, 25%) of sodium methoxide (9.2 g, 43 mmol). The reaction mixture was slowly warmed to room temperature and stirred for 18 h. The reaction was quenched with aqueous HCl solution (1 N). The pH of the mixture was adjusted to 6-7, then the mixture was evaporated. The residue was partitioned between ethyl acetate and water. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extract was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (30-50% ethyl acetate in hexanes) to give the product **(113)** as a white solid (2.5 g, 39%).

MS (M+H) = 447.2.

Preparation of (114):

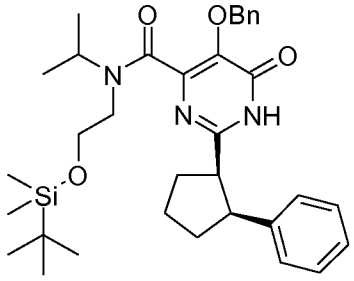


Step 6: Racemic 5-benzyloxy-6-oxo-2-((1R,2S)-2-phenyl-cyclopentyl)-1,6-dihydro-pyrimidine-4-carboxylic acid

To a solution of racemic 5-benzyloxy-6-oxo-2-((1R,2S)-2-phenyl-cyclopentyl)-1,6-dihydro-pyrimidine-4-carboxylic acid tert-butyl ester **(113)** (2.5 g, 5.6 mmol) in tetrahydrofuran (45 mL) and water (15 mL) and methanol (15 mL) was added LiOH (1.8 g, 75 mmol). The reaction mixture was heated at 80 °C for 4 h. TLC analysis indicated the completion of the reaction, and the mixture was concentrated to a small volume, and then extracted with ethyl acetate. The aqueous portion was acidified with aqueous HCl solution (1 N) to pH 2-3, and then extracted with ethyl acetate and dichloromethane. The combined organic extract was washed with brine, dried over $MgSO_4$, and concentrated to give the crude product **(114)** as a white solid (1.75 g, 80%), which was used directly without further purification.

MS (M+H) = 391.2.

Preparation of (115):

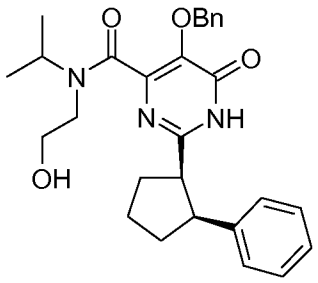


Step 7: Racemic 5-benzyloxy-6-oxo-2-((1R,2S)-2-phenyl-cyclopentyl)-1,6-dihydro-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide

To a stirred solution of racemic 5-benzyloxy-6-oxo-2-((1R,2S)-2-phenyl-cyclopentyl)-1,6-dihydro-pyrimidine-4-carboxylic acid (**114**) (1.75 g, 4.5 mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amine **(8b)** (1.95 g, 9.0 mmol) in pyridine (40 mL) was slowly added $POCl_3$ (0.84 mL, 9.0 mmol) at –10 °C. The reaction mixture was stirred at 0 °C for 2 h. The mixture was loaded into a pad of silica gel and directly purified by chromatography (40-60% ethyl acetate in hexanes) to give the product **(115)** as a white solid (1.84 g, 70%).

MS (M+H) = 590.3.

Preparation of (116):

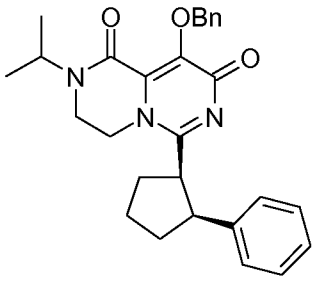


Step 8: Racemic 5-benzyloxy-6-oxo-2-((1R,2S)-2-phenyl-cyclopentyl)-1,6-dihydro-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide

To a stirred solution of racemic 5-benzyloxy-6-oxo-2-((1R,2S)-2-phenyl-cyclopentyl)-1,6-dihydro-pyrimidine-4-carboxylic acid_[2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide (**115**) (1.84 g, 3.1 mmol) in tetrahydrofuran (10 mL) was added aqueous HCl (1 N, 3.1 mL, 3.1 mmol). The reaction mixture was stirred at room temperature for 1 h. The mixture was neutralized with aqueous saturated $NaHCO_3$ solution to pH 7, and then extracted with ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extract was dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (50-80% ethyl acetate in hexanes) to give the product **(116)** as a white foam (1.2 g, 81%).

MS (M+H) = 476.2.

Preparation of (117):



Step 9: Racemic 9-benzyloxy-2-isopropyl-6-((1R,2S)-2-phenyl-cyclopentyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a stirred solution of racemic 5-benzyloxy-6-oxo-2-((1R,2S)-2-phenyl-cyclopentyl)-1,6-dihydro-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(116)** (1.2 g, 2.5 mmol) in dichloromethane (50 mL) was added triphenylphosphine (0.66 g, 2.5 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 min. Then diisopropyl azodicarboxylate (DIAD) (0.49 mL, 2.5 mmol) was added. The reaction mixture was stirred at room temperature for 2 h. The mixture was concentrated, and the residue was purified by chromatography (50-100% ethyl acetate in hexanes) to give the product **(117)** as a white solid (0.3 g, 26%).

MS (M+H) = 458.2.

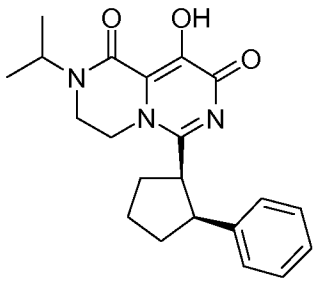
Preparation of (118) and (119):

Step 10: Chiral 9-hydroxy-2-isopropyl-6-((1R,2S)-2-phenyl-cyclopentyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione & chiral 9-hydroxy-2-isopropyl-6-((1S,2R)-2-phenyl-cyclopentyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a solution of racemic 9-benzyloxy-2-isopropyl-6-((1R,2S)-2-phenyl-cyclopentyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(117)** (0.3 g, 0.66 mmol) in methanol (10 mL) was added concentrated HCl (aq 37%, 5 mL). The reaction mixture was stirred at room temperature for 48 h, then concentrated to dryness. To the residue was added aqueous saturated $NaHCO_3$ solution, the mixture was extracted with 10% methanol in dichloromethane twice. The combined organic extract was concentrated. The residue was purified first by

reverse phase chromatography (C18 column, 50% MeCN in water), and then separated by chiral SFC into two enantiomers.

Chiral 9-hydroxy-2-isopropyl-6-((1R,2S)-2-phenyl-cyclopentyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(118)**:

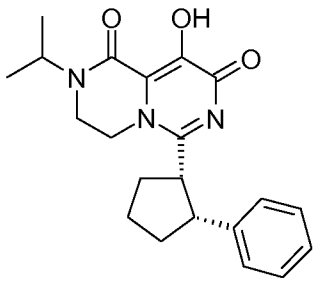


as a white solid (37 mg, 15%).

MS (M+H) = 368.2

^{1}H NMR (DMSO–d_6) δ: 12.40 (br. s., 1H), 7.27 (d, J = 4.3 Hz, 4H), 6.95 – 7.24 (m, 1H), 4.65 (s, 1H), 3.89 – 4.16 (m, 2H), 3.41 – 3.66 (m, 3H), 3.19 – 3.36 (m, 1H), 2.06 – 2.30 (m, 2H), 1.72 – 1.95 (m, 4H), 0.86 – 1.27 (m, 6H)

Chiral 9-hydroxy-2-isopropyl-6-((1S,2R)-2-phenyl-cyclopentyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(119)**:



as a white solid (41 mg, 17%).

MS (M+H) = 368.2.

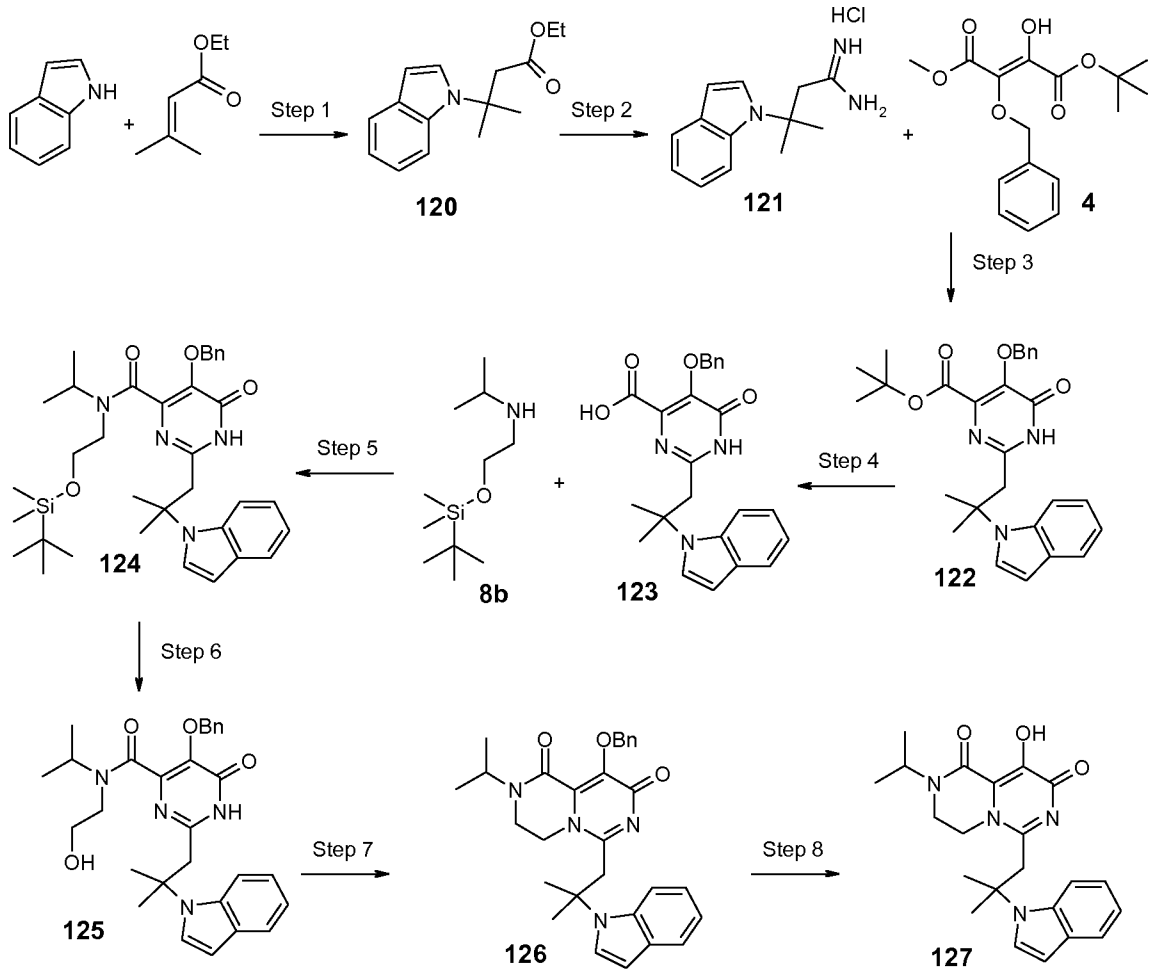
^{1}H NMR (DMSO-d_6) δ: 12.39 (s, 1H), 7.27 (d, J = 4.3 Hz, 4H), 7.08 – 7.22 (m, 1H), 4.51 – 4.79 (m, 1H), 3.89 – 4.15 (m, 2H), 3.41 – 3.66 (m, 3H), 3.19 – 3.36 (m, 1H), 1.95 – 2.33 (m, 2H), 1.63 – 1.90 (m, 4H), 0.91 – 1.36 (m, 6H)

Example 127

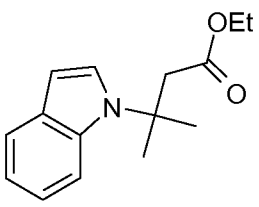
9-Hydroxy-6-(2-indol-1-yl-2-methyl-propyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 17.

Scheme 17



Preparation of (120):

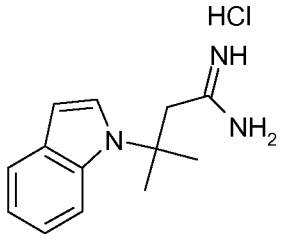


Step 1: 3-Indol-1-yl-3-methyl-butyric acid ethyl ester

To a solution of ethyl 3,3-dimethylacrylate (Aldrich, 1 g, 7.8 mmol) and indole (0.3 g, 2.6 mmol) in anhydrous dichloromethane (20 mL) was added potassium tert-butoxide (0.9 g, 7.7 mmol). The reaction mixture was heated at 50 °C for 24 h, then cooled to room temperature. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extract was washed with water, dried over $MgSO_4$, and conecntrated. The residue was purified by chromatography (10-20% ethyl acetate in hexanes) to give the product **(120)** as a white solid.(0.4 g, 64%).

MS (M+H) = 246.2.

Preparation of (121):

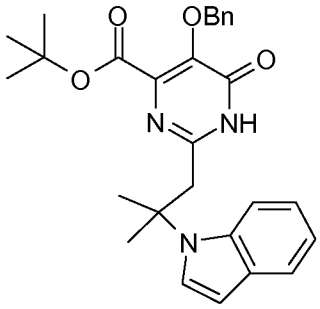


Step 2: 3-Indol-1-yl-3-methyl-butyramidine

To a stirred suspension of NH_4Cl (0.44 g, 8.2 mmol) in anhydrous toluene (40 mL) was added trimethylaluminum (2M in toluene, 4.1 mL, 8.2 mmol) at 0 °C. The mixture was then warmed to room temperature and stirred for 2 h. A solution of 3-indol-1-yl-3-methyl-butyric acid ethyl ester **(120)** (0.4 g, 1.6 mmol) in toluene (10 mL) was added to the above reaction mixture and stirred at 80 °C for 18 h. After completion of the reaction, the mixture was quenched with a suspension of silica gel in chloroform. The mixture was stirred at room temperature for 0.5 h, then filtered through a sintered funnel. The silica gel was washed with methanol. The combined filtrate was concentrated under reduced pressure. The crude product was purified by chromatography (10-100% methanol in dichloromethane) to give the product **(121)** as a brown solid (0.4 g, 100%).

MS (M+H) = 216.3

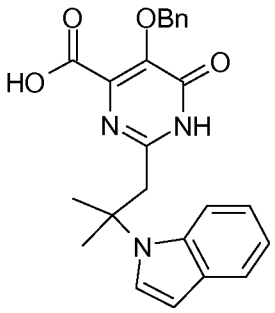
Preparation of (122):



Step 3: 5-Benzyloxy-2-(2-indol-1-yl-2-methyl-propyl)-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid tert-butyl ester

To a stirred solution of 3-indol-1-yl-3-methyl-butyramidine hydrochloride **(121)** (0.4 g, 1.6 mmol) and (E)-2-benzyloxy-3-hydroxy-but-2-enedioic acid 4-tert-butyl ester 1-methyl ester **(4)** (0.5 g, 1.6 mmol) in anhydrous methanol (40 mL) at 0 °C was added a methanolic solution (Aldrich, 25%) of sodium methoxide (1 g, 4.8 mmol). The reaction mixture was slowly warmed to room temperature and stirred for 18 h. The reaction was quenched with aqueous HCl solution (1 N). The pH of the mixture was adjusted to 6-7, then the mixture was evaporated. The residue was partitioned between ethyl acetate and water. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extract was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (30-50% ethyl acetate in hexanes) to give the product **(122)** as a white solid (0.18 g, 24%).

Preparation of (123):

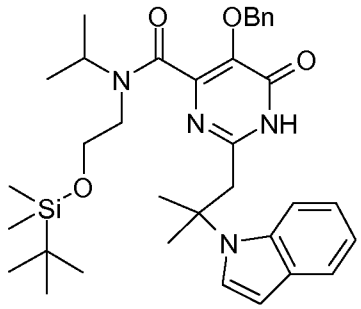


Step 4: 5-Benzyloxy-2-(2-indol-1-yl-2-methyl-propyl)-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid

To a solution of 5-benzyloxy-2-(2-indol-1-yl-2-methyl-propyl)-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid tert-butyl ester **(122)** (0.18 g, 0.38 mmol) in tetrahydrofuran (30 mL) and water (10 mL) and methanol (10 mL) was added LiOH (46 mg, 1.9 mmol). The reaction mixture was heated at 80 °C for 4 h. TLC analysis indicated the completion of reaction. The mixture was concentrated to a small volume, and then extracted with ethyl acetate. The aqueous potion was acidified with aqueous HCl solution (1 N) to pH 3, then extracted with ethyl acetate and dichloromethane. The combined organic extract was washed with brine, dried over $MgSO_4$, and concentrated to give the crude product **(123)** as an off-white solid (0.14 g, 88%), which was used directly without further purification.

MS (M+H) = 418.

Preparation of (124):

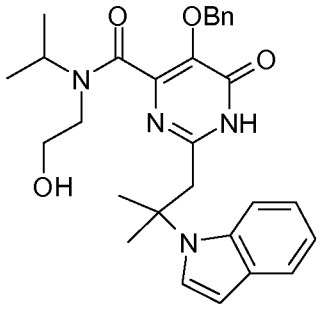


Step 5: 5-Benzyloxy-2-(2-indol-1-yl-2-methyl-propyl)-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide

To a stirred solution of 5-benzyloxy-2-(2-indol-1-yl-2-methyl-propyl)-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid **(123)** (0.14 g, 0.34 mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amine **(8b)** (0.15 g, 0.67 mmol) in pyridine (20 mL) at –10 °C was slowly added $POCl_3$ (0.06 g, 0.67 mmol) . The reaction mixture was stirred at 0 °C for 2 h. The mixture was loaded into a pad of silica gel and directly purified by chromatography (40-60% ethyl acetate in hexanes) to give the product **(124)** as a white solid (0.16 g, 77%).

MS (M+H) = 617.3.

Preparation of (125):

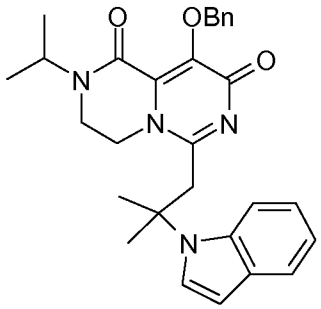


Step 6: 5-Benzyloxy-2-(2-indol-1-yl-2-methyl-propyl)-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide

To a stirred solution of 5-benzyloxy-2-(2-indol-1-yl-2-methyl-propyl)-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(124)** (0.16 g, 0.26 mmol) in tetrahydrofuran (10 mL) was added aqueous HCl (1 N, 1 mL, 1 mmol). The reaction mixture was stirred at room temperature for 1 h. The mixture was neutralized with aqueous saturated $NaHCO_3$ solution to pH 7, then extracted with ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extract was dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (0-10% methanol in ethyl acetate) to give the product **(125)** as a white solid (98 mg, 75%).

MS (M+H) = 503.2.

Preparation of (126):

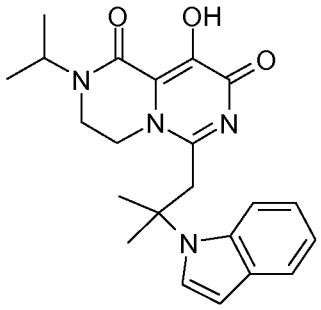


Step 7: 9-Benzyloxy-6-(2-indol-1-yl-2-methyl-propyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a stirred solution of 5-benzyloxy-2-(2-indol-1-yl-2-methyl-propyl)-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(125)** (98 mg, 0.2 mmol) in dichloromethane (20 mL) was added triphenylphosphine (51 g, 0.2 mmol). The mixture was stirred at room temperature for 10 min. Then diisopropyl azodicarboxylate (DIAD) (0.038 mL, 0.2 mmol) was added. The reaction mixture was stirred at room temperature for 2 h. The mixture was concentrated, and the residue was purified by chromatography (0-10% methanol in ethyl acetate) to give the product **(126)** as a white solid (43 mg, 46%).

MS (M+H) = 485.2.

Preparation of (127):



Step 8: 9-Hydroxy-6-(2-indol-1-yl-2-methyl-propyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a solution of 9-benzyloxy-6-(2-indol-1-yl-2-methyl-propyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(126)** (43 mg, 0.09 mmol) in methanol (10 mL) was added concentrated HCl (aq 37%, 5 mL). The reaction mixture was stirred at room temperature for 24 h, then concentrated to dryness. The residue was purified by reverse phase chromatography (20-50% MeCN-TFA in water-TFA) to give the title compound **(127)** as trifluoroacetic acid salt: off-white solid (22 mg, 63%).

MS (M+H) = 395.2.

^{1}H NMR (DMSO-d_6) δ: 12.43(s, 1H), 6.74 – 7.86 (m, 5H), 6.45 (d, J = 3.3 Hz, 1H), 4.62 – 4.74 (m, 1H), 3.35 (s, 2H), 2.81 – 2.89 (m, 2H), 2.48 – 2.52 (m, 2H), 1.11 – 1.28 (m, 6H), 0.95 – 1.06 (m, 6H)

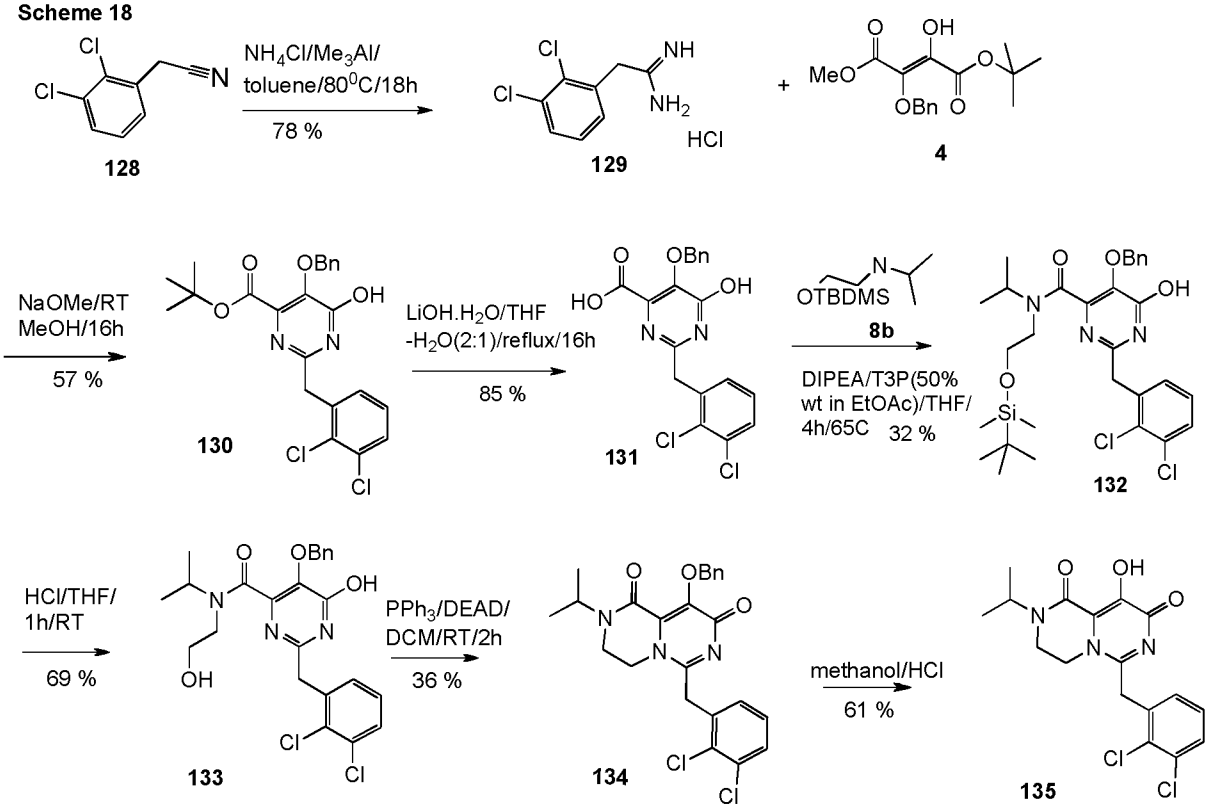
Example 135

6-(2,3-Dichlorobenzyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

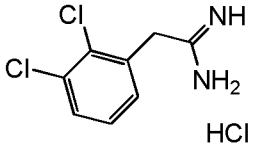
The synthetic procedure used in this preparation is outlined in Scheme 18.

Synthetic route for 135:

Scheme 18



Preparation of (129):

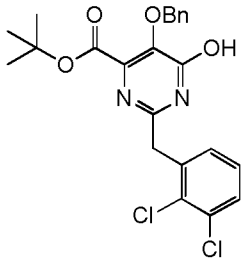


Step 1: 2-(2,3-Dichlorophenyl)-acetamidine hydrochloride

To a stirred suspension of NH_4Cl (4.29g, 80.21mmol) in dry toluene (120mL) was added trimethyl aluminium (2M in toluene, 41mL, 80.21mmol) at 5 °C. The mixture was then warmed to room temperature and stirred for 2h. A solution of (2,3-dichlorophenyl)-acetonitrile **(128)** (5g, 26.73mmol) in toluene (25mL) was added to the mixture and stirred for 14h at 80°C. After completion of the reaction, it was quenched with a suspension of silica gel in chloroform and the reaction mixture was stirred for half an hour at room temperature and filtered through a sintered funnel. The silica gel was washed with methanol and the combined filtrate was concentrated under reduced pressure to get 2-(2,3-dichlorophenyl)-acetamidine hydrochloride salt **(129)** (5g, 78%) as an off-white solid.

LCMS: 203 (M+H).

Preparation of (130):

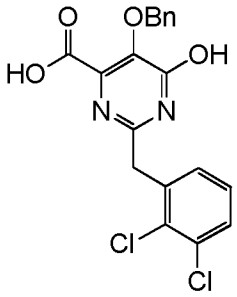


Step 2: 5-Benzyloxy-2-(2,3-dichlorobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester

To a stirred solution of 2-(2,3-dichlorophenyl)-acetamidine hydrochloride salt **(129)** (10g, 41.84mmol) and (E)-2-benzyloxy-3-hydroxy-but-2-enedioic acid 4-tert-butyl ester 1-methyl ester **(4)** (19.33g, 62.76 mmol) in methanol (300mL) was added sodium methoxide (6.7g, 125.52mmol) at 0 °C. Then the reaction mixture was allowed to warm to room temperature, and was stirred for 16h. After completion of the reaction, it was quenched with 1N HCl, the methanol was evaporated and water was added. The mixture was extracted with ethyl acetate and the separated organic part was dried over sodium sulfate and concentrated under reduced pressure to get a crude product, which was purified by a normal silica column using 30% ethyl acetate in hexane to get 5-benzyloxy-2-(2,3-dichlorobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester **(130)** (10g, 57.8%) as a brown solid.

LCMS: 461 (M+H).

Preparation of (131):

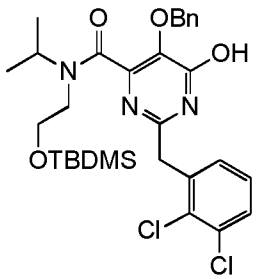


Step 3: 5-Benzyloxy-2-(2,3-dichlorobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid

To a stirred solution of 5-benzyloxy-2-(2,3-dichlorobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester **(130)** (10g, 21.69 mmol) in a mixture of THF-water (2:1, 90mL) was added lithium hydroxide, monohydrate (4.55g, 108.42mmol). The mixture was refluxed for 18h. After completion of the reaction, the volume was reduced by evaporation as much as possible, water was added, and the residue was washed with ethyl acetate to remove non-acidic impurities. The separated aqueous part was acidified with 2(N) HCl to bring the pH to approx. 5 to 6. The acidified aqueous part was extracted with dichloromethane, the separated organic part was dried over sodium sulfate and concentrated under reduced pressure to get 5-benzyloxy-2-(2,3-dichlorobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid **(131)** (7.5g, 85.32%) as a white solid.

LCMS: 405.4(M+H).

Preparation of (132):



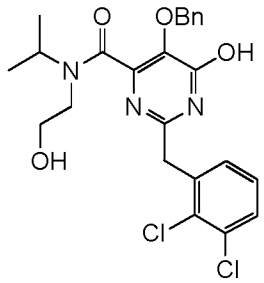
Step 4: 5-Benzyloxy-2-(2,3-dichlorobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide

To a stirred solution of 5-benzyloxy-2-(2,3-dichlorobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid **(131)** (5.5 g, 13.58 mmol) in tetrahydrofuran (70mL) were added N,N-

diisopropylethylamine (9.36 mL, 54.32 mmol) and T_3P (17.3 mL, 27.16 mmol) followed by [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amine **(8b)** (5.89g, 27.16 mmol) at room temperature. The mixture was heated at 65°C for 4h. After completion of the reaction, water was added and the mixture was extracted with ethyl acetate. The separated organic part was dried and concentrated to get a crude product which was purified by a normal silica column using 10 to 20% ethyl acetate in hexane to obtain 5-benzyloxy-2-(2,3-dichlorobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide (132) (2.7g, 32.8%) as a light yellow solid.

LCMS: 604.2 (M+H).

Preparation of (133):

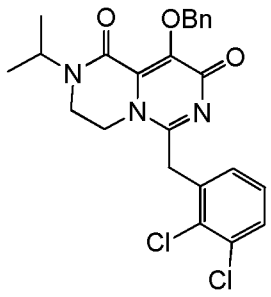


Step 5: 5-Benzyloxy-2-(2,3-dichlorobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide

To a stirred solution of 5-benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(132)** (3g, 4.967mmol) in tetrahydrofuran (45mL) was added 1(N) HCl (7.5ml, 7.5mmol) at room temperature and the mixture was stirred for 60 min at room temperature. After completion of the reaction, the mixture was neutralized with 1N sodium hydroxide aqueous solution, extracted with ethyl acetate, dried over sodium sulfate and concentrated under reduced pressure to get a crude product which was purified by a normal silica column using 60% ethyl acetate in hexane to get 5-benzyloxy-2-biphenyl-2-ylmethyl-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide **(133)** (1.7g, 69.8%) as a white solid.

LCMS: 490.2 (M+H).

Preparation of (134):

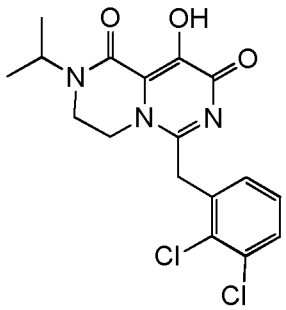


Step 6: 9-Benzyloxy-6-(2,3-dichlorobenzyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a stirred solution of 5-benzyloxy-2-(2,3-dichlorobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(133)** (200 mg, 0.408mmol) in dichloromethane (5mL) was added triphenyl phosphine (161mg, 0.612mmol) at room temperature and the mixture was stirred for 10 min. Then DEAD (106mg, 0.612mmol) was added at room temperature and the mixture was stirred for another 2h. After completion of the reaction, the mixture was concentrated under reduced pressure to get a crude product, which was purified by a normal silica column using 2% methanol in dichloromethane to afford 9-benzyloxy-6-(2,3-dichlorobenzyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(134)** (70mg, 36.3%) as a white solid.

LCMS: 472 (M+H).

Preparation of (135):



Step 7: 6-(2,3-Dichlorobenzyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a stirred solution of 9-benzyloxy-6-(2,3-dichlorobenzyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(134)** (70mg, 0.095mmol) in methanol (3mL) was added

concentrated HCl (3mL) and the reaction mixture was stirred for 5 h at room temperature. After completion of the reaction, the mixture was evaporation and the residue was basified with saturated aqueous $NaHCO_3$ solution. The mixture was extracted with 10% methanol in dichloromethane, the organic part was separated. The drying over sodium sulfate was conducted and concentration to get a crude product, which was washed with ether followed by pentene to get 6-(2,3-dichlorobenzyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(135)** (35mg, 61.7%) as a brown colored solid.

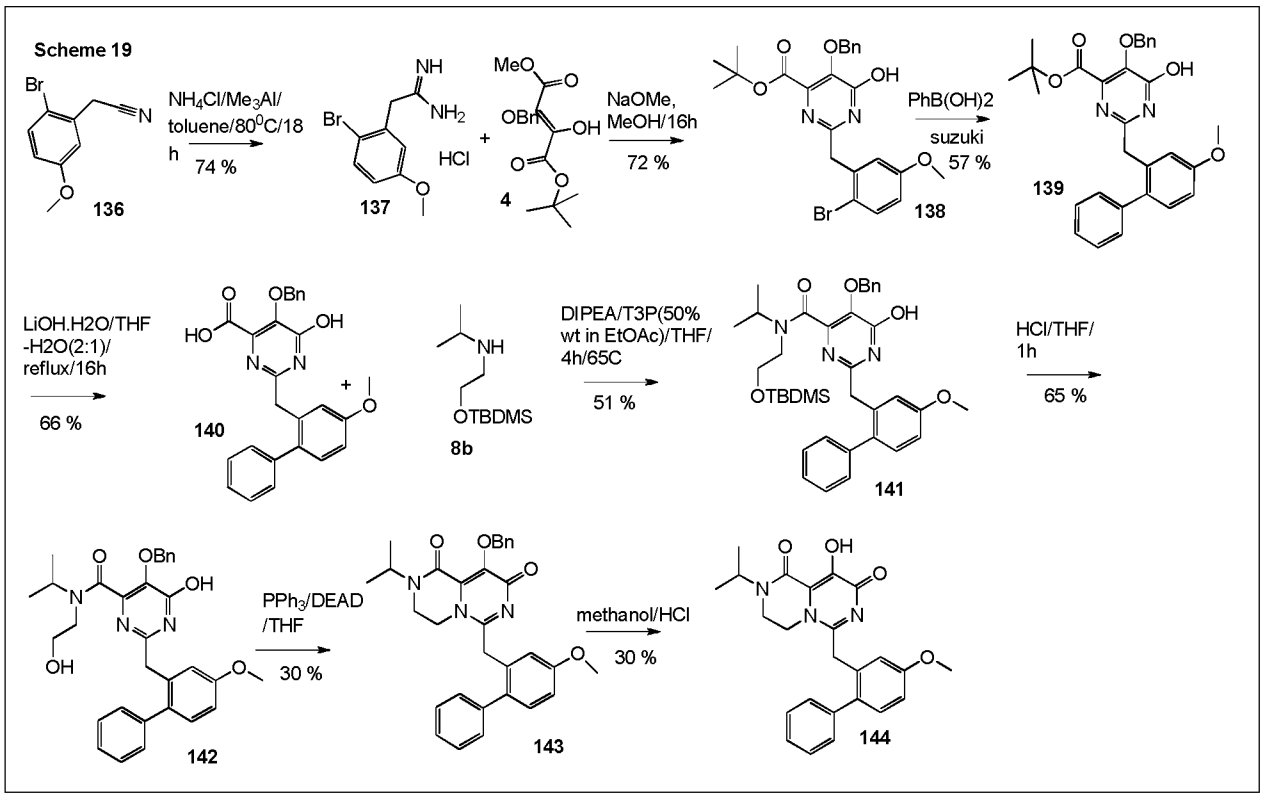
LCMS: 381.8 (M+H).

Example 144

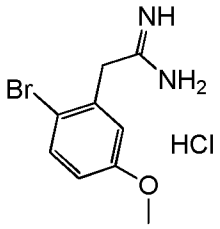
9-Hydroxy-2-isopropyl-6-(4-methoxy-biphenyl-2-ylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 19.

Synthetic route for 144:



Preparation of (137):

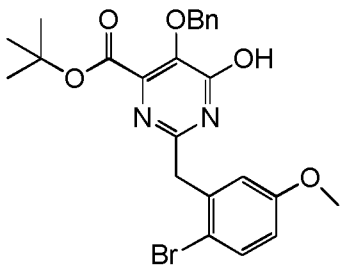


Step 1: 2-(2-Bromo-5-methoxy-phenyl)-acetamidine hydrochloride salt.

To a stirred suspension of NH_4Cl (3.58g, 66.37mmol) in dry toluene (100mL) was added trimethyl aluminium (2M in toluene, 33.18mL, 66.37mmol) at 5 °C, then the mixture was warmed to room temperature and stirred for 2h. A solution of (2-bromo-5-methoxy-phenyl)-acetonitrile **(136)** (5g, 22.12mmol) in toluene (25mL) was added to the above reaction mixture and the mixture was then stirred for 14h at 80°C. After completion of the reaction, it was quenched with a suspension of silica gel in chloroform and the reaction mixture was stirred for half an hour at room temperature and filtered through a sintered funnel, the silica gel was washed with methanol and the combined filtrate was concentrated under reduced pressure to get 2-(2-bromo-5-methoxyphenyl)-acetamidine hydrochloride salt as a crude product **(137)** (4g, 74.37%) a as white solid.

LCMS: 244 (M+H).

Preparation of (138):



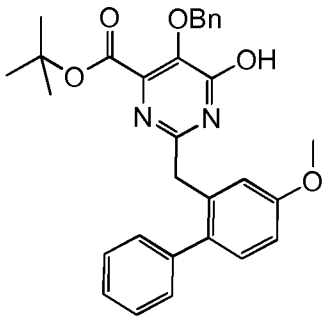
Step 2: 5-Benzyloxy-2-(2-bromo-5-methoxybenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester

5-Benzyloxy-2-(2-bromo-5-methoxybenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester **(138)** (6.5g, 72.3%) as a yellow solid was synthesized from 2-(2-bromo-5-methoxy-phenyl)-acetamidine hydrochloride salt. **(137)** (5g, 17.92mmol) and (E)-2-benzyloxy-3-

hydroxy-but-2-enedioic acid 4-tert-butyl ester 1-methyl ester **(4)** (8.28g, 26.88mmol) following the procedure as described for 5-benzyloxy-2-(2,3-dichlorobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester **(138)**.

LCMS: 503.4(M+H).

Preparation of (139):

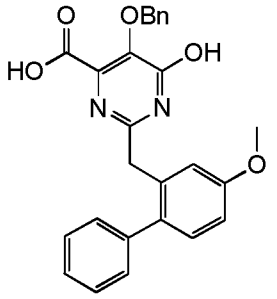


Step 3: 5-Benzyloxy-6-hydroxy-2-(4-methoxybiphenyl-2-ylmethyl)-pyrimidine-4-carboxylic acid tert-butyl ester

To a stirred solution of 5-benzyloxy-2-(2-bromo-5-methoxybenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester **(138)** (3g, 5.988mmol) in n-butanol : water (3:1, 12mL) were added phenyl boronic acid (1.096g, 8.982mmol), X-Phos (427mg, 0.898mmol), K_3PO_4 (4.44g, 20.958mmol) and $Pd(dba)_2$ (275mg, 0.479mmol).The reaction mixture was refluxed for 10h. After completion of the reaction, the mixture was evaporated to get a crude product which was purified by a normal silica column using 2% methanol in dichloromethane to afford 5-benzyloxy-6-hydroxy-2-(4-methoxybiphenyl-2-ylmethyl)-pyrimidine-4-carboxylic acid tert-butyl ester **(139)** (1.7g, 56.94%) as an off-white solid.

LCMS: 499.2(M+H).

Preparation of (140):

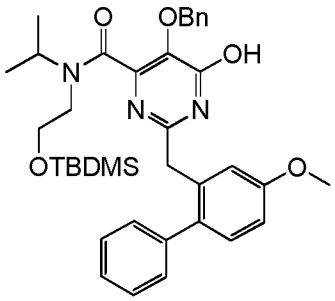


Step 4: 5-Benzyloxy-6-hydroxy-2-(4-methoxy-biphenyl-2-ylmethyl)-pyrimidine-4-carboxylic acid

5-Benzyloxy-6-hydroxy-2-(4-methoxy-biphenyl-2-ylmethyl)-pyrimidine-4-carboxylic acid **(140)** (700mg, 65.6%) as a white solid was synthesized from 5-benzyloxy-6-hydroxy-2-(4-methoxybiphenyl-2-ylmethyl)-pyrimidine-4-carboxylic acid tert-butyl ester **(139)** (1.2g, 2.41mmol) following the procedure as described for 5-benzyloxy-2-(2,3-dichlorobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid **(140)**.

LCMS: 441.4(M+H).

Preparation of (141):

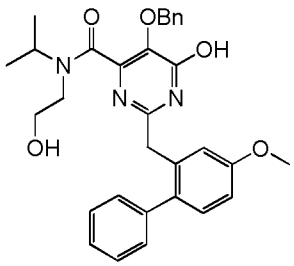


Step 5: 5-Benzyloxy-6-hydroxy-2-(4-methoxybiphenyl-2-ylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide

5-Benzyloxy-6-hydroxy-2-(4-methoxybiphenyl-2-ylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(141)** (520mg, 51.15%) as a yellow sticky liquid was synthesized from 5-benzyloxy-6-hydroxy-2-(4-methoxybiphenyl-2-ylmethyl)-pyrimidine-4-carboxylic acid **(140)** (700mg, 1.584mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amine **(8b)** (687mg, 3.167mmol) following the procedure as described for 5-benzyloxy-2-(2,3-dichlorobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(141)**.

LCMS: 642.2(M+H).

Preparation of (142):

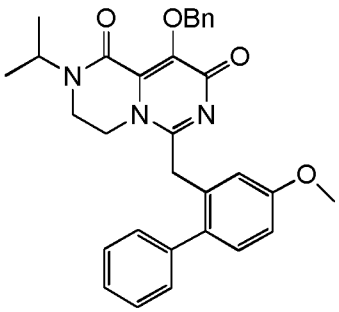


Step 6: 5-Benzyloxy-6-hydroxy-2-(4-methoxybiphenyl-2-yl-methyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide

5-Benzyloxy-6-hydroxy-2-(4-methoxy-biphenyl-2-yl-methyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(142)** (280mg, 65.42%) was synthesized from 5-benzyloxy-6-hydroxy-2-(4-methoxy-biphenyl-2-ylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(141)** (520mg, 0.861mmol) following the procedure as described for 5-benzyloxy-2-biphenyl-2-yl-methyl-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide **(142)**.

LCMS: 526.6(M+H).

Preparation of (143):



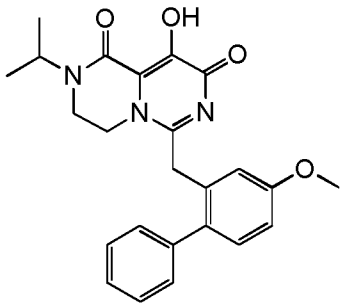
Step 7: 9-Benzyloxy-2-isopropyl-6-(4-methoxy-biphenyl-2-ylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

9-Benzyloxy-2-isopropyl-6-(4-methoxy-biphenyl-2-ylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(143)** (33mg, 29.68%) as a white solid was synthesized from 5-

benzyloxy-6-hydroxy-2-(4-methoxybiphenyl-2-ylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(142)** (115mg, 0.218 mmol) following the procedure as described for 9-benzyloxy-6-(2,3-dichlorobenzyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione**(143)**.

LCMS: 510(M+H).

Preparation of (144):



Step 8: 9-Hydroxy-2-isopropyl-6-(4-methoxy-biphenyl-2-ylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

9-Hydroxy-2-isopropyl-6-(4-methoxy-biphenyl-2-ylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(144)** (18mg, 29.69%) as a white solid was synthesized from 9-benzyloxy-2-isopropyl-6-(4-methoxy-biphenyl-2-ylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(143)** (82mg, 0.161mmol) following the procedure as described for 6-(2,3-dichlorobenzyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(144)**.

LCMS: 420.2(M+H).

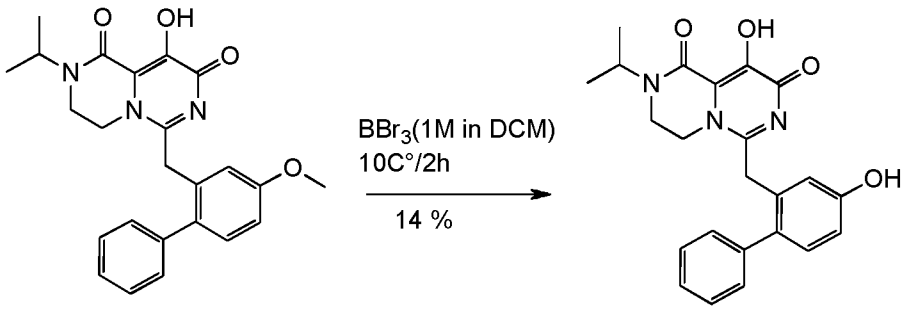
Example 145

9-Hydroxy-6-(4-hydroxy-biphenyl-2-ylmethyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 20.

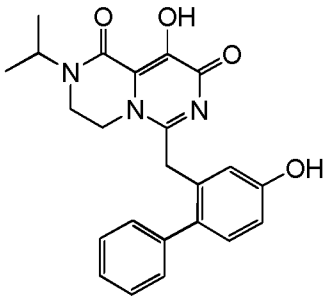
Synthetic route for (145):

Scheme 20



144 **145**

Preparation of (145):



9-Hydroxy-6-(4-hydroxy-biphenyl-2-ylmethyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a stirred solution of 9-hydroxy-2-isopropyl-6-(4-methoxy-biphenyl-2-ylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(145)** (230mg, 0.548mmol) in dichloromethane (10mL) was added BBr_3 (1M in dichloromethane, 1.64mL, 1.64mmol) at ice temperature under nitrogen and the mixture was allowed to stirred for 2 h at room temperature. On completion of the reaction, the mixture was evaporated under reduced pressure and the residue was diluted with dichloromethane (100mL) and water. The separated organic layer was washed with saturated $NaHCO_3$ solution (50mL), water (50mL), brine (50mL), and dried over sodium sulfate and concentrated under reduced pressure. The obtained crude product was purified by preparative HPLC to obtain 9-hydroxy-6-(4-hydroxy-biphenyl-2-ylmethyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(145)** (32mg, 14.39%) as an off-white solid.

LCMS: 406.4(M+H).

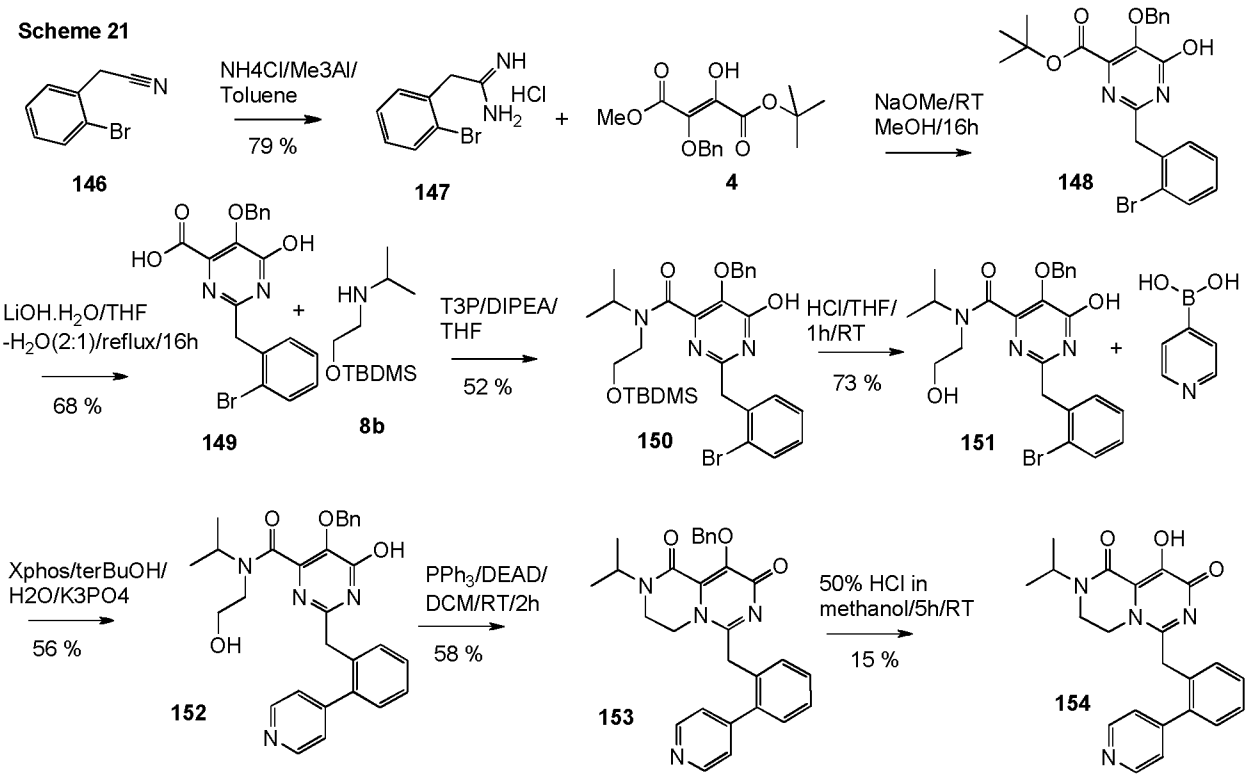
Example 154

9-Hydroxy-2-isopropyl-6-(2-pyridin-4-yl-benzyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

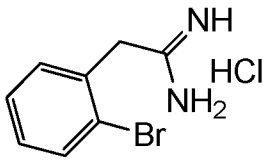
The synthetic procedure used in this preparation is outlined in Scheme 21.

Synthetic route for (154):

Scheme 21



Preparation of (147)

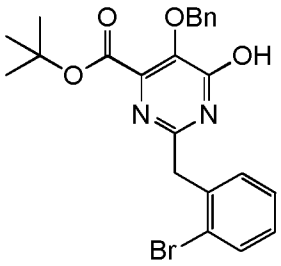


Step 1: 2-(2-Bromo-phenyl)-acetamidine hydrochloride salt

2-(2-Bromo-phenyl)-acetamidine hydrochloride salt **(147)** (20g, 78.58%) as a white solid was synthesized from (2-bromo-phenyl)-acetonitrile **(146)** (5g, 25.50mmol) following the procedure as described for 2-(2-bromo-5-methoxy-phenyl)-acetamidine hydrochloride salt as a crude product **(147).**

LCMS: 215(M+H).

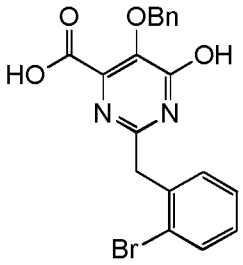
Preparation of (148):



Step 2: 5-Benzyloxy-2-(2-bromobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester

5-Benzyloxy-2-(2-bromobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester **(148)** (28g, crude) as a brown solid was synthesized from 2-(2-bromophenyl)-acetamidine hydrochloride salt **(147)** (17.76g, 71.32mmol) and (E)-2-benzyloxy-3-hydroxy-but-2-enedioic acid 4-tert-butyl ester 1-methyl ester **(4)** (32.95g, 106.98mmol) following the procedure as described for 5-benzyloxy-2-(2,3-dichlorobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester **(130)**. The product was used without purification for further synthesis.

Preparation of (149):

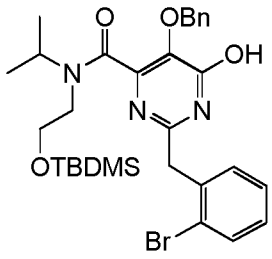


Step 3: 5-Benzyloxy-2-(2-bromobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid

5-Benzyloxy-2-(2-bromobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid **(149)** (16.5g, 68%) as a brown solid was synthesized from 5-benzyloxy-2-(2-bromobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester **(148)** (30g, 63.69mmol) following the procedure as described for 5-benzyloxy-2-(2,3-dichlorobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid **(131).**

LCMS: 415.2(M+H).

Preparation of (150):

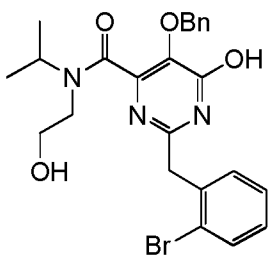


Step 4: 5-Benzyloxy-2-(2-bromobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid 2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide

5-Benzyloxy-2-(2-bromobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid 2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(150)** (382mg, 51.6%) as an off-white solid was synthesized from 5-benzyloxy-2-(2-bromobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid **(149)** (500mg, 1.20mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amine **(8b)** (523.6mg, 2.40mmol) following the procedure as described for 5-benzyloxy-2-(2,3-dichlorobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(132).**

LCMS: 616.2(M+H).

Preparation of (151):

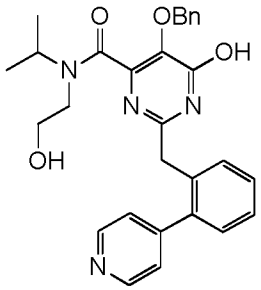


Step 5: 5-Benzyloxy-2-(2-bromobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide

5-Benzyloxy-2-(2-bromobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(151)** (1.3g, 72.5%) as an off-white solid was synthesized from 5-benzyloxy-2-(2-bromobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid 2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(150)** (2.2g, 3.57mmol) following the procedure as described for 5-Benzyloxy-2-(2,3-dichlorobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(133).**

LCMS: 500.2(M+H).

Preparation of (152):

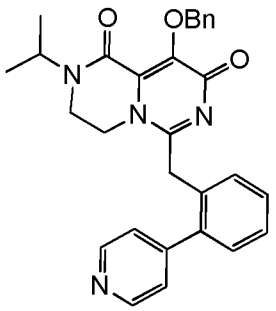


Step 6: 5-Benzyloxy-6-hydroxy-2-(2-pyridin-4-yl-benzyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide

5-Benzyloxy-6-hydroxy-2-(2-pyridin-4-yl-benzyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(152)** (251mg, 56.02%) as an off-white solid was synthesized from 5-benzyloxy-2-(2-bromobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(151)** (450mg, 0.89mmol) and pyridine-4-boronic acid (165.78mg, 1.34mmol) following the procedure as described for 5-benzyloxy-6-hydroxy-2-(4-methoxybiphenyl-2-ylmethyl)-pyrimidine-4-carboxylic acid tert-butyl ester **(139).**

LCMS: 499(M+H).

Preparation of (153)

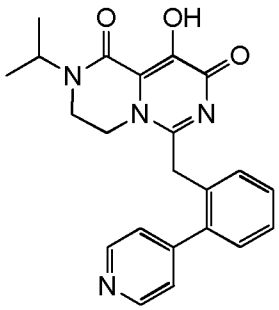


Step 7: 9-Benzyloxy-2-isopropyl-6-(2-pyridin-4-yl-benzyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

9-Benzyloxy-2-isopropyl-6-(2-pyridin-4-yl-benzyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(153)** (83mg, 57.73%) as an off-white solid was synthesized from 5-benzyloxy-6-hydroxy-2-(2-pyridin-4-yl-benzyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(152)** (150mg, 0.90mmol) following the procedure as described for 9-benzyloxy-6-(2,3-dichlorobenzyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(134).**

LCMS: 481.2(M+H).

Preparation of (154):



Step 8: 9-Hydroxy-2-isopropyl-6-(2-pyridin-4-yl-benzyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

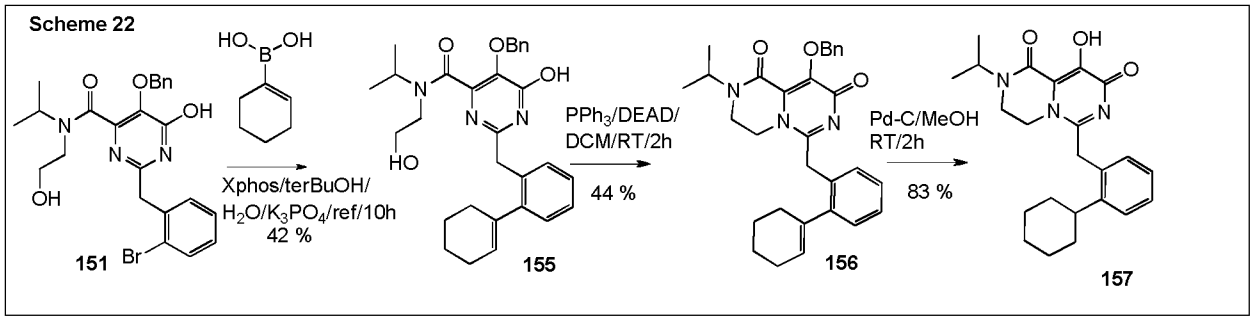
9-Hydroxy-2-isopropyl-6-(2-pyridin-4-yl-benzyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(154)** (30mg, 14.77%) as a light yellow solid was synthesized from 9-benzyloxy-2-isopropyl-6-(2-pyridin-4-yl-benzyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(153)** (250mg, 0.52mmol) following the procedure as described for 6-(2,3-dichlorobenzyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(135).**

LCMS: 391.2(M+H).

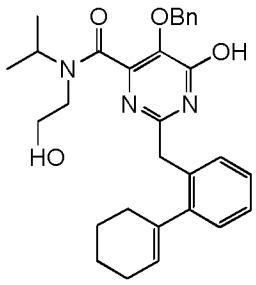
Example 157

6-(2-Cyclohexyl-benzyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 22.



Preparation of (155)

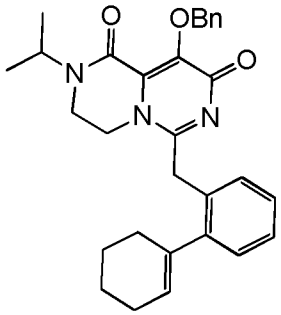


5-Benzyloxy-2-(2-cyclohex-1-enyl-benzyl)-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide

5-Benzyloxy-2-(2-cyclohex-1-enyl-benzyl)-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(155)** (210mg, 41.9%) as a colorless sticky liquid was synthesized from 5-benzyloxy-2-(2-bromobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(151)** (500mg, 0.999mmol) and cyclohexene boronic acid (188.84mg, 1.49mmol) following the procedure as described for 5-benzyloxy-6-hydroxy-2-(4-methoxy-biphenyl-2-ylmethyl)-pyrimidine-4-carboxylic acid tert-butyl ester **(139).**

LCMS: 502.2(M+H).

Preparation of (156)

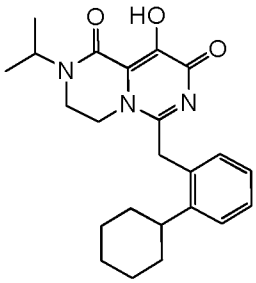


9-Benzyloxy-6-(2-cyclohex-1-enyl-benzyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

9-Benzyloxy-6-(2-cyclohex-1-enyl-benzyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(156)** (42.5mg, 44.15%) as an off-white solid was synthesized from 5-benzyloxy-2-(2-cyclohex-1-enyl-benzyl)-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(155)** (100mg, 0.199mmol) following the procedure as described for 9-benzyloxy-6-(2,3-dichlorobenzyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(134).**

LCMS: 484.2(M+H).

Preparation of (157)



6-(2-Cyclohexyl-benzyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

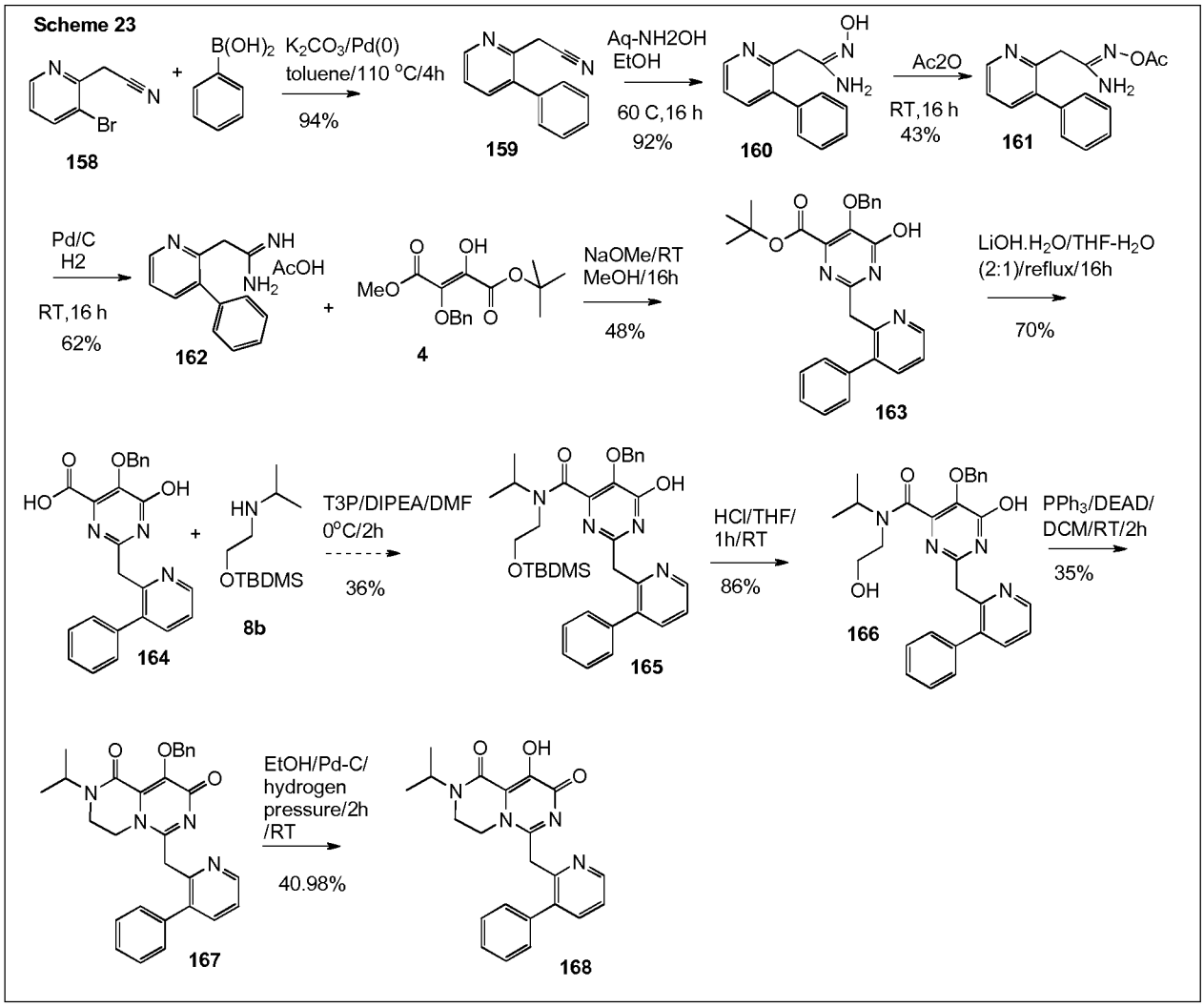
To a stirred solution of 9-benzyloxy-6-(2-cyclohex-1-enyl-benzyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(156)** (170mg, 0.352mmol) in methanol (20mL) was added Pd/C(10%) (170mg) and hydrogenated under balloon pressure for 2h at room temperature. After completion of the reaction, the mixture was filtered through a celite pad, washed with methanol (30mL), evaporated under reduced pressure to get a crude product which was purified by preparative HPLC to get 6-(2-cyclohexyl-benzyl)-9hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(157)** (115mg, 82.72%) as an off-white solid.

LCMS: 396(M+H).

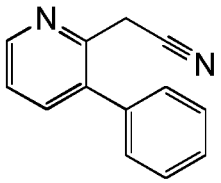
Example 168

9-Hydroxy-2-isopropyl-6-(3-phenyl-pyridin-2-ylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 23.



Preparation of (159):



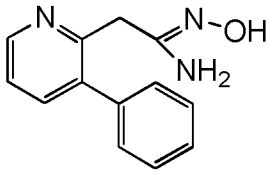
Step 1: (3-Phenyl-pyridin-2-yl)-acetonitrile

To a stirred solution of (3-bromo-pyridin-2-yl)-acetonitrile **(158)** (1 g, 5.07 mmol) and phenyl boronic acid (928 mg g, 7.16 mmol) in a solvent mixture of toluene (25 mL) and ethanol (25 mL) was added K_2CO_3 (2.1 g, 15.23 mmol). The mixture was degassed by argon, X-Phos (484 mg, 1.01 mmol) and $Pd(PPh_3)_4$ (586 mg g, 0.51 mmol) were added and the mixture was again degassed. The reaction mixture was refluxed (110 °C) for 4h. Silica thin layer chromatography

was performed (30% ethylacetate in hexane, R_f=0.45). The catalyst was filtered off through a celite bed, washing with ethylacetate (3 x 50 mL) was conducted, the mixture was concentrated, the crude product was purified by a CombiFlash column (eluted at 15% ethylacetate in hexane) to get (3-phenyl-pyridin-2-yl)-acetonitrile **(159)** (930 mg, 94.34%) as a light yellow solid.

LCMS:195.2 (M+H).

Preparation of (160):

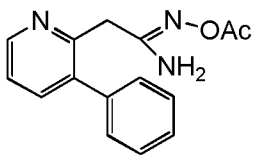


Step 2: N-Hydroxy-2-(3-phenyl-pyridin-2-yl)-acetamidine

To a stirred solution of (3-phenyl-pyridin-2-yl)-acetonitrile **(159)** (4.9 g, 25.26 mmol) in ethanol (250 mL) was added 50% aqueous NH_2OH (3.4 mL, 50.51 mmol) and the mixture was heated at 60 °C for 16 h. Silica thin layer chromatography was performed (40% ethylacetate in hexane, R_f=0.2). Ethanol was evaporated, water (50 mL) was added, the mixture was extracted with etylacetate (3 x 50 mL), dried and concentrated to get N-hydroxy-2-(3-phenyl-pyridin-2-yl)-acetamidine **(160)** (5.3 g, 92.33%, crude) as a yellow solid.

LCMS: 228.0 (M+H).

Preparation of (161):

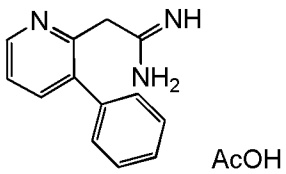


Step 3: 2-(3-phenylpyridin-2-yl)ethanimidamido acetate

Ac_2O (30 mL) was added to N-hydroxy-2-(3-phenyl-pyridin-2-yl)-acetamidine **(160)** (5.3 g, 23.35 mmol) at room temperature. A purple colored solution was formed, after a few hours a dark brown solution was formed which was stirred for 6 h at room temperature. Silica thin layer chromatography was performed (100% ethylacetate, R_f=0.6). Cold water was added, the mixture was extracted with ethylacetate (3 x 50 mL), the organic part was dried and concentrated, the crude product was purified by a CombiFlash column (eluted at 50% ethylacetate in hexane) to get 2-(3-phenylpyridin-2-yl)ethanimidamido acetate **(161)** (2.7 g, 42.94% pure and 2 g mixture) as a yellow solid.

LCMS: 269.8 (M+H).

Preparation of (162):

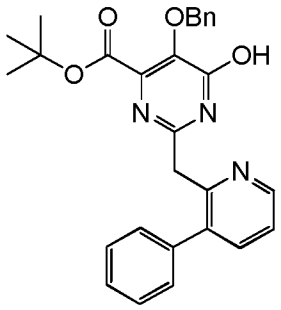


Step 4: 2-(3-Phenyl-pyridin-2-yl)-acetamidine with acetic acid

To a stirred degassed solution of **(161)** (2.7 g, 10.04 mmol) in ethanol (135 mL) was added 10% Pd-C (270 mg), the mixture was stirred 16 h under H_2 (hydrogen bubbler) at room temperature. Silica thin layer chromatography was performed (ethylacetate, R_f=0.1). The reaction mixture was filtered through celite, washed with 10% methanol in dichloromethane (5 x 100 mL), dried and concentrated. The yellow solid was washed with 10% ethylacetate in hexane (3 x 30 mL) to get pure 2-(3-phenyl-pyridin-2-yl)-acetamidine with acetic acid **(162)** (1.7 g, 62.5%) as an off-white solid.

LCMS: 212.0(M+H).

Preparation of (163):

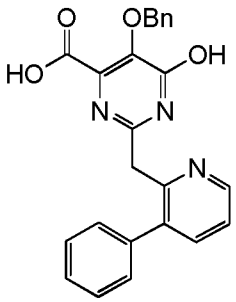


Step 5: 5-Benzyloxy-6-hydroxy-2-(3-phenyl-pyridin-2-ylmethyl)-pyrimidine-4-carboxylic acid tert-butyl ester

To a stirred solution of 2-(3-phenyl-pyridin-2-yl)-acetamidine **(162)** (300 mg, 1.10 mmol) and (E)-2-benzyloxy-3-hydroxy-but-2-enedioic acid 4-tert-butyl ester **(4)** (511 mg, 1.66 mmol) in methanol (5 mL) was added sodium methoxide (1.3 mL, 3.32 mmol) at 0 °C, then the reaction mixture was allowed to warm to room temperature, stirred for 16 h. Silica thin layer chromatography was performed (50% ethylacetate in hexane, R_f=0.3). After completion of the reaction, it was quenched with water, methanol was evaporated and water (30 mL) was added. The mixture was extracted with ethyl acetate (3 x 30 mL) and the separated organic part was dried and concentrated to get a crude product, which was purified by a CombiFlash column (eluted at 90% ethyl acetate in hexane) to get 5-benzyloxy-6-hydroxy-2-(3-phenyl-pyridin-2-ylmethyl)-pyrimidine-4-carboxylic acid tert-butyl ester **(163)** (250 mg, 48.1%) as a yellow sticky product.

LCMS: 470.2 (M+H).

Preparation of (164):

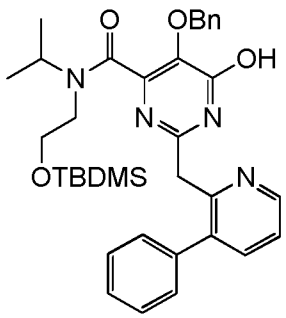


Step 6: 5-Benzyloxy-6-hydroxy-2-(3-phenyl-pyridin-2-ylmethyl)-pyrimidine-4-carboxylic acid

5-Benzyloxy-6-hydroxy-2-(3-phenyl-pyridin-2-ylmethyl)-pyrimidine-4-carboxylic **(164)** (370 mg, 69.96%) as an off-white solid was synthesized from 5-benzyloxy-6-hydroxy-2-(3-phenyl-pyridin-2-ylmethyl)-pyrimidine-4-carboxylic acid tert-butyl ester **(163)** (600 mg, 1.28 mmol) following the procedure as described for 5-benzyloxy-2-(2,3-dichlorobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid **(131)**. Ssilica thin layer chromatography was performed (5% methanol in dichloromethane, R_f=0.1).

LCMS: 414.4 (M+H).

Preparation of (165):

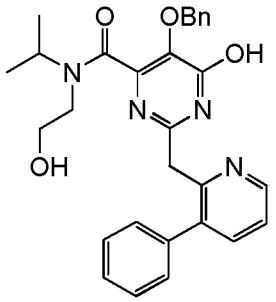


Step 7: 5-Benzyloxy-6-hydroxy-2-(3-phenyl-pyridin-2-ylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide

To a stirred solution of 5-benzyloxy-6-hydroxy-2-(3-phenyl-pyridin-2-ylmethyl)-pyrimidine-4-carboxylic acid **(164)** (370 mg, 0.89 mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amine **(8b)** (292 mg, 1.34 mmol) in dimethylformamide (5 mL) was added N,N-diisopropylethylamine (0.5 mL, 2.69 mmol), the mixture was cooled to 0 °C, T_3P (50 wt% in ethylacetate) (1.8 g, 2.69 mmol) was added, and the mixture was stirred for 16 h at room temperature. Silica thin layer chromatography was performed (5% methanol in dichloromethane, R_f=0.3). Water (100 mL) was added, the mixture was extracted with ethylacetate, dried and concentrated, and purified by a CombiFlash column (eluted at 2-5% MeOH in DCM) to get 5-benzyloxy-6-hydroxy-2-(3-phenyl-pyridin-2-ylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(165)** (200 mg, 36.46%) as a yellow sticky product.

LCMS:613.2 (M+H).

Preparation of (166):

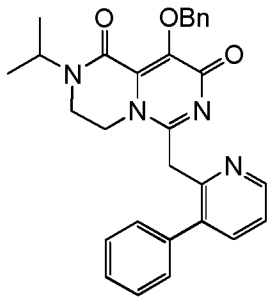


Step 8: 5-Benzyloxy-6-hydroxy-2-(3-phenyl-pyridin-2-ylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide

5-Benzyloxy-6-hydroxy-2-(3-phenyl-pyridin-2-ylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(166)** (140 mg, 85.93 %) as a light yellow sticky solid was synthesized from 5-benzyloxy-6-hydroxy-2-(3-phenyl-pyridin-2-ylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(165)** (200 mg, 0.33 mmol) following the procedure as described for 5-benzyloxy-2-(2,3-dichlorobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(132)**. Silica thin layer chromatography was performed (5% methanol in dichloromethane, R_f=0.4).

LCMS:499.0 (M+H).

Preparation of (167):

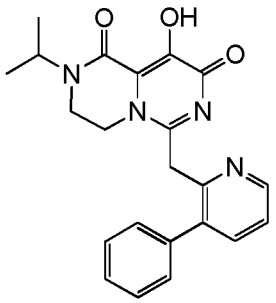


Step 9: 9-Benzyloxy-2-isopropyl-6-(3-phenyl-pyridin-2-ylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a stirred solution of 5-benzyloxy-6-hydroxy-2-(3-phenyl-pyridin-2-ylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(166)** in tetrahydrofuran (20 mL) were added triphenyl phosphine (66 mg, 0.25 mL) and DTAD (58 mg, 0.25 mmol) at room temperature. A yellow clear solution was formed, which was sonicated for 20 min. It was stirred at room temperature for 24 h. Silica thin layer chromatography was performed (5% methanol in dichloromethane, R_f=0.2). The mixture was concentrated under reduced pressure to get a crude product, which was purified by a preparative thin layer chromatography plate (mobile phase 5% methanol in dichloromethane) to get pure 9-benzyloxy-2-isopropyl-6-(3-phenyl-pyridin-2-ylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(167)** (17 mg, 35.23%) as a yellow sticky solid.

LCMS: 481.3 (M+H).

Preparation of (168):



Step 10: 9-Hydroxy-2-isopropyl-6-(3-phenyl-pyridin-2-ylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

9-Hydroxy-2-isopropyl-6-(3-phenyl-pyridin-2-ylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(168)** (12 mg, 40.98 %) as a light yellow solid was synthesized from 9-benzyloxy-2-isopropyl-6-(3-phenyl-pyridin-2-ylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(167)** (36 mg, 0.07 mmol) following the procedure as described for 9-hydroxy-2-isopropyl-6-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(168)**.

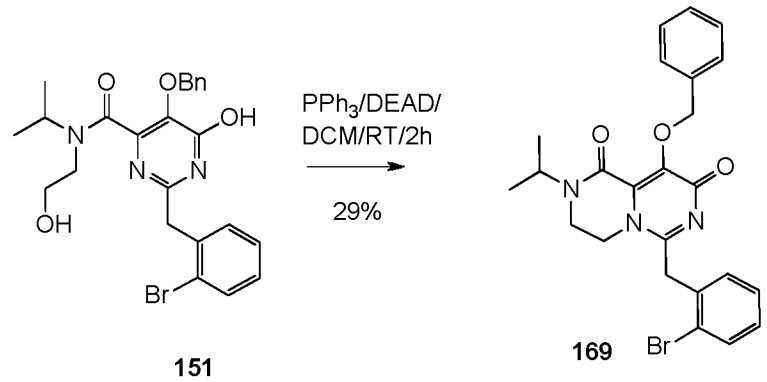
LCMS: 391.0 (M+H).

Example 169 (intermediate)

9-Benzyloxy-6-(2-bromobenzyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

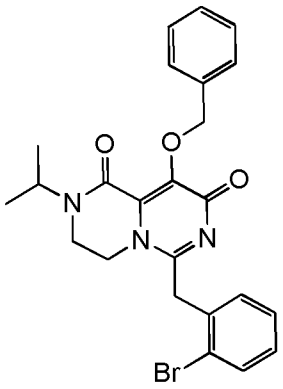
The synthetic procedure used in this preparation is outlined in Scheme 24.

Scheme 24



151 **169**

Preparation of (169):



9-Benzyloxy-6-(2-bromobenzyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a stirred solution of 5-benzyloxy-2-(2-bromobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(151)** (400mg, 0.8mmol) in dichloromethane (10mL) was added triphenyl phosphine (310.55mg, 1.18mmol) at room temperature. The mixture was stirred for 10 min. Then DEAD (0.186mL, 1.18mmol) was added at room temperature and the mixture was stirred for another 2h. After completion of the reaction, the mixture was concentrated under reduced pressure to get a crude product, which was purified using a

normal silica column using 2% methanol in dichloromethane to afford 9-benzyloxy-6-(2-bromobenzyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(169)** (112mg, 29%) as a white solid.

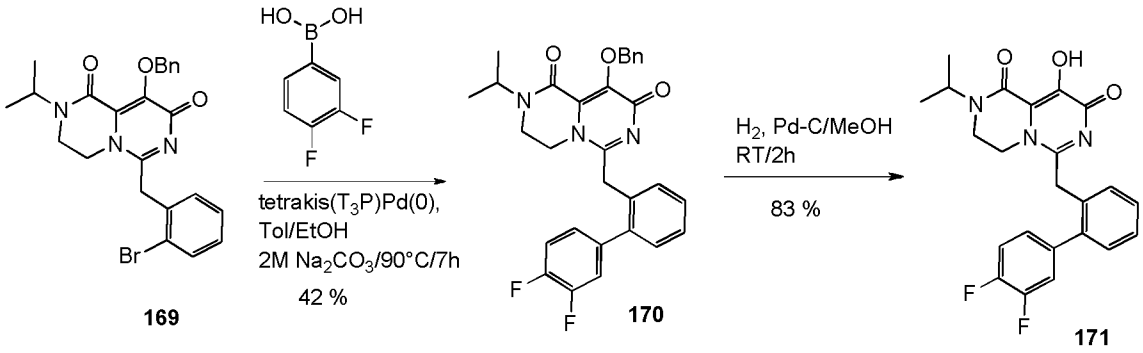
LCMS: 482.0 (M+H).

Example 171

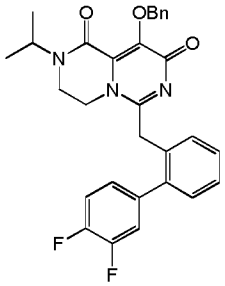
6-[[2-(3,4-Difluorophenyl)phenyl]methyl]-9-hydroxy-2-isopropyl-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 25.

Scheme 25



Preparation of (170)

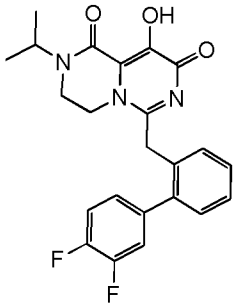


Step 1: 9-Benzyloxy-6-[[2-(3,4-difluorophenyl)phenyl]methyl]-2-isopropyl-3,4-dihydropyrazino-[1,2-c]pyrimidine-1,8-dione

9-Benzyloxy-6-[(2-bromophenyl)methyl]-2-isopropyl-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione **(169)** (150 mg, 0.311 mmol) and 3,4-difluorphenylboronic acid (56.5 mg, 0.358 mmol) were suspended in a mixture of toluene/ethanol (10ml/1ml), treated at room temperature under argon with tetrakis(triphenylphosphine)palladium(0) (14.4 mg, 12.4 µmol) and 2M sodium carbonate solution (342 µl, 684 µmol) and the reaction mixture was then heated at 90°C for 7 h. The reaction was quenched with water and the mixture was extracted twice with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by chromatography over 25 g silica gel with methanol/dichloromethane (gradient: 0 to10% methanol). All fractions containing product were combined and concentrated to afford 9-benzyloxy-6-[[2-(3,4-difluorophenyl)phenyl]methyl]-2-isopropyl-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione (160 mg) as a white solid.

LC/HR-MS: $(M+H)^+$ = 516.20993.

Preparation of (171)



Step 2: 6-[[2-(3,4-Difluorophenyl)phenyl]methyl]-9-hydroxy-2-isopropyl-3,4-dihydropyrazino-[1,2-c]pyrimidine-1,8-dione

9-Benzyloxy-6-[[2-(3,4-difluorophenyl)phenyl]methyl]-2-isopropyl-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione **(170)** (160 mg) in methanol (20 ml) was hydrogenated over 10% Pd/C (20.6 mg) at room temperature and at atmospheric pressure for 2 h. The catalyst was filtered off, the filtrate was concentrated *in vacuo* to give the desired product as a light yellow foam (112 mg).

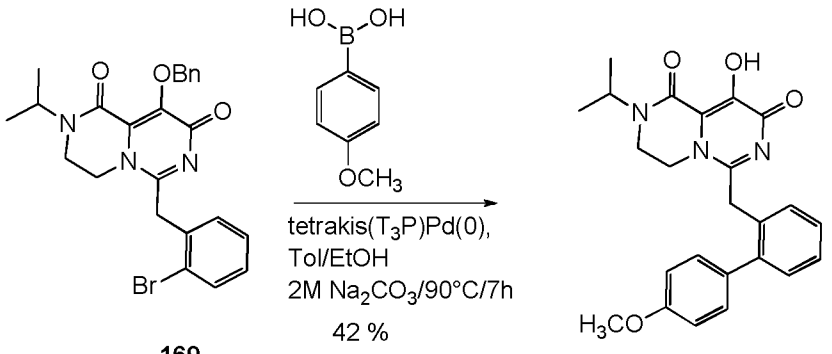
LC/HR-MS: $(M+H)^+$ = 426.16318.

Example 172

9-Hydroxy-2-isopropyl-6-[[2-(4-methoxyphenyl)phenyl]methyl]-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione

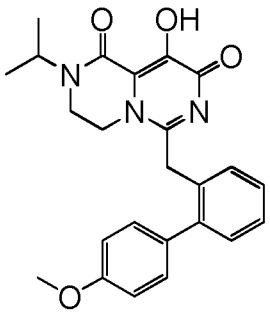
The synthetic procedure used in this preparation is outlined in Scheme 26.

Scheme 26



169 **172**

Preparation of (172)



9-Hydroxy-2-isopropyl-6-[[2-(4-methoxyphenyl)phenyl]methyl]-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione

The title compound **(172)** was prepared in analogy to example **170** from 9-benzyloxy-6-[(2-bromophenyl)methyl]-2-isopropyl-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione **(169)** (120 mg) and 4-methoxyphenylboronic acid (45.4 mg). The product could be obtained directly from the coupling reaction (step 1). White solid (20 mg).

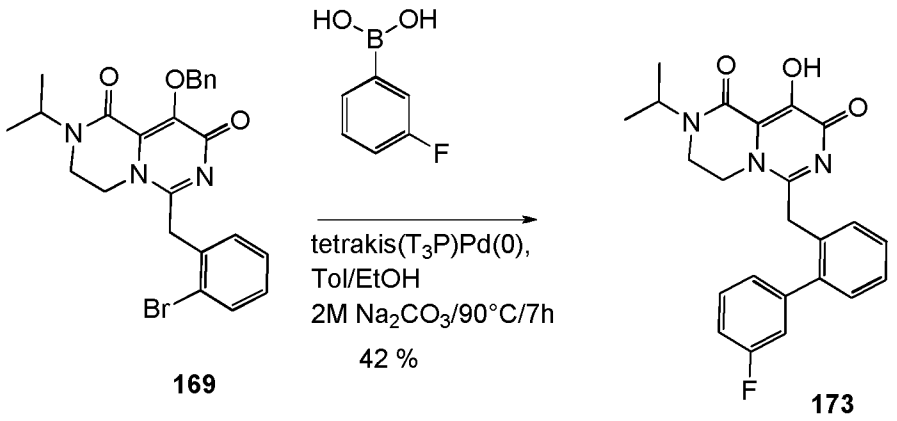
LC/MS: $(M+H)^+$ = 420.

Example 173

6-[[2-(3-Fuorophenyl)phenyl]methyl]-9-hydroxy-2-isopropyl-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione

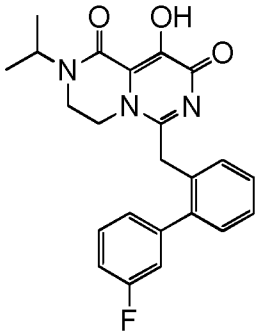
The synthetic procedure used in this preparation is outlined in Scheme 27.

Scheme 27



169 **173**

Preparation of (173)



6-[[2-(3-Fuorophenyl)phenyl]methyl]-9-hydroxy-2-isopropyl-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione

The title compound **(173)** was prepared in analogy to example **170** from 9-benzyloxy-6-[(2-bromophenyl)methyl]-2-isopropyl-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione **(169)** (150 mg) and 3-fluorophenylboronic acid (50 mg). The product could be obtained directly from the coupling reaction (step 1). White solid (20 mg).

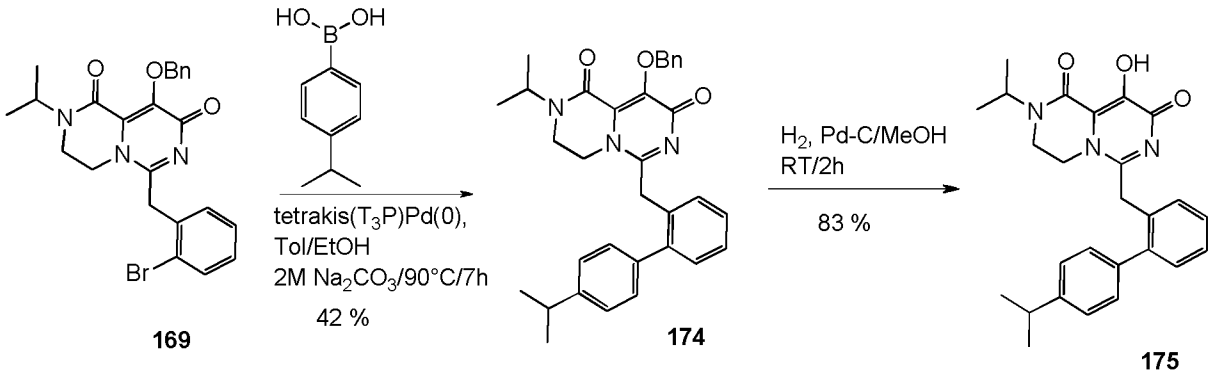
LC/HR-MS: $(M+H)^+$ = 408.17294.

Example 175

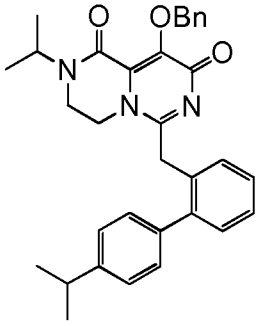
9-Hydroxy-2-isopropyl-6-[[2-(4-isopropylphenyl)phenyl]methyl]-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 28.

Scheme 28



Preparation of (174)



Step 1: 9-Benzyloxy-2-isopropyl-6-[[2-(4-isopropylphenyl)phenyl]methyl]-3,4-dihydropyrazino-[1,2-c]pyrimidine-1,8-dione

The title compound **(174)** was obtained in analogy to example **(170)** from 9-benzyloxy-6-[(2-bromophenyl)methyl]-2-isopropyl-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione **(169)** (150 mg) and 4-isopropylphenylboronic acid (58.7 mg) as a white foam (150 mg).

LC/HR-MS: $(M+H)^+$ = 522.27619.

Preparation of (175)

Step 2: 9-Hydroxy-2-isopropyl-6-[[2-(4-isopropylphenyl)phenyl]methyl]-3,4-dihydropyrazino-[1,2-c]pyrimidine-1,8-dione

The desired title compound was obtained in analogy to **(171)** from 9-benzyloxy-2-isopropyl-6-[[2-(4-isopropylphenyl)phenyl]methyl]-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione **(174)** (80 mg) as an off-white solid (57.2 mg).

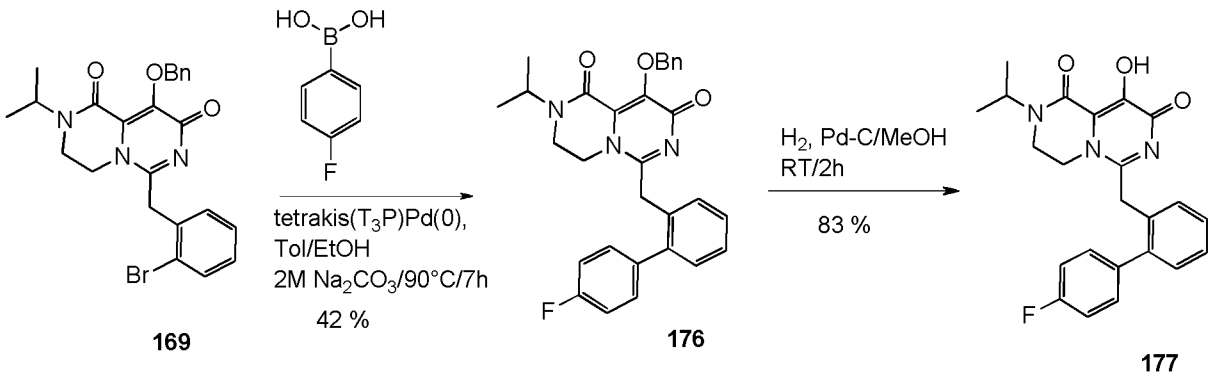
LC/HR-MS: $(M+H)^+$ = 432.22910.

Example 177

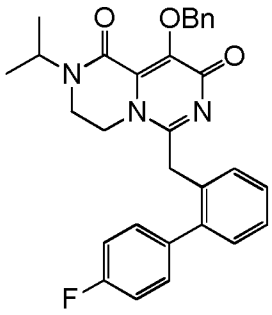
6-[[2-(4-Fluorophenyl)phenyl]methyl]-9-hydroxy-2-isopropyl-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 29.

Scheme 29



Preparation of (176)

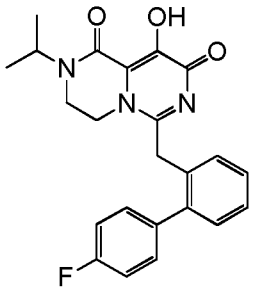


Step 1: 9-Benzyloxy-6-[[2-(4-fluorophenyl)phenyl]methyl]-2-isopropyl-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione

The title compound **(176)** was obtained in analogy to example **(170)** from 9-benzyloxy-6-[(2-bromophenyl)methyl]-2-isopropyl-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione **(169)** (150 mg) and 4-fluorophenylboronic acid (50 mg) as an off-white solid (120 mg).

LC/HR-MS: $(M+H)^+$ = 498.2196.

Preparation of (177)



Step 2: 6-[[2-(4-fluorophenyl)phenyl]methyl]-9-hydroxy-2-isopropyl-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione

The title compound **(177)** was obtained in analogy to example **(171)** from 9-benzyloxy-6-[[2-(4-fluorophenyl)phenyl]methyl]-2-isopropyl-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione (120 mg) **(176)** as an amorphous off-white solid, 34.2 mg.

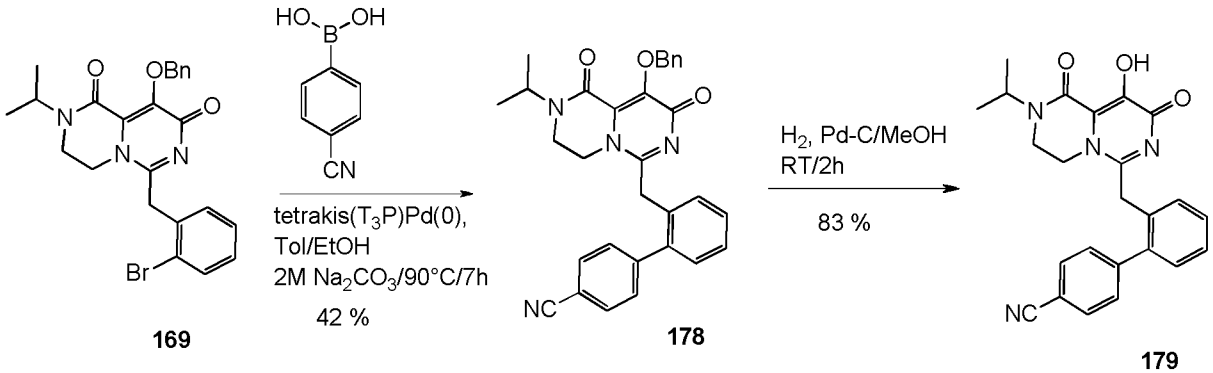
LC/HR-MS: $(M+H)^+$ = 408.17303.

Example 179

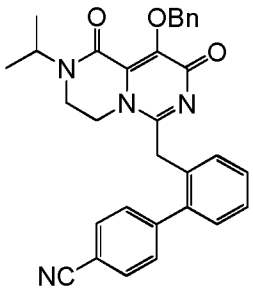
4-[2-[(9-hydroxy-2-isopropyl-1,8-dioxo-3,4-dihydropyrazino[1,2-c]pyrimidin-6-yl)methyl]phenyl]-benzonitrile

The synthetic procedure used in this preparation is outlined in Scheme 30.

Scheme 30



Preparation of (178)



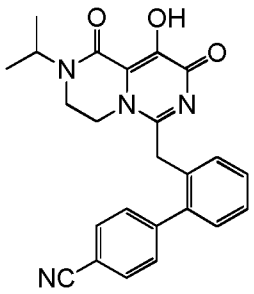
Step 1: 4-[2-[(9-benzyloxy-2-isopropyl-1,8-dioxo-3,4-dihydropyrazino[1,2-c]pyrimidin-6-yl)methyl]phenyl]benzonitrile

The title compound **(178)** was obtained in analogy to example **(170)** from 9-benzyloxy-6-[(2-bromophenyl)methyl]-2-isopropyl-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione **(169)** (150 mg) and 4-cyanophenylboronic acid (52.5 mg) as an off-white solid (45 mg).

LC/HR-MS: $(M+H)^+$ = 505.2244.

Preparation of (179)

181



Step 2: 4-[2-[(9-hydroxy-2-isopropyl-1,8-dioxo-3,4-dihydropyrazino[1,2-c]pyrimidin-6-yl)methyl]phenyl]benzonitrile

The title compound **(179)** was obtained in analogy to example **(171)** from 4-[2-[(9-benzyloxy-2-isopropyl-1,8-dioxo-3,4-dihydropyrazino[1,2-c]pyrimidin-6-yl)methyl]phenyl] (40 mg) **(178)** as an amorphous white solid, 11.4 mg.

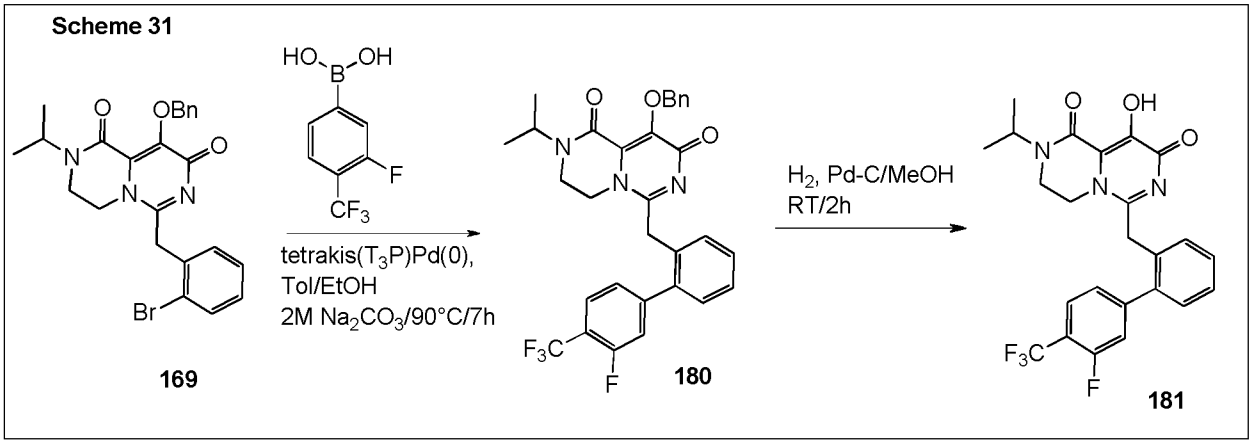
LC/HR-MS: $(M+H)^+$ = 415.17719.

Example 181

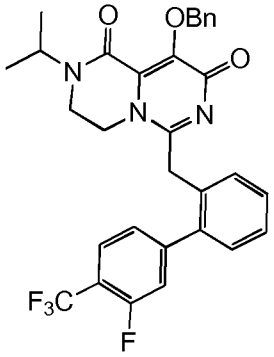
6-[[2-[3-fluoro-4-(trifluoromethyl)phenyl]phenyl]methyl]-9-hydroxy-2-isopropyl-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 31.

Scheme 31



Preparation of (180)

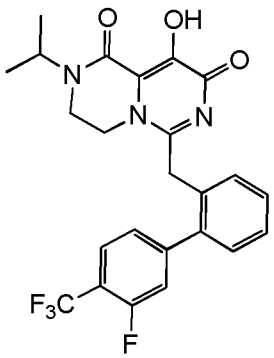


Step 1: 9-Benzyloxy-6-[[2-[3-fluoro-4-(trifluoromethyl)phenyl]phenyl]methyl]-2-isopropyl-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione

The title compound **(180)** was obtained in analogy to example **(170)** from 9-benzyloxy-6-[(2-bromophenyl)methyl]-2-isopropyl-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione **(169)** (150 mg) and 3-fluoro-4-trifluoromethyl-phenylboronic acid (74.3 mg) as an amorphous light yellow solid (142 mg).

LC/HR-MS: $(M+H)^+$ = 566.2049.

Preparation of (181)



Step 2: 6-[[2-[3-fluoro-4-(trifluoromethyl)phenyl]phenyl]methyl]-9-hydroxy-2-isopropyl-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione

The title compound **(181)** was obtained in analogy to example **(171)** from 9-benzyloxy-6-[[2-[3-fluoro-4-(trifluoromethyl)phenyl]phenyl]methyl]-2-isopropyl-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione **(180)** as an amorphous white solid, 18 mg.

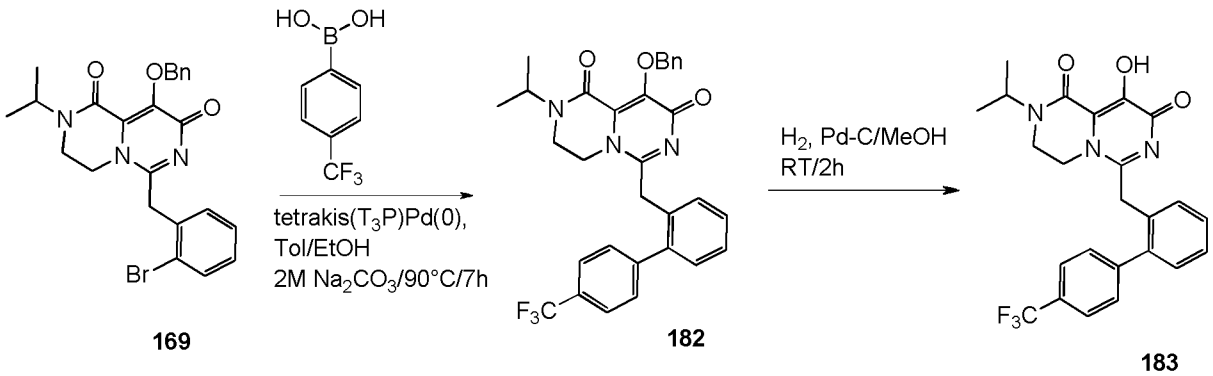
LC/HR-MS: $(M+H)^+$ = 476.15986.

Example 183

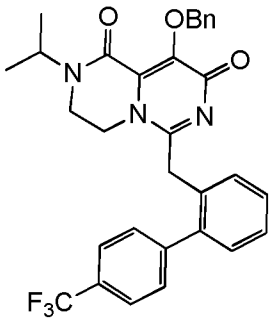
9-Hydroxy-2-isopropyl-6-[[2-[4-(trifluoromethyl)phenyl]phenyl]methyl]-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 32.

Scheme 32



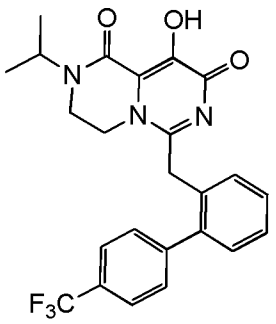
Preparation of (182)



Step 1: 9-Benzyloxy-2-isopropyl-6-[[2-[4-(trifluoromethyl)phenyl]phenyl]methyl]-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione

The title compound **(182)** was obtained in analogy to example **(170)** from 9-benzyloxy-6-[(2-bromophenyl)methyl]-2-isopropyl-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione **(169)** (150 mg) and 4-trifluoromethyl-phenylboronic acid (68 mg) as an off-white solid (151 mg) which was directly used in the subsequent reaction step.

Preparation of (183)



Step 2: 9-Hydroxy-2-isopropyl-6-[[2-[4-(trifluoromethyl)phenyl]phenyl]methyl]-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione

The title compound **(183)** was obtained in analogy to example **(171)** from 9-benzyloxy-2-isopropyl-6-[[2-[4-(trifluoromethyl)phenyl]phenyl]methyl]-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione (140 mg) **(182)** as an off-white solid, 22.8 mg.

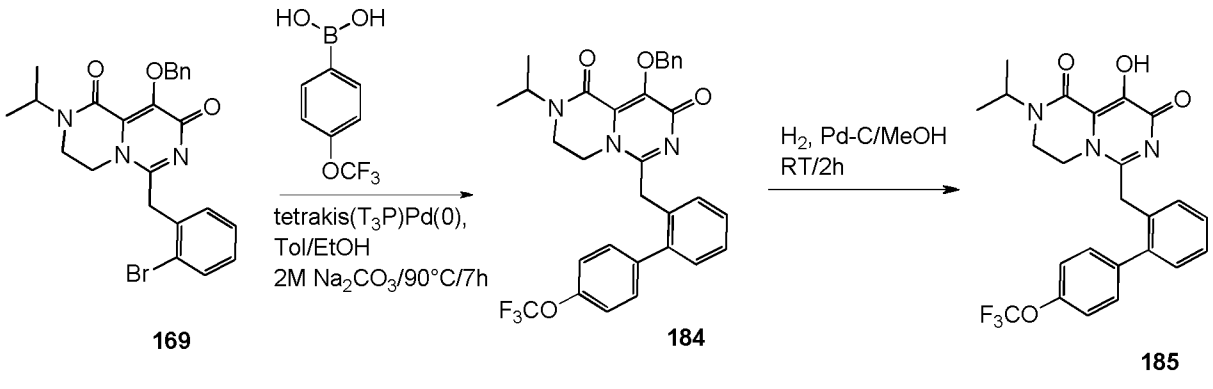
LC/HR-MS: $(M+H)^+$ = 458.16956.

Example 185

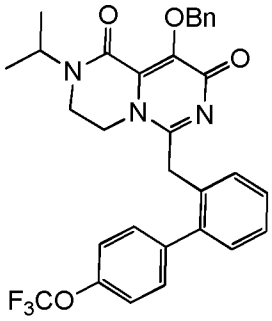
9-Hydroxy-2-isopropyl-6-[[2-[4-(trifluoromethoxy)phenyl]phenyl]methyl]-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 33.

Scheme 33



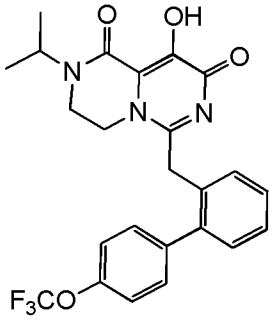
Preparation of (184)



Step 1: 9-Benzyloxy-2-isopropyl-6-[[2-[4-(trifluoromethoxy)phenyl]phenyl]methyl]-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione

The title compound **(184)** was obtained in analogy to example **(170)** from 9-benzyloxy-6-[(2-bromophenyl)methyl]-2-isopropyl-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione **(169)** (150 mg) and 4-trifluoromethoxy-phenylboronic acid (73.6 mg) as a white solid (150 mg). The crude product was directly used in the next reaction step.

Preparation of (185)



Step 2: 9-Hydroxy-2-isopropyl-6-[[2-[4-(trifluoromethoxy)phenyl]phenyl]methyl]-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione

The title compound **(185)** was obtained in analogy to example **(171)** from 9-benzyloxy-2-isopropyl-6-[[2-[4-(trifluoromethoxy)phenyl]phenyl]methyl]-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione (150 mg) **(184)** as an off-white solid, 9 mg.

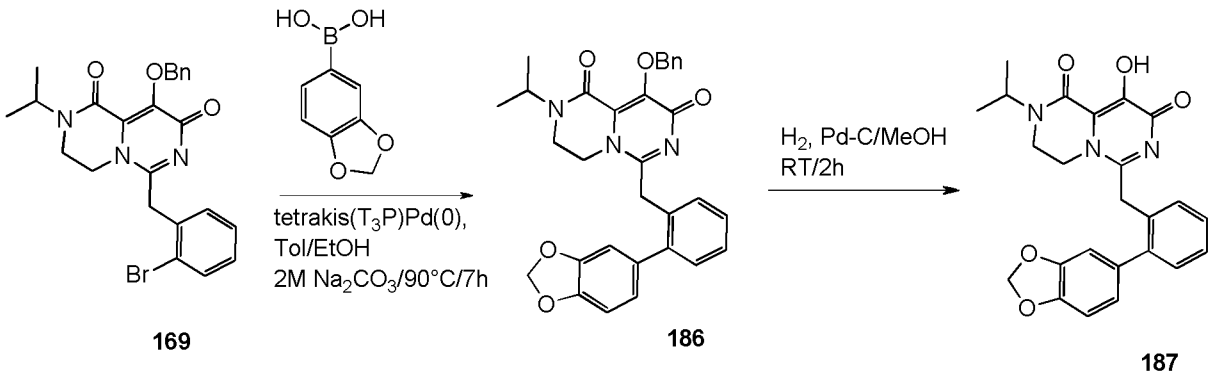
LC/HR-MS: $(M+H)^+$ = 474.16440.

Example 187

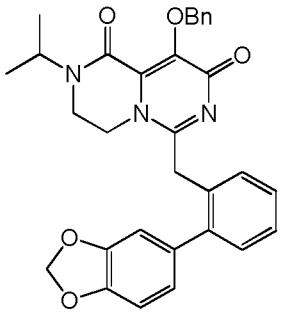
6-[[2-(1,3-Benzodioxol-5-yl)phenyl]methyl]-9-hydroxy-2-isopropyl-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 34.

Scheme 34



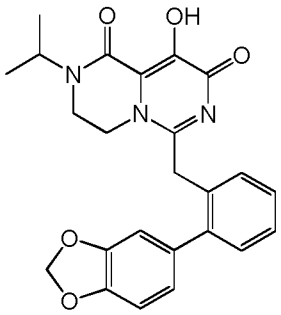
Preparation of (186)



Step 1: 6-[[2-(1,3-benzodioxol-5-yl)phenyl]methyl]-9-benzyloxy-2-isopropyl-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione

The title compound **(186)** was obtained in analogy to example **(170)** from 9-benzyloxy-6-[(2-bromophenyl)methyl]-2-isopropyl-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione **(169)** (150 mg) and 1,3-benzodioxol-5-ylboronic acid (59.3 mg). The crude material (130 mg) was directly used in the next reaction step.

Preparation of (187)



Step 2: 6-[[2-(1,3-benzodioxol-5-yl)phenyl]methyl]-9-hydroxy-2-isopropyl-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione

The title compound **(187)** was obtained in analogy to example **(171)** from 9-benzyloxy-2-isopropyl-6-[[2-[4-(trifluoromethoxy)phenyl]phenyl]methyl]-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione (130 mg) **(186)** as an off-white solid, 7 mg.

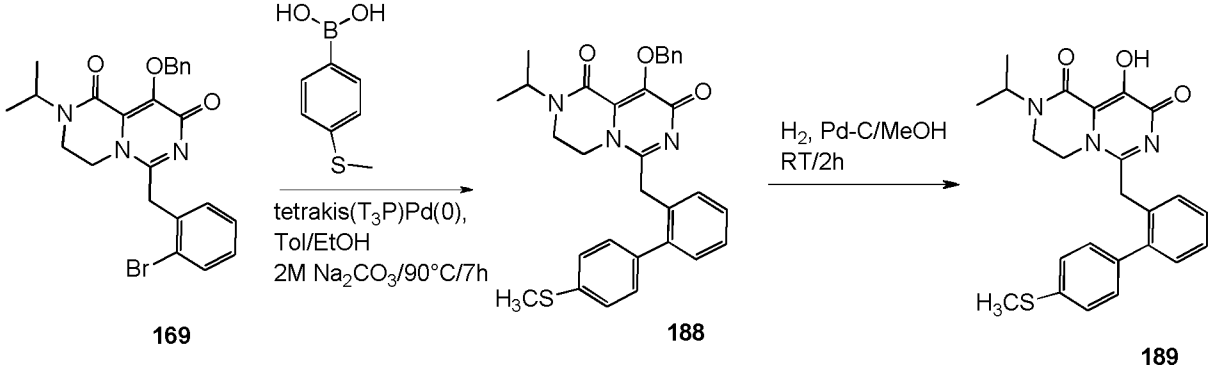
LC/HR-MS: $(M+H)^+$ = 434.17153.

Example 189

9-Hydroxy-2-isopropyl-6-[[2-(4-methylsulfanylphenyl)phenyl]methyl]-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione

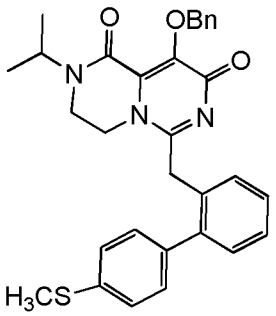
The synthetic procedure used in this preparation is outlined in Scheme 35.

Scheme 35



169 188 189

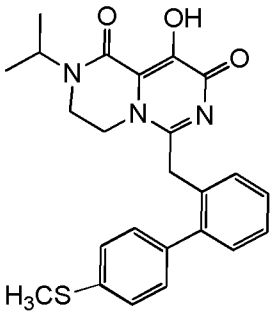
Preparation of (188)



Step 1: 9-Benzyloxy-2-isopropyl-6-[[2-(4-methylsulfanylphenyl)phenyl]methyl]-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione

The title compound **(188)** was obtained in analogy to example **(170)** from 9-benzyloxy-6-[(2-bromophenyl)methyl]-2-isopropyl-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione **(169)** (150 mg) and 4-(methylthio)phenylboronic acid (115 mg) as a light yellow solid (152 mg). The material was directly used in the subsequent reaction step.

Preparation of (189)



Step 2: 9-Hydroxy-2-isopropyl-6-[[2-(4-methylsulfanylphenyl)phenyl]methyl]-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione

The title compound **(189)** was obtained in analogy to example **(171)** from 9-benzyloxy-2-isopropyl-6-[[2-[4-(trifluoromethoxy)phenyl]phenyl]methyl]-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione (100 mg) **(188)** as an off-white solid, 68.4 mg.

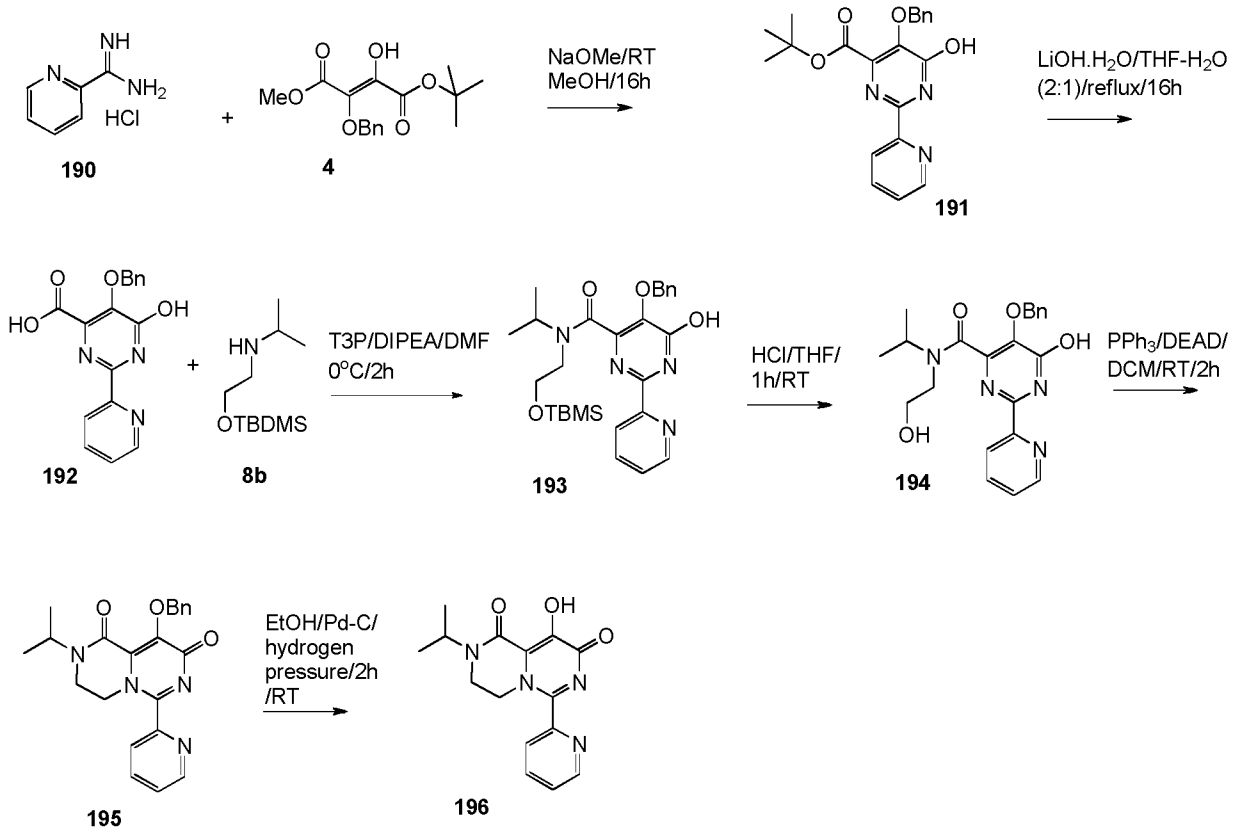
LC/HR-MS: $(M+H)^+$ = 436.1708.

Example 196

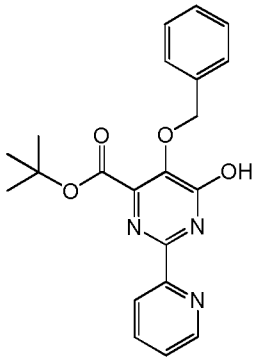
9-Hydroxy-2-isopropyl-6-(2-pyridyl)-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 36.

Scheme 36



Preparation of (191)

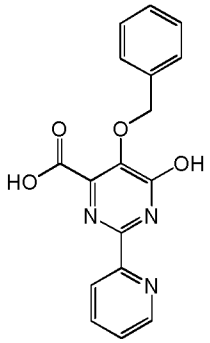


Step 1: tert-Butyl 5-benzyloxy-6-hydroxy-2-(2-pyridyl)pyrimidine-4-carboxylate

The title compound **(191)** was obtained in analogy to example **(163)** from pyridine-2-carboximidamide HCl **(190)** and 4-tert-butyl 1-methyl 2-(benzyloxy)-3-hydroxyfumarate **(4)** as an off-white solid.

LC/HR-MS: $(M+H)^+$ = 338.114.

Preparation of (192)

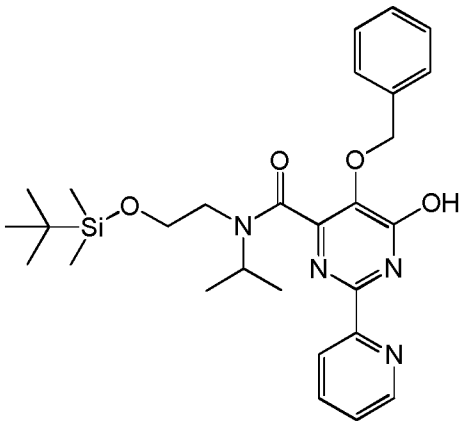


Step 2: 5-Benzyloxy-6-hydroxy-2-(2-pyridyl)pyrimidine-4-carboxylic acid

The title compound **(192)** was obtained in analogy to **(164)** from tert-butyl 5-benzyloxy-6-hydroxy-2-(2-pyridyl)pyrimidine-4-carboxylate **(191)** as a white solid.

LC/HR-MS: $(M+H)^+$ = 338.114.

Preparation of (193)

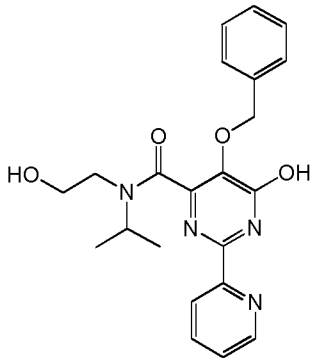


Step 3: 5-Benzyloxy-N-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-6-hydroxy-N-isopropyl-2-(2-pyridyl)pyrimidine-4-carboxamide

The title compound **(193)** was obtained in analogy to **(165)** from 5-benzyloxy-6-hydroxy-2-(2-pyridyl)pyrimidine-4-carboxylic acid **(192)** and N-[2-[tert-butyl(dimethyl)silyl]oxyethyl]propan-2-amine **(8b)** as a white solid.

LC/HR-MS: $(M+H)^+$ = 523.27392.

Preparation of (194)

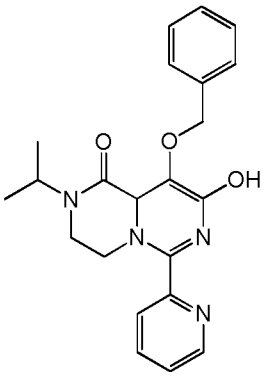


Step 4: 5-Benzyloxy-6-hydroxy-N-(2-hydroxyethyl)-N-isopropyl-2-(2-pyridyl)pyrimidine-4-carboxamide

The title compound was obtained in analogy to **(166)** from 5-benzyloxy-N-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-6-hydroxy-N-isopropyl-2-(2-pyridyl)pyrimidine-4-carboxamide **(193)** on treatment with 1M HCl in tetrahydrofuran as a light yellow gum.

LC/HR-MS: $(M+H)^+$ = 409.1880.

Preparation of (195)

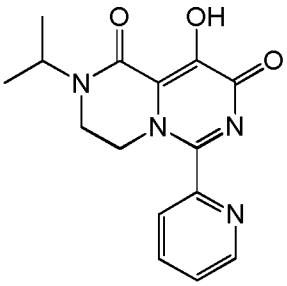


Step 5: 9-Benzyloxy-8-hydroxy-2-isopropyl-6-(2-pyridyl)-4,9a-dihydro-3H-pyrazino[1,2-c]pyrimidin-1-one

The title compound was prepared in analogy to **(167)** from 5-benzyloxy-6-hydroxy-N-(2-hydroxyethyl)-N-isopropyl-2-(2-pyridyl)pyrimidine-4-carboxamide **(194)** as a light yellow gum.

LC/HR-MS: $(M+H)^+$ = 391.1769.

Preparation of (196)



Step 6: 9-Hydroxy-2-isopropyl-6-(2-pyridyl)-3,4-dihydropyrazino[1,2-c]pyrimidine-1,8-dione

The title compound was prepared in analogy to **(168)** from 9-benzyloxy-8-hydroxy-2-isopropyl-6-(2-pyridyl)-4,9a-dihydro-3H-pyrazino[1,2-c]pyrimidin-1-one **(195)** as an off-white solid.

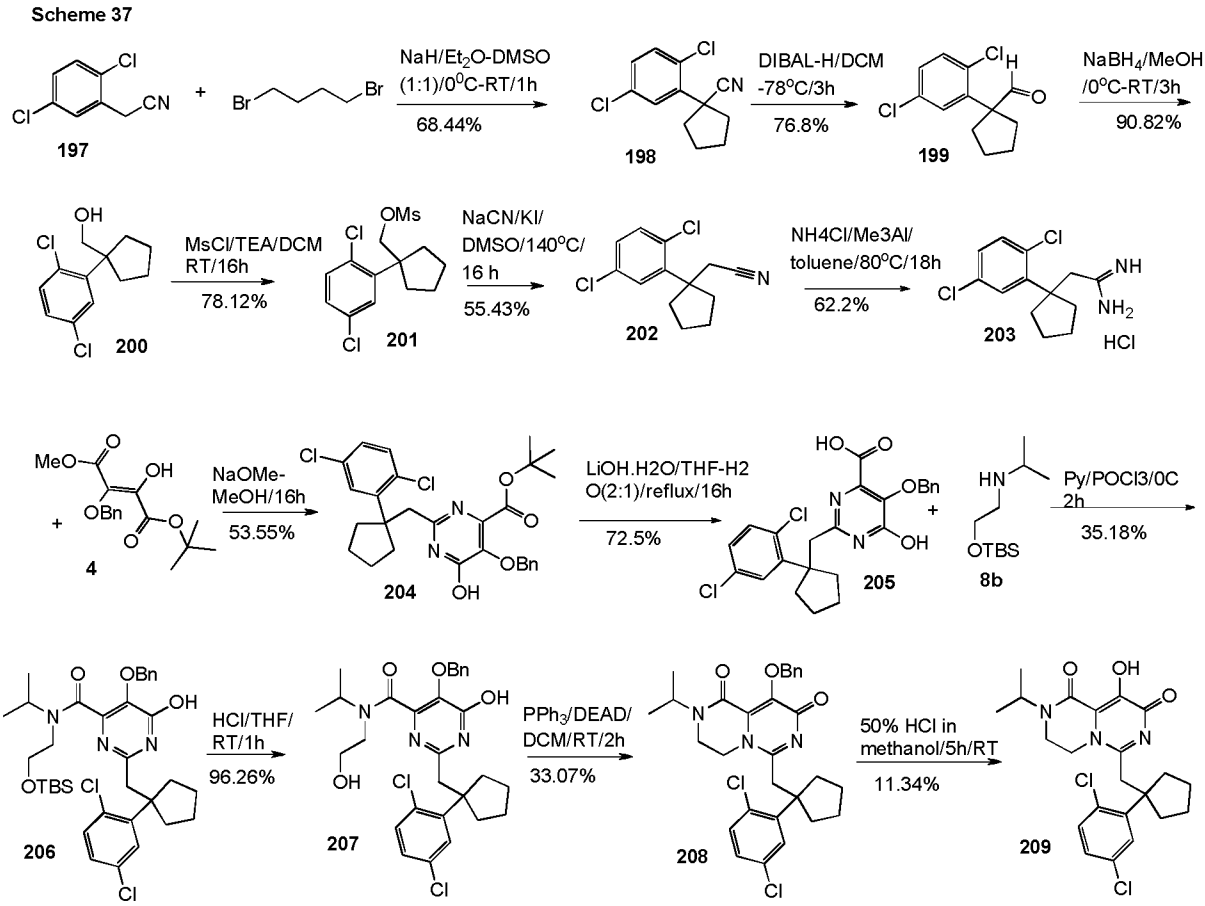
LC/HR-MS: $(M+H)^+$ = 301.13013.

Example 209

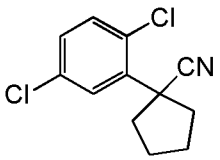
6-[1-(2,5-Dichloro-phenyl)-cyclopentylmethyl]-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 37.

Scheme 37



Preparation of (198):



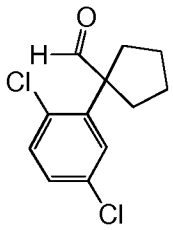
Step 1: 1-(2,5-Dichloro-phenyl)-cyclopentanecarbonitrile

To a suspension of NaH (60% w/w suspension in paraffin oil) (14.19 g, 354.76 mmol) in dimethyl sulfoxide (300 mL), was added (2,5-dichloro-phenyl)-acetonitrile **(197)** (30g,

161.256mmol) and 1,4-dibromobutane (19.34mL, 161.26mmol) by dissolving in dimethyl sulfoxide-ether (1:1, 600mL) dropwise at 0°C. The reaction mixture was stirred at room temperature for 1h. Silica thin layer chromatography was conducted (10% ethyl acetate in hexane, Rf = 0.8). After completion of the reaction, water (500mL) and 10% HCl solution (200mL) were added and the mixture was extracted with ethyl acetate. The organic part was dried, and evaporated to get a crude residue, which was purified with silica gel (normal, 100-200 mesh) column chromatography using a gradient eluent of 2 to 10% ethylacetate in hexane to get pure **(198)** (26.5g, 68.44%) as a white solid.

GCMS: 239 (M).

Preparation of (199):

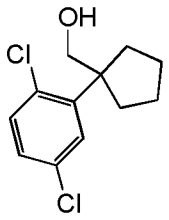


Step 2: 1-(2,5-Dichloro-phenyl)-cyclopentanecarbaldehyde

To a stirred solution of 1-(2,5-dichloro-phenyl)-cyclopentanecarbonitrile **(198)** (32g, 133.891mmol) in DCM (350mL), was added DIBAL (25% in toluene, 191.0mL, mmol) for 1 h at -70°C and the reaction mixture was stirred 2 h at the same temperature (silica TLC, 10% ethyl acetate in hexane, Rf = 0.7). Reaction mixture was quenched with saturated potassium sodium tartarate solution very slowly and stirred at room temperature for 16 h. It was extracted with DCM, washed with brine and dried, concentrated to get the crude residue which was purified over normal silica gel (100-200 mesh) column chromatography using gradient eluent 2-20% ethylacetate in hexane to get 1-(2,5-dichloro-phenyl)-cyclopentanecarbaldehyde **(199)** (25g, 76.8%), as colorless liquid.

GCMS: 242(M)

Preparation of (200):

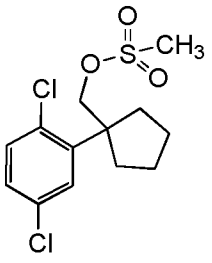


Step 3: [1-(2,5-Dichloro-phenyl)-cyclopentyl]-methanol

A solution of 1-(2,5-dichlorophenyl)-cyclopentanecarbaldehyde **(199)** (25g, 103.305mmol) in methanol (300mL), was cooled in ice bath, $NaBH_4$ (7.816g, 206.612mmol) was added portionwise and the mixture was stirred for 3h at room temperature. Silica thin layer chromatography was performed (10% ethyl acetate in hexane, Rf = 0.5). After completion of the reaction, it was quenched with saturated NH_4Cl solution (100mL), methanol was removed from the reaction mixture under reduced pressure, the residue was diluted with water and the mixture was extracted with dichloromethane, the combined organic layer was washed with brine, dried, and concentrated. The concentrate was purified using normal silica gel (100-200 mesh) column chromatography using a gradient eluent of 2 to 10% ethylacetate in hexane to get [1-(2,5-dichlorophenyl)-cyclopentyl]-methanol **(200)** (23g, 90.82%) as a colorless liquid.

GCMS: 244 (M).

Preparation of (201):



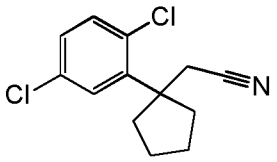
Step 4: Methanesulfonic acid 1-(2,5-dichlorophenyl)-cyclopentylmethyl ester

To a stirred solution of [1-(2,5-dichlorophenyl)-cyclopentyl]-methanol **(200)** (23g, 95.04mmol) in dry dichloromethane (250mL) was added dry triethylamine (26.42mL, 190.083mmol) slowly, then mesyl chloride (8.785mL, 114.05mmol) was added and the mixture was stirred for 16h at

room temperature. Silica thin layer chromatography was performed (10% ethyl acetate in hexane, Rf = 0.5). After completion of the reaction, the mixture was diluted with water, and extracted with dichloromethane. The combined organic layer was washed with brine, and dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude product was purified using normal silica gel (100-200 mesh) column chromatography using a gradient eluent of 2 to 10% ethylacetate in hexane to get pure methanesulfonic acid 1-(2,5-dichlorophenyl)-cyclopentylmethyl ester **(201)** (24g, 78.12%) as a white solid.

GCMS: 322(M).

Preparation of (202):

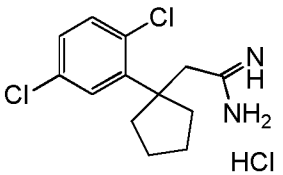


Step 5: [1-(2,5-Dichlorophenyl)-cyclopentyl]-acetonitrile

To a stirred solution of methanesulfonic acid 1-(2,5-dichlorophenyl)-cyclopentylmethyl ester **(201)** (24g, 74.53mmol) in dimethyl sulfoxide (200mL) KI (1.237g, 7.453mmol) and NaCN (5.478g, 111.801mmol) were added. The mixture was heated to 140°C and stirred for 5h. Silica TLC was performed (10% ethyl acetate in hexane, Rf = 0.6). The reaction mixture was cooled to room temperature, diluted with water, extracted with ethyl acetate, washed with brine, dried, concentrated. The obtained crude product was purified using normal silica gel (100-200 mesh) column chromatography using a gradient eluent of 2 to 10% ethylacetate in hexane to get pure [1-(2,5-dichlorophenyl)-cyclopentyl]-acetonitrile **(202)** (10.5g, 55.43%) as a white solid.

GCMS: 253(M).

Preparation of (203):

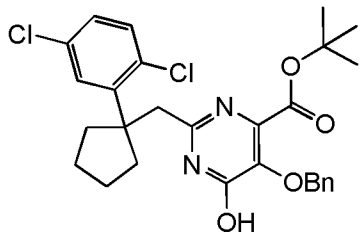


Step 6: 2-[1-(2,5-Dichlorophenyl)-cyclopentyl]-acetamidine hydrochloride

To a suspension of NH_4Cl (1.939g, 35.573mmol) in toluene (30mL) was added dropwise a solution of $AlMe_3$ (2 M in toluene; 9.48mL, 18.972mmol) at 0°C and the mixture was stirred for 2h at room temperature prior to the addition of a solution of [1-(2,5-dichlorophenyl)-cyclopentyl]-acetonitrile **(202)** in toluene (20mL). It was then heated to 80°C for 16h. Silica thin layer chromatography was performed (40% ethyl acetate in hexane, Rf = 0.1). The cooled reaction mixture was poured into a slurry of normal silica gel (100-200 mesh; 8 g) in $CHCl_3$ (60 mL), followed by vigorous stirring for 30 min. The mixture was filtered off and the cake was rinsed with MeOH. The combined filtrate was evaporated and the crude residue was taken in 10% methanol in dichloromethane (100 mL). The mixture was stirred for 30 min. The suspended solid was removed by filtration and the filtrate was evaporated. The crude product was triturated in diethylether and the solid was collected by filtration, dried under vacuum to afford 2-[1-(2,5-dichlorophenyl)-cyclopentyl]-acetamidine hydrochloride **(203)** (2.0g, 62.2%) as a white solid.

LCMS: 271 (M+H).

Preparation of (204):



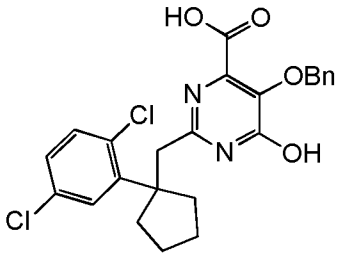
Step 7: 5-Benzyloxy-2-[1-(2,5-dichlorophenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester

To a stirred solution of 2-[1-(2,5-dichlorophenyl)-cyclopentyl]-acetamidine hydrochloride **(2=3)** (2.0, 7.407mmol) and (E)-2-benzyloxy-3-hydroxy-but-2-enedioic acid 4-tert-butyl ester **(4)** (3.422g, 11.111mmol) in methanol (50mL) NaOMe (25% in methanol; 4.8mL) was added dropwise at 0°C and stirred at room temperature for 16h. Silica thin layer chromatography was performed (40% ethyl acetate in hexane, Rf = 0.6). The reaction mixture was quenched with HCl (1N; 5mL), methanol was removed, the product was diluted with water and the mixture

was extracted with ethyl acetate. The combined organic part was dried, the product was concentrated and the crude product was purified using a normal silica gel column using a gradient eluent of 10 to 40% ethylacetate in hexane to get pure 5-benzyloxy-2-[1-(2,5-dichlorophenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester **(204)** (2.1g, 53.55%) as a yellow solid.

LCMS: 529.2 (M+H).

Preparation of (205):

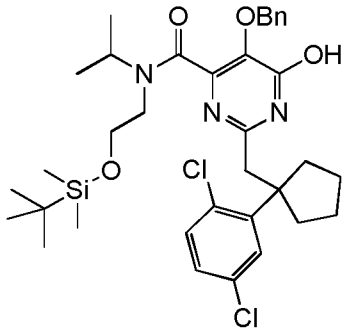


Step 8: 5-Benzyloxy-2-[1-(2,5-dichlorophenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid

To a stirred solution of 5-benzyloxy-2-[1-(2,5-dichlorophenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester **(204)** (2.0g, 3.788mmol) in tetrahydrofuran-H_2O (2:1) (30mL) Li(OH)•H_2O (1.591g, 37.88mmol) was added, then the reaction mixture was stirred under reflux for 16h. Silica thin layer chromatography was performed (40% ethyl acetate in hexane, Rf = 0.1). After completion of the reaction, volatiles were removed, the reaction mixture was diluted with water, the pH was adjusted to pH ~7 with 1N HCl, then the reaction mixture was extracted with ethylacetate. The organic part was dried with Na_2SO_4, then concentrated to get pure 5-benzyloxy-2-[1-(2,5-dichlorophenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid **(205)** (1.3g, 72.5%) as a white solid.

LCMS: 473.2(M+H)

Preparation of (206):

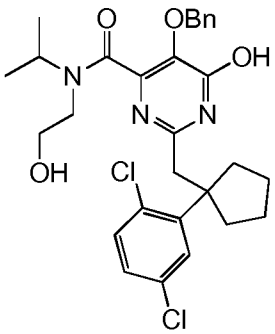


Step 9: 5-Benzyloxy-2-[1-(2,5-dichlorophenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide

To a stirred white suspension of 5-benzyloxy-2-[1-(2,5-dichlorophenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid **(205)** (500 mg, 1.05 mmol) in pyridine (5.5 mL) was added [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amine **(8b)** (344 mg, 1.58 mmol), cooled to -10°C, $POCl_3$ (0.3 mL, 3.17 mmol) was added at the same temperature. The mixture was stirred at 0°C for 2 h. Silica thin layer chromatography was performed (50% ethylacetate in hexane, R_f=0.8). After completion of the reaction, ice cooled-water (30 mL) was added to the reaction mixture at 0°C, a saturated solution of $NaHCO_3$ (pH~8) was added, the mixture was extracted with ethyl acetate (4 x 50 mL), the organic part was dried and concentrated, the crude product was purified by a CombiFlash column (eluted at 30%-50% ethylacetate in hexane) to get 5-benzyloxy-2-[1-(2,5-dichlorophenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(206)** (250 mg, 35.18%) as a yellow sticky mass.

LC-MS: 672.4 (M+H).

Preparation of (207):

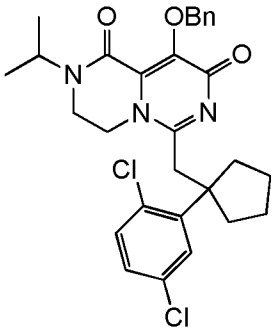


Step 10: 5-Benzyloxy-2-[1-(2,5-dichlorophenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide

To a stirred solution of 5-benzyloxy-2-[1-(2,5-dichlorophenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(206)** (250 mg, 0.37 mmol) in tetrahydrofuran (3.3 mL) was added 1(N) HCl (1.9 mL, 1.86 mmol) at room temperature and the mixture was stirred for 2 h at room temperature. Silica thin layer chromatography was performed (50% ethylacetate in hexane, R_f=0.2). After completion of the reaction, the mixture was basified (pH ~8) with a saturated solution of $NaHCO_3$, extracted with ethyl acetate, dried over sodium sulfate and concentrated to get a crude product which was purified by a CombiFlash column (eluted at 30% ethyl acetate in hexane) to get 5-benzyloxy-2-[1-(2,5-dichlorophenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(207)** (200 mg, 96.26%) as a white foam-like solid.

LC-MS: 558.0 (M+H).

Preparation of (208):



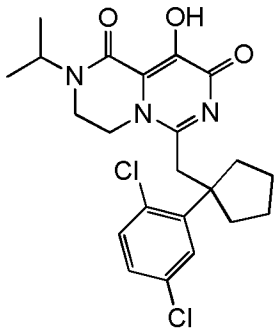
Step 11: 9-Benzyloxy-6-[1-(2,5-dichlorophenyl)-cyclopentylmethyl]-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a stirred solution of 5-benzyloxy-2-[1-(2,5-dichlorophenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(207)** (125 mg, 0.22 mmol) in tetrahydrofuran (5 mL) were added triphenyl phosphine (117 mg, 0.45 mmol) and DIAD (0.09 mL, 0.45 mmol) at room temperature, a yellow clear solution was formed, after 5 min it turned into a light yellow hazy solution. The solution was stirred for 2 h at room temperature. Silica thin layer chromatography was performed (100% ethylacetate, R_f=0.3). The mixture was concentrated under reduced pressure to get a crude product, which was purified by a

CombiFlash column (eluted at 2-5% methanol in dichloromethane) to get 9-benzyloxy-6-[1-(2,5-dichlorophenyl)-cyclopentylmethyl]-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(208)** (40 mg, 33.07%) as a white sticky solid.

LC-MS: 540.2 (M+H).

Preparation of (209):



Step 12: 6-[1-(2,5-Dichlorophenyl)-cyclopentylmethyl]-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

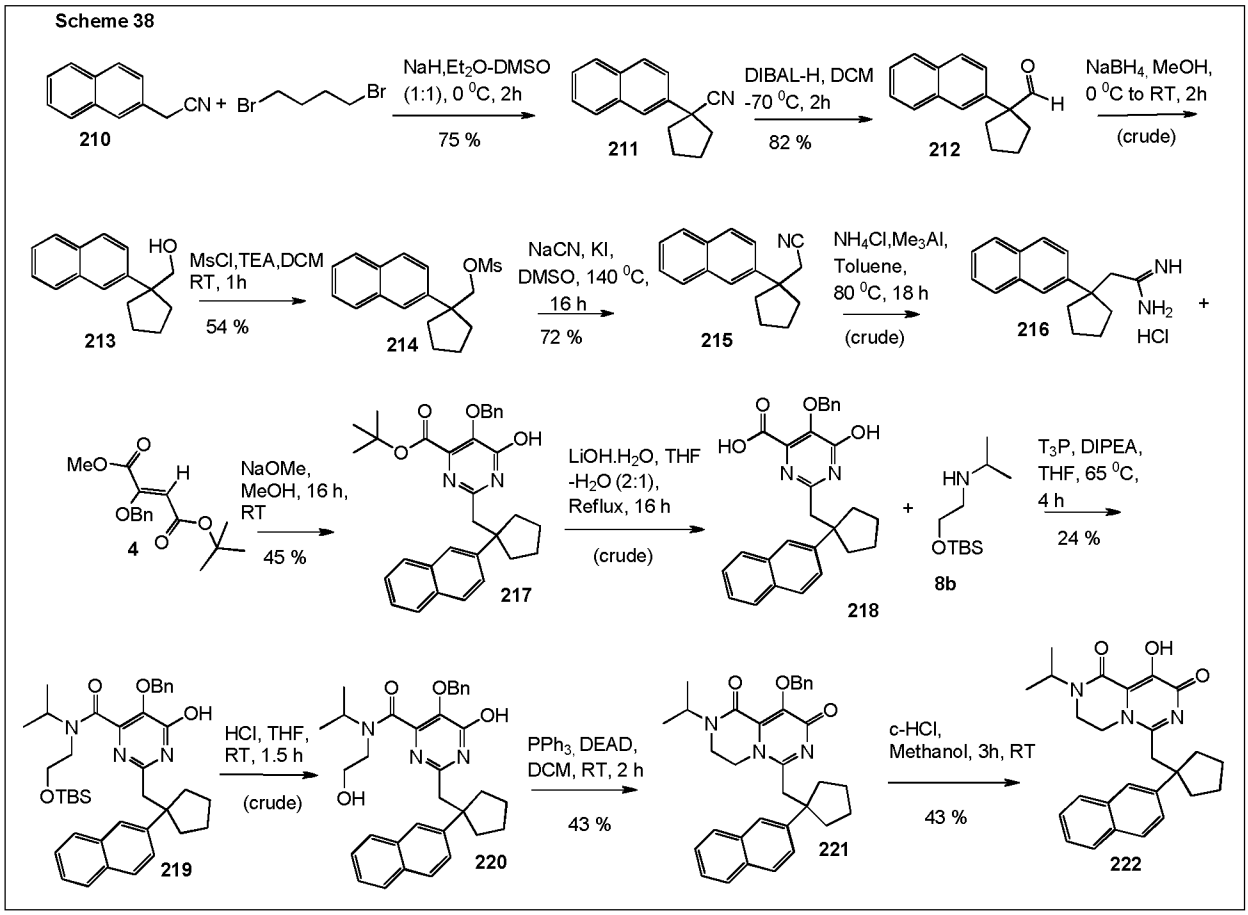
To a stirred solution of 9-benzyloxy-6-[1-(2,5-dichlorophenyl)-cyclopentylmethyl]-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(208)** (500 mg, 0.93 mmol) in methanol (5.5 mL) was added concentrated HCl (4 mL) and the mixture was stirred for 20 h. Silica thin layer chromatography was performed (100% ethylacetate, R_f=0.3). Methanol was removed, water was added, the mixture was basified (pH~8) with solid $NaHCO_3$, extracted with ethylacetate (3 x 20 mL), and the organic part was dried and concentrated. The crude product was purified by preparative HPLC purification to get 6-[1-(2,5-dichlorophenyl)-cyclopentylmethyl]-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c] pyrimidine-1,8-dione **(209)** (32 mg, 11.34%) as a light brown solid.

LC-MS: 450.0 (M+H).

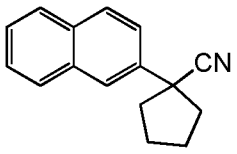
Example 222

9-Hydroxy-2-isopropyl-6-(1-naphthalen-2-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 38.



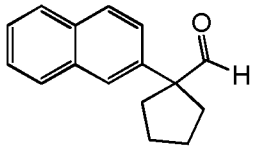
Preparation of (211):



Step:1 1-Naphthalen-2-yl-cyclopentanecarbonitrile

1-Naphthalen-2-yl-cyclopentanecarbonitrile **(211)** (25.0 g, 75.46 %) was synthesized as a white solid from naphthalen-2-yl-acetonitrile **(210)** (25.0 g, 149.7 mmol) and 1,4-dibromobutane (17.8 mL, 149.7 mmol) following the procedure described for 1-(2,5-dichlorophenyl)-cyclopentanecarbonitrile **(198).**

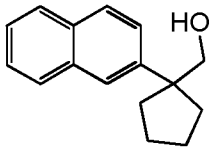
Preparation of (212):



Step 2: 1-Naphthalen-2-yl-cyclopentanecarbaldehyde

1-Naphthalen-2-yl-cyclopentanecarbaldehyde **(212)** (21.0 g, 82.77 %) was synthesized as a colourless liquid from 1-naphthalen-2-yl-cyclopentanecarbonitrile **(211)** (25.0 g, 113.12 mmol) following the procedure described for 1-(2,5-dichlorophenyl)-cyclopentanecarbaldehyde **(199).**

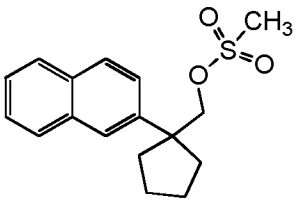
Preparation of (213):



Step 3: (1-Naphthalen-2-yl-cyclopentyl)-methanol

(1-Naphthalen-2-yl-cyclopentyl)-methanol **(213)** (22.0 g, crude) was synthesized as a colourless liquid from 1-naphthalen-2-yl-cyclopentanecarbaldehyde **(212)** (22.0 g, 98.21 mmol) following the procedure described for 1-(2,5-dichlorophenyl)-cyclopentane-methanol **(200).**

Preparation of (214):

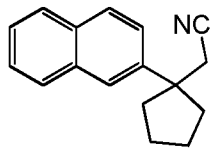


Step 4: Methanesulfonic acid 1-naphthalen-2-yl-cyclopentylmethyl ester

Methanesulfonic acid 1-naphthalen-2-yl-cyclopentylmethyl ester **(214)** (16.0 g, 54.0 %) was synthesized as a white solid from (1-naphthalen-2-yl-cyclopentyl)-methanol **(213)** (22.0 g,

97.34 mmol) following the procedure described for methanesulfonic acid 1-(2,5-dichlorophenyl)-cyclopentylmethyl ester **(201).**

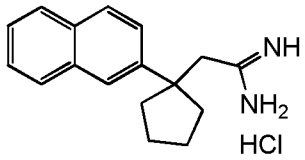
Preparation of (215):



Step 5: (1-Naphthalen-2-yl-cyclopentyl)-acetonitrile

(1-Naphthalen-2-yl-cyclopentyl)-acetonitrile **(215)** (9.0 g, 72.67 %) was synthesized as a brown solid from methanesulfonic acid 1-naphthalen-2-yl-cyclopentylmethyl ester **214)** (16.0 g, 52.63 mmol) following the procedure described for [1-(2,5-dichlorophenyl)-cyclopentyl]-acetonitrile **(202).**

Preparation of (216):

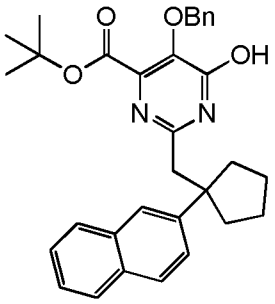


Step 6: 2-(1-Naphthalen-2-yl-cyclopentyl)-acetamidine hydrochloride

2-(1-Naphthalen-2-yl-cyclopentyl)-acetamidine hydrochloride **(216)** (5.0 g, crude) was synthesized as a white solid from (1-naphthalen-2-yl-cyclopentyl)-acetonitrile **(215)** (5.0 g, 21.27 mmol) following the procedure described for the HCl-salt of 2-[1-(2,5-dichlorophenyl)-cyclopentyl]-acetamidine hydrochloride **(203)**.

LC-MS: 252.8 (M+H).

Preparation of (217):

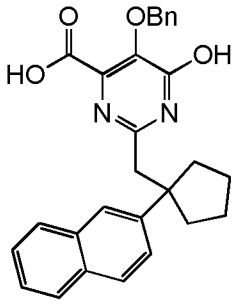


5-Benzyloxy-6-hydroxy-2-(1-naphthalen-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid tert-butyl ester

5-Benzyloxy-6-hydroxy-2-(1-naphthalen-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid tert-butyl ester **(217)** (4.0 g, 45.2 %) was synthesized as a white solid from 2-(1-naphthalen-2-yl-cyclopentyl)-acetamidine hydrochloride **(216)** (5.0 g, 17.33 mmol) following the procedure described for 5-benzyloxy-2-[1-(2,5-dichlorophenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester **(204)**

.

Preparation of (218):

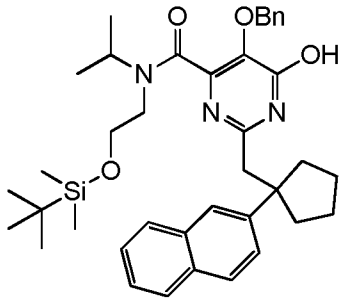


5-Benzyloxy-6-hydroxy-2-(1-naphthalen-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid

5-Benzyloxy-6-hydroxy-2-(1-naphthalen-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(218)** (300.0 mg, crude) was synthesized as a white solid from 5-benzyloxy-6-hydroxy-2-(1-naphthalen-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid tert-butyl ester **(217)** (300.0 mg, 0.588 mmol) following the procedure described for 5-benzyloxy-2-[1-(2,5-dichlorophenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid **(205)**.

LC-MS: 455.2 (M+H).

Preparation of (219):

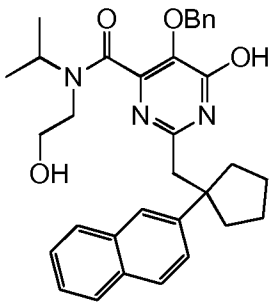


5-Benzyloxy-6-hydroxy-2-(1-naphthalen-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide

5-Benzyloxy-6-hydroxy-2-(1-naphthalen-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(219)** (300.0 mg, 24.5%) was synthesized as a colorless liquid from 5-benzyloxy-6-hydroxy-2-(1-naphthalen-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(218)** (850.0 mg, 1.87 mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amine **(8b)** (610.5 mg, 2.80 mmol) following the procedure described for 5-benzyloxy-2-[1-(2,5-dichlorophenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(206).**

LC-MS: 654.4 (M+H).

Preparation of (220):

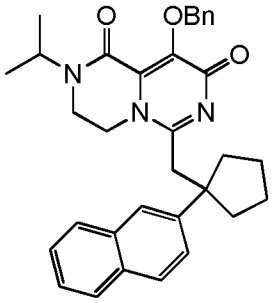


5-Benzyloxy-6-hydroxy-2-(1-naphthalen-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)isopropylamide

5-Benzyloxy-6-hydroxy-2-(1-naphthalen-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(220)** (80.0 mg, crude) was synthesized as a colorless liquid from 5-benzyloxy-6-hydroxy-2-(1-naphthalen-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(219)** (300.0 mg, 0.459 mmol) following the procedure described 5-benzyloxy-2-[1-(2,5-dichlorophenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(207).**

LC-MS: 540.2 (M+H).

Preparation of (221):

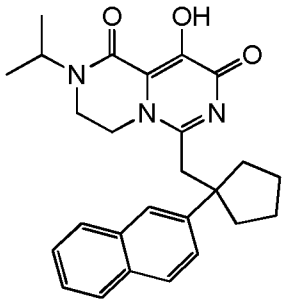


9-Benzyloxy-2-isopropyl-6-(1-naphthalen-2-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

9-Benzyloxy-2-isopropyl-6-(1-naphthalen-2-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(221)** (90.0 mg, 41.33 %) was synthesized as a white solid from 5-benzyloxy-6-hydroxy-2-(1-naphthalen-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(220)** (225.0 mg, 0.417 mmol) following the procedure described for 9-benzyloxy-6-[1-(2,5-dichlorophenyl)-cyclopentylmethyl]-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(208)**.

LC-MS: 522.0 (M+H).

Preparation of (222):



9-Hydroxy-2-isopropyl-6-(1-naphthalen-2-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

9-Hydroxy-2-isopropyl-6-(1-naphthalen-2-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(222)** (50.0 mg, 43.12 %) was synthesized as a light pink solid from 9-benzyloxy-2-isopropyl-6-(1-naphthalen-2-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(221)** (140.0 mg, 0.269 mmol) following the procedure described for 6-[1-(2,5-dichlorophenyl)-cyclopentylmethyl]-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c] pyrimidine-1,8-dione **(209)**.

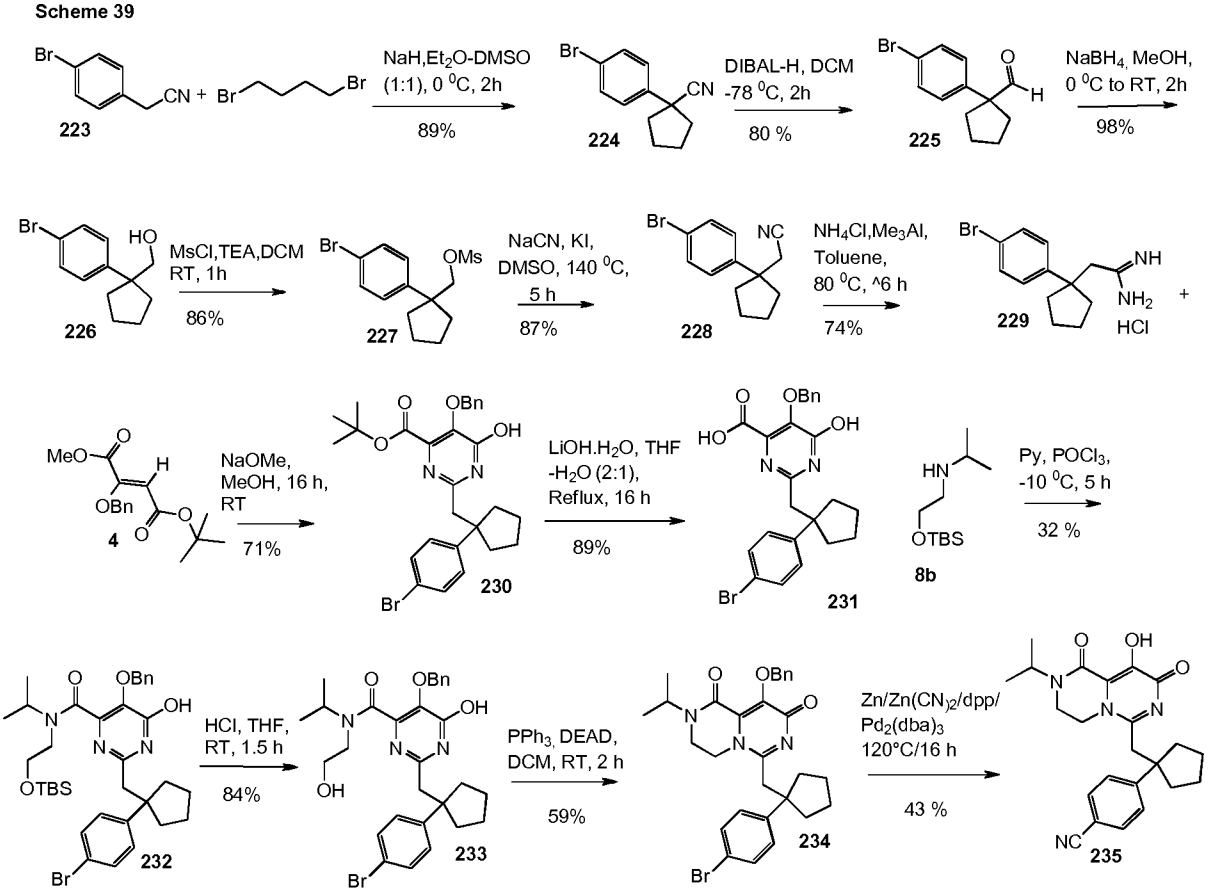
LC-MS: 432.0 (M+H).

Example 235

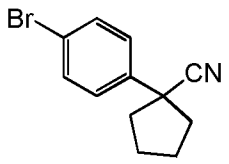
4-[1-(9-Hydroxy-2-isopropyl-1,8-dioxo-1,3,4,8-tetrahydro-2H-pyrazino[1,2-c]pyrimidin-6-ylmethyl)-cyclopentyl]-benzonitrile

The synthetic procedure used in this preparation is outlined in Scheme 39.

Scheme 39



Preparation of (224):

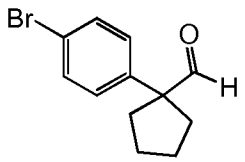


1-(4-Bromo-phenyl)-cyclopentanecarbonitrile

To a suspension of NaH (2.55 g, 63.75 mmol, 60%) in DMSO (50 mL) were added dropwise a mixture of 4-bromophenyl-acetonitrile **(223)** (5 g, 25.51 mmol) and 1,4-dibromobutane (3.04 mL, 25.51 mmol) dissolved in DMSO:Ether (1:1) (50 mL) at 0 °C and the reaction mixture was stirred at this temperature for 2 h. After completion of the reaction, water (20 mL) and 10% HCl solution (50 mL) was added to the mixture and extracted with ethyl acetate (2x200 ml). The organic layer was dried over Na_2SO_4, concentrated and purified by 100-200 silica column chromatography using hexane as the eluent to give 1-(4-bromo-phenyl)-cyclopentanecarbonitrile **(224)** (5.7 g, 89%) as white crystalline solid.

GC-MS: 250 (M+)

Preparation of (225):

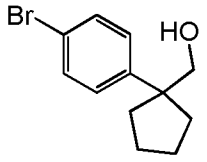


1-(4-Bromo-phenyl)-cyclopentanecarbaldehyde

To a stirred solution of 1-(4-bromo-phenyl)-cyclopentanecarbonitrile **(224)** (5.7 g, 22.78 mmol) in dichloromethane (50 mL), was added slowly DIBAL-H (33 mL, 56.96 mmol, 25% in toluene) at -70 °C. The reaction mixture was stirred at this temperature for 2 h. After completion of the reaction, it was quenched by slow addition of aqueous potassium sodium tartarate tetrahydrate solution (20 mL). The reaction mixture was stirred at room temperature for 16 h. The mixture was extracted with DCM thrice, organic part was dried over Na_2SO_4 and concentrated. The crude product was purified by 100-200 silica column chromatography using hexane as the eluent to give 1-(4-bromo-phenyl)-cyclopentanecarbaldehyde **(225)** (4.7 g, 81%) as white solid.

GC-MS: 253 (M+).

Preparation of (226):

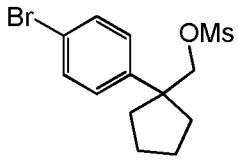


[1-(4-Bromo-phenyl)-cyclopentyl]-methanol

To a stirred solution of 1-(4-bromo-phenyl)-cyclopentanecarbaldehyde **(225)** (51.0 g, 201.47 mmol) in methanol (400 mL), was added $NaBH_4$ (15.31 g, 402.94 mmol) portion wise at 0 °C. The reaction mixture was then stirred at room temperature for 2 h. After completion, solvent was concentrated, diluted with water and the crude product was extracted with ethyl acetate

(2x300 mL). The organic part was dried over Na_2SO_4 and evaporated to give [1-(4-bromo-phenyl)-cyclopentyl]-methanol **(226)** (50.8 g, 98%) as white solid which was sufficiently pure to use for the next step.

Preparation of (227):

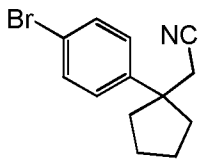


Methanesulfonic acid 1-(4-bromo-phenyl)-cyclopentylmethyl ester

To a stirred of [1-(4-bromo-phenyl)-cyclopentyl]-methanol **(226)** (47.0 g, 184.19 mmol) in dichloromethane (300 mL) was added Et_3N (51.3 mL, 368.39 mmol) followed by mesyl chloride (17.1 mL, 221.03 mmol) dropwise at 0 °C, stirred at room temperature for 1 h. The reaction was quenched by the addition of water, extracted with DCM, washed with water, dried over Na_2SO_4 and concentrated. The crude was purified by 100-200 silica column chromatography using 5% ethyl acetate in hexane as the eluent to give methanesulfonic acid 1-(4-bromo-phenyl)-cyclopentylmethyl ester **(227)** (52.8 g, 86%) as a white solid.

GC-MS: 334 (M+).

Preparation of (228):



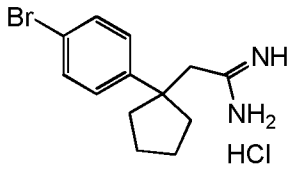
[1-(4-Bromo-phenyl)-cyclopentyl]-acetonitrile

To a stirred solution of methanesulfonic acid 1-(4-bromo-phenyl)-cyclopentylmethyl ester **(227)** (20 g, 60.01 mmol) in DMSO (100 mL) were added KI (0.99 g, 6.00 mmol) and NaCN (4.41 g, 90.02 mmol). Reaction mixture was then stirred at 140 °C for 5 h. After completion of the reaction, it was diluted with water, extracted with ethyl acetate (2x250 mL) and the organic layer was washed with water and brine. It was then dried over Na_2SO_4, and concentrated. The

crude product was purified by 100-200 silica column chromatography using 5% ethyl acetate in hexane as the eluent to give [1-(4-bromo-phenyl)-cyclopentyl]-acetonitrile **(228)** (13.9 g, 87%) as colorless thick liquid.

GC-MS: 264 (M+).

Preparation of (229):

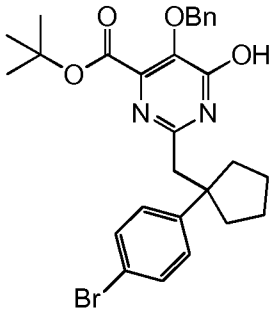


HCl-salt of 2-[1-(4-Bromo-phenyl)-cyclopentyl]-acetamidine

To a suspension of NH_4Cl (1.21 g, 43.65 mmol) in toluene (30 mL) was added dropwise a solution of trimethyl aluminium (1.64 g, 43.65 mmol, 2 M in toluene) at 0 °C and stirred for 2 h at room temperature prior to the addition of a solution of [1-(4-bromo-phenyl)-cyclopentyl]-acetonitrile **(228)** (2.0 g, 7.57 mmol) in toluene (10 mL). The resulting solution was heated to 80 °C for 16 h. The cooled reaction mixture was poured into a slurry of silica gel (10 g) in $CHCl_3$ (20 mL), followed by vigorous stirring for 30 min. The silica gel was filtered off and the cake was rinsed in turn with MeOH. The solvent was evaporated and the crude was taken in 10% MeOH in dichloromethane (200 mL) and stirred for 30 min. The solid suspension was removed by filtration and the filtrate was evaporated. The crude product was triturated in diethyl ether and the solid was collected by filtration, dried under vacuum to afford HCl-salt of 2-[1-(4-bromo-phenyl)-cyclopentyl]-acetamidine **(229)** (1.78 g, 74%) as white solid.

LC-MS: 281.0 (M+H).

Preparation of (230):

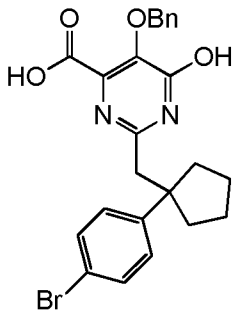


5-Benzyloxy-2-[1-(4-bromo-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester

To a mixture of HCl-salt of 2-[1-(4-bromo-phenyl)-cyclopentyl]-acetamidine **(229)** (6.5 g, 20.47 mmol) and (E)-2-benzyloxy-3-hydroxy-but-2-enedioic acid 4-tert-butyl ester 1-methyl ester **(4)** (9.47 g, 30.71 mmol) in MeOH (100 mL) was added sodium methoxide (3.32 g, 23.73 mmol, 25% in MeOH) at 0 °C. Then the reaction mixture was allowed to warm to room temperature and was stirred for 16 h. After completion of the reaction, solvent was reduced and the crude product was dissolved in dichloromethane (150 mL). Organic part was washed with 1 N HCl, separated and dried over Na_2SO_4. After evaporation the crude product was purified by 100-200 silica gel column chromatography using 20% ethyl acetate in hexane as the eluent to give 5-benzyloxy-2-[1-(4-bromo-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester **(230)** (7.9 g, 71%) as yellow solid.

LC-MS: 541.4 (M+H).

Preparation of (231):

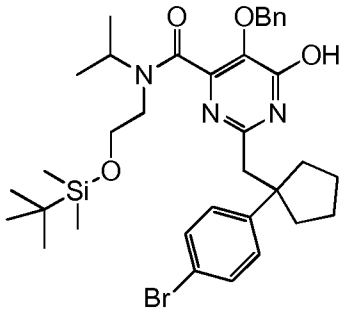


5-Benzyloxy-2-[1-(4-bromo-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid

To a stirred solution of 5-benzyloxy-2-[1-(4-bromo-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester **(230)** (7.9 g, 14.64 mmol) in THF (200 mL) was added aqueous solution (100 mL) of $LiOH.H_2O$ (6.15 g, 146.44 mmol). Resulting mixture was refluxed for 16 h. After completion of the reaction the organic solvent was removed on rotary evaporator and water (30 mL) was added. Aqueous solution was acidified (pH 5) with concentrated HCl at 0 °C to give white solid which was filtered off. The solid residue was triturated in diethyl ether and filtered. After drying, 5-benzyloxy-2-[1-(4-bromo-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid **(231)** was obtained (6.3 g, 89%) as white solid.

LC-MS: 485.2 (M+H).

Preparation of (232):

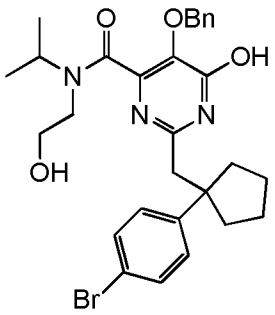


5-Benzyloxy-2-[1-(4-bromo-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide

To a stirred solution of 5-benzyloxy-2-[1-(4-bromo-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid **(231)** (2.0 g, 4.14 mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amine **(8b)** (2.7 g, 12.41 mmol) in pyridine (25 ml), was added $POCl_3$ (1.16 ml, 12.41 ml) at -10 °C. The reaction mixture was stirred at this temperature for 5 h. After completion of the reaction, it was quenched with water and the mixture was extracted with EtOAc. The organic part was washed with water, separated and dried over Na_2SO_4. After evaporation, the crude product was purified by 100-200 silica gel column chromatography using 30% EtOAc in hexane as the eluent to give 5-benzyloxy-2-[1-(4-bromo-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(232)** (0.9 g, 32%) as brown solid.

LC-MS: 684.6 (M+H).

Preparation of (233):

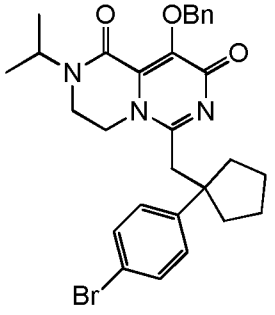


5-Benzyloxy-2-[1-(4-bromo-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide

To a stirred solution of 5-benzyloxy-2-[1-(4-bromo-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(232)** (1.0 g, 1.46 mmol) in THF (10 mL) was added HCl (37 % Aq, 1.70 mmol) and the reaction mixture was stirred at room temperature for 1.5 h. After completion of the reaction, mixture was diluted with ethyl acetate (30 mL), washed with water, separated and dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by 100-200 silica gel column chomatography using 60% ethyl acetate in hexane followed by 5% MeOH in DCM as the eluent to 5-benzyloxy-2-[1-(4-bromo-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(233)** (0.7 g, 84%) as white solid.

LC-MS: 568.2 (M+H).

Preparation of (234):

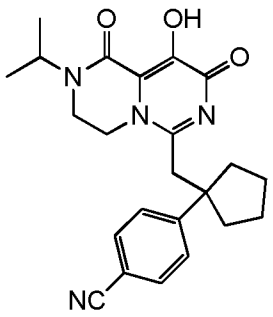


9-Benzyloxy-6-[1-(4-bromo-phenyl)-cyclopentylmethyl]-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a mixture of 5-benzyloxy-2-[1-(4-bromo-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(233)** (0.7 g, 1.23 mmol) and triphenyl phosphine (0.807 g, 3.08 mmol) in dry dichloromethane (10 mL) was added diethyl azidocarboxylate (0.58 mL, 3.69 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 h. After completion, the solvent was evaporated and the crude product was purified by 100-200 silica gel column chromatographey using 2% MeOH in dichloromethane as the eluent to give 9-benzyloxy-6-[1-(4-bromo-phenyl)-cyclopentylmethyl]-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(234)** (0.40 g, 59%) as white solid.

LC-MS: 550.2 (M+H).

Preparation of (235):



4-[1-(9-Hydroxy-2-isopropyl-1,8-dioxo-1,3,4,8-tetrahydro-2H-pyrazino[1,2-c]pyrimidin-6-ylmethyl)-cyclopentyl]-benzonitrile

To a stirred solution of 9-benzyloxy-6-[1-(4-bromo-phenyl)-cyclopentylmethyl]-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(234)** (100mg, 0.182 mmol) in NMP(1 mL), in a sealed tube was purged by argon for 10 min. To this suspension, Zn (1.188 mg, 0.018 mmol), dppf (3.021mg, 0.0050mmol), $Zn(CN)_2$ (17.067 mg, 0.145 mmol) and $Pd_2(dba)_3$ (3.327mg, 0.0040mmol) were added and heated at 120°C for 16 h. After completion of reaction, it was diluted with water and extracted with ethyl acetate, washed with water, followed by brine, separated , dried over sodium sulphate and evaporated to get crude which was purified by normal silica column using 10% methanol in DCM containing 10% ammonia to

get 4-[1-(9-hydroxy-2-isopropyl-1,8-dioxo-1,3,4,8-tetrahydro-2H-pyrazino[1,2-c]pyrimidin-6-ylmethyl)-cyclopentyl]-benzonitrile **(235)** (41mg, 55.53%) as an off-white solid.

LC-MS: 407 (M+H).

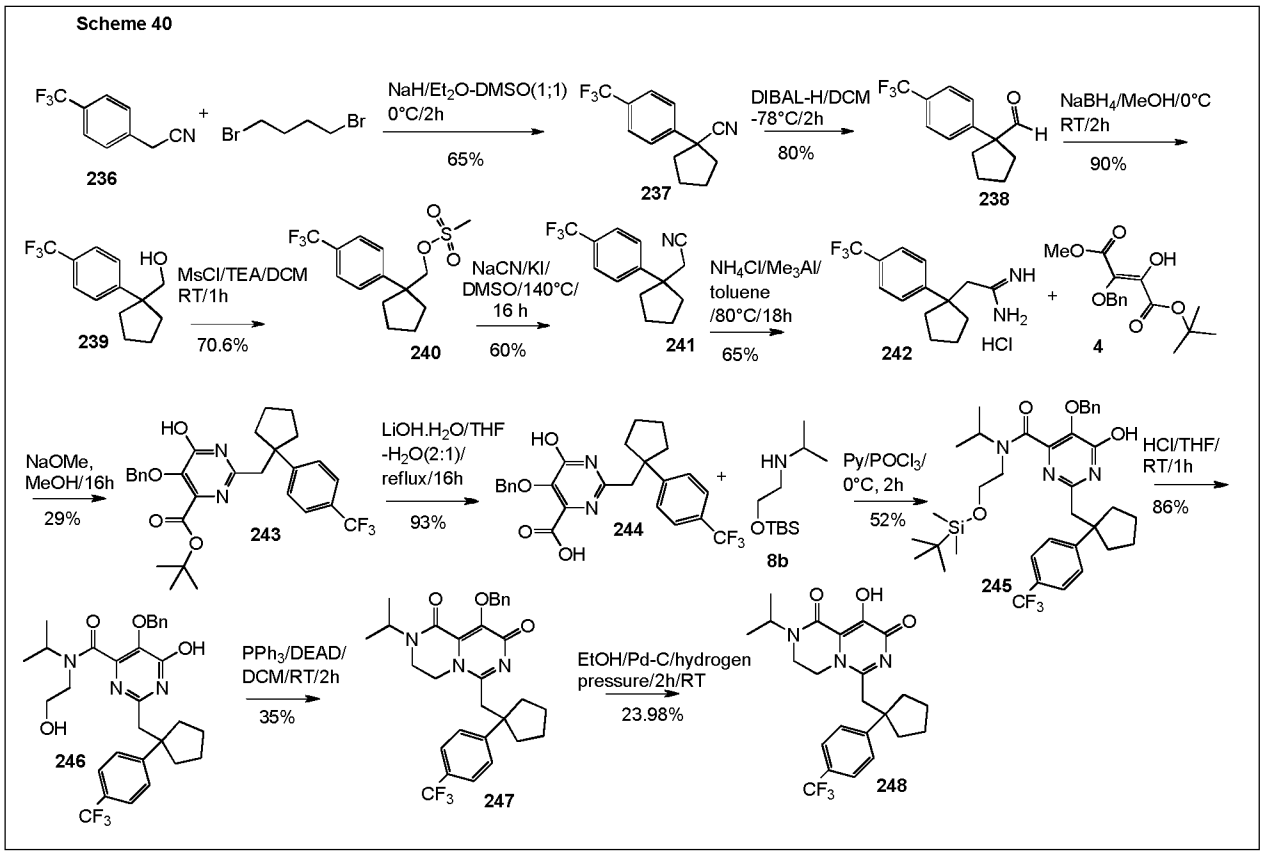
Example 248

9-Hydroxy-2-isopropyl-6-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

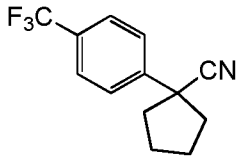
The synthetic procedure used in this preparation is outlined in Scheme 40.

Synthetic route for 248:

Scheme 40



Preparation of (237):

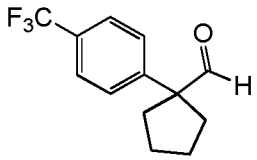


1-(4-Trifluoromethyl-phenyl)-cyclopentanecarbonitrile

To a suspension of NaH (8.18 g, 135.13 mmol, 60%) in DMSO (100 mL) were added dropwise a mixture of (4-trifluoromethyl-phenyl)-acetonitrile **(236)** (25 g, 135.13 mmol) and 1,4-dibromobutane (16 mL, 135.13 mmol) dissolved in DMSO:Ether (1:1) (300 mL) at 0 °C and the reaction mixture was stirred at this temperature for 2 h. After completion of the reaction, water (100 mL) and 10% HCl solution (50 mL) was added to the mixture and extracted with ethyl acetate (2x400 ml). The organic layer was dried over Na_2SO_4, concentrated and purified by 100-200 slica cloumn chromatography using hexane as the eluent to give 1-(4-trifluoromethyl-phenyl)-cyclopentanecarbonitrile **(237)** (21 g, 65%) as colorless liquid

GC-MS: 239 (M/H).

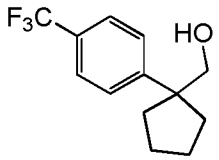
Preparation of (238):



1-(4-Trifluoromethyl-phenyl)-cyclopentanecarbaldehyde

To a stirred solution of 1-(4-trifluoromethyl-phenyl)-cyclopentanecarbonitrile **(237)** (21 g, 87.86 mmol) in dichloromethane (300 mL), was added slowly DIBAL (130 mL, 219.66 mmol, 25% in toluene) at -70 °C. The reaction mixture was stirred at this temperature for 2 h. After completion of the reaction, it was quenched by slow addition of aqueous potassium sodium tartarate tetrahydrate solution (130 mL). The reaction mixture was stirred at room temperature for 16 h. The mixture was extracted with DCM; organic part was dried over Na_2SO_4 and concentrated. The crude product was purified by 100-200 silica column chromatography using hexane as the eluent to give 1-(4-trifluoromethyl-phenyl)-cyclopentanecarbaldehyde **(238)** (17 g, 80%) as colorless liquid.

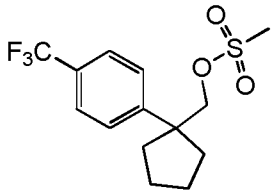
Preparation of (239):



[1-(4-Trifluoromethyl-phenyl)-cyclopentyl]-methanol

To a stirred solution of 1-(4-trifluoromethyl-phenyl)-cyclopentanecarbaldehyde **(238)** (17.0 g, 70.24 mmol) in methanol (200 mL), was added $NaBH_4$ (5.33 g, 140.5 mmol) portion wise at 0 °C. The reaction mixture was then stirred at room temperature for 2 h. After completion of reaction, solvent was concentrated and the crude product was diluted with water and extracted with ethyl acetate (2x300 mL). The organic part was dried over Na_2SO_4 and evaporated to give [1-(4-trifluoromethyl-phenyl)-cyclopentyl]-methanol **(239)** (15g, 90%) as white solid which was used for the next step without further purification.

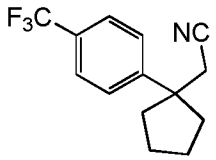
Preparation of (240):



Methanesulfonic acid 1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl ester

To a stirred of 1-(4-trifluoromethyl-phenyl)-cyclopentyl]-methanol **(239)** (15 g, 61.47 mmol) in dichloromethane (200 mL) was added Et_3N (17.1 mL, 123 mmol) followed by mesyl chloride (5.7 mL, 73.77 mmol) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 1 h. After completion, the reaction was quenched by the addition of water. The reaction mixture was diluted with dichloromethane. The organic part was washed with water, separated, dried over Na_2SO_4 and finally concentrated. The crude product was purified by 100-200 silica column chromatography using 10% ethyl acetate in hexane as the eluent to give methanesulfonic acid 1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl ester **(240)** (14 g, 70.6%) as a white solid.

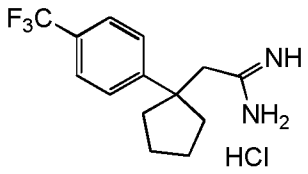
Preparation of (241):



[1-(4-Trifluoromethyl-phenyl)-cyclopentyl]-acetonitrile

To a stirred solution of methanesulfonic acid 1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl ester **(240)** (7g, 21.73 mmol) in DMSO (200 mL) were added KI (0.361 g, 2.17 mmol) and NaCN (1.6 g, 32.6 mmol). Reaction mixture was then stirred at 140 °C for 6 h. After completion of the reaction, it was diluted with water, extracted with ethyl acetate (2x300 mL) and the organic layer was washed with water and brine. It was then dried over Na_2SO_4, and concentrated. The crude product was purified by 100-200 silica column chromatography using 5% ethyl acetate in hexane as the eluent to give [1-(4-trifluoromethyl-phenyl)-cyclopentyl]-acetonitrile **(241)** (3.3 g, 60%) as colorless thick liquid.

Preparation of (242):



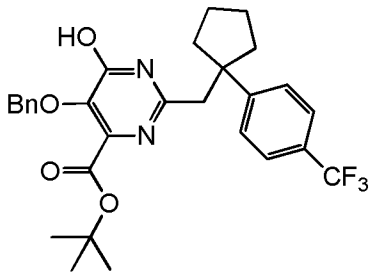
2-(1-p-Tolyl-cyclopentyl)-acetamidine (hydrochloride salt)

To a stirred suspension of NH_4Cl (1.3 g, 23.69 mmol) in dry toluene (30 mL) was added trimethylaluminium (2M solution in toluene) dropwise at 0 °C, stirred at 0 °C for 15 min, stirred at room temperature for 2h. The solution of [1-(4-trifluoromethyl-phenyl)-cyclopentyl]-acetonitrile **(241)** (2 g, 7.89 mmol) in toluene (10 mL) was added dropwise at the room temperature and heated at 80 °C for 16 h, the reaction mixture was cooled to 0 °C, Reaction mixture was poured into the slurry of silica gel (4 g) in $CHCl_3$ (4 mL), stirred vigorously for 30 min at 0°C, solid was filtered off through a celite, washed with methanol (5 x 100 mL), filtrate was concentrated, crude was taken in 10% MeOH in DCM (200 mL), stirred for 30 min. The solid was discarded by filtration and filtrate was concentrated. The crude was suspended in

ether, solid was collected by filtration, dried to get 2-(1-p-tolyl-cyclopentyl)-acetamidine (hydrochloride salt) **(242)** (1.4 g, 65.59 %) as light yellow solid.

LC-MS: 271.0 (M+H).

Preparation of (243):

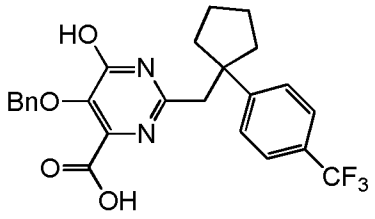


5-Benzyloxy-6-hydroxy-2-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-pyrimidine-4-carboxylic acid tert-butyl ester

To a stirred solution of 2-(1-p-tolyl-cyclopentyl)-acetamidine (HCl salt) **(242)** (600 mg, 1.96 mmol) and (E)-2-benzyloxy-3-hydroxy-but-2-enedioic acid 4-tert-butyl ester **(4)** (907 mg, 2.94 mmol) in methanol (10.6 mL) was added sodium methoxide (25 wt% in MeOH) (1.3 mL, 5.88 mmol) at 0°C then the reaction mixture allowed to warm to room temperature, stirred for 16 h. Silica thin layer chromatography was performed (30% ethylacetate in hexane, R_f=0.4). After completion of the reaction, it was quenched with water, methanol was evaporated and water (30 mL) was added. The mixture was extracted with ethyl acetate (3 x30 mL) and separated organic part was dried and concentrated to get crude, which was purified by CombiFlash column (eluted at 90% ethyl acetate in hexane) to get 5-benzyloxy-6-hydroxy-2-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-pyrimidine-4-carboxylic acid tert-butyl ester **(243)** (300 mg, 28.95%) as an off-white solid.

LC-MS: 539.2 (M+H).

Preparation of (244):

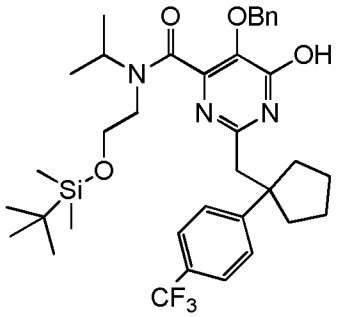


5-Benzyloxy-6-hydroxy-2-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-pyrimidine-4-carboxylic acid

To a stirred solution 5-benzyloxy-6-hydroxy-2-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-pyrimidine-4-carboxylic acid tert-butyl ester **(243)** (250 mg, 0.53 mmol) in the mixture of THF-water (2:1, 10 mL) was added lithium-hydroxide, monohydrate (477 mg, 11.36 mmol) refluxed for 20 h. Very faint starting ester was remained. Silica thin layer chromatography was performed (50% ethylacetate in hexane, R_f=0.1).Volatiles were evaporated, added water (10 mL), aqueous part was extracted with ethylacetate (2 x 30 mL), ethylacetate part was discarded, aqueous was acidified with 1(N) HCl to bring pH around 5-6. Acidified aqueous part was extracted with ethylacetate (3 x 30 mL), dried and concentrated to get 5-benzyloxy-6-hydroxy-2-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-pyrimidine-4-carboxylic acid **(244)** (250 mg, 93.13%) as an off-white solid.

LC-MS: 473.2 (M+H).

Preparation of (245):

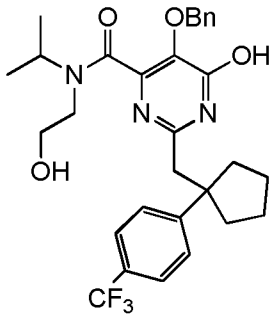


5-Benzyloxy-6-hydroxy-2-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide

5-Benzyloxy-6-hydroxy-2-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(245)** (187 mg, 52.55%) as yellow sticky solid was synthesized from 5-benzyloxy-6-hydroxy-2-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-pyrimidine-4-carboxylic acid **(244)** (250 mg, 0.53 mmol) and 2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amine **(8b)** following the procedure as described for 5-benzyloxy-2-[1-(2,5-dichlorophenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(206)**.

LCMS: 672.2 (M+H).

Preparation of (246):

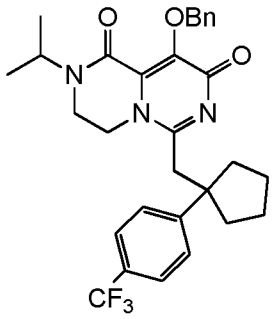


5-Benzyloxy-6-hydroxy-2-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide

5-Benzyloxy-6-hydroxy-2-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(246)** (110 mg, 70.79%) as white sticky solid was synthesized from 5-benzyloxy-6-hydroxy-2-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(245)** (187 mg, 0.28 mmol) and 1(N) HCl (0.05 mL, 1.39 mmol) following the procedure as described for 5-benzyloxy-2-[1-(2,5-dichlorophenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(207)**.

LCMS: 558.2 (M+H).

Preparation of (247):

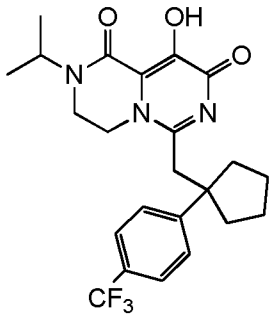


9-Benzyloxy-2-isopropyl-6-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

9-Benzyloxy-2-isopropyl-6-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(247)** (40 mg, 45.93 %) as white sticky solid was synthesized from 5-benzyloxy-6-hydroxy-2-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(246)** (90 mg, 0.16 mmol) following the procedure as described for 9-benzyloxy-6-[1-(2,5-dichlorophenyl)-cyclopentylmethyl]-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(208).** Silica thin layer chromatography was performed (ethylacetate, R_f=0.3).

LCMS:540.2 (M+H).

Preparation of (248):



9-Hydroxy-2-isopropyl-6-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a stirred degassed solution of 9-benzyloxy-2-isopropyl-6-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(247)** in EtOH (10 mL) was added 10% Pd-C (5 mg) and stirred for 2 h under H_2 baloon pressure. Silica thin layer chromatography was performed (5% MeOH I DCM, R_f=0.4). Pd-C was filterred off through a small bed of celite, washed with ethanol (5 x 20 mL), ethanol was evaporated, crude was purified by prep-TLC plate (mobile phase 5% MeOH in DCM) to get 9-hydroxy-2-isopropyl-6-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(248)** (8 mg, 23.98%) as an off-white solid.

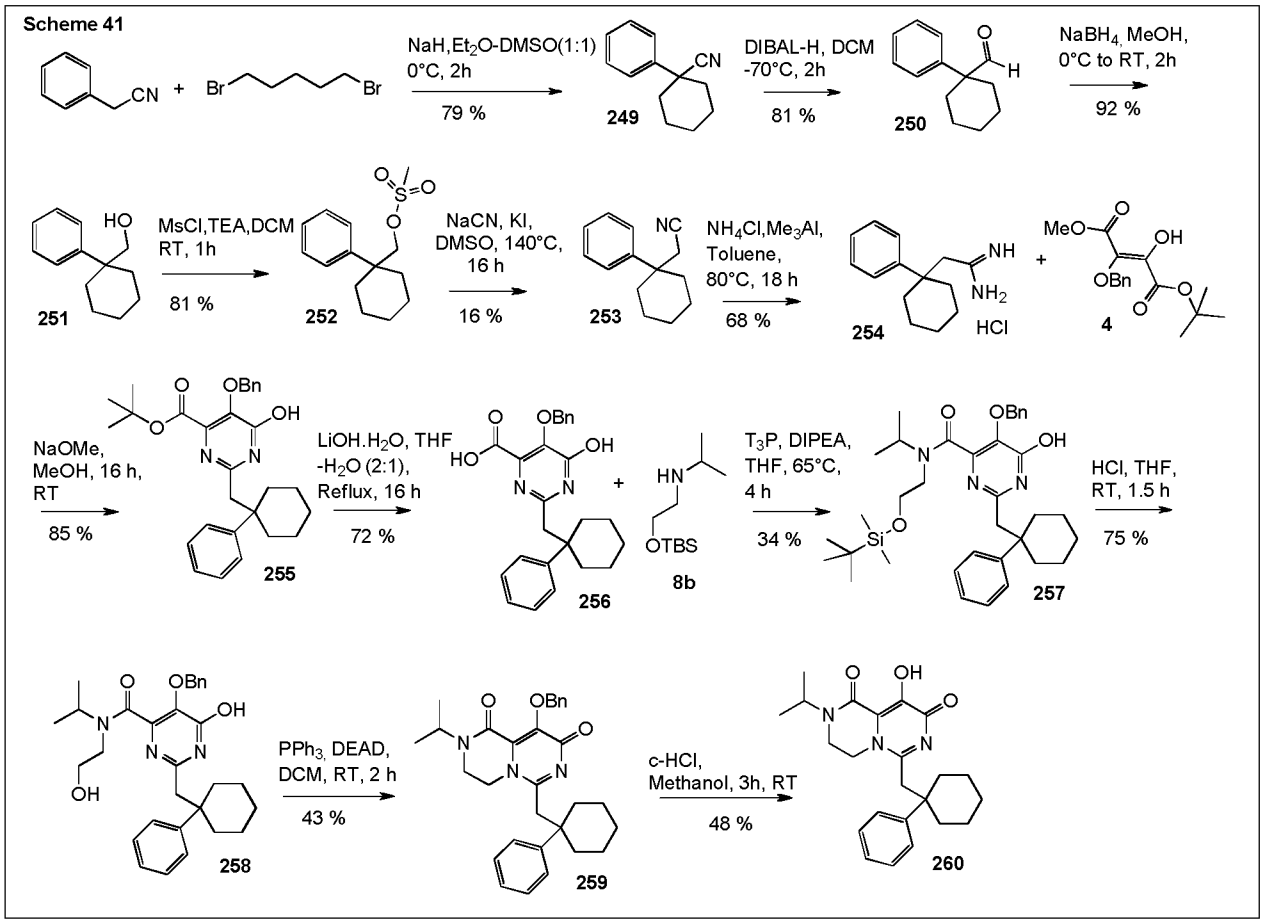
LCMS: 450.0 (M+H).

Example 260

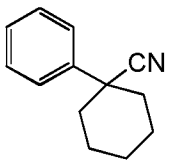
9-Hydroxy-2-isopropyl-6-(1-phenyl-cyclohexylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 41.

Synthetic route for 260



Preparation of (249):



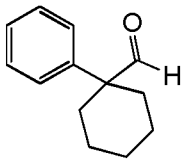
1-Phenyl-cyclohexanecarbonitrile

To a suspension of NaH (42.7 g, 1067.0 mmol, 60 %) in DMSO (600.0 mL) were added dropwise a mixture of phenylacetonitrile (50.0 g, 426.8 mmol) and 1,5-dibromopentane (58.1 mL, 426.8 mmol) dissolved in DMSO:Ether (1:1) (200.0 mL) at 0 °C and the reaction mixture was stirred at this temperature for 2 h. After completion of the reaction, water and 10 % HCl solution was added to the mixture and extracted with ethyl acetate. The combined organic layer was then washed with water, brine, dried over sodium sulphate and concentrated under

reduced pressure to get the crude. It was then purified by normal silica gel column chromatography (using hexane) to get 1-phenyl-cyclohexanecarbonitrile (**249)** (52.0 g, 65.76 %) as colorless oil.

GC-MS: 185.0 (m/z).

Preparation of (250):

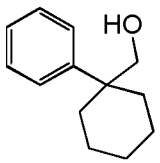


1-Phenyl-cyclohexanecarbaldehyde

To a stirred solution of 1-phenyl-cyclohexanecarbonitrile **(249)** (20.0 g, 107.9 mmol) in dichloromethane (200.0 mL) was added slowly DIBAL-H (153.5 mL, 269.87 mmol, 25 % in toluene) at -70 °C and stirred for 2 h. After completion of the reaction, it was quenched by slow addition of aqueous potassium sodium tartarate tetrahydrate solution and the reaction mixture was stirred at room temperature for 16 h. Then, it was extracted with DCM, organic layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to get the crude. It was purified by normal silica gel column chromatography (using hexane) to get 1-phenyl-cyclohexanecarbaldehyde **(250)** (16.48 g, 81.09 %) as colorless oil.

GC-MS: 188.0 (m/z).

Preparation of (251):

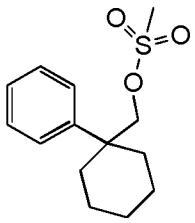


(1-Phenyl-cyclohexyl)-methanol

To a stirred solution of 1-phenyl-cyclohexanecarbaldehyde **(250)** (16.4 g, 87.1 mmol) in methanol (200.0 mL) was added $NaBH_4$ (6.62 g, 174.2 mmol) portion wise at 0 °C. The reaction mixture was then stirred at room temperature for 2 h. After completion of the reaction, the solvent was concentrated and the crude product was extracted with ethyl acetate. The organic layer was then washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to get (1-phenyl-cyclohexyl)-methanol **(251)** (15.2 g, 91.7 %) as white solid which was sufficiently pure to use for the next step.

GC-MS: 190.0 (m/z).

Preparation of (252):

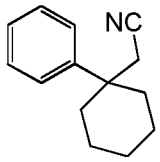


Methanesulfonic acid 1-phenyl-cyclohexylmethyl ester

To a stirred of (1-phenyl-cyclohexyl)-methanol **(251)** (43.0 g, 225.97 mmol) in dichloromethane (250.0 mL) was added Et_3N (63.0 mL, 451.9 mmol) followed by mesyl chloride (21.0 mL, 271.16 mmol) drop-wise at 0 °C and stirred at room temperature for 1 h. After completion of the reaction, it was quenched by the addition of water and extracted with dichloromethane. The organic layer was then washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to get the crude. It was purified by normal silica gel column chromatography (using 5% ethyl acetate in hexane) to get methanesulfonic acid 1-phenyl-cyclohexylmethyl ester **(252)** (49.3 g, 81.0 %) as a white solid.

GC-MS: 268.0 (m/z).

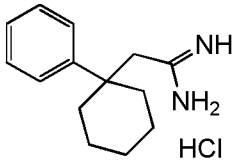
Preparation of (253):



(1-Phenyl-cyclohexyl)-acetonitrile

To a stirred solution of methanesulfonic acid 1-phenyl-cyclohexylmethyl ester **(252)** (20.0 g, 74.52 mmol) in DMSO (100.0 mL) were added KI (1.24 g, 7.45 mmol) and NaCN (5.48 g, 111.78 mmol) and stirred at 140 °C for 16 h. After completion of the reaction, it was diluted with water, extracted with ethyl acetate and the organic layer was washed with water and brine. It was then dried over Na_2SO_4 and concentrated. The crude product was purified by normal silica gel column chromatography (using 5 % ethyl acetate in hexane) to get (1-phenyl-cyclohexyl)-acetonitrile **(253)** (2.4 g, 16.1 %) as colorless liquid.

Preparation of (254):



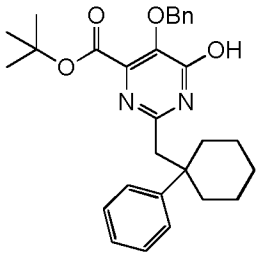
HCl-salt of 2-(1-phenyl-cyclohexyl)-acetamidine

To a suspension of NH_4Cl (2.34 g, 43.65 mmol) in toluene (20.0 mL) was added drop-wise a solution of trimethyl aluminium (3.15 g, 43.65 mmol, 2 M in toluene) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h prior to the addition of a solution of (1-phenyl-cyclohexyl)-acetonitrile **(253)** (2.9 g, 14.55 mmol) in toluene (10.0 mL). The resulting solution was heated to 80 °C for 16 h. The cooled reaction mixture was poured into a slurry of silica-gel (10.0 g) in $CHCl_3$ (20.0 mL) followed by vigorous stirring for 30 min. The silica gel was filtered off and the cake was rinsed in turn with MeOH. The solvent was evaporated and the crude was taken in 10 % MeOH in dichloromethane (200.0 mL) and stirred for 30 min. The solid suspension was removed by filtration and the filtrate was evaporated. The crude product was triturated in diethyl ether and the solid was collected by

filtration, dried under vacuum to afford HCl-salt of 2-(1-phenyl-cyclohexyl)-acetamidine **(254)** (2.5 g, 68.0 %) as white solid.

LC-MS: 217.2 (M+H).

Preparation of (255):

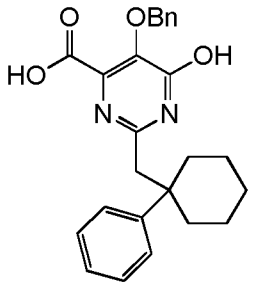


5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclohexylmethyl)-pyrimidine-4-carboxylic acid tert-butyl ester

To a mixture of HCl-salt of 2-(1-phenyl-cyclohexyl)-acetamidine **(254)** (2.0 g, 7.91 mmol) and (E)-2-benzyloxy-3-hydroxy-but-2-enedioic acid 4-tert-butyl ester 1-methyl ester (**9**) (3.66 g, 11.86 mmol) in MeOH (50.0 mL) was added sodium methoxide (1.28 g, 23.73 mmol, 25 % in MeOH) at 0 °C. Then the reaction mixture was allowed to warm to room temperature and was stirred for 16 h. After completion of the reaction, solvent was reduced and the crude product was dissolved in dichloromethane and extracted with DCM. The organic layer was washed with 1 N HCl and with water and brine. It was then dried over Na_2SO_4 and concentrated. The crude product was purified by normal silica gel column chromatography (using 10% ethyl acetate in hexane) to get 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclohexylmethyl)-pyrimidine-4-carboxylic acid tert-butyl ester **(255)** (3.2 g, 85.0 %) as yellowish thick liquid which turned into solid after keeping in room temperature.

LC-MS: 475.2 (M+H).

Preparation of (256):

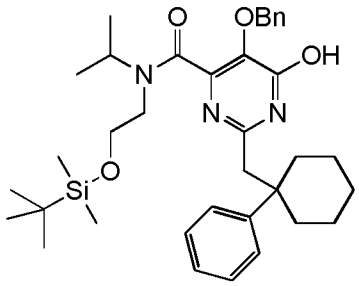


5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclohexylmethyl)-pyrimidine-4-carboxylic acid

To a stirred solution of 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclohexylmethyl)-pyrimidine-4-carboxylic acid tert-butyl ester **(255)** (2.5 g, 5.27 mmol) in THF (60.0 mL) was added aqueous solution (30.0 mL) of $LiOH.H_2O$ (2.21 g, 52.67 mmol) and refluxed for 16 h. After completion of the reaction, the organic solvent was removed on rotary evaporator and water (10.0 mL) was added. Aqueous solution was acidified with concentrated HCl (pH = 5.0) at 0 °C to give white solid which was filtered off. The solid residue was triturated in diethyl ether and filtered. After drying 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclohexylmethyl)-pyrimidine-4-carboxylic acid **(256)** was obtained (1.6 g, 72.58 %) as white solid.

LC-MS: 417.4 (M-H).

Preparation of (257):



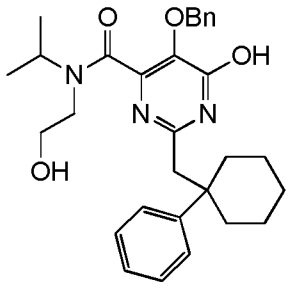
5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclohexylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide

To a stirred solution of 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclohexylmethyl)-pyrimidine-4-carboxylic acid **(256)** (0.5 g, 1.19 mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-

amine **(8b)** (0.78 g, 3.58 mmol) in dry THF (20.0 mL) were added propylphophonic anhydride (0.76 g, 2.39 mmol, 50% in ethyl acetate) and diisopropyl ethylamine (0.8 mL, 4.78 mmol) at room temperature and heated at 65 °C for 4 h. After completion of the reaction, mixture was portioned between ethyl acetate and water. Organic layer was separated and dried over Na_2SO_4 and concentrated under reduced pressure to get crude product which was purified by normal silica gel column chromatography (using 30 % ethyl acetate in hexane) to get 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclohexylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(257)** (0.25 g, 34.0 %) as colorless liquid.

LC-MS: 618.2 (M+H).

Preparation of (258):

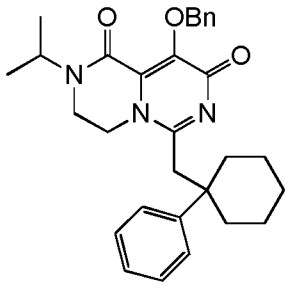


5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclohexylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide

To a stirred solution of 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclohexylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(257)** (0.7 g, 1.13 mmol) in THF (10.0 mL) was added HCl (0.062 g, 1.70 mmol) and the reaction mixture was stirred at room temperature for 1.5 h. After completion of the reaction, mixture was extracted with ethyl acetate. The combined organic layer was washed with water, separated and dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by normal silica gel column chromatography (using 60 % ethyl acetate in hexane followed by 5 % MeOH in EtOAc) to get 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclohexylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(258)** (0.43 g, 75.0 %) as white solid.

LC-MS: 504.2 (M+H).

Preparation of (259):

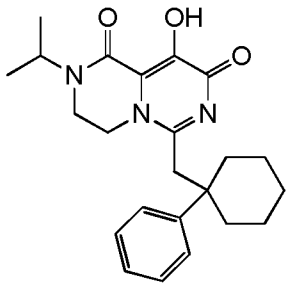


9-Benzyloxy-2-isopropyl-6-(1-phenyl-cyclohexylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a mixture of 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclohexylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(258)** (0.43 g, 0.85 mmol) and triphenyl phosphine (0.45 g, 1.71 mmol) in dry dichloromethane (10.0 mL) was added diethyl azidocarboxylate (0.34 mL, 2.13 mmol) at room temperature and stirred for 2 h. After completion of the reaction, the solvent was evaporated and the crude product was purified by normal silica gel column chromatography (using 2% MeOH in dichloromethane) to get 9-benzyloxy-2-isopropyl-6-(1-phenyl-cyclohexylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(259)** (0.18 g, 43.0 %) as white solid.

LC-MS: 486.2 (M+H).

Preparation of (260):



9-Hydroxy-2-isopropyl-6-(1-phenyl-cyclohexylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To the stirred solution of 9-benzyloxy-2-isopropyl-6-(1-phenyl-cyclohexylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione (**259)** (0.18 g, 0.37 mmol) in MeOH (5.0 mL) was added con- HCl (5.0 mL) and the reaction mixture was stirred at room temperature for 3 h. After completion of the reaction, solvent was reduced and the crude was extracted with 10 % MeOH in DCM. The organic part was washed with saturated $NaHCO_3$ solution, separated and dried over Na_2SO_4. After evaporation, the crude product was purified by normal silica gel column chromatography (using 3% MeOH in dichloromethane) to get 9-hydroxy-2-isopropyl-6-(1-phenyl-cyclohexylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(260)** (70.0 mg, 48.0 %) as white solid.

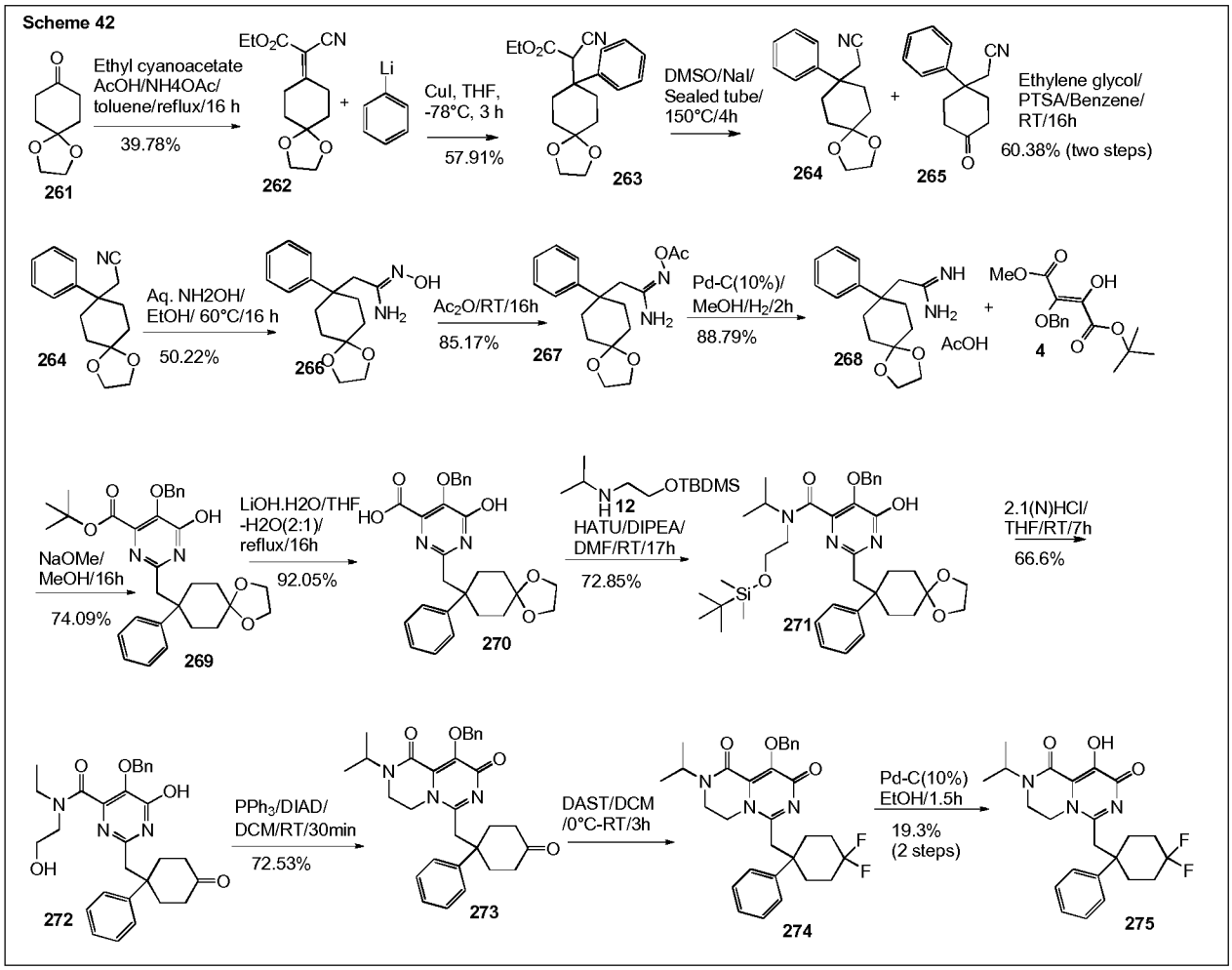
LC-MS: 396.2 (M+H).

Example 275

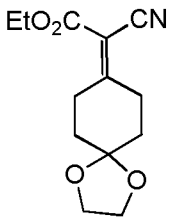
6-(4,4-Difluoro-1-phenyl-cyclohexylmethyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 42.

Synthetic route for 275



Synthesis of (262):



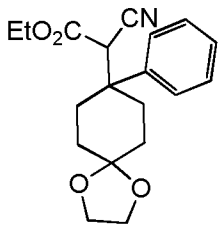
Cyano-(1,4-dioxa-spiro[4.5]dec-8-ylidene)-acetic acid ethyl ester

To a stirred solution of 1,4-dioxa-spiro[4.5]decan-8-one **(261)** (5.0 g, 32.01 mmol) and cyano-acetic acid ethyl ester (3.99g, 35.31 mmol) in toluene (50 mL) were added acetic acid (0.3 mL, 5.09 mmol) and ammonium acetate (123mg, 1.60 mmol). A Dean Stark trap and reflux

condenser were attached to the reaction flask and the mixture was heated to reflux and stirred for 16 h, the reaction mixture was cooled to 0°C, quenched with saturated aqueous NaHCO3 (100ml). The aqueous layer was extracted with EtOAc (2x200ml) and the combined organic layer was dried with sodium sulfate, filtered and concentrated under reduced pressure. The crude yellow oil was re-crystallized with 20% ethyl acetate in hexane to afford pure cyano-(1,4-dioxa-spiro[4.5]dec-8-ylidene)-acetic acid ethyl ester **(262)** (3.2 g, 39.78%) as light yellow solid.

LCMS; 330.2 (M+H)

Synthesis of (263):

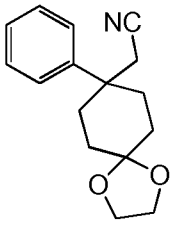


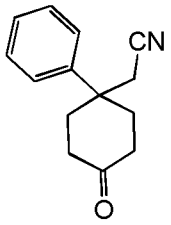
Cyano-(8-phenyl-1,4-dioxa-spiro[4.5]dec-8-yl)-acetic acid ethyl ester

To a stirred suspension of CuI (5.67g, 29.88mmol) in THF (70mL) was added phenyl lithium (1.8M dibutyl ether) (33.2mL, 59.76mmol) at -78°C and the resulting mixture was allowed to stir at -30°C for 2h. To the resulting reaction mixture at -78°c was added the pre cooled solution of Cyano-(1,4-dioxa-spiro[4.5]dec-8-ylidene)-acetic acid ethyl ester **(262)** in THF (30mL) and resulting mixture was allowed to stir at -30°C for 1h. Reaction was monitored by silica TLC (P-anisoldehyde active). Reaction mixture was quenched with sat.NH4Cl solution and reaction mixture was diluted with ethyl acetate and separates the organic layer. Organic part was dried over Na_2SO_4 and concentrated under reduced pressure, The resulted crude was purified over silica gel (normal, 100-200 mesh) column chromatography using gradient eluent 2% to 10% Ethylacetate in Hexane to get cyano-(8-phenyl-1,4-dioxa-spiro[4.5]dec-8-yl)-acetic acid ethyl ester **(263)** (3.8g, 57.91%), as colorless gummy liquid.

LCMS: 330.2 (M+H).

Synthesis of (264+265):

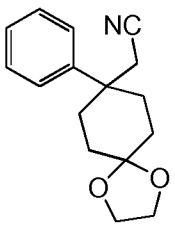




(4-Oxo-1-phenyl-cyclohexyl)-acetonitrile + (8-Phenyl-1,4-dioxa-spiro[4.5]dec-8-yl)-acetonitrile

To a solution of cyano-(8-phenyl-1,4-dioxa-spiro[4.5]dec-8-yl)-acetic acid ethyl ester **(263)** (500 mg, 1.52 mmol) in DMSO (5mL) was added NaI (910 mg, 6.07 mmol) and taken in a sealed tube. The reaction mixture was then heated at 150°C for 3 h [silica TLC; ethyl acetate: hexane =1:4, Rf = 0.3 (p-anysaldehyde active)] indicated that the formation of desired product along with the ketal de-protected product. To the reaction mass was added ethyl acetate (50ml) and washed with brine (3x25 ml). The organic layer was dried and concentrated in vacuo to get crude mixture shows formation of (4-oxo-1-phenyl-cyclohexyl)-acetonitrile **(265)** and (8-phenyl-1,4-dioxa-spiro[4.5]dec-8-yl)-acetonitrile **(264)** (400 mg, crude mixture) as brown sticky liquid which was used directly in the next step with out further purification.

Synthesis of (264):



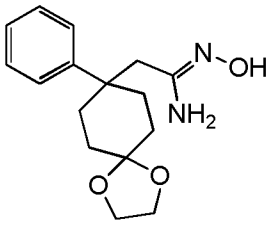
(8-Phenyl-1,4-dioxa-spiro[4.5]dec-8-yl)-acetonitrile

To a stirred solution of (4-oxo-1-phenyl-cyclohexyl)-acetonitrile **(265)** and (8-phenyl-1,4-dioxa-spiro[4.5]dec-8-yl)-acetonitrile **(264)** (350 mg, crude mixture) in benzene (50 mL) was added catalytic amount of PTSA (31.2mg, 0.164mmol) and ethanediol (0.28mL, 4.92mmol) and was stirred at room temperature for 16h [silica TLC; ethyl acetate-hexane=1:4; Rf = 0.4 (p-anysaldehyde active)]. The reaction was diluted with ethyl acetate (50ml) and washed with brine (2x50mL). The organic part was dried and concentrated in vacuo to get crude mass

which was purified over silica gel (normal, 100-200 mesh) column chromatography using gradient eluent of 5% to 10% ethyl acetate in hexane to get pure (8-phenyl-1,4-dioxa-spiro[4.5]dec-8-yl)-acetonitrile **(264)** (0.25g, 60.38%, two step yield) as yellow liquid.

LCMS; 258.2 (M+H)

Synthesis of (266):

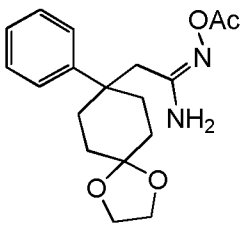


N-Hydroxy-2-(8-phenyl-1,4-dioxa-spiro[4.5]dec-8-yl)-acetamidine

To a stirred solution of 8-phenyl-1,4-dioxa-spiro[4.5]decane-8-carbonitrile **(264)** (1.5 g, 5.83 mmol) in ethanol (30 mL) was added NH_2OH (50% aqueous solution, 1.1 mL, 17.49 mmol) and heated at 60°C for 16 h Silica thin layer chromatography was performed (ethyl acetate : Hexane=1:1, Rf = 0.15). The reaction mass concentrated in vacuo to crude mass which was triturated with diethyl ether to get pure N-hydroxy-2-(8-phenyl-1,4-dioxa-spiro[4.5]dec-8-yl)-acetamidine **(266)** (850 mg, 50.22%) as an off-white solid which was used in the next step without further purification.

LCMS: 291.2 (M+H).

Synthesis of (267):

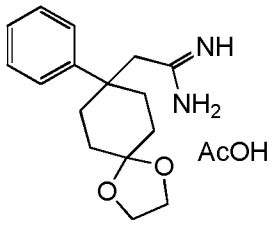


(Z)-(1-amino-2-{8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl}ethylidene)amino acetate

A mixture of N-hydroxy-2-(8-phenyl-1,4-dioxa-spiro[4.5]dec-8-yl)-acetamidine **(266)** (600 mg, 2.01 mmol) and acetic anhydride (2 mL) was stirred at room temperature for 16h (TLC, ethyl acetate :Hexane=7:3/UV/SiO_2, Rf = 0.4). The reaction mixture was diluted with ethyl acetate (50mL), washed with water (2x25mL), brine (25mL), dried and concentrated in vacuo to get crude mass which was purified by CombiFlash using a gradient eluent mixture of ethyl acetate and hexane to get pure (Z)-(1-amino-2-{8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl}ethylidene)amino acetate **(267)** (585 mg, 85.17%) as white sticky solid.

LCMS; 333.3 (M+H)

Synthesis of (268):

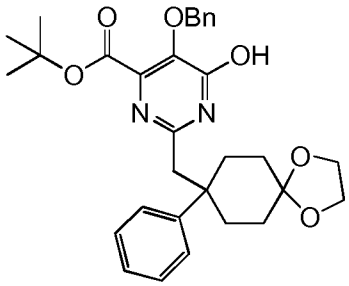


2-(8-Phenyl-1,4-dioxa-spiro[4.5]dec-8-yl)-acetamidine; compound with acetic acid

To a stirred solution of (Z)-(1-amino-2-{8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl}ethylidene)amino acetate **(267)** (1.4g, 4.21 mmol) in methanol was added Pd-C (10%) under nitrogen atmosphere and the mixture was kept under hydrogen atmosphere of balloon pressure at room temperature for 2 h (reaction was monitored by LCMS). The reaction mass was filtered and the filtrate was concentrated in vacuo to get a sticky mass which was triturated with diethyl ether to get pure 2-(8-phenyl-1,4-dioxa-spiro[4.5]dec-8-yl)-acetamidine; compound with acetic acid **(268)** (1.25 g, 88.79%) as white solid.

LCMS: 275.3 (M+H)

Synthesis of (269):

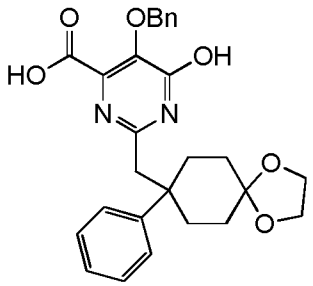


5-Benzyloxy-6-hydroxy-2-(8-phenyl-1,4-dioxa-spiro[4.5]dec-8-ylmethyl)-pyrimidine-4-carboxylicacid tert-butyl ester

A mixture of 2-(8-phenyl-1,4-dioxa-spiro[4.5]dec-8-yl)-acetamidine; compound with acetic acid **(268)** (500mg, 1.5mmol) and 2-benzyloxy-3-hydroxy-but-2-enedioic acid 4-tert-butyl ester 1-methyl ester **(4)** (553mg, 1.8mmol) in methanol (15mL) was cooled to 0°C followed by the addition of NaOMe (25% in methanol) (1mL, 4.5mmol) and stirred at room temperature for 16h Silica thin layer chromatography was performed (ethyl acetate :hexane = 7:3, Rf = 0.6). The reaction mixture was diluted with ethyl acetate (40 ml) and washed with brine (2x20mL), dried and concentrated in vacuo to get crude mixture which was purified over normal silica gel (100-200 mesh) column chromatography using gradient eluent (30-50% ethyl acetate in hexane) to get pure 5-benzyloxy-6-hydroxy-2-(8-phenyl-1,4-dioxa-spiro[4.5]dec-8-ylmethyl)-pyrimidine-4-carboxylic acid tert-butyl ester **(269)** (590mg, 74.09%) as brown sticky mass.

LCMS: 533.4 (M+H)

Synthesis of (270):

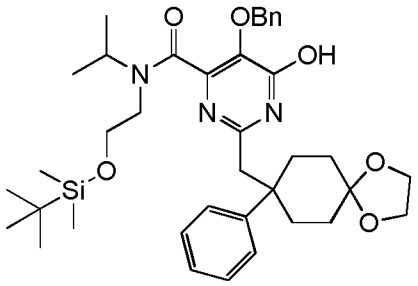


5-Benzyloxy-6-hydroxy-2-(8-phenyl-1,4-dioxa-spiro[4.5]dec-8-ylmethyl)-pyrimidine-4-carboxylic acid

A mixture of 5-benzyloxy-6-hydroxy-2-(8-phenyl-1,4-dioxa-spiro[4.5]dec-8-ylmethyl)-pyrimidine-4-carboxylic acid tert-butyl ester **(269)** (850mg, 1.60mmol), $LiOH.H_2O$ (670mg, 15.96mmol) in THF-water (5:1, 48mL) was refluxed for 20h Silica thin layer chromatography was performed (MeOH : DCM = 1:9, Rf = 0.1). From the reaction mixture THF was removed in vacuo and residue was diluted with water (25 mL); cooled in ice water, neutralized (pH~7) with 1(N) aqueous HCl and extracted with ethyl acetate (2x50 mL). The combined organic parts was washed with brine (25 mL), dried and concentrated in vacuo to get pure 5-benzyloxy-6-hydroxy-2-(8-phenyl-1,4-dioxa-spiro[4.5]dec-8-ylmethyl)-pyrimidine-4-carboxylic acid **(270)** (700mg, 92.05%) as yellow solid.

LCMS; 477.4 (M+H)

Synthesis of (271):

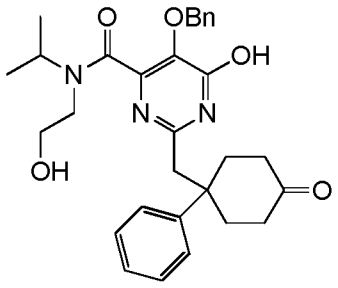


5-Benzyloxy-6-hydroxy-2-(8-phenyl-1,4-dioxa-spiro[4.5]dec-8-ylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide

To a stirred solution of 5-benzyloxy-6-hydroxy-2-(8-phenyl-1,4-dioxa-spiro[4.5]dec-8-ylmethyl)-pyrimidine-4-carboxylic acid **(270)** (600 mg, 1.26 mmol) in DMF (12 mL) were added [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amine **(8b)** (411 mg, 1.89 mmol), DIPEA (0.63 mL, 3.78 mmol) and HATU (574 mg, 1.51 mmol) and stirred at room temperature for 17h (TLC, ethyl acetate :hexane = 1:1/UV/SiO_2, Rf = 0.6). Reaction mass was diluted with ethyl acetate (100mL), washed with brine (3x50mL), dried and concentrated in vacuum to get crude mass which was purified normal silica gel (100-200 mesh) column chromatography using gradient polarity eluent (1-2% MeOH in DCM) to get pure 5-benzyloxy-6-hydroxy-2-(8-phenyl-1,4-dioxa-spiro[4.5]dec-8-ylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(271)** (620 mg, 72.85%) as brown sticky solid.

LCMS; 676.3 (M+H)

Synthesis of (272):

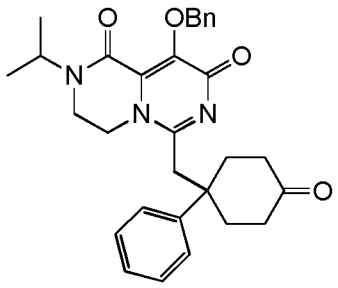


5-Benzyloxy-6-hydroxy-2-(4-oxo-1-phenyl-cyclohexylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide

To a solution of 5-benzyloxy-6-hydroxy-2-(8-phenyl-1,4-dioxa-spiro[4.5]dec-8-ylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(271)** (500 mg, 0.74 mmol) in THF (30.0 mL) was added 2.1(N) aqueous HCl (6.0 mL) and stirred at room temperature for 7 h Silica thin layer chromatography was performed (only EtOAc; Rf = 0.25). Reaction mass was concentrated in vacuum and diluted with ethyl acetate (50 mL), washed with aqueous $NaHCO_3$ solution (20 mL), brine (30 mL), dried and concentrated in vacuum to get crude mass which was purified by CombiFlash using gradient eluent mixture of mathanol and DCM to get pure 5-benzyloxy-6-hydroxy-2-(4-oxo-1-phenyl-cyclohexylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(272)** (255 mg, 66.6%) as white sticky solid.

LCMS; 518.3 (M+H)

Synthesis of (273):

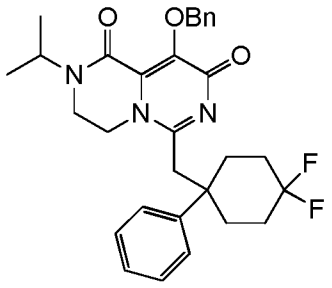


9-Benzyloxy-2-isopropyl-6-(4-oxo-1-phenyl-cyclohexylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a solution of 5-benzyloxy-6-hydroxy-2-(4-oxo-1-phenyl-cyclohexylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(272)** (200 mg, 0.39 mmol) in DCM (25.0 mL) was added PPh_3 (152 mg, 0.58 mmol) and DIAD (0.12 mL, 0.58 mmol) at room temperature and stirred for 30 min (silica TLC, 5%MeOH in EtOA, Rf = 0.5). Reaction mixture was concentrated under reduced pressure. Purified by normal silica gel (100-200 mesh) column chromatography using gradient polarity mobile phase (50% EtOAc in hexane to 5% MeOH in DCM) to get pure 9-benzyloxy-2-isopropyl-6-(4-oxo-1-phenyl-cyclohexylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(273)** (140 mg, 72.53%) as white solid.

LCMS; 500.2 (M+H)

Synthesis of (274):

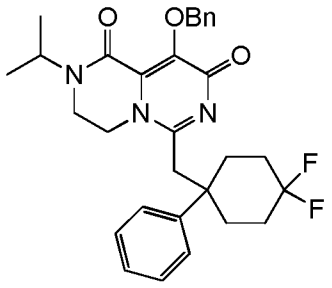


9-Benzyloxy-6-(4,4-difluoro-1-phenyl-cyclohexylmethyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

A solution of 9-benzyloxy-2-isopropyl-6-(4-oxo-1-phenyl-cyclohexylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(273)** (120 mg, 0.24 mmol) in DCM (8 mL) was added to a solution of dimethylaminosulfer trifluoride (0.18 mL, 1.80 mmol) in DCM (12 mL) at 0°C and stirred for 3 h at room temperature Silica thin layer chromatography was performed (5%MeOH in EtOAc, Rf = 0.2). Reaction mixture was cooled to 0°C and quenched with saturated aqueous $NaHCO_3$ solution (1 mL) and water (30 mL). Extracted with DCM (40 mL x 2), dried and concentrated in vacuum to get crude mass which was purified by preparative TLC (silica) using developing solvent 3% methanol in DCM to get 9-benzyloxy-6-(4,4-difluoro-1-phenyl-cyclohexylmethyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(274)** (80 mg, mixture)as brown sticky solid. LCMS indicated mixture. Next step was preceded with this mixture.

LCMS; 522.0 (M+H)

Synthesis of (275):



6-(4,4-Difluoro-1-phenyl-cyclohexylmethyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

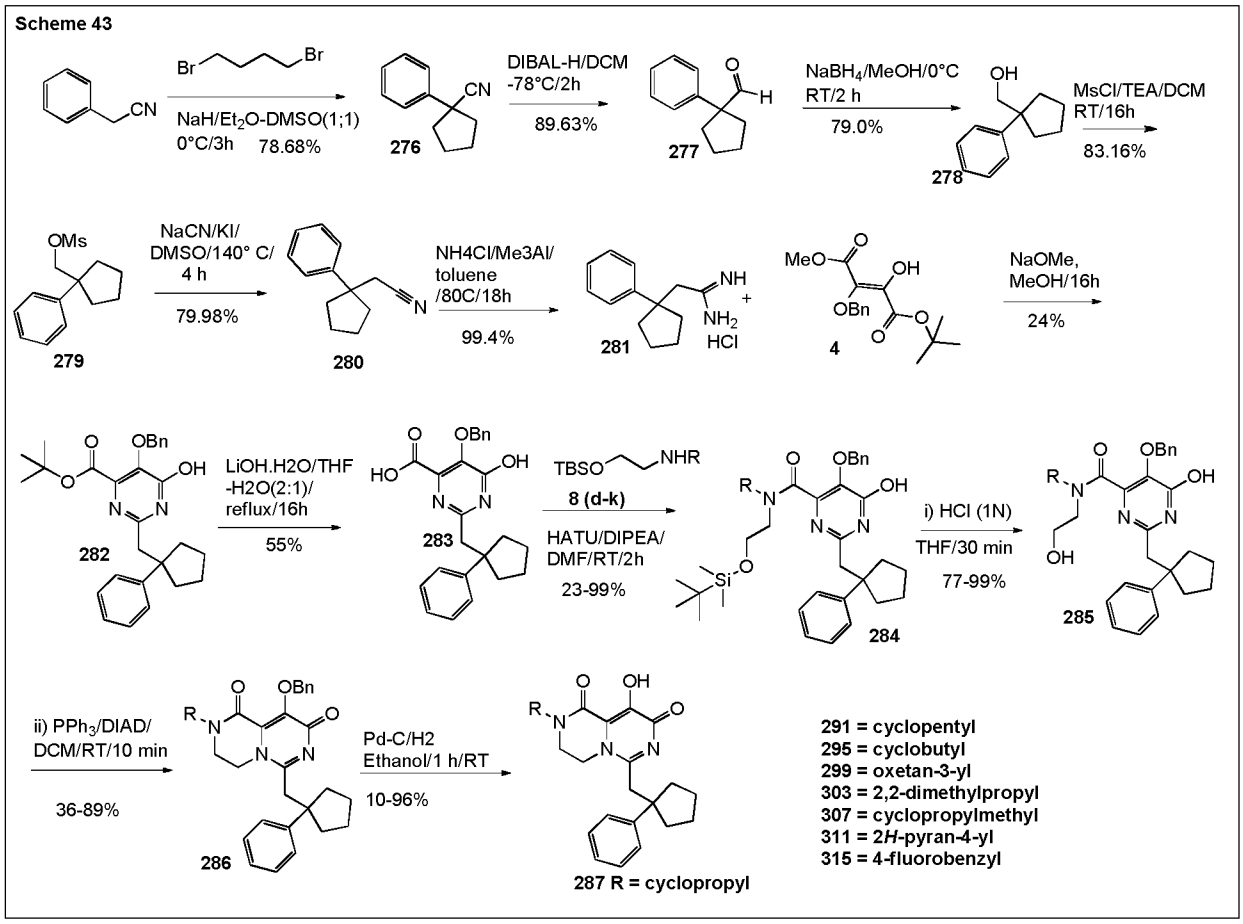
A solution of 9-benzyloxy-6-(4,4-difluoro-1-phenyl-cyclohexylmethyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(274)** in ethanol was degassed by argon followed by the addition of Pd-C (10%) under argon atmosphere and the reaction was stirred at room temperature under H2 atmosphere for 1.5 h. Reaction mass was filtered through celite bed and the filtrate was concentrated under reduced pressure to get crude mixture which was purified by preparative HPLC to get pure 6-(4,4-difluoro-1-phenyl-cyclohexylmethyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(275)** [20mg, 19.3% (2 steps)] as brown sticky solid.

LCMS; 330.2 (M+H)

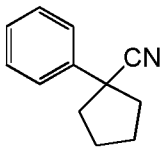
General procedure for examples 287 to 315

The synthetic procedures are outlined in Scheme 43.

General synthetic route for 287, 291, 295, 299, 303, 307, 311 and 315



Synthesis of (276):

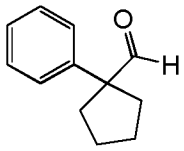


1-Phenyl-cyclopentanecarbonitrile

To a suspension of sodium hydride (60%) (7.5 g, 187.79 mmol) in DMSO (100 mL) was added dropwise a mixture of phenyl acetonitrile (10 g, 85.36 mmol) and 1,4-dibromobutane (18.43 g, 187.79 mmol) dissolved in DMSO: ether (120 mL, 1:1) at 0 °C stirred for 30 min at same temperature, then stirred at room temperature for 3 h. After completion of the reaction, it was quenched with 1 N HCl (10 mL), water (100 mL) was added, extracted with ethyl acetate (3 x 100 mL), separated organic part was washed with water (3 x 100 mL) and brine (100 mL),

organic part was dried and concentrated to get crude which was purified by CombiFlash column (eluted at 3% ethyl acetate in hexane) to afford 1-phenyl-cyclopentanecarbonitrile **(276)** (11.5 g, 78.68%) as colorless liquid.

Synthesis of (277):

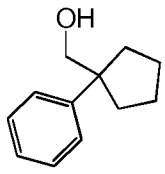


1-Phenyl-cyclopentanecarbaldehyde

To a stirred solution of 1-phenyl-cyclopentanecarbonitrile **(276)** (12.5 g, 73.00 mmol) in DCM (125 mL), was added DIBAL (25% in toluene) (104 mL, 182.50 mmol) at -78°C and stirred for 2 h at the same temperature. After completion of the reaction, it was quenched with saturated solution of potassium sodium tartrate (75 mL) and stirred for 16 h at room temperature, DCM part was separated, aqueous part was re-extracted with DCM (1x100 mL), dried, and concentrated, crude was purified by Combi-Flash column (eluted at 5% ethyl acetate in hexane) to get 1-phenyl-cyclopentanecarbaldehyde **(277)** (11.4 g, 89.63%) as colorless liquid.

GC-MS: 174 (m/z).

Synthesis of (278):



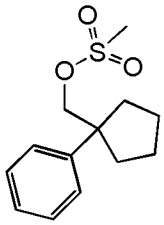
(1-Phenyl-cyclopentyl)-methanol]

To a stirred solution of 1-phenyl-cyclopentanecarbaldehyde **(277)** (11.5 g, 71.82 mmol) in methanol (150 mL) was added $NaBH_4$ at 0°C portion wise and was stirred at room temperature for 2 h. After completion of the reaction, it was quenched with saturated aqueous solution of ammonium chloride (20 mL), MeOH was removed, diluted with water (100 mL), extracted with ethyl acetate (3 x 100 mL) and separated organic part was dried and

concentrated. Crude was purified by Combi-Flash column (eluted at 5-10% ethylacetate in hexane) to get (1-phenyl-cyclopentyl)-methanol] **(278)** (10 g, 79.0%) as white solid.

GC-MS: 176 (m/z).

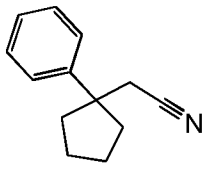
Synthesis of (279):



Methanesulfonic acid 1-phenyl-cyclopentylmethyl ester

To a stirred solution of (1-phenyl-cyclopentyl)-methanol] **(278)** (10 g, 56.73 mmol) in DCM (110 mL) was added triethyl amine (16 mL, 113.47 mmol) followed by mesyl chloride (5.3 mL, 68.08 mmol) at 0 °C, it was stirred at room temperature for 16 h. After completion of reaction it was diluted with DCM (50 mL), washed with water (100 mL), saturated aqueous sodium bicarbonate solution (50 mL) and brine (50 mL). Separated organic part was dried and concentrated. Crude was purified by Combi-Flash column (eluted at 10-20% ethylacetate in hexane) to get methanesulfonic acid 1-phenyl-cyclopentylmethyl ester **(279)** (12g, 83.16%) as yellow semi solid.

Synthesis of (280):



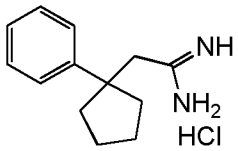
(1-Phenyl-cyclopentyl)-acetonitrile

To a stirred solution of methanesulfonic acid 1-phenyl-cyclopentylmethyl ester **(279)** (12 g, 47.24 mmol) in DMSO (36 mL) were added KI (784 mg, 4.72 mmol) and NaCN (3.5 g, 70.87 mmol) and stirred for 140°C for 4 h, stirred at room temperature for 16 h, After completion of

reaction, water (100 mL) was added. Extracted with ethyl acetate (3 x 100 mL), combined organic part was washed with saturated ferrous sulphate solution (100 mL), water (3 x 100 mL), brine (100 mL), dried and concentrated , crude was purified by Combi-Flash column (eluted at 10-20% ethylacetate in hexane) to get (1-phenyl-cyclopentyl)-acetonitrile **(280)** (7 g, 79.98%) as light yellow liquid.

GC-MS: 185 (m/z).

Synthesis of (281):

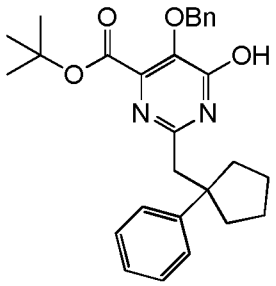


2-(1-Phenyl-cyclopentyl)-acetamidine hydrochloride

To a stirred suspension of NH_4Cl (2 g, 37.29 mmol) in dry toluene (50 mL) was added tri-methyl aluminium (2M in toluene) (18.6 mL, 37.29 mmol) at 5°C then warm to room temperature and stirred for 2 h. A solution of (1-phenyl-cyclopentyl)-acetonitrile **(280)** (2.3 g, 12.4 mmol) in toluene (10 mL) was added to reaction mass and stirred at 80°C for 14 h. After completion of the reaction, it was quenched with suspension of silica gel (8 g) in chloroform (8 mL) at 0 ^{0}Cand reaction mixture was stirred for 30 min at room temperature and filtered through a short bed of celite, washed with methanol and combined filtrate was concentrated. Residue was stirred with 10% MeOH in DCM (200 mL), white solid was discarded by filtration, filtrate was concentrated to get 2-(1-phenyl-cyclopentyl)-acetamidine hydrochloride salt **(281)** 2.5 g, 99.4% (crude yield) as yellow gummy oil.

LC-MS: 203.2 (M+H)

Synthesis of (282):

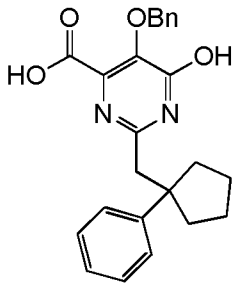


5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid tert-butyl ester

To a stirred solution of 2-(1-phenyl-cyclopentyl)-acetamidine hydrochloride salt **(281)** (500 mg, 2.09 mmol) and (E)-3-benzyloxy-2-hydroxy-4-oxo-pent-2-enoic acid tert-butyl ester **(4)** (970 mg, 3.15 mmol) in methanol (10 mL) was added sodium methoxide solution (25% in MeOH) (1.4 mL, 6.29 mmol) at 0°C then the reaction mixture allowed to warm slowly to room temperature, was stirred for 16h. After completion of the reaction, it was quenched with 1N HCl (5 mL), methanol was evaporated and water (20 mL) was added. The mixture was extracted with ethyl acetate (3 x 20 mL) and separated organic part was dried and concentrated to get crude, which was purified by Combi-Flash column (eluted at 10-20% ethylacetate in hexane) to get 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid tert-butyl ester **(282)** (230 mg, 23.82%) as white solid.

LC-MS: 461.1 (M+H).

Synthesis of (283):



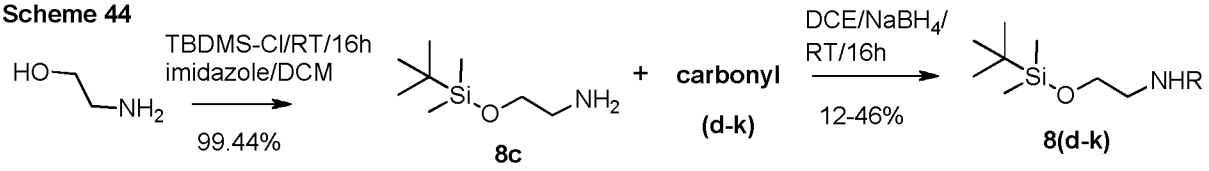
5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid

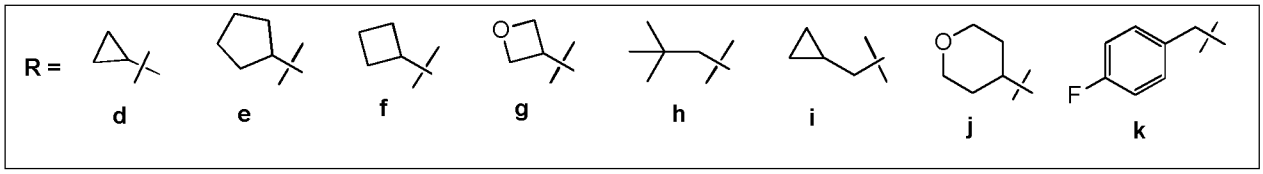
To a stirred solution 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid tert-butyl ester **(282)** (1.6 g. 3.48 mmol) in the mixture of THF:Water (2:1) (90 mL) was added lithium-hydroxide monohydrate (2.9 g, 69.57 mmol), refluxed for 18 h. After completion of reaction, volatile was vaporated, added water (30 mL), washed with ethyl acetate (2x 20 mL) to remove non acidic impurities. Separated aqueous part was acidified with 1(N) HCl to bring pH around 5 to 6. Acidified aqueous part was extracted with ethylacetatye (4 x 50 mL), dried and concentrated to get 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(283)** (780 mg, 55.44%) as white solid.

LC-MS: 405.2 (M+H).

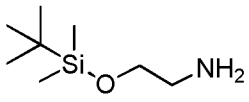
Synthesis of 8 (c-k):

Scheme 44





Synthesis of (8c):



2-(tert-Butyl-dimethyl-silanyloxy)-ethylamine

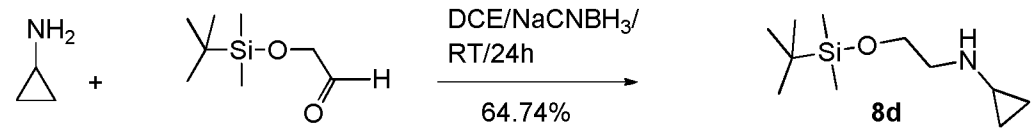
To a stirred solution of 2-amino-ethanol (55 g, 900.46 mmol) in DCM (1000 mL) were added DIPEA (220 mL, 1260.64 mmol) and tert-butyl-chloro-dimethyl-silane (135.7 g, 900.46 mmol) at 0 ^{0}C, stirred for 16 h at room temperature. After completion of reaction, water (500 mL) was added and extracted with DCM. Separated organic part was washed with water (2 x 100 mL), brine (100 mL), dried and concentrated to get 2-(tert-butyl-dimethyl-silanyloxy)-ethylamine **(8c)** (157 g, 99.44%) as light yellow oil.

Example 287

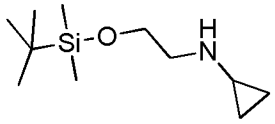
2-Cyclopropyl-9-hydroxy-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Schemes 43 and 45.

Scheme 45



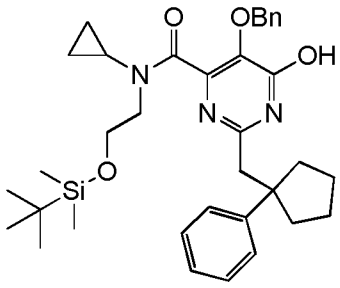
Synthesis of (8d):



[2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-cyclopropyl-amine

To a stirred solution of cyclopropylamine (500 mg, 8.76 mmol) in DCE (10 mL) were added tert-butyl-dimethyl-silanyloxy)-acetaldehyde (553 mg, 3.16 mmol), and acetic acid (0.02 mL, 0.29 mmol) at 0 °C, stirred 30 min at the same temperature, $NaCNBH_3$ (360 mg, 5.74 mmol) was added portion wise at 0 °C, stirred for 24 h at room temperature, quenched with water, extracted with DCM (3 x 30 mL), organic part was concentrated, dried and crude was purified by Combi-Flash column (eluted at 10-20% ethylacetate in hexane) to get [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropyl-amine **(8d)** (400 mg, 21.2%) as light yellow liquid.

Synthesis of (284):

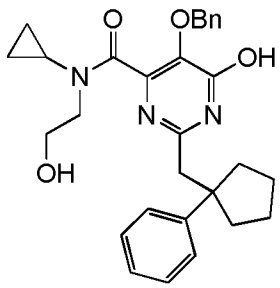


5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropyl-amide

To a stirred solution mixture of 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(283)** (300 mg, 0.74 mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropyl-amine **(8d)** (329 mg, 1.48 mmol) in DMF (5 mL) were added DIPEA (0.4 mL, 2.22 mmol) and HATU (423 mg, 1.11 mmol), stirred at room temperature for 1 h, water (50 mL) was added, extracted with ethylacetate (3 x 20 mL), combined organic part was washed with water (3 x 50 mL), brine (2x 30 mL), dried and concentrated. Crude was purified by Combi-Flash column (eluted at 20-30% ethylacetate in hexane) to get 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropyl-amide **(284)** (430 mg, 96.32%) as yellow solid.

LC-MS: 602.2 (M+H).

Synthesis of (285):

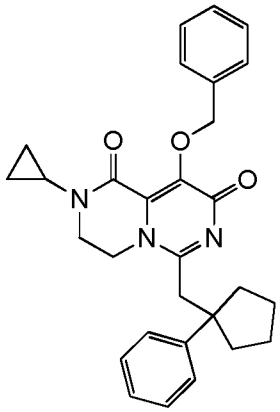


5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid cyclopropyl-(2-hydroxyethyl)-amide

To a stirred solution of 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropyl-amide **(284)** (430 mg, 0.69 mmol) in THF (20 mL) was added 1(N) HCl (3.5 mL. 3.48 mmol) at room temperature and was stirred for 30 min. After completion of the reaction, solid $NaHCO_3$ was added, basified upto pH~8, water (10 mL) was added, extracted with ethyl acetate (3 x 30 mL), organic part was dried and concentrated to get 5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid cyclopropyl-(2-hydroxyethyl)-amide **(285)** (300 mg, 88.4%) as light yellow sticky mass.

LC-MS: 488.0 (M+H).

Synthesis of (286):

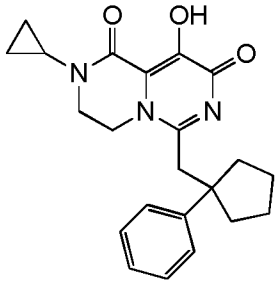


9-Benzyloxy-2-cyclopropyl-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a stirred solution of 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid cyclopropyl-(2-hydroxyethyl)-amide **(285)** (300 mg, 0.62 mmol) in DCM (30 mL) were added triphenyl phosphine (242 mg, 0.92 mmol) and DIAD (0.2 mL, 1.23 mmol) at room temperature, stirred for 10 min at room temperature. It was concentrated under reduced pressure to get crude, which was purified by Combi-Flash column (TPP-oxide was eluted in ethylacetate and product was eluted at 2% MeOH in DCM). It was again purified by prep-TLC plate to remove traces of TPP-oxide (mobile phase ethylacetate) 9-benzyloxy-2-cyclopropyl-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(286)** (180 mg, 62.3%) as white sticky solid.

LC-MS: 470.0 (M+H).

Synthesis of (287):



2-Cyclopropyl-9-hydroxy-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

Solution of 9-benzyloxy-2-cyclopropyl-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(286)** (180 mg, 0.38 mmol) in ethanol (20 mL) was degassed, added Pd-C (10%) (15 mg) and hydrogenated for 1 h. Catalyst was filtered of, washed with ethanol (3 x 20 mL) and DCM (2x 15 mL), Combined solvent was concentrated, solid was washed with n-pentane to get pure 2-cyclopropyl-9-hydroxy-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(287)** (140 mg, 96.25%) as white solid.

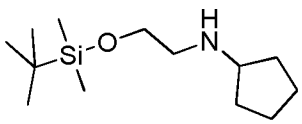
LC-MS: 380.0 (M+H).

Example 291

2-Cyclopentyl-9-hydroxy-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Schemes 43.

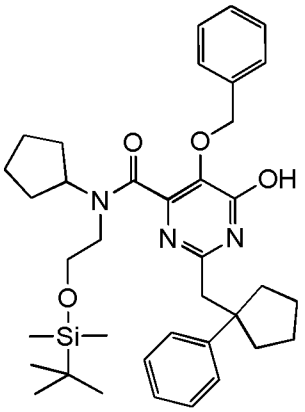
Synthesis of (8e):



[2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-cyclopentyl-amine

To a stirred solution of cyclopropylamine (1 g, 13.15 mmol) in DCE (20 mL) were added 2-(tert-butyl-dimethyl-silanyloxy)acetaldehyde (2.3 mg, 2.30 mmol), and acetic acid (0.08 mL, 0.29 mmol) at 0 °C, stirred 24 h at room temperature, $NaBH_4$ (995 mg, 26.29 mmol) was added portion wise at 0 °C, stirred for 2 h at room temperature, quenched with water, extracted with DCM (3 x 30 mL), organic part was dried and concentrated, crude was purified by Combi-Flash column (eluted at 10-20% ethylacetate in hexane) to get [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopentylamine **(8e)** (1.2 g, 37.48%) as yellow oil.

Synthesis of (288):

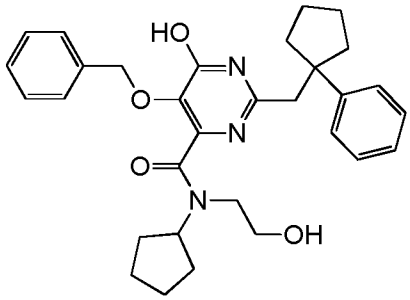


5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopentyl-amide

To a stirred solution mixture of 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(283)** (100 mg, 0.25 mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopentyl-amine **(8e)** (72 mg, 0.29 mmol) in DMF (2.5 mL) were added DIPEA (0.1 mL, 0.74 mmol) and HATU (141 mg, 0.37 mmol), stirred at room temperature for 20 h, water (25 mL) was added, extracted with ethylacetate (3 x 20 mL), combined organic part was washed with water (3 x 50 mL), brine (2x 30 mL), dried and concentrated. Crude was purified by Combi-Flash column (eluted at 20-30% ethylacetate in hexane) to get 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopentyl-amide **(288)** (97 mg, 62.28 %) as light yellow sticky solid.

LC-MS: 630.4 (M+H).

Synthesis of (289):

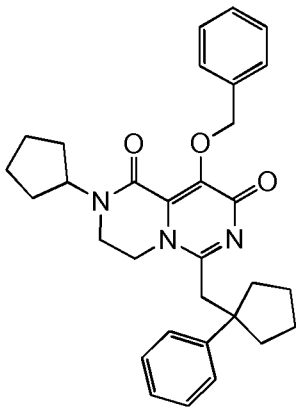


5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid cyclopentyl-(2-hydroxyethyl)-amide

This compound was prepared following the same method as 5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid cyclopropyl-(2-hydroxyethyl)-amide **(285)** from 5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopentyl-amide **(288)** (250 mg, 0.39 mmol).Off-white sticky solid (180 mg, 87.83%).

LC-MS: 516.4 (M+H).

Synthesis of (290):

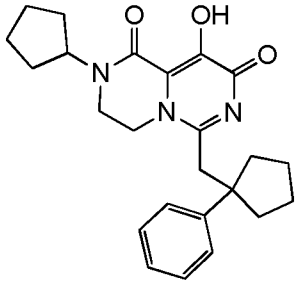


9-Benzyloxy-2-cyclopentyl-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

This compound was prepared following the same method as 9-benzyloxy-2-cyclopropyl-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(286)** from 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid cyclopentyl-(2-hydroxyethyl)-amide **(289)** (175 mg, 0.34 mmol).Off-white sticky solid (80 mg, 47.31%).

LC-MS: 498.4 (M+H).

Synthesis of (291):



2-Cyclopentyl-9-hydroxy-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

This compound was prepared following the same method as 2-cyclopropyl-9-hydroxy-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(287)** from 9-benzyloxy-2-cyclopentyl-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(290)** (80 mg, 0.16 mmol).White solid (16 mg, 24.42%).

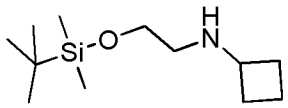
LC-MS: 408.2 (M+H).

Example 295

2-Cyclobutyl-9-hydroxy-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Schemes 43.

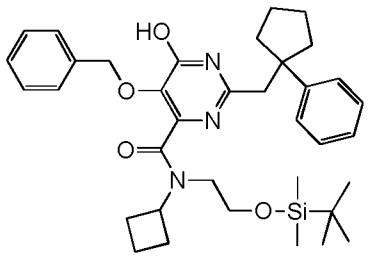
Synthesis of (8f):



[2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-cyclobutyl-amine

This compound was prepared following the same method as [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopentyl-amine **(8e)** from cyclobutylamine (1 g, 14.27 mmol) and 2-(tert-butyl-dimethyl-silanyloxy)acetaldehyd (2.6 mg, 14.26 mmol) as yellow gummy mass (400mg, 12.22%).

Synthesis of (292):

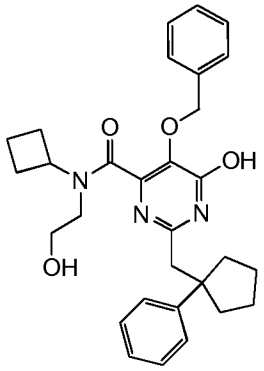


5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclobutyl-amide

To a stirred solution mixture of 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(283)** (300 mg, 0.74 mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclobutyl-amine **(8e)** (204 mg, 0.89 mmol) in DMF (5 mL) were added DIPEA (0.4 mL, 2.22 mmol) and HATU (423 mg, 1.11 mmol), stirred at room temperature for 1 h, water (50 mL) was added, extracted with ethylacetate (3 x 20 mL), combined organic part was washed with water (3 x 50 mL), brine (2x 30 mL), dried and concentrated. Crude was purified by Combi-Flash column (eluted at 20-30% ethylacetate in hexane) to get 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclobutyl-amide **(292)** (420 mg, 91.94%) as yellow sticky solid.

LC-MS: 616.4 (M+H).

Synthesis of (293):

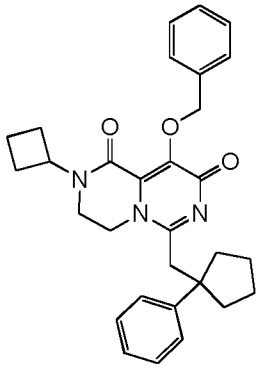


5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid cyclobutyl-(2-hydroxyethyl)-amide

This compound was prepared following the same method as 5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid cyclopropyl-(2-hydroxyethyl)-amide **(285)** from 5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid cyclobutyl-(2-hydroxyethyl)-amide **(292)** (420 mg, 0.68 mmol).White sticky solid (340 mg, 99.39%).

LC-MS: 502.2 (M+H).

Synthesis of (294):

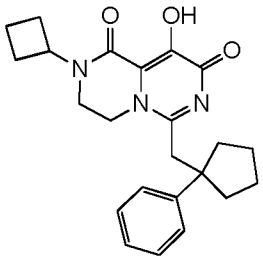


9-Benzyloxy-2-cyclobutyl-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

This compound was prepared following the same method as 9-benzyloxy-2-cyclopropyl-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(286)** from 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid cyclobutyl-(2-hydroxyethyl)-amide **(293)** (100 mg, 0.19 mmol). White solid (35 mg, 36.3%).

LC-MS: 484.2 (M+H).

Synthesis of (295):



2-Cyclobutyl-9-hydroxy-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

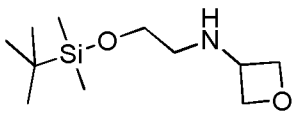
This compound was prepared following the same method as 2-cyclopropyl-9-hydroxy-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(287)** from 9-benzyloxy-2-cyclobutyl-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(294)** (140 mg, 0.29 mmol).White solid (48 mg, 42.14%). LC-MS: 394.2 (M+H).

Example 299

9-Hydroxy-2-oxetan-3-yl-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Schemes 43.

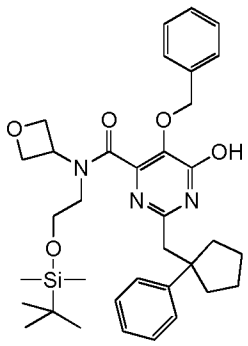
Synthesis of (8g):



[2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-oxetan-3-yl-amine

To a stirred solution of oxetan-3-one (1 g, 13.87 mmol) in MeOH (40 mL) were added 2-(tert-butyl-dimethyl-silanyloxy)-ethylamine (2.7 mg, 15.27 mmol), stirred for 30 min at room temperature, Cooled the reaction mixture, $Na(CN)BH_3$ was added portion wise, stirred at room temperature for 2 h, quenched with water, extracted with DCM (3 x 30 mL), organic part was concentrated, dried and purified by Combi-Flash column (eluted at 20-50% ethylacetate in hexane) to get [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-oxetan-3-yl-amine **(8g)** (1.5 g, 46.71%) as light yellow oil.

Synthesis of (296):

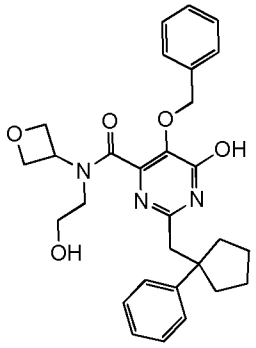


5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-oxetan-3-yl-amide

To a stirred solution mixture of 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(283)** (158 mg, 0.39 mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-oxetan-3-yl-amine **(8g)** (104 mg, 0.47 mmol) in DMF (3 mL) were added DIPEA (0.2 mL, 1.17 mmol) and HATU (222 mg, 0.59 mmol), stirred at room temperature for 1 h, water (50 mL) was added, extracted with ethylacetate (3 x 20 mL), combined organic part was washed with water (3 x 50 mL), brine (2x 30 mL), dried and concentrated. Crude was purified by Combi-Flash column (eluted at 20-30% ethylacetate in hexane) to get 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-oxetan-3-yl-amide **(296)** (240 mg, 99.43%) as yellow gummy mass.

LC-MS: 618.2 (M+H).

Synthesis of (297):

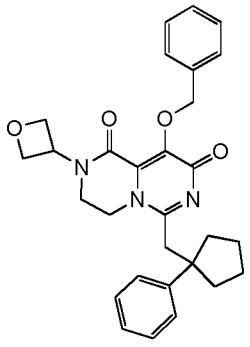


5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-oxetan-3-yl-amide

To a stirred solution of 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-oxetan-3-yl-amide **(296)** (240 mg, 0.39 mmol) in THF (20 mL) was added 1(M) TBAF in THF (1.2 mL, 1.16 mmol) at room temperature and was stirred for 60 min at room temperature. After completion of the reaction, it was concentrated, purified by Combi-Flash column (eluted at 5% MeOH in DCM) to get 5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-oxetan-3-yl-amide **(297)** as an off-white sticky solid (150 mg, 76.68%).

LC-MS: 504.2 (M+H).

Synthesis of (298):

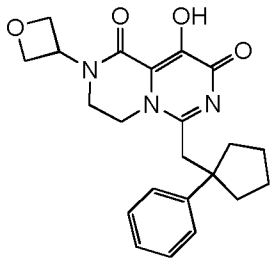


9-Benzyloxy-2-oxetan-3-yl-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

This compound was prepared following the same method as 9-benzyloxy-2-cyclopropyl-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(286)** from 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-oxetan-3-yl-amide **(297)** (150 mg, 0.28 mmol).Off-white solid (110 mg, 80.65%).

LC-MS: 486.2 (M+H).

Synthesis of (299):



9-Hydroxy-2-oxetan-3-yl-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

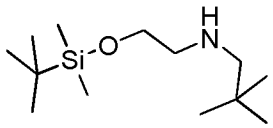
This compound was prepared following the same method as 2-cyclopropyl-9-hydroxy-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(287)** from 9-benzyloxy-2-oxetan-3-yl-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(298)** (100 mg, 0.21 mmol).White solid (8 mg, 9.82%). LC-MS: 396.2 (M+H).

Example 303

2-(2,2-Dimethyl-propyl)-9-hydroxy-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Schemes 43.

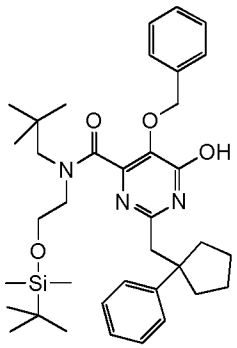
Synthesis of (8h):



[2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-(2,2-dimethyl-propyl)-amine

This compound was prepared following the same method as [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopentyl-amine **(8e)** from 2,2-dimethyl-propionaldehyde (1 g, 11.61 mmol) and 2-(tert-butyl-dimethyl-silanyloxy)-ethylamine **(8c)** (2.0 g, 11.6 mmol) as colorless oil (1.1 g, 38.6%).

Synthesis of (300):



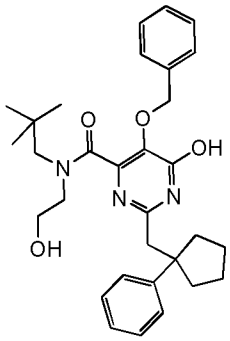
5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-(2,2-dimethyl-propyl)-amide

To a stirred solution mixture of 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(283)** (230 mg, 0.57 mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-(2,2-dimethyl-propyl)-amine **(8h)** (167 mg, 0.68 mmol) in DMF (2.2 mL) were added DIPEA (0.3 mL, 1.70 mmol) and HATU (324 mg, 0.85 mmol), stirred at room temperature for 20 h, water (75 mL) was added, extracted with ethylacetate (3 x 20 mL), combined organic part was washed with water (3 x 50 mL), brine (2x 30 mL), dried and concentrated. Crude was purified by Combi-Flash column (eluted at 20-30% ethylacetate in hexane) to get 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-

silanyloxy)-ethyl]-(2,2-dimethyl-propyl)-amide **(300)** (310 mg, 86.27%) as an off-white sticky solid.

LC-MS: 632.6 (M+H).

Synthesis of (301):

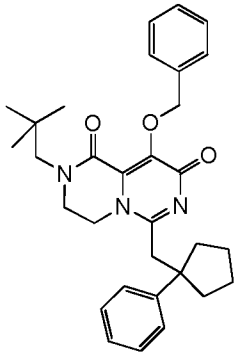


5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2,2-dimethyl-propyl)-(2-hydroxyethyl)-amide

This compound was prepared following the same method as 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid cyclopropyl-(2-hydroxyethyl)-amide **(285)** from 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-(2,2-dimethyl-propyl)-amide **(300)** (350 mg, 0.55 mmol).Light yellow sticky solid (270 mg, 94.03%).

LC-MS: 518.2 (M+H).

Synthesis of (302):

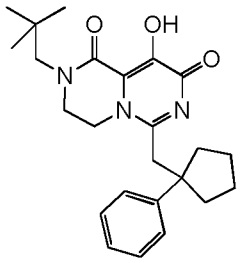


9-Benzyloxy-2-(2,2-dimethyl-propyl)-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

This compound was prepared following the same method as 9-benzyloxy-2-cyclopropyl-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(286)** from 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2,2-dimethyl-propyl)-(2-hydroxyethyl)-amide **(301)** (140 mg, 0.27 mmol).Off-white sticky solid (120 mg, 88.8%).

LC-MS: 500.4 (M+H).

Synthesis of (303):



2-(2,2-Dimethyl-propyl)-9-hydroxy-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

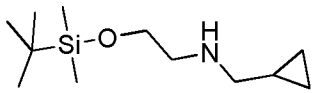
This compound was prepared following the same method as 2-cyclopropyl-9-hydroxy-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(287)** from 9-benzyloxy-2-(2,2-dimethyl-propyl)-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(302)** (120 mg, 0.24 mmol).White solid (30 mg, 30.5%). LC-MS: 410.2 (M+H).

Example 307

2-Cyclopropylmethyl-9-hydroxy-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Schemes 43.

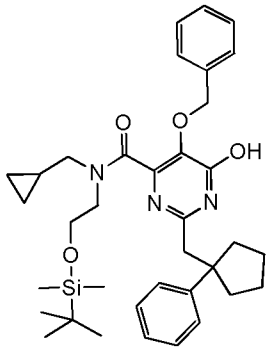
Synthesis of (8i):



[2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-cyclopropylmethyl-amine

This compound was prepared following the same method as [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopentyl-amine **(8e)** from cyclopropanecarbaldehyde (300 mg, 4.23 mmol) and 2-(tert-butyl-dimethyl-silanyloxy)-ethylamine **(8c)** (975 mg, 5.56 mmol). Colourless liquid (280 mg, 28.51%).

Synthesis of (304):

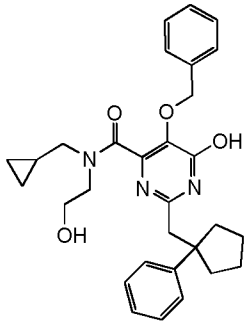


5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropylmethyl-amide

To a stirred solution mixture of 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(283)** (250 mg, 0.62 mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropylmethyl-amine **(8i)** (170 mg, 0.74 mmol) in DMF (3 mL) were added DIPEA (0.3 mL, 1.85 mmol) and HATU (352 mg, 0.93 mmol), stirred at room temperature for 20 h, water (75 mL) was added, extracted with ethylacetate (3 x 20 mL), combined organic part was washed with water (3 x 50 mL), brine (2x 30 mL), dried and concentrated. Crude was purified by Combi-Flash column (eluted at 20-30% ethylacetate in hexane) to get 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropylmethyl-amide **(304)** (380 mg, 99.82 %) as light yellow sticky solid.

LC-MS: 616.2 (M+H).

Synthesis of (305):

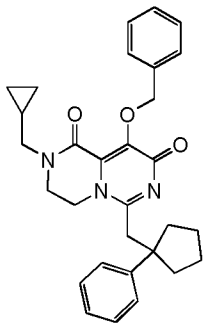


5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid cyclopropylmethyl-(2-hydroxyethyl)-amide

This compound was prepared following the same method as 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid cyclopropyl-(2-hydroxyethyl)-amide **(285)** from 5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropylmethyl-amide **(304)** (380 mg, 0.62 mmol).Light yellow sticky solid (300 mg, 96.93%).

LC-MS: 502.2 (M+H).

Synthesis of (306):

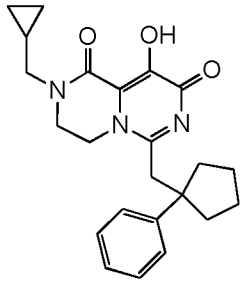


9-Benzyloxy-2-cyclopropylmethyl-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

This compound was prepared following the same method as 9-benzyloxy-2-cyclopropyl-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(286)** from 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid cyclopropylmethyl-(2-hydroxyethyl)-amide **(305)** (150 mg, 0.29 mmol).Colourless sticky solid (65 mg, 44.95%).

LC-MS: 484.4 (M+H).

Synthesis of (307):



2-Cyclopropylmethyl-9-hydroxy-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

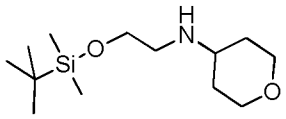
This compound was prepared following the same method as 2-cyclopropyl-9-hydroxy-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(287)** from 9-benzyloxy-2-cyclopropylmethyl-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(306)** (130 mg, 0.32 mmol).White solid (20 mg, 16%). LC-MS: 394.2 (M+H).

Example 311

9-Hydroxy-6-(1-phenyl-cyclopentylmethyl)-2-(tetrahydro-pyran-4-yl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Schemes 43.

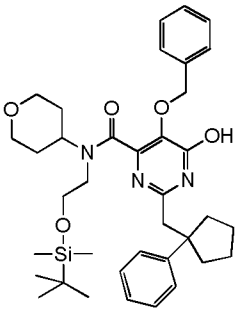
Synthesis of (8j):



[2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-(tetrahydro-pyran-4-yl)-amine

To a stirred cooled solution of tetrahydro-pyran-4-one (2 g, 19.98 mmol) in MeOH (30 mL) were added 2-(tert-butyl-dimethyl-silanyloxy)-ethylamine **(8c)** (2.5 mg, 13.98 mmol) stirred for 1 h at room temperature, cooled the reaction mixture, $Na(CN)BH_3$ (2.5 g, 39.96 mmol) was added portion wise, stirred at room temperature for 20 h, quenched with water, MeOH was removed, extracted with DCM (3 x 30 mL), organic part was concentrated, dried and purified by Combi-Flash column (eluted at 20-50% ethylacetate in hexane) to get [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-(tetrahydro-pyran-4-yl)-amine **(8j)** (2.5 g, 48.23 mmol) as light yellow oil.

Synthesis of (308):



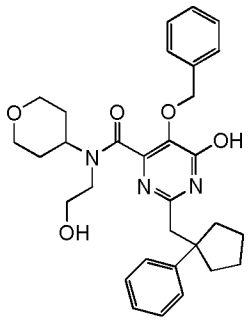
5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-(tetrahydro-pyran-4-yl)-amide

To a stirred solution mixture of 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(283)** (400 mg, 0.99 mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-(tetrahydro-pyran-4-yl)-amine **(8j)** (513 mg, 1.98 mmol) in DMF (6 mL) were added DIPEA (0.5 mL, 2.97 mmol) and HATU (564 mg, 1.48 mmol), stirred at room temperature for 1 h, water (75 mL) was added, extracted with ethylacetate (3 x 20 mL), combined organic part was washed with water (3 x 50 mL), brine (2x 30 mL), dried and concentrated. Crude was

purified by Combi-Flash column (eluted at 20-30% ethylacetate in hexane) to get 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-(tetrahydro-pyran-4-yl)-amide **(308)** (540mg, 84.53 %) as colorless sticky solid.

LC-MS: 646.2 (M+H).

Synthesis of (309):

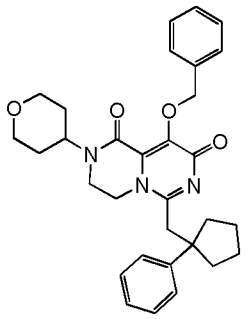


5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-(tetrahydro-pyran-4-yl)-amide

This compound was prepared following the same method as 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid cyclopropyl-(2-hydroxyethyl)-amide **(285)** from 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-(tetrahydro-pyran-4-yl)-amide **(308)** (540 mg, 0.83 mmol).White solid (400 mg, 89.99%).

LC-MS: 532.2 (M+H).

Synthesis of (310):

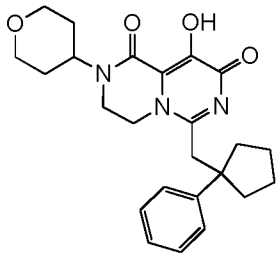


9-Benzyloxy-6-(1-phenyl-cyclopentylmethyl)-2-(tetrahydro-pyran-4-yl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

This compound was prepared following the same method as 9-benzyloxy-2-cyclopropyl-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(286)** from 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-(tetrahydro-pyran-4-yl)-amide **(309)** (440 mg, 0.90 mmol).White solid (260 mg, 56.1%).

LC-MS: 514.0 (M+H).

Synthesis of (311):



9-Hydroxy-6-(1-phenyl-cyclopentylmethyl)-2-(tetrahydro-pyran-4-yl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

This compound was prepared following the same method as 2-cyclopropyl-9-hydroxy-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(287)** from 9-benzyloxy-6-(1-phenyl-cyclopentylmethyl)-2-(tetrahydro-pyran-4-yl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(310)** (240 mg, 0.47 mmol).White solid (180mg, 90.96%).

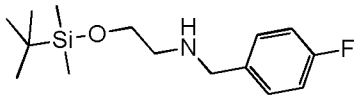
LC-MS: 424.0 (M+H).

Example 315

2-(4-Fluoro-benzyl)-9-hydroxy-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Schemes 43.

Synthesis of (8k):

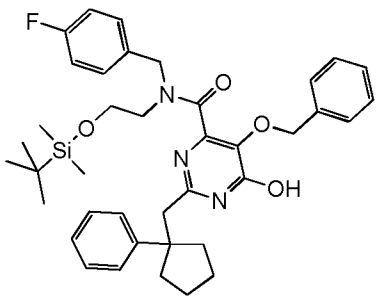


[2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-(4-fluoro-benzyl)-amine

This compound was prepared following the same method as [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopentyl-amine **(8e)** from 4-fluorobenzaldehyde (1 g, 8.06 mmol) and 2-(tert-butyl-dimethyl-silanyloxy)-ethylamine **(8c)** (1.8 g, 10.48 mmol). Light yellow liquid (800 mg, 35.03%).

LC-MS: 283.8

Synthesis of (312):

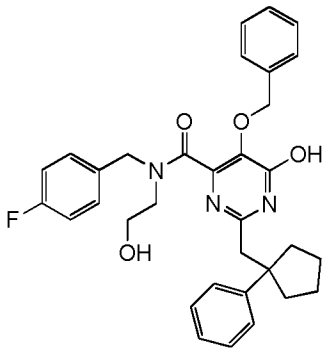


5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-(4-fluoro-benzyl)-amide

To a stirred solution mixture of 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(283)** (250 mg, 0.62 mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-(4-fluoro-benzyl)-amine **(8k)** (210 mg, 0.74 mmol) in DMF (5 mL) was added T_3P (50 wt % in ethyl acetate) (1.3 g, 1.85 mmol) at 0 ^{0}C, stirred at room temperature for 20 h, water (20 mL) was added, extracted with ethylacetate (3 x 20 mL), combined organic part was washed with water (3 x 50 mL), brine (2x 30 mL), dried and concentrated. Crude was purified by Combi-Flash column (eluted at 20-30% ethylacetate in hexane) to 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-(4-fluoro-benzyl)-amide **(312)** (96 mg, 23.18 %) as colourless sticky solid.

LC-MS: 668.0 (M-H).

Synthesis of (313):

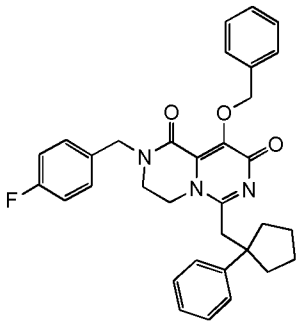


5-Benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (4-fluoro-benzyl)-(2-hydroxyethyl)-amide

This compound was prepared following the same method as 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid cyclopropyl-(2-hydroxyethyl)-amide **(285)** from 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-(4-fluoro-benzyl)-amide **(312)** (146 mg, 0.22 mmol).Colourless sticky solid (116 mg, 95.66%).

LC-MS: 556.4 (M+H).

Synthesis of (314):

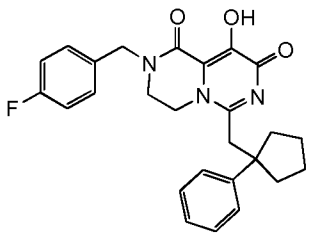


9-Benzyloxy-2-(4-fluoro-benzyl)-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

This compound was prepared following the same method as 9-benzyloxy-2-cyclopropyl-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(286)** from 5-benzyloxy-6-hydroxy-2-(1-phenyl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (4-fluoro-benzyl)-(2-hydroxyethyl)-amide **(313)** (91 mg, 0.16 mmol). Colorless sticky solid (46 mg, 52.2%).

LC-MS: 538.2 (M+H).

Synthesis of (315):



2-(4-Fluoro-benzyl)-9-hydroxy-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

This compound was prepared following the same method as 2-cyclopropyl-9-hydroxy-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(287)** from 9-benzyloxy-2-(4-fluoro-benzyl)-6-(1-phenyl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-

c]pyrimidine-1,8-dione **(314)** (45 mg, 0.08 mmol). It was purified by prep-TLC plate (mobile phase 5% MeOH in DCM) to get **15h** as white solid (8 mg, 21.33%).

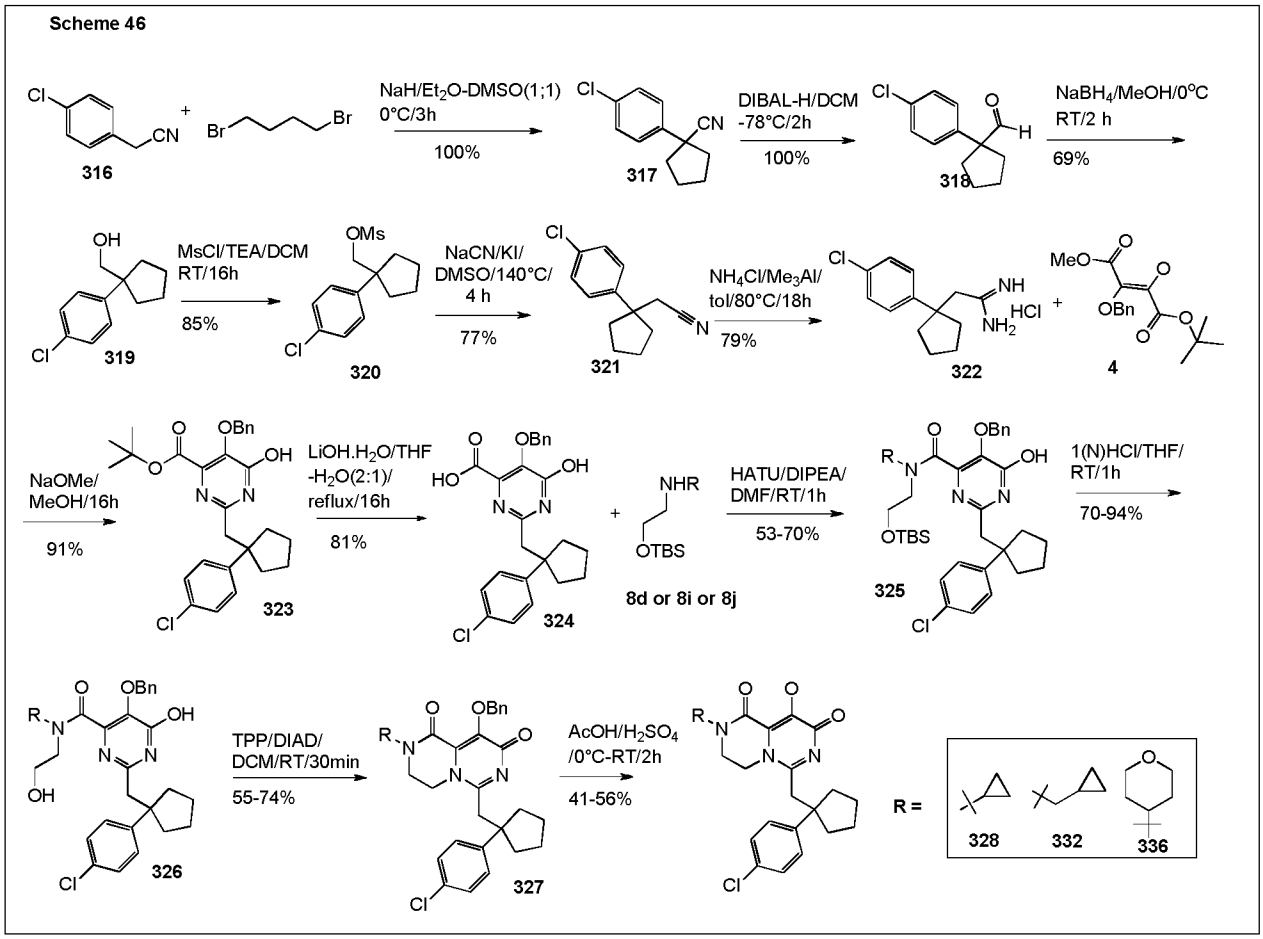
LC-MS: 448.2 (M+H).

General procedure for examples 317 to 315

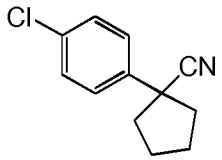
The synthetic procedures are outlined in Scheme 46.

General synthetic route for 317, 291, 295, 299, 303, 307, 311 and 315

Scheme 46



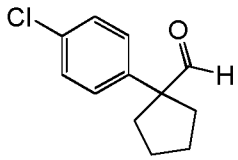
Synthesis of (317):



1-(4-Chloro-phenyl)-cyclopentanecarbonitrile

To a suspension of sodium hydride (60% suspension in mineral oil) (14.5g, 362.96 mmol) in DMSO (250 mL) was added dropwise a mixture of (4-chlorophenyl)acetonitrile **(316)** (25 g, 164.98 mmol) and 1,4-dibromobutane (35.6 g, 164.98 mmol) dissolved in DMSO: ether (1:1; 300mL) at 0°C stirred for 30min at same temperature, then stirred it at room temperature for 3h. After completion of the reaction, it was quenched with HCl (1N; 25 mL), water (200 mL), extracted with ethyl acetate (3x100mL), separated organic part was washed with water (3x100mL) and brine (100 mL), dried and concentrated to get crude which was purified by silica CombiFlash column (3-5% ethyl acetate in hexane used as eluent) to afford 1-(4-chloro-phenyl)-cyclopentanecarbonitrile **(317)** (33.9 g, 100%) as light yellow oil.

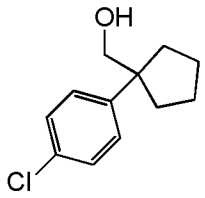
Synthesis of (318):



1-(4-Chloro-phenyl)-cyclopentanecarbaldehyde

To a stirred solution of 1-(4-chloro-phenyl)-cyclopentanecarbonitrile **(317)** (20 g, 97.24 mmol) in DCM (270 mL), was added DIBAL-H (25% in toluene) (138 mL, 243.09 mmol) at -78°C and stirred for 2h at the same temperature. After completion of the reaction, it was quenched with saturated solution of potassium sodium tartrate (75mL) and stirred for 16h at room temperature, DCM part was separated, aqueous part was re-extracted with DCM (1x100 mL), combined organic parts was dried, and concentrated. Obtained crude was purified by silica CombiFlash column (5% ethyl acetate in hexane was used as eluent) to get 1-(4-chloro-phenyl)-cyclopentanecarbaldehyde **(318)** (20.2 g, 100%) as light yellow oil.

Synthesis of (319):

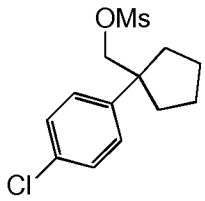


[1-(4-Chloro-phenyl)-cyclopentyl]-methanol

To a stirred solution of 1-(4-chloro-phenyl)-cyclopentanecarbaldehyde **(318)** (19g, 91.06 mmol) in methanol (250mL) was added $NaBH_4$ (6.9 g, 182.13 mmol) portion wise at 0°C, stirred at room temperature for 2 h. After completion of the reaction, it was quenched with saturated aqueous solution of ammonium chloride (20mL), MeOH was removed, residue was diluted with water (100mL). The mixture was extracted with ethyl acetate (3 x 100mL); combined organic parts was dried and concentrated. Crude was purified by silica CombiFlash column (5% ethylacetate in hexane was used as eluent) to get [1-(4-chloro-phenyl)-cyclopentyl]-methanol **(319)** (13.3 g, 69%) as colourless oil.

GC-MS: 210 (M+).

Synthesis of (320):

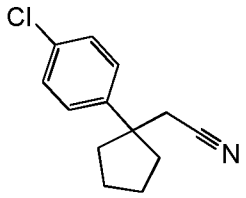


Methanesulfonic acid 1-(4-chloro-phenyl)-cyclopentylmethyl ester

To a stirred solution of 1-(4-chloro-phenyl)-cyclopentyl]-methanol **(319)** (12 g, 56.95 mmol) in DCM (110 mL) was added triethyl amine (16 mL, 113.90 mmol) followed by mesyl chloride (5.3 mL, 68.34 mmol) at 0°C, it was stirred at room temperature for 4 h, diluted with DCM (50 mL), washed with water (100 mL), saturated aqueous sodium bicarbonate solution (50 mL) and finally brine (50 mL). The organic part was dried, concentrated and purified by

CombiFlash column (eluted at 10-20% ethylacetate in hexane) to get methanesulfonic acid 1-(4-chloro-phenyl)-cyclopentylmethyl ester **(320)** (14 g, 85%) as light yellow crystalline solid.

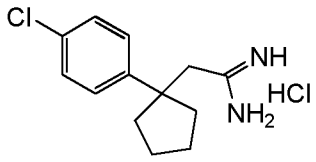
Synthesis of (321):



[1-(4-Chloro-phenyl)-cyclopentyl]-acetonitrile

To a stirred solution of methanesulfonic acid 1-(4-chloro-phenyl)-cyclopentylmethyl ester **(320)** (14 g, 48.48 mmol) in DMSO (50 mL) were added KI (805 mg, 4.85 mmol) and NaCN (3.6 g, 72.72 mmol) and stirred for 130°C for 4 h. After completion of reaction, cold water (200 mL) was added. extracted with ethyl acetate (3 x 100 mL), combined organic parts was washed with saturated ferrous sulphate solution (2 x 100 mL), water (2 x 100 mL), brine (100 mL), dried and concentrated , crude was purified by CombiFlash column (10-20% ethylacetate in hexane was used as eluent) to get [1-(4-chloro-phenyl)-cyclopentyl]-acetonitrile **(321)** (8.2 g, 77%) as light yellow liquid.

Synthesis of (322):

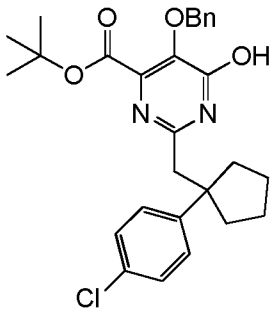


2-[1-(4-Chloro-phenyl)-cyclopentyl]-acetamidine, hydrochloride

To a stirred suspension of NH_4Cl (5.9 g, 111.97 mmol) in toluene (200 mL) was added tri-methylaluminium (2M in toluene) (56mL, 111.96mmol) at 5°C, warmed at room temperature and stirred for 2h. A solution of [1-(4-chloro-phenyl)-cyclopentyl]-acetonitrile **(321)** (8.2 g, 37.32 mmol) in toluene (20 mL) was added to the reaction mixture at room temperature and heated at 80°C for 14h. After completion of the reaction, it was quenched with suspension of silica gel (32g) in chloroform (32mL) at 0°C, quenched mixture was stirred for 30 min at room

temperature and filtered through a pad of celite. Residue was washed with methanol (5x50mL) and the combined filtrate was concentrated. The residue was stirred in 10% MeOH in DCM (150 mL), resulted white suspended solid was discarded by filtration and filtrate was concentrated to get 2-(1-phenyl-cyclopentyl)-acetamidine, hydrochloride **(322)** (7 g, 79%, crude) as yellow gummy oil.

Synthesis of (323):

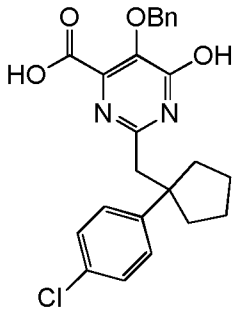


5-Benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester

To a stirred solution of 2-[1-(4-chloro-phenyl)-cyclopentyl]-acetamidine; hydrochloride **(322)** (3.1g, 11.34mmol) in methanol (25mL) was added (E, Z)-2-benzyloxy-3-hydroxy-but-2-enedioic acid 4-tert-butyl ester 1-methyl ester **(4)** (4.19g, 13.61mmol) and cooled to 0°C. To this reaction mixture was then added NaOMe (25% in methanol) (7.4mL, 34.03mmol) and stirred at room temperature for 16h (TLC; ethyl acetate: hexane = 1:1, Rf = 0.5). The reaction mixture was diluted with ethyl acetate (300mL), washed with water (60mL), brine (60mL), dried and concentrated in vacuo to get crude mass which was purified by CombiFlash eluted with gradient polarity mobile phase (hexane to 50% EtOAc in hexane) to get pure 5-benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester **(323)** (5.1g, 91%) as light brown solid.

LC-MS: 495.2(M+H)

Synthesis of (324):



5-Benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid

To a solution of 5-benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester **(323)** (4.82g, 9.74mmol) in THF (90mL) and water (45mL) was added $LiOH.H_2O$ (4.086g, 97.37mmol) and heated to reflux for 20h (reaction was monitored by LCMS). THF was removed in vacuo and reaction was diluted with water (100mL), extracted with ethyl acetate (2x50mL). Aqueous layer was acidified with 1(N) HCl to pH~3. White solid was separated by filtration and dried in vacuo to get pure 5-benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid **(324)** (3.47g, 81%).

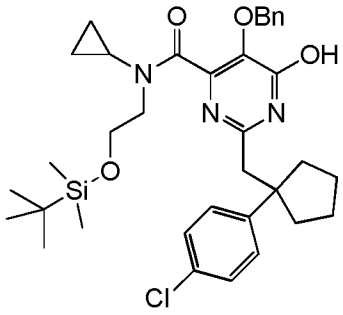
LC-MS: 439.0(M+H)

Example 328

6-[1-(4-Chloro-phenyl)-cyclopentylmethyl]-2-cyclopropyl-9-hydroxy-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Schemes 46.

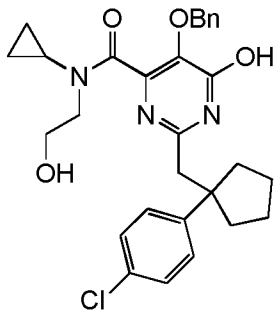
Synthesis of (325):



5-Benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropyl-amide

5-Benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid **(324)** (150.0mg, 0.34mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropyl-amine **(8d)** (110.4mg, 0.51mmol) were taken in DMF (3ml), HATU (123.3mg, 0.41mmol) and DIPEA (132.5mg, 1.03mmol) were added at room temperature and stirred for 16h Silica thin layer chromatography was performed (40% EtOAc in hexane; Rf = 0.4). To the reaction water (10ml) was added and stirred for 5 min and the aqueous mixture was extracted with EtOAc (2x15ml). Combined extracts was washed with water (3X10ml), dried and concentrated under reduced pressure. Obtained crude was purified by normal silica gel column chromatography (100-200 mesh) using 30% EtOAc in haxane as mobile phase to get pure 5-benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropyl-amide **(325)** (120mg, 55%) as yellow sticky solid.

Synthesis of (326):

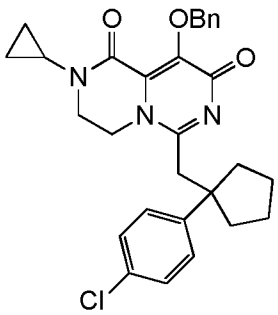


5-Benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid cyclopropyl -(2-hydroxyethyl)-amide

To a stirred solution of 5-benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropyl-amide **(325)** (100mg, 0.16mmol) in THF was added 1(N) HCl (5ml) at room temperature and was stirred for 30 min Silica thin layer chromatography was performed (60% EtOAc in hexane; Rf = 0.4). After completion of the reaction, solid $NaHCO_3$ was added to the reaction mixture, basified up to pH~8, extracted with ethylacetate (3 x 30 mL), combined extracts were dried and concentrated to get 5-benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid cyclopropyl -(2-hydroxyethyl)-amide **(326)** as brown sticky mass, it was used in the next step without purification.

LC-MS: 522.0(M+H).

Synthesis of (327):

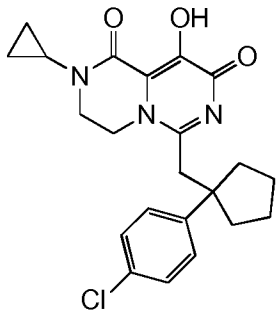


9-Benzyloxy-6-[1-(4-chloro-phenyl)-cyclopentylmethyl]-2-cyclopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

5-Benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid cyclopropyl -(2-hydroxyethyl)-amide **(326)** (90mg, 0.17mmol) and triphenylphosphine (90.5mg, 0.35mmol) were taken in DCM (3ml) at room temperature, DIAD (52.34mg, 0.26mmol) was added slowly and stirred for 1h. To the reaction mixture, DCM (15ml) was added and washed with water (10ml) and brine (10ml). Organic part was dried and concentrated under reduced pressure. Obtained residue was purified by normal silica column using 30% EtOAc in hexane to get 9-benzyloxy-6-[1-(4-chloro-phenyl)-cyclopentylmethyl]-2-cyclopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(327)** (130mg, 56%; 2 steps) as yellow sticky solid.

LC-MS: 504.0(M+H)

Synthesis of (328):



6-[1-(4-Chloro-phenyl)-cyclopentylmethyl]-2-cyclopropyl-9-hydroxy-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

9-benzyloxy-6-[1-(4-chloro-phenyl)-cyclopentylmethyl]-2-cyclopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(327)** (30 mg, 0.06 mmol) was taken in AcOH (1 mL), to the reaction H_2SO_4 (0.2 mL) was added slowly at 0°C and stirred it at room temperature for 1h. Reaction was quenched with aqueous saturated $NaHCO_3$ and extracted with EtOAc (2x15ml), combined extracts was dried and concentrated under reduced pressure. Obtained crude was purified by prep HPLC to get 6-[1-(4-chloro-phenyl)-cyclopentylmethyl]-2-cyclopropyl-9-hydroxy-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(328)** as an off-white solid (14mg, 57%).

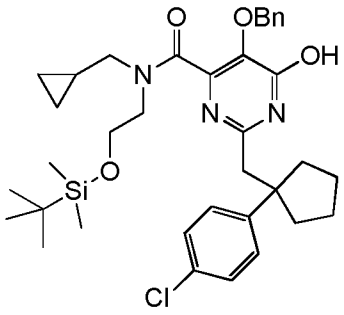
LC-MS: 414.0(M+H)

Example 332

6-[1-(4-Chloro-phenyl)-cyclopentylmethyl]-2-cyclopropylmethyl-9-hydroxy-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Schemes 46.

Synthesis of (329):

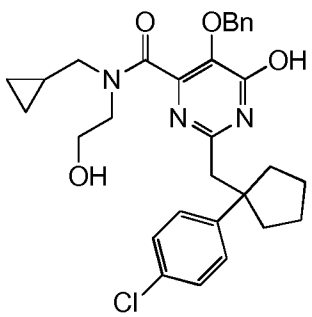


5-Benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropylmethyl-amide

To a stirred solution of 5-benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid **(324)** (350mg, 0.79mmol) in DMF (7.5mL) were added [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropylmethyl-amine **(8i)** (274mg, 1.19mmol) DIPEA (0.4mL), 2.39mmol) and HATU (364mg, 0.96mmol) and stirred at room temperature for 1h Silica thin layer chromatography was performed (ethyl acetate: hexane=1:1/UV/SiO_2, Rf =0.5). Reaction mass was diluted with ethyl acetate (60mL), washed with brine (3 x 30mL), dried and concentrated in vacuo to get crude mass of 5-benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropylmethyl-amide **(329)** (600mg) which was used directly in the next step without further purification.

LC-MS: 650.4(M+H)

Synthesis of (330):

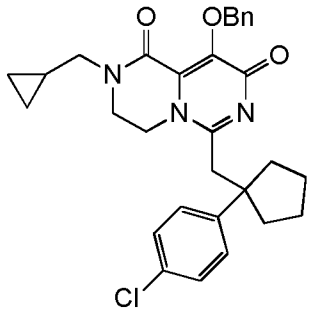


5-Benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid cyclopropylmethyl-(2-hydroxyethyl)-amide

To a stirred solution of 5-benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropylmethyl-amide **(329)** (580mg, crude) in THF (30mL) was added 1(N) aq.HCl (6mL) at room temperature and stirred for 1h (TLC; 100%ethyl acetate/UV/SiO_2, Rf =0.2). THF was removed in vacuo and the crude mass was dissolved in ethyl acetate (50mL) and washed with $NaHCO_3$ solution (10mL), water (20mL) and brine (20mL); dried and concentrated in vacuo to get crude mass which was purified by CombiFlash using gradient eluent mixture of ethyl acetate and hexane to get pure 5-benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid cyclopropylmethyl-(2-hydroxyethyl)-amide **(330)** (390mg, 94% two steps) as an off-white sticky solid.

LC-MS: 536.0(M+H)

Synthesis of (331):

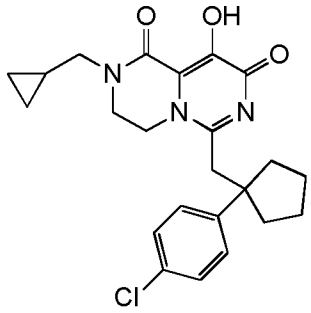


9-Benzyloxy-6-[1-(4-chloro-phenyl)-cyclopentylmethyl]-2-cyclopropylmethyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a solution of 5-benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid cyclopropylmethyl-(2-hydroxyethyl)-amide **(330)** (390mg, 0.73mmol) in DCM (30mL) was added PPh_3 (286mg, 1.09mmol) and DIAD (0.22mL, 1.09mmol) at room temperature and stirred for 30 minutes (TLC; 5%methanol in ethyl acetate/UV/SiO_2, Rf =0.05). DCM was removed in vacuo and the crude mass was purified by silica gel (normal, 100-200 mesh) column chromatography using gradient eluent of 1% to 5% methanol in DCM to get pure 9-benzyloxy-6-[1-(4-chloro-phenyl)-cyclopentylmethyl]-2-cyclopropylmethyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(331)** (280mg, 74%) as white sticky solid.

LC-MS: 518.0(M+H)

Synthesis of (332):



6-[1-(4-Chloro-phenyl)-cyclopentylmethyl]-2-cyclopropylmethyl-9-hydroxy-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a solution of 9-benzyloxy-6-[1-(4-chloro-phenyl)-cyclopentylmethyl]-2-cyclopropylmethyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(331)** (200mg, 0.38mmol) in acetic acid (6.0mL) was added H_2SO_4 (0.05mL) at 0°C and was stirred at room temperature for 2h (TLC; 5%methanol in DCM/UV/SiO_2, Rf =0.3). H_2SO_4 was quenched with $NaHCO_3$ solution, diluted with water and extracted with ethyl acetate (2 x 50mL). The organic part was washed with water (40mL) and brine (40mL); dried and concentrated in vacuo to get brownish gummy mass which was dissolved in DCM (1mL). 5mL of hexane was added to the solution and the solid appeared was allowed to settle down. Liquid phase was removed by decantation and the solid was triturated with diethyl ether and n-pentane to get pure 6-[1-(4-chloro-phenyl)-cyclopentylmethyl]-2-cyclopropylmethyl-9-hydroxy-3,4-dihydro-2H-pyrazino [1,2-c] pyrimidine-1,8-dione **(332)** (86mg, 52%) as light brown solid.

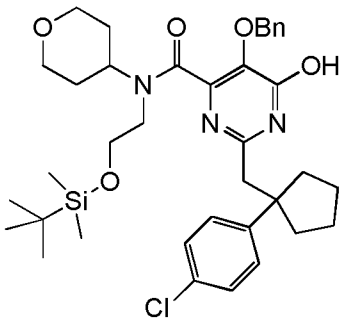
LC-MS: 427.8(M+H)

Example 336

6-[1-(4-Chloro-phenyl)-cyclopentylmethyl]-9-hydroxy-2-(tetrahydro-pyran-4-yl)-3,4-dihydro-2H-pyrazino [1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Schemes 46.

Synthesis of (333):

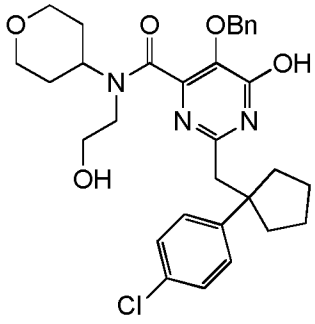


5-Benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-(tetrahydro-pyran-4-yl)-amide

5-Benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid **(324)** (150mg, 0.34mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-(tetrahydro-pyran-4-yl)-amine **(8j)** were taken in DMF (3ml), HATU (195.2mg, 0.51mmol) and DIPEA (110.4mg, 0.86mmol) were added at room temperature and stirred for 16h (monitored by LC/MS). To the reaction water was added (10ml) and stirred for 5 min. aqueous mixture was extracted with EtOAc (2x15ml). Combined extracts was washed with water (3X10ml), dried and concentrated under reduced pressure. Obtained crude was purified by normal silica gel column chromatography (100-200 mesh) using 30% EtOAc in hexane as mobile phase to get pure 5-benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-(tetrahydro-pyran-4-yl)-amide **(333)** (130mg, 56%) as yellow sticky solid.

LC-MS: 680.2(M+H).

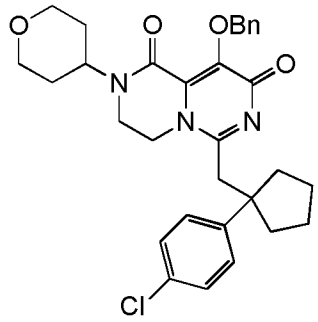
Synthesis of (334):



5-Benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-(tetrahydro-pyran-4-yl)-amide

To a stirred solution of 5-benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-(tetrahydro-pyran-4-yl)-amide **(333)** in THF (3ml) was added 1(N) HCl (1ml) at room temperature and stirred for 30 min at room temperature Silica thin layer chromatography was performed (ethyl acetate : hexane=3:2, Rf = 0.4). After completion of the reaction, solid $NaHCO_3$ was added; basified up to pH~8, extracted with ethylacetate (3 x 30 mL), combined extracts was dried and concentrated to get 5-benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-(tetrahydro-pyran-4-yl)-amide **(334)** proceeded to the next step without purification.

Synthesis of (335):

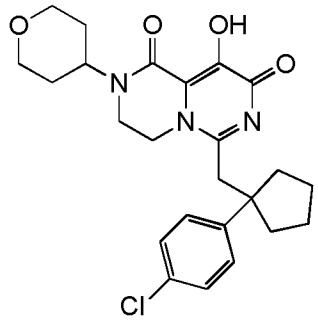


9-Benzyloxy-6-[1-(4-chloro-phenyl)-cyclopentylmethyl]-2-(tetrahydro-pyran-4-yl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

5-Benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-(tetrahydro-pyran-4-yl)-amide **(334)** (90mg, 0.16mmol) and triphenylphosphine were taken in DCM (3ml) at room temperature, DIAD was added slowly and stirred for 1h Silica thin layer chromatography was performed (ethyl acetate: hexane = 1:1, Rf = 0.6). To the reaction mixture DCM (15ml) was added and it was washed with water (10ml) and brine (10ml). Organic part was dried and concentrated under reduced pressure. Obtained residue was purified by normal silica gel (100-20 mesh) column chromatography suing 30% EtOAc in hexane to get 9-benzyloxy-6-[1-(4-chloro-phenyl)- cyclopentylmethyl]-2-(tetrahydro-pyran-4-yl)- 3,4-dihydro-2H- pyrazino[1,2-c] pyrimidine-1,8-dione **(335)** (50mg, 60%; 2 steps yield).

LC-MS: 548.0 (M+H)

Preparation of (336):



6-[1-(4-Chloro-phenyl)-cyclopentylmethyl]-9-hydroxy-2-(tetrahydro-pyran-4-yl)-3,4-dihydro-2H-pyrazino [1,2-c]pyrimidine-1,8-dione **(16252)**

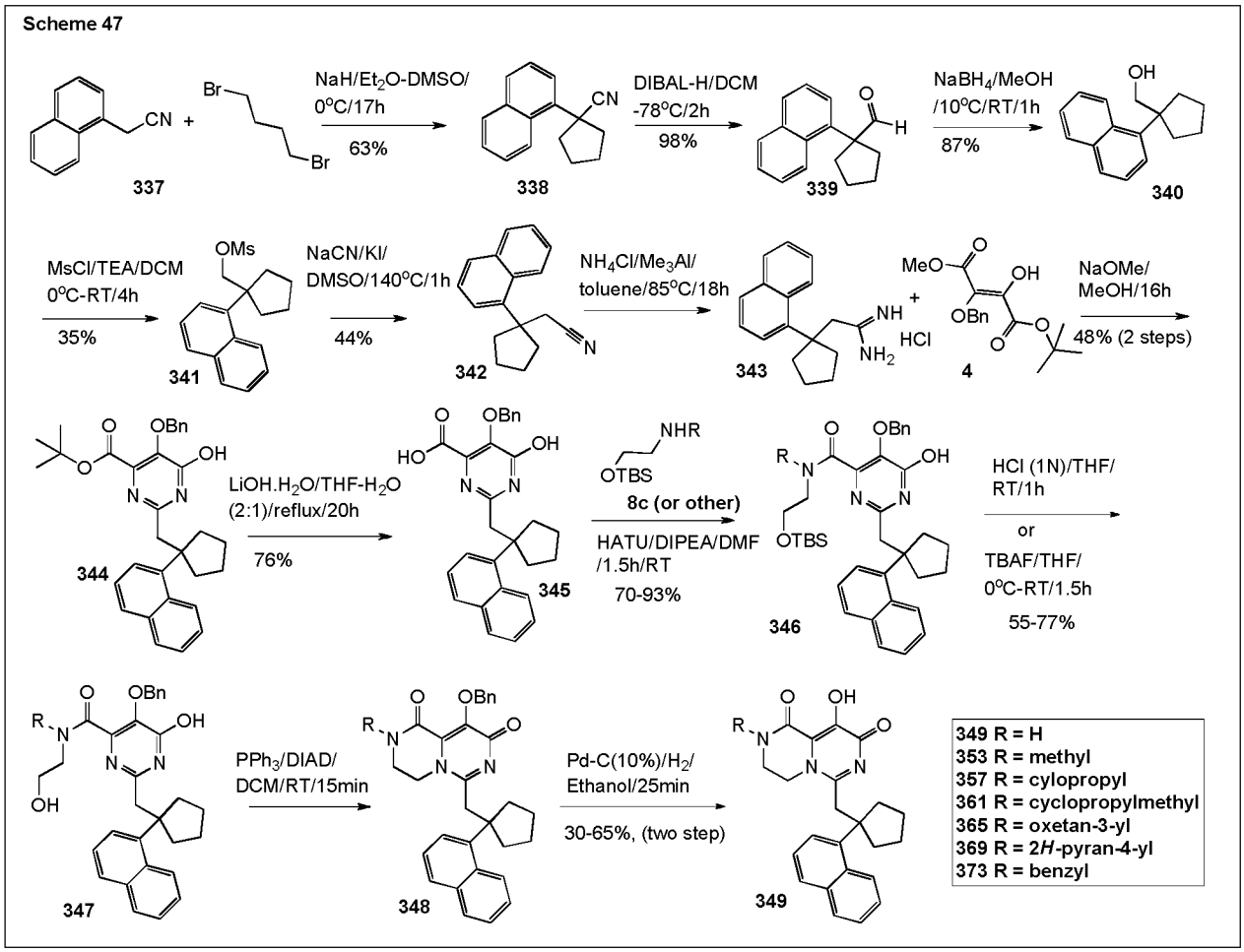
To a stirred solution of 9-benzyloxy-6-[1-(4-chloro-phenyl)-cyclopentylmethyl]-2-(tetrahydro-pyran-4-yl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(335)** in acetic acid (1mL), Conc. H_2SO_4 (0.001mL, 0.02mmol) was added and stirred for 4h, at room temperature (monitored by LCMS). After completion of the reaction, volatiles was removed from the reaction mixture, it was quenched with ice cold water (5mL), saturated aqueous $NaHCO_3$ (adjusted pH to 8) was added. Quenched mixture was extracted with ethyl acetate (2X15mL). Combined extracts was dried, concentrated; resulted residue was washed with 10% DCM in ether, to get 6-[1-(4-chloro-phenyl)-cyclopentylmethyl]-9-hydroxy-2-(tetrahydro-pyran-4-yl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(336)** (19mg, 41%), as an off-white solid.

LCMS: 457.8 (M+H).

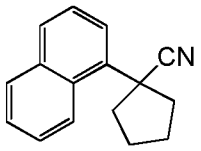
General procedure for examples 337 to 373

The synthetic procedures are outlined in Scheme 47.

General synthetic route for 349, 353, 357, 361, 365, 369, 373



Synthesis of (338):

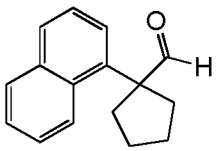


1-Naphthalen-1-yl-cyclopentanecarbonitrile

To a suspension of sodium hydride (60% in mineral oil, 5.24g, 131.6mmol) in DMSO (50mL) was added dropwise a mixture of naphthalen-1-yl-acetonitrile **(337)** (10.0g, 59.8mmol) and 1,4-dibromo-butane (12.91g, 59.8mmol) dissolved in DMSO-ether (1:1; 120mL) at 0°C and stirred for 30 min at the same temperature and then stirred at room temperature for 4h (silica TLC, 10% ethyl acetate in hexane, Rf = 0.65). The reaction mass was quenched with HCl

[1(N); 20mL] at 0°C. Ethyl acetate (400mL) was added and washed with water (500mL), brine (2 x 200ml), dried and concentrated in vacuo to get crude mass which was purified by CombiFlash using gradient eulent; mixture of ethyl acetate and hexane to get pure 1-naphthalen-1-yl-cyclopentanecarbonitrile **(338)** (8.4g, 63%) as white solid.

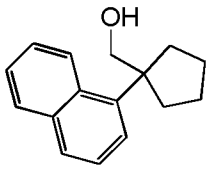
Synthesis of (339):



1-Naphthalen-1-yl-cyclopentanecarbaldehyde

To a solution of 1-naphthalen-1-yl-cyclopentanecarbonitrile **(338)** (10.5g, 47.4mmol) in DCM (150mL) was added dropwise DIBAL-H(25% in toluene, 67.5mL, 118.6mmol) at -78°C and stirred for 2 h at the same temperature (silica TLC, 5% ethyl acetate in hexane; Rf = 0.6). The reaction mass was quenched with saturated aqueous solution of potassium sodium tarterate (35mL) and stirred for 17h at room temperature. Reaction mixture was filtered, residue was washed with DCM; organic phase was separated, aqueous part was back extracted with DCM (100mL). Combined organic part was dried, filtered and concentrated in vacuo to get crude mass which was purified by CombiFlash using gradient eluent mixture of ethyl acetate and hexane to get pure 1-naphthalen-1-yl-cyclopentanecarbaldehyde **(339)** (10.4g, 98%) as colorless sticky liquid.

Synthesis of (340):

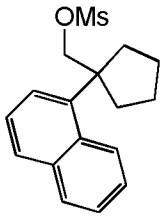


(1-Naphthalen-1-yl-cyclopentyl)-methanol

A solution of 1-naphthalen-1-yl-cyclopentanecarbaldehyde **(339)** (10.g, 44.6mmol) in methanol (150mL) was cooled to 0°C and $NaBH_4$ (3.373g, 89.2mmol) was added in portions (8 portions). After the addition was completed the reaction mixture was allowed to stirred at room

temperature for 1h (silica TLC, 10% ethyl acetate in hexane; Rf = 0.3). The reaction mass was quenched with aqueous NH_4Cl solution and concentrated in vacuo as much as possible; diluted with water (100mL) and extracted with ethyl acetate (2 x 100mL). Organic part was washed with brine (50mL), dried and concentrated in vacuo to get crude mass which was purified by CombiFlash using gradient eluent mixture of ethyl acetate and hexane to get pure (1-naphthalen-1-yl-cyclopentyl)-methanol **(340)** (8.75g, 87%) as white solid.

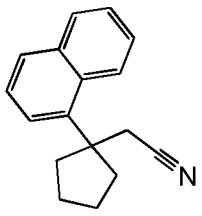
Synthesis of (341):



Methanesulfonic acid 1-naphthalen-1-yl-cyclopentylmethyl ester

To a solution of (1-naphthalen-1-yl-cyclopentyl)-methanol **(340)** (9.0g, 39.8mmol) in DCM (180mL) was added TEA (11.0mL, 79.5mL) and cooled to 0°C. To this reaction mixture was added mesylchloride and stir at room temperature for 18h (silica TLC, 10% ethyl acetate in hexane; Rf = 0.2). Reaction mass was diluted with DCM (100mL), washed with water (2 x 100mL), brine (100mL), dried and concentrated in vacuum to get crude mass which was purified by Combi-Flash using gradient eluent; mixture of ethyl acetate and hexane to get pure methanesulfonic acid 1-naphthalen-1-yl-cyclopentylmethyl ester **(341)** (4.25g, 35%) as white solid.

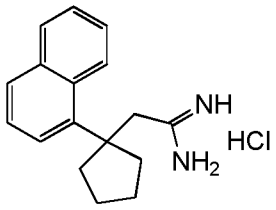
Synthesis of (342):



(1-Naphthalen-1-yl-cyclopentyl)-acetonitrile

To a stirred solution of methanesulfonic acid 1-naphthalen-1-yl-cyclopentylmethyl ester **(341)** (2.1g, 6.90mmol) in DMSO (10.0mL) were added KI (115mg, 0.69mmol) and NaCN (507mg, 10.35mmol) and stirred at 140°C for 2h (silica TLC, 10% ethyl acetate in hexane; Rf = 0.5). Reaction mass was cooled to room temperature, quenched with $FeSO_4$ solution (15mL) and diluted with water (100 mL). The solid was separated through filtration and washed well with ethyl acetate. The biphasic layer was separated in a separating funnel. The organic part was washed with brine (2 x 50mL), dried and concentrated in vacuo to get crude mass which was purified by Combi-Flash using a mixture of ethyl acetate and hexane as gradient eluent to get pure (1-naphthalen-1-yl-cyclopentyl)-acetonitrile **(342)** (710mg, 44%) as yellow gummy liquid.

Synthesis of (343):

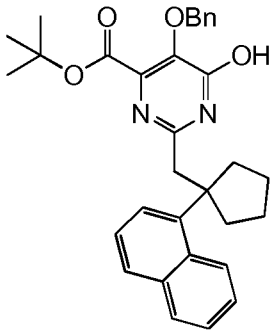


2-(1-Naphthalen-1-yl-cyclopentyl)-acetamidine; hydrochloride

To a stirred suspension of NH_4Cl (2.659g, 49.72mmol) in dry toluene (80mL) was added tri-methyl aluminum (2M in toluene, 25.0mL, 49.72mmol) slowly at 5°C then warm to room temperature and stirred for 2h. A solution of (1-naphthalen-1-yl-cyclopentyl)-acetonitrile **(342)** (3.9g, 16.57mmol) in toluene (5mL) was added to above reaction mass and stirred for 18h at 85°C (reaction was monitored by LC-MS). The reaction mixture was cooled to 0°C and quenched with suspension of silica gel in chloroform and then stirred for 0.5h at room temperature. Filtered through sintered funnel, residue was washed well with methanol and combined filtrate was concentrated under reduced pressure to get the crude mass; 10% methanol in DCM was added to the residue again filtered off the insoluble material and filtrate was concentrated in vacuum to get semi pure 2-(1-naphthalen-1-yl-cyclopentyl)-acetamidine; hydrochloride **(343)** (4.5g) as brown sticky mass. Proceeded to the next step; with out purification.

LC-MS: 252.6 (M+H)

Synthesis of (344):

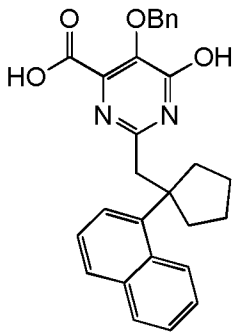


5-Benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid tert-butyl ester

To a stirred solution of 2-(1-naphthalen-1-yl-cyclopentyl)-acetamidine; hydrochloride **(343)** (4.5g, crude) in methanol (30mL) were added (E,Z)-2-benzyloxy-3-hydroxy-but-2-enedioic acid 4-tert-butyl ester 1-methyl ester **(4)** (5.759g, 18.7mmol) and cooled to 0°C in a ice bath. To this reaction mixture was then added NaOMe (25% in methanol, 10.1mL, 46.74mmol) and stirred at room temperature for 18h (silica TLC, 50% ethyl acetate in hexane; Rf = 0.5). The reaction mixture was diluted with ethyl acetate (100mL), washed with water (50mL), brine (50mL), dried and concentrated under vacuum to get crude mass which was purified by CombiFlash eluted with gradient mixture of ethyl acetate and hexane to get pure 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid tert-butyl ester **(344)** (4.1g, 48%, 2 steps) as brown sticky mass.

LC-MS: 511.0 (M+H)

Synthesis of (345):



5-Benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid

To a solution of 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid tert-butyl ester **(344)** (3.9g, 7.64mmol) in THF (60mL) and water (12mL) was added $LiOH.H_2O$ (3.2g, 76.4 mmol) and heated to reflux for 20h (reaction was monitored by LCMS), THF was removed from the reaction mixture under vacuum and the residue was diluted with water (50mL). Aqueous layer was washed with ethyl acetate (2 x 50mL) and then acidified with 1(N) HCl to pH~3. White solid was separated by filtration and dried in vacuum to get pure 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(345)** (2.65g, 76%) as white solid.

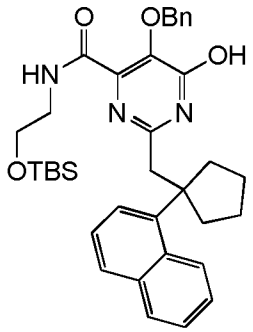
LC-MS: 455.0 (M+H)

Example 349

9-Hydroxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Schemes 47.

Synthesis of (346):



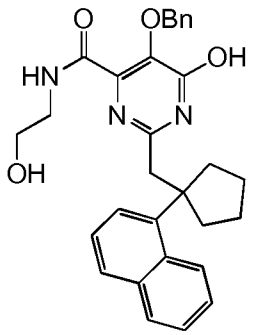
5-Benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-amide

To a stirred solution of '5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(345)** (250mg, 0.55mmol) in DMF (7.5mL) were added DIPEA (0.27mL, 1.65mmol), 2-(tert-butyl-dimethyl-silanyloxy)-ethylamine **(8c)** (145mg, 0.83mmol)

and HATU (251mg, 0.66mmol) and stirred at room temperature for 1.5h (silica TLC, 50% ethyl acetate in hexane, Rf = 0.5). Reaction mass was diluted with ethyl acetate (60ml), washed with brine (3 x 30mL), dried and concentrated in vacuo to get crude mass which was purified by CombiFlash using gradient eluent mixture of ethyl acetate and hexane to get pure 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-amide **(346)** (315mg, 94%) as white solid.

LC-MS: 612.2 (M+H)

Synthesis of (347):

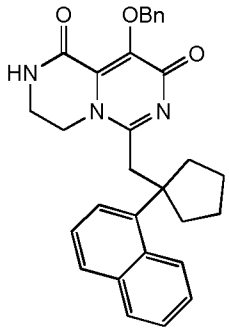


5-Benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-amide

To a stirred solution of 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-amide **(346)** (290mg, 0.48mmol) in THF (15.0mL) was added 1(N) HCl (3.0mL) at room temperature and stirred for 1h at the same temperature (silica TLC, 5% methanol in DCM/SiO_2/UV, Rf=0.5). THF was removed in vacuum and the solid obtained was filtered through sintered funnel, washed with water, ether and dried in vacuum to get pure 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-amide **(347)** (140mg, 59%) as white solid.

LC-MS: 498.4 (M+H)

Synthesis of (348):

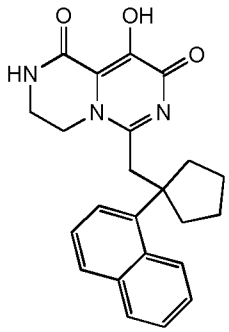


9-Benzyloxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a solution mixture of 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-amide **(347)** (140mg, 0.28mmol) and DIAD (0.28mL, 1.41mmol) in DCM (70mL) was added PPh_3 (443mg, 1.69mmol) at room temperature and stirred for 15min at the same temperature. Yellow color disappeared (silica TLC, ethyl acetate 100%; Rf = 0.2). DCM was removed in vacuum to get 9-benzyloxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(348)** (650mg, crude) which was used directly in the next step with out purification.

LC-MS: 480.0 (M+H)

Synthesis of (349):



9-Hydroxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

A solution of 9-benzyloxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(348)** (650mg, crude) in ethanol (50mL) was degassed by nitrogen and followed by the addition of Pd-C (10%) (100mg) and again degassed by nitrogen. The reaction mixture was then stirred under hydrogen atmosphere of balloon pressure for 25min at room temperature (reaction was monitored by LCMS). The reaction mass was the filtered through celite bed and the filtrate was concentrated in vacuo to obtain crude sticky mass. The crude mass was dissolved in DCM (5mL), and hexane (20mL) was added dropwise with constant stirring to get a solid precipitated. The solid was separated by decantation and washed well with diethyl ether and then with n-pentane and dried in vacuum to get pure 9-hydroxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(349)** (48mg, 44%, two step yield) as an off-white solid.

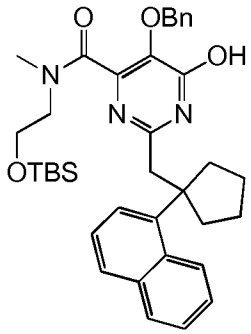
LC-MS: 390.3 (M+H)

Example 353

9-Hydroxy-2-methyl-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Schemes 47.

Synthesis of (350):



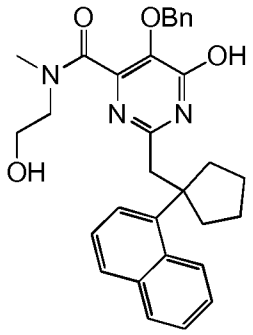
5-Benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide

To a stirred solution of 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(345)** (300mg, 0.66mmol) in DMF (7.5mL) were added DIPEA

(0.33mL, 1.98mmol), [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amine **(8a)** (187mg, 0.99mmol) and HATU (301mg, 0.79mmol) and stirred at room temperature for 1.5h (silica TLC, 50% ethyl acetate in hexane/SiO_2/UV, Rf=0.6). Reaction mass was diluted with ethyl acetate (100ml), washed with brine (3 x 50mL), dried and concentrated in vacuo to get crude mass which was purified by Combi-Flash using ethyl acetate and hexane mixture as eluting solvent to get pure 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(350)** (310mg, 75%) as light yellow sticky solid.

LC-MS: 625.8 (M+H)

Synthesis of (351):

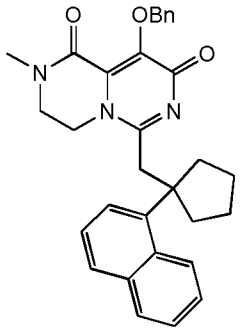


5-Benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide

To a stirred solution of 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(350)** (280mg, 0.45mmol) in THF (30.0mL) was added 1(N) HCl (6.0mL) at room temperature and stirred for 1h at the same temperature (silica TLC, 5% methanol in DCM, Rf = 0.5). THF was removed under vacuum; residue was diluted with water and extracted with ethyl acetate (2 x 25mL). Organic layer was washed with $NaHCO_3$ solution (10mL), water (20mL) and brine (20mL); dried and concentrated in vacuum to get crude mass which was purified by CombiFlash using gradient eluent of ethyl acetate and hexane mixture to get pure 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide **(351)** (145mg, 63%) as white solid.

LC-MS: 512.0 (M+H)

Synthesis of (352):

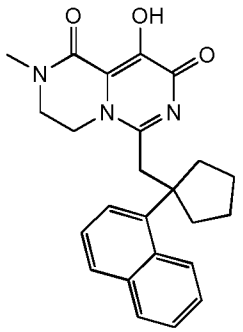


9-Benzyloxy-2-methyl-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a solution of 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide **(351)** (85mg, 0.17mmol) in DCM (20mL) was added PPh_3 (174mg, 0.67mmol) and cooled to 0°C followed by the addition of DIAD (0.2mL, 0.1mmol) and stirred for 15 min at the same temperature (silica TLC, 5% methanol in ethyl acetate; Rf = 0.3). DCM was removed in vacuum and the crude mass was purified by silica gel (normal, 100-200 mesh) column chromatography using gradient eluent mixture of 50% ethyl acetate in hexane to 100% ethyl acetate to get 9-benzyloxy-2-methyl-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(352)** (85mg, semi pure) as white sticky solid.

LC-MS: 494.0 (M+H)

Synthesis of (353): (16251)



9-Hydroxy-2-methyl-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

This compound was prepared by following the same method as pure 9-hydroxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(349)** from 9-benzyloxy-2-methyl-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(352)** (85mg, 0.17mmol). Yield was 35mg, 50% (white solid)

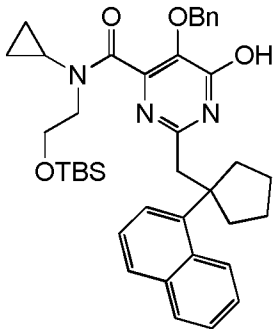
LC-MS: 404.2 (M+H)

Example 357

2-Cyclopropyl-9-hydroxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Schemes 47.

Synthesis of (354):

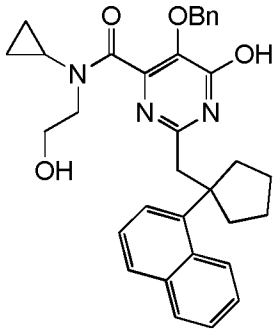


5-Benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropyl-amide

This compound was prepared following the same method as 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(350)** from 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(345)** (250mg, 0.55mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropyl-amine **(8d)** (177mg, 0.83mmol). Yield was 279mg, 78% (white sticky mass).

LC-MS: 652.2 (M+H)

Synthesis of (355):

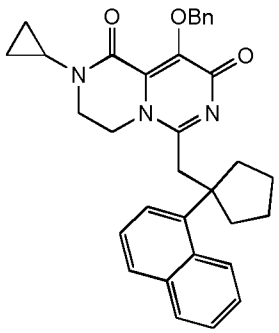


5-Benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid cyclopropyl-(2-hydroxyethyl)-amide

This compound was prepared following the same method as 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide **(351)** from 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropyl-amide **(354)** (270mg, 0.41mmol). Yield was 150mg, 67% (white solid)

LC-MS: 538.0 (M+H)

Synthesis of (356):



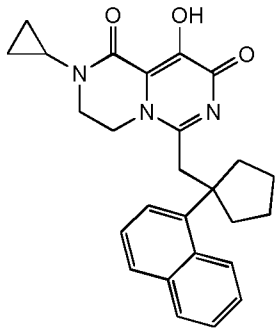
9-Benzyloxy-2-cyclopropyl-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a solution of 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid cyclopropyl-(2-hydroxyethyl)-amide **(355)** (120mg, 0.22mmol) and DIAD (0.22mL, 1.12mmol) in DCM (30mL) was added PPh_3 (351mg, 1.34mmol) at room temperature and stirred for 15min at the same temperature. Yellow color disappeared (silica

TLC 5% methanol in ethyl acetate, Rf = 0.2). DCM was removed in vacuo and the crude mass was purified by silica gel (normal, 100-200 mesh) column chromatography using gradient eluent mixture of 1% to 5% methanol in DCM to get pure 9-benzyloxy-2-cyclopropyl-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(356)** (106mg, 92%) as white solid.

LC-MS: 519.9 (M+H)

Synthesis of (357): (16271)



2-Cyclopropyl-9-hydroxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

This compound was prepared by following the same method as pure 9-hydroxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(349)** from 9-benzyloxy-2-cyclopropyl-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(356)** (100mg, 0.18mmol). Yield was 40mg, 52% (white solid)

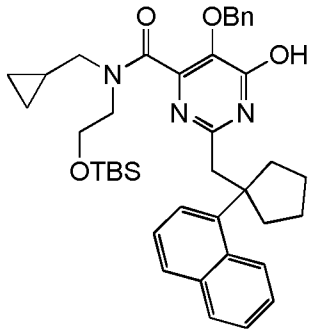
LC-MS: 429.8 (M+H)

Example 361

2-Cyclopropylmethyl-9-hydroxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Schemes 47.

Synthesis of (358):

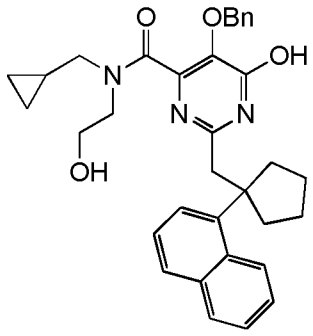


5-Benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropylmethyl-amide

This compound was prepared by following the same method as 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(350)** from '5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(345)** (225mg, 0.50mmol) and [2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-cyclopropylmethyl-amine **(8i)** (170mg, 0.74mmol). Yield was 307mg, 93% (white solid).

LC-MS: 666.0 (M+H)

Synthesis of (359):



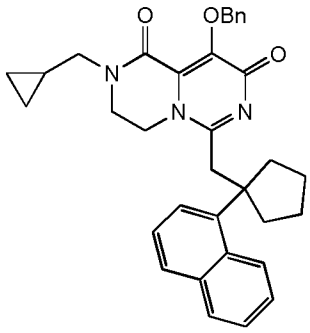
5-Benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid cyclopropyl methyl-(2-hydroxyethyl)-amide

This compound was prepared following the same method as 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-

amide **(351)** from 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropylmethyl-amide **(358)** (350mg, 0.53mmol). Yield was 225mg, 78% (white solid)

LC-MS: 552.2 (M+H)

Synthesis of (360):

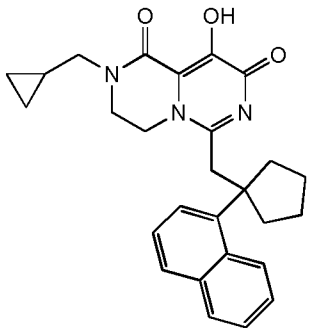


9-Benzyloxy-2-cyclopropylmethyl-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

This compound was prepared following the same method as 9-benzyloxy-2-methyl-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(352)** from 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid cyclopropylmethyl-(2-hydroxyethyl)-amide **(359)** (150mg, 0.27mmol). Yield was 94mg, semi pure (white sticky solid)

LC-MS: 534.0 (M+H)

Synthesis of (361): (16250)



2-Cyclopropylmethyl-9-hydroxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

This compound was prepared by following the same method as pure 9-hydroxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(349)** from 9-benzyloxy-2-cyclopropylmethyl-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(360)** (100mg, 0.19mmol). Yield was 42mg, 51% (white solid)

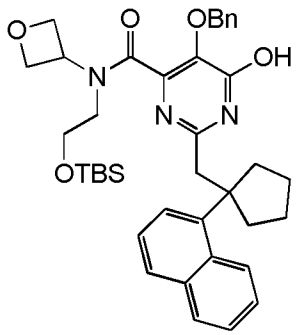
LC-MS: 444.0 (M+H)

Example 365

9-Hydroxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-2-oxetan-3-yl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Schemes 47.

Synthesis of (362):



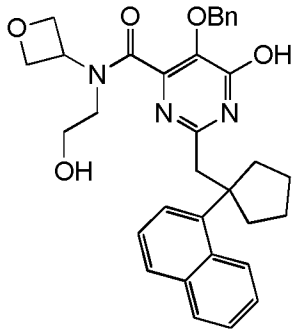
5-Benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-oxetan-3-yl-amide

This compound was prepared following the same method as 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(350)** from '5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(345)** (325mg, 0.72mmol) and [2-(tert-butyl-

dimethyl-silanyloxy)-ethyl]-oxetan-3-yl-amine **(8g)** (248mg, 1.07mmol). Yield was 340mg, 71% (colorless sticky mass).

LC-MS: 668.4 (M+H)

Synthesis of (363):

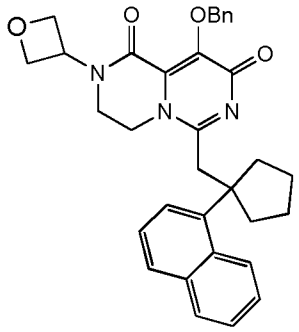


5-Benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-oxetan-3-yl-amide

To a solution of 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-oxetan-3-yl-amide **(362)** (290mg, 0.43mmol) in THF (10mL) was added TBAF (1M in THF, 1.3mL, 13mmol) at 0°C and stirred at room temperature for 1.5h (silica TLC, ethyl acetate: hexane=1:1/SiO_2/UV, Rf=0.3). THF was removed in vacuum and the crude mass was diluted with ethyl acetate (50mL); washed with water (25mL), brine (25mL), dried and concentrated in vacuum to get crude mass which was purified by CombiFlash using gradient eluent mixture of ethyl acetate and hexane to get pure 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-oxetan-3-yl-amide **(363)** (175mg, 73%) as white solid.

LC-MS: 554.0 (M+H)

Synthesis of (364):

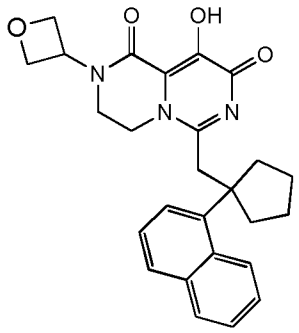


9-Benzyloxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-2-oxetan-3-yl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

This compound was prepared following the same method as pure 9-benzyloxy-2-cyclopropyl-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(356)** from 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-oxetan-3-yl-amide **(363)** (140mg, 0.25mmol). Yield was 131mg, 97% (white solid)

LC-MS: 536.0 (M+H)

Synthesis of (365): (16272)



9-Hydroxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-2-oxetan-3-yl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

A solution of 9-benzyloxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-2-oxetan-3-yl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(364)** (125mg, 0.23mmol) in ethanol (60mL) was degassed by nitrogen and followed by the addition of Pd-C (10%) (40mg) and again degassed

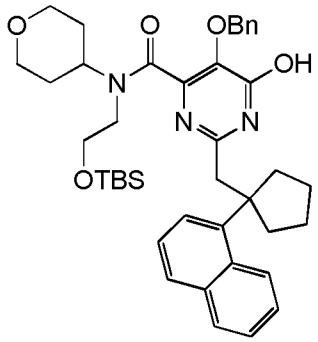
by nitrogen. The reaction mixture was then stirred under hydrogen atmosphere of balloon pressure for 25mins at room temperature. The reaction mass was the filtered through celite bed and the filtrate was concentrated in vacuo to get crude sticky mass which was purified by preparative TLC plate using developing solvent 3% methanol in DCM to get pure 9-hydroxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-2-oxetan-3-yl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(365)** (32mg, 31%) as an off-white solid.
LC-MS: 446.2 (M+H)

Example 369

9-Hydroxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-2-(tetrahydro-pyran-4-yl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Schemes 47.

Synthesis of (366):

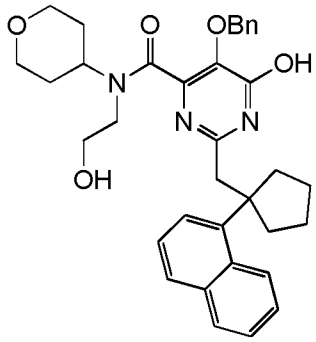


5-Benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-(tetrahydro-pyran-4-yl)-amide

This compound was prepared following the same method as 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(350)** from '5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(345)** (300mg, 0.66mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-(tetrahydro-pyran-4-yl)-amine **(8j)** (257mg, 0.99mmol). Yield was 320mg, 70% (colorless sticky mass).

LC-MS: 696.2 (M+H)

Synthesis of (367):

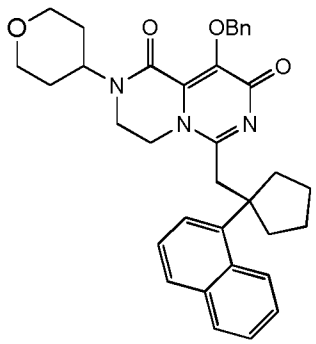


5-Benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-(tetrahydro-pyran-4-yl)-amide

This compound was prepared following the same method as 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide **(351)** from 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-(tetrahydro-pyran-4-yl)-amide **(366)** (300mg, 0.43mmol). Yield was 140mg, 56% (white solid)

LC-MS: 582.2 (M+H)

Synthesis of (368):

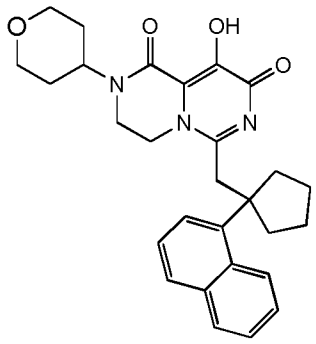


9-Benzyloxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-2-(tetrahydro-pyran-4-yl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

This compound was prepared following the same method as pure 9-benzyloxy-2-cyclopropyl-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(356)** from 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-(tetrahydro-pyran-4-yl)-amide **(367)** (110mg, 0.2mmol). Purification was done on silica gel (normal, 100-200 mesh) using 1% to 5% methanol in DCM as gradient eluent. Yield was 96mg, 90% (white solid)

LC-MS: 534.0 (M+H)

Synthesis of (369): (16261)



9-Hydroxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-2-(tetrahydro-pyran-4-yl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

This compound was prepared by following the same method as pure 9-hydroxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(349)** from 9-benzyloxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-2-(tetrahydro-pyran-4-yl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(368)** (85mg, 0.15mmol). Yield was 55mg, 77% (white solid)

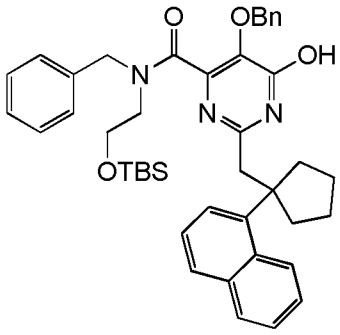
LC-MS: 473.8 (M+H)

Example 373

2-Benzyl-9-hydroxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Schemes 47.

Synthesis of (370):

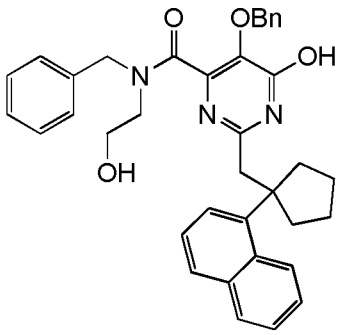


5-Benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid benzyl-[2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-amide

This compound was prepared by following the same method as 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(350)** from 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(345)** (250mg, 0.55mmol) and benzyl-[2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-amine **(8l)** (219mg, 0.83mmol). Yield was 358mg, 93% (colorless sticky mass).

LC-MS: 702.4 (M+H)

Synthesis of (371):

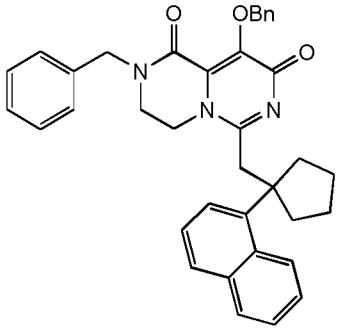


5-Benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid benzyl-(2-hydroxyethyl)-amide

This compound was prepared following the same method as 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide **(351)** from 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid benzyl-[2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-amide **(370)** (380mg, 0.54mmol). Yield was 190mg, 60% (white solid)

LC-MS: 588.0 (M+H)

Synthesis of (372):

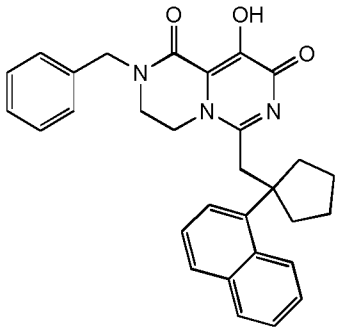


2-Benzyl-9-benzyloxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

This compound was prepared following the same method as pure 9-Benzyloxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-2-(tetrahydro-pyran-4-yl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(368)** from 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid benzyl-(2-hydroxyethyl)-amide **(371)** (155mg, 0.26mmol). Yield was 122mg, mixture (white sticky solid)

LC-MS: 570 (M+H)

Synthesis of (373): (16279)



2-Benzyl-9-hydroxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

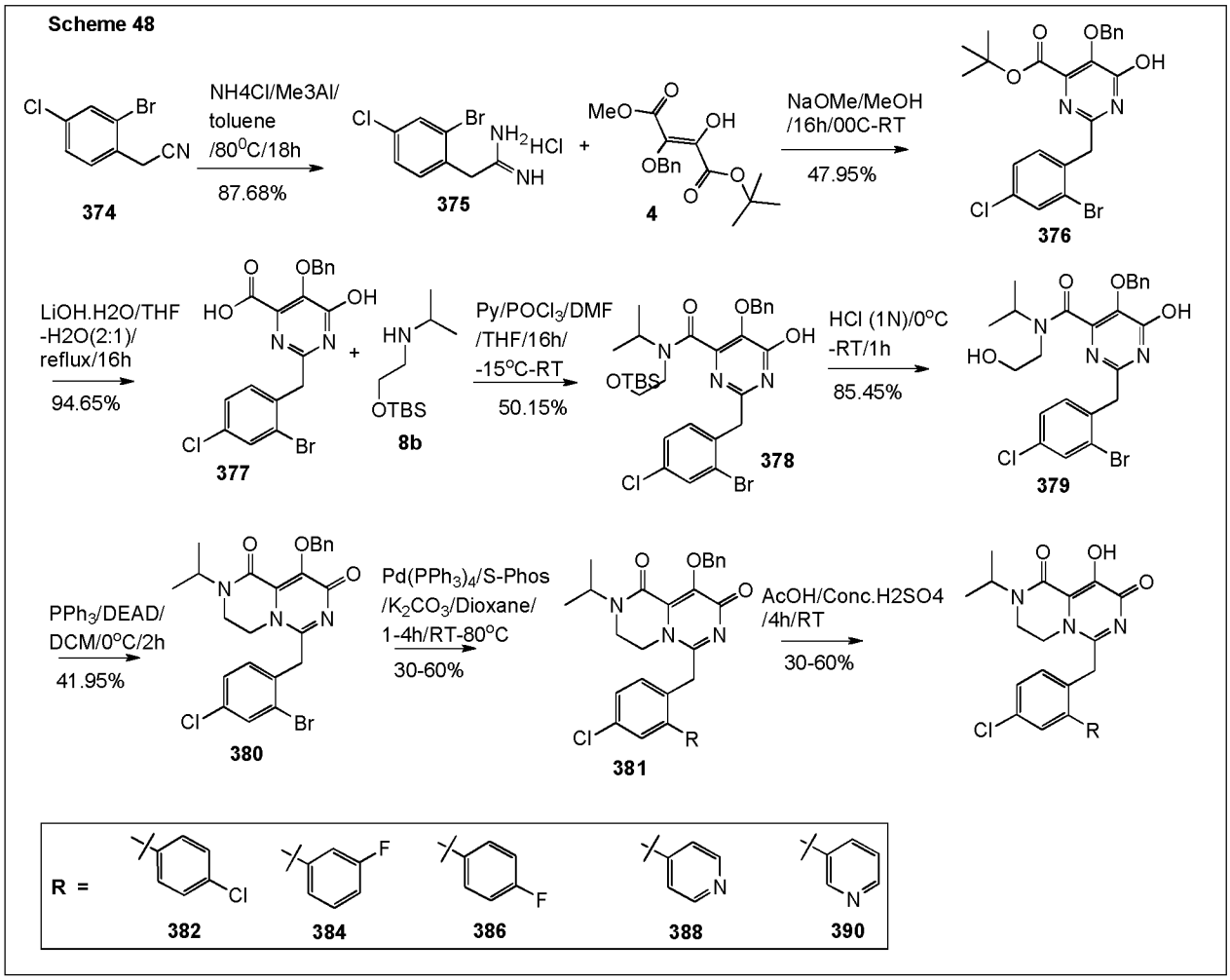
This compound was prepared following the same method as pure 9-hydroxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(349)** from 2-benzyl-9-benzyloxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(372)** (110mg, 0.19mmol). Yield was 35mg, 47% (light brown solid)

LC-MS: 479.9 (M+H)

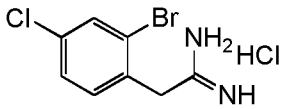
General procedure for examples 374 to 390

The synthetic procedures are outlined in Scheme 48.

General synthetic route for 382, 384, 386, 388, 390



Preparation of (375):



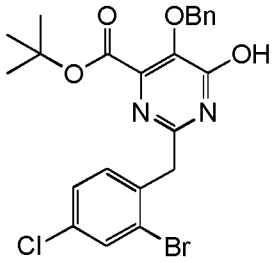
2-(2-Bromo-4-chloro-phenyl)-acetamidine hydrochloride

To a stirred suspension of NH_4Cl (9.241g, 169.565mmol) in dry toluene (120mL) was added tri-methyl aluminum (2M) (45.23mL, 90.435mmol) at 5°C, then warmed to room temperature and stirred for 2h. A solution of (2-bromo-4-chloro-phenyl)-acetonitrile **(374)** (13g, 56.522mmol) in toluene (30mL) was added to above reaction mass and stirred for 14h at 80°C Silica thin layer chromatography was performed (10% MeOH in DCM; Rf = 0.2). After

completion of the reaction, it was quenched with suspension of silica gel (20g) in chloroform (200mL) and reaction mixture was stirred for half an h at room temperature and filtered, silica gel was washed with methanol (100mL) and combined filtrate was concentrated under reduced pressure to get 2-(2-bromo-4-chloro-phenyl)-acetamidine hydrochloride **(375)** (14.0g, 87.68%) as White solid.

LCMS: 248.8 (M+H)

Preparation of (376):

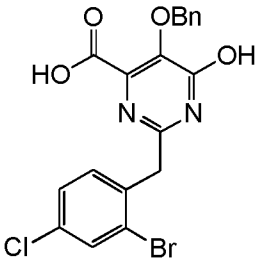


5-Benzyloxy-2-(2-bromo-4-chlorobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester

To a stirred solution of 2-(2-bromo-4-chloro-phenyl)-acetamidine hydrochloride (375) (7g, 24.823mmol) and 2-benzyloxy-3-hydroxy-but-2-enedioic acid 4-tert-butyl ester 1-methyl ester (4) (11.47g, 37.23mmol) in methanol (100mL) add NaOMe (16.1mL) (25% in methanol) dropwise at 0°C. Reaction mixture was allowed to warm to room temperature, stirred for 16h Silica thin layer chromatography was performed (50% EtOAc in hexane; Rf = 0.5). Reaction mixture was quenched with (1N) HCl (5mL), methanol was removed under reduced pressure, residue was diluted with water (200mL), extracted with EtOAc (2X250mL). Combined organic parts was dried, concentrated. Obtained crude was purified by normal silica (100-200 mesh) column to get 5-benzyloxy-2-(2-bromo-4-chlorobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester (376) (6.02g, 47.95%) as white solid.

LCMS: 507.2(M+H).

Preparation of (377):

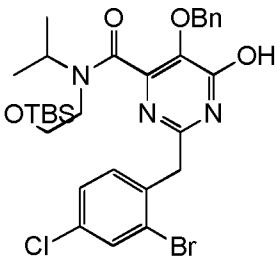


5-Benzyloxy-2-(2-bromo-4-chlorobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid

To a stirred solution of 5-benzyloxy-2-(2-bromo-4-chlorobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid tert-butyl ester (376) (14g, 27.723mmol) in THF-water (15:7, 220mL), $LiOH.H_2O$ (11.644g, 277.228) was added, refluxed for 16h Silica thin layer chromatography was performed (50% EtOAc in hexane; Rf = 0.1). After completion of the reaction, volatiles was removed, diluted with water (50mL), neutralized (pH 7) with (1N) HCl, filtered and resulted solid was dried to get 5-benzyloxy-2-(2-bromo-4-chlorobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid (377) (11.8g, 94.65%) as white solid.

LCMS: 451.2(M+H)

Preparation of (378):



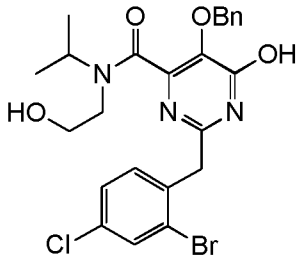
5-Benzyloxy-2-(2-bromo-4-chlorobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide

To a stirred solution of 5-benzyloxy-2-(2-bromo-4-chlorobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid (377) (4.0g, 8.9mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amine (8b) (5.8g, 26.73mmol), were taken in THF(150mL). To the reaction mixture pyridine (2.159mL, 26.726mmol) followed by $POCl_3$ (2.454mL, 26.726mmol) were added very slowly, at -15°C, stirred for 2h at same temperature. To the reaction 2 drops of DMF was added, reaction mixture was allowed to stir at room temperature for 16h Silica thin layer

chromatography was performed (50% EtOAc in hexane; Rf = 0.5). After completion of the reaction, it was quenched with ice cold water (150mL), extracted with EtOAc (2X250mL), combined organic parts was dried, concentrated, resulted crude residue was column purified (normal silica 100-200 mesh) to get 5-benzyloxy-2-(2-bromo-4-chlorobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide (378) (2.9g, 50.15%) as colorless gummy liquid.

LCMS: 648.2(M+H).

Preparation of (379):

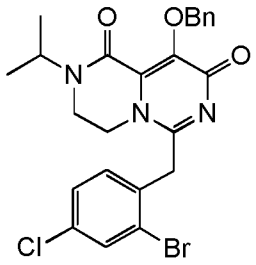


5-Benzyloxy-2-(2-bromo-4-chlorobenzyl)-6-hydroxy-pyrimidine-4-carboxylicacid(2-hydroxyethyl)-isopropyl-amide

To a stirred solution of 5-benzyloxy-2-(2-bromo-4-chlorobenzyl)-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide (378) (5.7g, 8.80mmol) in THF (50mL), (1N) HCl (15mL) was added, stirred for 1h at room temperature Silica thin layer chromatography was performed (70% EtOAc in hexane; Rf = 0.2). After completion of the reaction, volatiles was removed, residue was diluted with water (30mL) and $NaHCO_3$ was added to make pH~8, aqueous mixture was extracted with EtOAc (2X150mL), combined extracts was dried, concentrated, resulted residue was purified by column over normal silica gel (100-200) to get 5-benzyloxy-2-(2-bromo-4-chlorobenzyl)-6-hydroxy-pyrimidine-4-carboxylicacid(2-hydroxyethyl)-isopropyl-amide (379) (4.02g, 85.45%) as white solid.

LCMS: 533.8 (M+H).

Preparation of (380): (16291)



9-Benzyloxy-6-(2-bromo-4-chlorobenzyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a stirred solution of 5-benzyloxy-2-(2-bromo-4-chlorobenzyl)-6-hydroxy-pyrimidine-4-carboxylicacid(2-hydroxyethyl)-isopropyl-amide (379) (1.0g, 1.873mmol), TPP (1.717g, 6.554mmol) in DCM (120mL), DIAD (1.114, 5.618mmol) was added over 10h (dilution 0.19M; rate 3ml/h) at 0°C, then reaction was monitored by silica TLC Silica thin layer chromatography was performed (3% MeOH in DCM; Rf = 0.4). After completion of the reaction add 50mL water, extract with DCM (2X100mL), then organic part was dried over Na2SO4, then concentrated, resulted crude was column purified (using Amine bound silica) to get 9-benzyloxy-6-(2-bromo-4-chlorobenzyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione (380) (0.406g, 41.95%) as white solid.

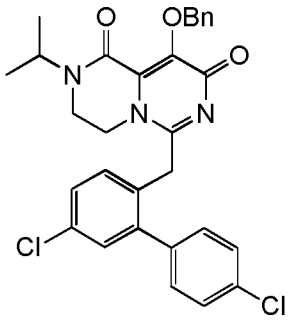
LCMS: 517.8(M+H).

Example 382

6-(5,4'-Dichloro-biphenyl-2-ylmethyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Schemes 48.

Preparation of (381):

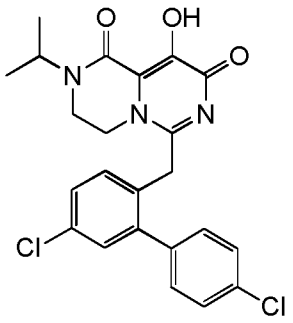


9-Benzyloxy-6-(5,4'-dichloro-biphenyl-2-ylmethyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

In a sealed tube stirred solution of 9-benzyloxy-6-(2-bromo-4-chlorobenzyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione (380) (80mg, 0.155mmol) in dioxane (3mL), 4-chlorophenyl boronicacid (24.248mg, 0.155mmol), and K_2CO_3(1N) [(64.279mg, 0.465mmol) dissolved in 0.7mL water] were added at room temperature, reaction was degassed for 30min with argon. To the reaction, $Pd(PPh_3)_4$ (17.916mg, 0.016mmol) was added, followed by S-Phos (12.729mg, 0.031mmol) and further degassed for another 10min. The reaction mass was heated at 80°C for 20 min (reaction was monitored by LCMS). After completion of the reaction, filtered, filtrate was diluted with water (5mL), then extract with Ethyl acetate, (2X 20mL), organic part was dried over Na_2SO_4, then concentrated, resulted crude was purified by column (using amine bound silica gel as stationary phase) to get 9-benzyloxy-6-(5,4'-dichloro-biphenyl-2-ylmethyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione (381) (42mg, 49.39%) as white solid.

LCMS: 548.0(M+H).

Preparation of (382): (16243)



6-(5,4'-Dichloro-biphenyl-2-ylmethyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a stirred solution of 9-benzyloxy-6-(5,4'-dichloro-biphenyl-2-ylmethyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione (10a) (35mg, 0.064mmol) in acetic acid (1mL), add conc. H_2SO_4 (0.001mL, 0.013mmol), reaction mixture was stirred for 4h, at room temperature (reaction was monitored by LC/MS). Volatiles were removed from the reaction mixture, residue was quenched with ice cold water (5mL), then add $NaHCO_3$ (adjust pH to 8), then extract with ethyl acetate (2X15mL), then organic part was dried, concentrated, resulted crude was purified by prep HPLC to get 6-(5,4'-dichloro-biphenyl-2-ylmethyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione (P046-03-EB-01) (18.1mg, 61.72%) as an off-white solid.

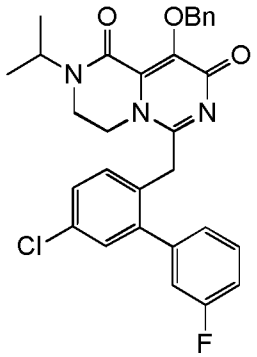
LCMS: 457.8(M+H).

Example 384

6-(5-Chloro-3'-fluoro-biphenyl-2-ylmethyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Schemes 48.

Preparation of (383):

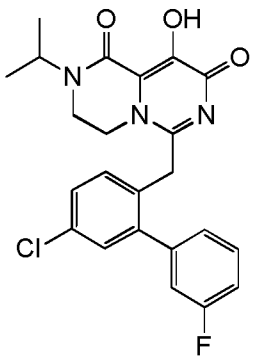


9-Benzyloxy-6-(5-chloro-3'-fluoro-biphenyl-2-ylmethyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

In a sealed tube, to the stirred solution of 9-benzyloxy-6-(2-bromo-4-chlorobenzyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione (380) (100mg, 0.194mmol) in dioxane (3mL), 3-fluorophenyl boronicacid (27.132mg, 0.194mmol), and K_2CO_3(1N) [(80.349mg, 0.581mmol) dissolved in 1.06mL water] were added at room temperature. Reaction mixture was de-gassed with argon by purging for 30min, $Pd(PPh_3)_4$ (22.395mg, 0.019mmol), followed by S-Phos (15.911mg, 0.039mmol) were added and further degassed for another 10min. The reaction mass was heated for 30 min at 80°C (monitored by LCMS). Reaction was filtered and diluted with water (5mL), extract with ethyl acetate, (2X 20mL). Combined extracts was dried, concentrated, resulted crude was purified by column (using amine bound silica gel) to get 9-benzyloxy-6-(5-chloro-3'-fluoro-biphenyl-2-ylmethyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione (383) (65mg, 63.04%) as an off-white solid.

LCMS: 532.0(M+H).

Preparation of (384): (16262)



6-(5-Chloro-3'-fluoro-biphenyl-2-ylmethyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a stirred solution of 9-benzyloxy-6-(5-chloro-3'-fluoro-biphenyl-2-ylmethyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione (383) (60mg, 0.113mmol) in acetic acid (1mL), Conc. H2SO4 (0.001mL, 0.023mmol) was added, stirred for 4h, at room temperature (monitored by LCMS).From the reaction volatiles were removed and quenched with ice cold water (5mL), aqueous saturated $NaHCO_3$ was added to adjust the pH up to 8. Quenched mass was extracted with ethyl acetate (2X15mL), combined organic part was dried, concentrated and purified by prep HPLC to get 6-(5-chloro-3'-fluoro-biphenyl-2-ylmethyl)-9-

hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione (384) (20.0mg, 40.06%) as an off-white solid.

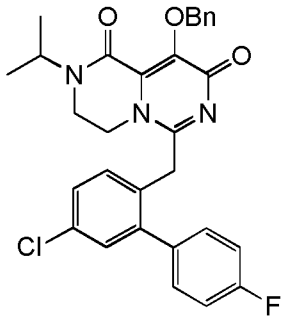
LCMS: 441.8(M+H).

Example 386

6-(5-Chloro-3'-fluoro-biphenyl-2-ylmethyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Schemes 48.

Preparation of (385):



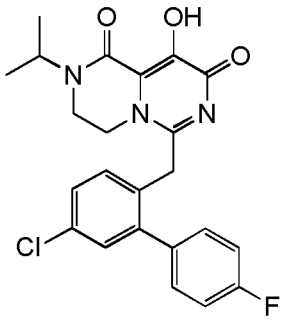
9-Benzyloxy-6-(5-chloro-4'-fluoro-biphenyl-2-ylmethyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c] pyrimidine-1,8-dione

In a sealed tube stirred solution of 9-benzyloxy-6-(2-bromo-4-chlorobenzyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione (380) (70mg, 0.136mmol) in dioxane (3mL) 4-fluorophenyl boronicacid (18.99mg, 0.14mmol), and K_2CO_3(1N) [(56.244mg, 0.407mmol) were added. It was dissolved in 0.82mL water] at room temperature and purged for 30min with argon. To the reaction $Pd(PPh_3)_4$ (15.676mg, 0.014mmol), followed by S-Phos (11.138mg, 0.027mmol) were added under argon. The reaction mixture was further degassed for another 10min, heated at 80°C for 30 min (monitored by LCMS). Reaction mixture was filtered through a pad of cellite, filtrate was diluted with water (5mL), extracted with ethyl acetate, (2X 20mL). Combined extracts was dried, concentrated, resulted crude was purified by column (using amine bound silica gel) to get 9-benzyloxy-6-(5-chloro-4'-fluoro-biphenyl-2-ylmethyl)-2-

isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione (385) (32mg, 44.34%) as an off-white solid.

LCMS: 532.2(M+H).

Preparation of (386): (16242)



6-(5-Chloro-4'-fluoro-biphenyl-2-ylmethyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a stirred solution of 9-benzyloxy-6-(5-chloro-4'-fluoro-biphenyl-2-ylmethyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione (385) (30mg, 0.056mmol) in acetic acid (1mL), conc. H_2SO_4 (0.001mL, 0.011mmol) was added and stirred for 4h at room temperature (monitored by LCMS). From the reaction, volatiles was removed and quenched with ice cold water (5mL), aqueous saturated $NaHCO_3$ was added to adjust the pH up to 8. Quenched mass was extracted with ethyl acetate (2X15mL), combined organic part was dried, concentrated and purified by prep HPLC to get 6-(5-chloro-4'-fluoro-biphenyl-2-ylmethyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-diol (386) (11.2mg, 44.86 mmol) as an off-white solid.

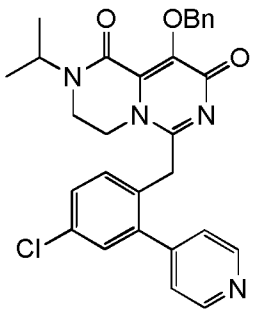
LCMS: 441.8(M+H).

Example 388

6-(4-Chloro-2-pyridin-4-yl-benzyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Schemes 48

Preparation of (387):

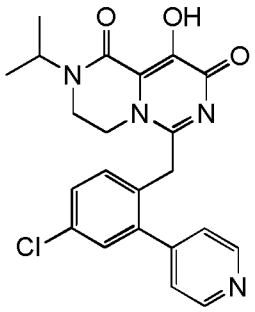


6-(4-Chloro-2-pyridin-4-yl-benzyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

In a sealed tube, to the stirred solution of 9-benzyloxy-6-(2-bromo-4-chlorobenzyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione (380) (100mg, 0.194mmol) in dioxane (4mL) pyridine 4-boronicacid (23.822mg, 0.194mmol), and K_2CO_3(1N) [(80.349mg, 0.581mmol) were added. It was dissolved in 0.82mL water] at room temperature and purged for 30min with argon. To the reaction $Pd(PPh_3)_4$ (22.395mg, 0.019mmol), followed by S-Phos (15.911mg, 0.039mmol) were added under argon. The reaction mixture was further degassed for another 10min, heated at 80°C for 4h (monitored by LCMS). Reaction mixture was filtered through a pad of cellite, filtrate was diluted with water (5mL), extracted with ethyl acetate, (2X 20mL). Combined extracts was dried, concentrated, resulted crude was purified by column (using amine bound silica gel) to get 9-benzyloxy-6-(4-chloro-2-pyridin-4-yl-benzyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione (387) (51mg, 51.1%) as an off-white solid.

LCMS: 515.0 (M+H).

Preparation of (388): (16274)



6-(4-Chloro-2-pyridin-4-yl-benzyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a stirred solution of 9-benzyloxy-6-(4-chloro-2-pyridin-4-yl-benzyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione (387) (50mg, 0.097mmol) in acetic acid (2mL), conc. H_2SO_4 (0.001mL, 0.019mmol) was added, reaction mixture was stirred for 4h at room temperature (monitored by LCMS). From the reaction, volatiles was removed and quenched with ice cold water (5mL), aqueous saturated $NaHCO_3$ was added to adjust the pH up to 8. Quenched mass was extracted with ethyl acetate (2X15mL), combined organic part was dried, concentrate and purified by prep HPLC to get 6-(4-chloro-2-pyridin-4-yl-benzyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione (388) (14.3mg, 31.45%) as an off-white solid.

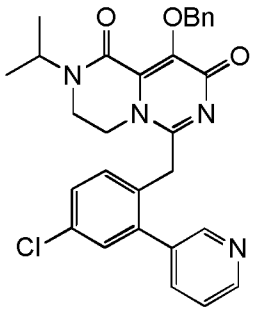
LCMS: 424.8(M+H).

Example 390

6-(4-Chloro-2-pyridin-3-yl-benzyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Schemes 48

Preparation of (389)

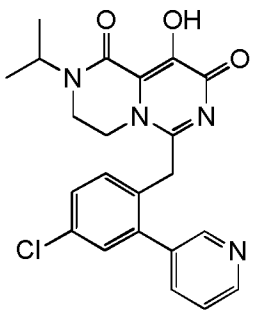


9-Benzyloxy-6-(4-chloro-2-pyridin-3-yl-benzyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

In a sealed tube, to the stirred solution of 9-benzyloxy-6-(2-bromo-4-chlorobenzyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione (380) (100mg, 0.194mmol) in the dioxane (3mL) pyridine 3-boronicacid (23.822mg, 0.194mmol), and K_2CO_3(1N) [(80.349mg, 0.581mmol) dissolved in 1.25mL water] were added at room temperature, argon was purged for 30min. Then $Pd(PPh_3)_4$ (22.395mg, 0.019mmol) , S-Phos (15.911mg, 0.039mmol) were added and further degassed for another 10min. The reaction mass was heated at 80°C for 4h (monitored by LCMS). Reaction mixture was filtered through a pad of cellite, filtrate was diluted with water (5mL), extracted with ethyl acetate, (2X 20mL). Combined extracts was dried, concentrated, resulted crude was purified by column (using amine bound silica gel) to get 9-benzyloxy-6-(4-chloro-2-pyridin-3-yl-benzyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione (389) (50mg, 50.1%) as an off-white solid.

LCMS: 515.0(M+H).

Preparation of (390): (16273)



6-(4-Chloro-2-pyridin-3-yl-benzyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

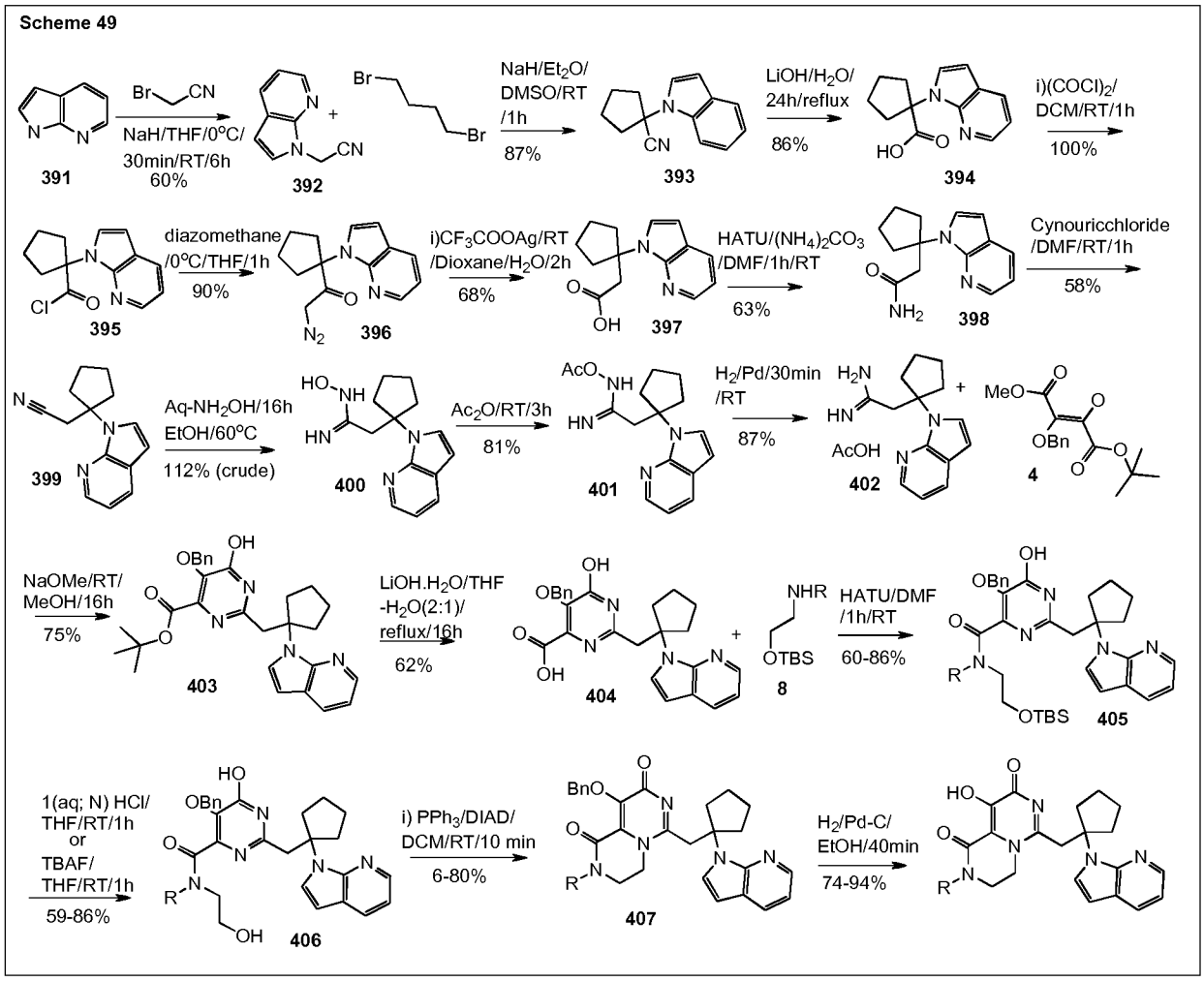
To a stirred solution of 9-benzyloxy-6-(4-chloro-2-pyridin-3-yl-benzyl)-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione (389) (45mg, 0.088mmol) in acetic acid (2mL), conc. H_2SO_4 (0.001mL, 0.018mmol) was added, reaction mixture was stirred for 4h at room temperature (monitored by LCMS). From the reaction, volatiles was removed and quenched with ice cold water (5mL), aqueous saturated $NaHCO_3$ was added to adjust the pH up to 8. Quenched mass was extracted with ethyl acetate (2X15mL), combined organic part was dried, concentrated and purified by prep HPLC to get 6-(4-chloro-2-pyridin-3-yl-benzyl)-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione (390) (12.0mg, 32.26%) as an off-white solid.

LCMS: 424.8(M+H).

General procedure for examples 391 to 428

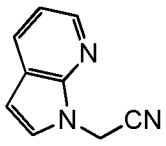
The synthetic procedures are outlined in Scheme 49.

General synthetic route for 408, 412, 416, 420, 424, 428



R = 408 412 416 420 424 428

Synthesis of (392):

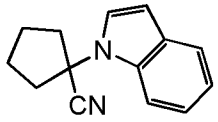


Pyrrolo[2,3-b]pyridin-1-yl-acetonitrile

To a suspension of sodium hydride (60%) (3.7 g, 93.12 mmol) in THF (60 mL) was added dropwise a mixture of 1H-pyrrolo[2,3-b]pyridine **(391=** (5 g, 42.33 mmol) and bromoacetonitrile (10 g, 84.65 mmol) dissolved in THF (40 mL) at 0 °C stirred for 30 min at same temperature, then stirred at room temperature for 6 h (TLC, 40% ethyl acetate in hexane, R_f = 0.5). After completion of the reaction, it was quenched with saturated ammonium chloride solution (100 mL), THF was removed, water (100 mL) was added, extracted with ethyl acetate (3 x 100mL), separated organic part was washed with brine (100 mL), dried and concentrated to get crude mass which was purified by Combi-Flash (eluted at 20% ethyl acetate in hexane) to afford pyrrolo[2,3-b]pyridin-1-yl-acetonitrile (**3**) (4g, 60%) as light brown solid.

LC-MS: 158.2 (M+H).

Synthesis of (393):

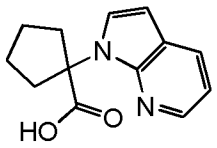


1-Pyrrolo[2,3-b]pyridin-1-yl-cyclopentanecarbonitrile

To a suspension of sodium hydride (60%) (8.6 g, 215.79 mmol) in DMSO (90 mL) was added dropwise a mixture of pyrrolo[2,3-b]pyridin-1-yl-acetonitrile **(392)** (15.4 g, 98.09 mmol) and 1,4-dibromo-butane (31.7 g, 147.13 mmol) dissolved in DMSO: ether (180 mL, 1:1) at 0 °C stirred for 30 min at same temperature, then stirred at room temperature for 24 h. (TLC, 40% ethyl acetate in hexane, R_f=0.6). After completion of the reaction, it was quenched with 1 N HCl (100 mL), water (100 mL) was added, extracted with ethyl acetate (3 x 100 mL), separated organic part was washed with water (3 x 100 mL) and brine (2 x 100 mL), organic part was dried and concentrated to get crude which was purified by Combi-Flash column (eluted at 10-20% ethyl acetate in hexane) to afford 1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentanecarbonitrile **(393)** (18 g, 87%) as light yellow crystalline solid.

LC-MS: 212.0 (M+H)

Synthesis of (394):

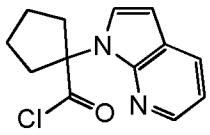


1-Pyrrolo[2,3-b]pyridin-1-yl-cyclopentanecarboxylic acid

To a stirred suspension of 1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentanecarbonitrile **(393)** (6.2 g, 29.35 mmol) in water (90 mL) was added $LiOH.H_2O$ (14 g, 334.56 mmol). The reaction mixture was refluxed for 24 h, (TLC, 30% ethyl acetate in hexane, R_f=0.3). It was cooled to 0 °C, aqueous part was acidified with HCl (6 N), to pH ~3; extracted with ethyl acetate (3 x 50 mL), dried and concentrated to get 1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentanecarboxylic acid **(394)** (5.8 g, 86%) as an off-white solid.

LC-MS: 231.0 (M+H)

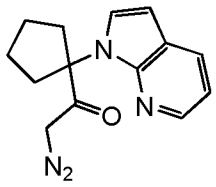
Synthesis of (395):



1-Pyrrolo[2,3-b]pyridin-1-yl-cyclopentanecarbonyl chloride

To a stiired solution of 1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentanecarboxylic acid **(394)** (1.2 g, 5.21 mmol) in DCM (80 mL) was added oxalyl chloride (1 mL, 11.47 mmol) at 0°C dropwise followed by DMF (0.1 mL). Stirred for 1h at room temperature. After completion, the reaction mixture is concentrated under argon atmosphere to get 1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentanecarbonyl chloride **(395)** (1.3 g, 100%, crude) as yellow solid which was directly used for the next step without analysis.

Synthesis of (396):

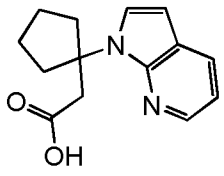


2-Diazo-1-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentyl)-ethanone

To a solution of 1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentanecarbonyl chloride **(395)** (1.2 g, 8.83 mmol) in THF (80mL) was added dropwise a solution of diazomethane [Synthesized freshly following standard condition; started from methylurea via formation of NMU and followed by KOH treatment] in ether (80 mL) at -5 °C, kept the stirring very slow. The reaction mixture was kept standing for 1 h at 0°C. (TLC, 30% ethyl acetate in hexane, R_f = 0.6). Volatiles were removed to get the crude and crude was purified by Combi-Flash column (eluted at 20-30% ethyl acetate in hexane) to get 2-diazo-1-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentyl)-ethanone **(396)** (1.1 g, 90%) as yellow sticky solid.

LC-MS: 254.8 (M+H).

Synthesis of (397):

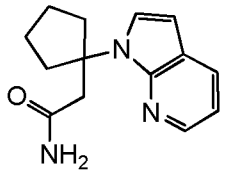


(1-Pyrrolo[2,3-b]pyridin-1-yl-cyclopentyl)-acetic acid

To a stirred solution of 2-diazo-1-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentyl)-ethanone **(396)** (0.95g, 3.82 mmol) in dioxane : water (10 : 1) (27.5 mL) was added silveracetate (319 mg, 1.91 mmol), stirred for 2 h at room temperature. (TLC, 30% ethyl acetate in hexane, R_f=0.2), filtered over celite bed, washed with ethylacetate (3 x 20 mL), and concentrated. Crude was purified by Combi-Flash column (eluted at 30% ethylacetate in hexane) to get (1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentyl)-acetic acid **(397)** (0.5g, 54%) as brown solid.

LC-MS: 245.2 (M+H)

Synthesis of (398):

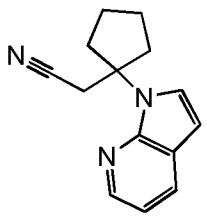


2-(1-Pyrrolo[2,3-b]pyridin-1-yl-cyclopentyl)-acetamide

To a stirred solution of (1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentyl)-acetic acid **(397)** (2.7g, 11.05 mmol) in DMF (60 mL) was added DIPEA (5.8 mL, 33.16 mmol) followed by $(NH_4)_2CO_3$ (5.2 g, 33.16 mmol) and HATU (6.3 g, 16.58 mmol), stirred for 1 h at room temperature (TLC, 50% ethyl acetate in hexane, R_f = 0.5), Water (200 mL) was added, extracted with ethyl acetate (2 x 200 mL), organic part was washed with water (2 x 100 mL), brine (2 x 100 mL), dried and concentrated. Crude was purified by Combi-Flash column (eluted at 30-40% ethylacetate in hexane) to get 2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentyl)acetamide **(398)** (1.7g, 63%) as yellow solid.

LC-MS: 244.1 (M+H)

Synthesis of (399):



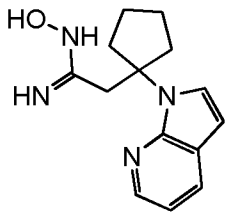
(1-Pyrrolo[2,3-b]pyridin-1-yl-cyclopentyl)-acetonitrile

To a stirred solution of 2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentyl)-acetamide **(398)** (1.6 g, 6.58 mmol) in DMF (25 mL) was added cyanuric chloride (728 mg, 3.95 mmol) at room temperature. The reaction mixture was stirred for 30 min at room temperature. (TLC, 30% ethyl acetate in hexane, R_f=0.8), Cold water was added, extracted with ethyl acetate (2 x 50

mL), washed with water (2 x 50 mL), brine (50 mL), dried and concentrated to get crude. Crude was purified by Combi-Flash column (eluted at 10-20% ethylacetate in hexane) to get (1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentyl)-acetonitrile **(399)** (861 mg, 58%) as light yellow thick oil.

LC-MS: 225.9 (M+H)

Synthesis of (400):

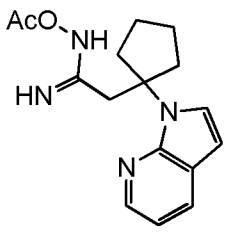


N-Hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentyl)-acetamidine

To a stirred solution of (1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentyl)-acetonitrile **(399)** (1.4 g, 6.21 mmol) in ethanol (50 mL) was added 50% aq NH_2OH (4 mL, 62.15 mmol) and heated at 60 °C for 16h. (TLC, 30% ethyl acetate in hexane, R_f=0.1). Ethanol was evaporated, water (50 mL) was added, extracted with etylacetate (3 x 50 mL), dried and concentrated to get crude N-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentyl)-acetamidine **(400)** (1.8g, 112%) as an off-white sticky liquid.

LC-MS: 258.9 (M+H)

Synthesis of (401):

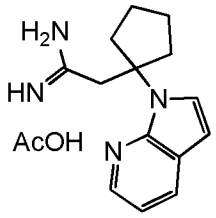


2-(1-{1H-pyrrolo[2,3-b]pyridin-1-yl}cyclopentyl)ethanimidamido acetate

Acetic anhydride (11.2 mL, 118.61 mmol) was added to N-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentyl)-acetamidine **(400)** (1.8 g, 6.98 mmol), stirred for 3 h at room temperature, (TLC, ethyl acetate, R_f=0.5), water (50 mL) was added, basified (pH~8) by solid $NaHCO_3$, extracted with ethylacetate (3 x 50 mL), dried and concentrated. Crude was purified by Combi-Flash column (eluted at 20-30% ethylacetate in hexane) to get 2-(1-{1H-pyrrolo[2,3-b]pyridin-1-yl}cyclopentyl)ethanimidamido acetate **(401)** (1.7 g, 81%) as an off-white solid.

LC-MS: 300.8 (M+H)

Synthesis of (402):

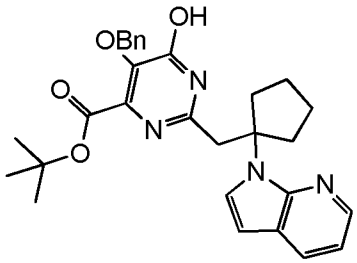


2-(1-Pyrrolo[2,3-b]pyridin-1-yl-cyclopentyl)-acetamidine; compound with acetic acid

To a stirred degassed solution of 2-(1-{1H-pyrrolo[2,3-b]pyridin-1-yl}cyclopentyl)ethanimidamido acetate **(401)** (500 mg, 1.67 mmol) in ethanol (20 mL) was added 10% Pd-C (50 mg), stirred 30 min under H_2 (hydrogen-bludder) at room temperature. (TLC, 50% ethyl acetate in hexane, R_f=0.1), The reaction mixture was filtered through celite bed, washed with 10% MeOH in DCM (5 x 50 mL), dried and concentrated to get 2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentyl)-acetamidine; compound with acetic acid **(402)** (437 mg, 87%) as an off-white solid.

LC-MS: 243.0 (M+H)

Synthesis of (403):

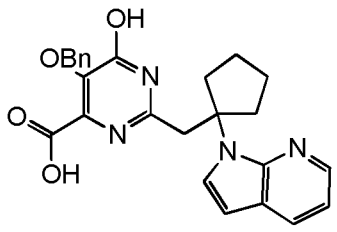


5-Benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid tert-butyl ester

To a stirred solution of 2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentyl)-acetamidine; compound with acetic acid **(402)** (800 mg, 2.65 mmol) and (E)-3-benzyloxy-2-hydroxy-4-oxo-pent-2-enoic acid tert-butyl ester **(4)** (978 mg, 3.18 mmol) in methanol (80 mL) was added sodium methoxide solution (25% in MeOH) (1.7 mL, 7.94 mmol) at 0°C then the reaction mixture allowed to warm slowly to room temperature, was stirred for 16h. (TLC, ethyl acetate, R_f=0.3). After completion of the reaction, methanol was evaporated to get crude, which was purified by Combi-Flash column (eluted at 60-70% ethylacetate in hexane) to get 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid tert-butyl ester **(403)** (1g, 75%) as light yellow solid.

LC-MS: 501.2 (M+H).

Synthesis of (404):



5-Benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid

To a stirred solution 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid tert-butyl ester **(403)** (900 mg. 1.8 mmol) in the mixture of THF:Water (2:1) (30 mL) was added lithium-hydroxide monohydrate (756 g, 18.0 mmol), refluxed for 24 h. (TLC, ethyl acetate, R_f=0.1) After completion of reaction, volatile was evaporated, aqueous part was washed with ethylacetate (3 x 30 mL), aqueous was acidified with HCl (6 N), to pH ~3; extracted with ethyl acetate (3 x 50 mL), dried and concentrated to get 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(404)** (500 mg, 62%) as an off-white sticky solid.

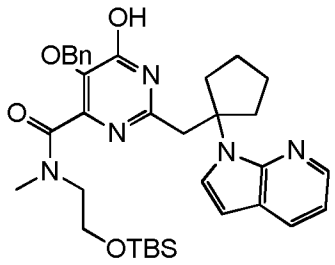
LC-MS: 445.0 (M+H).

Example 408

9-Hydroxy-2-methyl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 49.

Synthesis of (405):



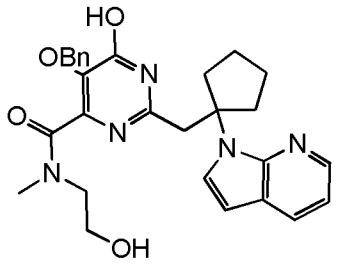
5-Benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide

To a stirred solution of 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(404)** (250 mg, 0.56 mmol) in DMF (5 mL) was added DIPEA (0.3 mL, 1.69 mmol) followed by [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amine **(8a)** (320 mg, 1.69 mmol) and HATU (320 mg, 0.84 mmol), stirred for 1 h, (TLC, ethyl acetate, R_f=0.5). Water (30 mL) was added, extracted with ethyl acetate (2 x 20 mL), organic part was washed with water (2 x 100 mL), brine (2 x 50 mL), dried and concentrated. Crude

was purified by Combi-Flash column (eluted at 30-40% ethylacetate in hexane) to get 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(405)** (300 mg, 87%) as light yellow sticky solid.

LC-MS: 616.4 (M+H).

Synthesis of (406):

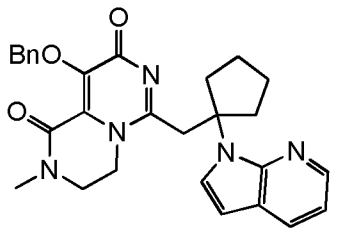


5-Benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide

To a stirred solution of 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(405)** (300 mg, 0.49 mmol) in THF (10 mL) was added 1(N) HCl (2.4 mL), stirred for 1 h at room temperature, after completion THF was removed, reaction mixture was basified with solid $NaHCO_3$ (pH~8), extracted with ethylacetate (3 x 20 mL), organic part was dried and concentrated, crude was purified by prep TLC (mobile phase ethylacetate) to get 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide **(406)** (210 mg, 86%) as light yellow sticky solid.

LC-MS: 502.1 (M+H).

Synthesis of (407):

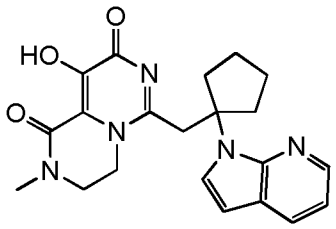


9-Benzyloxy-2-methyl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a stirred solution of 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide **(406)** (210 mg, 0.42 mmol) in DCM (30 mL) were added triphenyl phosphine (550 mg, 2.09 mmol) followed by DIAD (0.2 mL, 1.26 mmol) at room temperature, stirred for 10 min. (TLC, 5% MeOH in ethyl acetate, R_f=0.2). It was concentrated under reduced pressure to get crude, which was purified by Prep-TLC plate (mobile phase 5% MeOH in ethylacetate) to get 9-benzyloxy-2-methyl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(407)** (60 mg, 30%) as white solid.

LC-MS: 484.1 (M+H).

Synthesis of (408): (16281)



9-Hydroxy-2-methyl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

A solution of 9-benzyloxy-2-methyl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(407)** (60 mg, 0.12 mmol) in ethanol (10 mL) was degassed, added Pd-C (10%) (6 mg) and hydrogenated for 40 min (hydrogen bludder).(TLC, 5% MeOH in DCM, R_f=0.2). Catalyst was filtered of, washed with 10% DCM in ethanol (3 x 20 mL), combined solvents were concentrated, sticky solid was washed with pentane to get pure 9-hydroxy-2-methyl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(408)** (38 mg, 78%) as an off-white solid.

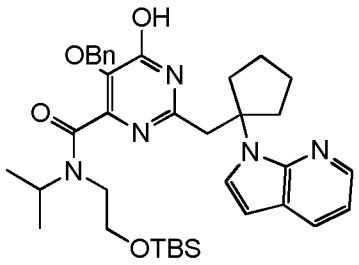
LC-MS: 394.2 (M+H).

Example 412

9-Hydroxy-2-isopropyl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 49.

Synthesis of (409):

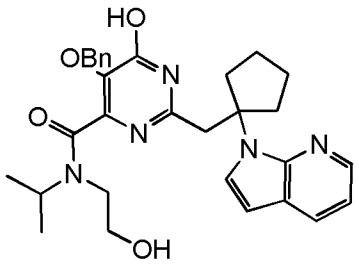


5-Benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide

5-Benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(409)** was prepared following the same method as for 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(405)** from 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(404)** (250 mg, 0.56 mmol) and [2-(tert-tutyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amine (367 mg, 1.69 mmol) **(8b)** to get off-white sticky solid (220 mg, 61%).

LC-MS: 644.5 (M+H).

Synthesis of (410):

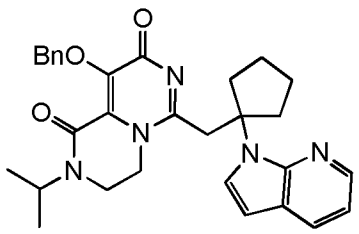


5-Benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide

5-Benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(410)** was prepared following the same method as 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide **(406)** from 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(409)** (220mg, 0.34 mmol) as an off-white sticky solid (110mg, 61%).

LC-MS: 530.2 (M+H).

Synthesis of (411):



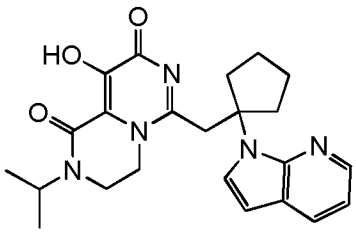
9-Benzyloxy-2-isopropyl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

9-Benzyloxy-2-isopropyl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(411)** was prepared following the same method as 9-benzyloxy-2-methyl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-

pyrazino[1,2-c]pyrimidine-1,8-dione **(407)** from 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(410)** (110 mg, 0.21 mmol) as an off-white solid (40 mg, 38%).

LC-MS: 512.1 (M+H).

Synthesis of (412): (16282)



9-Hydroxy-2-isopropyl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

9-Hydroxy-2-isopropyl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(412)** was prepared following the same method as 9-hydroxy-2-methyl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(408)** from 9-benzyloxy-2-isopropyl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino [1,2-c]pyrimidine-1,8-dione **(411)** (40 mg, 0.08 mmol) as an off-white solid (30 mg, 91%).

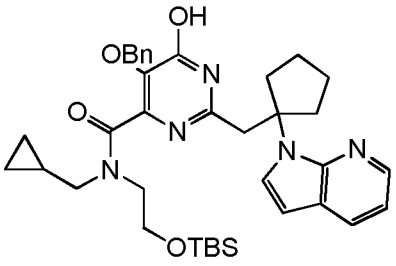
LC-MS: 422.1 (M+H).

Example 416

2-Cyclopropylmethyl-9-hydroxy-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 49.

Synthesis of (413):

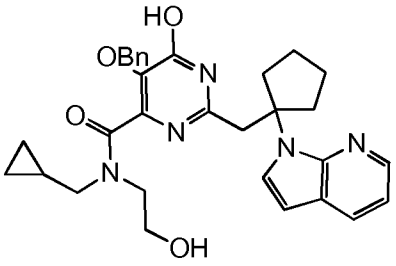


5-Benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropylmethyl-amide

5-Benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropylmethyl-amide **(413)** was prepared following the same method as 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(405)** from 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(404)** (200 mg, 0.45 mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropylmethyl-amine (134 mg, 0.58 mmol) **(8i)** to get off-white sticky solid (180 mg, 61%).

LC-MS: 656.0 (M+H).

Synthesis of (414):

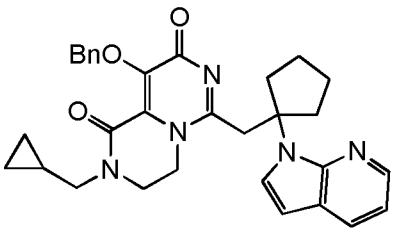


5-Benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid cyclopropylmethyl-(2-hydroxyethyl)-amide

5-Benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid cyclopropylmethyl-(2-hydroxyethyl)-amide **(414)** was prepared following the same method as 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide **(406)** from 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropylmethyl-amide **(413)** (170mg, 0.26mmol) as white sticky solid (140mg, crude).

LC-MS: 542.0 (M+H).

Synthesis of (415):

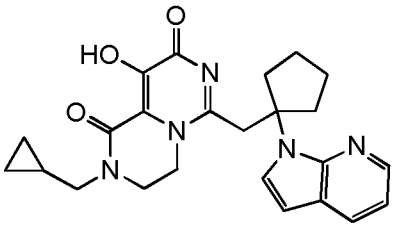


9-Benzyloxy-2-cyclopropylmethyl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

9-Benzyloxy-2-cyclopropylmethyl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(415)** was prepared following the same method as 9-benzyloxy-2-methyl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(407)** from 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid cyclopropylmethyl-(2-hydroxyethyl)-amide **(414)** (130 mg, 0.24 mmol) as white solid (56 mg, 46%).

LC-MS: 524.4 (M+H).

Synthesis of (416): (16289)



2-Cyclopropylmethyl-9-hydroxy-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

2-Cyclopropylmethyl-9-hydroxy-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(416)** was prepared following the same method as 9-hydroxy-2-methyl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(408)** from 9-benzyloxy-2-cyclopropylmethyl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentyl methyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(415)** (50 mg, 0.09 mmol) as an off-white solid (36 mg, 85%).

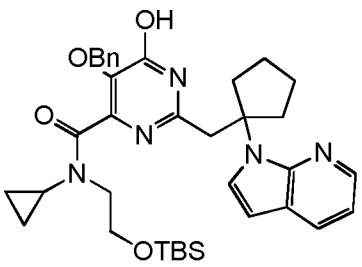
LC-MS: 434.3 (M+H).

Example 420

2-Cyclopropyl-9-hydroxy-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 49.

Synthesis of (417):

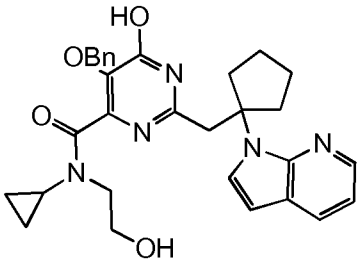


5-Benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropyl-amide

5-Benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropyl-amide **(417)** was prepared following the same method as 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(405)** from 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(404)** (150 mg, 0.34 mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropyl-amine (94 mg, 0.44 mmol) **(8d)** to get white sticky solid (96 mg, 44%).

LC-MS: 642.1 (M+H).

Synthesis of (418):

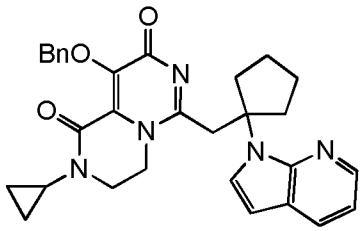


5-Benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid cyclopropyl-(2-hydroxyethyl)-amide

To a stirred solution of 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropyl-amide **(417)** (96 mg, .15 mmol) in THF (3 mL) was added TBAF 1(M) in THF (0.7 mL, 0.75 mmol) at room temperature, stirred for 1 h, THF was removed from the reaction mixture, diluted with ethyl acetate (50 mL), washed with water (2 x 30 mL), brine (30 mL), dried and concentrated to get 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid cyclopropyl-(2-hydroxyethyl)-amide **(418)** (60 mg, crude) as an off-white sticky solid.

LC-MS: 528.2(M+H).

Synthesis of (419):

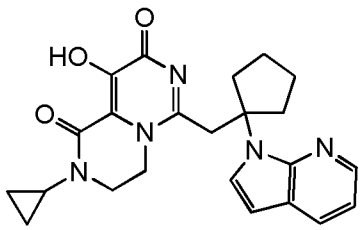


9-Benzyloxy-2-cyclopropyl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

9-Benzyloxy-2-cyclopropyl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(419)** was prepared following the same method as 9-benzyloxy-2-methyl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(407)** from 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid cyclopropyl-(2-hydroxyethyl)-amide **(418)** (60 mg, 0.11 mmol) as white sticky solid (45 mg, 80%).

LC-MS: 510.5 (M+H).

Synthesis of (420): (16303)



2-Cyclopropyl-9-hydroxy-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

2-Cyclopropyl-9-hydroxy-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(420)** was prepared following the same method as 9-hydroxy-2-methyl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(408)** from 9-Benzyloxy-2-cyclopropyl-6-(1-pyrrolo[2,3-

b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(419)** (45 mg, 0.09 mmol) as an off-white solid (35mg, 94%).

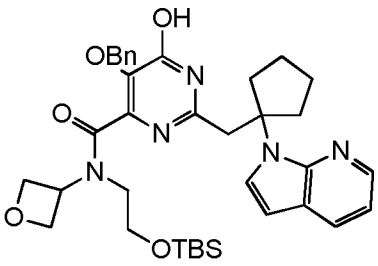
LC-MS: 420.0 (M+H).

Example 424

9-Hydroxy-2-oxetan-3-yl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 49.

Synthesis of (421):

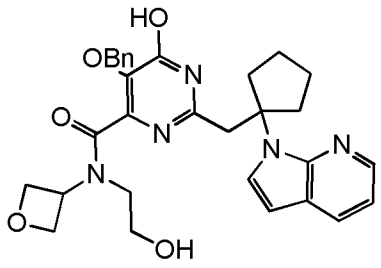


5-Benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-oxetan-3-yl-amide

5-Benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-oxetan-3-yl-amide **(421)** was prepared following the same method as 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(405)** from 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(404)** (125 mg, 0.28 mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-oxetan-3-yl-amine (98 mg, 0.42 mmol) **(8g)** to get white sticky solid (180 mg, 97%, mixture).

LC-MS: 658.1 (M+H).

Synthesis of (422):

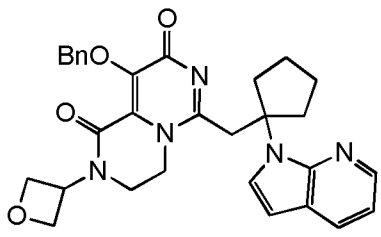


5-Benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-oxetan-3-yl-amide

5-Benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-oxetan-3-yl-amide **(422)** was prepared following the same method as 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid cyclopropyl-(2-hydroxyethyl)-amide **(418)** from 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-oxetan-3-yl-amide **(421)** (180 mg, 0.27 mmol) as light brown sticky solid (220 mg, crude).

LC-MS: 544.0 (M+H).

Synthesis of (423):



9-Benzyloxy-2-oxetan-3-yl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

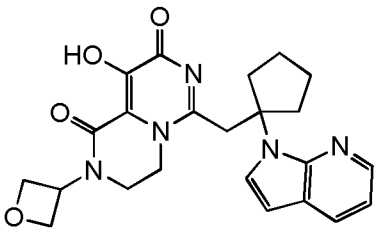
9-Benzyloxy-2-oxetan-3-yl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(423)** was prepared following the same method as 9-benzyloxy-2-methyl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-

pyrazino[1,2-c]pyrimidine-1,8-dione **(407)** from 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-oxetan-3-yl-amide **(422)** (200 mg, 0.40 mmol) as white sticky solid (13 mg, 6%).

LC-MS: 526.3 (M+H)

.

Synthesis of (424): (16297)



9-Hydroxy-2-oxetan-3-yl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

9-Hydroxy-2-oxetan-3-yl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(424)** was prepared following the same method as 9-hydroxy-2-methyl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(408)** from 9-Benzyloxy-2-oxetan-3-yl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(423)** (13 mg, 0.03 mmol) as an off-white solid (8mg, 74%).

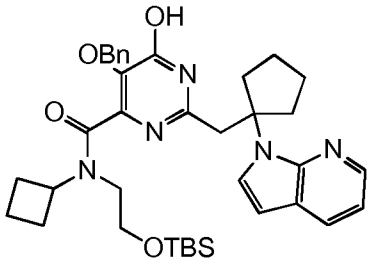
LC-MS: 436.1 (M+H).

Example 428

2-Cyclobutyl-9-hydroxy-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 49.

Synthesis of (425):

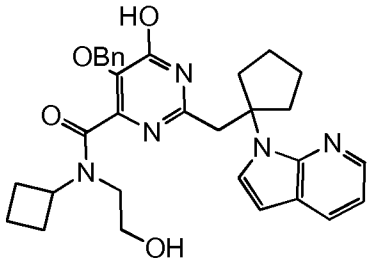


5-Benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclobutyl-amide

5-Benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclobutyl-amide **(425)** was prepared following the same method as 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(405)** from 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(8f)** (140 mg, 0.32 mmol) and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclobutyl-amine (108 mg, 0.47 mmol) to get white sticky solid (200 mg, 97%, impure).

LC-MS: 656.1 (M+H).

Synthesis of (426):

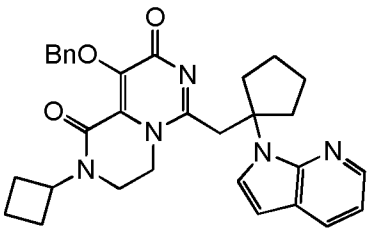


5-Benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid cyclobutyl-(2-hydroxyethyl)-amide

5-Benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid cyclobutyl-(2-hydroxyethyl)-amide **(426)** was prepared following the same method as 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid cyclopropyl-(2-hydroxyethyl)-amide **(418)** from 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclobutyl-amide **(425)** (200 mg, 0.30 mmol) as white solid (100 mg, 59%).

LC-MS: 542.4 (M+H).

Synthesis of (427):

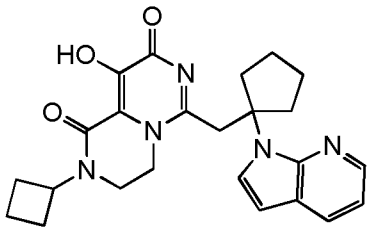


9-Benzyloxy-2-cyclobutyl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

9-Benzyloxy-2-cyclobutyl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(427)** was prepared following the same method as 9-benzyloxy-2-methyl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(407)** from 5-benzyloxy-6-hydroxy-2-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid cyclobutyl-(2-hydroxyethyl)-amide **(426)** (90mg, 0.17mmol) as an off-white solid (65 mg, 75%).

LC-MS: 524.4 (M+H).

Synthesis of (428): (16300)



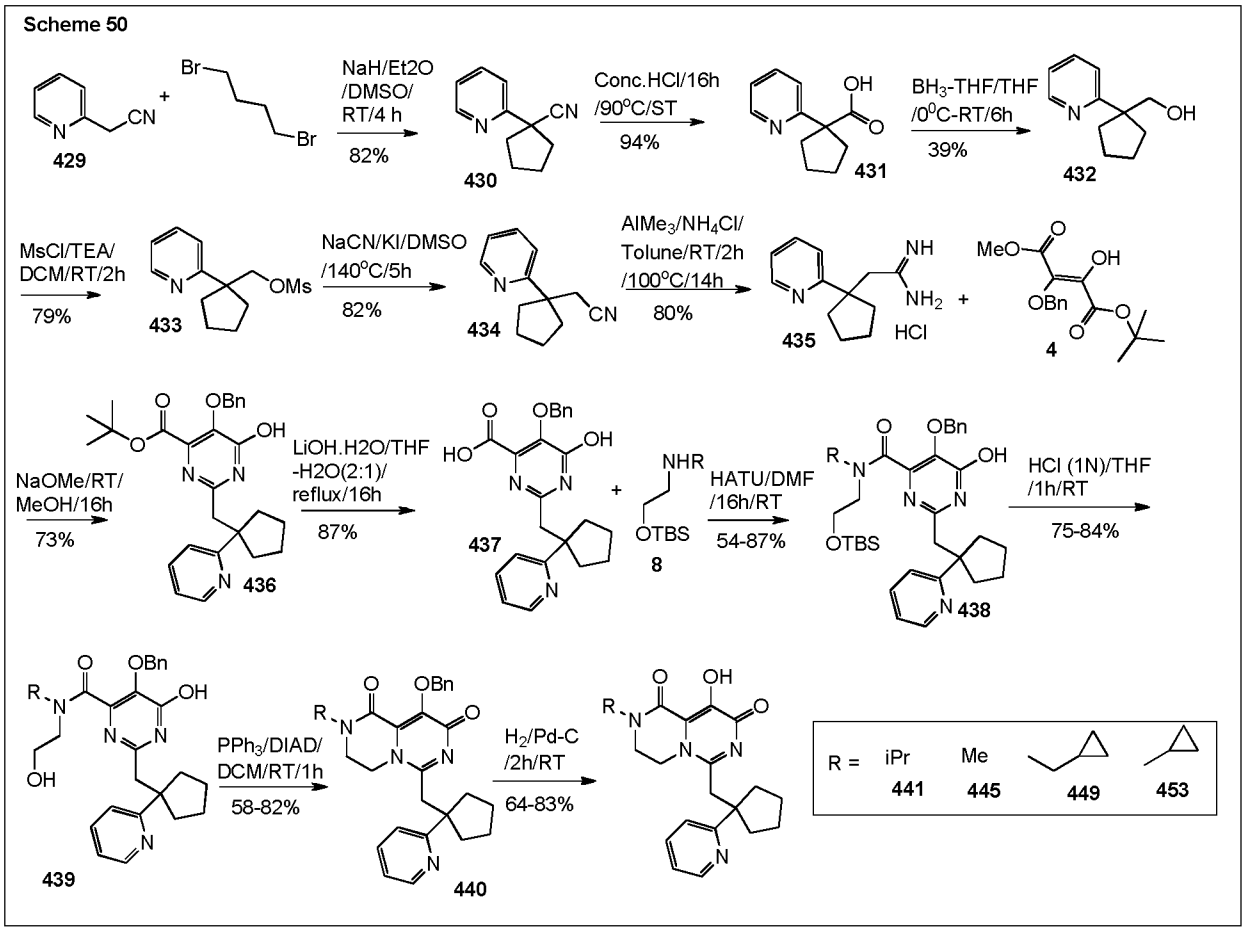
2-Cyclobutyl-9-hydroxy-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

2-Cyclobutyl-9-hydroxy-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(428)** was prepared following the same method as 9-hydroxy-2-methyl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(408)** from 9-benzyloxy-2-cyclobutyl-6-(1-pyrrolo[2,3-b]pyridin-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino [1,2-c]pyrimidine-1,8-dione **(427)** (55 mg, 0.10 mmol) as an off-white solid (37 mg, 81%). LC-MS: 434.2 (M+H).

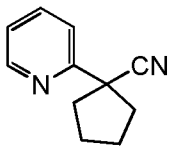
General procedure for examples 429 to 453

The synthetic procedures are outlined in Scheme 50.

General synthetic route for 441, 445, 449, 453



Preparation of (430):



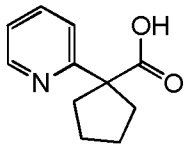
1-Pyridin-2-yl-cyclopentanecarbonitrile

To a suspension of sodium hydride (60%) (0.745g, 18.644mmol) in DMSO (10mL) was added dropwise a mixture of pyridin-2-yl-acetonitrile **(429)** (1g, 8.475mmol) and 1,4-dibromo-butane (1.831g,8.475mmol) dissolved in DMSO-ether (10mL, 1:1) at 0°C and stirred for 30 min at the same temperature and then stirred at room temperature for 4h. After completion of the reaction (monitored by silica TLC, Rf = 0.4, in 10% EtOAc/Hexane) it was quenched with HCl (1N; 10mL). Reaction mixture was diluted water (20mL) and extracted with EtOAc (2x50mL),

combined extracts was washed with water (20mL), brine (2x20mL), dried and concentrated in vacuo to get crude mass which was purified by combi-flash to get 1-pyridin-2-yl-cyclopentanecarbonitrile **(430)** (1.2g, 82%) as color less liquid.

LCMS: 173.0 (M+H)

Preparation of (431):

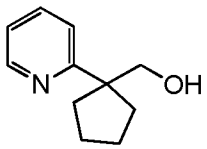


1-Pyridin-2-yl-cyclopentanecarboxylic acid

In a sealed tube 1-pyridin-2-yl-cyclopentanecarbonitrile (**3**) (10g, 58.14mmol) and HCl (12N; 70mL) were taken at room temperature, reaction mixture was stirred at 90°C for 16h Silica thin layer chromatography was performed (20% EtOAc/Hexane; Rf = 0.1). Reaction mixture was concentrated; azeotropped with toluene and residue was triturated with ether to get 1-pyridin-2-yl-cyclopentanecarboxylic acid **(431)** (10.5g, 94%) as white solid.

LCMS: 191.8 (M+H).

Preparation of (432):



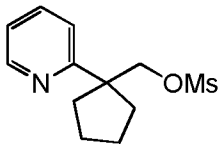
(1-Pyridin-2-yl-cyclopentyl)-methanol

To a stirred solution of 1-pyridin-2-yl-cyclopentanecarboxylic acid **(431)** (5g, 26.178mmol) in THF, added BH_3.THF (1M) (52.36mL) at 0°C, stirred for 1h, then this reaction mixture was allowed to stir at room temperature for 5h Silica thin layer chromatography was performed (50% EtOAc in Hexane; Rf = 0.5). Reaction was quenched with saturated NH_4Cl (30mL) at 0°C, reaction mass was diluted with water (50mL), extracted with 10% MeOH in DCM

(2X200mL), combined organic parts was dried, concentrated, resulted crude was purified by normal silica gel (100-200 mesh) column chromatography using 30% EtOAc in hexane as eluent to get (1-pyridin-2-yl-cyclopentyl)-methanol **(432)** (1.8g, 39%) as colorless liquid.

LCMS: 177.8 (M+H).

Preparation of (433):

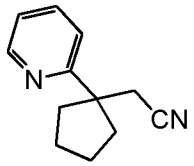


Methanesulfonic acid 1-pyridin-2-yl-cyclopentylmethyl ester

To a stirred solution of (1-pyridin-2-yl-cyclopentyl)-methanol **(432)** (1.8g, 10.169mmol) in DCM (20mL), TEA (2.827mL, 20.339mmol), and mesylchloride (0.94mL, 12.203mmol) were added at 0°C, it was allowed to stir for 2h at room temperature Silica thin layer chromatography was performed (50% EtOAc in hexane; Rf = 0.6). Reaction was quenched with water (30mL), extracted with DCM (2X70mL), organic part was dried, concentrated, resulted crude was purified by normal silica gel (100-200 mesh) column chromatography using 25% EtOAc in hexane as eluent to get methanesulfonic acid 1-pyridin-2-yl-cyclopentylmethyl ester **(433)** (2.05g, 79%) as white solid.

LCMS: 255.6 (M+H).

Preparation of (434):



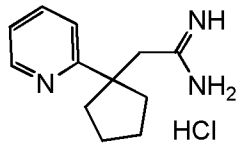
(1-Pyridin-2-yl-cyclopentyl)-acetonitrile

To a stirred solution of methanesulfonic acid 1-pyridin-2-yl-cyclopentylmethyl ester **(433)** (2g, 7.843mmol) in DMSO (15mL), KI (0.13g, 0.784mmol), NaCN (0.769g, 15.686mmol) were

added, reaction was subjected to heating at 140°C for 5h. Reaction mixture was quenched with ice cold water (50mL), and extracted with EtOAc (2x70mL), combined extracts was washed with brine, dried, concentrated, resulted crude was purified by normal silica gel (100-200 mesh) column chromatography using 15% EtOAc in hexane as eluent to get (1-pyridin-2-yl-cyclopentyl)-acetonitrile **(434)** (1.2g, 82%) as colorless liquid.

LCMS: 186.8 (M+H).

Preparation of (435):

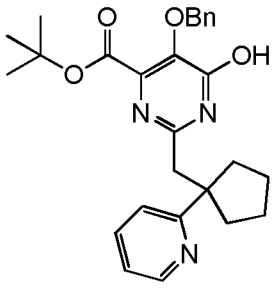


2-(1-Pyridin-2-yl-cyclopentyl)-acetamidine hydrochloride

To a stirred suspension of NH_4Cl (1.05g, 19.355mmol) in dry toluene (15mL) was added trimethyl aluminum (2M) (5.2mL, 10.323mmol) at 5°C then warm to room temperature and stirred for 2h. A solution of (1-pyridin-2-yl-cyclopentyl)-acetonitrile **(434)** (1.2g, 6.45mmol) in toluene (5mL) was added to above reaction mass and stirred for 14h at 100°C. After completion of the reaction, it was quenched with suspension of silica gel (5g) in chloroform (30mL) and reaction mixture was stirred for half an hour at room temperature. It was filtered through a sintered funnel, residue (silica gel) was washed with methanol (30mL), combined filtrate was concentrated, resulted crude mass was stirred with 10%MeOH in DCM (100mL), generated suspension was filtered; filtrate was concentrated under reduced pressure to get 2-(1-pyridin-2-yl-cyclopentyl)-acetamidine hydrochloride **(435)** (1.05g, 80%) as white solid.

LCMS: 203.9 (M+H).

Preparation of (436):

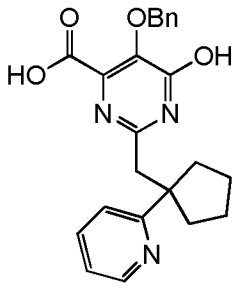


5-Benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid tert-butyl ester

To a stirred solution of 2-(1-pyridin-2-yl-cyclopentyl)-acetamidine hydrochloride **(435)** (1g, 3.55mmol) and 2-benzyloxy-3-hydroxy-but-2-enedioic acid 4-tert-butyl ester 1-methyl ester **(4)** (1.638g, 5.319mmol) in methanol (15mL), NaOMe (25% in methanol) (2.3mL, 10.638mmol) was added dropwise at 0°C. Then reaction mixture was allowed to stir at room temperature for 16h. Then reaction mixture was quenched with aqueous HCl (1N; 5mL), methanol was removed under reduced pressure, diluted with water (20mL) and extracted with EtOAc (2x50mL). Combined organic part was dried, concentrated, resulted was purified by normal silica gel (100-200 mesh) column chromatography using 30% EtOAc in hexane as eluent 5-benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid tert-butyl ester **(436)** (1.2g, 73%) as yellow sticky liquid.

LCMS: 461.9 (M+H).

Preparation of (437):



5-Benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid

To a stirred solution of 5-benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid tert-butyl ester **(436)** (1.2g, 2.60mmol) in THF-water (2:1; 24mL), $LiOH.H_2O$ (1.09g, 26.03mmol) was added, refluxed for 16h Silica thin layer chromatography was performed (50% EtOAc in hexane, Rf = 0.1). From the reaction mixture volatiles were removed, residue was diluted with water (20mL), pH was adjusted to 7 with (1N) aqueous HCl. Resulted precipitate filtered and dried. Obtained solid was triturated with ether to get 5-benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(437)** (920mg, 87%) as white solid.

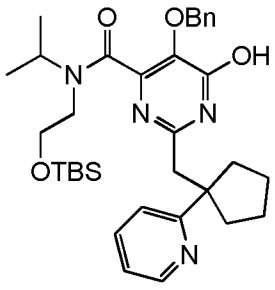
LCMS: 406.1 (M+H).

Example 441

9-Hydroxy-2-isopropyl-6-(1-pyridin-2-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 50.

Preparation of (438):



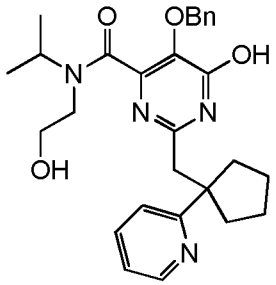
5-Benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylicacid[2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide

To a stirred solution of 5-benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(437)** (180mg, 0.44mmol) in DMF (5mL), DIPEA (0.22mL, 1.33mmol), HATU (253.5mg, 0.667mmol), and [2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amine **(8b)** were added, then this reaction mixture was allowed to stir for 16h at room temperature Silica thin layer chromatography was performed (50% EtOAc in hexane; Rf = 0.5). Reaction was

quenched with ice cold water (20mL), extracted with EtOAc (2x30mL), combined extracts was dried, concentrated under vacuo, resulted crude was purified by normal silica gel (100-200 mesh) column chromatography using 30-40% ethylacetate in hexane as gradient polarity mobile phase to get 5-benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylicacid[2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(438)** (160mg, 60%) as yellow gummy liquid.

LCMS: 605.1 (M+H).

Preparation of (439):

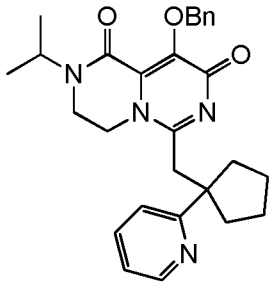


5-Benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylicacid (2-hydroxyethyl)-isopropyl-amide

To a stirred solution 5-benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylicacid[2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(438)** (150mg, 0.248mmol) of in THF (4mL), was added 1N HCl (1mL), then this reaction mixture was stirred for 1h, at room temperature, After completion of the reaction, volatile substances were removed the from the reaction, then dilute with water (10mL) and adjust with NaHCO3 to pH8, then extract with EtOAc (2 X 30mL), then organic part was dried over Na2SO4, then concentrated, resulted crude was purified by normal silica gel (100-200 mesh) column chromatography using 50-60% ethylacetate in hexane as gradient polarity mobile phase to get 5-benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylicacid (2-hydroxyethyl)-isopropyl-amide **(439)** (100mg, 82%) as white sticky liquid.

LCMS: 491.2 (M+H).

Preparation of (440):

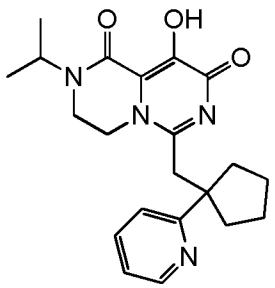


9-Benzyloxy-2-isopropyl-6-(1-pyridin-2-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a stirred solution of 5-benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylicacid (2-hydroxyethyl)-isopropyl-amide **(439)** (70mg, 0.143mmol), in DCM (10mL), TPP (131mg, 0.5mmol) DIAD (0.084mL, 0.429mmol) were added, stirred for 1h at room temperature Silica thin layer chromatography was performed (100% EtOAc, Rf =0.2). After completion of the reaction water (10mL) was added, extract with DCM (2X30mL). then organic part was dried over Na_2SO_4, then concentrated, resulted crude was purified by normal silica gel (100-200 mesh) column chromatography using 70-80% ethylacetate in hexane as gradient polarity mobile phase to get 9-benzyloxy-2-isopropyl-6-(1-pyridin-2-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(440)** (60.0mg, 90.2%) as white sticky liquid.

LCMS: 473.1 (M+H).

Preparation of (441):



9-Hydroxy-2-isopropyl-6-(1-pyridin-2-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a stirred solution of 9-benzyloxy-2-isopropyl-6-(1-pyridin-2-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(440)** (50mg, 0.106mmol) in ethanol (5mL), Pd-C(10% w/w, 10mg) was added, reaction mixture was allowed to stir for 1h, in hydrogen atmosphere at balloon pressure Silica thin layer chromatography was performed (10%MeOH in DCM; Rf = 0.3). After completion of the reaction, reaction mixture was filtered through celite bed, and concentrated resulted crude purified by normal silica gel (100-200 mesh) column chromatography using 2-5% MeOH in DCM as gradient polarity mobile phase to get 9-hydroxy-2-isopropyl-6-(1-pyridin-2-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(441)** (26mg, 64%) as an off-white solid.

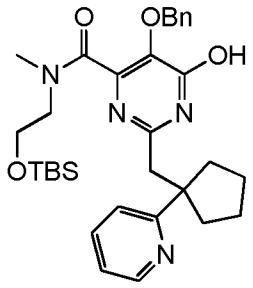
LCMS: 383.0 (M+H).

Example 445

9-Hydroxy-2-methyl-6-(1-pyridin-2-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 50.

Preparation of (442):



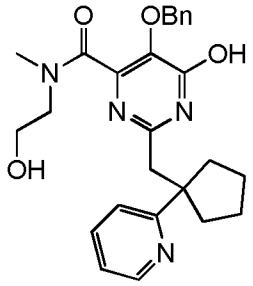
5-Benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide

To a stirred solution of 5-benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(437)** (200mg, 0.494mmol) in DMF (7mL), DIPEA (0.245mL, 1.481mmol), HATU (281.7mg, 0.741mmol), and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amine **(8a)** were added, then this reaction mixture was allowed to stir for 16h at room temperature Silica

thin layer chromatography was performed (70% EtOAc in hexane, Rf = 0.5). Reaction mixture was quenched with ice cold water (20mL), extracted with EtOAc (2X50mL), organic part was dried, concentrated, resulted crude was purified by normal silica gel (100-200 mesh) column chromatography using 30-40% ethylacetate in hexane as gradient polarity mobile phase to get 5-benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(442)** (220mg, 77%) as yellow gummy liquid.

LCMS: 577.1 (M+H).

Preparation of (443):

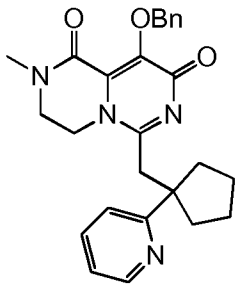


5-Benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylicacid (2-hydroxyethyl)-methyl-amide

To a stirred solution 5-benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(442)** (180mg, 0.313mmol) of in THF (10mL), was added 1N HCl (2mL), then this reaction mixture was stirred for 1h, at room temperature, After completion of the reaction, volatiles were removed the from the reaction mixture, residue was diluted with water (10mL) and pH was adjusted with $NaHCO_3$ to ~8, quenched mass was extracted with EtOAc (2 X 50mL), combined extracts was dried, concentrated, resulted crude was purified by normal silica gel (100-200 mesh) column chromatography using 50-60% ethylacetate in hexane as gradient polarity mobile phase to get 5-benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide **(443).**

LCMS: 463.0 (M+H).

Preparation of (444):

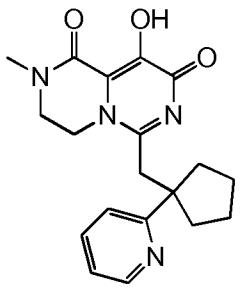


9-Benzyloxy-2-methyl-6-(1-pyridin-2-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a stirred solution of 5-benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide **(443)** (90mg, 0.195mmol), in DCM (10mL), TPP (178.64mg, 0.682mmol) DIAD (0.115mL, 0.584mmol) were added, stirred for 1h at room temperature Silica thin layer chromatography was performed (3%MeOH in EtOAc; Rf = 0.2). After completion of the reaction water (5mL) was added, extracted with DCM (2X30mL), organic part was dried, concentrated, resulted crude was purified by normal silica gel (100-200 mesh) column chromatography using 60-70% ethylacetate in hexane as gradient polarity mobile phase to get 9-benzyloxy-2-methyl-6-(1-pyridin-2-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(444)** (71mg, 82%) as white solid.

LCMS: 445.0 (M+H).

Preparation of (445):



9-Hydroxy-2-methyl-6-(1-pyridin-2-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a stirred solution of 9-benzyloxy-2-methyl-6-(1-pyridin-2-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(444)** (60mg, 0.135mmol) in ethanol (5mL), Pd-C (10%, w/w; 10mg) was added, reaction mixture was allowed to stir for 1h, in hydrogen atmosphere at balloon pressure, Silica thin layer chromatography was performed (10%MeOH in DCM, Rf = 0.3). After completion of the reaction, reaction mixture was filtered through celite bed, and concentrated resulted crude was triturated with 70% EtOAc in hexane to get 9-hydroxy-2-methyl-6-(1-pyridin-2-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(445)** (31mg, 65%) as white solid.

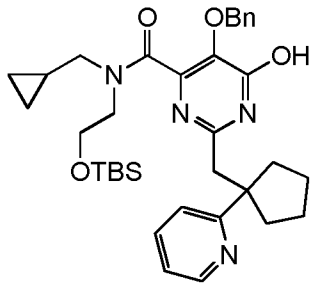
LCMS: 355.0 (M+H).

Example 449

2-Cyclopropylmethyl-9-hydroxy-6-(1-pyridin-2-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 50.

Preparation of (446):



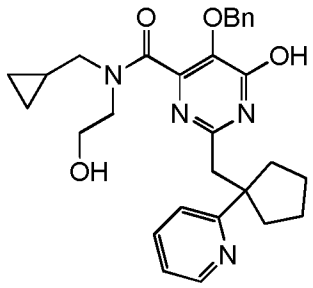
5-Benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylicacid[2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropylmethyl-amide

To a stirred solution of 5-benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(437)** (150mg, 0.37mmol) in DMF (5mL), DIPEA (0.184mL, 1.111mmol), HATU (211.24mg, 0.556mmol), and [2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-cyclopropylmethyl-amine **(8i)** were added, then this reaction mixture was allowed to stir for 16h at room temperature Silica thin layer chromatography was performed (50% EtOAc in

hexane; Rf = 0.5), Reaction was quenched with ice cold water (25mL) then extracted with EtOAc (2X 30mL), organic part was dried, concentrated, resulted crude was purified by normal silica gel (100-200 mesh) column chromatography using 30-40% ethylacetate in hexane as gradient polarity mobile phase to get 5-benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylicacid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropylmethyl-amide **(446)** (198mg, 87%) as colorless gummy liquid.

LCMS: 617.2 (M+H).

Preparation of (447):

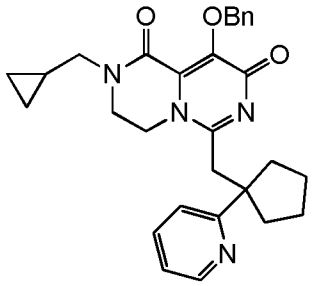


5-Benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylicacidcyclopropylmethyl-(2-hydroxyethyl)-amide

To a stirred solution 5-benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylicacid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropylmethyl-amide **(446)** (200mg, 0.325mmol) of in THF (10mL), was added (1N) aqueous HCl (2mL), it was stirred for 1h, at room temperature, After completion of the reaction, volatiles were removed, diluted with water (10mL) and pH was adjusted using $NaHCO_3$ to ~8, it was extracted with EtOAc (2 X 30mL), then organic part was dried, concentrated, resulted crude was purified by normal silica gel (100-200 mesh) column chromatography using 50-60% ethylacetate in hexane as gradient polarity mobile phase to get 5-benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid cyclopropylmethyl-(2-hydroxyethyl)-amide **(447)** (123mg, 75%) as colorless gummy liquid.

LCMS: 503.1 (M+H).

Preparation of (448):

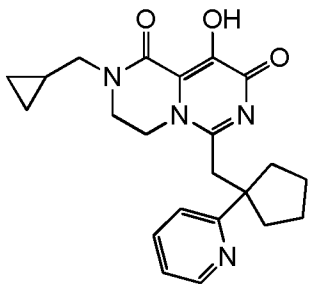


9-Benzyloxy-2-cyclopropylmethyl-6-(1-pyridin-2-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimdine-1,8-dione

To a stirred solution of 5-benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylicacidcyclopropylmethyl-(2-hydroxyethyl)-amide **(447)** (80mg, 0.159mmol), in DCM (5mL), TPP (146.13mg, 0.558mmol), DIAD (0.094mL, 0.478mmol) were added, stirred for 1h at room temperature Silica thin layer chromatography was performed (100% EtOAc; Rf = 0.2). After completion of the reaction water (5mL) was added, extracted with DCM (2X30mL), dried, concentrated, resulted crude was purified by normal silica gel (100-200) column chromatography using 60-70% ethylacetate in hexane as gradient polarity mobile phase to get 9-benzyloxy-2-cyclopropylmethyl-6-(1-pyridin-2-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimdine-1,8-dione **(448)** (45.0mg, 58%) as white solid.

LCMS: 485.0 (M+H).

Preparation of (449):



2-Cyclopropylmethyl-9-hydroxy-6-(1-pyridin-2-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a stirred solution of 9-benzyloxy-2-cyclopropylmethyl-6-(1-pyridin-2-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimdine-1,8-dione **(448)** (40mg, 0.083mmol) in ethanol (3mL), Pd-C (10%, w/w, 10mg) was added, then reaction mixture was allowed stir for 1h, in hydrogen atmosphere at balloon pressure Silica thin layer chromatography was performed (10%MeOH in DCM; Rf = 0.3). After completion of the reaction, reaction mixture was filtered through celite bed, and concentrated, resulted crude was triturated with 70% EtOAc in hexane to get 9-hydroxy-2-methyl-6-(1-pyridin-2-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(449)** (27mg, 83%) as an off-white solid.

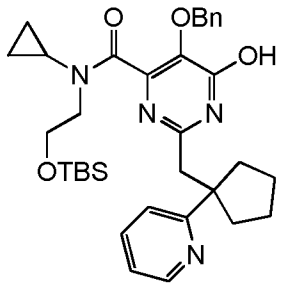
LCMS: 395.0 (M+H).

Example 453

2-Cyclopropyl-9-hydroxy-6-(1-pyridin-2-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

The synthetic procedure used in this preparation is outlined in Scheme 50.

Preparation of (450):



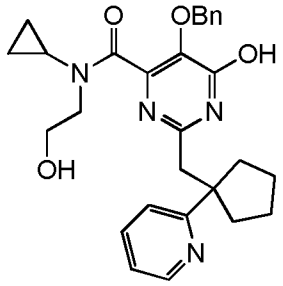
5-Benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropyl-amide

To a stirred solution of 5-benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(437)** (150mg, 0.494mmol) in DMF (5mL), DIPEA (0.184mL, 1.111mmol), HATU (211.24mg, 0.556mmol), and [2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-cyclopropyl-amine (crude) **(8d)** (239mg) were added, then this reaction mixture was allowed to stir for 16h at room temperature Silica thin layer chromatography was performed (50% EtOAc in hexane;

Rf = 0.5). Reaction was quenched with ice cold water (25mL), extracted with EtOAc (2X 30mL), organic part was dried, then concentrated, crude was purified by normal silica gel (100-200 mesh) column chromatography using 30-40% ethylacetate in hexane as gradient polarity mobile phase to get 5-benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylicacid[2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropyl-amide **(450)** (120mg, 54%) as yellow sticky liquid.

LCMS: 603.0 (M+H).

Preparation of (451):

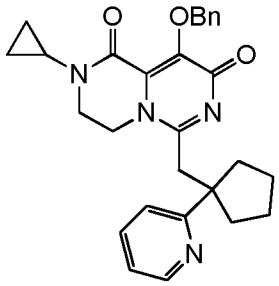


5-Benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylicacidcyclopropyl-(2-hydroxyethyl)-amide

To a stirred solution 5-benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclopropyl-amide **(450)** (120mg, 0.199mmol) of in THF (6mL), was added (1N) aqueous HCl (1.5mL), stirred for 1h, at room temperature. After completion of the reaction, volatiles were removed, residue was diluted with water (10mL) and pH was adjusted by using $NaHCO_3$ to ~8, extracted with EtOAc (2 X 30mL), combined extracts was dried, concentrated, resulted crude was purified by normal silica gel (100-200 mesh) column chromatography using 50-60% ethylacetate in hexane as gradient polarity mobile phase to get 5-benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylicacidcyclopropyl-(2-hydroxyethyl)-amide **(451)** (80mg, 82%) as colorless gummy liquid.

LCMS: 489.1 (M+H).

Preparation of (452):

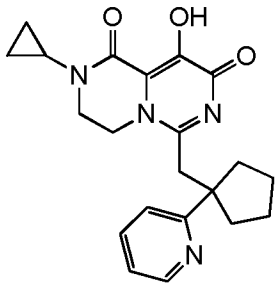


9-Benzyloxy-2-cyclopropyl-6-(1-pyridin-2-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a stirred solution of 5-benzyloxy-6-hydroxy-2-(1-pyridin-2-yl-cyclopentylmethyl)-pyrimidine-4-carboxylicacidcyclopropyl-(2-hydroxyethyl)-amide **(451)** (80mg, 0.164mmol), in DCM (6mL), TPP (150.33mg, 0.574mmol) and, DIAD (0.097mL, 0.492mmol) were added, stirred for 1h at room temperature Silica thin layer chromatography was performed (100%EtOAc, Rf = 0.2). After completion of the reaction water (5mL) was added, extracted with DCM (2X25mL), combined extarcts was dried, concentrated, to get crude 9-benzyloxy-2-cyclopropyl-6-(1-pyridin-2-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(452)** (270mg, Crude) as yellow gummy liquid.

LCMS: 471.0 (M+H).

Preparation of (453):



2-Cyclopropyl-9-hydroxy-6-(1-pyridin-2-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione

To a stirred solution of 9-benzyloxy-2-cyclopropyl-6-(1-pyridin-2-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(452)** (250mg, crude) in aceticacid (4mL), Conc.H_2SO_4 (0.001mL) was added and stirred for 2h at room temperature (monitored by LCMS). Volatiles were removed from the reaction mixture, quenched with ice water (10mL), pH was adjusted to ~ 8 using $NaHCO_3$, extracted with 10% MeOH in DCM (2x40mL), organic part was dried, concentrated resulted crude was purified by prep HPLC to get 2-cyclopropyl-9-hydroxy-6-(1-pyridin-2-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(453)** (17.3mg, 30% 2 steps) as an off-white solid.

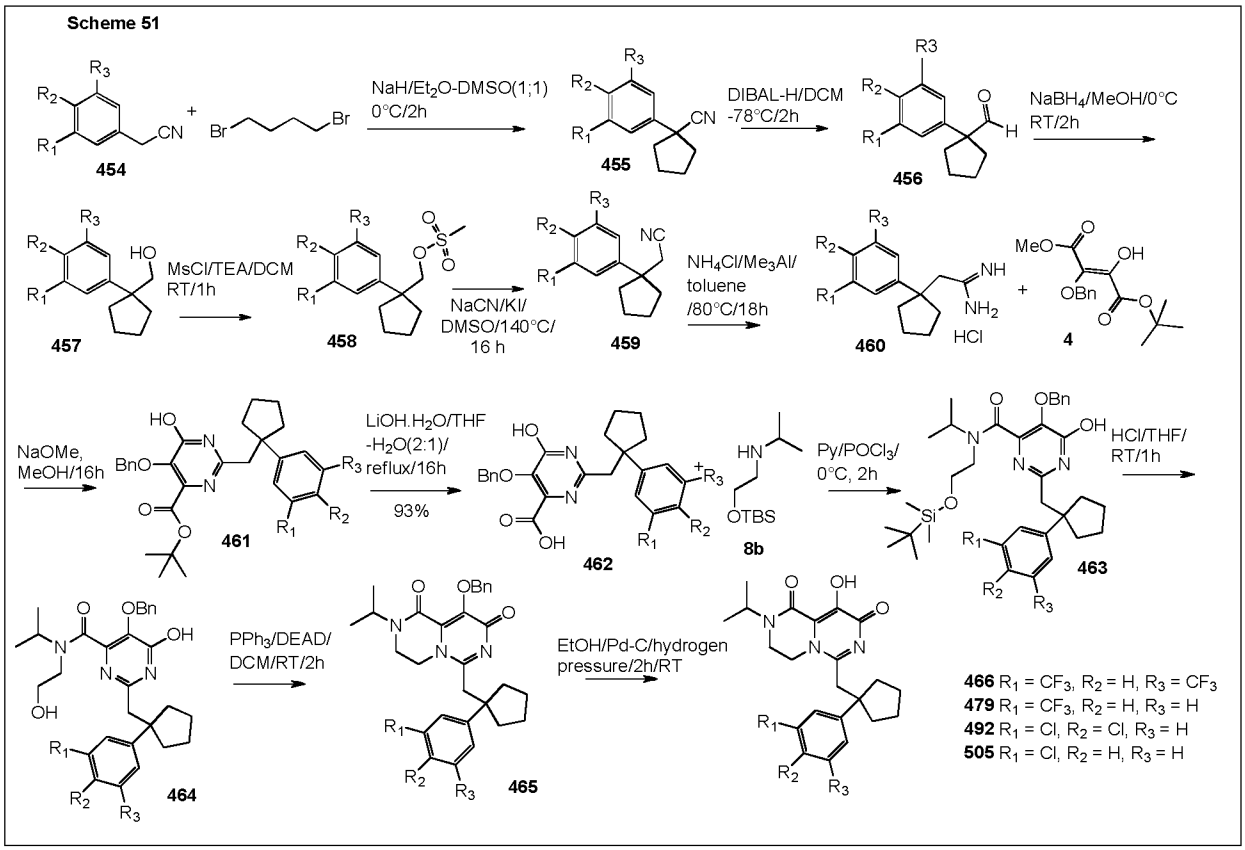
LCMS: 380.9 (M+H).

General procedure for examples 454 to 505

The synthetic procedures are outlined in Scheme 51.

General synthetic route for 466, 479, 492, 505

Scheme 51

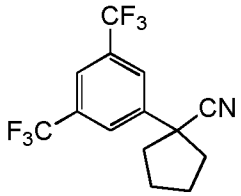


Example 466

6-((1-(3,5-bis(trifluoromethyl)phenyl)cyclopentyl)methyl)-9-hydroxy-2-isopropyl-3,4-dihydro-1*H*-pyrazino[1,2-c]pyrimidine-1,8(2*H*)-dione

The synthetic procedure used in this preparation is outlined in Scheme 51.

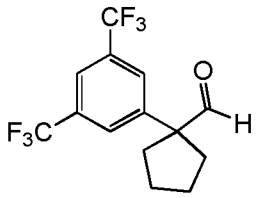
Preparation of (455):



Step:1 1-(3,5-bis(trifluoromethyl)phenyl)cyclopentanecarbonitrile

1-(3,5-bis(trifluoromethyl)phenyl)cyclopentanecarbonitrile **(455)** was synthesized from 2-(3,5-bis(trifluoromethyl)phenyl)acetonitrile **(454)** and 1, 4-dibromobutane following the procedure described for 1-(4-trifluoromethyl-phenyl)-cyclopentanecarbonitrile **(237).**

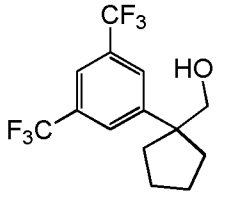
Preparation of (456):



Step 2: 1-(3,5-bis(trifluoromethyl)phenyl)cyclopentanecarbaldehyde

1-(3,5-bis(trifluoromethyl)phenyl)cyclopentanecarbaldehyde **(456)** was synthesized as a colourless liquid from 1-(3,5-bis(trifluoromethyl)phenyl)cyclopentanecarbonitrile **(455)** following the procedure described for 1-(4-trifluoromethyl-phenyl)-cyclopentanecarbaldehyde **(238).**

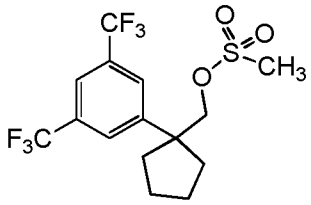
Preparation of (457):



Step 3: ((1-(3,5-bis(trifluoromethyl)phenyl)cyclopentyl)methanol

(1-(3,5-bis(trifluoromethyl)phenyl)cyclopentyl)methanol **(457)** was synthesized as a colourless liquid from 1-(3,5-bis(trifluoromethyl)phenyl)cyclopentanecarbaldehyde **(456)** following the procedure described for 1-(4-trifluoromethyl-phenyl)-cyclopentane-methanol **(239).**

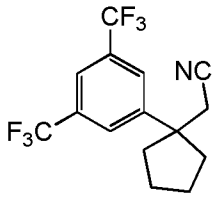
Preparation of (458):



Step 4: (1-(3,5-bis(trifluoromethyl)phenyl)cyclopentyl)methyl methanesulfonate

(1-(3,5-bis(trifluoromethyl)phenyl)cyclopentyl)methyl methanesulfonate **(458)** was synthesized from ((1-(3,5-bis(trifluoromethyl)phenyl)cyclopentyl)methanol **(457)** following the procedure described for Methanesulfonic acid 1-(4-trifluoromethyl -phenyl)-cyclopentylmethyl ester **(240).**

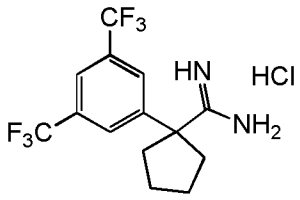
Preparation of (459):



Step 5: 2-(1-(3,5-bis(trifluoromethyl)phenyl)cyclopentyl)acetonitrile

2-(1-(3,5-bis(trifluoromethyl)phenyl)cyclopentyl)acetonitrile **(459)** was synthesized as a brown solid from (1-(3,5-bis(trifluoromethyl)phenyl)cyclopentyl)methyl methanesulfonate **(458)** following the procedure described for [1-(4-trifluoromethyl-phenyl)-cyclopentyl]-acetonitrile **(241).**

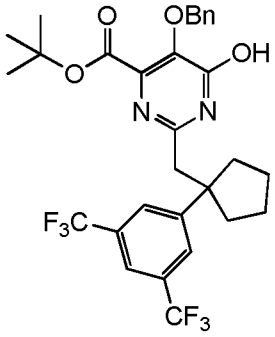
Preparation of (460):



Step 6: 2-(1-(3,5-bis(trifluoromethyl)phenyl-cyclopentyl)-acetamidine hydrochloride

2-(1-(3,5-bis(trifluoromethyl)phenyl-cyclopentyl)-acetamidine hydrochloride **(460)** was synthesized as a white solid from 2-(1-(3,5-bis(trifluoromethyl)phenyl)cyclopentyl)acetonitrile **(459)** following the procedure described for HCl-salt of 2-[1-(4-trifluoromethyl-phenyl)-cyclopentyl]-acetamidine hydrochloride **(242)**.

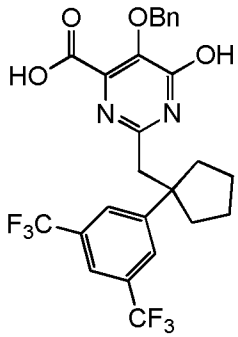
Preparation of (461):



tert-butyl 5-(benzyloxy)-2-((1-(3,5-bis(trifluoromethyl)phenyl)cyclopentyl)methyl)-6-hydroxypyrimidine-4-carboxylate

tert-butyl 5-(benzyloxy)-2-((1-(3,5-bis(trifluoromethyl)phenyl)cyclopentyl)methyl)-6-hydroxypyrimidine-4-carboxylate **(461)** was synthesized as a white solid from 2-(1-(3,5-bis(trifluoromethyl)phenyl-cyclopentyl)-acetamidine hydrochloride **(460)** following the procedure described for 5-benzyloxy-2-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid *tert*-butyl ester **(243)**

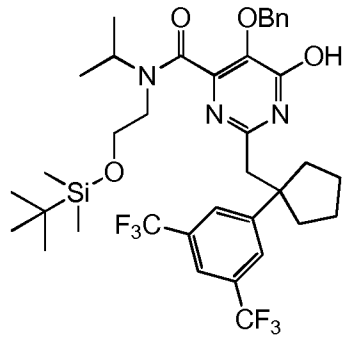
Preparation of (462):



5-(benzyloxy)-2-((1-(3,5-bis(trifluoromethyl)phenyl)cyclopentyl)methyl)-6-hydroxypyrimidine-4-carboxylic acid

5-(benzyloxy)-2-((1-(3,5-bis(trifluoromethyl)phenyl)cyclopentyl)methyl)-6-hydroxypyrimidine-4-carboxylic acid **(462)** was synthesized as a white solid from *tert*-butyl 5-(benzyloxy)-2-((1-(3,5-bis(trifluoromethyl)phenyl)cyclopentyl)methyl)-6-hydroxypyrimidine-4-carboxylate **(461)** following the procedure described for 5-benzyloxy-2-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid **(244)**.

Preparation of (463):

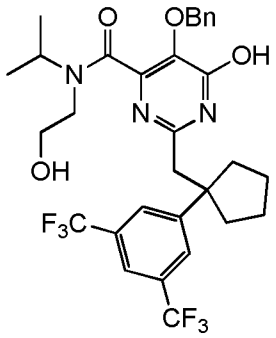


5-(benzyloxy)-2-((1-(3,5-bis(trifluoromethyl)phenyl)cyclopentyl)methyl)-N-(2-((tert-butyldimethylsilyl)oxy)ethyl)-6-hydroxy-N-isopropylpyrimidine-4-carboxamide

5-(benzyloxy)-2-((1-(3,5-bis(trifluoromethyl)phenyl)cyclopentyl)methyl)-N-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-6-hydroxy-N-isopropylpyrimidine-4-carboxamide **(463)** was synthesized from 5-(benzyloxy)-2-((1-(3,5-bis(trifluoromethyl)phenyl)cyclopentyl)methyl)-6-

hydroxypyrimidine-4-carboxylic acid **(462)** and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amine **(8b)** following the procedure described for 5-benzyloxy-2-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(245).**

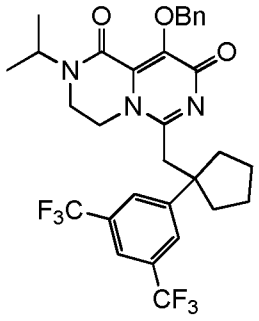
Preparation of (464):



5-(benzyloxy)-2-((1-(3,5-bis(trifluoromethyl)phenyl)cyclopentyl)methyl)-6-hydroxy-N-(2-hydroxyethyl)-N-isopropylpyrimidine-4-carboxamide

5-(benzyloxy)-2-((1-(3,5-bis(trifluoromethyl)phenyl)cyclopentyl)methyl)-6-hydroxy-N-(2-hydroxyethyl)-N-isopropylpyrimidine-4-carboxamide **(464)** was synthesized form 5-(benzyloxy)-2-((1-(3,5-bis(trifluoromethyl)phenyl)cyclopentyl)methyl)-N-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-6-hydroxy-N-isopropylpyrimidine-4-carboxamide **(463)** following the procedure described 5-benzyloxy-2-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(246).**

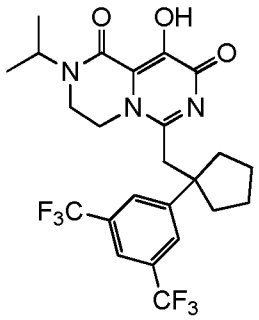
Preparation of (465):



9-(benzyloxy)-6-((1-(3,5-bis(trifluoromethyl)phenyl)cyclopentyl)methyl)-2-isopropyl-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione

9-(benzyloxy)-6-((1-(3,5-bis(trifluoromethyl)phenyl)cyclopentyl)methyl)-2-isopropyl-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione **(465)** was synthesized as a white solid from 5-(benzyloxy)-2-((1-(3,5-bis(trifluoromethyl)phenyl)cyclopentyl)methyl)-6-hydroxy-N-(2-hydroxyethyl)-N-isopropylpyrimidine-4-carboxamide **(464)** following the procedure described for 9-benzyloxy-6-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(247)**.

Preparation of (466):



6-((1-(3,5-bis(trifluoromethyl)phenyl)cyclopentyl)methyl)-9-hydroxy-2-isopropyl-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione

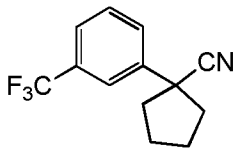
6-((1-(3,5-bis(trifluoromethyl)phenyl)cyclopentyl)methyl)-9-hydroxy-2-isopropyl-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione **(466)** was synthesized as a white solid from 9-(benzyloxy)-6-((1-(3,5-bis(trifluoromethyl)phenyl)cyclopentyl)methyl)-2-isopropyl-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione **(465)** following the procedure described for 6-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(248)**.

Example 479

9-hydroxy-2-isopropyl-6-((1-(3-(trifluoromethyl)phenyl)cyclopentyl)methyl)-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione

The synthetic procedure used in this preparation is outlined in Scheme 51.

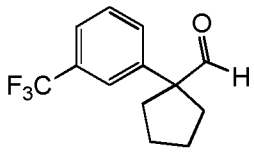
Preparation of (468):



Step:1 1-(3-(trifluoromethyl)phenyl)cyclopentanecarbonitrile

1-(3-(trifluoromethyl)phenyl)cyclopentanecarbonitrile **(468)** was synthesized from 2-(3-(trifluoromethyl)phenyl)acetonitrile **(467)** and 1,4-dibromobutane following the procedure described for 1-(4-trifluoromethyl-phenyl)-cyclopentanecarbonitrile **(237).**

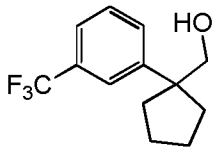
Preparation of (469):



Step 2: 1-(3-(trifluoromethyl)phenyl)cyclopentanecarbaldehyde

1-(3-(trifluoromethyl)phenyl)cyclopentanecarbaldehyde **(469)** was synthesized from 1-(3-(trifluoromethyl)phenyl)cyclopentanecarbonitrile **(468)** following the procedure described for 1-(4-trifluoromethyl-phenyl)-cyclopentanecarbaldehyde **(238).**

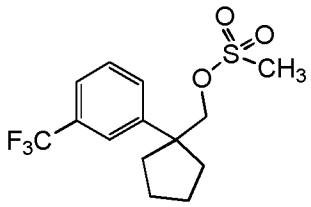
Preparation of (470):



Step 3: ((1-(3-(trifluoromethyl)phenyl)cyclopentyl)methanol

(1-(3-(trifluoromethyl)phenyl)cyclopentyl)methanol **(470)** was synthesized from 1-(3-(trifluoromethyl)phenyl)cyclopentanecarbaldehyde **(469)** following the procedure described for 1-(4-trifluoromethyl-phenyl)-cyclopentane-methanol **(239).**

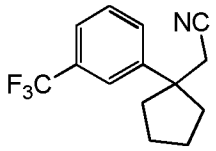
Preparation of (471):



Step 4: 1-(3-(trifluoromethyl)phenyl)cyclopentyl)methyl methanesulfonate

(1-(3-(trifluoromethyl)phenyl)cyclopentyl)methyl methanesulfonate **(471)** was synthesized from ((1-(3-(trifluoromethyl)phenyl)cyclopentyl)methanol **(470)** following the procedure described for Methanesulfonic acid 1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl ester **(240).**

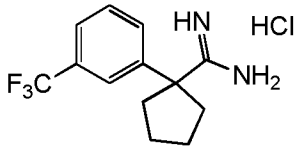
Preparation of (472):



Step 5: 2-(1-(3-(trifluoromethyl)phenyl)cyclopentyl)acetonitrile

2-(1-(3-(trifluoromethyl)phenyl)cyclopentyl)acetonitrile **(471)** was synthesized from (1-(3-(trifluoromethyl)phenyl)cyclopentyl)methyl methanesulfonate **(470)** following the procedure described for [1-(4-trifluoromethyl-phenyl)-cyclopentyl]-acetonitrile **(241).**

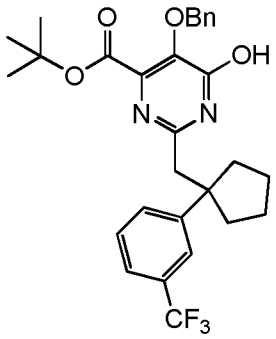
Preparation of (473):



Step 6: 2-(1-(3-(trifluoromethyl)phenyl-cyclopentyl)-acetamidine hydrochloride

2-(1-(3-(trifluoromethyl)phenyl-cyclopentyl)-acetamidine hydrochloride **(473)** was synthesized from 2-(1-(3-(trifluoromethyl)phenyl)cyclopentyl)acetonitrile **(472)** following the procedure described for HCl-salt of 2-[1-(4-trifluoromethyl-phenyl)-cyclopentyl]-acetamidine hydrochloride **(242)**.

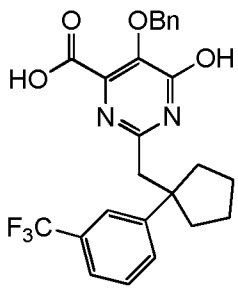
Preparation of (474):



tert-butyl 5-(benzyloxy)-6-hydroxy-2-((1-(3-(trifluoromethyl)phenyl)cyclopentyl)methyl)pyrimidine-4-carboxylate

tert-butyl 5-(benzyloxy)-6-hydroxy-2-((1-(3-(trifluoromethyl)phenyl)cyclopentyl)methyl)pyrimidine-4-carboxylate **(474)** was synthesized as a white solid from 2-(1-(3-(trifluoromethyl)phenyl-cyclopentyl)-acetamidine hydrochloride **(473)** following the procedure described for 5-benzyloxy-2-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid *tert*-butyl ester **(243)**

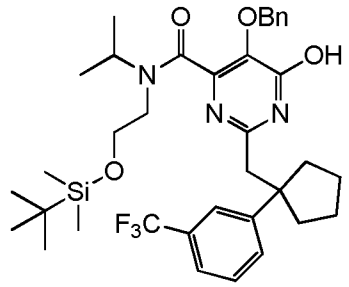
Preparation of (475):



5-(benzyloxy)-6-hydroxy-2-((1-(3-(trifluoromethyl)phenyl)cyclopentyl)methyl)pyrimidine-4-carboxylic acid

5-(benzyloxy)-6-hydroxy-2-((1-(3-(trifluoromethyl)phenyl)cyclopentyl)methyl)pyrimidine-4-carboxylic acid **(475)** was synthesized as a white solid from tert-butyl 5-(benzyloxy)-6-hydroxy-2-((1-(3-(trifluoromethyl)phenyl)cyclopentyl)methyl)pyrimidine-4-carboxylate **(474)** following the procedure described for 5-benzyloxy-2-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid **(244)**.

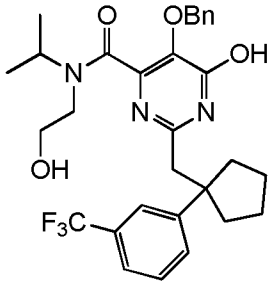
Preparation of (476):



5-(benzyloxy)-N-(2-((tert-butyldimethylsilyl)oxy)ethyl)-6-hydroxy-N-isopropyl-2-((1-(3-(trifluoromethyl)phenyl)cyclopentyl)methyl)pyrimidine-4-carboxamide

5-(benzyloxy)-N-(2-((tert-butyldimethylsilyl)oxy)ethyl)-6-hydroxy-N-isopropyl-2-((1-(3-(trifluoromethyl)phenyl)cyclopentyl)methyl)pyrimidine-4-carboxamide **(476)** was synthesized from 5-(benzyloxy)-6-hydroxy-2-((1-(3-(trifluoromethyl)phenyl)cyclopentyl)methyl)pyrimidine-4-carboxylic acid **(475)** and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amine **(8b)** following the procedure described for 5-benzyloxy-2-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(245)**.

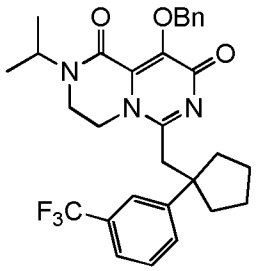
Preparation of (477):



5-(benzyloxy)-6-hydroxy-N-(2-hydroxyethyl)-N-isopropyl-2-((1-(3-(trifluoromethyl)phenyl)cyclopentyl)methyl)pyrimidine-4-carboxamide

5-(benzyloxy)-6-hydroxy-N-(2-hydroxyethyl)-N-isopropyl-2-((1-(3-(trifluoromethyl)phenyl)cyclopentyl)methyl)pyrimidine-4-carboxamide **(477)** was synthesized from 5-(benzyloxy)-N-(2-((tert-butyldimethylsilyl)oxy)ethyl)-6-hydroxy-N-isopropyl-2-((1-(3-(trifluoromethyl)phenyl)cyclopentyl)methyl)pyrimidine-4-carboxamide **(476)** following the procedure described 5-benzyloxy-2-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(246).**

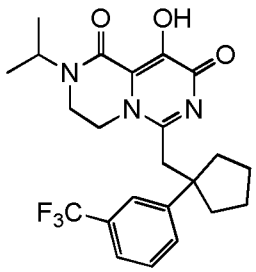
Preparation of (478):



9-(benzyloxy)-2-isopropyl-6-((1-(3-(trifluoromethyl)phenyl)cyclopentyl)methyl)-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione

9-(benzyloxy)-2-isopropyl-6-((1-(3-(trifluoromethyl)phenyl)cyclopentyl)methyl)-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione **(478)** was synthesized as a white solid from 5-(benzyloxy)-6-hydroxy-N-(2-hydroxyethyl)-N-isopropyl-2-((1-(3-(trifluoromethyl)phenyl)cyclopentyl)methyl)pyrimidine-4-carboxamide **(477)** following the procedure described for 9-benzyloxy-6-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(247)**.

Preparation of (479):



9-hydroxy-2-isopropyl-6-((1-(3-(trifluoromethyl)phenyl)cyclopentyl)methyl)-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione

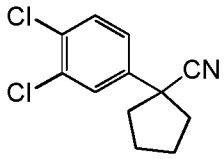
9-hydroxy-2-isopropyl-6-((1-(3-(trifluoromethyl)phenyl)cyclopentyl)methyl)-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione **(479)** was synthesized as a white solid from 9-(benzyloxy)-2-isopropyl-6-((1-(3-(trifluoromethyl)phenyl)cyclopentyl)methyl)-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione **(478)** following the procedure described for 6-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(248)**.

Example 492

6-((1-(3,4-dichlorophenyl)cyclopentyl)methyl)-9-hydroxy-2-isopropyl-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione

The synthetic procedure used in this preparation is outlined in Scheme 51.

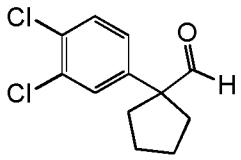
Preparation of (481):



Step:1 1-(3,4-dichlorophenyl)cyclopentanecarbonitrile

1-(3,4-dichlorophenyl)cyclopentanecarbonitrile **(481)** was synthesized from 2-(3,4-dichlorophenyl)acetonitrile **(480)** and 1,4-dibromobutane following the procedure described for 1-(4-trifluoromethyl-phenyl)-cyclopentanecarbonitrile **(237).**

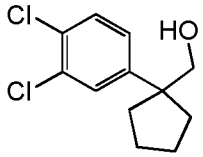
Preparation of (482):



Step 2: 1-(3,4-dichlorophenyl)cyclopentanecarbaldehyde

1-(3,4-dichlorophenyl)cyclopentanecarbaldehyde **(482)** was synthesized from 1-(3,4-dichlorophenyl)cyclopentanecarbonitrile **(481)** following the procedure described for 1-(4-trifluoromethyl-phenyl)-cyclopentanecarbaldehyde **(238).**

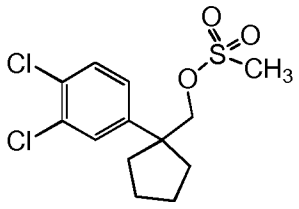
Preparation of (483):



Step 3: (1-(3,4-dichlorophenyl)cyclopentyl)methanol

(1-(3,4-dichlorophenyl)cyclopentyl)methanol **(483)** was synthesized from 1-(3,4-dichlorophenyl)phenyl)cyclopentanecarbaldehyde **(482)** following the procedure described for 1-(4-trifluoromethyl-phenyl)-cyclopentane-methanol **(239).**

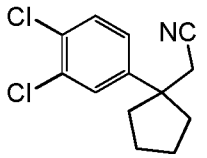
Preparation of (484):



Step 4: 1-(3,4-dichlorophenyl)cyclopentyl)methyl methanesulfonate

(1-(3,4-dichlorophenyl)cyclopentyl)methyl methanesulfonate **(484)** was synthesized from (1-(3,4-dichlorophenyl)cyclopentyl)methanol **(483)** following the procedure described for Methanesulfonic acid 1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl ester **(240).**

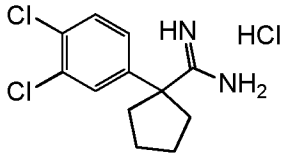
Preparation of (485):



Step 5: 2-(1-(3,4-dichlorophenyl)cyclopentyl)acetonitrile

2-(1-(3,4-dichlorophenyl)cyclopentyl)acetonitrile **(485)** was synthesized from (1-(3,4-dichlorophenyl)cyclopentyl)methyl methanesulfonate **(484)** following the procedure described for [1-(4-trifluoromethyl-phenyl)-cyclopentyl]-acetonitrile **(241).**

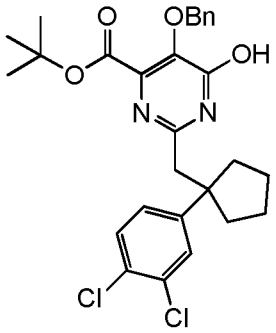
Preparation of (486):



Step 6: 2-(1-(3,4-dichlorophenyl)-cyclopentyl)-acetamidine hydrochloride

2-(1-(3,4-dichlorophenyl)-cyclopentyl)-acetamidine hydrochloride **(486)** was synthesized from 2-(1-(3,4-dichlorophenyl)cyclopentyl)acetonitrile **(485)** following the procedure described for HCl-salt of 2-[1-(4-trifluoromethyl-phenyl)-cyclopentyl]-acetamidine hydrochloride **(242)**.

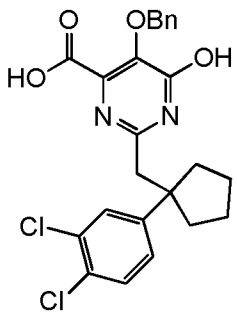
Preparation of (487):



tert-butyl 5-(benzyloxy)-2-((1-(3,4-dichlorophenyl)cyclopentyl)methyl)-6-hydroxypyrimidine-4-carboxylate

tert-butyl 5-(benzyloxy)-2-((1-(3,4-dichlorophenyl)cyclopentyl)methyl)-6-hydroxypyrimidine-4-carboxylate **(487)** was synthesized as a white solid from 2-(1-(3,4-dichlorophenyl)-cyclopentyl)-acetamidine hydrochloride **(486)** following the procedure described for 5-benzyloxy-2-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid *tert*-butyl ester **(243)**

Preparation of (488):

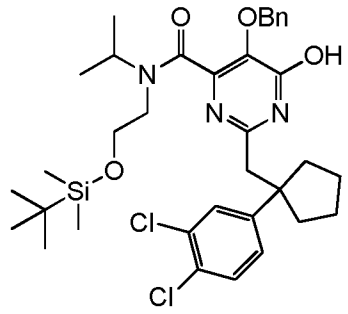


5-(benzyloxy)-2-((1-(3,4-dichlorophenyl)cyclopentyl)methyl)-6-hydroxypyrimidine-4-carboxylic acid

5-(benzyloxy)-2-((1-(3,4-dichlorophenyl)cyclopentyl)methyl)-6-hydroxypyrimidine-4-carboxylic acid **(488)** was synthesized as a white solid from tert-butyl 5-(benzyloxy)-2-((1-(3,4-dichlorophenyl)cyclopentyl)methyl)-6-hydroxypyrimidine-4-carboxylate **(487)** following the

procedure described for 5-benzyloxy-2-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid **(244)**.

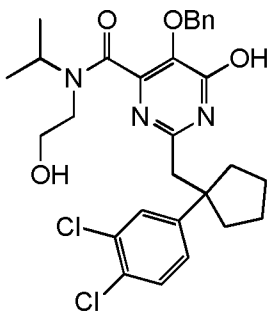
Preparation of (489):



5-(benzyloxy)-N-(2-((tert-butyldimethylsilyl)oxy)ethyl)-2-((1-(3,4-dichlorophenyl)cyclopentyl)methyl)-6-hydroxy-N-isopropylpyrimidine-4-carboxamide

5-(benzyloxy)-N-(2-((tert-butyldimethylsilyl)oxy)ethyl)-2-((1-(3,4-dichlorophenyl)cyclopentyl)methyl)-6-hydroxy-N-isopropylpyrimidine-4-carboxamide **(489)** was synthesized from 5-(benzyloxy)-2-((1-(3,4-dichlorophenyl)cyclopentyl)methyl)-6-hydroxypyrimidine-4-carboxylic acid **(488)** and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amine **(8b)** following the procedure described for 5-benzyloxy-2-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(245).**

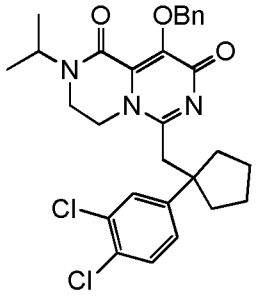
Preparation of (490):



5-(benzyloxy)-2-((1-(3,4-dichlorophenyl)cyclopentyl)methyl)-6-hydroxy-N-(2-hydroxyethyl)-N-isopropylpyrimidine-4-carboxamide

5-(benzyloxy)-2-((1-(3,4-dichlorophenyl)cyclopentyl)methyl)-6-hydroxy-N-(2-hydroxyethyl)-N-isopropylpyrimidine-4-carboxamide **(490)** was synthesized from 5-(benzyloxy)-N-(2-((tert-butyldimethylsilyl)oxy)ethyl)-2-((1-(3,4-dichlorophenyl)cyclopentyl)methyl)-6-hydroxy-N-isopropylpyrimidine-4-carboxamide **(489)** following the procedure described 5-benzyloxy-2-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(246).**

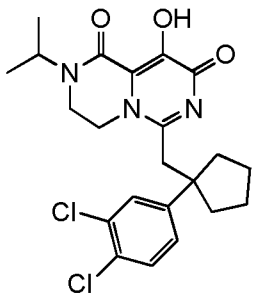
Preparation of (491):



9-(benzyloxy)-6-((1-(3,4-dichlorophenyl)cyclopentyl)methyl)-2-isopropyl-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione

9-(benzyloxy)-6-((1-(3,4-dichlorophenyl)cyclopentyl)methyl)-2-isopropyl-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione **(491)** was synthesized as a white solid from 5-(benzyloxy)-2-((1-(3,4-dichlorophenyl)cyclopentyl)methyl)-6-hydroxy-N-(2-hydroxyethyl)-N-isopropylpyrimidine-4-carboxamide **(490)** following the procedure described for 9-benzyloxy-6-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(247)**.

Preparation of (492):



6-((1-(3,4-dichlorophenyl)cyclopentyl)methyl)-9-hydroxy-2-isopropyl-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione

6-((1-(3,4-dichlorophenyl)cyclopentyl)methyl)-9-hydroxy-2-isopropyl-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione **(492)** was synthesized as a white solid from 9-(benzyloxy)-6-((1-(3,4-dichlorophenyl)cyclopentyl)methyl)-2-isopropyl-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione **(491)** following the procedure described for 6-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(248)**.

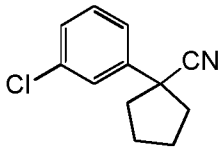
LC/HR-MS: $(M+H)^+$ = 450.1358

Example 505

6-((1-(3-chlorophenyl)cyclopentyl)methyl)-9-hydroxy-2-isopropyl-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione

The synthetic procedure used in this preparation is outlined in Scheme 51.

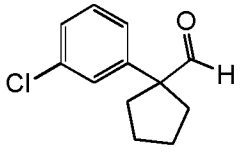
Preparation of (494):



Step:1 1-(3-chlorophenyl)cyclopentanecarbonitrile

1-(3-chlorophenyl)cyclopentanecarbonitrile **(494)** was synthesized from 2-(3-chlorophenyl)acetonitrile **(493)** and 1,4-dibromobutane following the procedure described for 1-(4-trifluoromethyl-phenyl)-cyclopentanecarbonitrile **(237).**

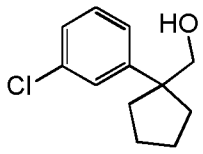
Preparation of (495):



Step 2: 1-(3-chlorophenyl)cyclopentanecarbaldehyde

1-(3-chlorophenyl)cyclopentanecarbaldehyde **(495)** was synthesized from 1-(3-chlorophenyl)cyclopentanecarbonitrile **(494)** following the procedure described for 1-(4-trifluoromethyl-phenyl)-cyclopentanecarbaldehyde **(238).**

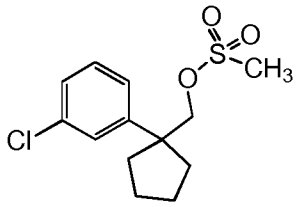
Preparation of (496):



Step 3: (1-(3-chlorophenyl)cyclopentyl)methanol

(1-(3-chlorophenyl)cyclopentyl)methanol **(496)** was synthesized from 1-(3-chlorophenyl)phenyl)cyclopentanecarbaldehyde **(495)** following the procedure described for 1-(4-trifluoromethyl-phenyl)-cyclopentane-methanol **(239).**

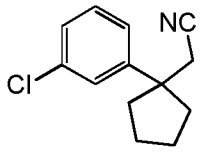
Preparation of (497):



Step 4: 1-(3-chlorophenyl)cyclopentyl)methyl methanesulfonate

(1-(3-chlorophenyl)cyclopentyl)methyl methanesulfonate **(497)** was synthesized from (1-(3-chlorophenyl)cyclopentyl)methanol **(496)** following the procedure described for Methanesulfonic acid 1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl ester **(240).**

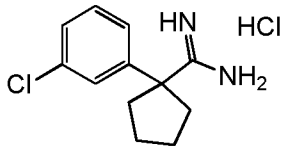
Preparation of (498):



Step 5: 2-(1-(3-chlorophenyl)cyclopentyl)acetonitrile

2-(1-(3-chlorophenyl)cyclopentyl)acetonitrile **(498)** was synthesized from (1-(3-chlorophenyl)cyclopentyl)methyl methanesulfonate **(497)** following the procedure described for [1-(4-trifluoromethyl-phenyl)-cyclopentyl]-acetonitrile **(241).**

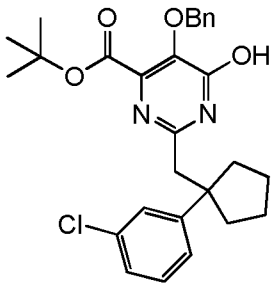
Preparation of (499):



Step 6: 2-(1-(3-chlorophenyl)-cyclopentyl)-acetamidine hydrochloride

2-(1-(3-chlorophenyl)-cyclopentyl)-acetamidine hydrochloride **(499)** was synthesized from 2-(1-(3-chlorophenyl)cyclopentyl)acetonitrile **(498)** following the procedure described for HCl-salt of 2-[1-(4-trifluoromethyl-phenyl)-cyclopentyl]-acetamidine hydrochloride **(242)**.

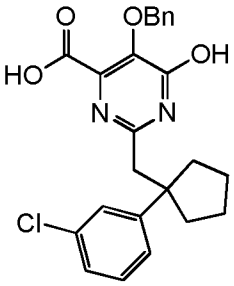
Preparation of (500):



tert-butyl 5-(benzyloxy)-2-((1-(3-chlorophenyl)cyclopentyl)methyl)-6-hydroxypyrimidine-4-carboxylate

tert-butyl 5-(benzyloxy)-2-((1-(3-chlorophenyl)cyclopentyl)methyl)-6-hydroxypyrimidine-4-carboxylate **(500)** was synthesized as a white solid from 2-(1-(3-chlorophenyl)-cyclopentyl)-acetamidine hydrochloride **(499)** following the procedure described for 5-benzyloxy-2-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid *tert*-butyl ester **(243)**

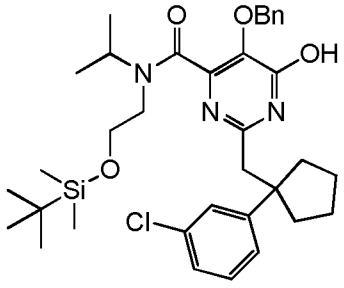
Preparation of (501):



5-(benzyloxy)-2-((1-(3-chlorophenyl)cyclopentyl)methyl)-6-hydroxypyrimidine-4-carboxylic acid

5-(benzyloxy)-2-((1-(3-chlorophenyl)cyclopentyl)methyl)-6-hydroxypyrimidine-4-carboxylic acid **(501)** was synthesized as a white solid from tert-butyl 5-(benzyloxy)-2-((1-(3-chlorophenyl)cyclopentyl)methyl)-6-hydroxypyrimidine-4-carboxylate **(500)** following the procedure described for 5-benzyloxy-2-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid **(244)**.

Preparation of (502):

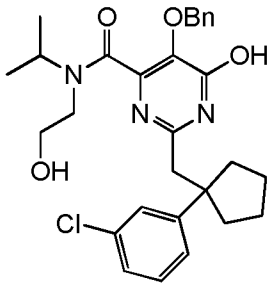


5-(benzyloxy)-N-(2-((tert-butyldimethylsilyl)oxy)ethyl)-2-((1-(3-chlorophenyl)cyclopentyl)methyl)-6-hydroxy-N-isopropylpyrimidine-4-carboxamide

5-(benzyloxy)-N-(2-((tert-butyldimethylsilyl)oxy)ethyl)-2-((1-(3-chlorophenyl)cyclopentyl)methyl)-6-hydroxy-N-isopropylpyrimidine-4-carboxamide **(502)** was synthesized from 5-(benzyloxy)-2-((1-(3-chlorophenyl)cyclopentyl)methyl)-6-hydroxypyrimidine-4-carboxylic acid **(501)** and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amine **(8b)** following the procedure described for 5-benzyloxy-2-[1-(4-trifluoromethyl-

phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amide **(245).**

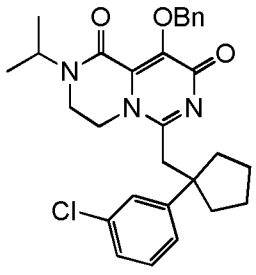
Preparation of (503):



5-(benzyloxy)-2-((1-(3-chlorophenyl)cyclopentyl)methyl)-6-hydroxy-N-(2-hydroxyethyl)-N-isopropylpyrimidine-4-carboxamide

5-(benzyloxy)-2-((1-(3-chlorophenyl)cyclopentyl)methyl)-6-hydroxy-N-(2-hydroxyethyl)-N-isopropylpyrimidine-4-carboxamide **(503)** was synthesized from 5-(benzyloxy)-N-(2-((tert-butyldimethylsilyl)oxy)ethyl)-2-((1-(3-chlorophenyl)cyclopentyl)methyl)-6-hydroxy-N-isopropylpyrimidine-4-carboxamide **(502)** following the procedure described 5-benzyloxy-2-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-isopropyl-amide **(246).**

Preparation of (504):

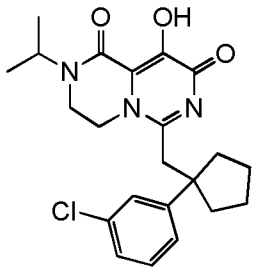


9-(benzyloxy)-6-((1-(3-chlorophenyl)cyclopentyl)methyl)-2-isopropyl-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione

9-(benzyloxy)-6-((1-(3-chlorophenyl)cyclopentyl)methyl)-2-isopropyl-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione **(504)** was synthesized as a white solid from 5-

(benzyloxy)-2-((1-(3-)cyclopentyl)methyl)-6-hydroxy-N-(2-hydroxyethyl)-N-isopropylpyrimidine-4-carboxamide **(503)** following the procedure described for 9-benzyloxy-6-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(247)**.

Preparation of (505):



6-((1-(3-chlorophenyl)cyclopentyl)methyl)-9-hydroxy-2-isopropyl-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione

6-((1-(3-chlorophenyl)cyclopentyl)methyl)-9-hydroxy-2-isopropyl-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione **(505)** was synthesized as a white solid from 9-(benzyloxy)-6-((1-(3-chlorophenyl)cyclopentyl)methyl)-2-isopropyl-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione **(504)** following the procedure described for 6-[1-(4-trifluoromethyl-phenyl)-cyclopentylmethyl]-9-hydroxy-2-isopropyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(248)**.

LC/HR-MS: $(M+H)^+$ = 416.1740

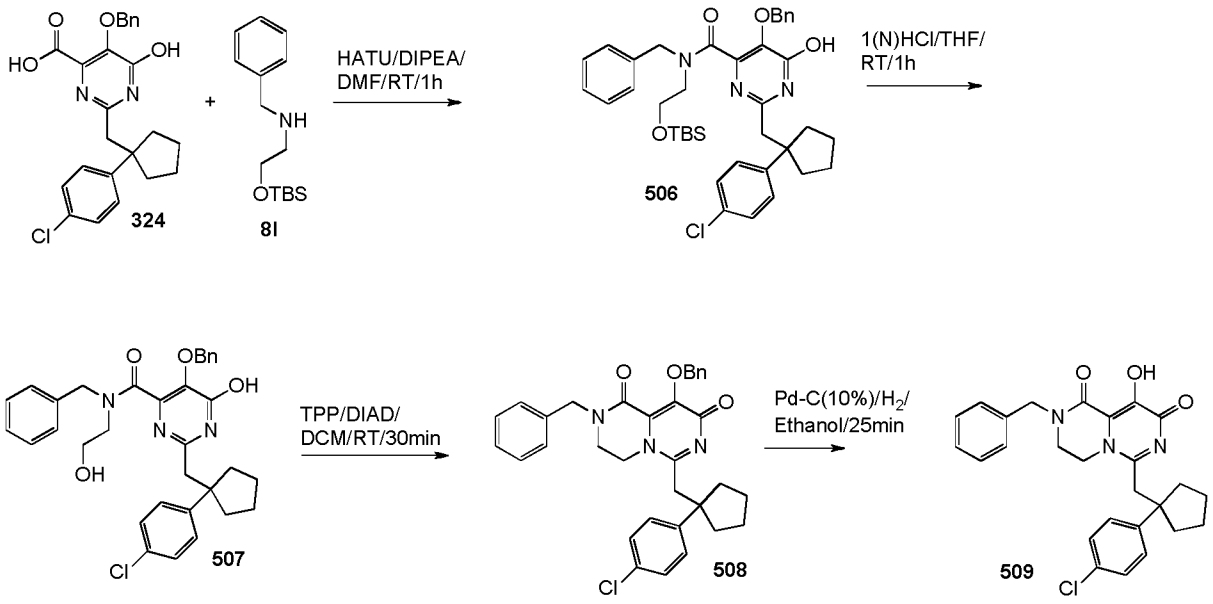
Example 509

2-benzyl-6-((1-(4-chlorophenyl)cyclopentyl)methyl)-9-hydroxy-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione

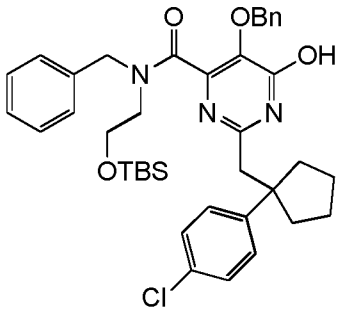
The synthetic procedure used in this preparation is outlined in Scheme 52.

Synthetic route for 509:

Scheme 52



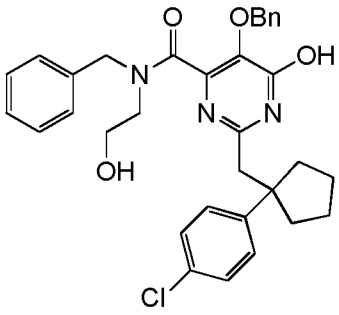
Synthesis of (506):



N-benzyl-5-(benzyloxy)-N-(2-((tert-butyldimethylsilyl)oxy)ethyl)-2-((1-(4-chlorophenyl)cyclopentyl)methyl)-6-hydroxypyrimidine-4-carboxamide

This compound was prepared by following the same method as 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(350)** from 5-Benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid **(324)** and benzyl-[2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-amine **(8I)**.

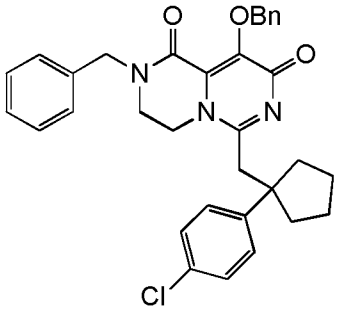
Synthesis of (507):



N-benzyl-5-(benzyloxy)-2-((1-(4-chlorophenyl)cyclopentyl)methyl)-6-hydroxy-N-(2-hydroxyethyl)pyrimidine-4-carboxamide

This compound was prepared following the same method as 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide **(351)** from N-benzyl-5-(benzyloxy)-N-(2-((tert-butyldimethylsilyl)oxy)ethyl)-2-((1-(4-chlorophenyl)cyclopentyl)methyl)-6-hydroxypyrimidine-4-carboxamide **(506).**

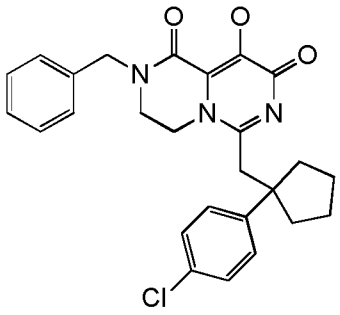
Synthesis of (508):



2-benzyl-9-(benzyloxy)-6-((1-(4-chlorophenyl)cyclopentyl)methyl)-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione

This compound was prepared following the same method as pure 9-Benzyloxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(348)** from N-benzyl-5-(benzyloxy)-2-((1-(4-chlorophenyl)cyclopentyl)methyl)-6-hydroxy-N-(2-hydroxyethyl) pyrimidine-4-carboxamide **(507)**.

Synthesis of (509): (16048)



2-benzyl-6-((1-(4-chlorophenyl)cyclopentyl)methyl)-9-hydroxy-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione

This compound was prepared following the same method as pure 9-hydroxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(349)** from 2-benzyl-9-(benzyloxy)-6-((1-(4-chlorophenyl)cyclopentyl)methyl)-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione **(508)**.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.62 (d, *J*=5.52 Hz, 2 H) 1.72 - 1.90 (m, 4 H) 2.23 - 2.37 (m, 4 H) 2.69 (d, *J*=1.76 Hz, 1 H) 2.89 (s, 2 H) 3.09 (d, *J*=5.27 Hz, 2 H) 3.31 (s, 8 H) 3.52 (d, *J*=6.02 Hz, 2 H) 4.63 (s, 2 H) 7.17 - 7.47 (m, 9 H)

LC/HR-MS: $(M+H)^+$ = 464.1743

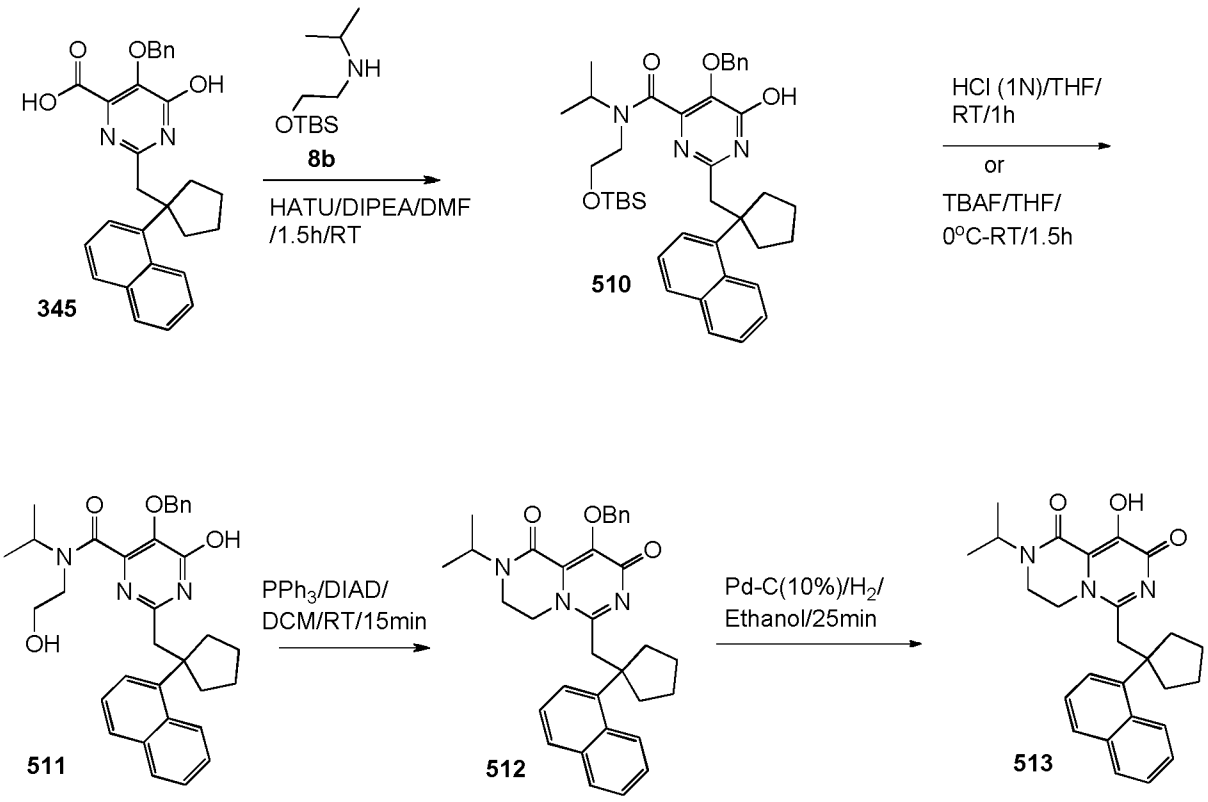
Example 513

9-hydroxy-2-isopropyl-6-((1-(naphthalen-1-yl)cyclopentyl)methyl)-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione

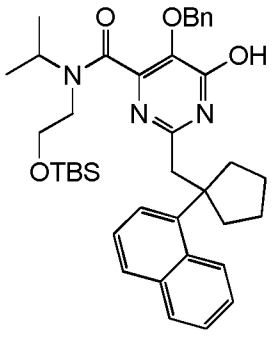
The synthetic procedure used in this preparation is outlined in Scheme 53.

Synthetic route for 513:

Scheme 53



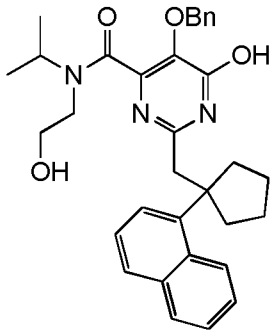
Synthesis of (510):



5-(benzyloxy)-N-(2-((tert-butyldimethylsilyl)oxy)ethyl)-6-hydroxy-N-isopropyl-2-((1-(naphthalen-1-yl)cyclopentyl)methyl)pyrimidine-4-carboxamide

This compound was prepared by following the same method as 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-amide **(350)** from 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid **(345)** and [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-isopropyl-amine **(8b)**.

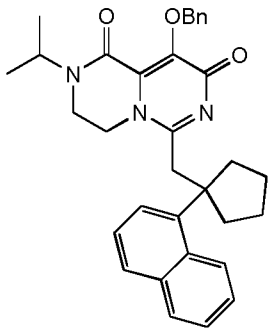
Synthesis of (511):



5-(benzyloxy)-6-hydroxy-N-(2-hydroxyethyl)-N-isopropyl-2-((1-(naphthalen-1-yl)cyclopentyl)methyl) pyrimidine-4-carboxamide

This compound was prepared following the same method as 5-benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-methyl-amide **(351)** from 5-(benzyloxy)-N-(2-((tert-butyldimethylsilyl)oxy)ethyl)-6-hydroxy-N-isopropyl-2-((1-(naphthalen-1-yl)cyclopentyl)methyl)pyrimidine-4-carboxamide **(510).**

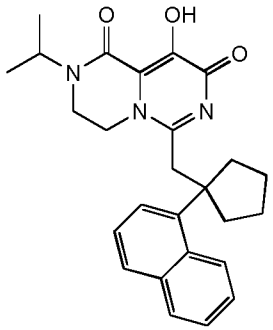
Synthesis of (512):



9-(benzyloxy)-2-isopropyl-6-((1-(naphthalen-1-yl)cyclopentyl)methyl)-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione

This compound was prepared following the same method as pure 9-Benzyloxy-2-methyl-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(352)** from 5-(benzyloxy)-6-hydroxy-N-(2-hydroxyethyl)-N-isopropyl-2-((1-(naphthalen-1-yl)cyclopentyl)methyl) pyrimidine-4-carboxamide **(511)**.

Synthesis of (513):



9-hydroxy-2-isopropyl-6-((1-(naphthalen-1-yl)cyclopentyl)methyl)-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione

This compound was prepared following the same method as pure 9-hydroxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(349)** from 9-(benzyloxy)-2-isopropyl-6-((1-(naphthalen-1-yl)cyclopentyl)methyl)-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione **(512)**.

Orange foam: LC/ MS: $(M+H)^+$ = 432

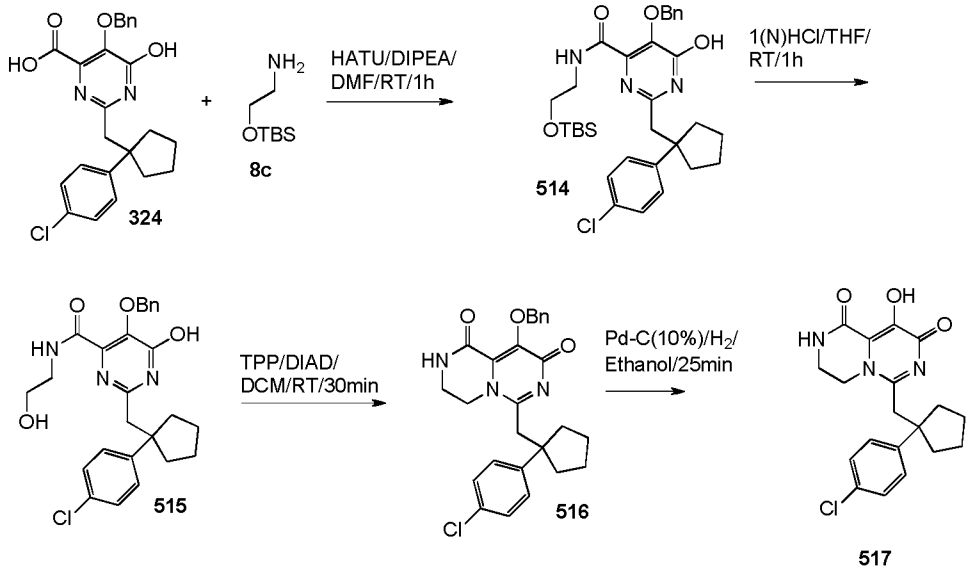
Example 517

6-((1-(4-chlorophenyl)cyclopentyl)methyl)-9-hydroxy-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione

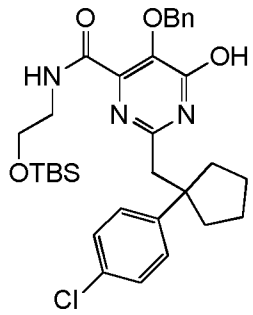
The synthetic procedure used in this preparation is outlined in Scheme 53.

Synthetic route for 517:

Scheme 53



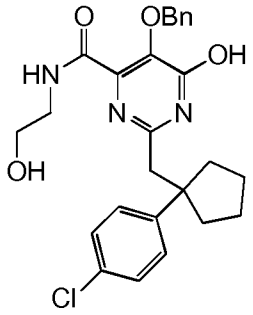
Synthesis of (514):



5-(benzyloxy)-N-(2-((tert-butyldimethylsilyl)oxy)ethyl)-2-((1-(4-chlorophenyl)cyclopentyl)methyl)-6-hydroxypyrimidine-4-carboxamide

This compound was prepared by following the same method as 5-Benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-amide **(346)** from 5-Benzyloxy-2-[1-(4-chloro-phenyl)-cyclopentylmethyl]-6-hydroxy-pyrimidine-4-carboxylic acid **(324)** and 2-(tert-butyl-dimethyl-silanyloxy)-ethylamine **(8c)**.

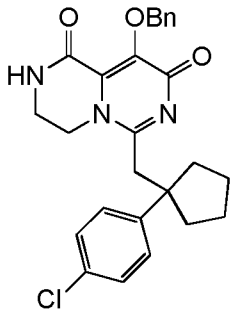
Synthesis of (515):



5-(benzyloxy)-2-((1-(4-chlorophenyl)cyclopentyl)methyl)-6-hydroxy-N-(2-hydroxyethyl)pyrimidine-4-carboxamide

This compound was prepared following the same method as 5-Benzyloxy-6-hydroxy-2-(1-naphthalen-1-yl-cyclopentylmethyl)-pyrimidine-4-carboxylic acid (2-hydroxyethyl)-amide **(347)** from 5-(benzyloxy)-N-(2-((tert-butyldimethylsilyl)oxy)ethyl)-2-((1-(4-chlorophenyl)cyclopentyl)methyl)-6-hydroxypyrimidine-4-carboxamide **(514).**

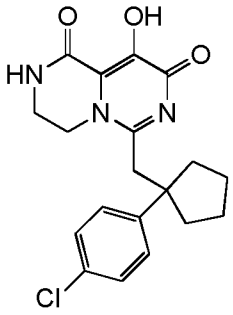
Synthesis of (516):



9-(benzyloxy)-6-((1-(4-chlorophenyl)cyclopentyl)methyl)-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione

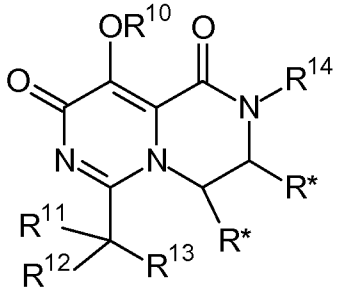
This compound was prepared following the same method as pure 9-Benzyloxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(348)** from 5-(benzyloxy)-2-((1-(4-chlorophenyl)cyclopentyl)methyl)-6-hydroxy-N-(2-hydroxyethyl)pyrimidine-4-carboxamide **(515)**.

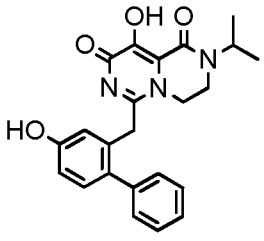
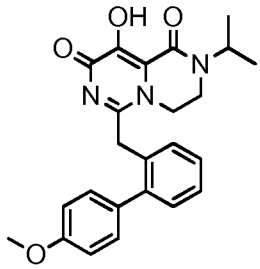
Synthesis of (517): (16246)

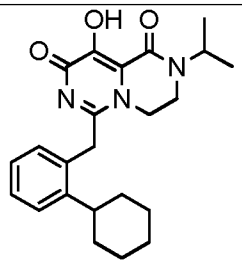
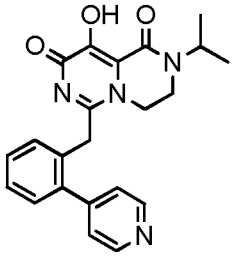
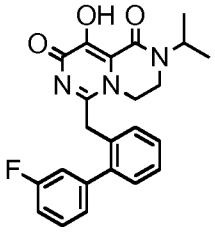
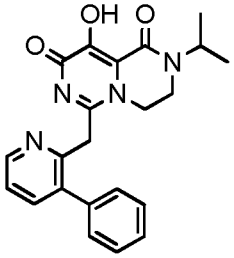
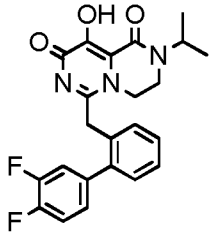
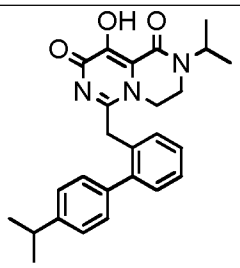
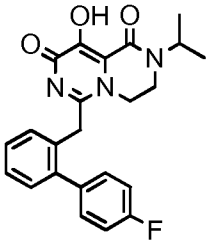
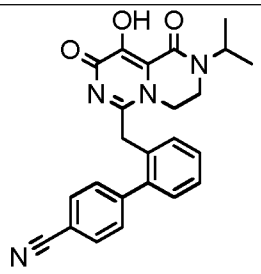
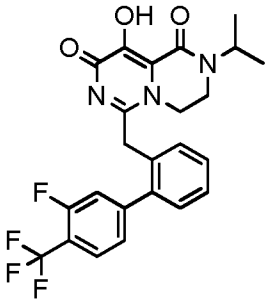
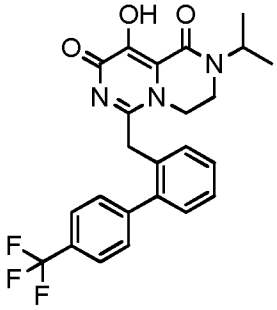


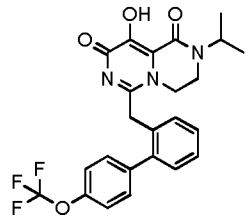
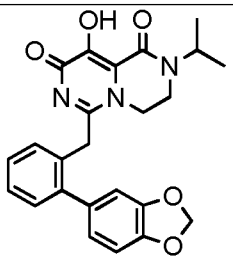
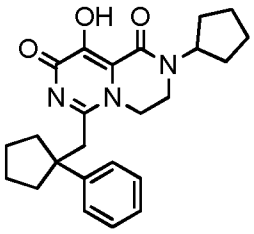
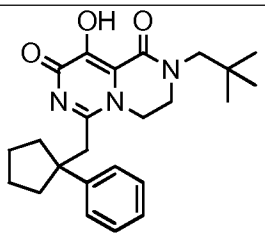
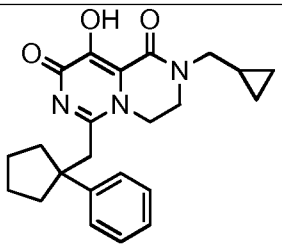
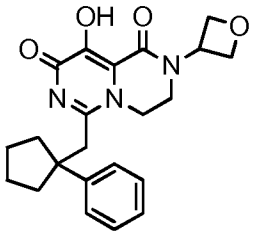
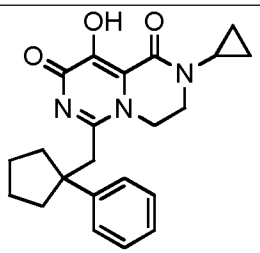
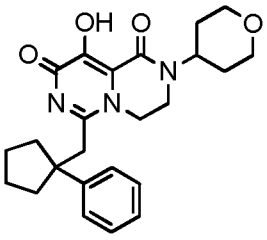
6-((1-(4-chlorophenyl)cyclopentyl)methyl)-9-hydroxy-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione

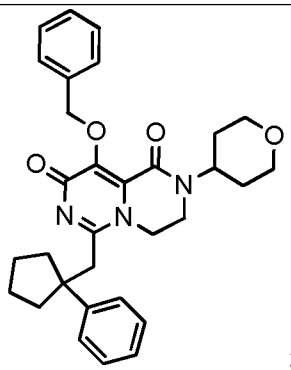
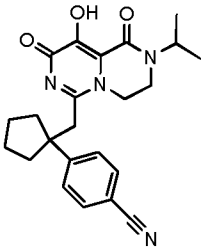
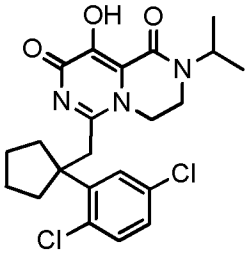
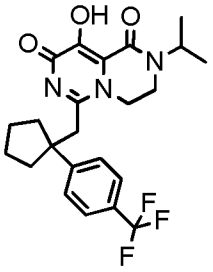
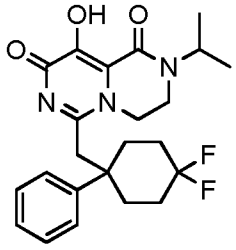
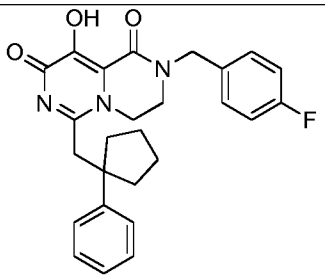
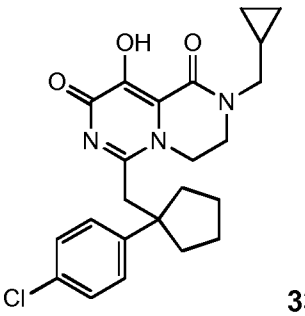
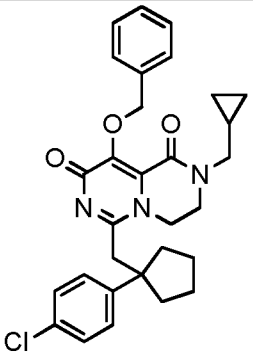
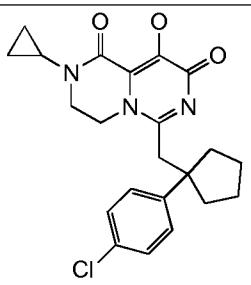
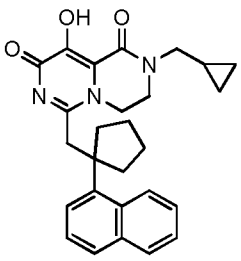
This compound was prepared following the same method as pure 9-Hydroxy-6-(1-naphthalen-1-yl-cyclopentylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione **(349)** from 9-(benzyloxy)-6-((1-(4-chlorophenyl)cyclopentyl)methyl)-3,4-dihydro-1H-pyrazino[1,2-c]pyrimidine-1,8(2H)-dione **(517)**.

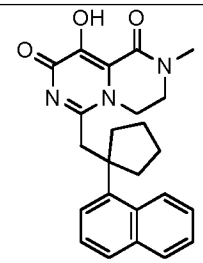
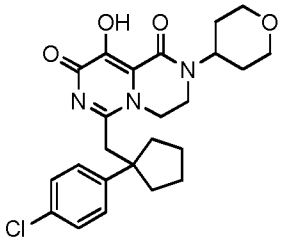
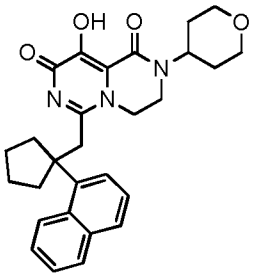
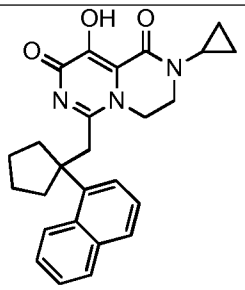
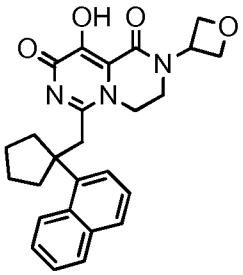
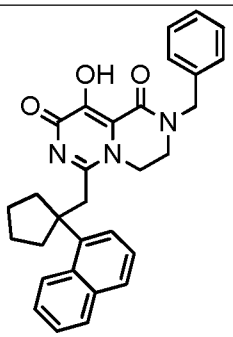
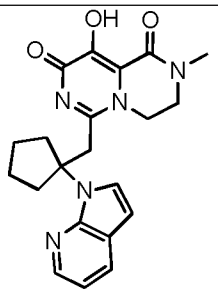
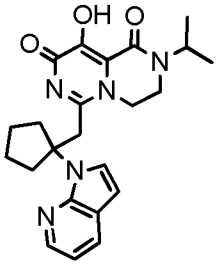
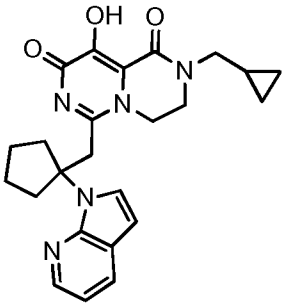
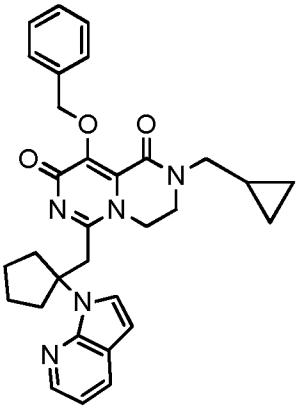


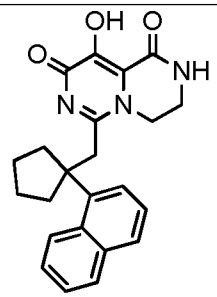
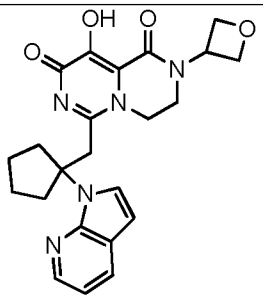
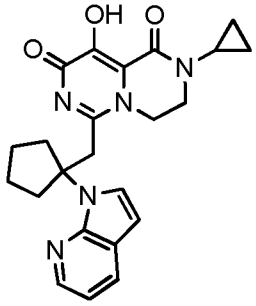
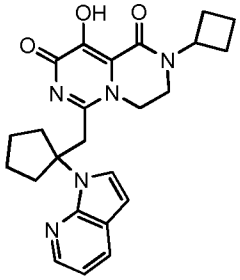
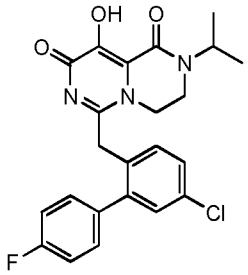
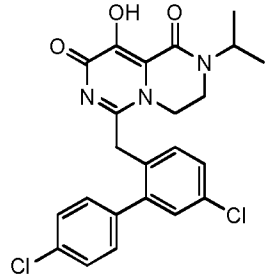
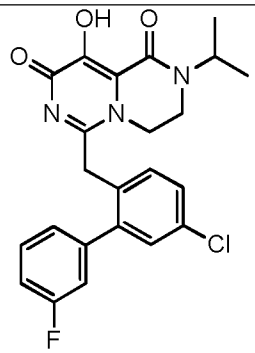
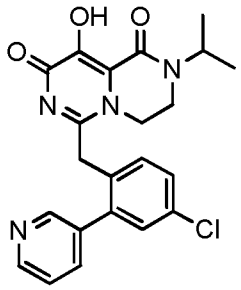
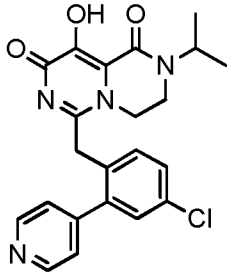
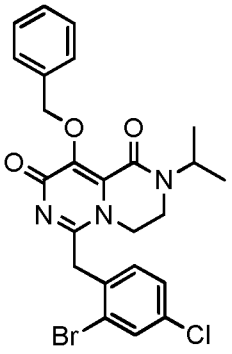
Formula, no.	FRET	Formula, no.	FRET
 **145**	IC_{50}= 0.146 µM	 **172**	IC_{50}=0.122 µM
	IC_{50}=0.114 µM		IC_{50}=0.094 µM

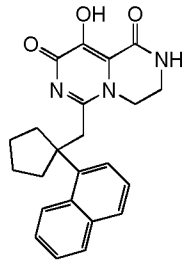
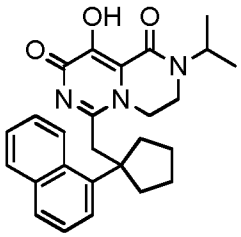
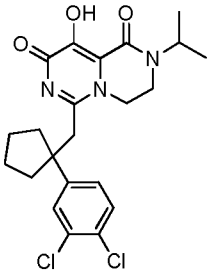
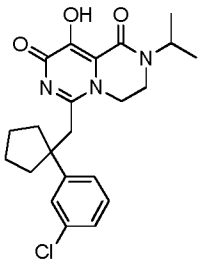
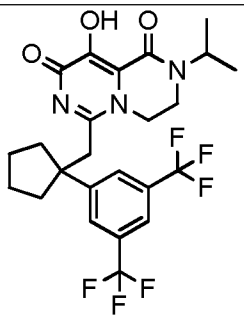
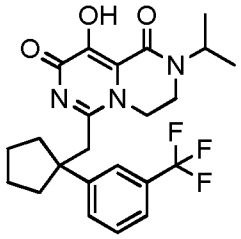
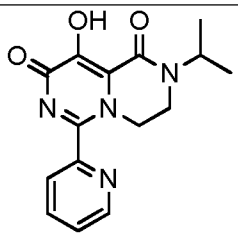
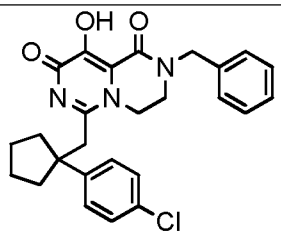
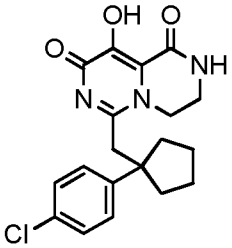
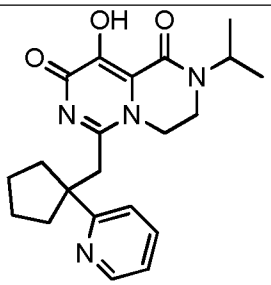
 **157**		 **154**	
 **173**	IC_{50}=0.38 μM	 **168**	IC_{50}=0.38 μM
 **171**	IC_{50}=1.06 μM	 **175**	IC_{50}=0.70 μM
 **177**	IC_{50}=1.55 μM	 **179**	IC_{50}=0.30 μM
 **181**	IC_{50}=0.38 μM	 **183**	IC_{50}=0.32 μM

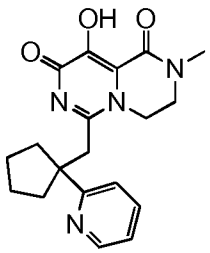
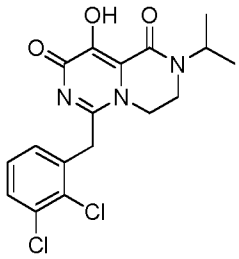
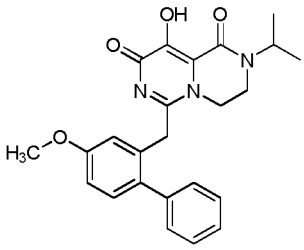
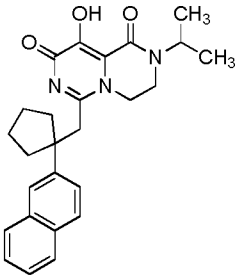
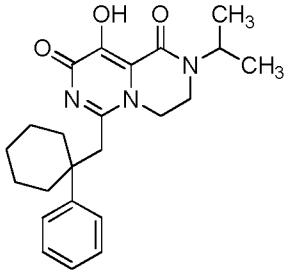
 **185**	IC_{50}=0.55 μM	 **187**	IC_{50}=0.229 μM
 **291**	IC_{50}=0.521 μM	 **189**	IC_{50}=0.116 μM
 **295**	IC_{50}=0.102 μM	 **303**	IC_{50}=0.143 μM
 **307**	IC_{50}=0.138 μM	 **299**	IC_{50}=0.134 μM
 **287**	IC_{50}=0.098 μM	 **311**	IC_{50}=0.043 μM

 **310**	IC_{50}>25 μM	 **235**	IC_{50}=0.041 μM
 **209**	IC_{50}=0.295 μM	 **248**	IC_{50}=0.262 μM
 **275**	IC_{50}=0.084 μM	 **315**	IC_{50}=0.422 μM
 **332**	IC_{50}=0.205 μM	 **331**	IC_{50}>25 μM
 **328**	IC_{50}=0.73 μM	 **361**	IC_{50}=0.14 μM

 **353**	IC_{50}=0.11 μM	 **336**	IC_{50}=0.06 μM
 **369**	IC_{50}=0.11 μM	 **357**	IC_{50}=0.104 μM
 **365**	IC_{50}>25 μM	 **373**	IC_{50}=0.67 μM
 **408**	IC_{50}=0.08 μM	 **412**	IC_{50}=0.02 μM
 **416**	IC_{50}=0.141 μM	 **415**	IC_{50}>25 μM

 **349**	IC_{50}=0.162 μM	 **424**	IC_{50}=0.108 μM
 **420**	IC_{50}=0.092 μM	 **428**	IC_{50}=0.173 μM
 **386**	IC_{50}=0.436 μM	 **382**	IC_{50}=0.266 μM
 **384**	IC_{50}=0.058 μM	 **390**	IC_{50}=0.081 μM
 **388**	IC_{50}=0.110 μM	 **380**	IC_{50}>25 μM

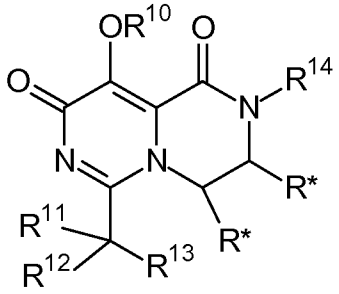
 **349**	IC_{50}=0.16 μM	 **513**	IC_{50}=0.27 μM
 **492**	IC_{50}=0.61 μM	 **505**	IC_{50}=0.32 μM
 **466**	IC_{50}=0.318 μM	 **479**	IC_{50}=0.46 μM
 **196**	IC_{50}=1.89 μM	 **509**	IC_{50}=0.99 μM
 **517**	IC_{50}=1.27 μM	 **441**	IC_{50}=0.097 μM

 **445**	IC_{50}=0.063 μM	 **135**	IC_{50}=0.35 μM
 **144**	IC_{50}=0.43 μM	 **222**	IC_{50}=0.11 μM
 **260**	IC_{50}=0.12 μM		

New PCT Patent Application
based on US 61/750,017
Savira pharmaceuticals GmbH et al.
Our ref.: U2797 PCT

CLAIMS

1. A compound having the general formula (I), optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof,



(I)

wherein

X^{10} is NR^{15}, $N(R^{15})C(O)$, $C(O)NR^{15}$, O, C(O), C(O)O, OC(O); $N(R^{15})SO_2$, $SO_2N(R^{15})$, S, SO, or SO_2;

R^{10} is –H, a $–C_{1–6}$ alkyl group or a $–C(O)–C_{1–6}$ alkyl group;

R^{11} is –H, a $–C_{1–6}$ alkyl group, or a $–C_{1–6}$ alkyl group which is substituted by one or more halogen atoms;

R^{12} is –H, a $–C_{1–6}$ alkyl group, or a $–C_{1–6}$ alkyl group which is substituted by one or more halogen atoms;

or wherein **R^{11}** and **R^{12}** can be joined together to form a 3- to 7-membered carbo- or heterocyclic ring;

R^{13} is $-R^{16}$, or $-X^{10}-R^{16}$;

R^{14} is –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl), $-C_{1-4}$ alkyl–(optionally substituted C_{3-7} cycloalkyl), or $-C_{1-4}$ alkyl–(optionally substituted aryl);

R^{15} is –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl), $-C_{1-4}$ alkyl–(optionally substituted C_{3-7} cycloalkyl), or $-C_{1-4}$ alkyl–(optionally substituted aryl);

R^{16} is –(optionally substituted hydrocarbon group which contains from 5 to 20 carbon atoms and optionally 1 to 4 heteroatoms selected from O, N and S and which contains at least one ring);

R^{17} is –H, $-C_{1-6}$ alkyl, or $-(CH_2CH_2O)_rH$;

R^{18} is –H, or $-C_{1-6}$ alkyl;

R is independently selected from $-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkyl, –Hal, $-CF_3$, –CN, $-COOR^{17}$, $-OR^{17}$, $-(CH_2)_qNR^{17}R^{18}$, $-C(O)-NR^{17}R^{18}$, and $-NR^{17}-C(O)-C_{1-6}$ alkyl;

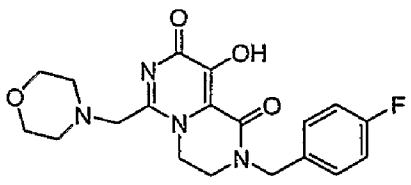
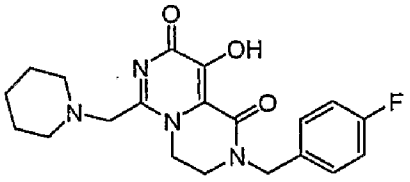
R* is independently selected from –H, $-C_{1-6}$ alkyl, and $-C_{3-7}$ cycloalkyl;

q is 0 to 4; and

r is 1 to 3;

wherein the alkyl group, aryl group, hydrocarbon group and/or cycloalkyl group can be optionally substituted with one or more substituents R;

with the proviso that the following compounds are disclaimed:


and

.

2. The compound according to claim 1, wherein R^{13} is $-R^{16}$.

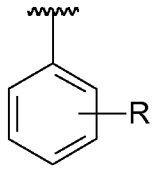
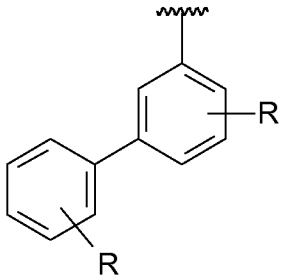
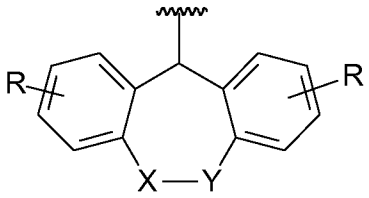
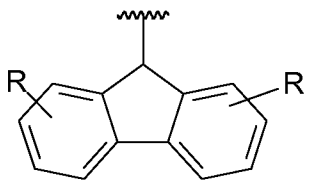
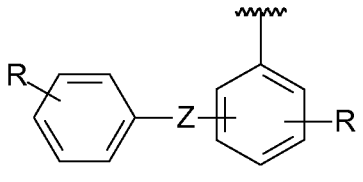
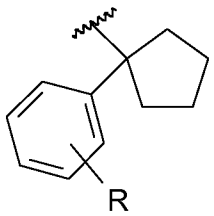
3. The compound according to claim 1, wherein R^{13} is $-X^{10}-R^{16}$ and X^{10} is $N(R^{15})SO_2$.

4. The compound according to any of claims 1 to 3, wherein R^{11} and R^{12} are –H.

5. The compound according to any of claims 1 to 4, wherein R^{10} is –H, or –(optionally substituted C_{1-6} alkyl).

6. The compound according to any of claims 1 to 5, wherein R^{14} is –H, –(optionally substituted C_{1-6} alkyl), or –(optionally substituted aryl).

7. The compound according to any of claims 1 to 6, wherein R^{16} is selected from






and


wherein

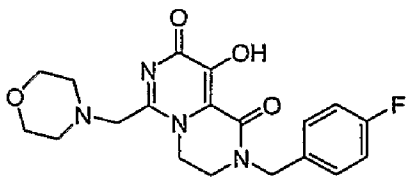
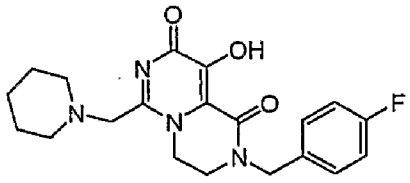
X is absent, CH_2, NH, C(O)NH, S or O;

Y is CH_2;

Z is O or S; and

R is independently selected from –H, $-C_{1-6}$ alkyl, $-CF_3$, –halogen, –CN, –OH, and $-O-C_{1-6}$ alkyl.

8. A pharmaceutical composition comprising:
a compound having the general formula (I) as defined in any of claims 1 to 7, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof,
and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s);
with the proviso that the following compounds are disclaimed:


and

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9. The pharmaceutical composition according to claim 8, which additionally comprises at least one further medicament which is selected from the group consisting of a polymerase inhibitor which is different from the compound having the general formula (I); neuramidase inhibitor; M2 channel inhibitor; alpha glucosidase inhibitor; ligand of another influenza target; antibiotics, anti-inflammatory agents, lipoxygenase inhibitors, EP ligands, bradykinin ligands, and cannabinoid ligands.

10. A compound having the general formula (I) as defined in any of claims 1 to 7, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof,
wherein the compound is for use in the treatment, amelioration or prevention of a viral disease caused by Herpesviridae, Filoviridae, Paramyxoviridae, Rhabdoviridae, Orthomyxoviridae, Bunyaviridae, Arenaviridae, Coronaviridae, Picornaviridae, Togaviridae, or Flaviviridae; and
wherein the compounds disclaimed in claim 1 are not disclaimed.

11. A method of treating, ameliorating or preventing a viral disease caused by Herpesviridae, Filoviridae, Paramyxoviridae, Rhabdoviridae, Orthomyxoviridae, Bunyaviridae, Arenaviridae, Coronaviridae, Picornaviridae, Togaviridae, or Flaviviridae; the method comprising administering to a patient in need thereof an effective amount of

a compound having the general formula (I) as defined in any of claims 1 to 7, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof; and wherein the compounds disclaimed in claim 1 are not disclaimed.

12. A compound having the general formula (I) as defined in any of claims 1 to 7, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof, wherein the compound is for use in the treatment, amelioration or prevention of influenza; and
wherein the compounds disclaimed in claim 1 are not disclaimed.

13. A method of treating, ameliorating or preventing influenza; the method comprising administering to a patient in need thereof an effective amount of a compound having the general formula (I) as defined in any of claims 1 to 7, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof; and
wherein the compounds disclaimed in claim 1 are not disclaimed.

14. The compound or method according to claim 10 or 11, wherein at least one further medicament which is selected from the group consisting of a polymerase inhibitor which is different from the compound having the general formula (I); neuramidase inhibitor; M2 channel inhibitor; alpha glucosidase inhibitor; ligand of another influenza target; antibiotics, anti-inflammatory agents, lipoxygenase inhibitors, EP ligands, bradykinin ligands, and cannabinoid ligands is administered concurrently with, sequentially with or separately from the compound having the general formula (I).

15. The compound, pharmaceutical composition or method according to any of claims 1 to 14, wherein the compound having the general formula (I) exhibits an IC_{50} of less than about 40 μM in the FRET endonuclease activity assay disclosed herein.