

**(12) STANDARD PATENT**  
**(19) AUSTRALIAN PATENT OFFICE**

(11) Application No. **AU 2019396499 B2**

(54) Title  
**Substituted xanthine derivatives**

(51) International Patent Classification(s)  
**C07D 473/06** (2006.01) **A61P 25/22** (2006.01)  
**A61P 25/16** (2006.01) **A61P 25/24** (2006.01)  
**A61P 25/18** (2006.01) **A61P 25/28** (2006.01)

(21) Application No: **2019396499** (22) Date of Filing: **2019.12.10**

(87) WIPO No: **WO20/120450**

(30) Priority Data

|                   |                   |              |
|-------------------|-------------------|--------------|
| (31) Number       | (32) Date         | (33) Country |
| <b>18212060.0</b> | <b>2018.12.12</b> | <b>EP</b>    |

(43) Publication Date: **2020.06.18**

(44) Accepted Journal Date: **2024.10.10**

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(56) Related Art  
**WO 2014/143799 A2**



## (51) International Patent Classification:

C07D 473/06 (2006.01) A61P 25/22 (2006.01)

A61P 25/24 (2006.01) A61P 25/28 (2006.01)

A61P 25/16 (2006.01) A61P 25/18 (2006.01)

TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

## (21) International Application Number:

PCT/EP2019/084375

## (22) International Filing Date:

10 December 2019 (10.12.2019)

## (25) Filing Language:

English

## (26) Publication Language:

English

## (30) Priority Data:

18212060.0 12 December 2018 (12.12.2018) EP

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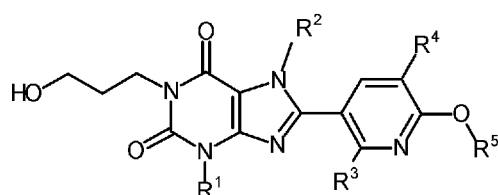
(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS,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

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ,

## Published:

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

(54) Title: SUBSTITUTED XANTHINE DERIVATIVES



(I)

(57) Abstract: The present invention relates to compounds of formula (I) a process for their manufacture, pharmaceutical compositions containing them and their use in therapy, particularly in the treatment of conditions having an association with TRPC5 containing ion channels. R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> have meanings given in the description.



## SUBSTITUTED XANTHINE DERIVATIVES

### FIELD OF THE INVENTION

The present invention relates to substituted xanthine derivatives, pharmaceutical compositions containing them and their use in therapy, particularly in the treatment or prevention of conditions having an association with TRPC5 containing ion channels.

### BACKGROUND OF THE INVENTION

A variety of ion channel proteins exist to mediate ion flux across cellular membranes. The proper expression and function of ion channel proteins is essential for the maintenance of cell function, and the intracellular communication. Numerous diseases are the result of misregulation of membrane potential or aberrant calcium handling. Given the central importance of ion channels in modulating membrane potential and ion flux in cells, identification of agents that can promote or inhibit particular ion channels are of great interest as research tools and as possible therapeutic agents.

Cation channels such as the transient receptor potential (TRP) cation channel subfamily C, member 5 (TRPC5) modulate the flux of calcium and sodium ions across cellular membranes. Sodium and calcium influx leads to a depolarization of the cell. This increases the probability that voltage-gated ion channels will reach the threshold required for activation. As a result, activation of non-selective cation channels can increase electrical excitability and increase the frequency of voltage-dependent events. Voltage-dependent events include, but are not limited to, neuronal action potentials, cardiac action potentials, smooth muscle contraction, cardiac muscle contraction, and skeletal muscle contraction.

Calcium influx caused by the activation of non-selective cation channels such as TRPC5 also alters the intracellular free calcium concentration. Calcium is a ubiquitous second messenger molecule within the cell and the alterations in intracellular calcium levels have profound effects on signal transduction and gene expression. Thus, activation of non-selective cation channels such as TRPC5 can lead to changes in gene expression and cellular phenotype. Gene expression events include, but are not limited to, production of mRNAs encoding cell surface receptors, ion channels, and kinases. These changes in gene expression can lead to hyperexcitability in that cell.

Homomeric TRPC5 ion channels are signal transduction gated,  $\text{Ca}^{2+}$ -permeable channels predominantly expressed in neurons. TRPC5 forms homomultimeric structures such as

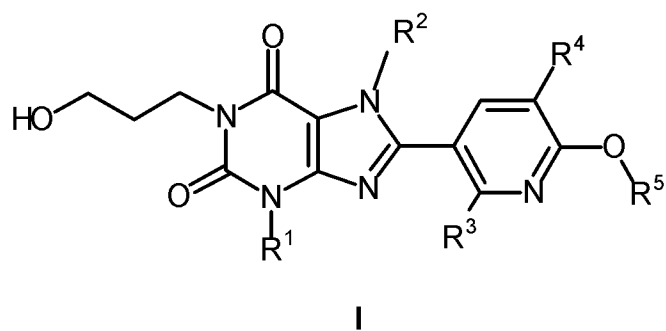
tetramers (i.e., TRPC5 homomultimers) and heteromultimeric structures such as tetramers (i.e., TRPC5-TRPC1 heteromultimers). Unless expressly stated otherwise, when the term TRPC5 is used herein, for example, when identifying a modulator of TRPC5 such as a TRPC5 antagonist, the term TRPC5 is used generically so as to include either or both of a TRPC5 homomultimer or a heteromultimer (e.g. TRPC5-TPRC1 or TRPC5-TRPC4 heteromultimer). Examples of TRPC5 in the literature include the following: Nature 2008 Jan. 3; 451 (7174):69-72; Mol Pharmacol. 2008 Jan.; 73 (1):42-9; J Biol Chem. 2007 Nov. 16; 282 (46):33868-78; Biochem Biophys Res Commun. 2008 Jan. 11; 365 (2):239-45; J Biol Chem. 2006 Nov. 3; 281 (44):33487-96; Eur J Pharmacol. 2005 Mar. 14; 510 (3):217- 22; J Biol Chem. 2006 Feb. 24; 281 (8):4977-82; Biochem Soc Trans. 2007 February; 35 (Pt.1):101-4; Handb Exp Pharmacol. 2007; (179):109-23; J Biol Chem. 2005 Mar. 25; 280 (12):10997-1006; J Physiol. 2006 Jan. 15; 570 (Pt 2):219-35; and Nat Neurosci. (2003) 6: 837- 45.

Modulating the function of TRPC5 proteins provides a means of modulating calcium homeostasis, sodium homeostasis, membrane polarization, and/or intracellular calcium levels, and compounds that can modulate TRPC5 function are useful in many aspects, including, but not limited to, maintaining calcium homeostasis, modulating intracellular calcium levels, modulating membrane polarization, and treating or preventing diseases, disorders, or conditions associated with calcium and/or sodium homeostasis or dyshomeostasis.

Compounds inhibiting TRPC5 containing ion channels are for example useful for treating conditions such as a neuropsychiatric disorder, a neurodegenerative disorder, nephropathy, and seizure disorder by modulating the activity of the transient receptor potential cation channel subfamily C, member 5 (TRPC5), which can exist in homomultimeric form as well as heteromultimeric form with other ion channels such as TRPC1 or TRPC3 (i.e. TRPC5-TRPC1 and TRPC1-TRPC3-TRPC5). WO 2014/143799 discloses xanthine derivatives that inhibit TRPC5. They modulate the function of TRPC5 by inhibiting a TRPC5-mediated ion flux or by inhibiting the inward current, the outward current, or both currents mediated by TRPC5.

## DETAILED DESCRIPTION OF THE INVENTION

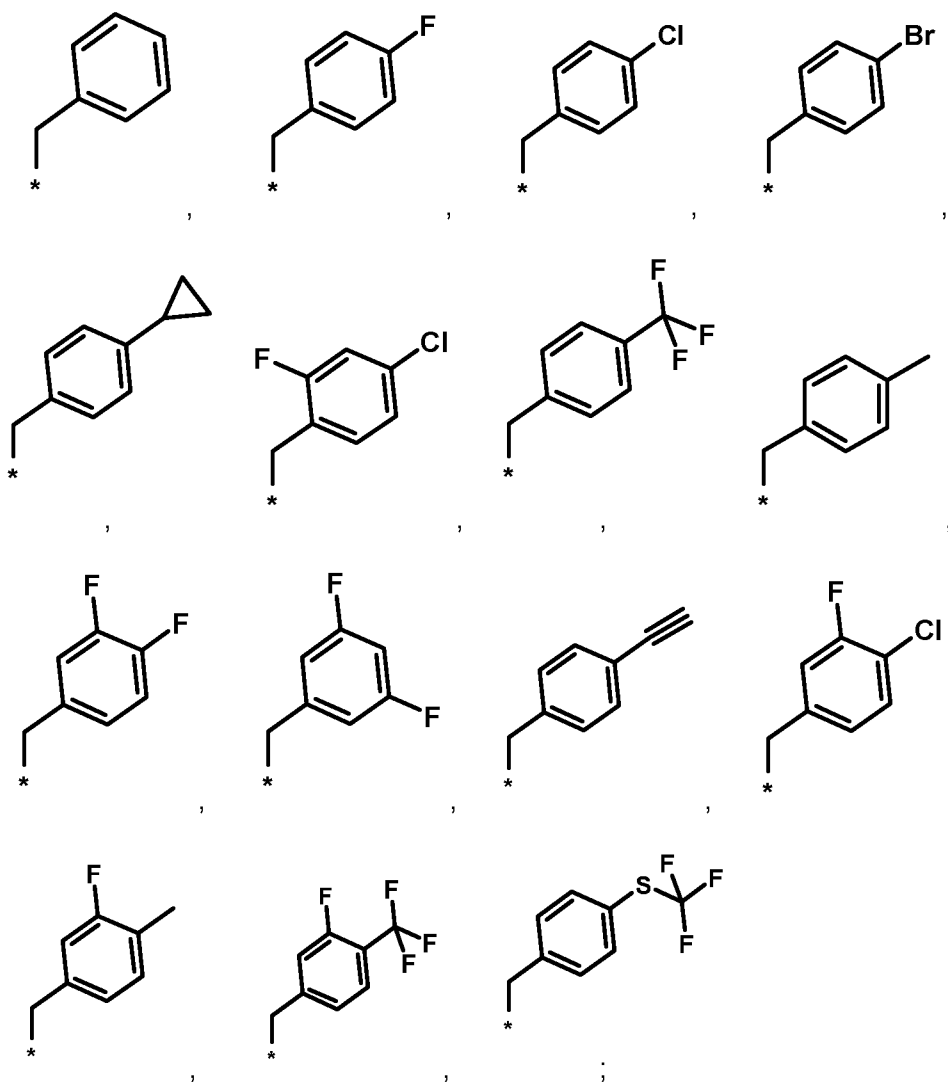
The present invention provides novel substituted xanthine derivatives of formula I



in which

$R^1$  represents ethyl, isopropyl, isobutyl, cyclobutyl;

5  $R^2$  represents

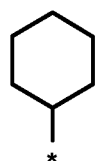


**R<sup>3</sup>** represents hydrogen, fluoro, C<sub>1</sub>-C<sub>3</sub>-alkyl optionally substituted with one or more fluorine atoms;

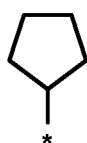
**R<sup>4</sup>** represents hydrogen or fluoro;

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$R^5$  represents



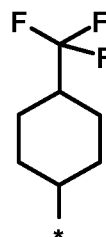
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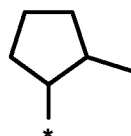
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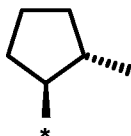
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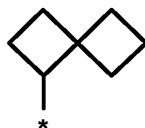
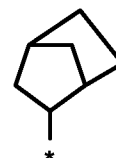
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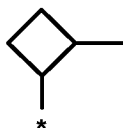
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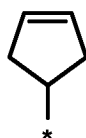
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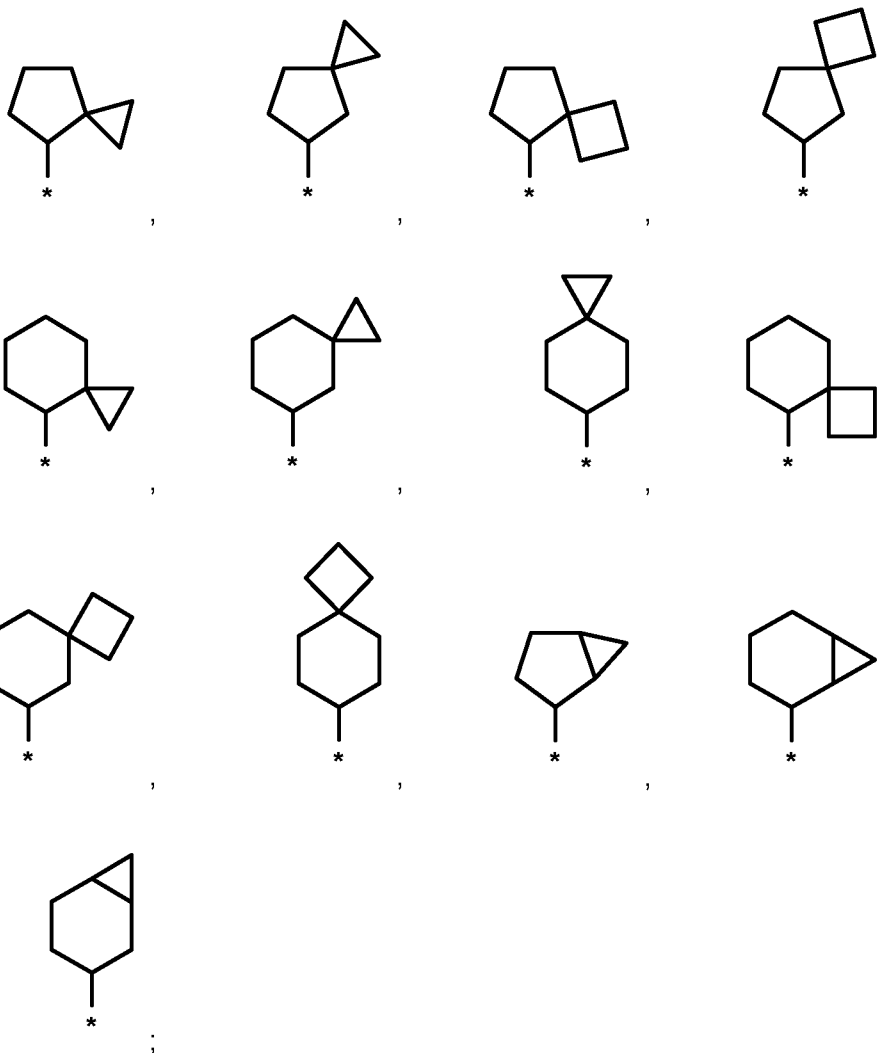
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which groups

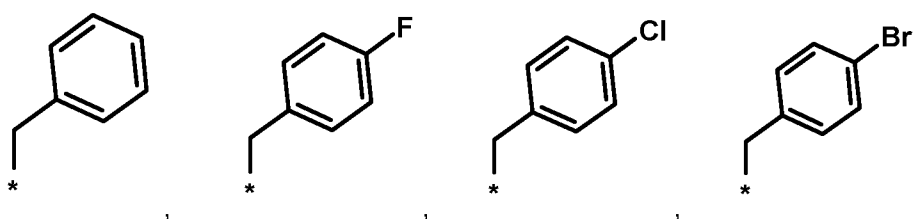
are optionally substituted with one or more fluorine atoms and/or one or more C<sub>1</sub>-C<sub>3</sub>-alkyl fluorinated with one or more fluorine atoms;

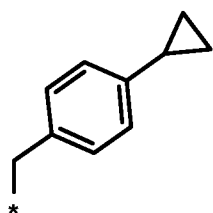
5 or a physiologically acceptable salt thereof.

In another embodiment, in the general formula I,

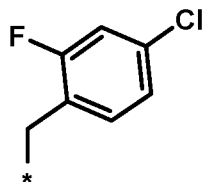
R<sup>1</sup> represents ethyl, isopropyl, isobutyl, cyclobutyl;

R<sup>2</sup> represents

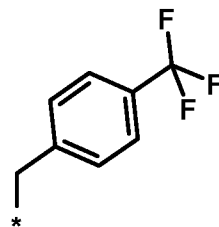




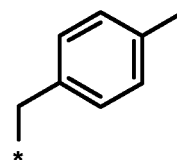
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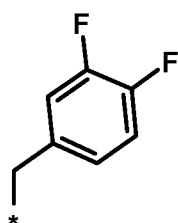
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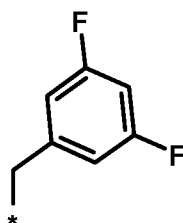
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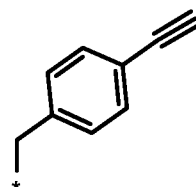
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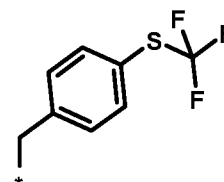
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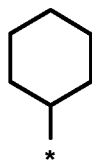
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$R^3$  represents hydrogen, fluoro, methyl, ethyl,  $-CF_3$ ;

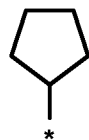
$R^4$  represents hydrogen or fluoro;

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$R^5$  represents



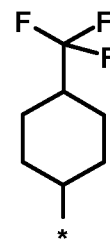
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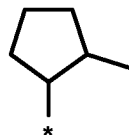
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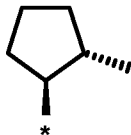
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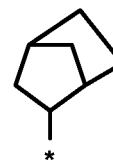
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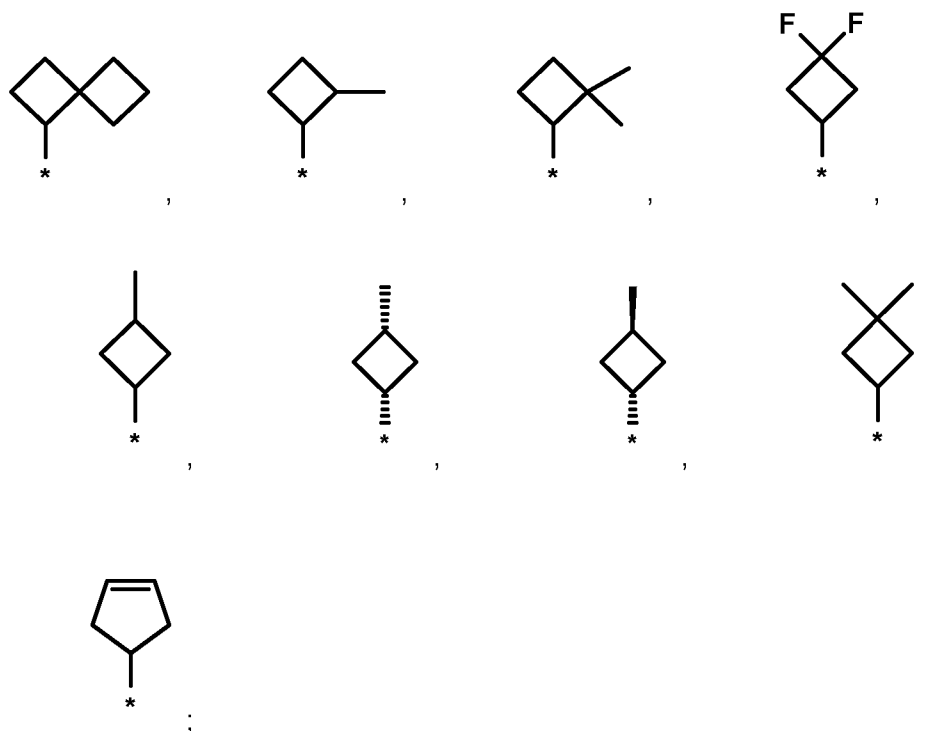
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or a physiologically acceptable salt thereof.

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Compounds of the present invention are potent TRPC5-inhibitors. They differ from the structurally closest compounds disclosed in WO 2014/143799 in that the C8-position of the xanthine in the compounds of the present invention is substituted with a 3-pyridyl group rather than with a phenyl group.

10

The compounds of the present invention modulate the function of TRPC5 by inhibiting a TRPC5-mediated ion flux or by inhibiting the inward current, the outward current, or both currents mediated by TRPC5. They are characterized by a higher potency for inhibition of TRPC5, when compared to the closest prior art compounds in WO 2014/143799.

15

The present invention thus provides compounds for use in the treatment of a TRPC5 mediated disorder.

The present invention further provides methods of treating a TRPC5 mediated disorder in a human subject comprising administering to the subject a compound or composition of a compound of the present invention or a pharmaceutically acceptable salt thereof.

- 5 In one aspect, the invention relates to a method for treating a condition for which reduced TRPC5 activity can reduce the severity of the condition, by administering a TRPC5 antagonist, such as a compound as described herein that inhibits a TRPC5-mediated current and/or a TRPC5-mediated ion flux. Described herein are compounds, which are TRPC5 antagonists that have a measured IC<sub>50</sub> for inhibition of TRPC5 of 5 nanomolar or less. In certain embodiments,
- 10 the compounds described herein, which are TRPC5 antagonists inhibit one or both of inward and outward TRPC5-mediated currents with an IC<sub>50</sub> of 5 nanomolar or less. In certain embodiments, the compounds described herein inhibit at least 95% of a TRPC5-mediated current or a TRPC5-mediated ion flux when administered at 1 micromolar or less.
- 15 In another aspect, the compounds described herein, which are TRPC5 antagonists can be used to inhibit a function of TRPC5, for example a TRPC5-mediated current and/or a TRPC5-mediated ion flux. In some embodiments, the compounds described herein can be used to inhibit a TRPC5 mediated current *in vitro*, for example in cells in culture. In other embodiments, the compounds described herein can be used to inhibit a TRPC5 mediated current *in vivo*. In
- 20 certain embodiments, the compounds described herein inhibit both an inward and an outward TRPC5-mediated current.

## DEFINITIONS

Terms not specifically defined herein should be given the meanings that would be given to them by one skilled in the art in light of the disclosure and the context.

5

The terms “antagonist” and “inhibitor” are used interchangeably to refer to an agent that decreases or suppresses a biological activity, such as to repress an activity of an ion channel, such as TRPC5. TRPC5 ion channels as described herein include homomultimeric and heteromultimeric structures (e.g. homomultimeric TRPC5 and heteromeric TRPC5-TRPC1 or  
10 TRPC5-TRPC4). TRPC5 antagonists include inhibitors having any combination of the structural and/or functional properties disclosed herein.

An “effective amount” of, e.g. a TRPC5 antagonist, with respect to the subject methods of inhibition or treatment, refers to an amount of the antagonist in a preparation which, when  
15 applied as part of a desired dosage regimen brings about a desired clinical or functional result. Without being bound by theory, an effective amount of a TRPC5 antagonist for use in the methods of the present invention includes an amount of a TRPC5 antagonist effective to decrease one or more *in vitro* or *in vivo* function of a TRPC5 channel. Exemplary functions include, but are not limited to, membrane polarization (e.g. an antagonist may promote  
20 hyperpolarization of a cell), ion flux, ion concentration in a cell, outward current, and inward current. Compounds that antagonize TRPC5 function include compounds that antagonize an *in vitro* or *in vivo* functional activity of TRPC5. When a particular functional activity is only readily observable in an *in vitro* assay, the ability of a compound to inhibit TRPC5 function in that *in vitro* assay serves as a reasonable proxy for the activity of that compound. In certain  
25 embodiments, an effective amount is an amount sufficient to inhibit a TRPC5-mediated current and/or an amount sufficient to inhibit TRPC5 mediated ion flux.

The TRPC5 antagonists for use in the methods of the present invention may be characterized according to their activity, or lack of activity, against one or more other ion channels. When  
30 other ion channels are referred to, inhibition of a function of such other ion channels is defined similarly. For example, inhibition of an ion channel or an activity of an ion channel means the antagonist inhibits one or more functional activities of the other ion channel. Such functions include the current mediated by the particular ion channel, ion flux, or membrane polarization.

35 The terms “compound” and “agent” are used interchangeably to refer to the inhibitors/antagonists of the invention.

The compounds described herein can be asymmetric (e.g., having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present invention that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically active starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis.

Resolution of racemic mixtures of compounds can be carried out by any of numerous methods known in the art. An example method includes fractional recrystallization using a "chiral resolving acid" which is an optically active, salt-forming organic acid. Suitable resolving agents for fractional recrystallization methods are, for example, optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids such as  $\beta$ -camphorsulfonic acid. Other resolving agents suitable for fractional crystallization methods include stereoisomerically pure forms of  $\alpha$ -methylbenzylamine (e.g., *S*- and *R*-forms, or diastereomerically pure forms), 2-phenylglycinol, norephedrine, ephedrine, N-methylephedrine, cyclohexylethylamine, and 1,2-diaminocyclohexane.

Resolution of racemic mixtures can also be carried out by elution on a column packed with an optically active resolving agent (e.g., dinitrobenzoylphenylglycine). Suitable elution solvent composition can be determined by one skilled in the art. Compounds of the invention also include tautomeric forms, such as keto-enol tautomers.

Unless specifically indicated, throughout the specification and the appended claims, a given chemical formula or name shall encompass tautomers and all stereo, optical and geometrical isomers (e.g. enantiomers, diastereoisomers, *E/Z* isomers) and racemates thereof, as well as mixtures in different proportions of the separate enantiomers, mixtures of diastereoisomers, or mixtures of any of the foregoing forms where such isomers and enantiomers exist.

Compounds of the invention can also include all isotopes of atoms occurring in the intermediates or final compounds. For example, the compound of the invention may be radiolabeled with radioactive isotopes, such as for example tritium ( $^3\text{H}$ ) or carbon-14 ( $^{14}\text{C}$ ). All isotopic variations, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound forms a salt with an acid or a base.

Examples for acids forming a pharmaceutically acceptable salt with a parent compound containing a basic moiety include mineral or organic acids such as benzenesulfonic acid, benzoic acid, citric acid, ethanesulfonic acid, fumaric acid, gentisic acid, hydrobromic acid, hydrochloric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, 4-methyl-benzenesulfonic acid, phosphoric acid, salicylic acid, succinic acid, sulfuric acid or tartaric acid. Also included are the salts of amino acids such as arginate, and salts of organic acids like glucuronic or galactunoric acids (see, for example, Berge et al., "Pharmaceutical Salts", Journal of Pharmaceutical Science, 1977, 66, 1-19).

Examples for cations and bases forming a pharmaceutically acceptable salt with a parent compound containing an acidic moiety include  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$ ,  $\text{NH}_4^+$ , L-arginine, 2,2'-iminobisethanol, L-lysine, *N*-methyl-D-glucamine or tris(hydroxymethyl)-aminomethane.

The neutral form of the compounds of the invention is preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

The terms "TRPC5", "TRPC5 protein", and "TRPC5 channel" are used interchangeably throughout the application. Unless expressly stated, the term TRPC5 includes homomultimeric structures (e.g. homomultimeric TRPC5) and heteromultimeric structures (e.g. heteromultimeric TRPC5-TRPC1).

## BIOLOGICAL ASSAYS

The biological activity of compounds is determined by the following methods:

### Assay A: Determination of TRPC5-inhibition

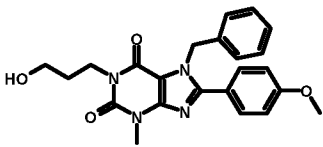
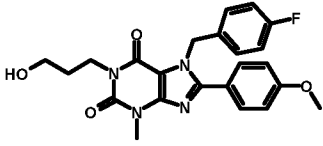
- 5 Patch clamp experiments permit the detection of currents through the TRPC5 channel in a cell line. In normal whole-cell patch clamp recordings, a glass electrode is brought into contact with a single cell and a high-resistance (gigaohm) seal is established with the cell membrane. The membrane is then ruptured to achieve the whole-cell configuration, permitting control of the voltage of the cell membrane and measurement of currents flowing across the membrane using
- 10 the amplifier attached to the electrode and resulting in the replacement of cytoplasm with the pipette solution. A perfusion system permits control of the extracellular solution, including the addition of blockers and activators of the current. The current can be activated by including 1.4  $\mu\text{M}$  free  $\text{Ca}^{2+}$  in the pipette (intracellular) solution, and 80  $\mu\text{M}$   $\text{LaCl}_3$  in the extracellular solution.
- 15 TRPC5 cells were induced 20-48 hours, removed from growth plates, and replated at low density (to attain good single-cell physical separation) on glass coverslips for measurement. In some cases, cells were grown in low density overnight on glass coverslips. Patch clamp recordings were made in the whole-cell mode with a holding potential of -40 mV. Every 5 seconds, a voltage ramp was applied from -120 to +100 mV, 400 ms in duration. Currents
- 20 elicited were quantified at -80 mV and +80 mV. The internal solution consisted of 140 mM cesium aspartate, 10 mM HEDTA, 2 mM  $\text{CaCl}_2$ , 2.27 mM  $\text{MgCl}_2$  and 10 mM HEPES, pH 7.2, with 1,400 nM calculated free  $\text{Ca}^{2+}$ . The external solution consisted of 150 mM NaCl, 4.5 mM 15 KCl, 1 mM  $\text{MgCl}_2$ , 2 mM  $\text{CaCl}_2$ , 10 mM HEPES, 10 mM glucose, 1 mM EGTA, pH 7.4. Upon addition of  $\text{LaCl}_3$ , TRPC5 current was induced only in TRPC5-expressing cells and not in
- 25 parental HEK293 TReX cells. Removal of the LaCh stimulus causes most of the current to go away. Potential blockers were tested for ability to block both inward and outward currents in the continued presence of  $\text{LaCl}_3$ .

- IC<sub>50</sub> of a compound of the invention was estimated by testing the compound 500 nM. When
- 30 500 nM of a compound showed no block, IC<sub>50</sub> was estimated as > 1  $\mu\text{M}$ . Compounds blocking 50% or more at 500 nM are retested at multiple concentrations, and the % block is fitted by standard equations to determine IC<sub>50</sub> accurately, using a 5/6 point concentration-response experiment.

## Biological Data

Table 1: *In vitro* potencies of the closest prior art compounds of WO2014/143799 determined in the Assay A (described above)

5

| Example                         | Structure                                                                          | Assay A<br>TRPC5<br>inhibition |
|---------------------------------|------------------------------------------------------------------------------------|--------------------------------|
| Example 441 in<br>WO2014/143799 |  | 324 nM                         |
| Example 465 in<br>WO2014/143799 |  | 52 nM                          |

Compounds of the present invention surprisingly show a much higher potency in TRPC5-inhibition when measured in the same assay (Assay A) than the closest prior art compounds (examples #441 and #465 in WO2014/143799).

10

The compounds of the present invention differ structurally from Examples 441 and 465 in WO 2014/143799, i.e. the closest prior art compounds, in that the C8-position of the xanthine in the presently claimed compounds is substituted with a 3-pyridyl rather than with a phenyl group as in Examples 441 and 465 of WO 2014/143799. Furthermore, the heteroaryl group in the presently claimed compounds is substituted with a cycloalkyl-O- group rather than with a methoxy-group, as in Examples 441 and 465 of WO 2014/143799. These structural differences unexpectedly result in a markedly increased potency in TRPC5-inhibition. (Tables 1 and 2).

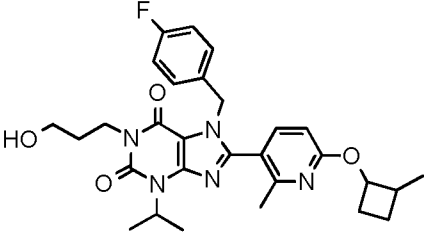
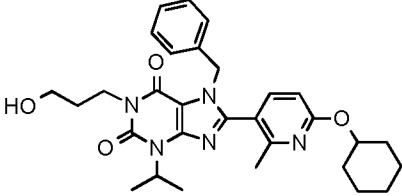
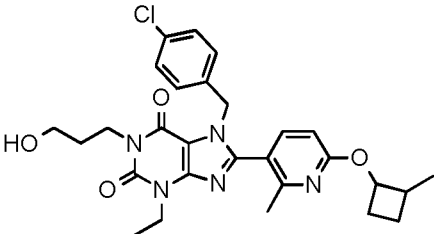
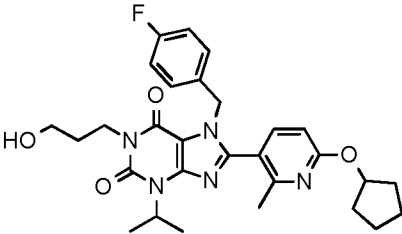
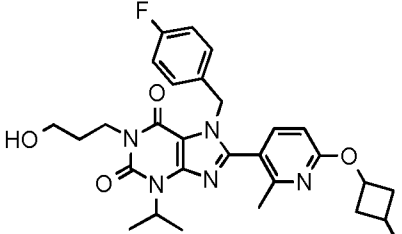
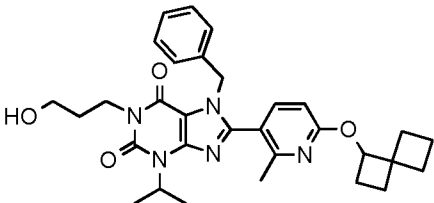
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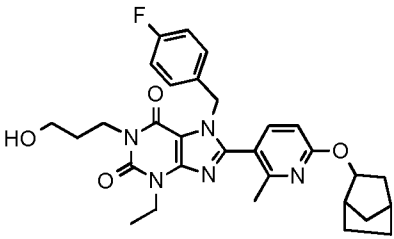
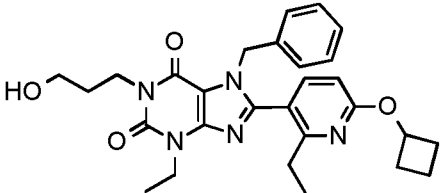
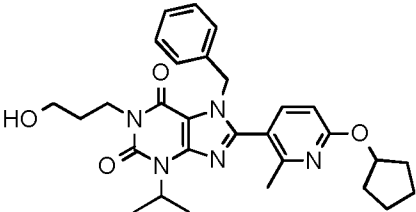
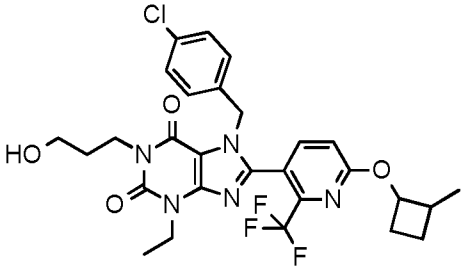
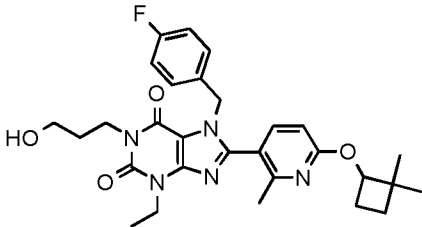
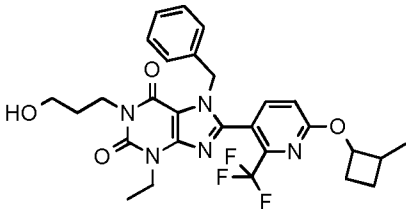
These results demonstrate that compounds of the present invention unexpectedly are superior to the structurally most similar example disclosed in WO2014/143799 (closest prior art compounds) in TRPC5 inhibition. Consequently, compounds of the present invention are more viable for human use.

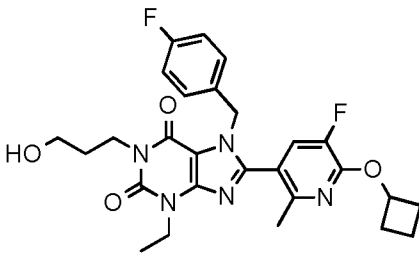
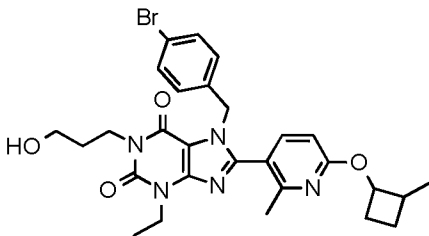
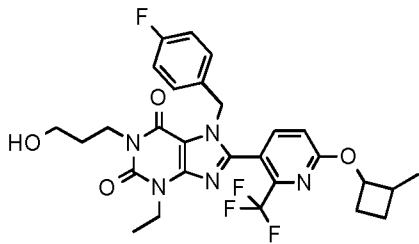
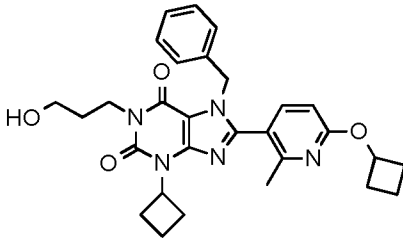
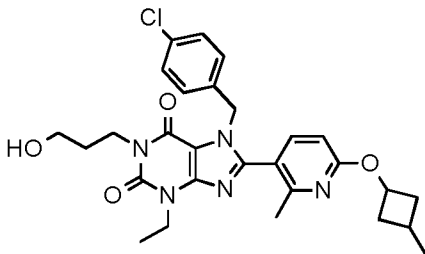
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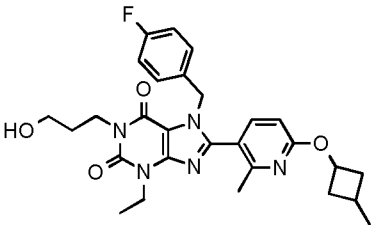
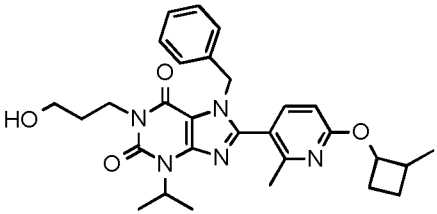
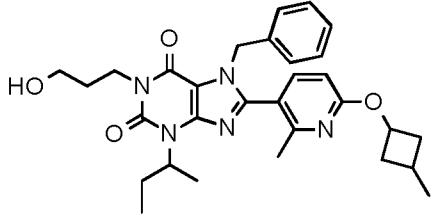
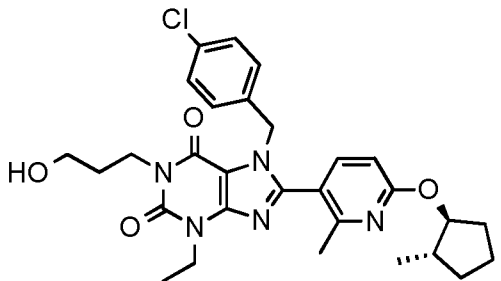
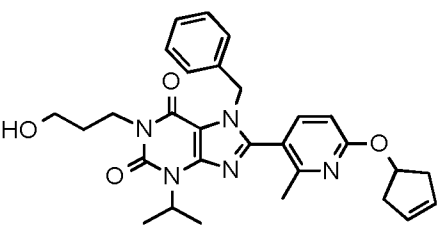
Table 2: *In vitro* potencies of compounds of the present invention determined in Assay A (described above)

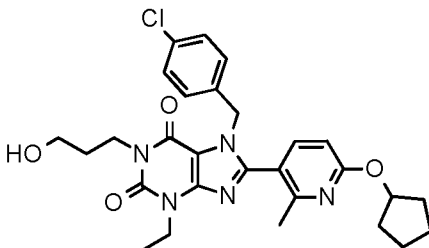
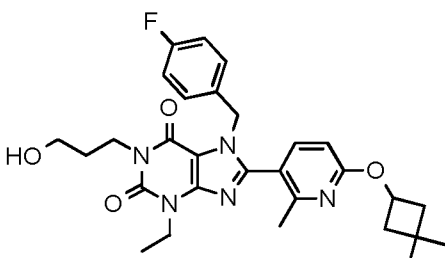
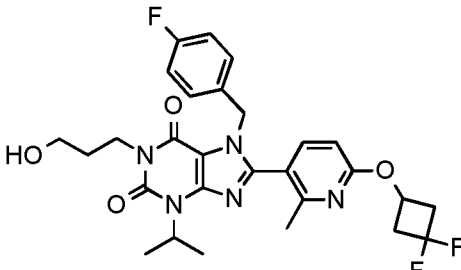
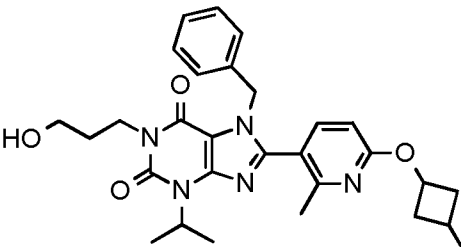
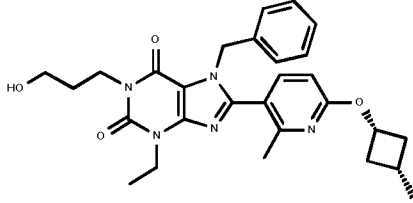
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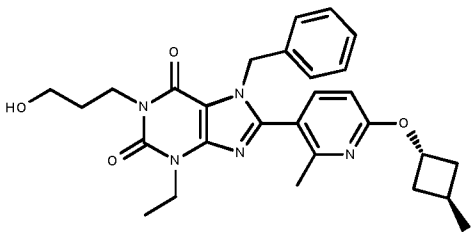
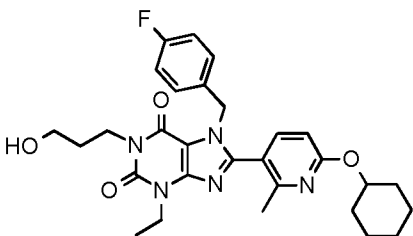
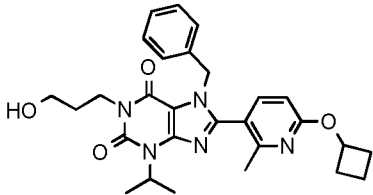
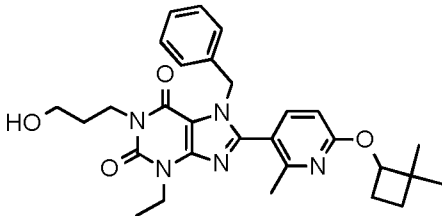
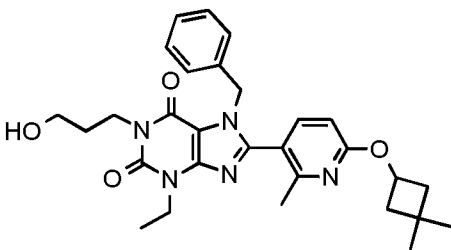
| Example | Structure                                                                           | Assay A TRPC5 inhibition |
|---------|-------------------------------------------------------------------------------------|--------------------------|
| 1       |    | < 0.032 nM               |
| 2       |    | 0.095 nM                 |
| 3       |   | 0.099 nM                 |
| 4       |  | < 0.1 nM                 |
| 5       |  | < 0.1 nM                 |
| 6       |  | < 0.1 nM                 |

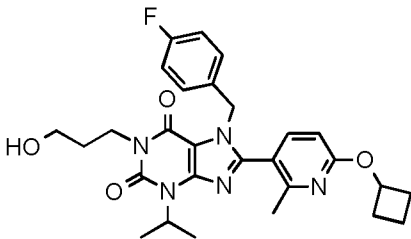
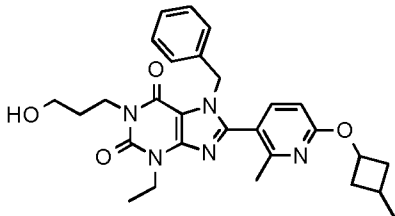
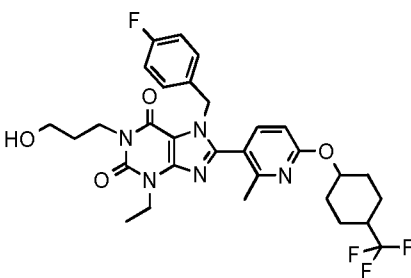
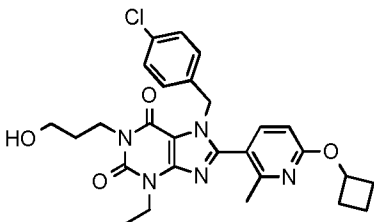
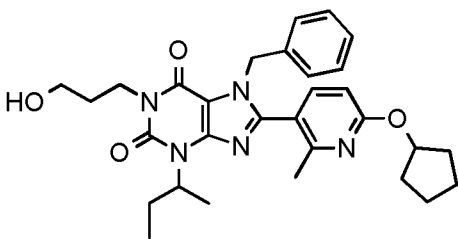
| Example | Structure                                                                           | Assay A TRPC5 inhibition |
|---------|-------------------------------------------------------------------------------------|--------------------------|
| 7       |    | 0.104 nM                 |
| 8       |    | 0.106 nM                 |
| 9       |   | 0.130 nM                 |
| 10      |  | 0.150 nM                 |
| 11      |  | 0.163 nM                 |
| 12      |  | 0.171 nM                 |

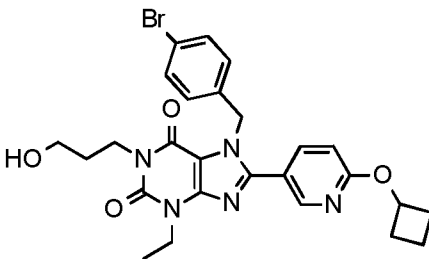
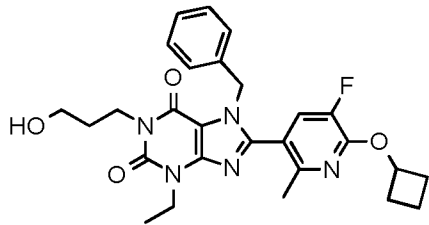
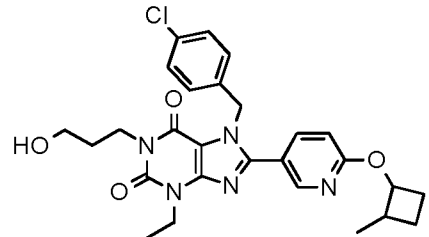
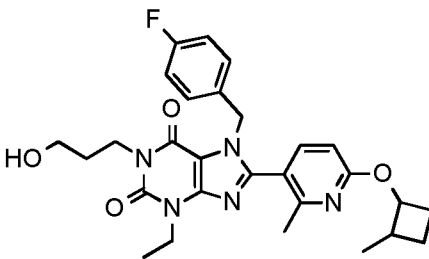
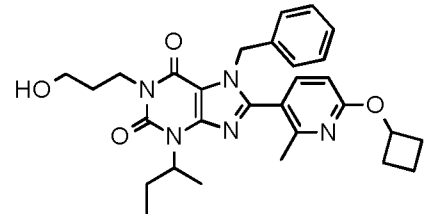
| Example | Structure                                                                           | Assay A TRPC5 inhibition |
|---------|-------------------------------------------------------------------------------------|--------------------------|
| 13      |    | 0.174 nM                 |
| 14      |    | 0.178 nM                 |
| 15      |   | 0.184 nM                 |
| 16      |  | 0.190 nM                 |
| 17      |  | 0.199 nM                 |

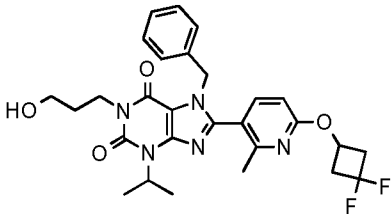
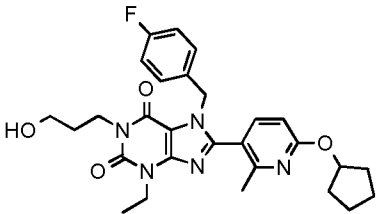
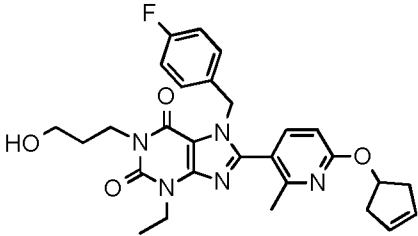
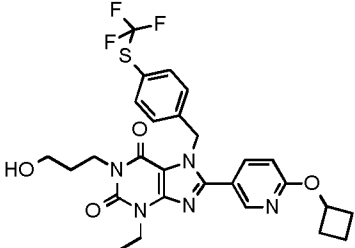
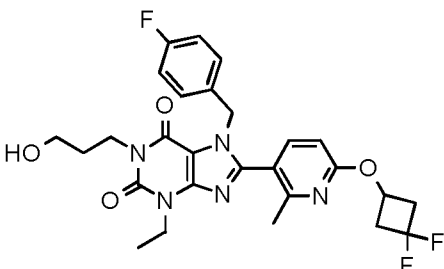
| Example | Structure                                                                                                         | Assay A TRPC5 inhibition |
|---------|-------------------------------------------------------------------------------------------------------------------|--------------------------|
| 18      |                                  | 0.207 nM                 |
| 19      |                                  | 0.236 nM                 |
| 20      |                                 | 0.246 nM                 |
| 21      |  <p>racemic trans-mixture</p> | 0.249 nM                 |
| 22      |                                | 0.265 nM                 |

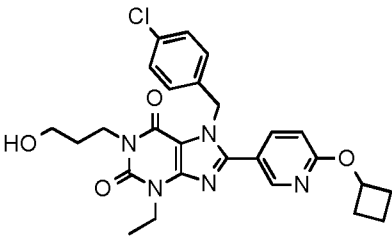
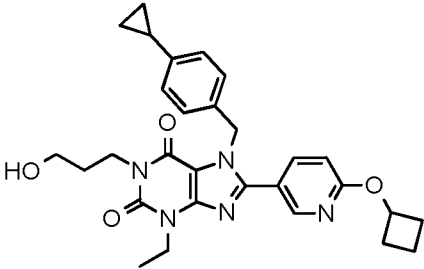
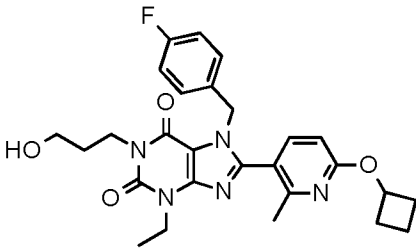
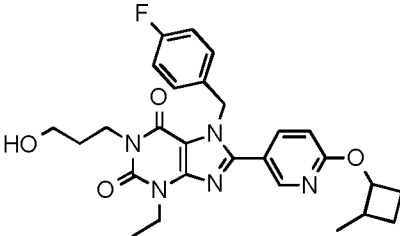
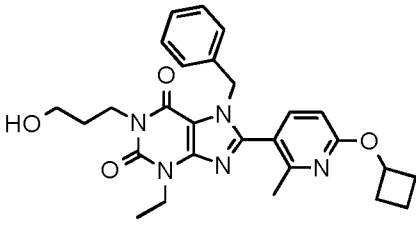
| Example | Structure                                                                           | Assay A TRPC5 inhibition |
|---------|-------------------------------------------------------------------------------------|--------------------------|
| 23      |    | 0.275 nM                 |
| 24      |    | 0.281 nM                 |
| 25      |   | 0.312 nM                 |
| 26      |  | < 0.32 nM                |
| 27      |  | 0.402 nM                 |

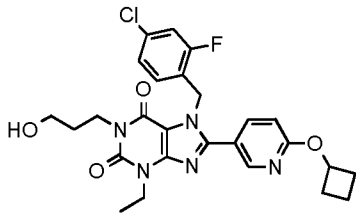
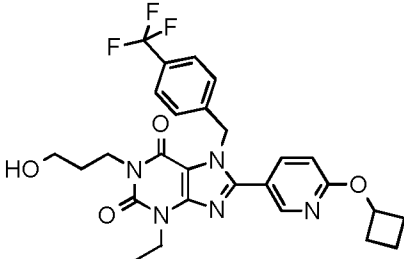
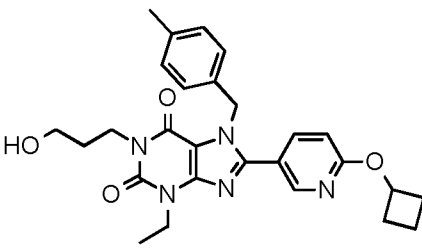
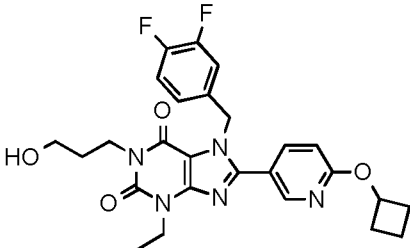
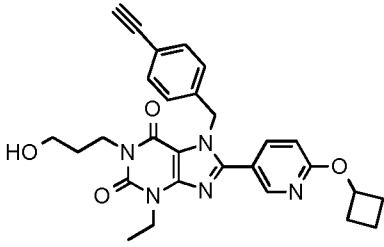
| Example | Structure                                                                           | Assay A TRPC5 inhibition |
|---------|-------------------------------------------------------------------------------------|--------------------------|
| 28      |   | 0.917 nM                 |
| 29      |    | 0.403 nM                 |
| 30      |   | 0.426 nM                 |
| 31      |  | 0.431 nM                 |
| 32      |  | 0.460 nM                 |

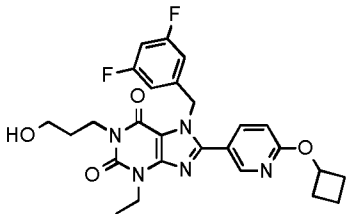
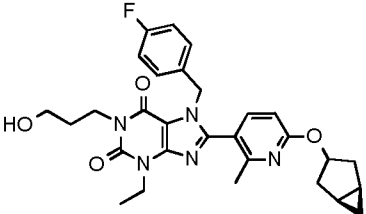
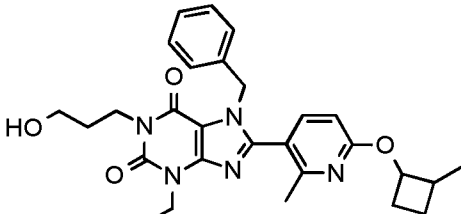
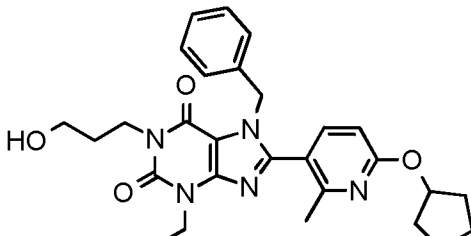
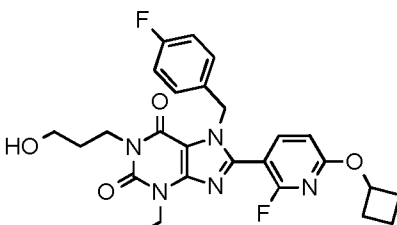
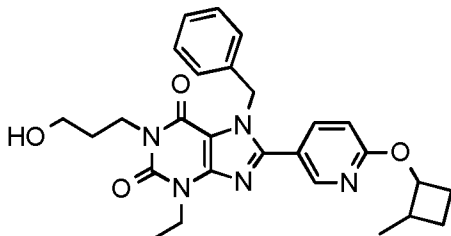
| Example | Structure                                                                           | Assay A TRPC5 inhibition |
|---------|-------------------------------------------------------------------------------------|--------------------------|
| 33      |    | 0.477 nM                 |
| 34      |    | 0.485 nM                 |
| 35      |   | 0.531 nM                 |
| 36      |  | 0.551 nM                 |
| 37      |  | 0.603 nM                 |

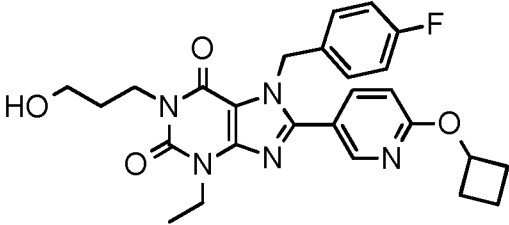
| Example | Structure                                                                           | Assay A TRPC5 inhibition |
|---------|-------------------------------------------------------------------------------------|--------------------------|
| 38      |    | 0.613 nM                 |
| 39      |    | 0.628 nM                 |
| 40      |   | 0.643 nM                 |
| 41      |  | 0.688 nM                 |
| 42      |  | 0.713 nM                 |

| Example | Structure                                                                           | Assay A TRPC5 inhibition |
|---------|-------------------------------------------------------------------------------------|--------------------------|
| 43      |    | 0.732 nM                 |
| 44      |    | 0.743 nM                 |
| 45      |   | 0.750 nM                 |
| 46      |  | 0.812 nM                 |
| 47      |  | 0.859 nM                 |

| Example | Structure                                                                           | Assay A TRPC5 inhibition |
|---------|-------------------------------------------------------------------------------------|--------------------------|
| 48      |    | 0.873 nM                 |
| 49      |    | 1.007 nM                 |
| 50      |   | 1.163 nM                 |
| 51      |  | 1.360 nM                 |
| 52      |  | 1.582 nM                 |

| Example | Structure                                                                           | Assay A TRPC5 inhibition |
|---------|-------------------------------------------------------------------------------------|--------------------------|
| 53      |    | 1.587 nM                 |
| 54      |    | 1.601 nM                 |
| 55      |   | 2.162 nM                 |
| 56      |  | 2.643 nM                 |
| 57      |  | 2.663 nM                 |

| Example | Structure                                                                            | Assay A TRPC5 inhibition |
|---------|--------------------------------------------------------------------------------------|--------------------------|
| 58      |     | 3.668 nM                 |
| 59      |     | 1.727 nM                 |
| 60      |    | 2.094 nM                 |
| 61      |  | 2.426 nM                 |
| 62      |   | 3.369 nM                 |
| 63      |   | 3.155 nM                 |

| Example | Structure                                                                          | Assay A TRPC5 inhibition |
|---------|------------------------------------------------------------------------------------|--------------------------|
| 64      |  | 2.715 nM                 |

### USE IN TREATMENT/ METHOD OF USE

The present invention is directed to compounds which are useful in the treatment of a disease, disorder and condition wherein the inhibition of the activity of the transient receptor potential cation channel TRPC5 is of therapeutic benefit. This includes but is not limited to the treatment and/or prevention of psychiatric, neurological or neurodegenerative conditions, pain, seizure, non-neuronal conditions, and cancer.

**Psychiatric conditions** include diseases associated with dysregulated emotional processing (e.g. borderline personality disorder or depressive disorders like major depression, major depressive disorder, psychiatric depression, dysthymia, and postpartum depression, and bipolar disorders), anxiety and fear-related disorders (e.g. post-traumatic stress disorder, panic disorder, agoraphobia, social phobias, generalized anxiety disorder, panic disorder, social anxiety disorder, obsessive compulsive disorder, and separation anxiety), memory disorders (e.g. Alzheimer's disease, amnesia, aphasia, brain injury, brain tumor, chronic fatigue syndrome, Creutzfeldt-Jakob disease, dissociative amnesia, fugue amnesia, Huntington's disease, learning disorders, sleeping disorders, multiple personality disorder, pain, post-traumatic stress disorder, schizophrenia, sports injuries, stroke, and Wernicke-Korsakoff syndrome), disorders associated with impaired impulse control and addiction.

**Neurological or neurodegenerative conditions** include e.g. Alzheimer's disease (AD), Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), and other brain disorders caused by trauma or other insults including aging.

**Pain disorders** include nociceptive pain, inflammatory pain, cancer pain, and neuropathic pain (e.g. cancer pain, osteoarthritic pain, rheumatoid arthritis pain, post-herpetic neuralgia, pain due to burns, and other indications). The pain can be chronic or acute.

**Seizures** may be induced by excitotoxicity of a variety of origins. Commonly excess neuronal firing can drive seizure activity. Compounds that reduce the hyperexcitability of relevant neuronal populations have significant potential in reducing seizure activity. Compounds of the invention that inhibit TRPC5 may reduce hyperexcitability and thus reduce seizure activity.

**Non-neuronal conditions** include nephropathy, proteinuric kidney disease, liver diseases such as hepatic dyslipidemia associated with cholestasis, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD) [WO2018/146485], itch, disorders associated with malfunction of the cardiovascular-vascular system or vascular permeability (e.g. pulmonary arterial hypertension, acute respiratory distress syndrome (ARDS), maladaptive cardiac remodeling, disorders associated with maladaptive blood pressure control like hypertension or hypotension, and other medical conditions such as diabetes, insulin resistance, metabolic syndrome and obesity. It is envisaged that the use for treatment of non-neuronal conditions may also extend to the use for cosmetic weight loss (WO2018/146485).

Another aspect of the invention relates to pharmaceutical compositions for use in a human patient, comprising an effective amount of a compound described herein (or a pharmaceutically acceptable salt thereof), and one or more pharmaceutically acceptable excipient(s). The invention further contemplates the use of the compounds described herein in the manufacture of a medicament or a pharmaceutical composition to treat or reduce the symptoms of any of the diseases or conditions provided in the specification. The compounds described herein can be used for treating a particular disease or condition and can be formulated for administration via a route appropriate for the particular disease or condition.

The applicable daily dose of compounds of the present invention may vary from 0.1 to 2000 mg. The actual pharmaceutically effective amount or therapeutic dose will depend on factors known by those skilled in the art such as age and weight of the patient, route of administration and severity of disease. In any case, the drug substance is to be administered at a dose and in a manner which allows a pharmaceutically effective amount to be delivered that is appropriate to the patient's condition.

## PHARMACEUTICAL COMPOSITIONS

Suitable compositions for administering the compounds of the present invention will be apparent to those with ordinary skill in the art and include for example tablets, pills, capsules, suppositories, lozenges, troches, solutions, syrups, elixirs, sachets, injectables, inhalatives, and

powders. The content of the pharmaceutically active compound(s) may vary in the range from 0.1 to 95 wt.-%, preferably 5.0 to 90 wt.-% of the composition as a whole.

Suitable tablets may be obtained, for example, by mixing a compound of the present invention with known excipients, for example inert diluents, carriers, disintegrants, adjuvants, surfactants, binders and/or lubricants and compressing the resulting mixture to tablets.

### COMBINATION THERAPY

The compounds of the present invention can be used alone or in combination with other active pharmaceutical ingredients. In particular, compounds according to the present invention can be combined with other treatment options known to be used in the art in connection with a treatment of any of the indications the treatment of which is in the focus of the present invention.

Among such active pharmaceutical ingredients or treatment options that are considered suitable for combination with the compounds and the treatment according to the present invention are antidepressants, mood stabilizers, typical and atypical antipsychotics, anxiolytics, antiepileptic drugs, sleeping agents, cognitive enhancers, stimulants, additional psychoactive drugs, anti-inflammatory drugs, analgesic drugs, chemotherapeutic drugs as well as active pharmaceutical ingredients used or potentially useful in the treatment of metabolic disorders, liver diseases and kidney diseases, the latter active pharmaceutical ingredients also including potential inhibitors of TRPC3 and/or TRPC6.

## EXPERIMENTAL SECTION

**List of abbreviations:**

|    |       |                                        |
|----|-------|----------------------------------------|
| 5  | ACN   | acetonitrile                           |
|    | conc  | concentrated                           |
|    | d     | day(s)                                 |
|    | DCM   | dichloromethane                        |
|    | DIPEA | N-ethyl-diisopropylamine               |
| 10 | DMAP  | 4-dimethylaminopyridine                |
|    | DMF   | N,N- dimethylformamide                 |
|    | DMSO  | dimethylsulfoxide                      |
|    | EtOAc | ethyl acetate                          |
|    | g     | gram                                   |
| 15 | h     | hour(s)                                |
|    | HOAc  | acetic acid                            |
|    | HPLC  | high performance liquid chromatography |
|    | MeOH  | Methanol                               |
|    | min   | minute(s)                              |
| 20 | mg    | milligram                              |
|    | mL    | milliliter                             |
|    | N     | normal                                 |
|    | rt    | room temperature                       |
|    | RT    | retention time                         |
| 25 | SFC   | supercritical fluid chromatography     |
|    | THF   | tetrahydrofuran                        |
|    | TFA   | trifluoroacetic acid                   |
|    | μL    | microliter                             |

**HPLC-Methods:**

|    |                  |                                      |
|----|------------------|--------------------------------------|
| 30 | Method Name:     | <b>A</b>                             |
|    | Column:          | XBridge BEH C18_ 2.1 x 30 mm, 1.7 μm |
|    | Column Supplier: | Waters                               |

| Gradient/Solvent | % Sol | % Sol [ACN] | Flow [mL/min] | Temp [°C] |
|------------------|-------|-------------|---------------|-----------|
|------------------|-------|-------------|---------------|-----------|

| Time [min] | [H <sub>2</sub> O, 0.1% TFA] |     |     |    |
|------------|------------------------------|-----|-----|----|
| 0.00       | 99                           | 1   | 1.6 | 60 |
| 0.02       | 99                           | 1   | 1.6 | 60 |
| 1.00       | 0                            | 100 | 1.6 | 60 |
| 1.10       | 0                            | 100 | 1.6 | 60 |

Method Name: **B**

Column: XBridge BEH Phenyl, 2.1 x 30 mm, 1.7 µm

Column Supplier: Waters

| Gradient/Solvent<br>Time [min] | % Sol<br>[H <sub>2</sub> O, 0.1%<br>NH <sub>3</sub> ] | % Sol<br>[Acetonitril] | Flow [mL/min] | Temp [°C] |
|--------------------------------|-------------------------------------------------------|------------------------|---------------|-----------|
| 0.00                           | 95                                                    | 5                      | 1.3           | 60        |
| 0.02                           | 95                                                    | 5                      | 1.3           | 60        |
| 1.00                           | 0                                                     | 100                    | 1.3           | 60        |
| 1.10                           | 0                                                     | 100                    | 1.3           | 60        |

5

Method Name: **C**

Column: XBridge C18, 4.6 x 30 mm, 3.5 µm

Column Supplier: Waters

| Gradient/Solvent<br>Time [min] | % Sol<br>[H <sub>2</sub> O, 0.1%<br>NH <sub>3</sub> ] | % Sol [ACN] | Flow [mL/min] | Temp [°C] |
|--------------------------------|-------------------------------------------------------|-------------|---------------|-----------|
| 0.00                           | 97                                                    | 3           | 5             | 60        |
| 0.02                           | 97                                                    | 3           | 5             | 60        |
| 1.60                           | 0                                                     | 100         | 5             | 60        |
| 1.70                           | 0                                                     | 100         | 5             | 60        |

10

Method Name: **D**

Column: XBridge BEH C18, 2.1 x 30 mm, 1.7 µm

Column Supplier: Waters

| Gradient/Solvent<br>Time [min] | % Sol<br>[H <sub>2</sub> O, 0.1%<br>NH <sub>3</sub> ] | % Sol [ACN] | Flow [mL/min] | Temp [°C] |
|--------------------------------|-------------------------------------------------------|-------------|---------------|-----------|
| 0.00                           | 95                                                    | 5           | 1.3           | 60        |
| 0.02                           | 95                                                    | 5           | 1.3           | 60        |
| 1.00                           | 0                                                     | 100         | 1.3           | 60        |
| 1.10                           | 0                                                     | 100         | 1.3           | 60        |

Method Name: **E**

Column: XBridge BEH C18\_2.1 x 30 mm\_2.5 µm

Column Supplier: Waters

| Gradient/Solvent<br>Time [min] | % Sol<br>[H <sub>2</sub> O, 0.1%<br>NH <sub>3</sub> ] | % Sol [ACN] | Flow [mL/min] | Temp [°C] |
|--------------------------------|-------------------------------------------------------|-------------|---------------|-----------|
| 0.00                           | 50                                                    | 50          | 1.3           | 60        |
| 0.02                           | 50                                                    | 50          | 1.3           | 60        |
| 1.00                           | 0                                                     | 100         | 1.3           | 60        |
| 1.10                           | 0                                                     | 100         | 1.3           | 60        |

5

Method Name: **F**

Column: Sunfire C18\_3.0 x 30 mm\_2.5 µm

Column Supplier: Waters

| Gradient/Solvent<br>Time [min] | % Sol<br>[H <sub>2</sub> O, 0.1%<br>TFA (v/v)] | % Sol [ACN] | Flow [mL/min] | Temp [°C] |
|--------------------------------|------------------------------------------------|-------------|---------------|-----------|
| 0.0                            | 95.0                                           | 5.0         | 1.5           | 60.0      |
| 1.3                            | 0.0                                            | 100.0       | 1.5           | 60.0      |
| 1.5                            | 0.0                                            | 100.0       | 1.5           | 60.0      |

10

Method Name: **G**

Column: XBridge BEH C18\_2.1 x 30 mm\_2.5 µm

Column Supplier: Waters

| Gradient/Solvent<br>Time [min] | % Sol<br>[H <sub>2</sub> O, 0.1%<br>NH <sub>3</sub> ] | % Sol [ACN] | Flow [mL/min] | Temp [°C] |
|--------------------------------|-------------------------------------------------------|-------------|---------------|-----------|
| 0.00                           | 95                                                    | 5           | 1.3           | 60        |
| 0.02                           | 95                                                    | 5           | 1.3           | 60        |
| 1.00                           | 0                                                     | 100         | 1.3           | 60        |
| 1.10                           | 0                                                     | 100         | 1.3           | 60        |

Method Name: **H**

Column: XBridge BEH C18\_2.1 x 30 mm\_1.7 µm

Column Supplier: Waters

| Gradient/Solvent<br>Time [min] | % Sol<br>[H <sub>2</sub> O, 0.1%<br>NH <sub>3</sub> ] | % Sol [ACN] | Flow [mL/min] | Temp [°C] |
|--------------------------------|-------------------------------------------------------|-------------|---------------|-----------|
| 0.00                           | 50                                                    | 50          | 1.3           | 60        |
| 0.02                           | 50                                                    | 50          | 1.3           | 60        |
| 1.00                           | 0                                                     | 100         | 1.3           | 60        |
| 1.10                           | 0                                                     | 100         | 1.3           | 60        |

5

Method Name: **I**

Column: Lux® Cellulose\_3 4.6 x 250 mm\_5 µm

Column Supplier: Phenomenex

| Gradient/Solvent<br>Time [min] | % Sol<br>[scCO <sub>2</sub> ] | % Sol<br>[MEOH<br>20mM<br>NH <sub>3</sub> ] | Flow<br>[mL/min] | Temp [°C] | Back<br>pressure<br>(PSI) |
|--------------------------------|-------------------------------|---------------------------------------------|------------------|-----------|---------------------------|
| 0.0                            | 90.0                          | 10.0                                        | 4.0              | 40.0      | 2175.0                    |
| 10.0                           | 90.0                          | 10.0                                        | 4.0              | 40.0      | 2175.0                    |

10

Method Name: **J**

Column: Chiralpak® IA\_4.6 x 250 mm\_5 µm

Column Supplier: Daicel

| Gradient/Solvent<br>Time [min] | % Sol<br>[scCO <sub>2</sub> ] | % Sol<br>[MEOH<br>20mM<br>NH <sub>3</sub> ] | Flow<br>[mL/min] | Temp [°C] | Back<br>pressure<br>(PSI) |
|--------------------------------|-------------------------------|---------------------------------------------|------------------|-----------|---------------------------|
| 0.0                            | 85.0                          | 15.0                                        | 4.0              | 40.0      | 2175.0                    |
| 10.0                           | 85.0                          | 15.0                                        | 4.0              | 40.0      | 2175.0                    |

Method Name: **K**

Column: Lux® Amylose-2\_4.6 x 250 mm\_5 µm

5 Column Supplier: Phenomenex

| Gradient/Solvent<br>Time [min] | % Sol<br>[scCO <sub>2</sub> ] | % Sol<br>[MEOH<br>20mM<br>NH <sub>3</sub> ] | Flow<br>[mL/min] | Temp [°C] | Back<br>pressure<br>(PSI) |
|--------------------------------|-------------------------------|---------------------------------------------|------------------|-----------|---------------------------|
| 0.0                            | 95.0                          | 5.0                                         | 4.0              | 40.0      | 2175.0                    |
| 10.0                           | 95.0                          | 5.0                                         | 4.0              | 40.0      | 2175.0                    |

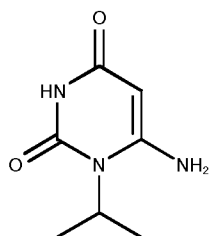
**NMR method:** NMR spectra were recorded on a Bruker AVANCE IIIHD 400 MHz

10 instrument using TopSpin 3.2 pl6 software. Chemical shifts are given in parts per million (ppm) downfield from internal reference trimethylsilane in δ units. Selected data are reported in the following manner: chemical shift (multiplicity, coupling constants (J), number of hydrogens). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), spt (septet), m (multiplet), br (broad).

15

### **Intermediates:**

Intermediate 1.1



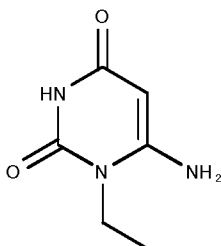
1.1

The reaction was performed under argon atmosphere and in dried glassware. Sodium [metal] (4.50 g, 196 mmol) was added in pieces to dry propan-2-ol (150 mL). The mixture was stirred 2 h and heated to 95°C. After the sodium was completely dissolved, isopropyl-urea (10.0 g, 97.9 mmol) and cyano-acetic acid ethyl ester (10.4 mL, 97.9 mmol) were added and the mixture was stirred overnight at 95°C. The mixture was cooled down and H<sub>2</sub>O (40.0 mL) was added and the pH was adjusted to 6 with conc HCl. Stirring was continued under ice cooling and N<sub>2</sub> atmosphere for 12 h. The obtained precipitate was filtered and dried to obtain 7.33 g of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 170

HPLC: RT = 0.23 min, Method F

Intermediate 1.2



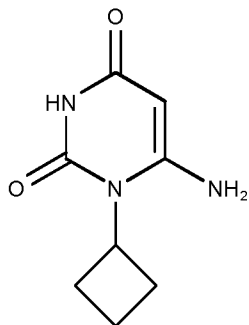
1.2

The reaction was performed under argon atmosphere and in dried glassware. Sodium (metal) (20.9 g, 908 mmol) was added in pieces to dry ethanol (600 mL). The mixture was stirred 3 d and heated to 60°C. After the sodium was completely dissolved, ethylurea (40.0 g, 454 mmol) and ethyl 2-cyanoacetate (48.3 mL, 454 mmol) were added and the mixture was stirred 4 d at reflux. The mixture was concentrated in vacuo, H<sub>2</sub>O (200 mL) was added and the pH was adjusted to 7 with conc HCl. Stirring was continued under ice cooling for 30 min. The obtained precipitate was filtered, washed with H<sub>2</sub>O and dried to obtain 48.59 g of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 156

HPLC: RT = 1.18 min, Method B

## Intermediate 1.3



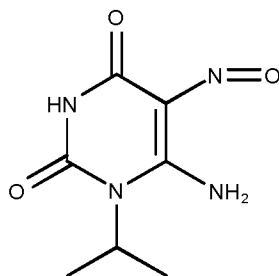
1.3

- 5 The reaction was performed under nitrogen atmosphere and in dried glassware. Sodium (metal) (0.6 g, 26.3 mmol) was added in pieces to dry propan-2-ol (20 mL). The mixture was stirred 1 h at 60°C. Then EtOH (5 mL, 60.7 mmol) was added and the mixture was stirred 30 min at 60°C. After the sodium was completely dissolved, cyclobutylurea (1.5 g, 13.1 mmol) and ethyl 2-cyanoacetate (1.4 mL, 13.1 mmol) were added and the mixture was stirred overnight at reflux. The mixture was concentrated in vacuo, H<sub>2</sub>O (5.0 mL) was added and the pH was adjusted to 7 with conc HCl. Stirring was continued under ice cooling and N<sub>2</sub> atmosphere for 45 min. The obtained precipitate was filtered and dried to obtain 1.61 g of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 182

- 15 HPLC: RT = 0.31 min, Method F

## Intermediate 2.1



2.1

- 20 To a mixture of intermediate 1.1 (1.00 g, 5.91 mmol) in HCl (1 mol/l, 16.5 mL, 16.5 mmol) NaNO<sub>2</sub> (571 mg, 8.28 mmol) in H<sub>2</sub>O (6.00 mL) was added dropwise. NaOH (4 N, about 4 mL) was added until the pH of the solution reached pH=9. The obtained

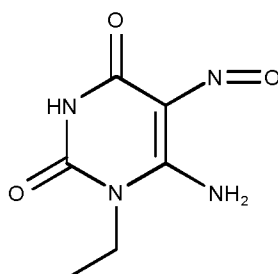
precipitate was filtered, washed with MeOH and tert-butylmethylether and dried to obtain 0.79 g of the product.

MS (ESI+): (M+H)<sup>+</sup> 199

HPLC: RT = 0.24 min, Method F

5

#### Intermediate 2.2



2.2

To a mixture of intermediate 1.2 (48.6 g, 0.304 mol) in HCl (1 mol/l, 800 mL, 800 mmol)

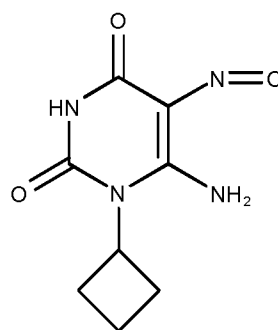
10  $\text{NaNO}_2$  (29.3 g, 0.425 mol) in  $\text{H}_2\text{O}$  (280 mL) was added dropwise. The mixture was stirred overnight at rt. Then the mixture was basified with NaOH (60%, about 15 mL).

The obtained precipitate was filtered, washed with MeOH and tert-butylmethylether and dried to obtain 43.8 g of the product.

MS (ESI+): (M+H)<sup>+</sup> 185

15 HPLC: RT = 0.09 min, Method B

#### Intermediate 2.3



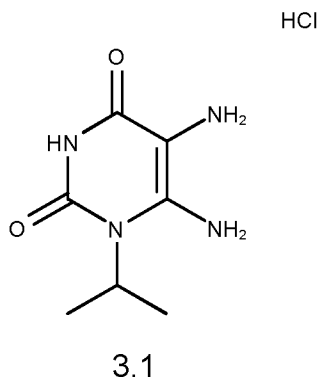
2.3

20 To a mixture of intermediate 1.3 (2.31 g, 0.013 mol) in HCl (1 mol/l, 16.5 mL, 16.5 mmol)  $\text{NaNO}_2$  (1.23 g, 0.018 mol) in  $\text{H}_2\text{O}$  (6 mL) was added dropwise. Then the mixture was neutralised with NaOH (4N). The obtained precipitate was filtered, washed with  $\text{H}_2\text{O}$  and tert-butylmethylether and dried to obtain 2.27 g of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 211

HPLC: RT = 0.30 min, Method F

### Intermediate 3.1

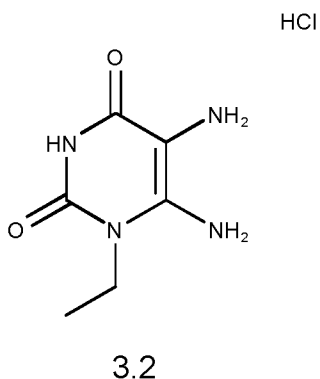


A mixture of intermediate 2.1 (8.04 g, 40.6 mmol), Pd/C (10%, 1.9 g), MeOH (120 mL), H<sub>2</sub>O (80 mL) and HCl solution (4 mol/L, 11.2 mL, 44.6 mmol) was hydrogenated at rt and 50 psi of H<sub>2</sub> for 4 h. The mixture was filtered, MeOH was evaporated, ACN was added and freeze dried to obtain 3.04 g of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 185

HPLC: RT = 0.01 min, Method D

### Intermediate 3.2

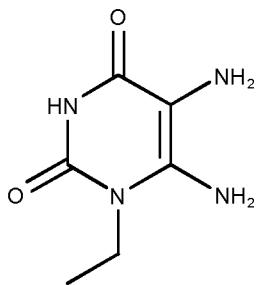


A mixture of intermediate 2.2 (43.3 g, 235 mmol), Pd/C (10%, 4.95 g), MeOH (400 mL), H<sub>2</sub>O (300 mL) and HCl solution (1 mol/L, 259 mL, 259 mmol) was hydrogenated at rt and 50 psi of H<sub>2</sub> for 1 d. The mixture was filtered, MeOH was evaporated, ACN was added and freeze dried to obtain 47.2 g of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 169/171

HPLC: RT = 0.08/0.1 min, Method B

## Intermediate 3.3



3.3

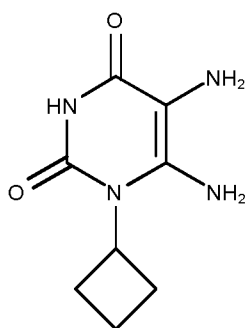
- 5 A mixture of intermediate 2.2 (31.0 g, 109 mmol), Pd/C (10%, 3.0 g), MeOH (270 mL), H<sub>2</sub>O (207 mL) and HCl solution (1 mol/L, 185 mL, 185 mmol) was hydrogenated at rt and 50 psi of H<sub>2</sub> for 1.5 d (temperature increased to 50°C). The mixture was filtered, MeOH was evaporated and freeze-dried. The residue was dissolved in H<sub>2</sub>O (390 mL) and NaHCO<sub>3</sub> was added until the pH reached 6-7. The obtained precipitate was filtered,  
 10 washed with cold H<sub>2</sub>O and tert-butylmethylether and dried to give 15.6 g of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 171

HPLC: RT = 0.14 min, Method F

## Intermediate 3.4

HCl



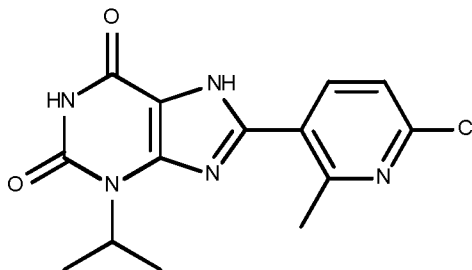
3.4

- 15 A mixture of intermediate 2.3 (1.0 g, 4.76 mmol), Pd/C (10%, 115 mg), MeOH (15 mL), H<sub>2</sub>O (7.5 mL) and HCl solution (1 mol/L, 5.23 mL, 5.23 mmol) was hydrogenated at rt and 50 psi of H<sub>2</sub> for 4 h. The mixture was filtered and the mixture was concentrated in vacuo. The crude product was purified by chromatography to obtain 1.24 g of the  
 20 product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 197

HPLC: RT = 0.15 min, Method F

Intermediate 4.1



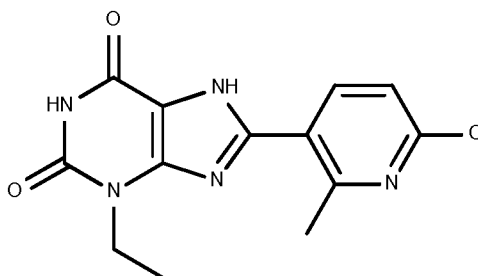
4.1

To a mixture of intermediate 3.1 (0.4 g, 1.8 mmol) in DMF (1.00 mL) and DMSO (1.00 mL) 6-chloro-2-methylpyridine-3-carbaldehyde (282 mg, 1.8 mmol) was added and the mixture was stirred 45 min at 100°C in the microwave. The mixture was cooled to rt,  
10 H<sub>2</sub>O was added and the obtained precipitate was filtered and dried to obtain 0.41 g of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 319

HPLC: RT = 0.70 min, Method F

15 Intermediate 4.2



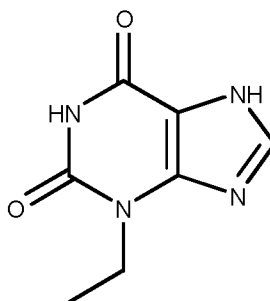
4.2

Intermediate 4.2 was prepared in an analogous manner to intermediate 4.1 using intermediate 3.2 and 6-chloro-2-methylpyridine-3-carbaldehyde.

20 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 306

HPLC: RT = 0.54 min, Method C

Intermediate 4.3



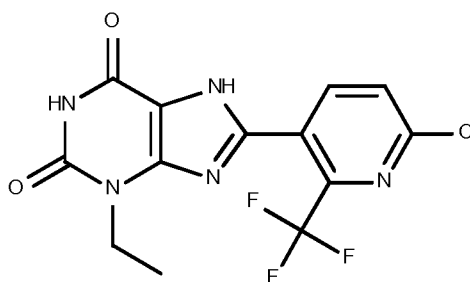
4.3

To a mixture of intermediate 3.3 (2.0 g, 10.6 mmol) in (diethoxymethoxy) ethane (16.5 mL) formic acid (0.535 mL, 12.2 mmol) was added and the mixture was stirred overnight  
5 at 150°C. The mixture was cooled in an icebath, the obtained precipitate was filtered, washed with tert-butylmethylether and dried to obtain 1.93 g of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 181

HPLC: RT = 0.27 min, Method F

#### 10 Intermediate 4.4



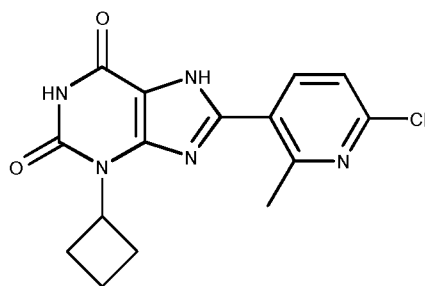
4.4

To a mixture of intermediate 3.2 (0.8 g, 3.1 mmol) in DMF (4.00 mL, 49.2 mmol) and DMSO (4.00 mL, 56.3 mmol) 6-chloro-2-(trifluoromethyl)pyridine-3- carbaldehyde (649  
15 mg, 3.1 mmol) was added and the mixture was stirred 45 min at 100°C in the microwave. H<sub>2</sub>O was added, the obtained precipitate was filtered and dried to obtain 1.10 g of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 360

HPLC: RT = 0.68 min, Method F

#### 20 Intermediate 4.6



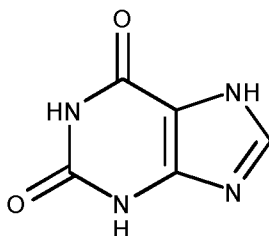
4.6

To a mixture of intermediate 3.4 (300 mg, 1.03 mmol) in DMF (1 mL, 12.3 mmol) and DMSO (1 mL, 14.1 mmol) 6-chloro-2-methylpyridine-3-carbaldehyde (160.5 mg, 1.03 mmol) was added and the mixture was stirred 45 min at 100°C in the microwave. H<sub>2</sub>O was added, the obtained precipitate was filtered and dried to obtain 0.31 g of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 332/334

HPLC: RT = 0.75 min, Method F

#### Intermediate 4.8



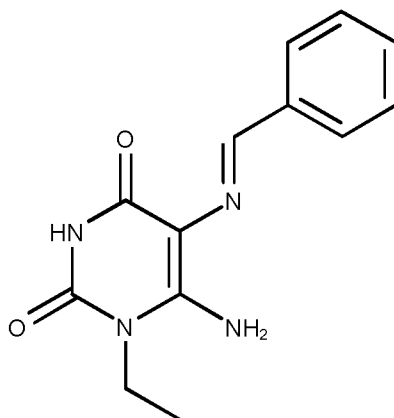
4.8

To a mixture of 5,6-diamino-1,2,3,4-tetrahydropyrimidine-2,4-dione-sulfate (8.45 g, 35.2 mmol) in (diethoxymethoxy) ethane (52.7 mL, 317 mmol) formic acid (3.08 mL, 70.4 mmol) was added and the mixture was stirred overnight at 150°C. The mixture was cooled, H<sub>2</sub>O was added and the obtained precipitate was filtered, washed with H<sub>2</sub>O and dried to obtain 5.83 g of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 153.1

HPLC: RT = 0.10 min, Method D

#### Intermediate 4.10



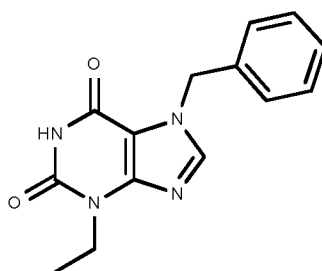
4.10

To a mixture of intermediate 3.2 (2.0 g, 8.23 mmol) in H<sub>2</sub>O (104 ml) benzaldehyde (1.67 mL, 16.46 mmol) was added and the mixture was stirred 1 h at rt. The obtained  
5 precipitate was filtered, washed with water and dried to obtain 2.27 g of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 259/260

HPLC: RT = 0.41 min, Method D

Intermediate 4.11



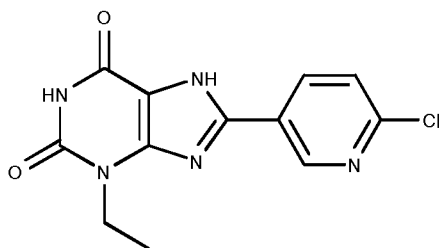
4.11

To a mixture of intermediate 23.1 (594 mg, 1.62 mmol) in (diethoxymethoxy)ethane (17.47 mL, 105 mmol) formic acid (170.6  $\mu$ L, 4.52 mmol) was added and the mixture was stirred 30 min at reflux. The mixture was cooled, H<sub>2</sub>O was added and the obtained  
15 precipitate was filtered and dried to obtain 241 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 271/272

HPLC: RT = 0.39 min, Method D

Intermediate 4.12



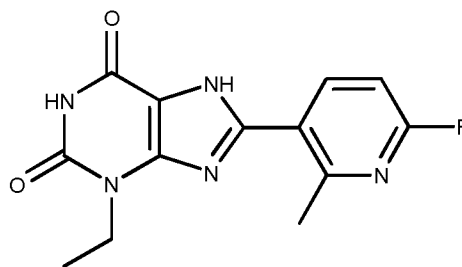
4.12

To a mixture of intermediate 3.2 (1.0 g, 4.84 mmol) in DMF (10 mL, 123 mmol) and DMSO (10 mL, 141 mmol) 6-chloropyridine-3-carbaldehyde (685 mg, 4.84 mmol) was added and the mixture was stirred 45 min at 100°C in the microwave. H<sub>2</sub>O was added, the obtained precipitate was filtered, washed with H<sub>2</sub>O and dried to obtain 1.0 g of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 292/294

HPLC: RT = 0.57 min, Method C

Intermediate 4.13



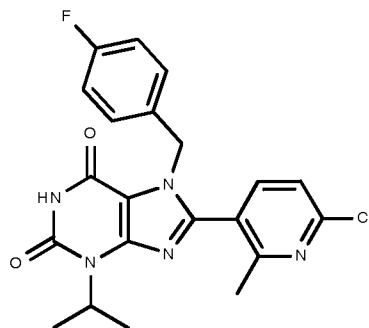
4.13

Intermediate 4.13 was prepared in an analogous manner to intermediate 4.12 using intermediate 3.2 and 6-fluoro-2-methylpyridine-3-carbaldehyde.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 290/291

HPLC: RT = 0.52 min, Method F

Intermediate 5.1



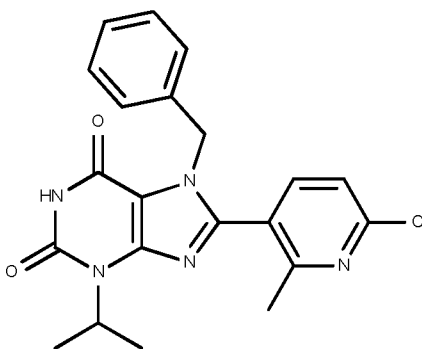
5.1

To a mixture of intermediate 4.1 (405 mg, 1.27 mmol) in DMF (3.00 mL), THF (3 mL) and DMSO (3 mL) DIPEA (0.262 mL, 1.52 mmol) and 1-(bromomethyl)-4-fluorobenzene (0.157 mL, 1.27 mmol) were added and the mixture was stirred 2.5 h at 80°C. The mixture was acidified with TFA and purified by chromatography to obtain 508 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 427

HPLC: RT = 0.88 min, Method F

#### Intermediate 5.2



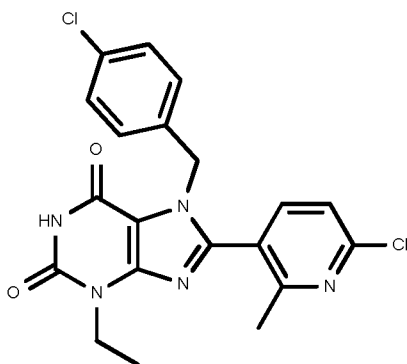
5.2

To a mixture of intermediate 4.1 (1.5 g, 4.47 mmol) in DMF (15.0 mL), DIPEA (0.923 mL, 5.37 mmol) and (bromomethyl)benzene (0.53 mL, 4.47 mmol) were added and the mixture was stirred 1 h at 80°C. H<sub>2</sub>O was added and extracted with EtOAc. The combined organic layers were dried and concentrated in vacuo to obtain 1.54 g of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 411/413

HPLC: RT = 0.9 min, Method F

#### Intermediate 5.3



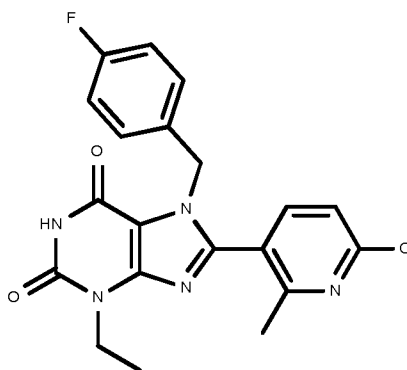
5.3

Intermediate 5.3 was prepared in an analogous manner to intermediate 5.1 using intermediate 4.2 and 1-(bromomethyl)-4-chlorobenzene.

5 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 430

HPLC: RT = 0.85 min, Method F

Intermediate 5.4



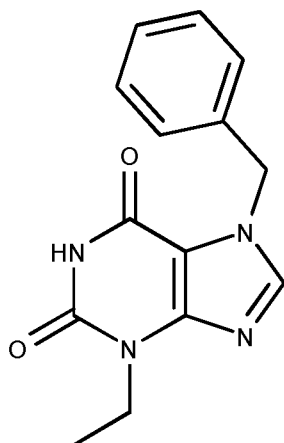
5.4

To a mixture of intermediate 4.2 (1.0 g, 3.27 mmol) in DMF (10.0 mL), DIPEA (0.675 mL, 3.93 mmol) and 1-(bromomethyl)-4-fluorobenzene (0.404 mL, 3.27 mmol) were added and the mixture was stirred 4 h at 80°C. The mixture was cooled, filtered and the filtrate was purified by chromatography to obtain 0.67 g of the product.

15 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 414/416

HPLC: RT = 0.79 min, Method F

Intermediate 5.5



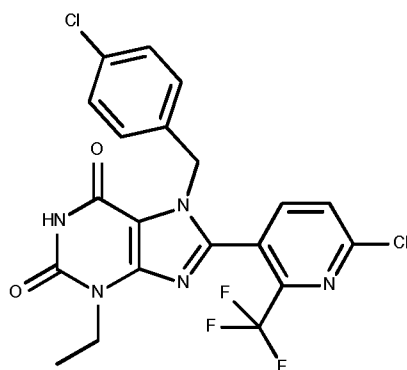
5.5

To a mixture of intermediate 4.3 (150 mg, 0.83 mmol) in THF (0.53 mL) and DMSO (0.53 mL) DIPEA (0.29 mL, 1.67 mmol) was added and the mixture was stirred 5 min at 80°C. Then (bromomethyl)benzene (0.99 mL, 0.83 mmol) was added and the mixture was stirred 1 h at 80°C. H<sub>2</sub>O was added and extracted with EtOAc. The combined organic layers were dried, concentrated in vacuo and purified by chromatography to obtain 85.0 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 271/272

HPLC: RT = 0.4 min, Method G

#### Intermediate 5.6



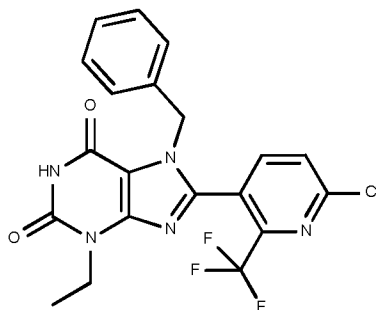
5.6

To a mixture of intermediate 4.4 (0.2 g, 0.56 mmol) in DMF (4.0 mL), DIPEA (0.115 mL, 0.67 mmol) and 1-(bromomethyl)-4-chlorobenzene (114 mg, 0.56 mmol) were added and the mixture was stirred 2.5 h at 80°C. The reaction mixture was filtered and purified by chromatography to obtain 226 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 484

HPLC: RT = 0.95 min, Method F

Intermediate 5.7



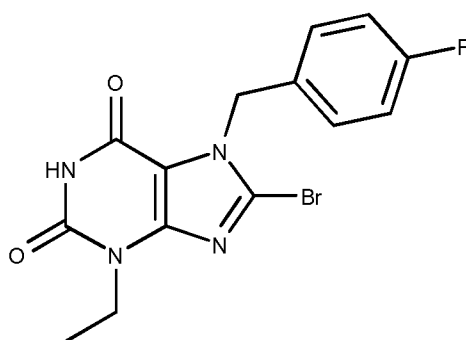
5.7

Intermediate 5.7 was prepared in an analogous manner to intermediate 5.6 using intermediate 4.4 and (bromomethyl) benzene.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 450

HPLC: RT = 0.87 min, Method F

Intermediate 5.9



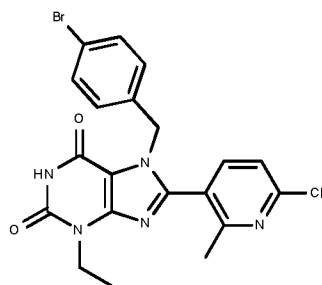
5.9

To a mixture of intermediate 13.1 (90 mg, 0.347 mmol) in DMF (1.0 mL), DIPEA (0.119 mL, 0.695 mmol) and 1-(bromomethyl)-4-fluorobenzene (0.043 mL, 0.347 mmol) were added and the mixture was stirred 1 h at rt. H<sub>2</sub>O was added, the obtained precipitate was filtered and dried to obtain 104 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 367/369

HPLC: RT = 0.74 min, Method F

Intermediate 5.10



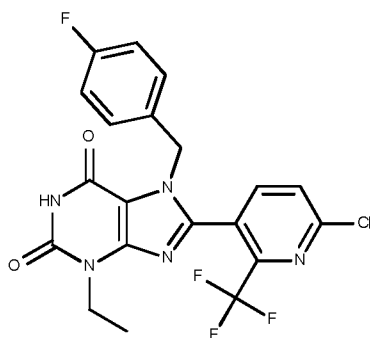
5.10

Intermediate 5.10 was prepared in an analogous manner to intermediate 5.6 using intermediate 4.2 and 1-bromo-4-(bromomethyl)benzene.

5 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 476

HPLC: RT = 0.88 min, Method F

Intermediate 5.11



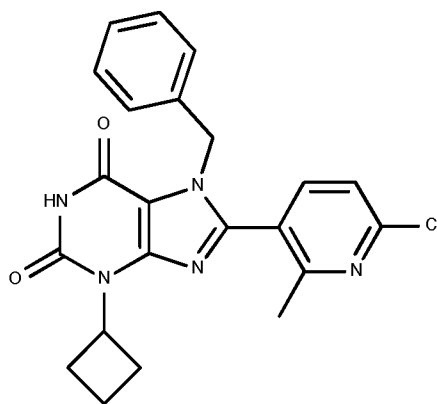
5.11

Intermediate 5.11 was prepared in an analogous manner to intermediate 5.6 using intermediate 4.4 and 1-(bromomethyl)-4-fluorobenzene.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 468

HPLC: RT = 0.90 min, Method F

Intermediate 5.12



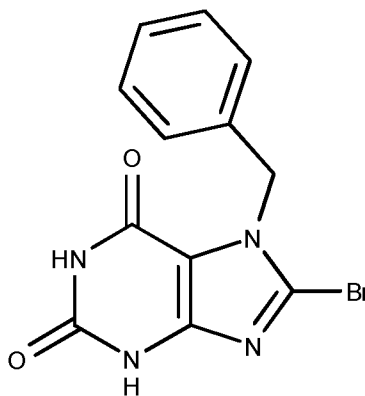
5.12

To a mixture of intermediate 4.6 (308 mg, 0.93 mmol) in DMF (5.0 mL), DIPEA (0.192 mL, 1.11 mmol) and (bromomethyl)benzene (110.3  $\mu$ L, 0.93 mmol) were added and the mixture was stirred 2 h at 80°C. The reaction mixture was purified by chromatography to obtain 282 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 422/424

HPLC: RT = 0.96 min, Method F

#### Intermediate 5.14



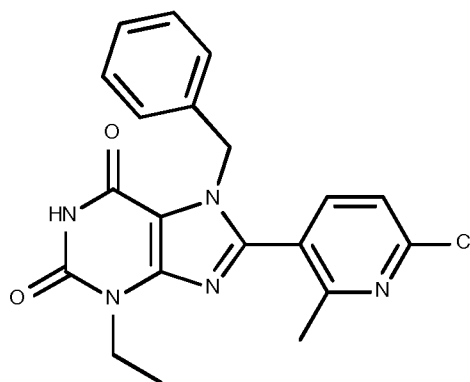
5.14

To a mixture of intermediate 13.2 (6.1 g, 13.2 mmol) in DMF (35 mL), THF (35 mL) and DMSO (35 mL) DIPEA (6.8 mL, 39.6 mmol) and (bromomethyl)benzene (1.67 mL, 14.5 mmol) were added and the mixture was stirred 45 min at rt. The mixture was filtered, concentrated in vacuo and purified by chromatography to obtain 1.70 g of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 321

HPLC: RT = 0.56 min, Method F

## Intermediate 5.15



5.15

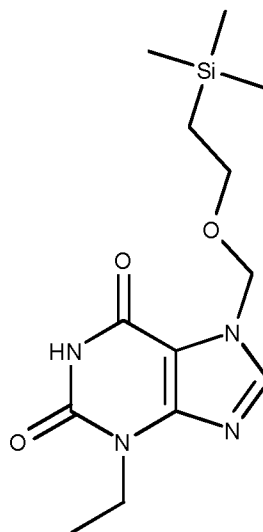
To a mixture of intermediate 4.2 (1.0 g, 3.27 mmol) in DMF (10.0 mL), DIPEA (0.675 mL, 3.93 mmol) and (bromomethyl)benzene (388.5  $\mu$ L, 3.27 mmol) were added and the mixture was stirred 4 h at 80°C. The reaction mixture was cooled, filtered and purified by chromatography to obtain 684 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 396/398

HPLC: RT = 0.78 min, Method F

10

## Intermediate 5.17



5.17

To a mixture of intermediate 4.3 (540 mg, 3 mmol) in DMSO (2 mL) and THF (2 mL) DIPEA (1.03 mL, 6 mmol) and [2-(chloromethoxy)ethyl]trimethylsilane (0.53 mL, 3

15

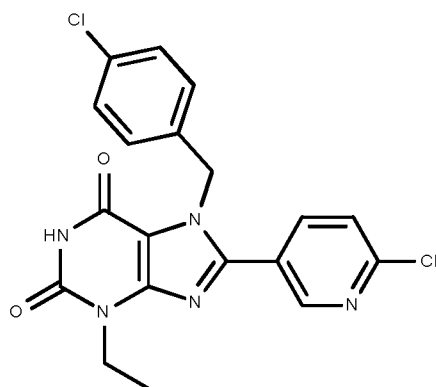
mmol) were added and the mixture was stirred 1 h at rt to obtain the crude product, which was used without further purification.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 311

HPLC: RT = 0.54 min, Method D

5

Intermediate 5.18



5.18

To a mixture of intermediate 4.12 (350 mg, 1.2 mmol) in DMF (3 mL, 37 mmol) DIPEA (247.7  $\mu$ L, 1.44 mmol) and 1-(bromomethyl)-4-chlorobenzene (246.6 mg, 1.2 mmol) were added and the mixture was stirred overnight at 80°C. The reaction mixture was filtered and purified by chromatography to obtain 148 mg of the product.

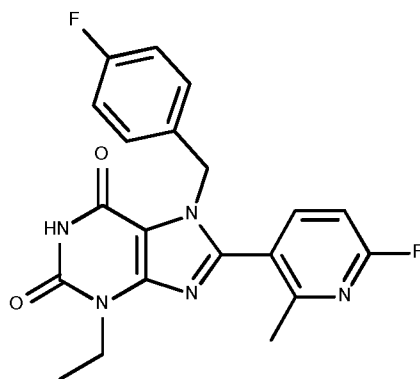
10

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 416/418

HPLC: RT = 0.85 min, Method F

15

Intermediate 5.19



5.19

To a mixture of intermediate 4.13 (426 mg, 1.47 mmol) in DMF (5 mL, 61.5 mmol) DIPEA (304  $\mu$ L, 1.77 mmol) and 1-(bromomethyl)-4-fluorobenzene (193  $\mu$ L, 1.47 mmol)

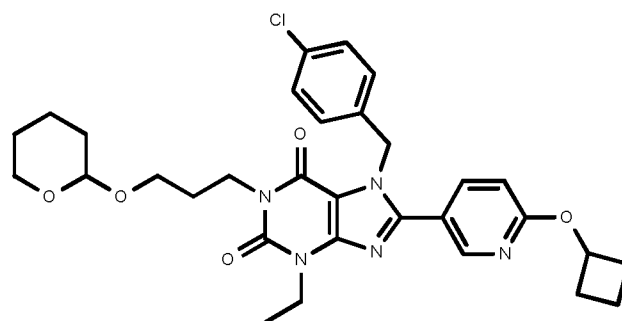
20

were added and the mixture was stirred 1 h at 80°C. The reaction mixture was filtered, H<sub>2</sub>O was added and extracted with EtOAc. The combined organic layers were dried and concentrated in vacuo. The crude product was purified by chromatography to obtain 344 mg of the product.

5 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 398/400

HPLC: RT = 0.73 min, Method F

Intermediate 5.20



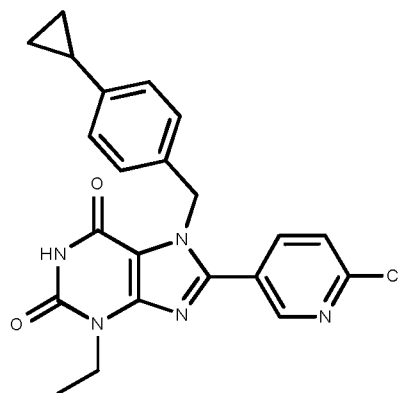
5.20

To a mixture of intermediate 22.1 (23.5 mg, 0.05 mmol) in THF (413  $\mu$ L, 5.2 mmol) and DMSO (413  $\mu$ L, 5.8 mmol) DIPEA (9.5  $\mu$ L, 0.06 mmol) and 1-(bromomethyl)-4-chlorobenzene (15.4 mg, 0.075 mmol) were added and the mixture was stirred at 50°C. The mixture was cooled and used without further purification.

15 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 594

HPLC: RT = 0.9 min, Method D

Intermediate 5.21



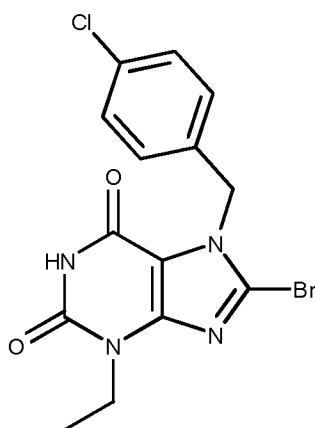
5.21

Intermediate 4.12 (300 mg, 1.03 mmol) was dissolved in DMF (1 mL), THF (1 mL) and DMSO (1 mL). DIPEA (581  $\mu$ L, 3.4 mmol) was added and the mixture was stirred 5 min at 80°C. Then intermediate 24.1 (217 mg, 1.03 mmol) was added and the mixture was stirred 1.5 h at 80°C. The reaction mixture was acidified with TFA, filtered, purified by chromatography and freeze dried to obtain 61.1 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 422

HPLC: RT = 0.91 min, Method F

#### Intermediate 5.23



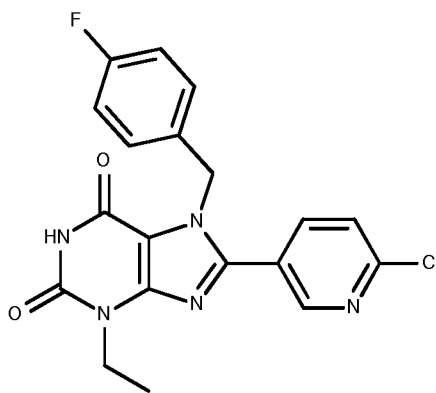
5.23

To a mixture of intermediate 13.1 (611 mg, 2.36 mmol) in DMF (5.75 mL) DIPEA (1.22 mL, 7.08 mmol) and 1-(bromomethyl)-4-chlorobenzene (484.6 mg, 2.36 mmol) were added and the mixture was stirred 1 h at rt. The mixture was purified by chromatography to obtain 850 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 385

HPLC: RT = 0.57 min, Method G

#### Intermediate 5.24



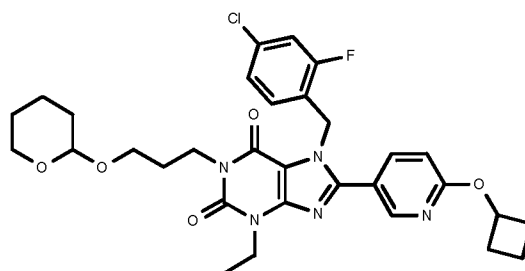
5.24

To a mixture of intermediate 4.12 (150 mg, 0.514 mmol) in DMF (3 mL) DIPEA (106  $\mu$ L, 0.617 mmol) and 1-(bromomethyl)-4-fluorobenzene (63.5  $\mu$ L, 0.514 mmol) were added  
 5 and the mixture was stirred overnight at 80°C. The mixture was cooled, filtered and purified by chromatography to obtain 54.0 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 400/402

HPLC: RT = 0.79 min, Method F

10 Intermediate 5.25



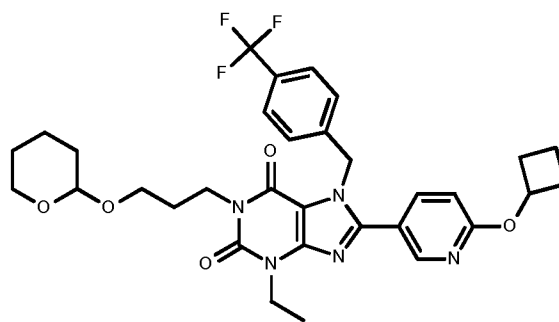
5.25

To a mixture of intermediate 22.1 (42.3 mg, 0.09 mmol) in THF (744  $\mu$ L, 9.27 mmol) and DMSO (740  $\mu$ L, 10.4 mmol) DIPEA (17  $\mu$ L, 0.10 mmol) and 1-(bromomethyl)-4-chloro-2-fluorobenzene (18.3  $\mu$ L, 0.135 mmol) were added and the mixture was stirred overnight  
 15 at 50°C. The mixture was cooled and used without further purification.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 614

HPLC: RT = 0.92 min, Method D

20 Intermediate 5.26



5.26

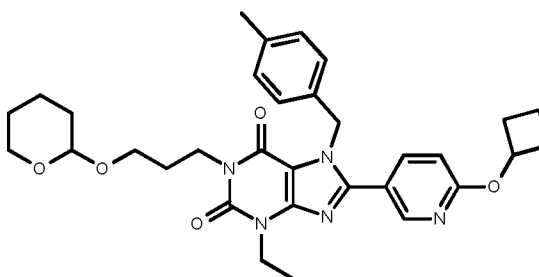
To a mixture of intermediate 22.1 (42.3 mg, 0.09 mmol) in THF (744  $\mu$ L, 9.27 mmol) and DMSO (740  $\mu$ L, 10.4 mmol) DIPEA (17  $\mu$ L, 0.10 mmol) and 1-(bromomethyl)-4-

5 (trifluoromethyl)benzene (20.9  $\mu$ L, 0.135 mmol) were added and the mixture was stirred overnight at 50°C. The mixture was cooled and used without further purification.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 628

HPLC: RT = 0.92 min, Method D

10 Intermediate 5.27



5.27

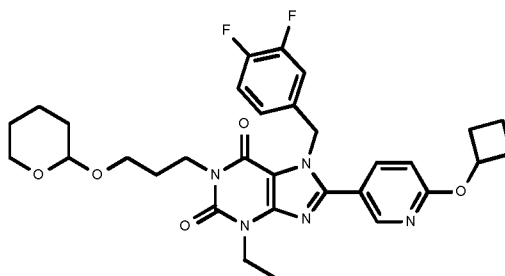
To a mixture of intermediate 22.1 (42.3 mg, 0.09 mmol) in THF (744  $\mu$ L, 9.27 mmol) and DMSO (740  $\mu$ L, 10.4 mmol) DIPEA (17  $\mu$ L, 0.10 mmol) and 1-(bromomethyl)-4-

15 methylbenzene (25 mg, 0.135 mmol) were added and the mixture was stirred overnight at 50°C. The mixture was cooled and used without further purification.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 574

HPLC: RT = 0.91 min, Method D

20 Intermediate 5.28



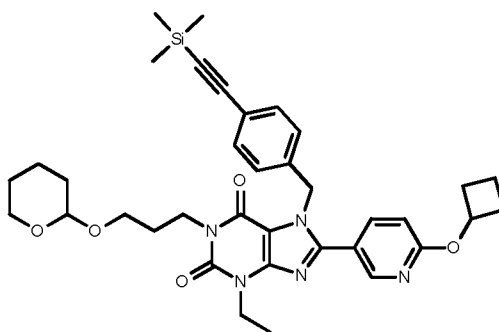
5.28

To a mixture of intermediate 22.1 (42.3 mg, 0.09 mmol) in THF (744  $\mu$ L, 9.27 mmol) and DMSO (740  $\mu$ L, 10.4 mmol) DIPEA (17  $\mu$ L, 0.10 mmol) and 4-(bromomethyl)-1,2-difluorobenzene (28 mg, 0.135 mmol) were added and the mixture was stirred overnight at 50°C. The mixture was cooled and used without further purification.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 596

HPLC: RT = 0.88 min, Method D

#### Intermediate 5.29



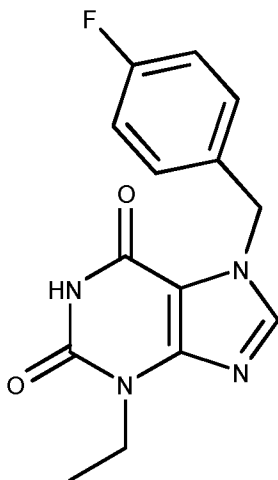
5.29

To a mixture of intermediate 22.1 (74 mg, 0.102 mmol) in THF (1 mL, 12.5 mmol) and DMSO (1 mL, 14.1 mmol) DIPEA (81  $\mu$ L, 0.47 mmol) and intermediate 24.2 (63 mg, 0.24 mmol) were added and the mixture was stirred 45 min at 50°C and overnight at 90°C. Additional DIPEA and intermediate 24.2 and ACN (2 mL) were added and the mixture was stirred 4 h at 90°C. The mixture was cooled, filtered and purified by chromatography to obtain 13.0 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 656

HPLC: RT = 0.97 min, Method A

#### Intermediate 5.30



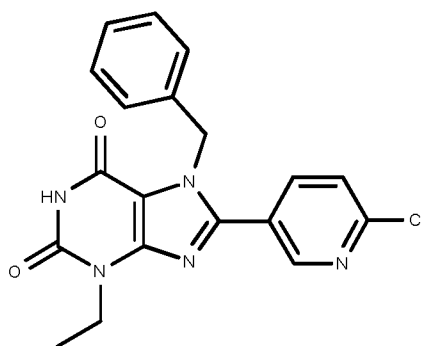
5.30

To a mixture of intermediate 4.3 (400 mg, 2.22 mmol) in THF (1.42 mL) and DMSO (1.42 mL) DIPEA (274  $\mu$ L, 4.44 mmol) and after 5 min at 80°C 1-(bromomethyl)-4-fluorobenzene (274  $\mu$ L, 2.22 mmol) were added and the mixture was stirred 1 h at 80°C. H<sub>2</sub>O was added and extracted with EtOAc. The combined organic layers were dried, concentrated in vacuo and purified by chromatography to obtain 268 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 289

HPLC: RT = 0.59 min, Method F

Intermediate 5.31



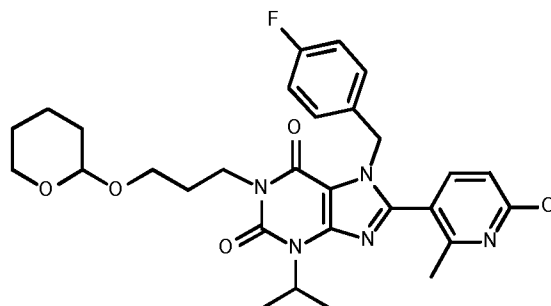
5.31

To a mixture of intermediate 4.12 (150 mg, 0.514 mmol) in DMF (3 mL, 37 mmol) DIPEA (106  $\mu$ L, 0.617 mmol) and (bromomethyl)benzene (61  $\mu$ L, 0.514 mmol) were added and the mixture was stirred overnight at 80°C. The mixture was cooled, filtered and purified by chromatography to obtain 57.0 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 382/384

HPLC: RT = 0.78 min, Method F

### Intermediate 6.1



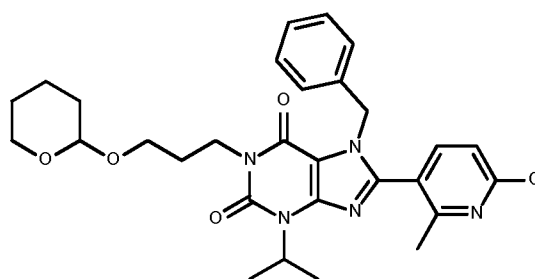
## 6.1

To a mixture of intermediate 5.1 (0.51 g, 1.19 mmol) in anhydrous DMF (2 mL)  $K_2CO_3$  (0.328 g, 2.38 mmol) and 2-(3-bromopropoxy)tetrahydro-2H-pyran (0.302 mL, 1.78 mmol) were added and the mixture was stirred for 1 h at 80°C.  $H_2O$  was added and extracted with EtOAc. The combined organic layers were dried, concentrated in vacuo and the crude product purified by chromatography to obtain 556 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 570

HPLC: RT = 0.83 min, Method D

### Intermediate 6.2



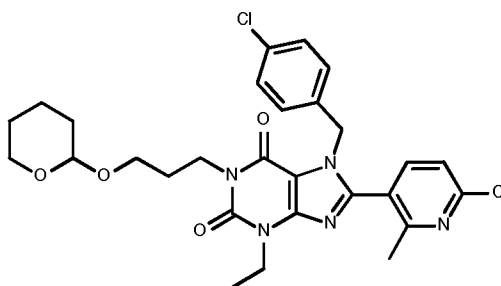
6.2

Intermediate 6.2 was prepared in an analogous manner to intermediate 6.1 using intermediate 5.2.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 553/554

HPLC: RT = 0.82 min, Method G

### Intermediate 6.3



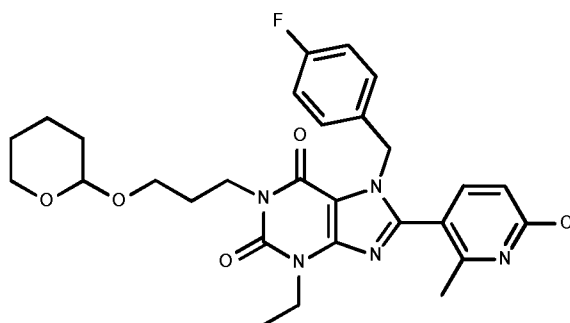
6.3

To a mixture of intermediate 5.3 (0.39 g, 0.91 mmol) in anhydrous DMF (2 mL)  $K_2CO_3$  (0.252 g, 1.82 mmol) and 2-(3-bromopropoxy)tetrahydro-2H-pyran (0.232 mL, 1.37 mmol) were added and the mixture was stirred for 2 h at 50°C.  $H_2O$  was added and extracted with EtOAc. The combined organic layers were dried, concentrated in vacuo and the crude product purified by chromatography to obtain 438 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 572

HPLC: RT = 1.38 min, Method C

Intermediate 6.4



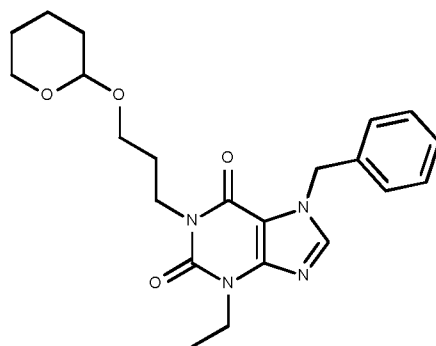
6.4

Intermediate 6.4 was prepared in an analogous manner to intermediate 6.1 using intermediate 5.4.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 556/558

HPLC: RT = 0.77 min, Method D

Intermediate 6.5



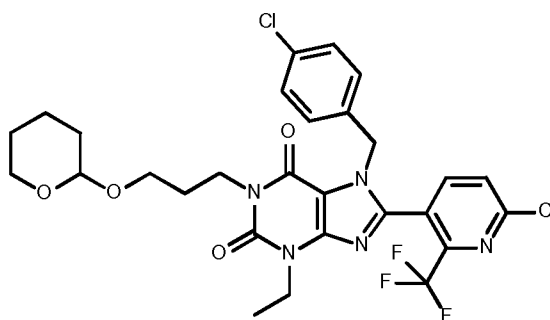
6.5

Intermediate 6.5 was prepared in an analogous manner to intermediate 6.1 using intermediate 5.5.

5 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 413/414

HPLC: RT = 0.63 min, Method G

Intermediate 6.6



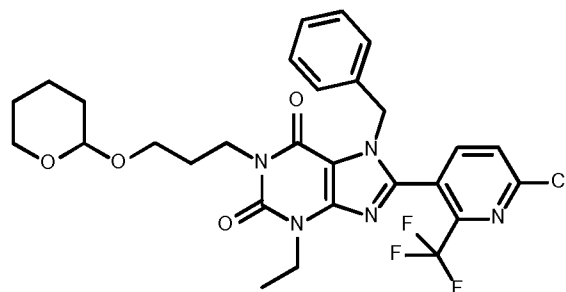
6.6

Intermediate 6.6 was prepared in an analogous manner to intermediate 6.3 using intermediate 5.6.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 626

HPLC: RT = 1.45 min, Method C

Intermediate 6.7



60

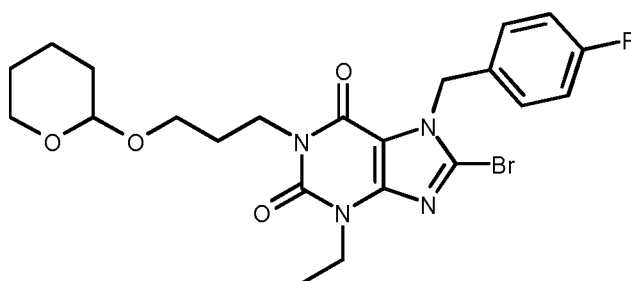
## 6.7

Intermediate 6.7 was prepared in an analogous manner to intermediate 6.3 using intermediate 5.7.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 592

5 HPLC: RT = 1.38 min, Method C

## Intermediate 6.9



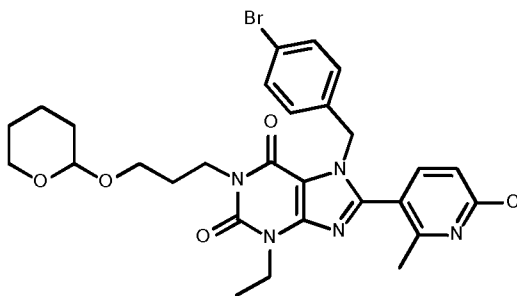
6.9

Intermediate 6.9 was prepared in an analogous manner to intermediate 6.3 using intermediate 5.9.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 510/511

HPLC: RT = 0.73 min, Method G

## Intermediate 6.10



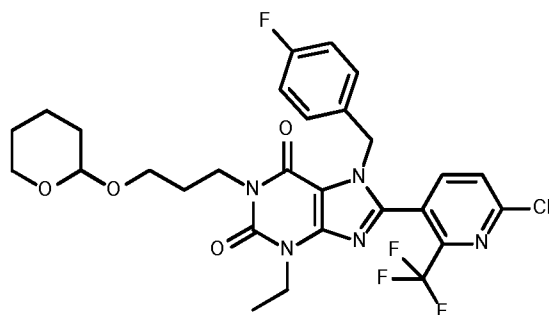
6.10

Intermediate 6.10 was prepared in an analogous manner to intermediate 6.3 using intermediate 5.10.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 618

HPLC: RT = 0.83 min, Method D

## Intermediate 6.11



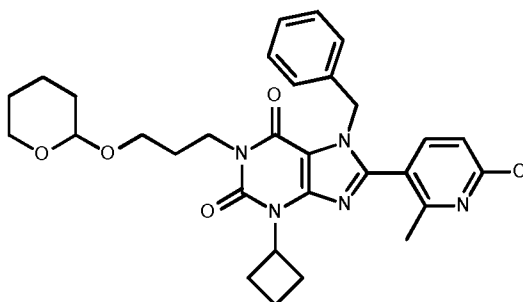
6.11

To a mixture of intermediate 5.11 (192 mg, 0.41 mmol) in anhydrous DMF (2 mL)  $K_2CO_3$  (114 mg, 0.82 mmol) and 2-(3-bromopropoxy)tetrahydro-2H-pyran (0.105 mL, 0.62 mmol) were added and the mixture was stirred for 2 h at 50°C.  $H_2O$  was added and extracted with EtOAc. The combined organic layers were dried, concentrated in vacuo and purified by chromatography to obtain 207 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 610

HPLC: RT = 1.40 min, Method C

### Intermediate 6.12



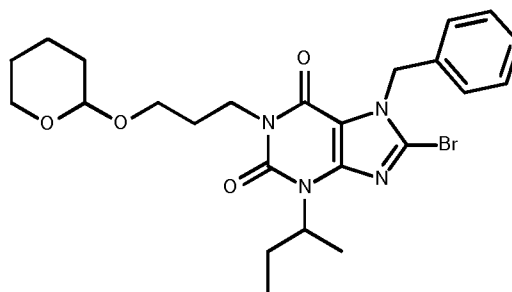
6.12

To a mixture of intermediate 5.12 (282 mg, 0.67 mmol) in anhydrous DMF (3 mL)  $K_2CO_3$  (277.2 mg, 2.01 mmol) and 2-(3-bromopropoxy)tetrahydro-2H-pyran (170.4  $\mu$ L, 1.00 mmol) were added and the mixture was stirred for 2 h at 80°C.  $H_2O$  was added and extracted with EtOAc. The combined organic layers were dried, concentrated in vacuo and purified by chromatography to obtain 321 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 564/566

HPLC: RT = 0.84 min, Method F

## Intermediate 6.14



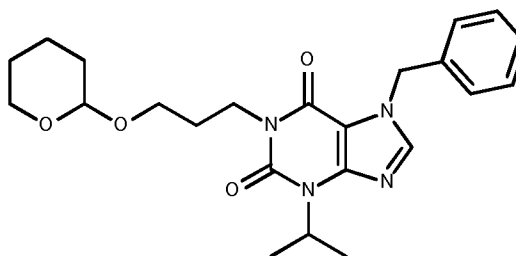
6.14

To a mixture of intermediate 19.1 (700 mg, 1.86 mmol) in THF (7.73 mL), DMSO (7.78 mL) and DMF (7.84 mL)  $K_2CO_3$  (769 mg, 0.006 mol) and 2-(3-bromopropoxy)tetrahydro-2H-pyrane (0.42 mL, 2.78 mmol) were added and the mixture was stirred for 1 h at 100°C. The mixture was cooled, diluted with ACN and purified by chromatography to obtain 811 mg of the product.

MS (ESI<sup>+</sup>): (M+H-THP)<sup>+</sup> 437

HPLC: RT = 0.84 min, Method G

## Intermediate 6.15



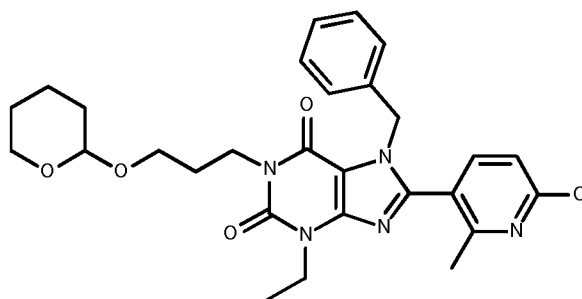
6.15

To a mixture of intermediate 19.2 (660 mg, 2.16 mmol) in anhydrous DMF (5 mL)  $K_2CO_3$  (0.9 g, 6.48 mmol) and 2-(3-bromopropoxy)tetrahydro-2H-pyrane (0.55 mL, 3.24 mmol) were added and the mixture was stirred for 2 h at 80°C.  $H_2O$  was added and extracted with EtOAc. The combined organic layers were dried, concentrated in vacuo and the crude product was purified by chromatography and freeze dried to obtain 767 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 427/428

HPLC: RT = 0.97 min, Method F

## Intermediate 6.16

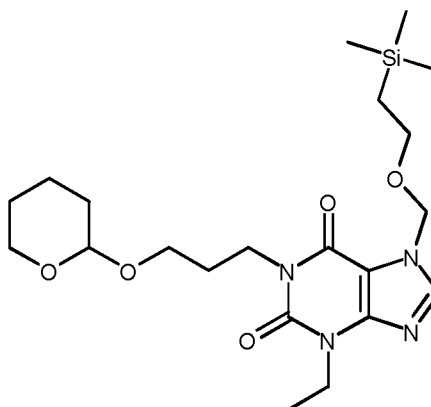


6.16

Intermediate 6.16 was prepared in an analogous manner to intermediate 6.11 using intermediate 5.15.

5 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 538/540  
HPLC: RT = 1.06 min, Method F

Intermediate 6.18

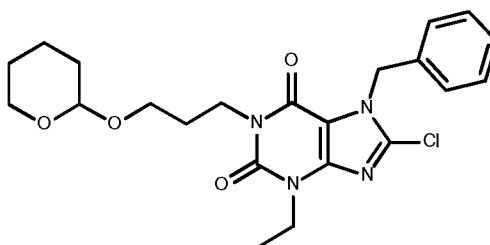


6.18

To the reaction mixture of intermediate 5.17 K<sub>2</sub>CO<sub>3</sub> (1244 mg, 9 mol) and 2-(3-bromopropoxy)tetrahydro-2H-pyran (764 μL, 4.5 mmol) were added and the mixture was stirred overnight at 90°C. The mixture was cooled and purified by chromatography to obtain 920 mg of the product.

15 MS (ESI<sup>+</sup>): (M+H-THP)<sup>+</sup> 369  
HPLC: RT = 0.75 min, Method D

Intermediate 6.19



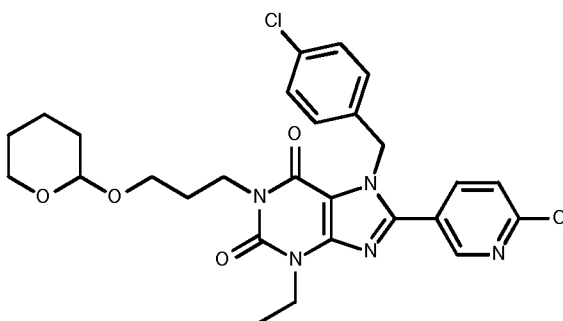
6.19

To a mixture of intermediate 11.5 (0.63 g, 2.08 mmol) in DMF (10 mL)  $K_2CO_3$  (0.86 g, 6.23 mmol) and 2-(3-bromopropoxy)tetrahydro-2H-pyran (0.53 mL, 3.12 mmol) were added and the mixture was stirred 2h at 80°C.  $H_2O$  was added and extracted with EtOAc. The combined organic layers were dried and concentrated in vacuo. The crude product was purified by chromatography and freeze dried to obtain 414 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 447/449

HPLC: RT = 0.73 min, Method G

#### Intermediate 6.20



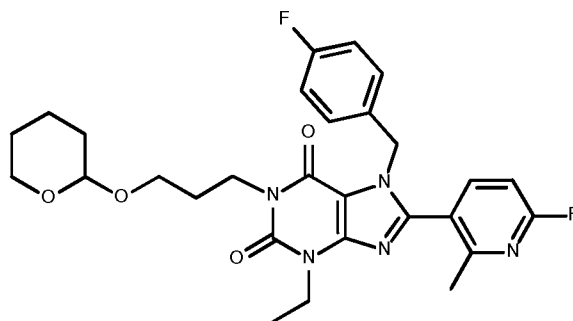
6.20

To a mixture of intermediate 5.18 (148 mg, 0.356 mmol) in anhydrous DMF (1 mL)  $K_2CO_3$  (98.3 mg, 0.711 mmol) and 2-(3-bromopropoxy)tetrahydro-2H-pyran (90.4  $\mu$ L, 0.533 mmol) were added and the mixture was stirred 2h at 50°C.  $H_2O$  was added and extracted with EtOAc. The combined organic layers were dried and concentrated in vacuo. The crude product was purified by chromatography and freeze dried to obtain 174 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 558/560

HPLC: RT = 1.38 min, Method C

#### Intermediate 6.21



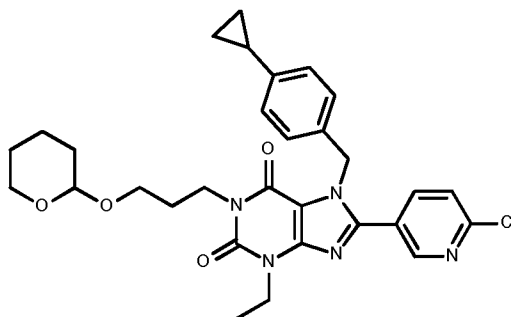
6.21

Intermediate 6.21 was prepared in an analogous manner to intermediate 6.19 using  
 5 intermediate 5.19.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 540/541

HPLC: RT = 0.69 min, Method D

Intermediate 6.22



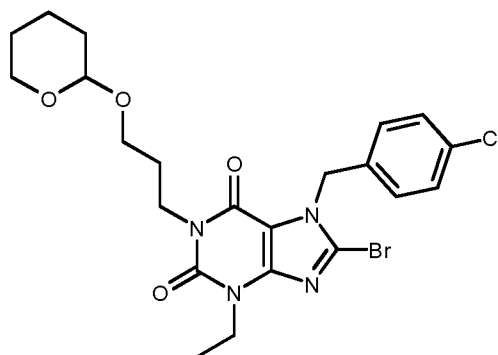
6.22

To a mixture of intermediate 5.21 (61 mg, 0.145 mmol) in DMF (2 mL) K<sub>2</sub>CO<sub>3</sub> (40 mg,  
 0.29 mmol) and 2-(3-bromopropoxy)tetrahydro-2H-pyran (36.8  $\mu$ L, 0.217 mmol) were  
 15 added and the mixture was stirred 2h at 50°C. H<sub>2</sub>O was added and extracted with  
 EtOAc. The combined organic layers were dried and concentrated in vacuo. The crude  
 product was purified by chromatography and freeze-dried to obtain 66 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 564

HPLC: RT = 1.17 min, Method F

Intermediate 6.24



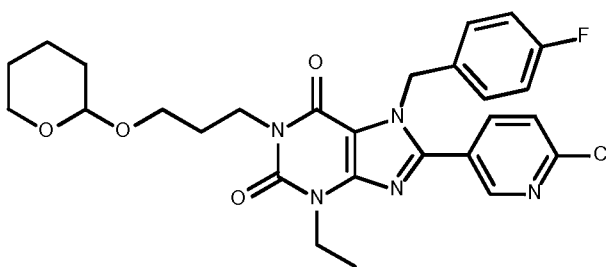
6.24

To a mixture of intermediate 5.23 (900 mg, 2.35 mmol) in DMF (3.81 mL)  $K_2CO_3$  (0.97 g, 7.04 mmol) and 2-(3-bromopropoxy)tetrahydro-2H-pyran (0.60 mL, 3.52 mmol) were added and the mixture was stirred for 1 h at 110°C. The mixture was cooled, filtered, diluted with ACN and purified by chromatography to obtain 1.15 g of the product.

MS (ESI<sup>+</sup>): (M+H-THP)<sup>+</sup> 527

HPLC: RT = 0.79 min, Method G

#### Intermediate 6.25



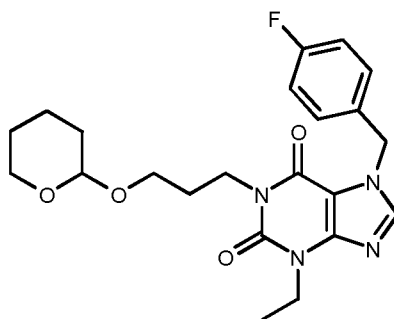
6.25

To a mixture of intermediate 5.24 (54 mg, 0.135 mmol) in DMF (1 mL)  $K_2CO_3$  (37 mg, 0.270 mmol) and 2-(3-bromopropoxy)tetrahydro-2H-pyran (34.3  $\mu$ L, 0.203 mmol) were added and the mixture was stirred for 2 h at 50°C.  $H_2O$  was added and extracted with EtOAc. The combined organic layers were dried and concentrated in vacuo. The crude product was purified by chromatography and freeze dried to obtain 55.0 mg the product.

MS (ESI<sup>+</sup>): (M+H-THP)<sup>+</sup> 542/544

HPLC: RT = 1.32 min, Method C

#### Intermediate 6.26



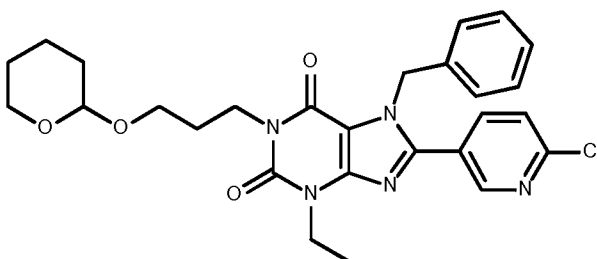
6.26

To a mixture of intermediate 5.30 (268 mg, 0.928 mmol) in DMF (3 mL)  $K_2CO_3$  (567 mg, 1.856 mmol) and 2-(3-bromopropoxy)tetrahydro-2H-pyran (0.24 mL, 1.392 mmol) were added and the mixture was stirred 1 h at 80°C.  $H_2O$  was added and extracted with EtOAc. The combined organic layers were dried, concentrated in vacuo and the crude product was purified by chromatography to obtain 345 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 431

HPLC: RT = 0.91 min, Method F

#### Intermediate 6.27



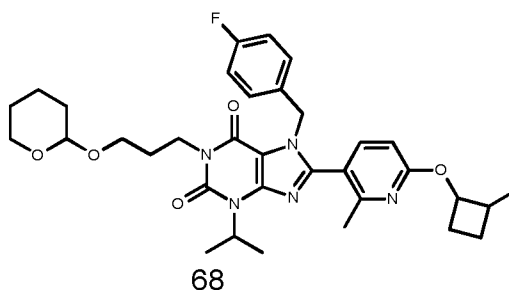
6.27

Intermediate 6.27 was prepared in an analogous manner to intermediate 6.25 using intermediate 5.31.

MS (ESI<sup>+</sup>): (M+H-THP)<sup>+</sup> 524/526

HPLC: RT = 1.31 min, Method C

#### Intermediate 7.1



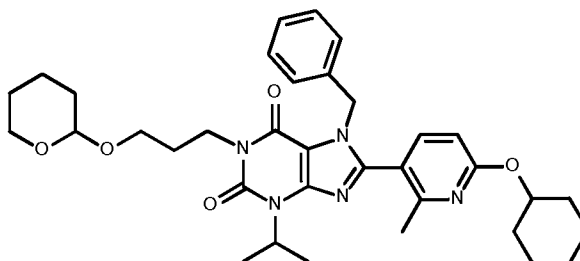
68

## 7.1

To a mixture of intermediate 6.1 (50 mg, 0.088 mmol) in dioxane (1 mL) 2-methylcyclobutan-1-ol (0.5 mL) and sodium hydride (55%, 7.7 mg, 0.175 mmol) were added. The mixture was stirred for 6 h at 100°C. H<sub>2</sub>O was added and extracted with EtOAc. The combined organic layers were dried and concentrated in vacuo and the resulting crude product was used without further purification.

HPLC: RT = 1.36 min, Method F

## Intermediate 7.2



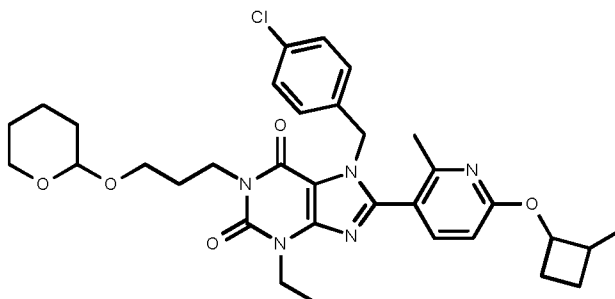
## 7.2

To a mixture of cyclohexanol (26.7  $\mu$ L, 0.254 mmol) and sodium hydride (11.1 mg, 0.254 mmol) in DMF (0.5 mL) intermediate 6.2 (70 mg, 0.127 mmol) was added and the reaction was stirred 1 h at 50°C. H<sub>2</sub>O was added and extracted with DCM. The combined organic layers were dried and concentrated in vacuo and the resulting crude product used without further purification.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 616/617

HPLC: RT = 0.75 min, Method E

## Intermediate 7.3



## 7.3

To a mixture of sodium hydride (55%, 7.6 mg, 0.18 mmol) in 2-methylcyclobutan-1-ol (0.5 mL) intermediate 6.3 (50 mg, 0.09 mmol) was added and the mixture was stirred 1.5

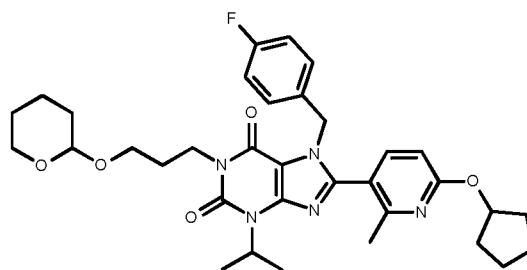
h at 100°C. H<sub>2</sub>O was added and extracted with EtOAc. The combined organic layers were dried and concentrated in vacuo and used without further purification.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 622

HPLC: RT = 1.65 min, Method C

5

Intermediate 7.4



7.4

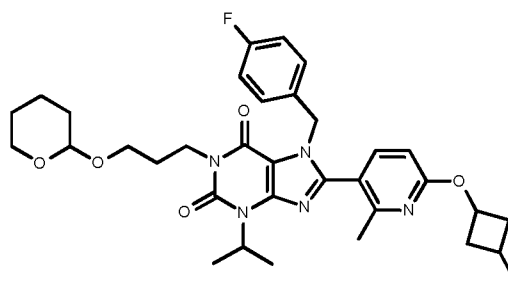
Intermediate 7.4 was prepared in an analogous manner to intermediate 7.1 using intermediate 6.1 and cyclopentanol.

10

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 621

HPLC: RT = 1.36 min, Method F

Intermediate 7.5



15

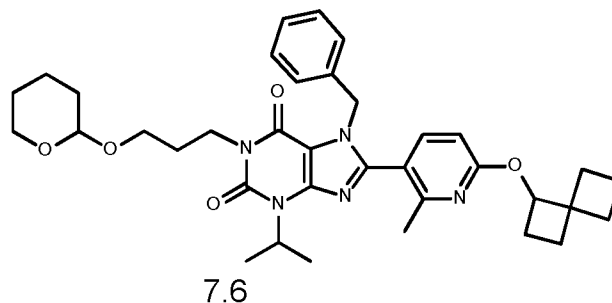
7.5

Intermediate 7.5 was prepared in an analogous manner to intermediate 7.1 using intermediate 6.1 and 3-methylcyclobutan-1-ol.

HPLC: RT = 1.35 min, Method F

20

Intermediate 7.6

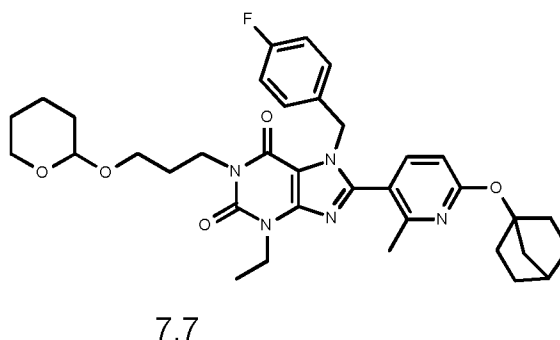


To a mixture of intermediate 6.2 (70 mg, 0.13 mmol) in DMF (0.5 mL) spiro[3.3]heptan-1-ol (28.5 mg, 0.25 mmol) and sodium hydride (55%, 11.1 mg, 0.25 mmol) were added. The mixture was stirred for 1 h at 50°C. H<sub>2</sub>O was added and extracted with DCM. The combined organic layers were dried and concentrated in vacuo and the crude product was used without further purification.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 628/629

HPLC: RT = 0.8 min, Method E

#### Intermediate 7.7

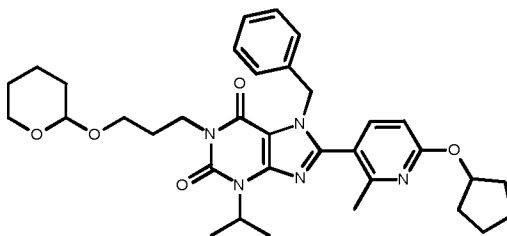


To a mixture of intermediate 6.4 (135 mg, 0.24 mmol) in dioxane (1 mL) bicyclo[2.2.1]heptan-2-ol (0.5 mL, 4.28 mmol) and sodium hydride (55%, 21.2 mg, 0.49 mmol) were added. The mixture was stirred for 3 h at 110°C. H<sub>2</sub>O was added and extracted with EtOAc. The combined organic layers were dried and concentrated in vacuo. The crude product was purified by chromatography to obtain 117 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 632

HPLC: RT = 0.98 min, Method G

#### Intermediate 7.8

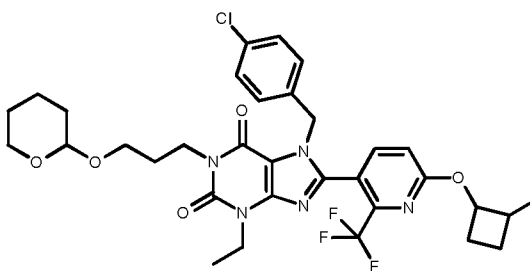


7.8

To a mixture of cyclopentanol (1 mL) and sodium hydride (55%, 15.8 mg, 0.36 mmol) in DMF (1 mL) intermediate 6.2 (100 mg, 0.18 mmol) was added and the reaction was stirred 1.5 h at 110°C. H<sub>2</sub>O was added and extracted with EtOAc. The combined organic layers were dried and concentrated in vacuo and used without further purification.

HPLC: RT = 0.98 min, Method D

### Intermediate 7.9



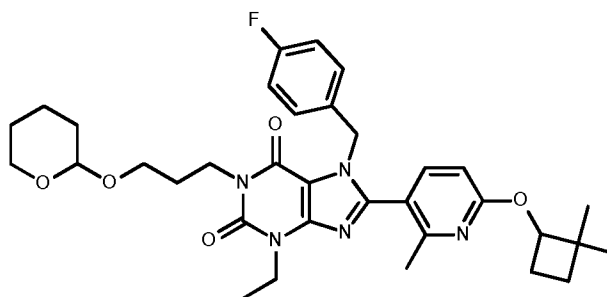
7.9

Intermediate 7.9 was prepared in an analogous manner to intermediate 7.3 using intermediate 6.6.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 676

HPLC: RT = 1.65 min, Method C

## Intermediate 7.11



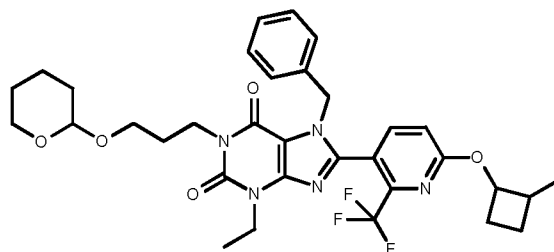
7.11

To a mixture of 2,2-dimethylcyclobutan-1-ol (0.5 mL) and sodium hydride (55%, 11 mg, 0.252 mmol) intermediate 6.4 (70 mg, 0.126 mmol) was added and the reaction was stirred 2 h at rt. H<sub>2</sub>O was added and extracted with DCM. The combined organic layers were dried and concentrated in vacuo and the crude product was used without further purification.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 620/621

HPLC: RT = 0.97 min, Method D

#### Intermediate 7.12



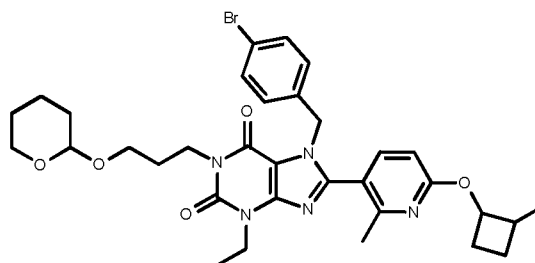
7.12

To a mixture of sodium hydride (55%, 13.3 mg, 0.30 mmol) in 2-methylcyclobutan-1-ol (0.5 ml) intermediate 6.7 (90 mg, 0.15 mmol) was added and the mixture was stirred 1.5 h at 100°C. H<sub>2</sub>O was added and extracted with EtOAc. The combined organic layers were dried, concentrated in vacuo and the crude product was purified by chromatography to obtain 33.0 mg the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 642

HPLC: RT = 1.62 min, Method C

#### Intermediate 7.14



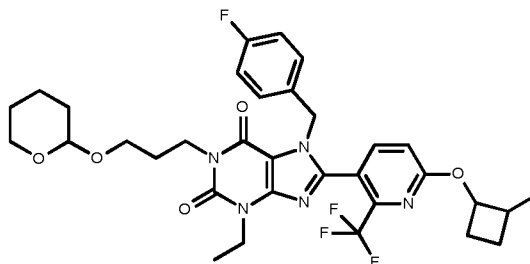
7.14

Intermediate 7.14 was prepared in an analogous manner to intermediate 7.11 using intermediate 6.10.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 668

HPLC: RT = 0.99 min, Method D

### Intermediate 7.15



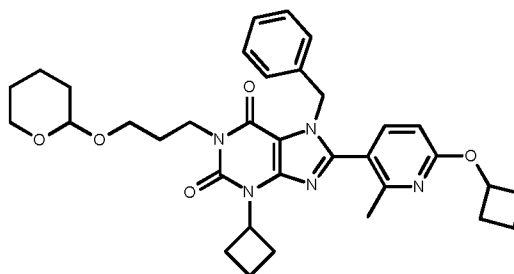
7.15

To a mixture of sodium hydride (55%, 12.9 mg, 0.30 mmol) in 2-methylcyclobutan-1-ol (0.3 ml) intermediate 6.11 (90 mg, 0.15 mmol) was added and the mixture was stirred 2 h at 100°C. H<sub>2</sub>O was added and extracted with EtOAc. The combined organic layers were dried, concentrated in vacuo and the resulting crude product was purified by chromatography to obtain 69.7 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 660

HPLC: RT = 1.61 min, Method C

### Intermediate 7.17



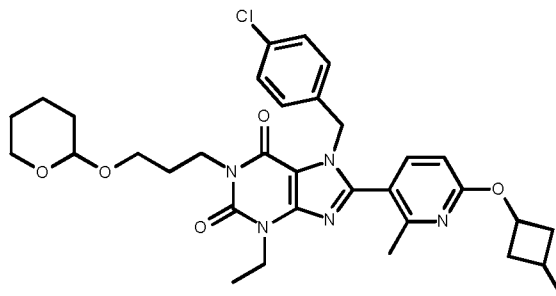
7.17

To a mixture of cyclobutanol (44.2 μL, 0.567 mmol) and sodium hydride (24.8 mg, 0.567 mmol) in DMF (1 mL) intermediate 6.12 (160 mg, 0.284 mmol) was added and the reaction was stirred 4.5 h at 50°C. H<sub>2</sub>O was added and extracted with EtOAc. The combined organic layers were dried and concentrated in vacuo and the resulting crude product was used without further purification.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 600/601

HPLC: RT = 0.99 min, Method G

## Intermediate 7.18



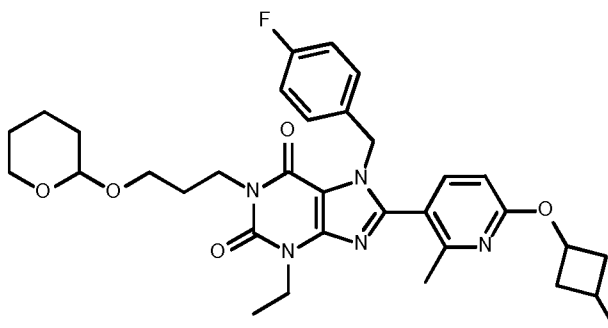
7.18

- 5 To a mixture of sodium hydride (55%, 12.2 mg, 0.28 mmol) in 3-methylcyclobutan-1-ol (0.3 ml) intermediate 6.3 (80 mg, 0.14 mmol) was added and the mixture was stirred 2 h at 100°C. H<sub>2</sub>O was added and extracted with EtOAc. The combined organic layers were dried and concentrated in vacuo and the resulting crude product was used without further purification.

10 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 622

HPLC: RT = 1.64 min, Method C

## Intermediate 7.20



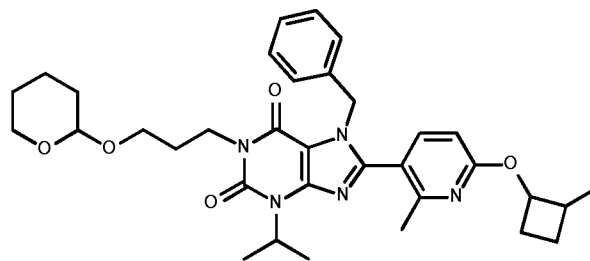
7.20

Intermediate 7.20 was prepared in an analogous manner to intermediate 7.11 using intermediate 6.4 and 3-methylcyclobutan-1-ol.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 606/607

20 HPLC: RT = 0.93 min, Method D

## Intermediate 7.21



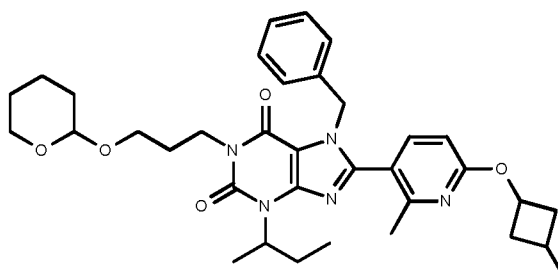
7.21

To a mixture of sodium hydride (55%, 14.2 mg, 0.33 mmol) in 2-methylcyclobutan-1-ol (0.5 ml) intermediate 6.2 (100 mg, 0.16 mmol) was added and the mixture was stirred 2 h at rt. H<sub>2</sub>O was added and extracted with DCM. The combined organic layers were dried and concentrated in vacuo and the resulting crude product was used without further purification.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 602/603

HPLC: RT = 1.68 min, Method C

Intermediate 7.22



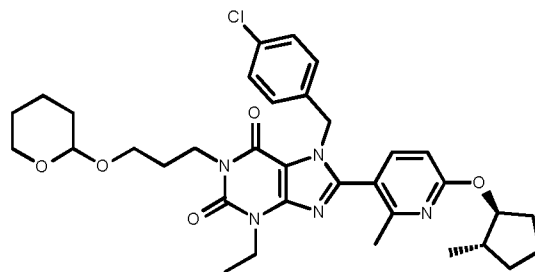
7.22

To a mixture of intermediate 15.2 (230 mg, 0.42 mmol) in THF (2.5 mL) 3-methylcyclobutan-1-ol (72 mg, ) sodium hydride (60%, 33.5 mg, 0.84 mmol) was added and stirred 1 h at rt, 30 min at 40°C and 1.5 h at 60°C. The mixture was cooled and used without further purification.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 616

HPLC: RT = 0.75 min, Method G

Intermediate 7.23



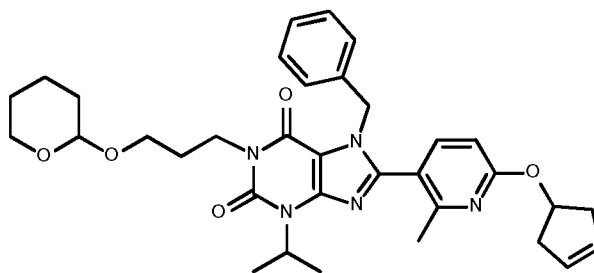
7.23

To a mixture of intermediate 6.3 (60 mg, 0.11 mmol) in dioxane (0.5 mL) trans-2-methylcyclopentan-1-ol (1 mL) and sodium hydride (55%, 9.2 mg, 0.21 mmol) were added. The mixture was stirred for 1.5 h at 100°C. H<sub>2</sub>O was added and extracted with EtOAc. The combined organic layers were dried and concentrated in vacuo to obtain 13.1 mg of the product as a racemic mixture.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 636

HPLC: RT = 0.76 min, Method H

#### Intermediate 7.24



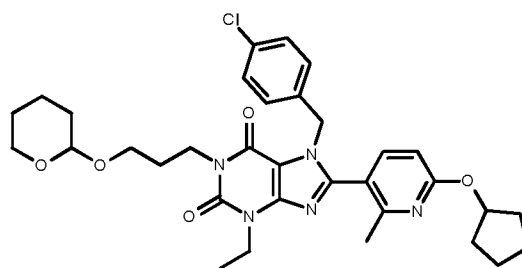
7.24

To a mixture of cyclopent-3-en-1-ol (21.3 mg, 0.25 mmol) and sodium hydride (11.1 mg, 0.25 mmol) in DMF (0.5 mL) intermediate 6.2 (70 mg, 0.13 mmol) was added and the reaction was stirred 1 h at 50°C. H<sub>2</sub>O was added and extracted with DCM. The combined organic layers were dried and concentrated in vacuo and used without further purification.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 600/601

HPLC: RT = 0.64 min, Method E

#### Intermediate 7.25



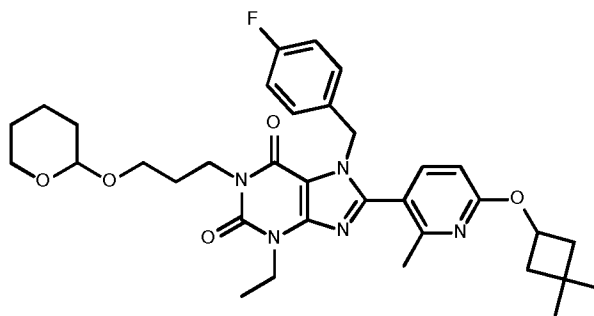
7.25

To a mixture of sodium hydride (55%, 11.6 mg, 0.266 mmol) in cyclopentanol (0.5 ml) intermediate 6.3 (76 mg, 0.133 mmol) was added and the mixture was stirred 1.5 h at 100°C. H<sub>2</sub>O was added and extracted with EtOAc. The combined organic layers were dried, concentrated in vacuo and purified by chromatography to obtain 26.2 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 622

HPLC: RT = 1.64 min, Method C

Intermediate 7.26



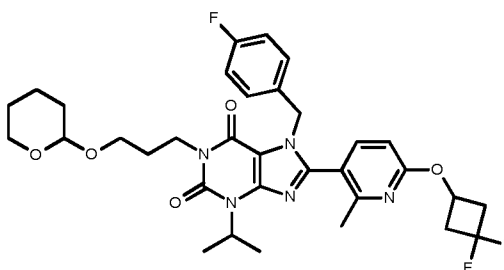
7.26

Intermediate 7.26 was prepared in an analogous manner to intermediate 7.21 using intermediate 6.4 and 3,3-dimethylcyclobutan-1-ol.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 620/621

HPLC: RT = 0.96 min, Method D

Intermediate 7.27



7.27

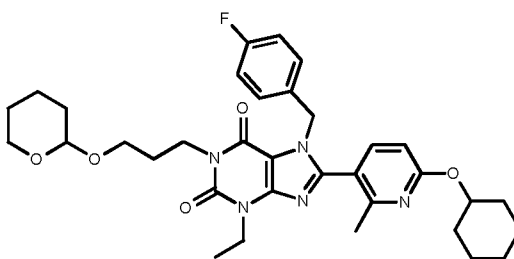
The reaction was performed under argon atmosphere.

A mixture of intermediate 6.1 (74 mg, 0.13 mmol), 5-(di-tert-butylphosphanyl)-1',3',5'-triphenyl-1'H-1,4'-bipyrazole (3.3 mg, 0.006 mmol), tris((1E,4E)-1,5-diphenylpenta-1,4-dien-3-one)dipalladium (4.8 mg, 0.005 mmol), Cs<sub>2</sub>CO<sub>3</sub> (42.3 mg, 0.13 mmol) and 3,3-difluorocyclobutan-1-ol (300 µL) in anhydrous dioxane (2 ml, 22.7 mmol) was stirred 45 min at 100°C in the microwave. The mixture was filtered, concentrated in vacuo, the resulting crude product was purified by chromatography and freeze dried to obtain 53.0 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 462/463

HPLC: RT = 0.9 min, Method G

Intermediate 7.28



7.28

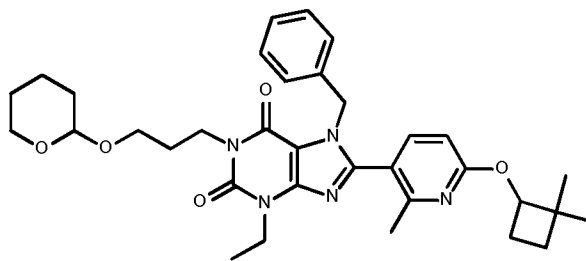
To a mixture of intermediate 6.4 (50 mg, 0.09 mmol) in cyclohexanol (0.5 mL, 4.8 mmol) and dioxane (1 ml, 11.3 mmol) sodium hydride (55%, 7.9 mg, 0.18 mmol) was added and the reaction was stirred 1 h at 110°C. H<sub>2</sub>O was added and extracted with EtOAc.

The combined organic layers were dried and concentrated in vacuo and the resulting crude product was used without further purification.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 620

HPLC: RT = 0.95 min, Method F

Intermediate 7.29



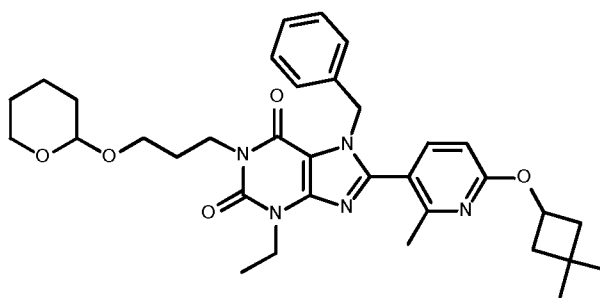
7.29

To a mixture of sodium hydride (55%, 11.4 mg, 0.26 mmol) in 2,2-dimethylcyclobutan-1-ol (0.5 ml) intermediate 6.16 (70 mg, 0.13 mmol) was added and the mixture was stirred 1 h at 50°C. H<sub>2</sub>O was added and extracted with DCM. The combined organic layers were dried, concentrated in vacuo and the resulting crude product used without further purification.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 602/603

HPLC: RT = 1.32 min, Method F

Intermediate 7.30



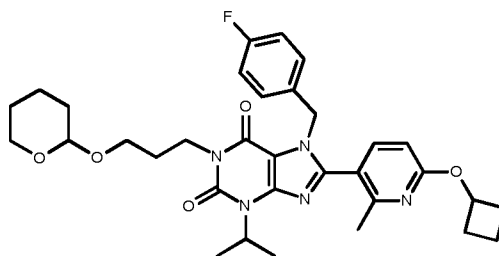
7.30

To a mixture of sodium hydride (55%, 11.4 mg, 0.26 mmol) in 3,3-dimethylcyclobutan-1-ol (0.5 ml) intermediate 6.16 (70 mg, 0.13 mmol) was added and the mixture was stirred 1 h at rt. Additional sodium hydride was added and the mixture was stirred 1h at 50°C. H<sub>2</sub>O was added and extracted with DCM. The combined organic layers were dried, concentrated in vacuo and the resulting crude product was used without further purification.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 602/603

HPLC: RT = 1.29 min, Method F

Intermediate 7.31



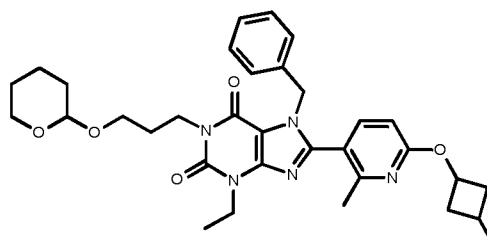
7.31

Intermediate 7.31 was prepared in an analogous manner to intermediate 7.21 using intermediate 6.1.

5 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 606

HPLC: RT = 0.85 min, Method D

Intermediate 7.32



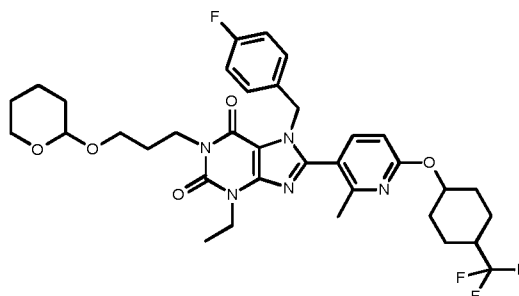
7.32

To a mixture of intermediate 6.16 (83 mg, 0.15 mmol) in dioxane (0.5 ml, 5.67 mmol) 3-methylcyclobutan-1-ol (0.5 mL) and sodium hydride (55%, 13.5 mg, 0.31 mmol) were added and the reaction was stirred 2 h at 100°C. H<sub>2</sub>O was added and extracted with EtOAc. The combined organic layers were dried and concentrated in vacuo and used without further purification.

15 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 588

HPLC: RT = 0.93 min, Method D

20 Intermediate 7.34



81

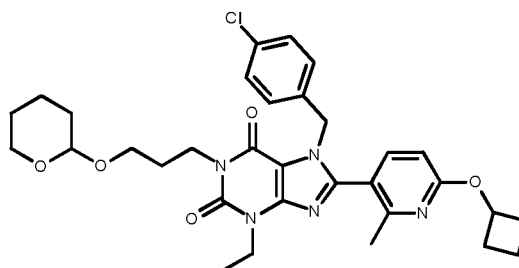
## 7.34

Intermediate 7.34 was prepared in an analogous manner to intermediate 7.6 using intermediate 6.4 and 4-(trifluoromethyl)cyclohexan-1-ol.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 688/689

5 HPLC: RT = 0.94 min, Method G

Intermediate 7.35



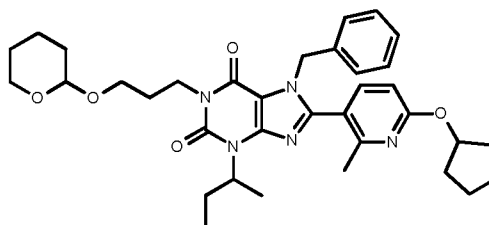
7.35

10 To a mixture of sodium hydride (55%, 12.7 mg, 0.29 mmol) in cyclobutanol (1.5 ml) intermediate 6.3 (83 mg, 0.145 mmol) was added and the mixture was stirred overnight at 100°C. H<sub>2</sub>O was added and extracted with EtOAc. The combined organic layers were dried, concentrated in vacuo and the resulting crude product used without further purification.

15 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 622

HPLC: RT = 1.64 min, Method C

Intermediate 7.36



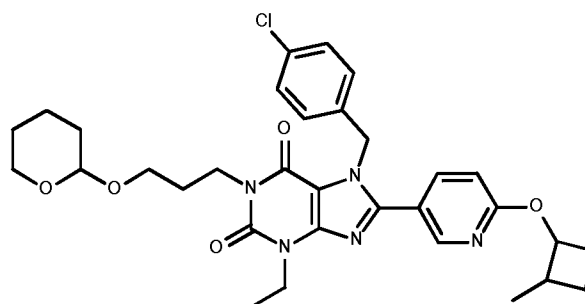
7.36

To a mixture of intermediate 15.2 (230 mg, 0.42 mmol) in THF (2.52 ml, 31.4 mmol) cyclopentanol (72 mg, 0.84 mmol) and sodium hydride (60%, 33.5 mg, 0.84 mmol) were added and the reaction was stirred 1 h at rt, 30 min at 40°C and 1.5 h at 60°C. The mixture was cooled and used without further purification.

25 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 616

HPLC: RT = 0.75 min, Method E

Intermediate 7.37



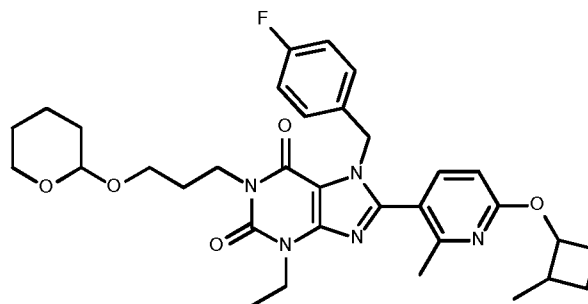
7.37

To a mixture of intermediate 6.20 (57 mg, 0.102 mmol) in dioxane (0.3 ml, 3.40 mmol) 2-methylcyclobutan-1-ol (0.2 mL) and sodium hydride (55%, 8.9 mg, 0.204 mmol) were added and the reaction was stirred 2 h at rt and 1 h at 40°C. H<sub>2</sub>O was added and extracted with DCM. The combined organic layers were dried, concentrated and the resulting crude product used without further purification.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 608/610

HPLC: RT = 1.62 min, Method C

Intermediate 7.38



7.38

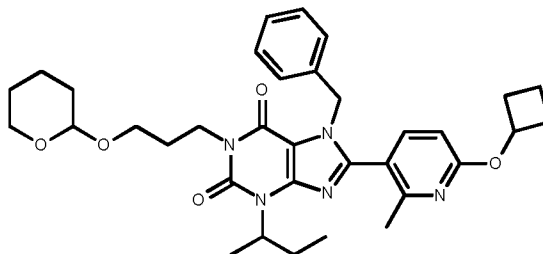
To a mixture of sodium hydride (55%, 9.3 mg, 0.214 mmol) in 2-methylcyclobutan-1-ol (0.3 ml) and DMF (0.3 mL) intermediate 6.4 (70 mg, 0.107 mmol) was added and the mixture was stirred 1 h at rt and 2 h at 50°C. H<sub>2</sub>O was added and extracted with DCM.

The combined organic layers were dried, concentrated in vacuo and the resulting crude product used without further purification.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 606/607

HPLC: RT = 1.6 min, Method C

## Intermediate 7.39



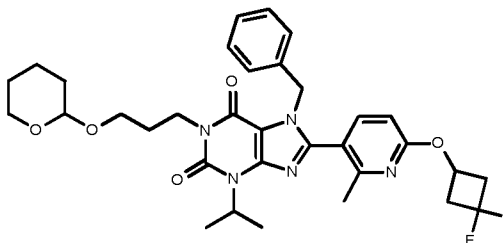
7.39

- 5 To a mixture of intermediate 15.2 (230 mg, 0.42 mmol) in THF (2.52 ml, 31.4 mmol) cyclobutanol (60.4 mg, 0.84 mmol) and sodium hydride (60%, 33.5 mg, 0.84 mmol) were added and the reaction was stirred 1 h at rt, 30 min at 40°C and 1.5 h at 60°C. The mixture was cooled and the resulting crude product was used without further purification.

10 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 602

HPLC: RT = 0.69 min, Method E

## Intermediate 7.40



7.40

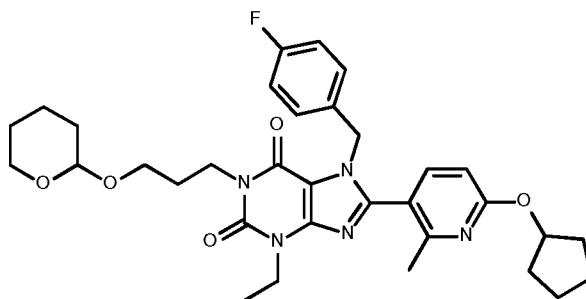
- 15 The reaction was performed under argon atmosphere.
- A mixture of intermediate 6.2 (70 mg, 0.127 mmol), 5-(di-tert-butylphosphanyl)-1',3',5'-triphenyl-1'H-1,4'-bipyrazole (3.21 mg, 0.006 mmol), tris((1E,4E)-1,5-diphenylpenta-1,4-dien-3-one)dipalladium (4.64 mg, 0.005 mmol), Cs<sub>2</sub>CO<sub>3</sub> (41.3 mg, 0.127 mmol) and 3,3-difluorocyclobutan-1-ol (250 mg) in anhydrous dioxane (2 ml, 22.7 mmol) was stirred 45 min at 100°C in the microwave. The mixture was filtered, concentrated in vacuo, purified by chromatography and freeze dried to obtain 61 mg of the product.
- 20

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 624/625

HPLC: RT = 0.9 min, Method G

25

## Intermediate 7.41



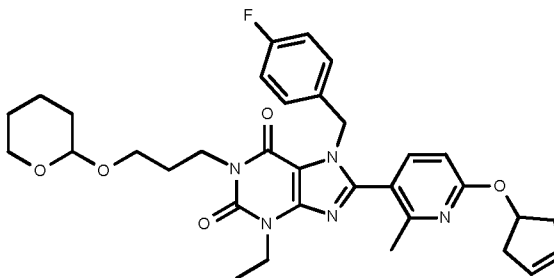
7.41

To a mixture of sodium hydride (55%, 11 mg, 0.252 mmol) in cyclopentanol (0.5 ml) intermediate 6.4 (70 mg, 0.126 mmol) was added and the mixture was stirred 2h at rt. H<sub>2</sub>O was added and extracted with DCM. The combined organic layers were dried, concentrated and the resulting crude product used without further purification.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 606/607

HPLC: RT = 0.93 min, Method D

## Intermediate 7.42



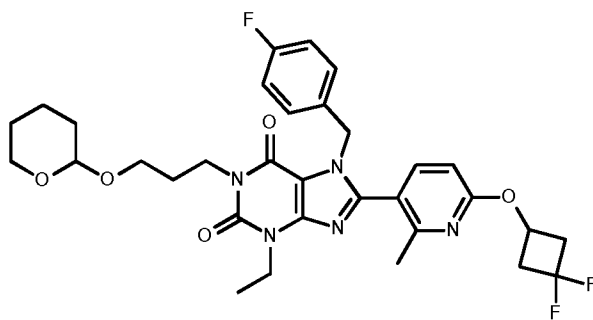
7.42

To a mixture of intermediate 6.4 (50 mg, 0.09 mmol) in dioxane (1 ml, 11.3 mmol) cyclopent-3-en-1-ol (0.5 mL) and sodium hydride (55%, 7.85 mg, 0.18 mmol) were added and the reaction was stirred 1 h at 110°C. H<sub>2</sub>O was added and extracted with EtOAc. The combined organic layers were dried, concentrated and the resulting crude product used without further purification.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 604

HPLC: RT = 0.88 min, Method G

## Intermediate 7.43



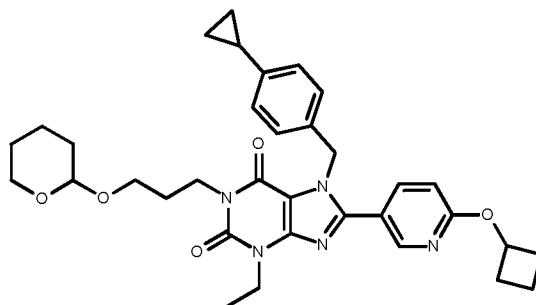
7.43

A mixture of intermediate 6.21 (80 mg, 0.126 mmol) and 3,3-difluorocyclobutan-1-ol (27.2 mg, 0.252 mmol) in anhydrous THF (0.5 ml, 6.2 mmol) was cooled to 0°, then potassium 2-methylpropan-2-olate (28.3 mg, 0.252 mmol) was added and the reaction was stirred 1 h under cooling. H<sub>2</sub>O was added and extracted with DCM. The combined organic layers were dried, concentrated and the resulting crude product used without further purification.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 628/629

HPLC: RT = 0.78 min, Method D

#### Intermediate 7.45

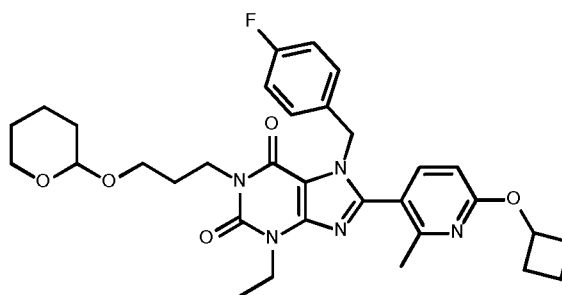


7.45

To a mixture of intermediate 6.22 (66 mg, 0.12 mmol) in dioxane (1 ml) cyclobutanol (0.5 mL) and sodium hydride (55%, 10.3 mg, 0.24 mmol) were added and the reaction was stirred 4.5 h at 110°C. H<sub>2</sub>O was added and extracted with EtOAc. The combined organic layers were dried, concentrated and the resulting crude product used without further purification.

HPLC: RT = 1.30 min, Method F

## Intermediate 7.47



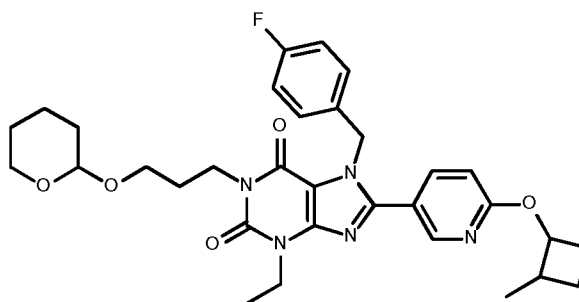
7.47

Intermediate 7.47 was prepared in an analogous manner to intermediate 7.41 using  
intermediate 6.4 and cyclobutanol.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 606

HPLC: RT = 0.9 min, Method D

## Intermediate 7.48



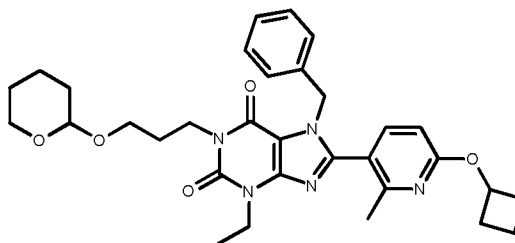
7.48

To a mixture of intermediate 6.25 (55 mg, 0.101 mmol) in dioxane (0.3 ml) 2-methylcyclobutan-1-ol (0.2 mL) and sodium hydride (55%, 8.86 mg, 0.203 mmol) were added and the reaction was stirred 1 h at 40°C. H<sub>2</sub>O was added and extracted with  
DCM. The combined organic layers were dried, concentrated and the resulting crude  
product was used without further purification.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 592/593

HPLC: RT = 1.56 min, Method C

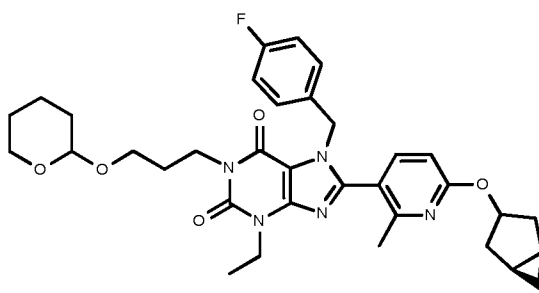
## Intermediate 7.49



To a mixture of intermediate 6.16 (83 mg, 0.154 mmol) in dioxane (0.5 ml) cyclobutanol (2.0 mL) and sodium hydride (55%, 13.5 mg, 0.309 mmol) were added and the reaction  
5 was stirred 2 h at 100°C. H<sub>2</sub>O was added and extracted with EtOAc. The combined organic layers were dried, concentrated and the resulting crude product was used without further purification.

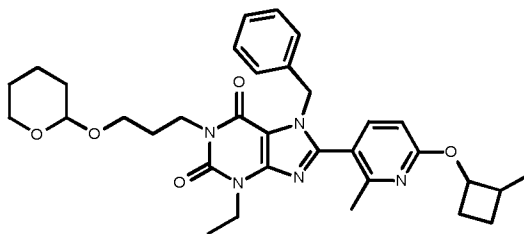
HPLC: RT = 0.89 min, Method D

10



To a mixture of intermediate 6.4 (70 mg, 0.126 mmol) in DMF (1 ml) cis-bicyclo[3.1.0]hexan-3-ol (61.8 mg, 0.629 mmol) and sodium hydride (55%, 11 mg, 0.252 mmol) were added and the reaction was stirred 1 h at 50°C. Additional sodium hydride and (1R,5S)-bicyclo[3.1.0]hexan-3-ol were added and the mixture was stirred 1 h at 50°C. H<sub>2</sub>O was added and extracted with DCM. The combined organic layers were dried, concentrated and the resulting crude product was used without further purification.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 618/619  
HPLC: RT = 0.94 min, Method G



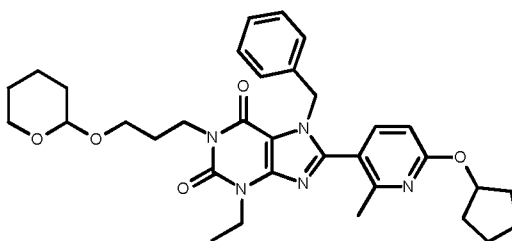
7.51

To a mixture of sodium hydride (55%, 13.8 mg, 0.316 mmol) in 2-methylcyclobutan-1-ol (0.5 ml) intermediate 6.16 (85 mg, 0.158 mmol) was added and the mixture was stirred 1.5 h at 100°C. H<sub>2</sub>O was added and extracted with EtOAc. The combined organic layers were dried, concentrated and the resulting crude product was used without further purification.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 588

HPLC: RT = 0.94 min, Method D

Intermediate 7.52



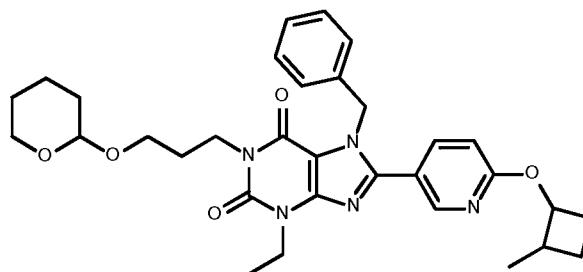
7.52

To a mixture of intermediate 6.16 (83 mg, 0.154 mmol) in dioxane (0.5 ml) cyclopentanol (0.5 mL) and sodium hydride (55%, 13.5 mg, 0.309 mmol) were added and the reaction was stirred 6 h at 100°C. H<sub>2</sub>O was added and extracted with EtOAc. The combined organic layers were dried, concentrated and the resulting crude product was used without further purification.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 588

HPLC: RT = 0.93 min, Method D

Intermediate 7.53



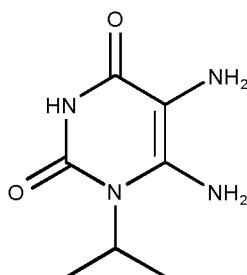
7.53

To a mixture of intermediate 6.27 (54 mg, 0.067 mmol) in dioxane (0.3 ml) 2-methylcyclobutan-1-ol (0.2 mL) and sodium hydride (55%, 5.9 mg, 0.134 mmol) were added and the reaction was stirred 2 h at rt and 1 h at 40°C. H<sub>2</sub>O was added and extracted with DCM. The combined organic layers were dried, concentrated in vacuo and the resulting crude product was used without further purification.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 574/575

HPLC: RT = 1.56 min, Method C

#### Intermediate 8.1



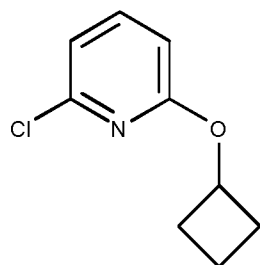
8.1

To a mixture of 2.1 (2.5 g, 12.62 mmol) in NaOH (1 mol/L, 30 mL, 30 mmol) hydrazine hydrate (1.16 mL, 23.34 mmol) was added and cooled to 0°C. Then raney nickel was added and the mixture was stirred for 1h at 0°C. The mixture was cooled, acidified to a pH of 7-8 with conc. HCl, the obtained precipitate was filtered, washed with H<sub>2</sub>O (50 mL) and tert-butylmethylether (50 mL) and dried to obtain 2.15 g the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 185

HPLC: RT = 0.15 min, Method F

#### Intermediate 9.1



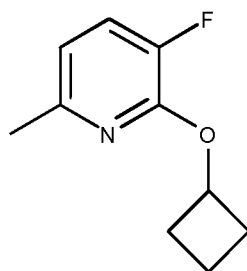
9.1

After stirring a mixture of cyclobutanol (0.31 mL, 3.8 mmol) and sodium hydride (91.2 mg, 3.8 mmol) for 5 min DMF (2 ml, 25 mmol) 2-chloro-6-fluoropyridine (250 mg, 1.9 mmol) was added and the mixture was stirred for 1h at rt. H<sub>2</sub>O was added and extracted with DCM. The combined organic layers were dried and concentrated in vacuo. The crude product was purified by chromatography to obtain 245 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 184/186

HPLC: RT = 0.69 min, Method F

#### Intermediate 9.2



9.2

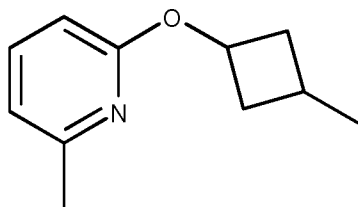
The reaction was performed under argon atmosphere.

To a mixture of Pd(OAc)<sub>2</sub> (118 mg, 0.526 mmol) and {[1,1'-binaphthalene]-2-yl}di-tert-butylphosphane (210 mg, 0.526 mmol) in anhydrous dioxane (20 mL, 227 mmol) 2-bromo-3-fluoro-6-methylpyridine (1.0 g, 5.263 mmol), cyclobutanol (821 µL, 10.526 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (1.715 g, 5.263 mmol) were added after 5 min. The reaction mixture was stirred 45 min at 140°C in the microwave. The mixture was filtered, concentrated in vacuo and purified by chromatography to obtain 270 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 182/183

HPLC: RT = 0.72 min, Method G

#### Intermediate 9.3



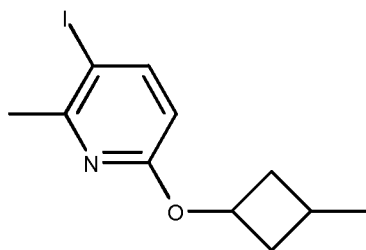
9.3

After stirring a mixture of 3-methylcyclobutan-1-ol (0.25 mL, 2.7 mmol) and sodium hydride (55%, 236 mg, 5.4 mmol) in DMF (5 mL, 61.5 mmol) for 10 min 2-fluoro-6-methylpyridine (300 mg, 2.7 mmol) was added and the mixture was stirred for 1 h at rt. H<sub>2</sub>O was added and extracted with diethylether. The combined organic layers were dried and concentrated and the resulting crude product was used without further purification.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 178/179

HPLC: RT = 0.54 min, Method F

#### Intermediate 9.4

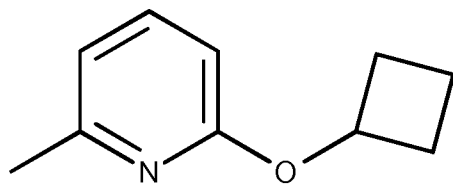


9.4

To a mixture of 6-fluoro-3-iodo-2-methylpyridine (237 mg, 1.0 mmol) and 3-methylcyclobutan-1-ol (103 mg, 1.2 mmol) in THF (2 mL, 25 mmol) (tert-butoxy)potassium (224 mg, 2.0 mmol) was added at 0°C. The mixture was stirred 15 min at 0°C. H<sub>2</sub>O was added and extracted with EtOAc. The combined organic layers were dried and concentrated in vacuo to obtain 250 mg of the product.

HPLC: RT = 1.407/1.724 min cis/trans, Method K

#### Intermediate 9.5



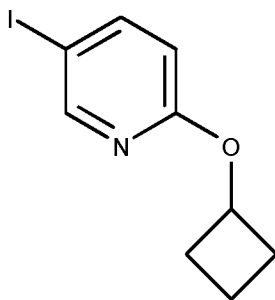
9.5

After stirring a mixture of cyclobutanol (1.05 mL, 13.5 mmol) and sodium hydride (55%, 1178 mg, 27 mmol) for 10 min DMF (10 ml, 123 mmol) 2-fluoro-6-methylpyridine (1.5 g, 13.5 mmol) was added and the mixture was stirred for 1h at rt. Additional sodium hydride was added and the mixture was stirred 1h at 50°C. H<sub>2</sub>O was added and extracted with diethylether. The combined organic layers were dried, concentrated and the resulting crude product was used without further purification.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 164

HPLC: RT = 0.38 min, Method F

#### Intermediate 9.6



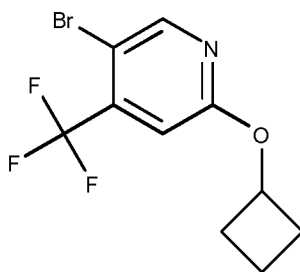
9.6

To a mixture of cyclobutanol (8.14 mL, 104.4 mmol) in THF (25.1 mL, 313.2 mmol) sodium hydride (60%, 835.2 mg, 20.8 mmol) was added and stirred for 20 min at 60°C. Then 2-chloro-5-iodopyridine (5.0 g, 20.8 mmol) was added and the mixture was stirred overnight at 60°C. The mixture was cooled, filtered and concentrated in vacuo. The crude product was purified by chromatography to obtain 2.60 g the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 276

HPLC: RT = 0.76 min, Method D

#### Intermediate 9.7



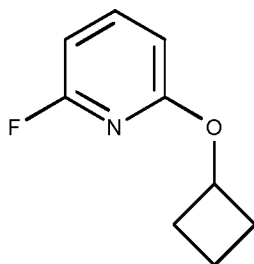
9.7

To a mixture of 5-bromo-2-chloro-4-(trifluoromethyl)pyridine (521 mg, 2.0 mmol) and cyclobutanol (313.2  $\mu$ L, 4 mmol) in THF (2.4 mL, 30 mmol) potassium 2-methylpropan-  
2-olate (247 mg, 2.2 mmol) was added and the mixture was stirred 20 min at rt. H<sub>2</sub>O was added and extracted with DCM. The combined organic layers were dried and concentrated in vacuo to obtain 845 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 297

HPLC: RT = 1.22 min, Method G

#### Intermediate 9.8



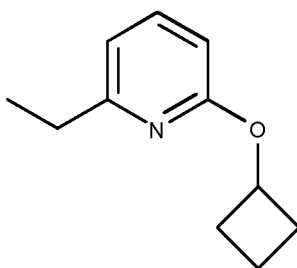
9.8

To a mixture of 2,6-difluoropyridine (1.0 g, 8.69 mmol) and cyclobutanol (627 mg, 8.69 mmol) in DMF (8 mL) sodium hydride (379 mg, 8.69 mmol) was added and the mixture was stirred overnight at rt. H<sub>2</sub>O was added and extracted with EtOAc. The combined organic layers were dried and concentrated in vacuo. The crude product was purified by chromatography to obtain 1.0 g of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 116

HPLC: RT = 0.58 min, Method F

#### Intermediate 10.1



10.1

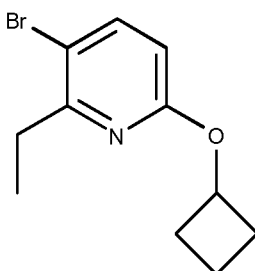
The reaction was performed under argon atmosphere.

To a mixture of intermediate 9.1 (1.52g, 8.28 mmol), potassium ethyltrifluoroboranuide  
5 (2.25g, 16.57 mmol) and  $K_2CO_3$  (3.43g, 24.85 mmol) in toluene/ $H_2O$  (10/1, 12 mL)  
 $Pd(OAc)_2$  (93 mg, 0.41 mmol) and X-Phos were added and the mixture was stirred for  
10 h at 140°C. The mixture was filtered, concentrated in vacuo and purified by  
chromatography to obtain 885 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 178/179

10 HPLC: RT = 0.54 min, Method F

Intermediate 11.1



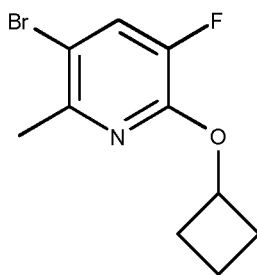
11.1

15 To a mixture of intermediate 10.1 (905 mg, 5.11 mmol) in anhydrous DMF (10 mL,  
122.9 mmol) 1-bromopyrrolidine-2,5-dione (909 mg, 5.11 mmol) was added and the  
mixture was stirred for 2.5 h at rt.  $Na_2S_2O_3$  solution (10%) was added and extracted with  
DCM. The combined organic layers were dried and concentrated in vacuo. The crude  
product was purified by chromatography to obtain 905 mg of the product.

20 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 256/258

HPLC: RT = 1.25 min, Method F

Intermediate 11.2

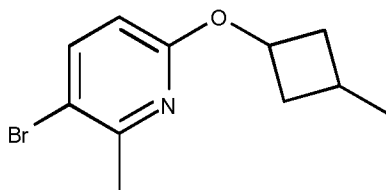


11.2

To a mixture of intermediate 9.2 (220 mg, 1.21 mmol) in anhydrous DMF (3 mL, 36.9 mmol) 1-bromopyrrolidine-2,5-dione (259 mg, 1.46 mmol) was added and the mixture  
 5 was stirred for 2 h at 60°C. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution (10%) was added and extracted with DCM. The combined organic layers were dried and concentrated in vacuo. The crude product was purified by chromatography to obtain 116 mg of the product.

HPLC: RT = 0.85 min, Method G

#### 10 Intermediate 11.3



11.3

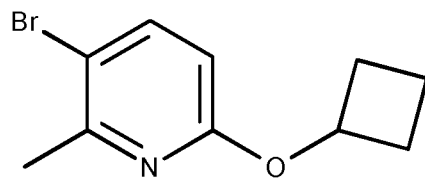
The reaction was performed under argon atmosphere.

To a mixture of intermediate 9.3 (478 mg, 2.7 mmol) in anhydrous THF (30 mL, 374  
 15 mmol) 1,3-dibromo-5,5-dimethylimidazolidine-2,4-dione (1.16 g, 4.05 mmol) was added and the mixture was stirred overnight at rt. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution was added, evaporated the THF and extracted with DCM. The combined organic layers were dried and concentrated in vacuo. The crude product was purified by chromatography to obtain 498 mg of the product.

20 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 256/258

HPLC: RT = 1.21 min, Method F

#### Intermediate 11.4



11.4

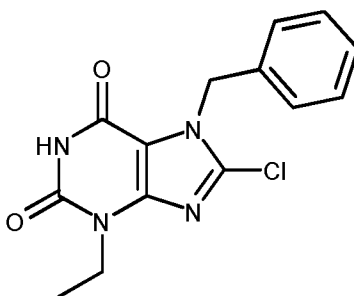
The reaction was performed under argon atmosphere.

To a mixture of intermediate 9.5 (2.59 g, 13.5 mmol) in anhydrous THF (100 mL, 1247 mmol) 1,3-dibromo-5,5-dimethylimidazolidine-2,4-dione (5.78 g, 20.2 mmol) was added and the mixture was stirred overnight at rt.  $\text{Na}_2\text{S}_2\text{O}_3$  solution was added, evaporated the THF and extracted with DCM. The combined organic layers were dried and concentrated in vacuo. The crude product was purified by chromatography to obtain 2.27 g of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 242/244

HPLC: RT = 1.14 min, Method F

Intermediate 11.5



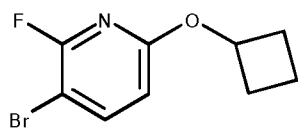
11.5

To a mixture of intermediate 4.11 (722 mg, 2.23 mmol) in anhydrous THF (25 mL) 1-chloropyrrolidine-2,5-dione (0.33 g, 2.45 mmol) was added and the mixture was stirred overnight at 60°C. The mixture was concentrated in vacuo,  $\text{H}_2\text{O}$  was added and the obtained precipitate was filtered and dried to obtain 633 mg the product.

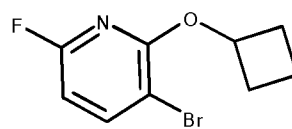
MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 305/307

HPLC: RT = 0.7 min, Method G

Intermediate 11.6



11.6.1



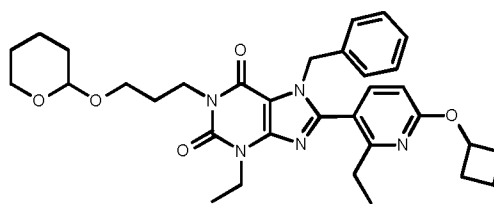
11.6.2

To a mixture of intermediate 9.8 (300mg, 1.79 mmol) in DCM (5 mL) 1-bromopyrrolidine-2,5-dione (319 mg, 1.79 mmol) was added and the mixture was stirred  
 5 1 h at 50°C. Additional 1-bromopyrrolidine-2,5-dione and DMF (1 mL) were added and the mixture was stirred overnight at 50°C and 3 d at rt. The mixture was concentrated in vacuo and purified by chromatography to obtain 389 mg of the product as a 70/30 (11.6.1/11.6.2) mixture of regioisomers.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 246

10 HPLC: RT = 1.09 min, Method F

#### Intermediate 12.1



12.1

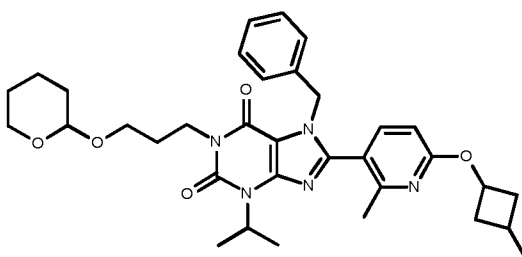
15 The reaction was performed under argon atmosphere.

To a mixture of intermediate 6.5 (107 mg, 0.22 mmol) and intermediate 11.1 (56.5 mg, 0.22 mmol) in anhydrous THF (195  $\mu$ L, 2.43 mmol) and anhydrous DMF (412  $\mu$ L, 5.07 mmol) K<sub>2</sub>CO<sub>3</sub> (61 mg, 0.44 mmol), tricyclohexylphosphane (25 mg, 0.088 mmol), Pd(OAc)<sub>2</sub> (10 mg, 0.044 mmol) and Cul (126 mg, 0.66 mmol) were added and the  
 20 mixture was stirred overnight at 130°C. MeOH was added, filtered and concentrated in vacuo. H<sub>2</sub>O was added and extracted with DCM. The combined organic layers were dried and concentrated in vacuo. The crude product was purified by chromatography to obtain 44.0 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 588/589

25 HPLC: RT = 0.95 min, Method G

#### Intermediate 12.2



12.2

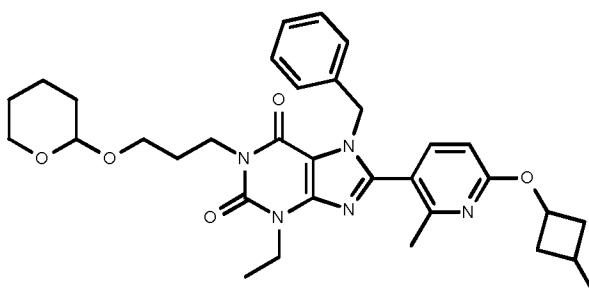
The reaction was performed under argon atmosphere.

To a mixture of intermediate 6.15 (100 mg, 0.234 mmol) and intermediate 11.3 (60.1 mg, 0.234 mmol) in anhydrous THF (200  $\mu$ L, 2.49 mmol) and anhydrous DMF (400  $\mu$ L, 4.92 mmol)  $K_2CO_3$  (65 mg, 0.469 mmol), tricyclohexylphosphane (26 mg, 0.094 mmol),  $Pd(OAc)_2$  (10.5 mg, 0.047 mmol) and  $CuI$  (134 mg, 0.703 mmol) were added and the mixture was stirred 2 d at 130°C.  $H_2O$  was added and extracted with EtOAc. The combined organic layers were dried and concentrated in vacuo. The crude product was purified by chromatography and freeze dried to obtain 35.0 mg the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 602

HPLC: RT = 1.32 min, Method F

#### Intermediate 12.3



12.3

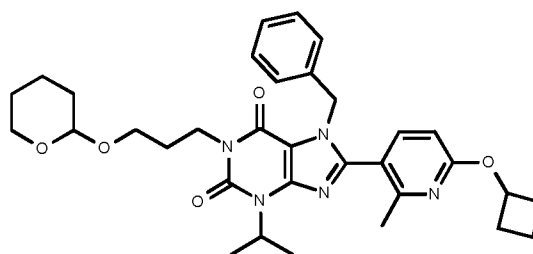
The reaction was performed under argon atmosphere.

To a mixture of intermediate 6.5 (310 mg, 0.752 mmol) and intermediate 9.4 (190 mg, 0.627 mmol) in anhydrous THF (2 mL, 25 mmol) and anhydrous DMF (2 mL, 25 mmol)  $K_2CO_3$  (173 mg, 1.254 mmol), tricyclohexylphosphane (70 mg, 0.251 mmol),  $Pd(OAc)_2$  (28 mg, 0.125 mmol) and  $CuI$  (358 mg, 1.88 mmol) were added and the mixture was stirred overnight at 125°C. The mixture was cooled and purified by silica column and further purified by chromatography to obtain 57.0 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 588

HPLC: RT = 0.92 min, Method D

Intermediate 12.4



12.4

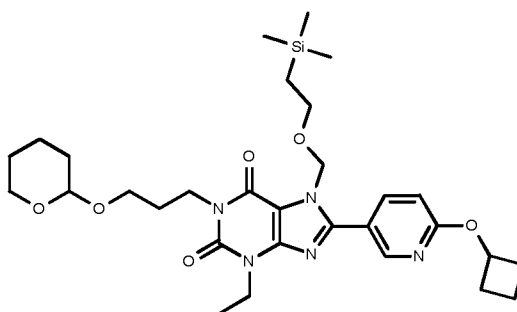
The reaction was performed under argon atmosphere.

To a mixture of intermediate 6.15 (220 mg, 0.52 mmol) and intermediate 11.4 (125 mg, 0.52 mmol) in anhydrous THF (400  $\mu$ L, 5 mmol) and anhydrous DMF (800  $\mu$ L, 9.8 mmol)  $K_2CO_3$  (143 mg, 1.03 mmol), tricyclohexylphosphane (58 mg, 0.206 mmol),  $Pd(OAc)_2$  (23 mg, 0.103 mmol) and  $CuI$  (295 mg, 1.55 mmol) were added and the mixture was stirred overnight at 130°C.  $H_2O$  was added, the mixture was basified with  $NH_3$  and extracted with EtOAc. The combined organic layers were dried and concentrated in vacuo. The crude product was purified by chromatography to obtain 121 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 589/590

HPLC: RT = 0.8 min, Method F

Intermediate 12.5



12.5

The reaction was performed under argon atmosphere.

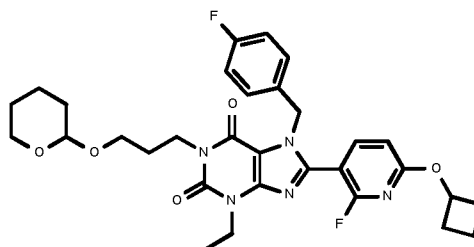
To a mixture of intermediate 6.18 (700 mg, 1.55 mmol) and intermediate 9.6 (850 mg, 3.09 mmol) in anhydrous THF (9.92 mL, 124 mmol) and anhydrous DMF (5 mL, 62 mmol)  $K_2CO_3$  (428 mg, 3.09 mmol), tricyclohexylphosphane (162 mg, 0.62 mmol),  $Pd(OAc)_2$  (69 mg, 0.309 mmol) and  $CuI$  (884 mg, 4.64 mmol) were added and the

mixture was stirred 4h at 180°C. H<sub>2</sub>O was added and extracted with DCM. The combined organic layers were dried and concentrated in vacuo. The crude product was purified by chromatography to obtain 221 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 600

5 HPLC: RT = 0.99 min, Method D

Intermediate 12.6



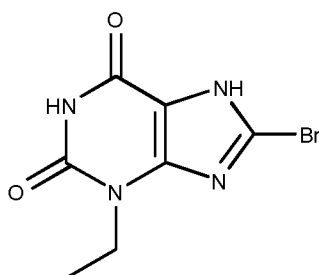
12.6

10 The reaction was performed under argon atmosphere.

To a mixture of intermediate 6.26 (80 mg, 0.19 mmol) and intermediate 11.6 (50.3 mg, 0.20 mmol) in anhydrous THF (164  $\mu$ L, 2.04 mmol) and anhydrous DMF (348  $\mu$ L, 4.27 mmol) K<sub>2</sub>CO<sub>3</sub> (51.4 mg, 0.372 mmol), tricyclohexylphosphane (20.9 mg, 0.074 mmol), Pd(OAc)<sub>2</sub> (8.3 mg, 0.037 mmol) and CuI (106 mg, 0.558 mmol) were added and the mixture was stirred overnight at 130°C. The mixture was filtered, washed with ACN and DMF and purified by chromatography to obtain 42.3 mg of the product.

15 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 596

Intermediate 13.1



13.1

To a mixture of intermediate 4.3 (230 mg, 1.277 mmol) in HOAc (5 mL) sodium acetate (209.5 mg, 2.553 mmol) was added and the mixture was warmed to 50°C. To this mixture a solution of dibromine (131  $\mu$ L, 2.553 mmol) in HOAc (5 mL) was added and

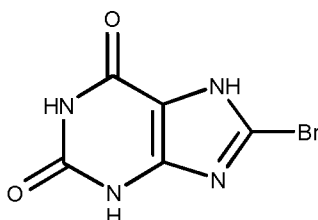
the reaction mixture was stirred for 1h at 50°C. Water was added, the obtained precipitate was filtered, washed with water and dried to obtain 90.0 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 261/262

HPLC: RT = 0.37 min, Method F

5

### Intermediate 13.2



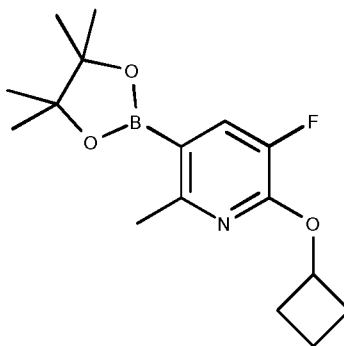
13.2

To a mixture of intermediate 4.8 (7.42 g, 35.74 mmol) in H<sub>2</sub>O (35.4 mL, 1.97 mol) dibromine (2.75 mL, 53.62 mmol) was added and the mixture was stirred overnight at 100°C in a closed vial. The mixture was cooled, H<sub>2</sub>O was added (200 mL) and the obtained precipitate was filtered, washed with H<sub>2</sub>O and tert-butylmethylether and dried to obtain 3.05 g of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 232

HPLC: RT = 0.24 min, Method F

### Intermediate 14.1



14.1

The reaction was performed under argon atmosphere.

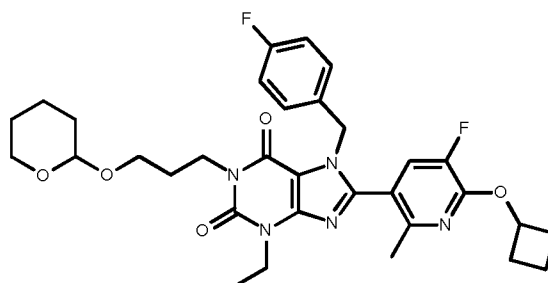
A mixture of intermediate 11.2 (76 mg, 0.292 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (80.2 mg), potassium acetate (86.1 mg, 0.877 mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (7.2 mg, 0.009 mmol) in dioxane (1 mL) was stirred overnight

at 50°C. The mixture was filtered and concentrated in vacuo. H<sub>2</sub>O was added and extracted with DCM. The combined organic layers were filtered over a silica column, dried and concentrated in vacuo to obtain 85.0 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 308/309

5 HPLC: RT = 0.94 min, Method G

#### Intermediate 15.1



15.1

The reaction was performed under argon atmosphere.

To a mixture of intermediate 6.9 (112 mg, 0.22 mmol) and intermediate 14.1 (104 mg, 0.22 mmol) in THF (2 mL, 25 mmol) K<sub>3</sub>PO<sub>4</sub> (1 mol/L, 0.44 mL, 0.44 mmol) was added and after 5 min dicyclohexyl[2',4',6'-tris(propan-2-yl)-[1,1'-

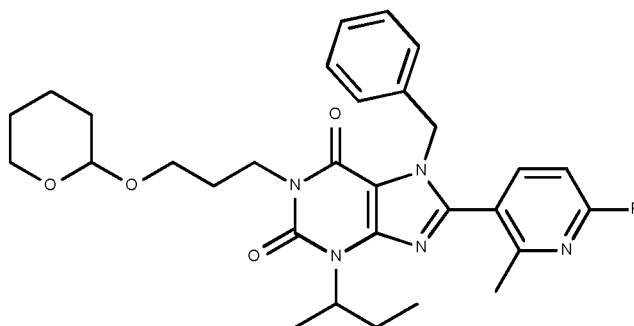
15 biphenyl]-2-yl]phosphane {2'-amino-[1,1'-biphenyl]-2-

yl}palladiumylum methanesulfonate (18.6 mg, 0.022 mmol) was added and the reaction mixture was stirred for 5h at 100°C. The mixture was filtered, washed with MeOH and concentrated in vacuo. The crude product was purified by chromatography to obtain 35 mg of the product.

20 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 610/611

HPLC: RT = 1.26 min, Method F

#### Intermediate 15.2



15.2

The reaction was performed under argon atmosphere.

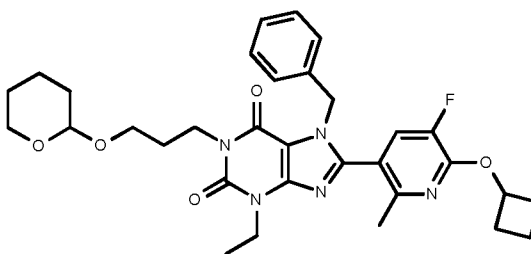
To a mixture of intermediate 6.14 (810 mg, 1.56 mmol) in dioxane (34.4 mL, 390 mmol)

[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with  
dichloromethane (1:1, 255 mg, 0.31 mmol) was added and after 5 min (6-fluoro-2-  
methylpyridin-3-yl)boronic acid (314 mg, 2.03 mmol) and  $\text{Cs}_2\text{CO}_3$  (2 mol/L, 1.56 mL,  
3.12 mmol) were added and the mixture was stirred 3 h at 100°C. The mixture was  
cooled, filtered and washed with MeOH/ACN (1/1). Thiopolymer (1g) was added, the  
mixture was filtered again and washed with MeOH/ACN (1/1). The crude product was  
purified by chromatography to obtain 700 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 550

HPLC: RT = 0.83 min, Method G

### Intermediate 15.3



15.3

The reaction was performed under argon atmosphere.

To a mixture of intermediate 6.19 (100 mg, 0.22 mmol) and intermediate 14.1 (82 mg,

0.17 mmol) in THF (2 mL, 25 mmol)  $\text{K}_3\text{PO}_4$  (0.5 mol/L, 0.9 mL, 0.45 mmol) was added  
and after 5 min (2-dicyclohexylphosphino-2',4',6'-trisisopropyl)-1,1'-biphenyl][2-(2'-  
amino-1,1'-biphenyl)]palladium(II) methanesulfonate (18.9 mg, 0.022 mmol) was added  
and the reaction mixture was stirred 5h at 100°C. The mixture was filtered, washed with

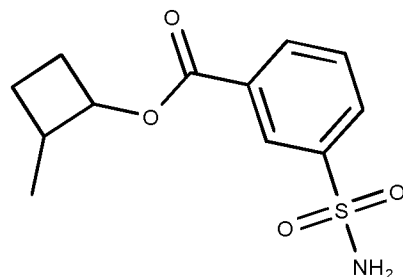
MeOH and concentrated in vacuo. The crude product was purified by chromatography to obtain 58.0 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 592/593

HPLC: RT = 0.9 min, Method G

5

Intermediate 16.1



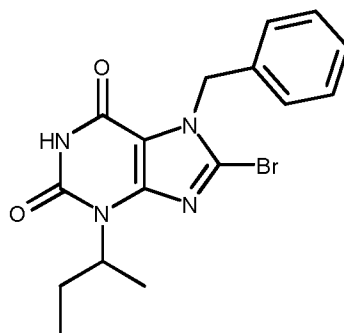
16.1

10 To a mixture of 3-sulfamoylbenzoic acid (70.1 mg, 0.348 mmol) and DMAP (4.4 mg, 0.036 mmol) in DMF (0.5 mL) 2-methylcyclobutan-1-ol (30 mg, 0.348 mmol) and DCC (86.5 mg, 0.415 mmol) were added and the mixture was stirred 1h. H<sub>2</sub>O was added and the mixture extracted with DCM. The combined organic layers were dried, concentrated in vacuo and purified by chromatography to obtain 21.0 mg the product as a  
15 diastereomeric mixture.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 268/269

HPLC: RT = 0.53/0.54 min, Method D

Intermediate 19.1



19.1

A mixture of intermediate 5.14 (1.7 g, 5.29 mmol) in DMF (22 mL, 270 mmol) was warmed to 50°C. Then sodium hydride (60%, 211.8 mg, 5.29 mmol) was added and

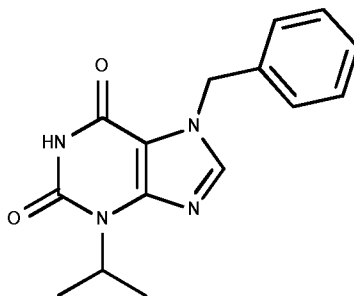
20

stirred 30 min at 50°C. Additional DMF (7.3 mL, 90 mmol) and 2-iodobutane (3.05 mL, 26.5 mmol) were added and the mixture was stirred 3h at 80°C. The mixture was cooled and purified by chromatography to obtain 700.0 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 379

5 HPLC: RT = 0.63 min, Method G

Intermediate 19.2



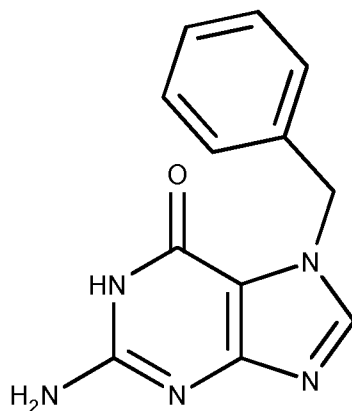
19.2

10 A mixture of intermediate 21.1 (2 g, 8.26 mmol) in DMF (45 mL, 553 mmol) was warmed to 50°C. Then sodium hydride (55%, 360.3 mg, 8.23 mmol) was added and stirred 1 h at 50°C. 2-iodopropane (4.13 mL, 41.28 mmol) were added and the mixture was stirred 1h at 80°C. The mixture was cooled, purified by chromatography and freeze dried to obtain 661 mg of the product.

15 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 285/286

HPLC: RT = 0.65 min, Method F

Intermediate 20.1



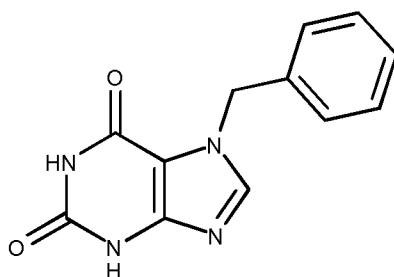
20.1

To a mixture of 2-amino-9-[(2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6,9-dihydro-1H-purin-6-one (60 g, 211.8 mmol) in DMSO (160 ml, 2.25 mol) (bromomethyl)benzene (30.2 ml, 254.2 mmol) was added dropwise and the mixture was stirred 4 h at 50°C. The mixture was cooled and HCl (4 mol/l, 122 mL, 487.2 mmol) was added dropwise and the mixture was stirred 2h at 70°C. The mixture was cooled, filtered, washed with MeOH and dried to obtain 41.8 g of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 242

HPLC: RT = 0.28 min, Method D

#### Intermediate 21.1



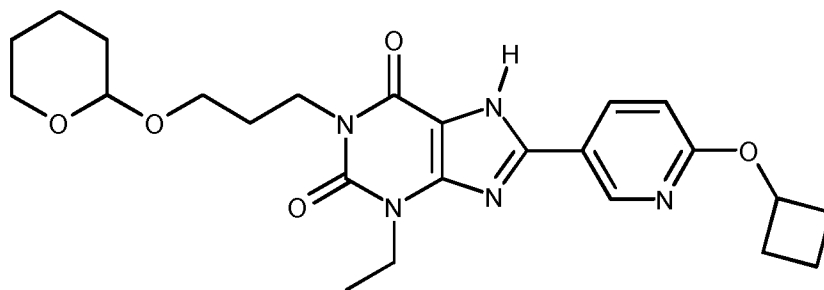
21.1

To a mixture of intermediate 20.1 (1.41g, 5.86 mmol) in AcOH (40 ml) NaNO<sub>2</sub> (404 mg, 5.86 mmol) in H<sub>2</sub>O (5 mL) was added dropwise at 50°C and the mixture was stirred 3h at 50°C. Additional NaNO<sub>2</sub> (404 mg, 5.86 mmol) in H<sub>2</sub>O (5 mL) was added and the mixture was stirred overnight at 70°C. The mixture was cooled, basified with NaHCO<sub>3</sub> solution and extracted with DCM. The combined organic layers were dried and concentrated in vacuo. The crude product was purified by chromatography and freeze dried to obtain 1.13 g of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 242

HPLC: RT = 0.32 min, Method A

#### Intermediate 22.1



107

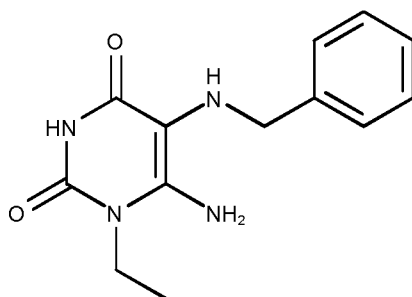
## 22.1

To a mixture of intermediate 12.5 (220 mg, 0.367 mmol) in THF (3.03 mL, 37.8 mmol) tetrabutylammonium fluoride (1 mol/L, 651 mg, 0.734 mmol) was added and the mixture was stirred overnight at 80°C. The mixture was cooled and used without further purification.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 386

HPLC: RT = 0.62 min, Method D

## Intermediate 23.1



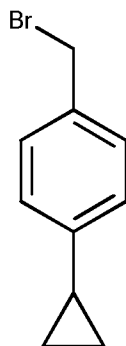
23.1

A mixture of intermediate 4.10 (0.89 g, 1.72 mmol), raney nickel (60 mg) and NaOH (1N, 60 mL, 1.5 mol) was hydrogenated at rt and 50 psi of H<sub>2</sub> for 2 d. The mixture was filtered and acidified with HCl. The obtained precipitate was filtered, washed with water and dried to obtain 62.0 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 261/262

HPLC: RT = 0.34 min, Method D

## Intermediate 24.1

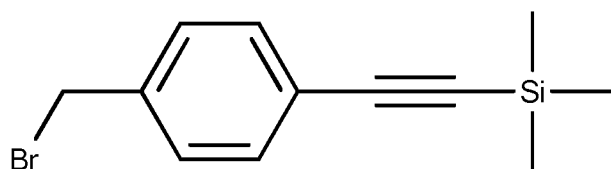


24.1

To a mixture of (4-cyclopropylphenyl)methanol (646 mg, 4.36 mmol) in DCM (5 mL) tribromophosphane (286.8  $\mu$ L, 3.05 mmol) and THF (1 mL) were added and the mixture was stirred 30 min at rt. Additional tribromophosphane was added and the mixture was basified with saturated  $\text{NaHCO}_3$  solution under ice cooling and extracted with DCM. The combined organic layers were dried and concentrated in vacuo to obtain 744 mg of the product.

HPLC: RT = 0.69 min, Method F

#### Intermediate 24.2

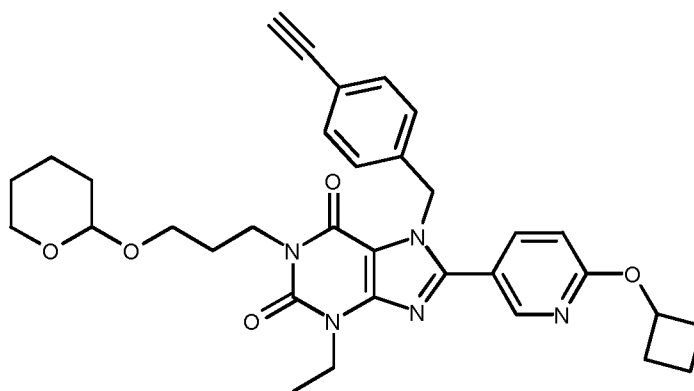


#### 24.2

To a mixture of {4-[2-(trimethylsilyl)ethynyl]phenyl}methanol (772.4 mg, 3.78 mmol) in chloroform (3 mL) tribromophosphane (355.3  $\mu$ L, 2.88 mmol) was added under ice cooling. The mixture was stirred overnight at rt.  $\text{H}_2\text{O}$  was added and extracted with DCM. The combined organic layers were dried and concentrated in vacuo. The crude product was purified by chromatography to obtain 150.0 mg of the product.

HPLC: RT = 1.20 min, Method F

#### Intermediate 25.1



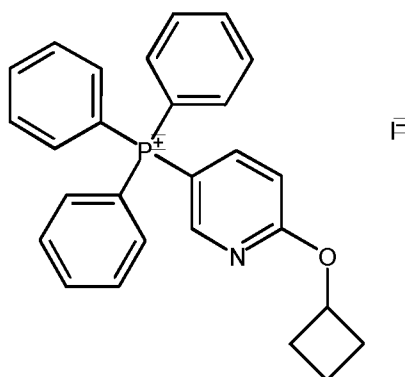
## 25.1

To a mixture of intermediate 5.29 (13 mg, 0.02 mmol) in MeOH (1 mL) and THF (1 mL)  $K_2CO_3$  (5.5 mg) was added and the mixture was stirred 2 h at rt and used without further purification in the next step.

5 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 584

HPLC: RT = 0.81 min, Method A

## Intermediate 26.1



F

## 26.1

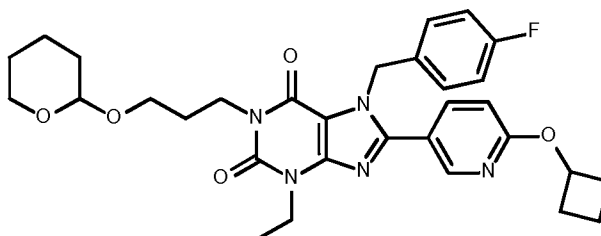
The reaction was performed under argon atmosphere.

A mixture of intermediate 9.6 (1.375 g, 5.00 mmol), tris(dibenzylideneacetone)-dipalladium(0) (45.8 mg, 0.05 mmol) and triphenylphosphane (1.31 g, 5.00 mmol) in xylol (3.37 mL, 28.5 mmol) was stirred 4.5 h at reflux. The mixture was cooled, EtOAc (100 mL) was added and heated to reflux. The mixture was cooled again and the obtained precipitate was filtered, washed with EtOAc and dried to obtain 2.20 g of the product.

15 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 410

HPLC: RT = 0.58 min, Method A

## Intermediate 27.1



## 27.1

The reaction was performed under argon atmosphere.

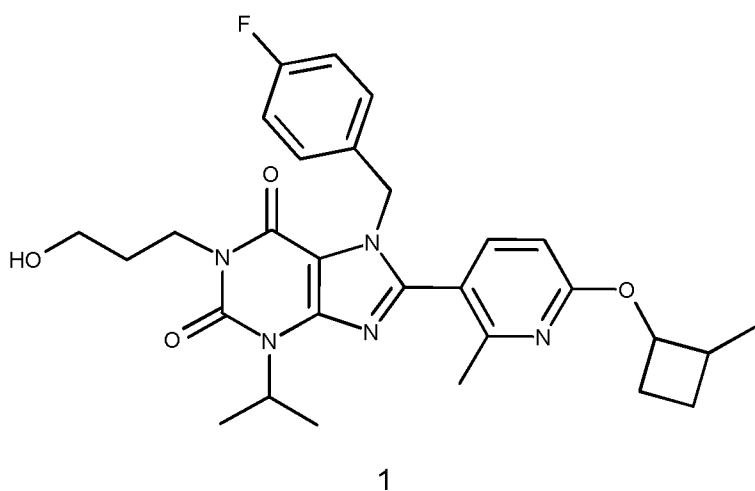
To a mixture of intermediate 26.1 (633 mg, 0.88 mmol) and Pd(OAc)<sub>2</sub> (40 mg, 0.18 mmol) in DMF (2.5 mL) was added a solution of intermediate 6.9 (450 mg, 0.88 mmol) and K<sub>2</sub>CO<sub>3</sub> (366 mg, 2.65 mmol) in DMF (3 mL) and the mixture was stirred 3 d at 120°C. The mixture was cooled, filtered over a celite pad, washed with DCM/MeOH (95/5), concentrated in vacuo and purified by chromatography to obtain 27.0 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 578

HPLC: RT = 0.87 min, Method D

### Examples:

#### Example 1

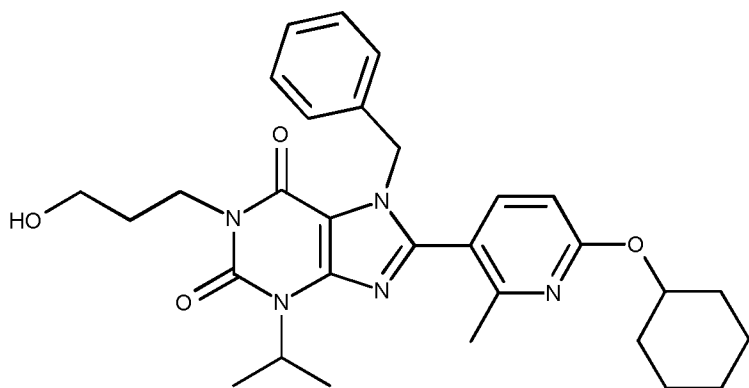


To a mixture of intermediate 7.1 (54.0 mg, 0.09 mmol) in MeOH (1.0 mL) and THF (1.0 mL) toluene-4-sulfonic acid hydrate (20.7 mg, 0.11 mmol) was added. The mixture was stirred 1 h at rt. The mixture was concentrated in vacuo and purified by chromatography to obtain 29.5 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 536

HPLC: RT = 0.84 min, Method F

#### Example 2



2

To a mixture of intermediate 7.2 (39.0 mg, 0.06 mmol) in MeOH (2.0 mL) toluene-4-sulfonic acid hydrate (0.06 g, 0.32 mmol) was added. The mixture was stirred 1 h at rt.

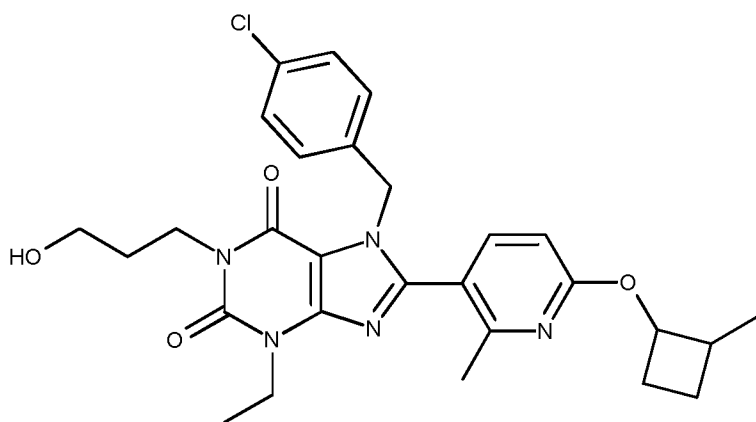
5 The mixture was purified by chromatography to obtain 23.0 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 533

HPLC: RT = 0.88 min, Method G

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 7.64 (d, *J*=8.4 Hz, 1H), 7.22-7.24 (m, 3H), 6.87-6.90 (m, 2H), 6.68 (d, *J*=8.4 Hz, 1H), 5.41 (s, 2H), 5.01-5.15 (m, 2H), 4.42 (t, *J*=5.3 Hz, 1H), 3.94-3.97  
10 (m, 2H), 3.43-3.48 (m, 2H), 2.05 (s, 3H), 1.91-1.99 (m, 2H), 1.69-1.75 (m, 4H), 1.24-1.56 (m, 12H).

### Example 3



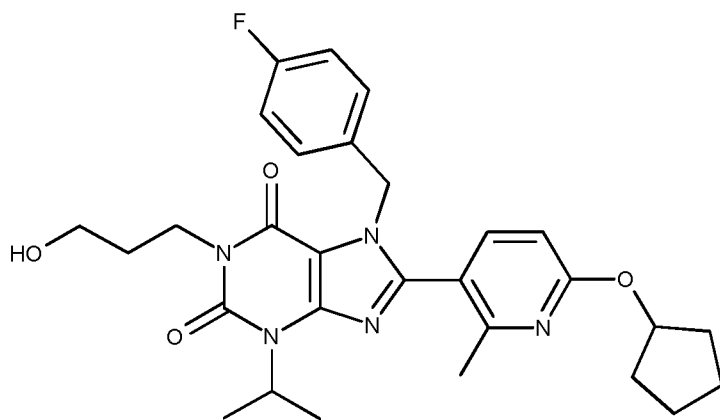
3

Example 3 was prepared in an analogous manner to example 1 using intermediate 7.3.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 539/541 (Cl isotope pattern)

RT = 1.44 min, Method C

### Example 4



4

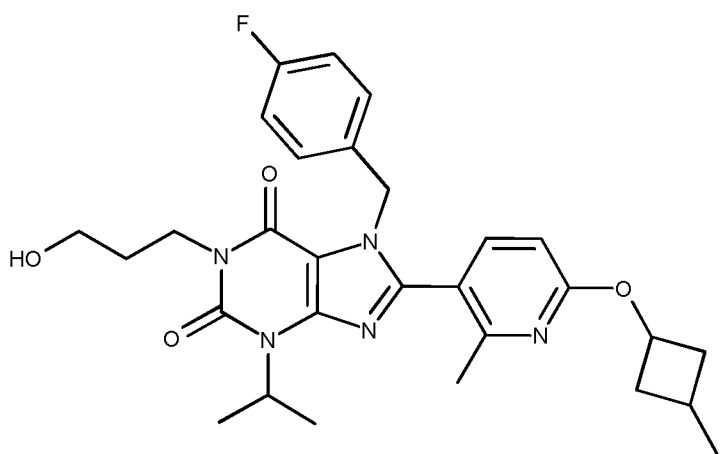
Example 4 was prepared in an analogous manner to example 1 using intermediate 7.4.

5 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 536

RT = 0.83 min, Method F

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 7.63 (d, *J*=8.5 Hz, 1H), 7.04-7.09 (m, 2H), 6.93-6.95 (m, 2H), 6.69 (d, *J*=8.5 Hz, 1H), 5.38-5.41 (m, 3H), 5.06-5.15 (m, 1H), 4.42 (t, *J*=5.3 Hz, 1H), 3.94-3.97 (m, 2H), 3.42-3.48 (m, 2H), 2.07 (s, 3H), 1.91-2.00 (m, 2H), 1.57-1.76 (m, 8H), 1.51 (d, *J*=6.8 Hz, 6H).

### Example 5



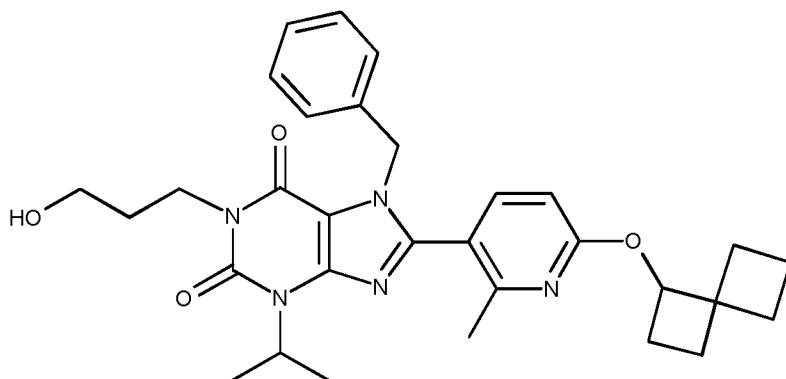
5

15 Example 5 was prepared in an analogous manner to example 1 using intermediate 7.5.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 536

RT = 0.83 min, Method F

### Example 6



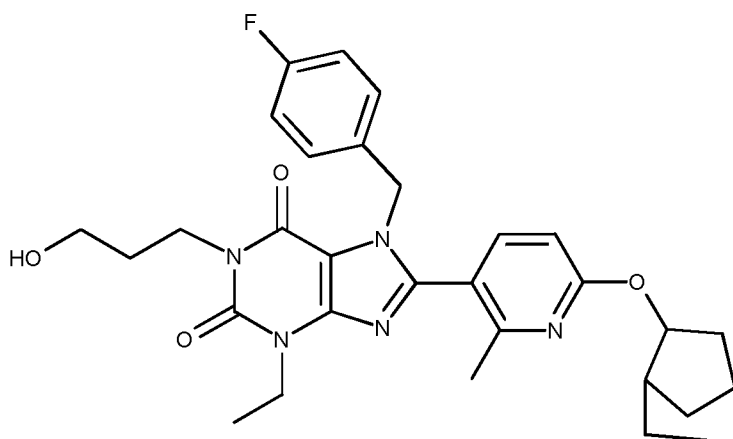
6

Example 6 was prepared in an analogous manner to example 1 using intermediate 7.6.

5 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 545

RT = 0.59 min, Method E

### Example 7



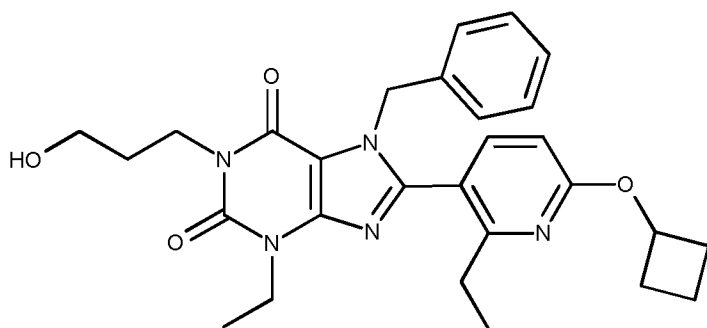
7

Example 7 was prepared in an analogous manner to example 1 using intermediate 7.7.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 548

RT = 0.84 min, Method G

15 Example 8



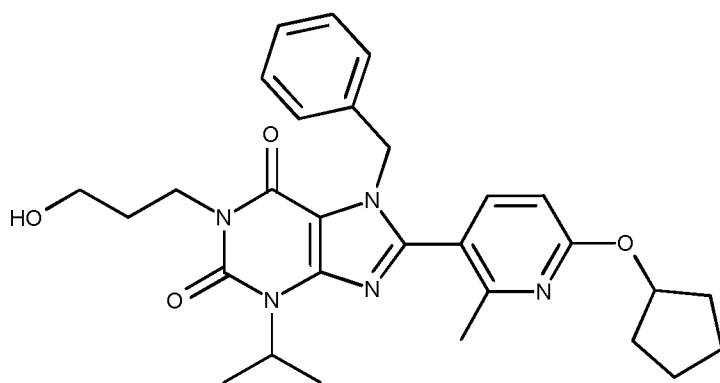
8

Example 7 was prepared in an analogous manner to example 2 using intermediate 12.1.

5 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 505

RT = 0.8 min, Method G

Example 9



9

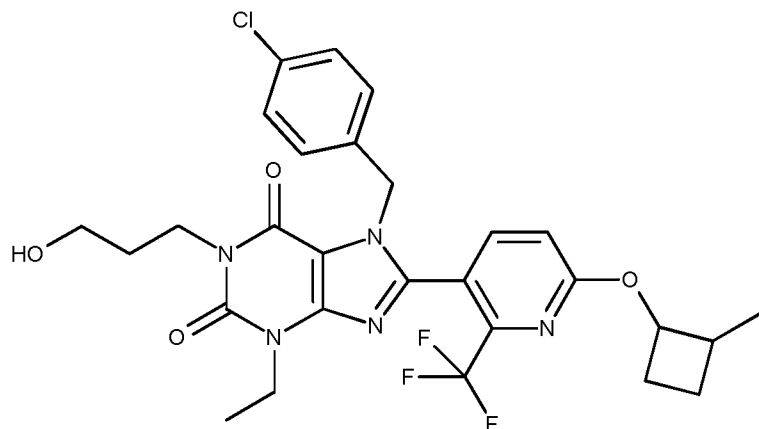
Example 9 was prepared in an analogous manner to example 1 using intermediate 7.8.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 518

RT = 0.85 min, Method D

1H NMR (DMSO-d<sub>6</sub>) δ 7.64 (d, J=8.5 Hz, 1H), 7.22-7.24 (m, 3H), 6.86-6.89 (m, 2H),  
 15 6.68 (d, J=8.5 Hz, 1H), 5.38-5.41 (m, 3H), 5.06-5.15 (m, 1H), 4.42 (t, J=5.3 Hz, 1H),  
 3.94-3.97 (m, 2H), 3.42-3.48 (m, 2H), 2.04 (s, 3H), 1.91-2.00 (m, 2H), 1.57-1.76 (m,  
 8H), 1.51 (d, J=7.0 Hz, 6H).

Example 10

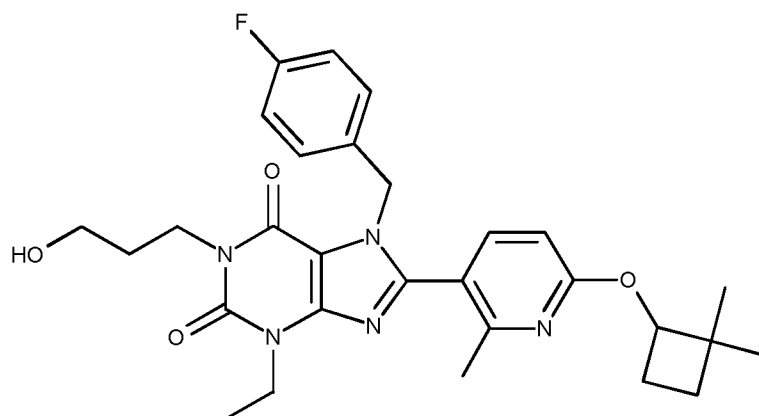


10

Example 10 was prepared in an analogous manner to example 1 using intermediate 7.9.

- 5 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 593/595 (Cl isotope pattern)  
RT = 1.47 min, Method C

Example 11

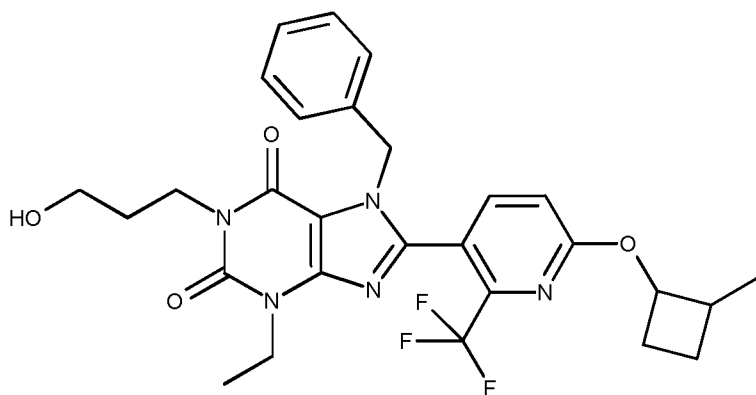


11

Example 11 was prepared in an analogous manner to example 2 using intermediate 7.11.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 537  
RT = 0.84 min, Method D

Example 12

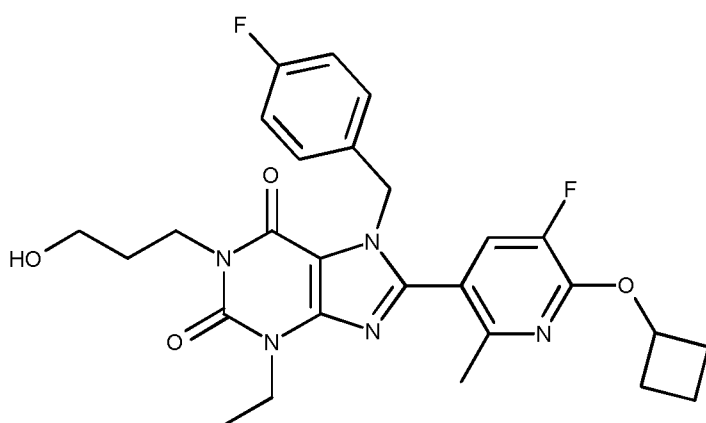


12

Example 12 was prepared in an analogous manner to example 1 using intermediate 7.12.

5 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 559  
RT = 1.41 min, Method C

### Example 13

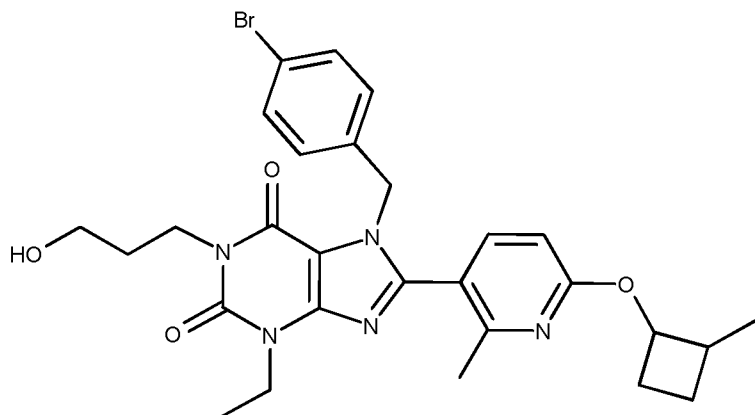


13

To a mixture of intermediate 15.1 (35.0 mg, 0.06 mmol) in MeOH (2.0 mL) toluene-4-sulfonic acid hydrate (0.055 g, 0.29 mmol) was added. The mixture was stirred 1 h at rt. The mixture was purified by chromatography to obtain 27.0 mg of the product.

10 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 527  
HPLC: RT = 0.78 min, Method G

### Example 14



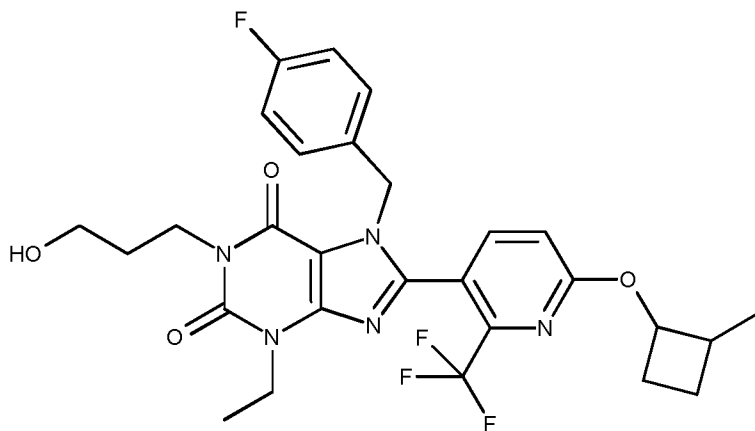
14

To a mixture of intermediate 7.14 (97 mg, 0.146 mmol) in MeOH (1.0 mL) and THF (1.0 mL) toluene-4-sulfonic acid hydrate (35 mg, 0.182 mmol) was added. The mixture was stirred 1.5 h at rt. The mixture was concentrated in vacuo and purified by chromatography to obtain 42.2 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 583/585 (Br isotope pattern)

HPLC: RT = 0.86 min, Method D

#### Example 15



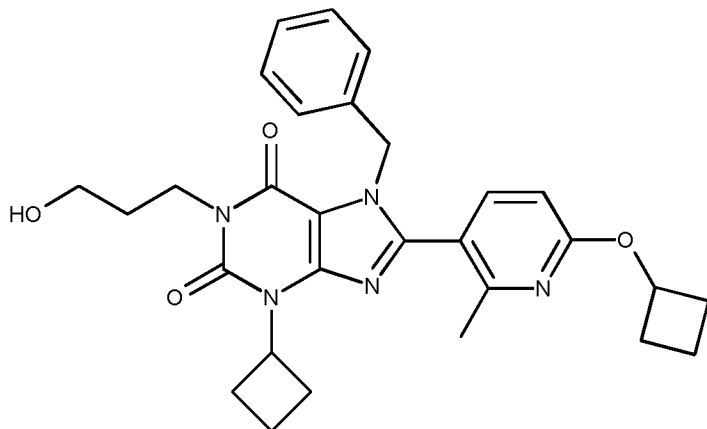
15

To a mixture of intermediate 7.15 (70 mg, 0.11 mmol) in MeOH (1.0 mL) and THF (1.0 mL) toluene-4-sulfonic acid hydrate (25 mg, 0.13 mmol) was added. The mixture was stirred 4 h at rt. The mixture was concentrated in vacuo and purified by chromatography to obtain 45.4 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 577

HPLC: RT = 1.42 min, Method C

### Example 16



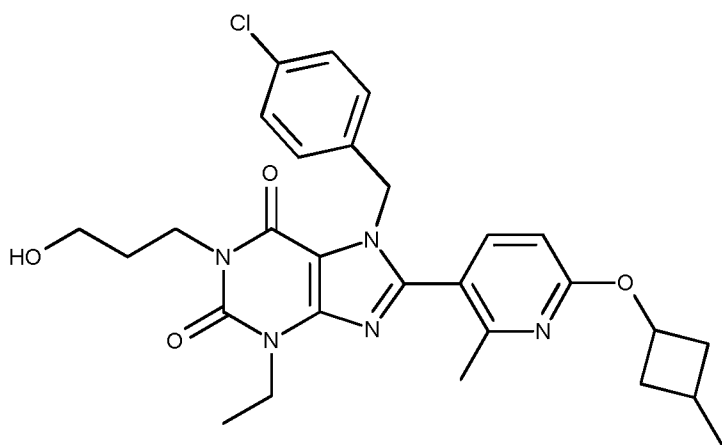
16

5 To a mixture of intermediate 7.17 (170 mg, 0.28 mmol) in MeOH (2.0 mL) toluene-4-sulfonic acid hydrate (0.27 g, 1.42 mmol) was added. The mixture was stirred 1 h at rt. The mixture was purified by chromatography and freeze dried to obtain 123 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 517

10 RT = 0.85 min, Method G

### Example 17



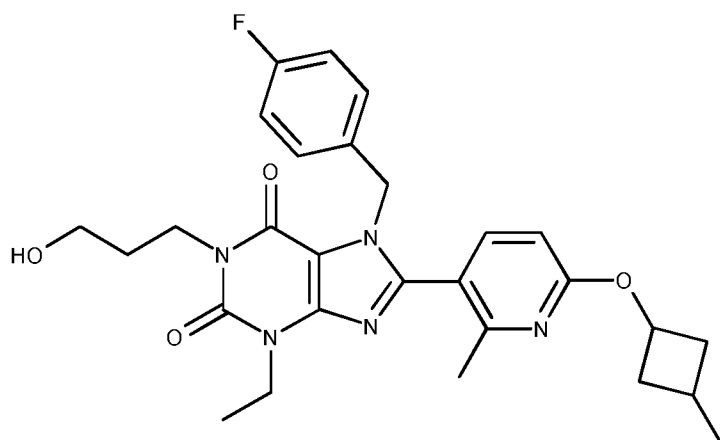
17

15 Example 17 was prepared in an analogous manner to example 15 using intermediate 7.18.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 539/541 (Cl isotope pattern)

RT = 0.84 min, Method C

## Example 18



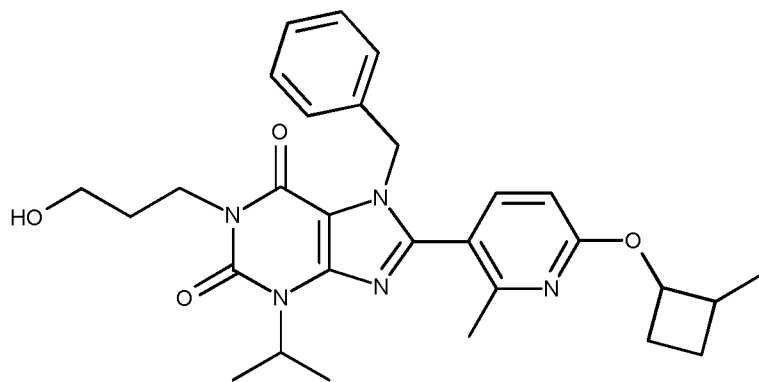
18

Example 18 was prepared in an analogous manner to example 16 using intermediate 7.20.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 523

RT = 0.8 min, Method D

## Example 19



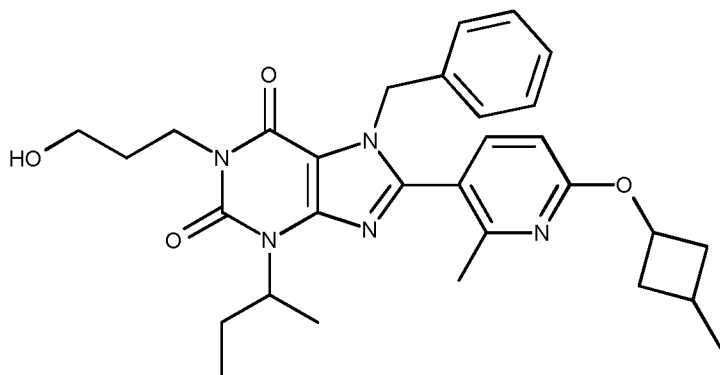
19

To a mixture of intermediate 7.21 (98 mg, 0.16 mmol) in THF (1.0 mL) toluene-4-sulfonic acid hydrate (0.155 g, 0.81 mmol) was added. The mixture was stirred 1 h at rt. The mixture was purified by chromatography and freeze dried to obtain 55.0 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 519

HPLC: RT = 1.48 min, Method C

## Example 20



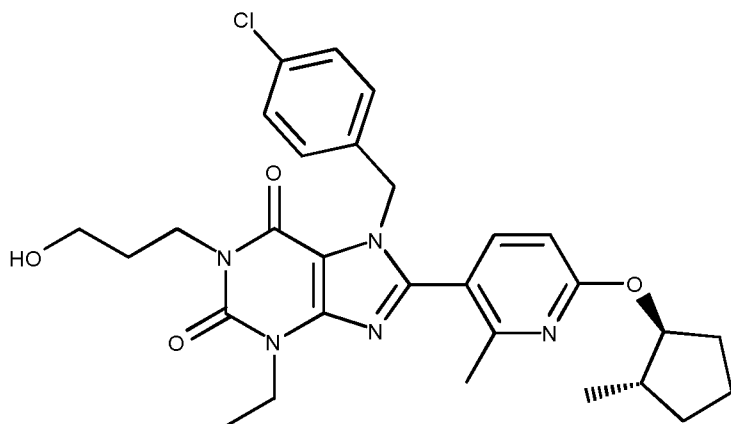
20

- 5 To a mixture of intermediate 7.22 (crude, 259 mg, 0.42 mmol) in ACN (1 mL) toluene-4-sulfonic acid hydrate (240mg, 1.26 mmol) and MeOH (5 mL, 0.125 mol) were added and the mixture was stirred 30 min at rt. The mixture was purified by chromatography to obtain 170 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 533

- 10 RT = 0.88 min, Method G

## Example 21



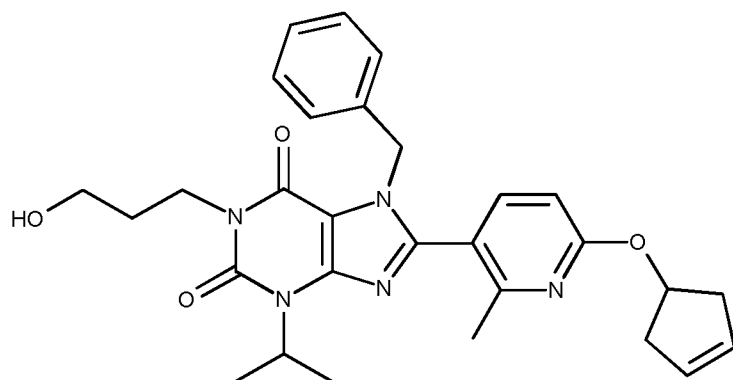
21

- 15 To a mixture of intermediate 7.23 (13 mg, 0.02 mmol) in MeOH (0.5 mL) and THF (0.5 mL) toluene-4-sulfonic acid hydrate (5 mg, 0.03 mmol) was added. The mixture was stirred 1.5 h at rt. The mixture was concentrated in vacuo and purified by chromatography to obtain 9.4 mg of the product as a racemic mixture.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 553/555 (Cl isotope pattern)

RT = 0.88 min, Method D

### Example 22



5

22

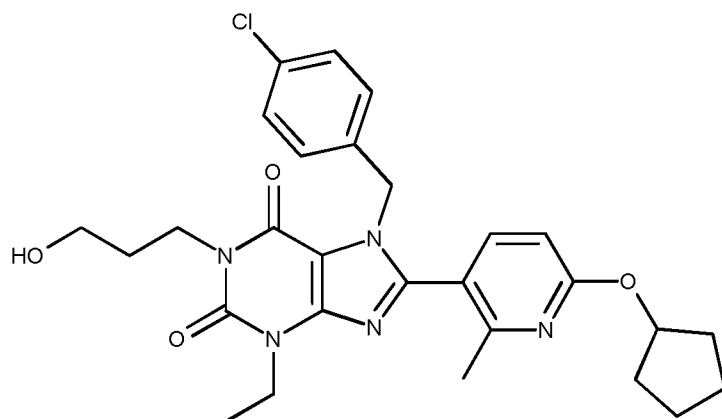
Example 22 was prepared in an analogous manner to example 16 using intermediate 7.24.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 517

RT = 0.41 min, Method E

10

### Example 23



23

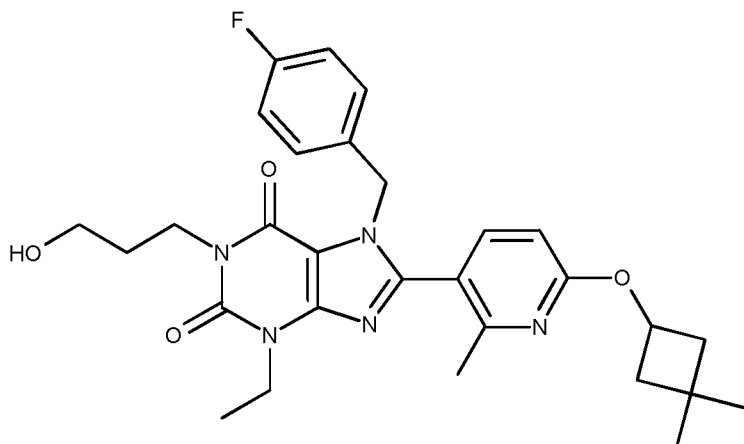
To a mixture of intermediate 7.25 (26 mg, 0.04 mmol) in MeOH (1 mL) and THF (1 mL) toluene-4-sulfonic acid hydrate (10 mg, 0.05 mmol) was added. The mixture was stirred 0.5 h at rt. The mixture was concentrated in vacuo and purified by chromatography to obtain 14.5 mg of the product.

15

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 539/541 (Cl isotope pattern)

RT = 1.42 min, Method C

## Example 24



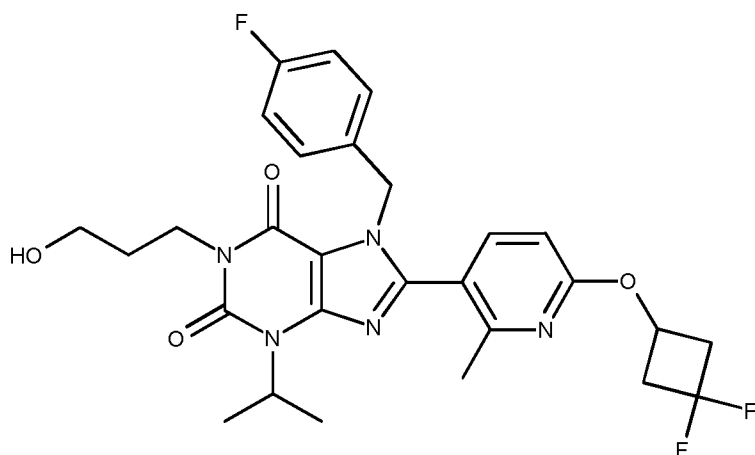
24

- 5 Example 24 was prepared in an analogous manner to example 16 using intermediate 7.26.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 537

RT = 0.82 min, Method D

## 10 Example 25



25

Example 25 was prepared in an analogous manner to example 16 using intermediate 7.27.

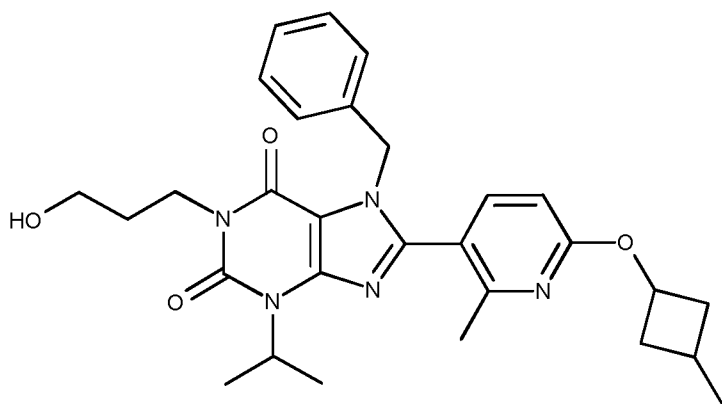
- 15 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 559

RT = 1.08 min, Method F

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 7.72 (d, *J*=8.5 Hz, 1H), 7.05-7.09 (m, 2H), 6.92-6.96 (m, 2H), 6.81 (d, *J*=8.5 Hz, 1H), 5.39 (s, 2H), 5.05-5.20 (m, 2H), 4.42 (t, *J*=5.3 Hz, 1H), 3.94-3.98 (m, 2H), 3.43-3.48 (m, 2H), 3.11-3.21 (m, 2H), 2.66-2.80 (m, 2H), 2.06 (s, 3H), 1.69-1.76 (m, 2H), 1.51 (d, *J*=6.9 Hz, 6H).

5

### Example 26



26

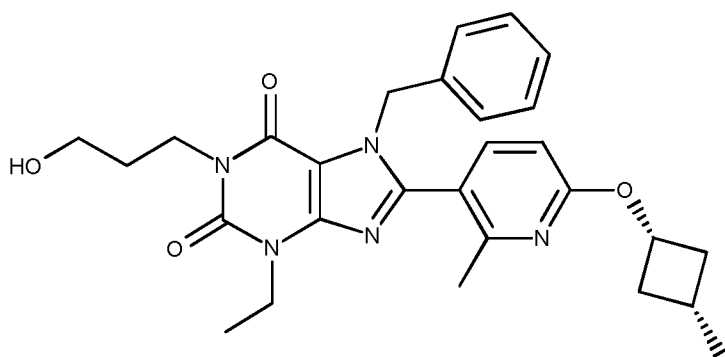
Example 26 was prepared in an analogous manner to example 16 using intermediate 12.2.

10

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 519

RT = 1.13 min, Method F

### Example 27



27

To a mixture of intermediate 12.3 (155 mg, 0.26 mmol) in MeOH (1.5 mL) toluene-4-sulfonic acid hydrate (100 mg, 0.53 mmol) was added. The mixture was stirred 3 h at rt. The mixture was concentrated in vacuo and purified by chromatography. Cis/trans isomers were separated by SFC (see example 28 for other isomer).

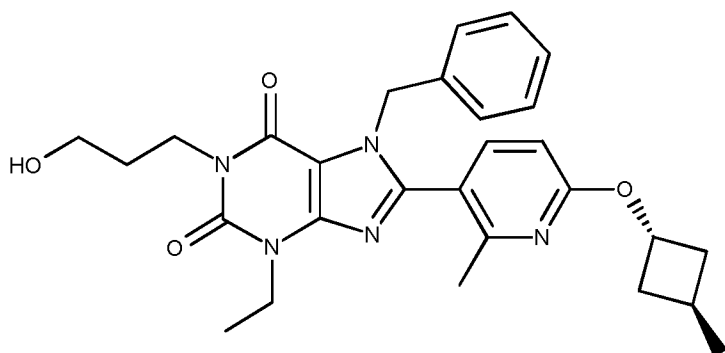
15

20

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 505

RT = 4.428 min, Method J

#### Example 28



5

30

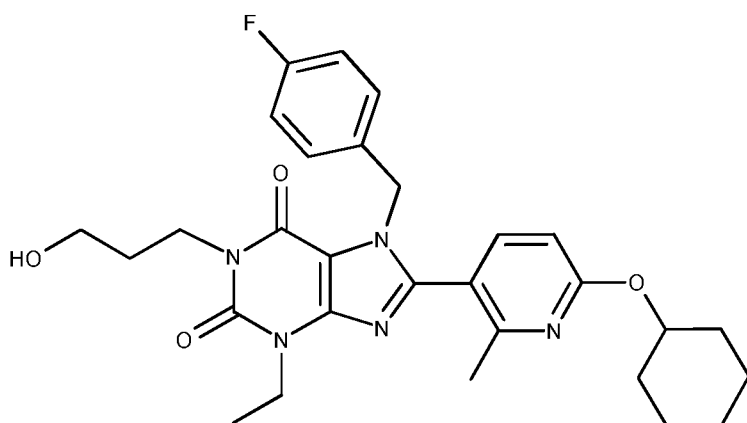
To a mixture of intermediate 12.3 (155 mg, 0.26 mmol) in MeOH (1.5 mL) toluene-4-sulfonic acid hydrate (100 mg, 0.53 mmol) was added. The mixture was stirred 3 h at rt. The mixture was concentrated in vacuo and purified by chromatography. Cis/trans isomers were separated by SFC (see example 27 for other isomer).

10

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 505

RT = 5.005 min, Method J

#### Example 29



15

29

To a mixture of intermediate 7.28 (55 mg, 0.09 mmol) in MeOH (1.0 mL) and THF (1.0 mL) toluene-4-sulfonic acid hydrate (21 mg, 0.11 mmol) was added. The mixture was

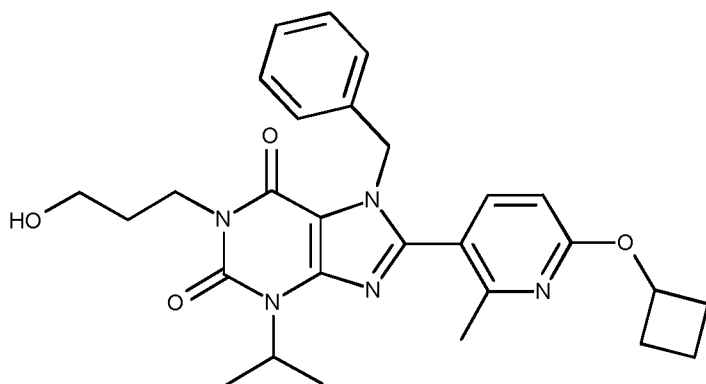
stirred 1 h at rt. The mixture was concentrated in vacuo and purified by chromatography to obtain 34.3 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 537

HPLC: RT = 0.82 min, Method D

5

### Example 30



30

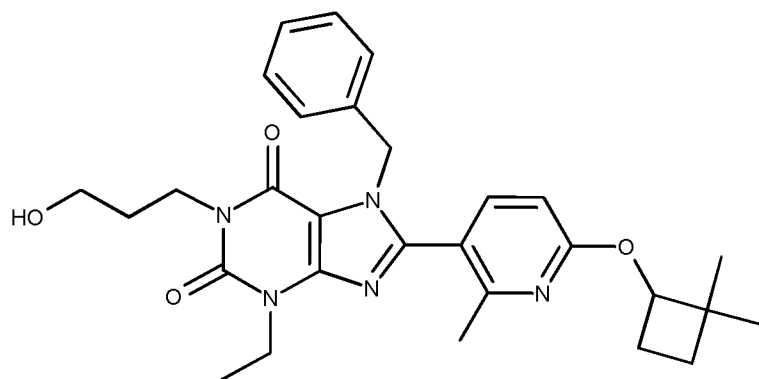
To a mixture of intermediate 12.4 (121 mg, 0.19 mmol) in MeOH (3.0 mL) toluene-4-sulfonic acid hydrate (182 mg, 0.96 mmol) was added. The mixture was stirred 1 h at rt. The mixture was concentrated in vacuo, purified by chromatography and freeze dried to obtain 95.0 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 505

HPLC: RT = 1.08 min, Method F

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 7.66 (d, *J*=8.5 Hz, 1H), 7.21-7.25 (m, 3H), 6.86-6.89 (m, 2H), 6.70 (d, *J*=8.5 Hz, 1H), 5.41 (s, 2H), 5.05-5.19 (m, 2H), 4.42 (t, *J*=5.3 Hz, 1H), 3.94-3.97 (m, 2H), 3.42-3.48 (m, 2H), 2.36-2.45 (m, 2H), 2.01-2.12 (m, 5H), 1.61-1.83 (m, 4H), 1.51 (d, *J*=7.0 Hz, 6H).

### Example 31

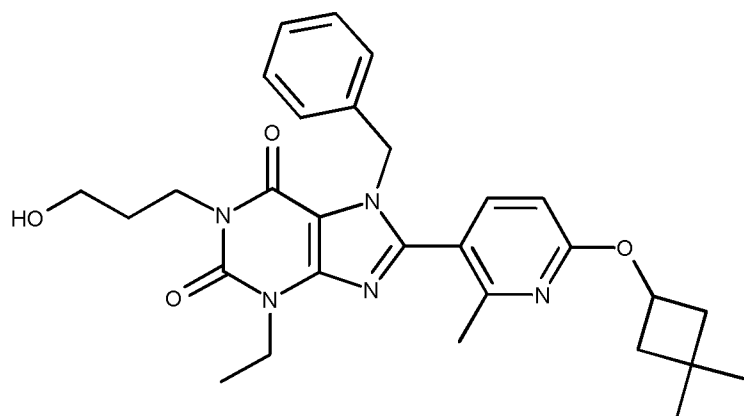


31

Example 31 was prepared in an analogous manner to example 30 using intermediate 7.29.

5 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 519  
RT = 0.85 min, Method D

Example 32

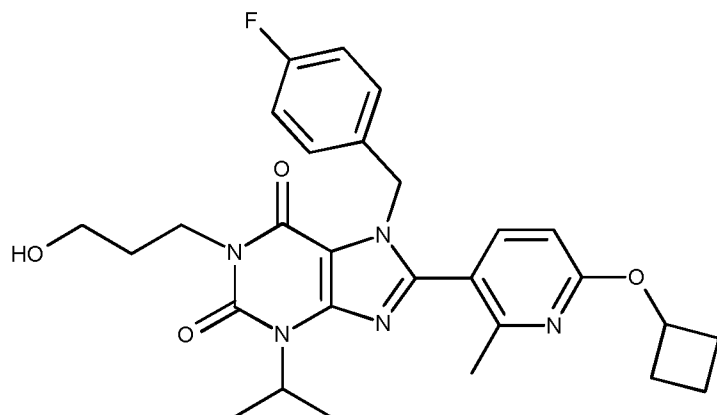


32

Example 32 was prepared in an analogous manner to example 30 using intermediate 7.30.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 519  
RT = 0.83 min, Method D

Example 33



33

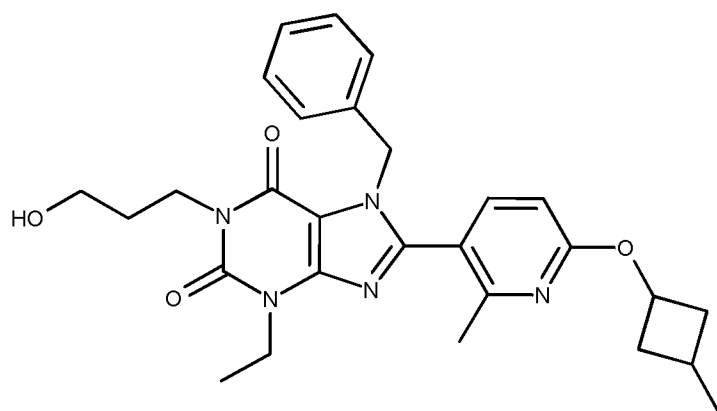
Example 33 was prepared in an analogous manner to example 29 using intermediate 7.31.

5 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 523

RT = 0.73 min, Method D

1H NMR (DMSO-d<sub>6</sub>) δ 7.65 (d, J=8.5 Hz, 1H), 7.04-7.09 (m, 2H), 6.92-6.95 (m, 2H),  
6.71 (d, J=8.4 Hz, 1H), 5.39 (s, 2H), 5.05-5.19 (m, 2H), 4.41-4.43 (m, 1H), 3.94-3.97 (m,  
2H), 3.42-3.48 (m, 2H), 2.36-2.45 (m, 2H), 2.01-2.12 (m, 5H), 1.61-1.83 (m, 4H), 1.51  
10 (d, J=7.0 Hz, 6H).

#### Example 34



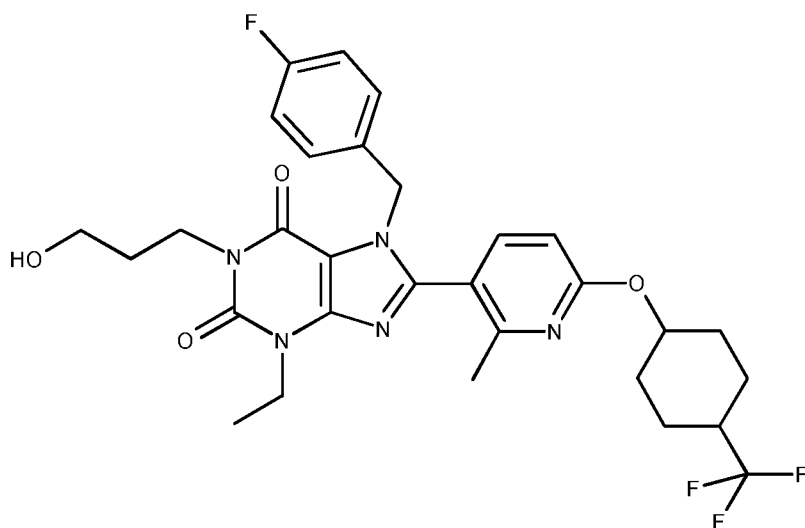
34

15 Example 34 was prepared in an analogous manner to example 29 using intermediate 7.32.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 505

RT = 0.79 min, Method D

## Example 35



5

35

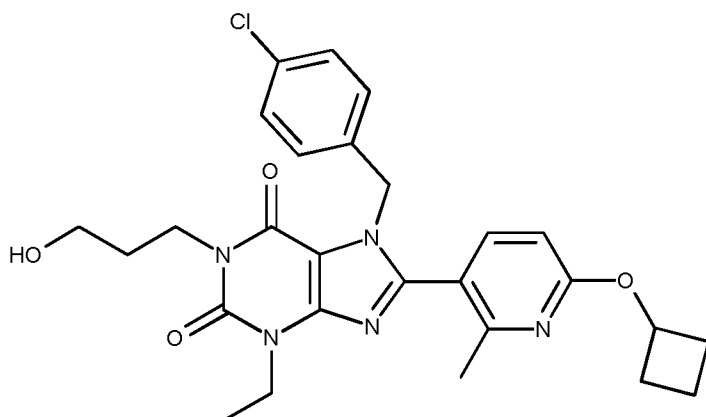
Example 35 was prepared in an analogous manner to example 30 using intermediate 7.34.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 605

RT = 0.72 min, Method D

10

## Example 36



36

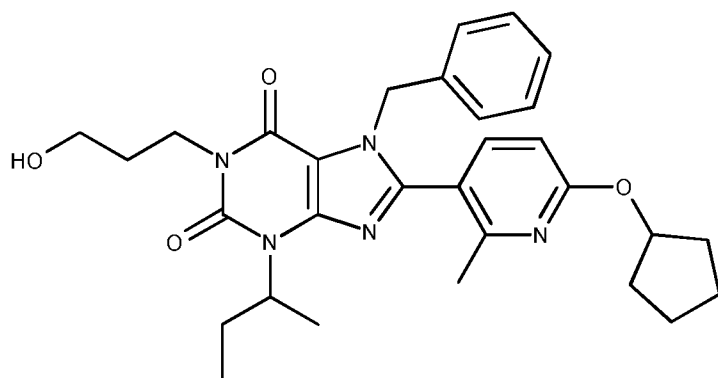
Example 36 was prepared in an analogous manner to example 29 using intermediate 7.35.

15

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 525/527 (Cl isotope pattern)

RT = 1.35 min, Method C

### Example 37



5

37

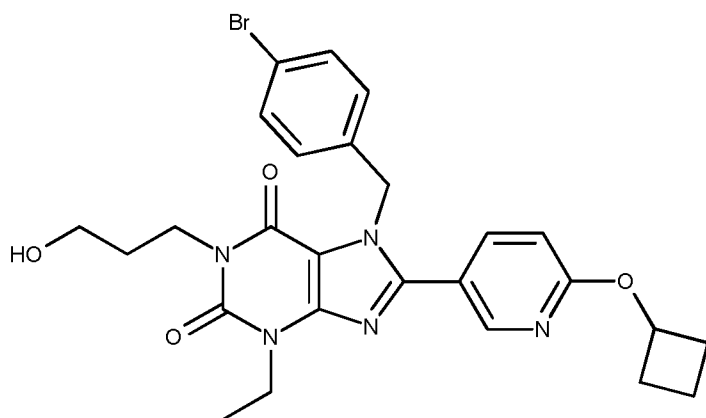
Example 37 was prepared in an analogous manner to example 30 using intermediate 7.36.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 533

RT = 0.88 min, Method G

10

### Example 38



38

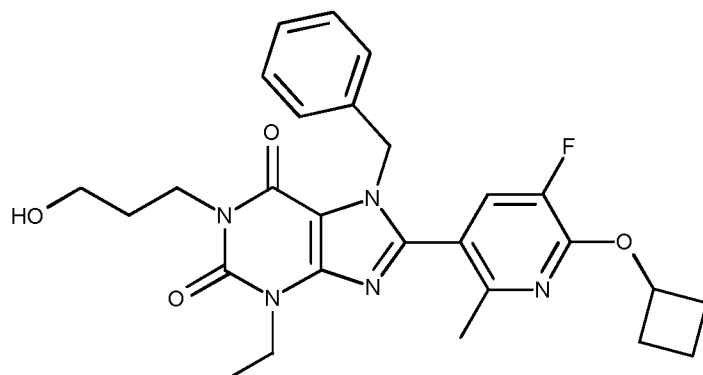
To a mixture of intermediate 22.1 (40 mg, 0.085 mmol) in THF (704  $\mu$ L) and DMSO (697  $\mu$ L) DIPEA (16.1  $\mu$ L, 0.094 mmol) and 1-bromo-4-(bromomethyl)benzene (32 mg, 0.128 mmol) were added. The mixture was stirred 1.5 h at 50°C. Additional DIPEA was added and the mixture was stirred 45 min at 90°C. Then additional 1-bromo-4-(bromomethyl)benzene was added and the mixture was stirred 1h at 90°C. The mixture was cooled and purified by chromatography to obtain 8.0 mg of the product.

15

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 555/557 (Br isotope pattern)

HPLC: RT = 0.78 min, Method D

### Example 39



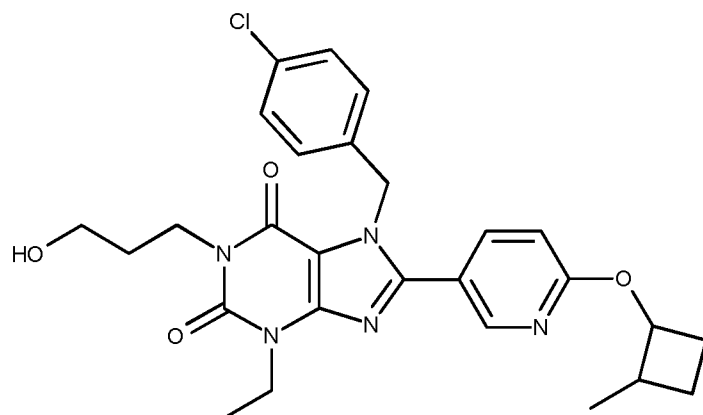
39

Example 39 was prepared in an analogous manner to example 30 using intermediate 15.3.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 509

RT = 0.77 min, Method G

### Example 40



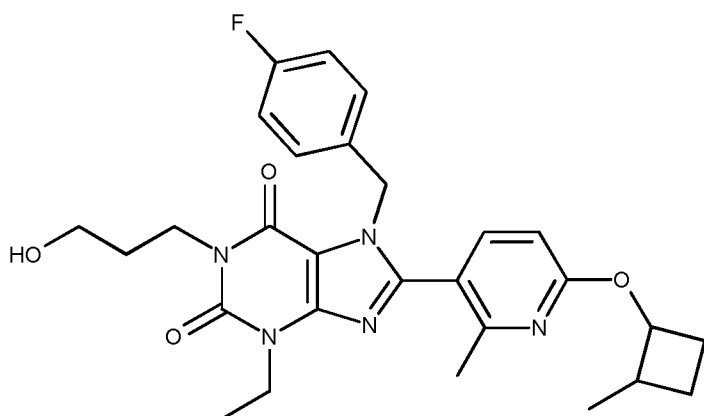
40

To a mixture of intermediate 7.37 (62 mg, 0.102 mmol) in THF (1.0 mL) toluene-4-sulfonic acid hydrate (182 mg, 0.96 mmol) was added. The mixture was stirred 1 h at rt. The mixture was concentrated in vacuo, purified by chromatography and freeze dried to obtain 40.0 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 526/528 (Cl isotope pattern)

HPLC: RT = 1.4 min, Method C

Example 41



5

41

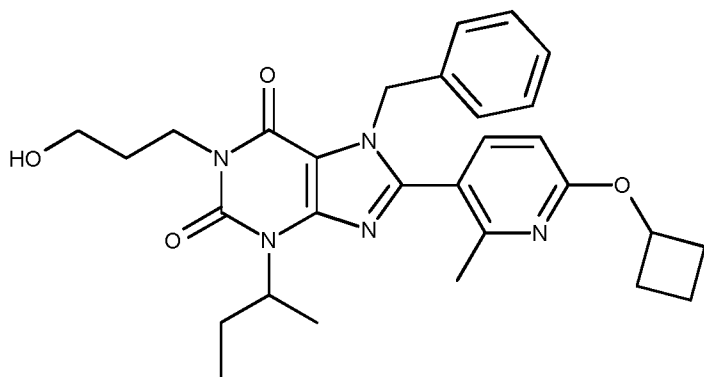
Example 41 was prepared in an analogous manner to example 40 using intermediate 7.38.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 523

RT = 1.37 min, Method C

10

Example 42



42

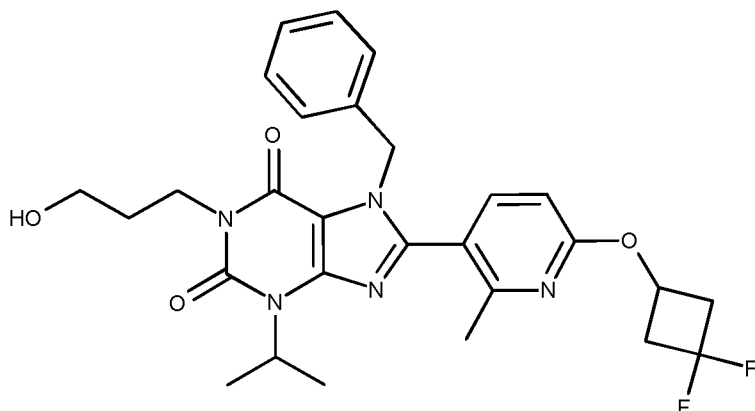
15

To a mixture of intermediate 7.39 (253 mg, 0.42 mmol) in ACN (1 ml), MeOH (5 ml) and toluene-4-sulfonic acid hydrate (240 mg, 1.26 mmol) were added and the mixture was stirred 30 min at rt. The mixture was purified by chromatography to obtain 181 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 519

RT = 0.84 min, Method G

## Example 43



43

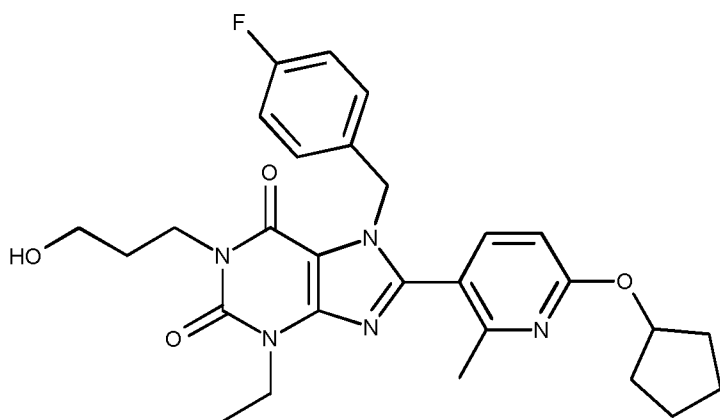
- 5 Example 43 was prepared in an analogous manner to example 30 using intermediate 7.40.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 541

RT = 1.07 min, Method F

- 1H NMR (DMSO-d<sub>6</sub>) δ 7.73 (d, J=8.5 Hz, 1H), 7.21-7.25 (m, 3H), 6.87-6.89 (m, 2H),  
 10 6.80 (d, J=8.2 Hz, 1H), 5.41 (s, 2H), 5.05-5.19 (m, 2H), 4.43 (t, J=5.0 Hz, 1H), 3.94-3.98 (m, 2H), 3.43-3.48 (m, 2H), 3.11-3.21 (m, 2H), 2.66-2.80 (m, 2H), 2.06 (s, 3H), 1.69-1.76 (m, 2H), 1.51 (d, J=6.9 Hz, 6H).

## Example 44



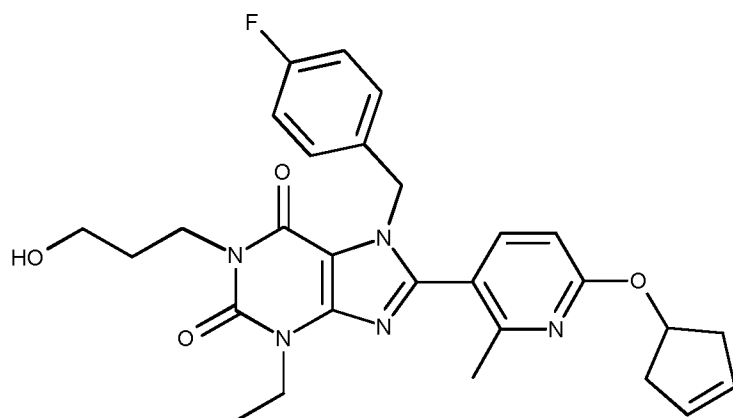
44

- 15 Example 44 was prepared in an analogous manner to example 30 using intermediate 7.41.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 523

RT = 0.79 min, Method D

#### Example 45



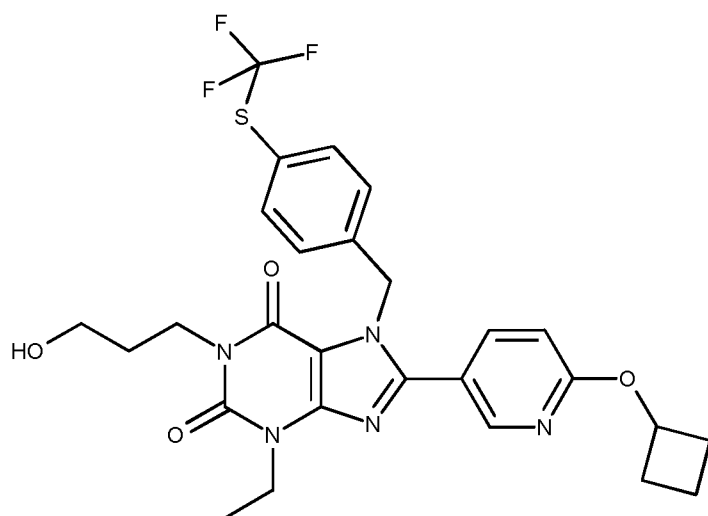
45

Example 45 was prepared in an analogous manner to example 29 using intermediate 7.42.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 521

RT = 0.74 min, Method D

#### Example 46



46

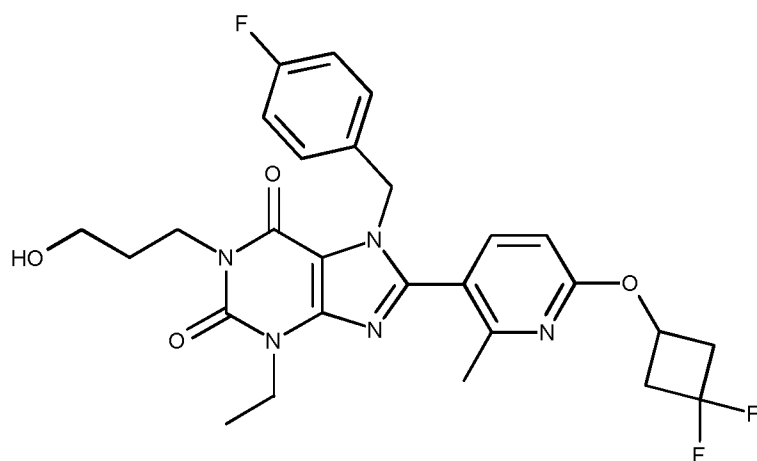
To a mixture of intermediate 22.1 (40 mg, 0.085 mmol) in THF (704  $\mu$ L) and DMSO (697  $\mu$ L) DIPEA (16.1  $\mu$ L, 0.094 mmol) and 4-(trifluoromethylthio)benzylchloride (29 mg,

0.128 mmol) were added. The mixture was stirred 1.5 h at 50°C. Additional DIPEA was added and the mixture was stirred 1.5 h at 90°C. Then additional 4-(trifluormethylthio)benzylchloride was added and the mixture was stirred 1h at 90°C. The mixture was cooled and purified by chromatography to obtain 7.0 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 577

HPLC: RT = 0.83 min, Method D

#### Example 47



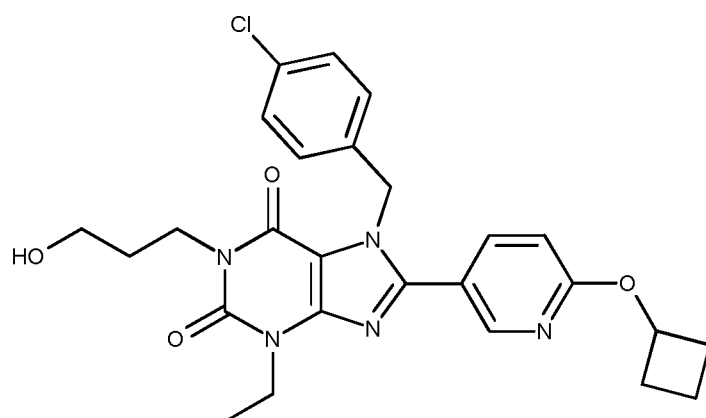
47

Example 47 was prepared in an analogous manner to example 30 using intermediate 7.43.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 545

RT = 0.67 min, Method D

#### Example 48



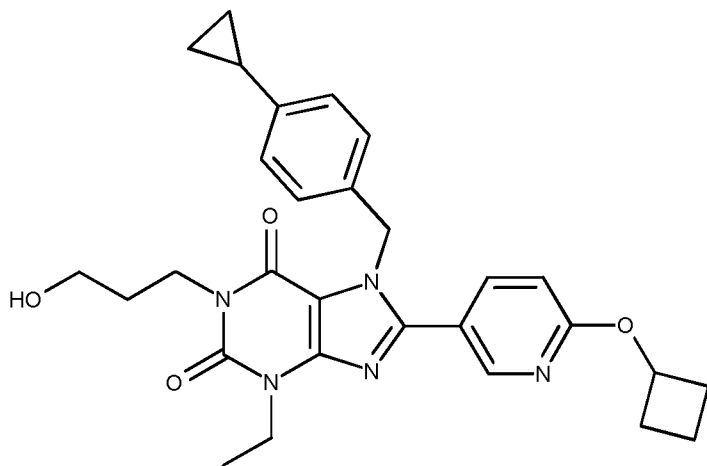
48

To the crude reaction mixture of intermediate 5.20 (29.7 mg, 0.05 mmol) toluene-4-sulfonic acid hydrate (28.5 mg, 0.15 mmol) and MeOH (0.5 mL) were added. The mixture was stirred overnight at rt. The mixture was purified by chromatography to obtain 18.3 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 511/513 (Cl isotope pattern)

HPLC: RT = 0.76 min, Method D

## Example 49



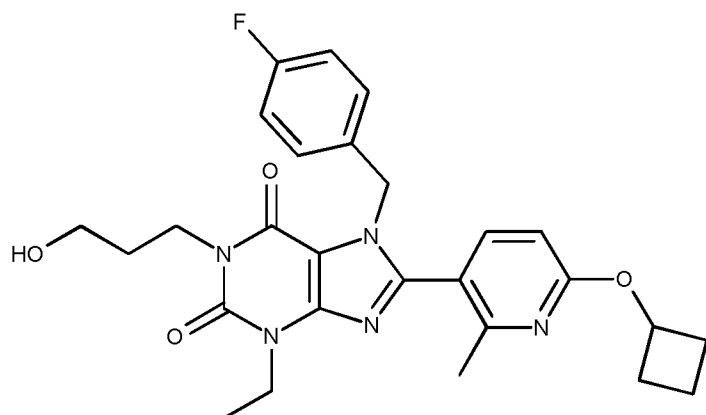
49

Example 49 was prepared in an analogous manner to example 29 using intermediate 7.45.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 517

RT = 1.11 min, Method F

## Example 50

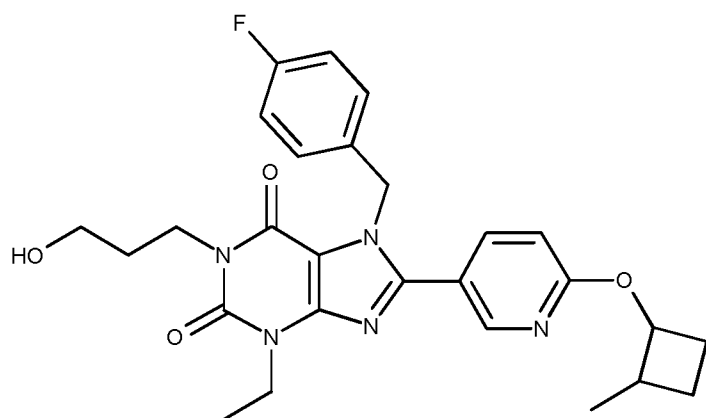


50

Example 50 was prepared in an analogous manner to example 30 using intermediate 7.47.

5 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 509  
RT = 0.75 min, Method D

#### Example 51

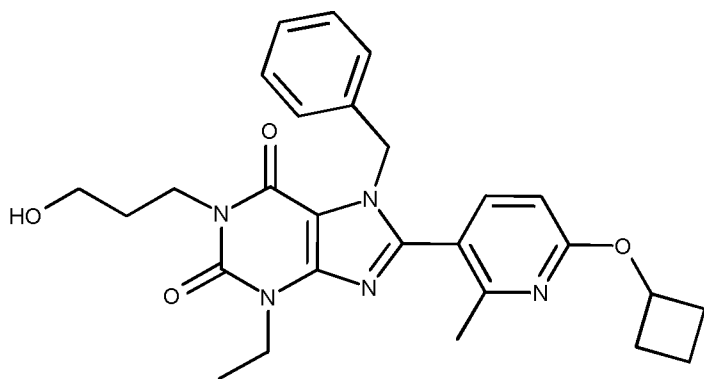


51

Example 51 was prepared in an analogous manner to example 40 using intermediate 6.25.

10 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 509  
15 RT = 1.34 min, Method C

#### Example 52



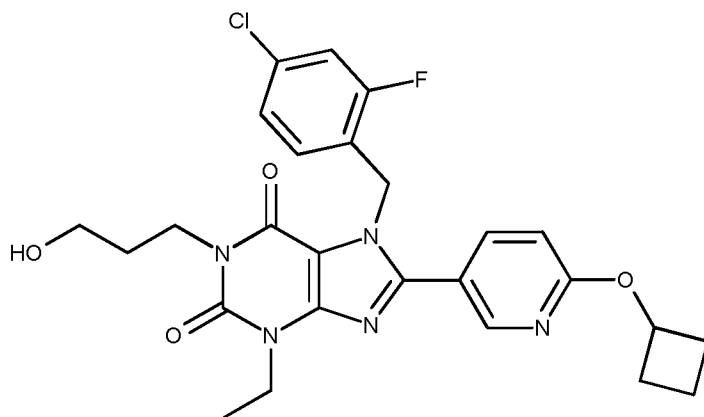
52

To a mixture of intermediate 7.49 (88 mg, 0.153 mmol) in MeOH (1 mL) and THF (1 mL) toluene-4-sulfonic acid hydrate (36.5 mg, 0.192 mmol) was added and the mixture was stirred 1 h at rt. The mixture was purified by chromatography to obtain 69.1 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 491

RT = 0.74 min, Method D

#### Example 53



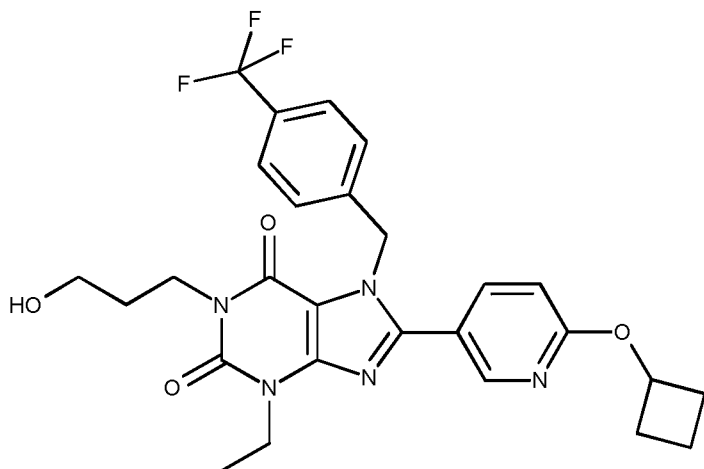
53

To the reaction mixture of intermediate 5.25 toluene-4-sulfonic acid hydrate (171.2 mg, 0.90 mmol) and MeOH (2 mL) were added. The mixture was stirred 1 h at rt. The mixture was purified by chromatography to obtain 41.0 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 529/531 (Cl isotope pattern)

HPLC: RT = 0.78 min, Method D

#### Example 54

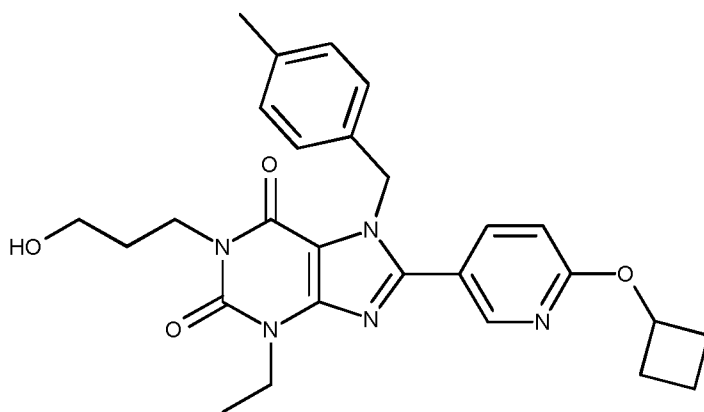


54

Example 54 was prepared in an analogous manner to example 53 using intermediate 5.26.

5 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 545  
RT = 0.79 min, Method D

Example 55

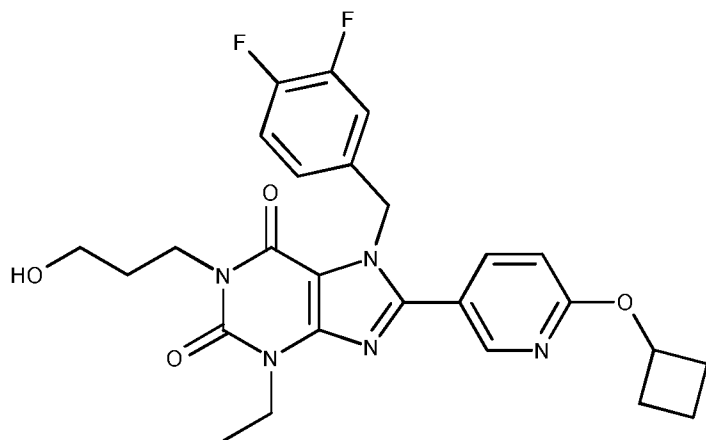


55

Example 55 was prepared in an analogous manner to example 53 using intermediate 5.27.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 491  
RT = 0.77 min, Method D

Example 56

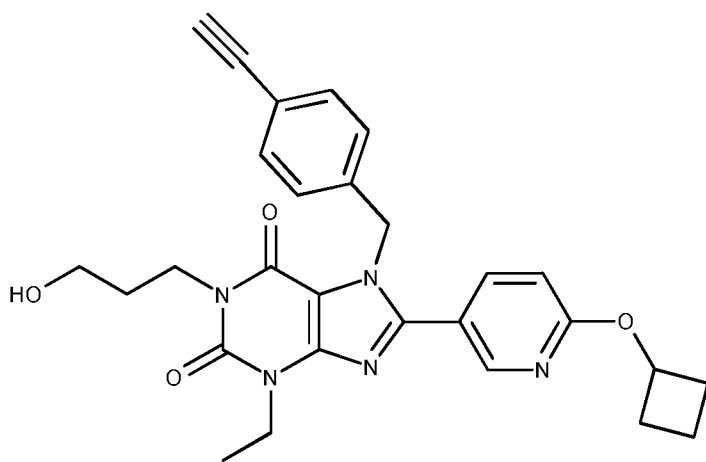


56

Example 56 was prepared in an analogous manner to example 53 using intermediate 5.28.

5 MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 513  
RT = 0.74 min, Method D

#### Example 57



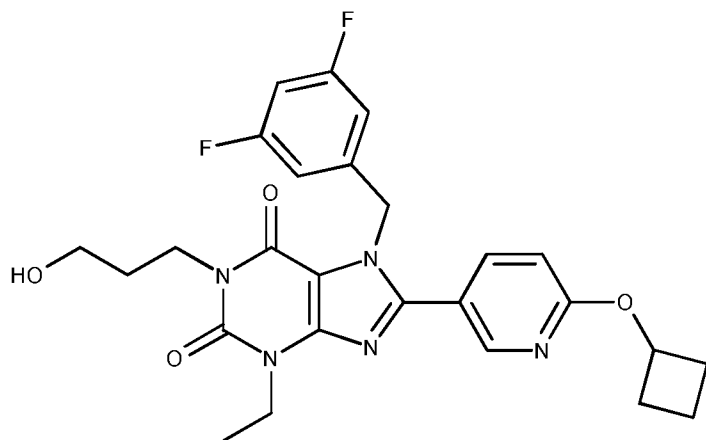
57

To the crude reaction mixture of intermediate 25.1 toluene-4-sulfonic acid hydrate (11.3 mg, 0.06 mmol) and MeOH (2 mL) were added. The mixture was stirred 1 h at rt. The mixture was purified by chromatography to obtain 5.8 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 501

15 HPLC: RT = 0.70 min, Method A

#### Example 58



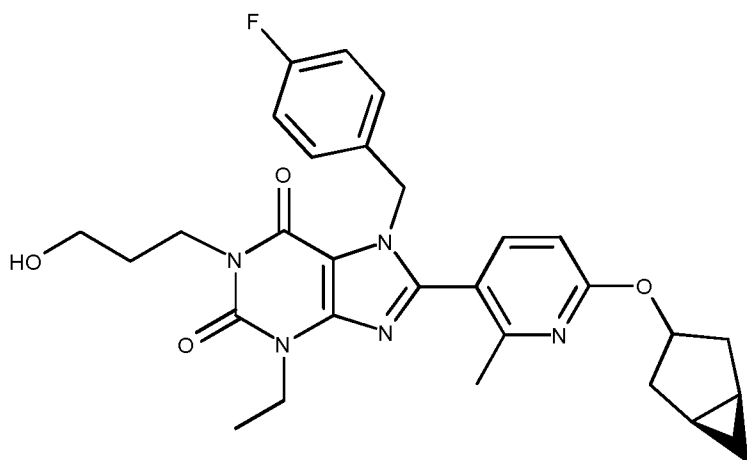
58

To a mixture of intermediate 22.1 (40 mg, 0.085 mmol) in THF (704  $\mu$ L) and DMSO (697  $\mu$ L) DIPEA (16.1  $\mu$ L, 0.094 mmol) and 1-(bromomethyl)-3,5-difluorobenzene (26.5 mg, 0.128 mmol) were added. The mixture was stirred 1.5 h at 50°C. Additional DIPEA was added and the mixture was stirred 2 h at 90°C. Then additional 1-(bromomethyl)-3,5-difluorobenzene was added and the mixture was stirred 1h at 90°C. The mixture was cooled and purified by chromatography to obtain 15.0 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 513

HPLC: RT = 0.74 min, Method D

### Example 59



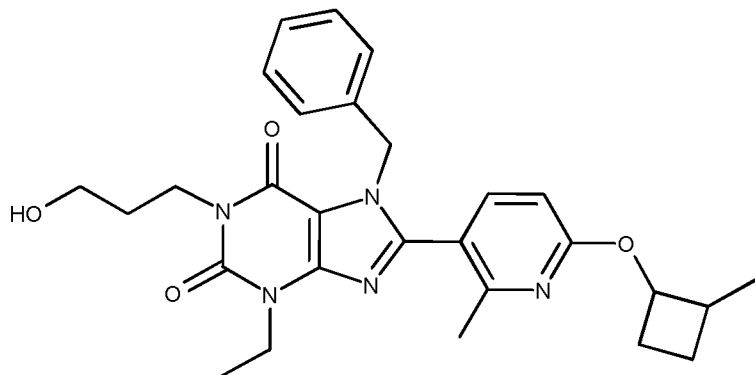
59

Example 59 was prepared in an analogous manner to example 53 using intermediate 7.50.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 535

RT = 1.09 min, Method F

### Example 60



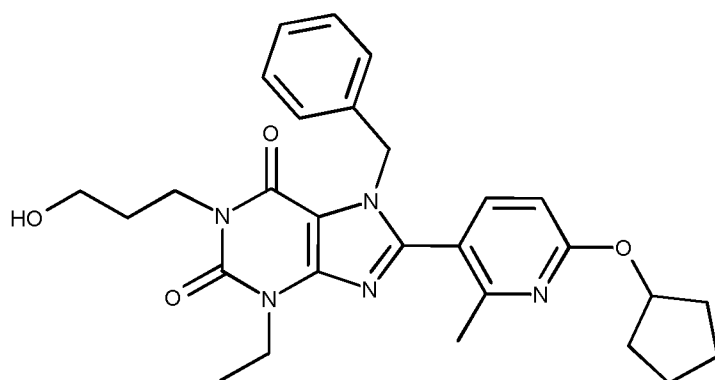
60

To a mixture of intermediate 7.51 (92 mg, 0.157 mmol) in MeOH (1 mL) and THF (1 mL) toluene-4-sulfonic acid hydrate (37.2 mg, 0.196 mmol) was added and the mixture was stirred 1.5 h at rt. The mixture was purified by chromatography to obtain 43.0 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 505

RT = 0.8 min, Method D

### Example 61



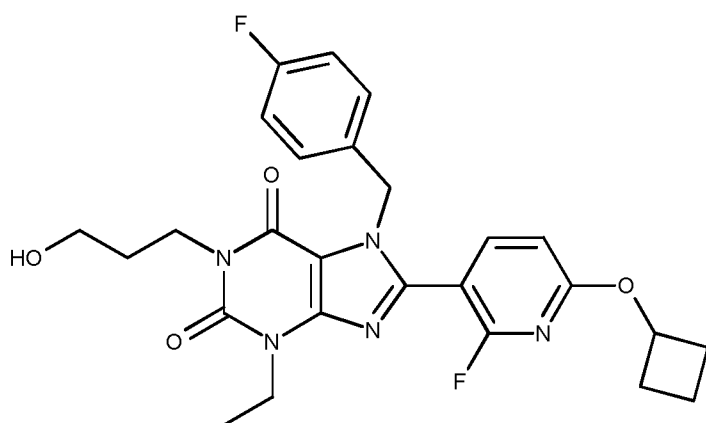
61

Example 61 was prepared in an analogous manner to example 54 using intermediate 7.52.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 505

RT = 0.78 min, Method D

## Example 62



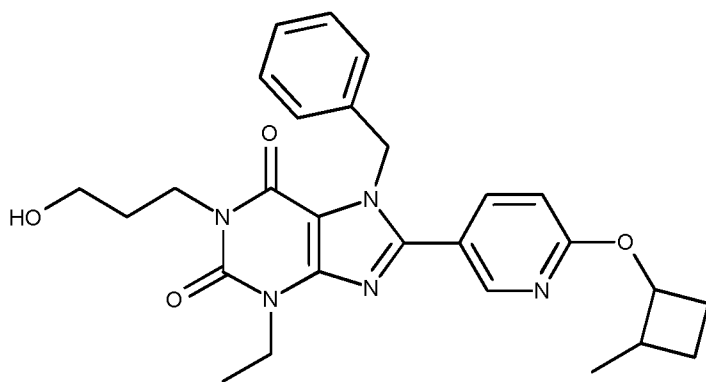
62

To a mixture of intermediate 12.6.1 (42 mg, 0.071 mmol) in MeOH (1 mL) and THF (1 mL) toluene-4-sulfonic acid hydrate (12.2 mg, 0.071 mmol) was added and the mixture was stirred 1 h at rt. The mixture was purified by chromatography to obtain 13.7 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 513

RT = 0.74 min, Method G

## Example 63



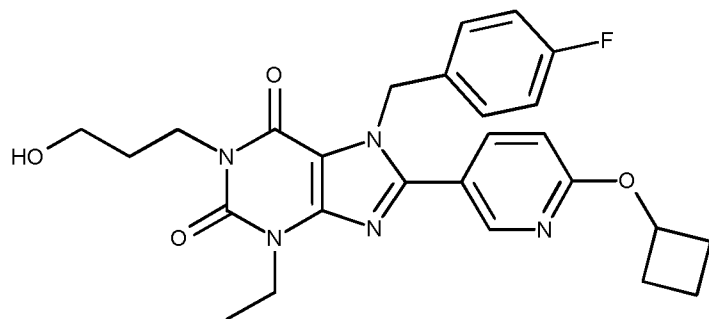
63

To a mixture of intermediate 7.53 (38 mg, 0.066 mmol) in THF (1 mL) toluene-4-sulfonic acid hydrate (63 mg, 0.331 mmol) was added and the mixture was stirred 1 h at rt. The mixture was purified by chromatography and freeze-dried to obtain 27.0 mg of the product.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 491

RT = 1.33 min, Method C

## Example 64



64

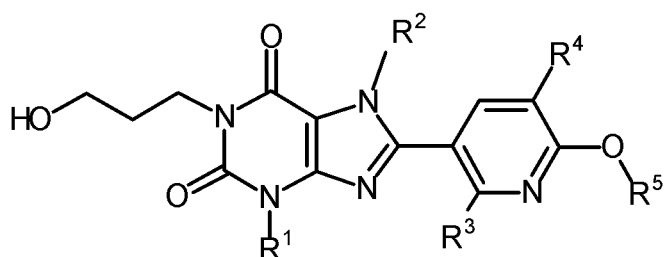
- 5 Example 64 was prepared in an analogous manner to example 53 using intermediate 27.1.

MS (ESI<sup>+</sup>): (M+H)<sup>+</sup> 495

RT = 0.73 min, Method D

## Claims

- 5 1. A compound of formula I

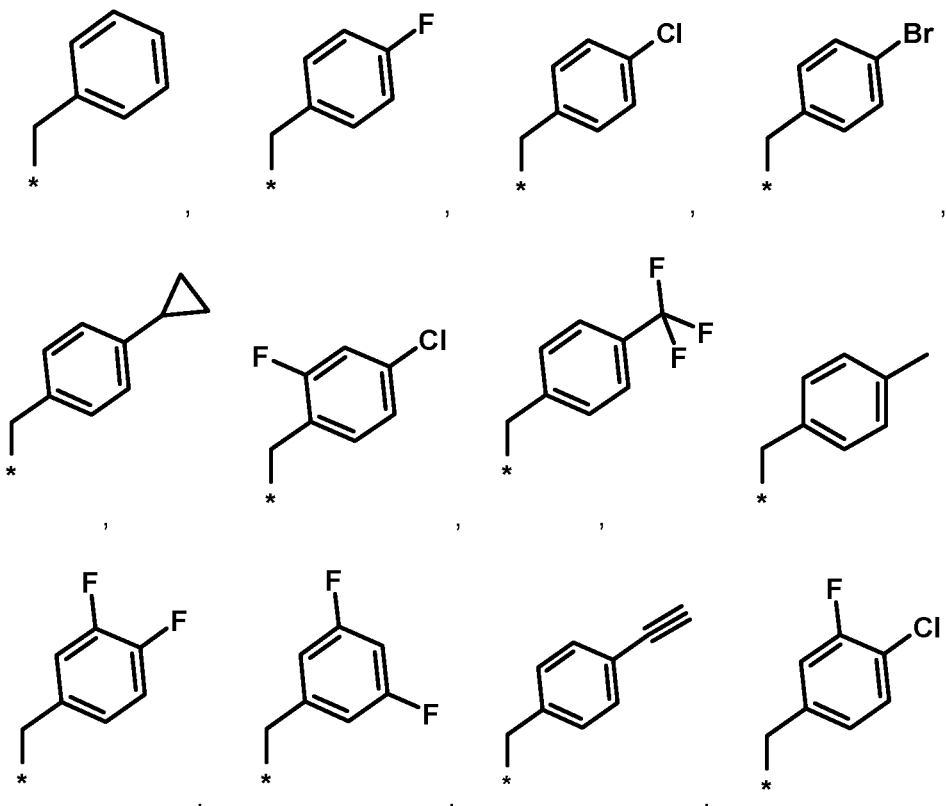


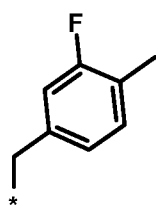
I

10 in which

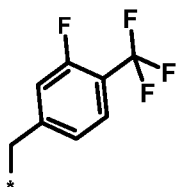
R¹ represents ethyl, isopropyl, isobutyl, cyclobutyl;

R² represents

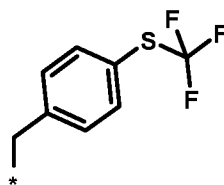




1



2



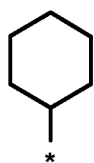
3

$R^3$  represents hydrogen, fluoro,  $C_1$ - $C_3$ -alkyl optionally substituted with one or more fluorine atoms;

5  $R^4$  represents hydrogen or fluoro;

$R^5$  represents

10



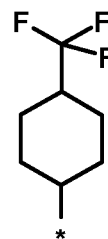
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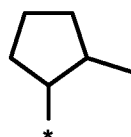
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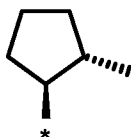
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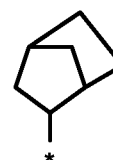
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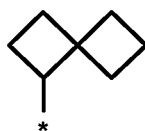
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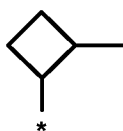
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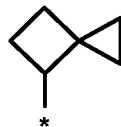
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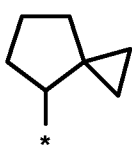
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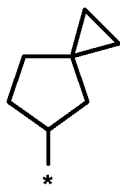
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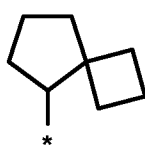
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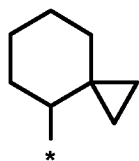
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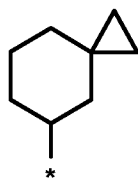
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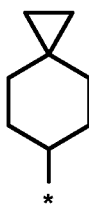
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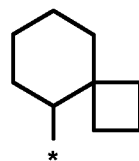
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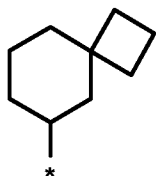
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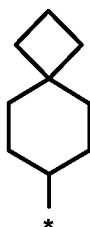
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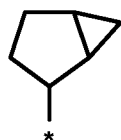
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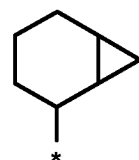
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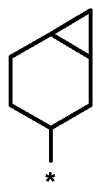
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which groups

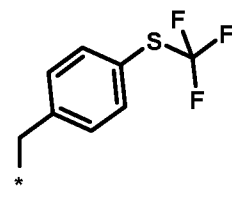
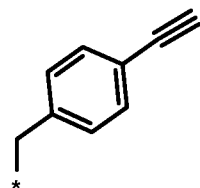
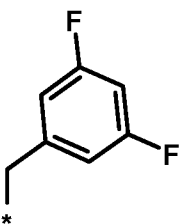
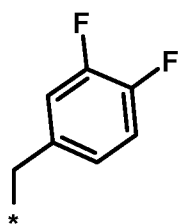
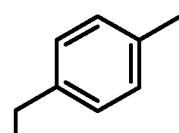
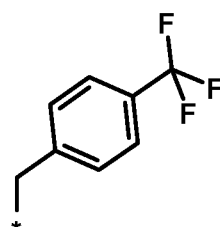
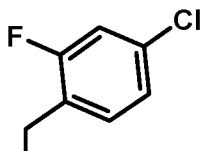
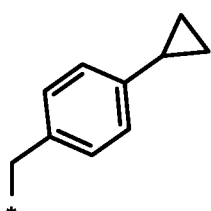
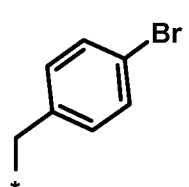
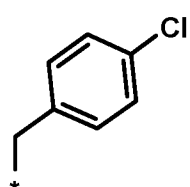
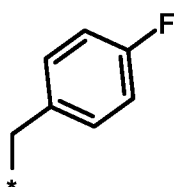
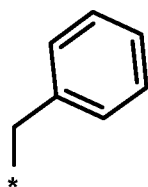
are optionally substituted with one or more fluorine atoms and/or one or more C<sub>1</sub>-C<sub>3</sub>-alkyl fluorinated with one or more fluorine atoms.

2. The compound according to claim 1

wherein

$R^1$  represents ethyl, isopropyl, isobutyl, cyclobutyl;

5  $R^2$  represents

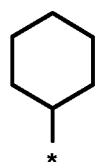


$R^3$  represents hydrogen, fluoro, methyl, ethyl,  $-CF_3$ ;

10  $R^4$  represents hydrogen or fluoro;

$R^5$  represents

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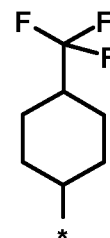
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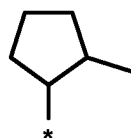
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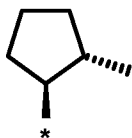
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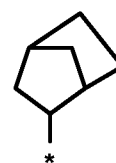
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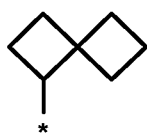
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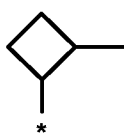
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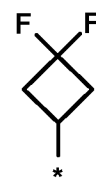
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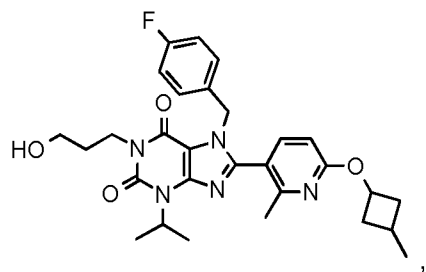
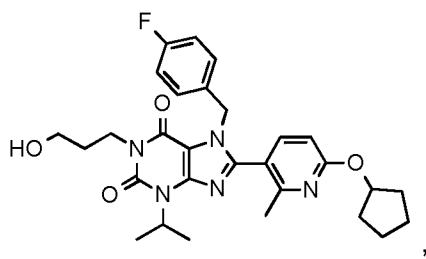
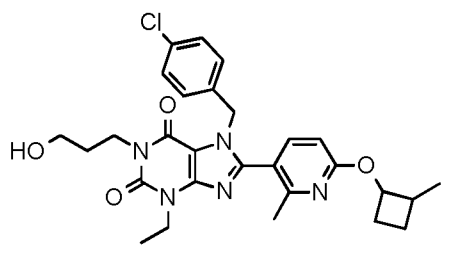
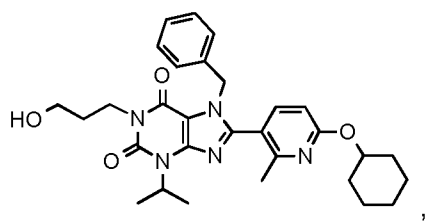
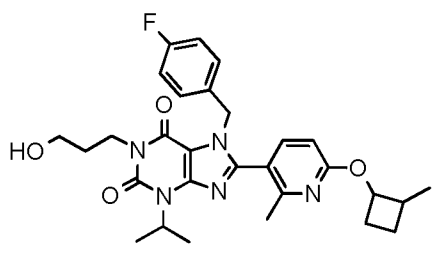


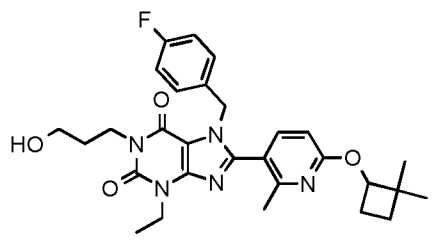
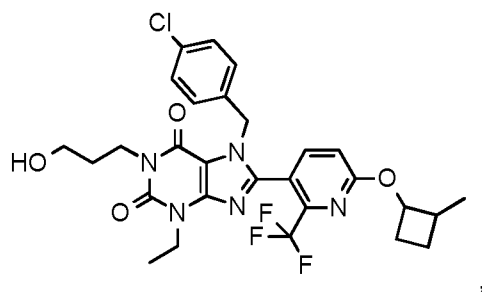
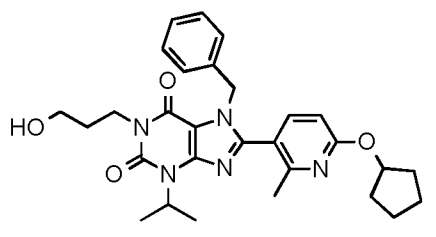
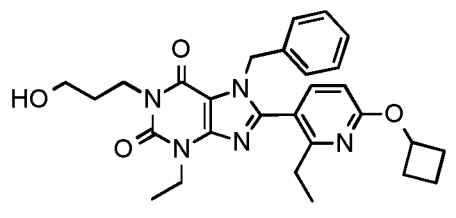
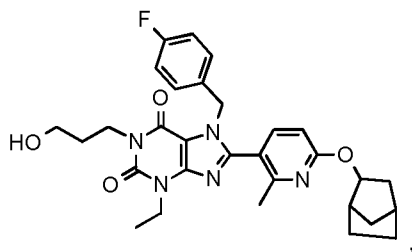
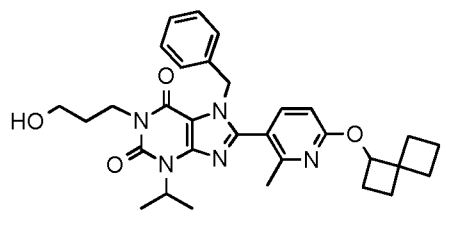
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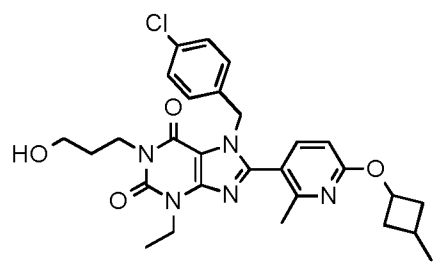
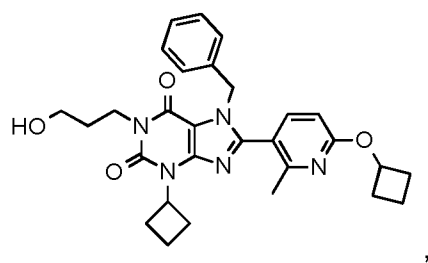
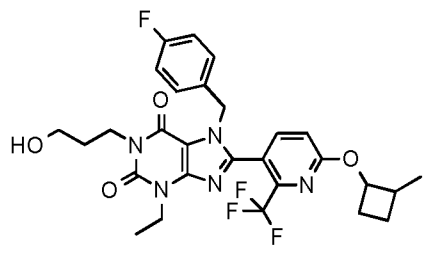
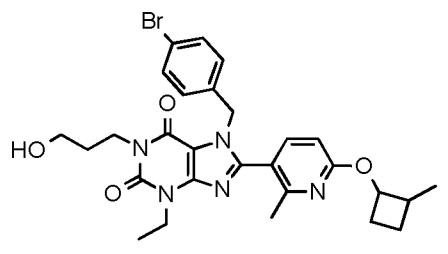
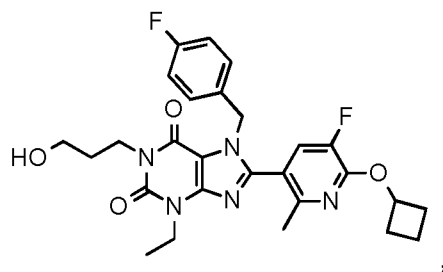
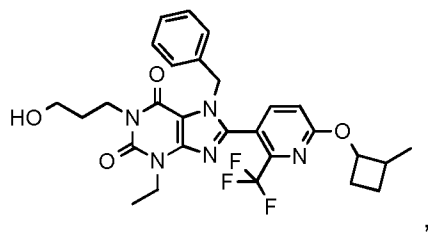


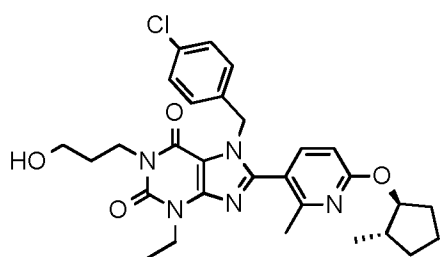
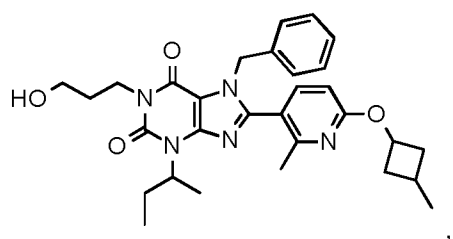
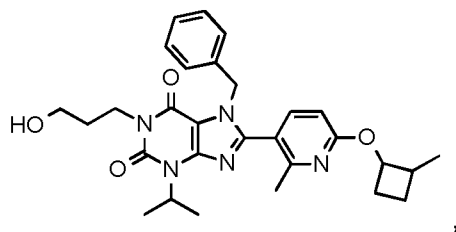
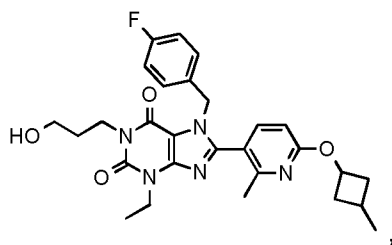
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3. The compound according to claim 1 or 2, namely a compound selected from the group consisting of

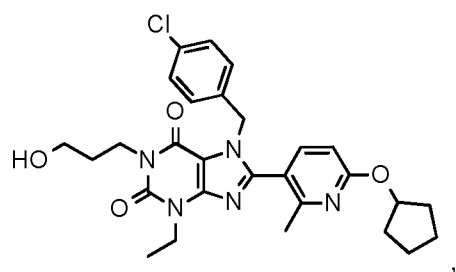
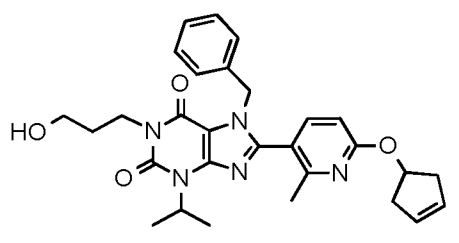


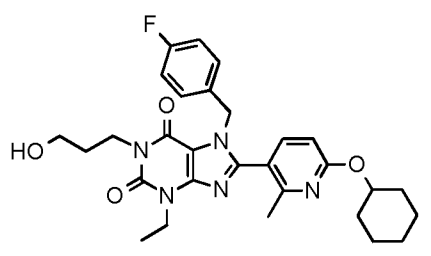
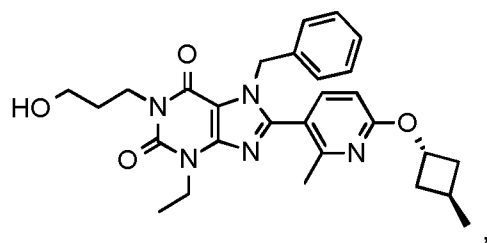
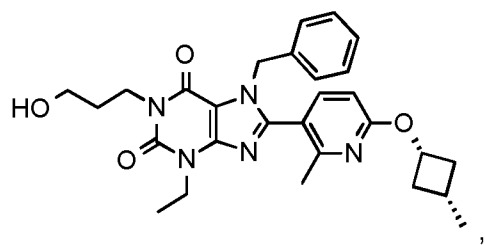
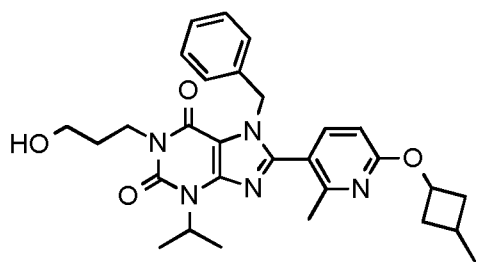
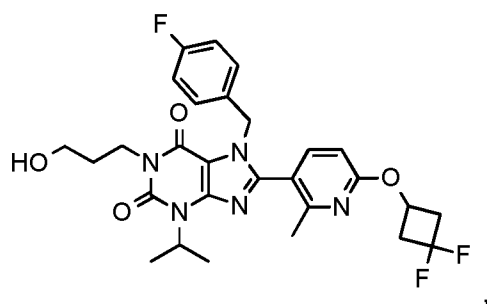
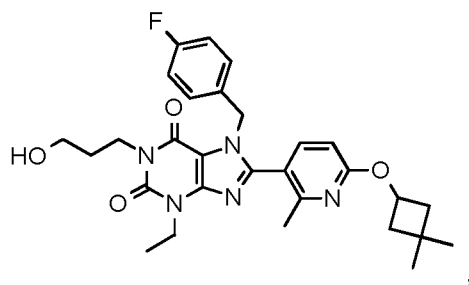


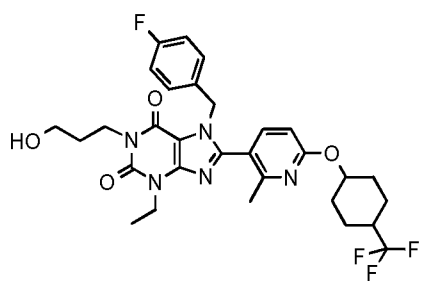
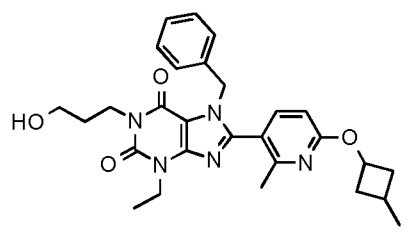
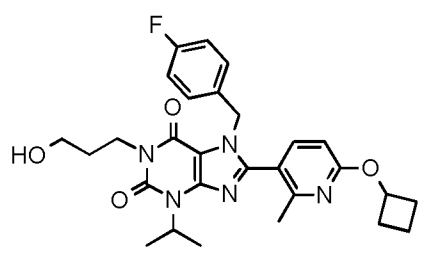
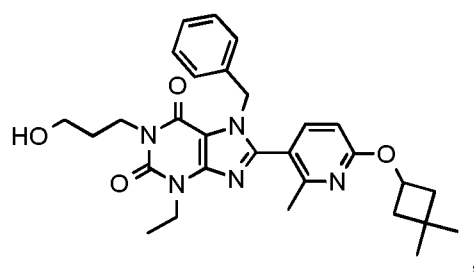
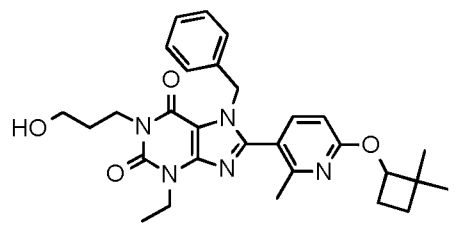
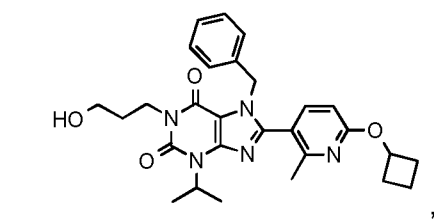


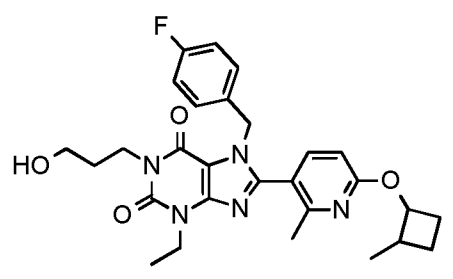
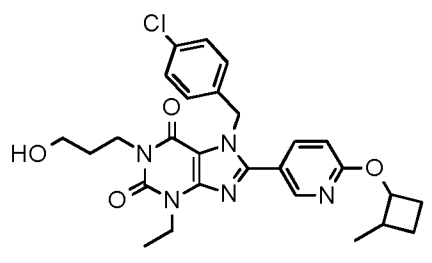
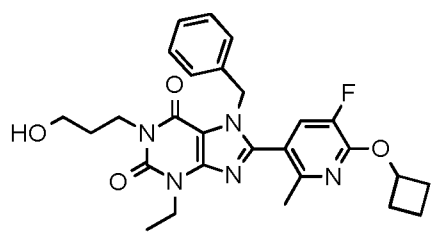
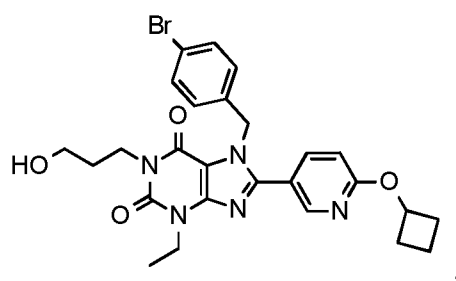
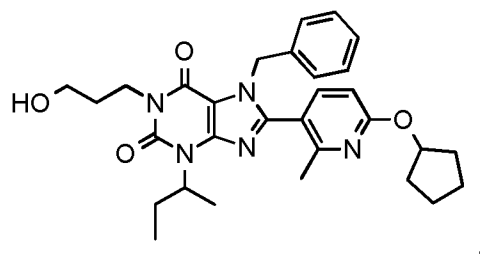
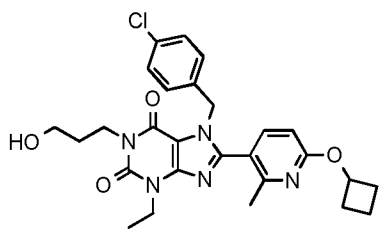


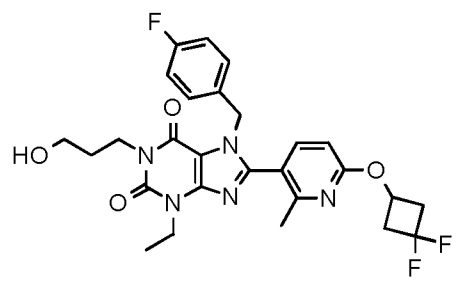
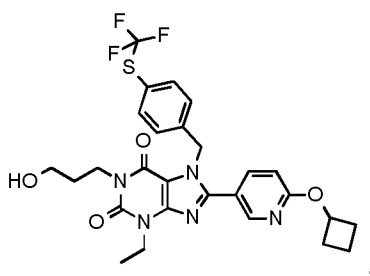
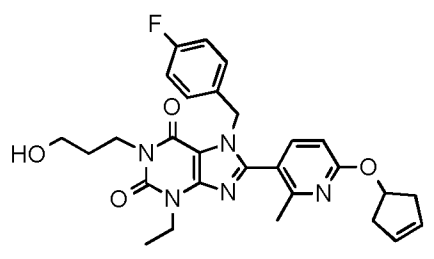
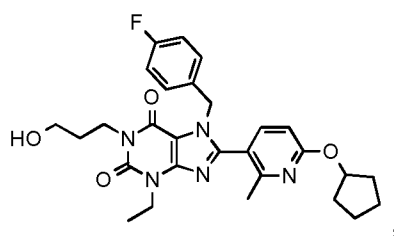
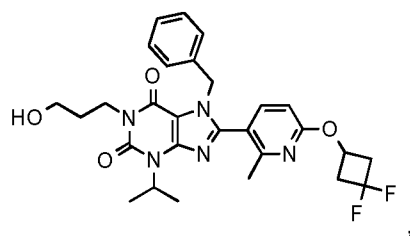
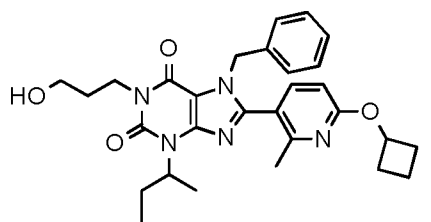
racemic trans-mixture

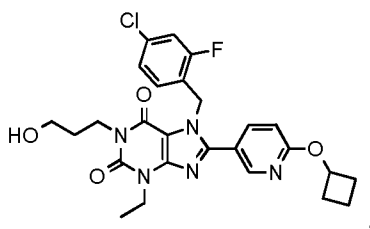
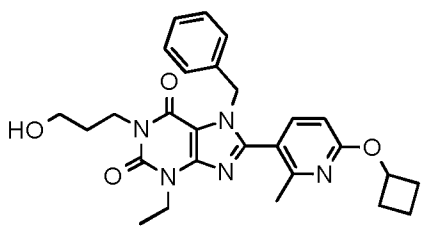
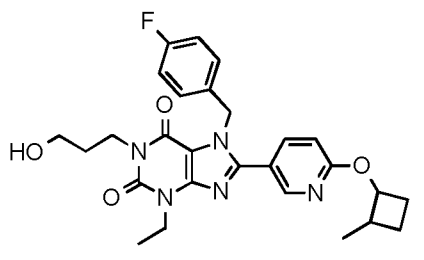
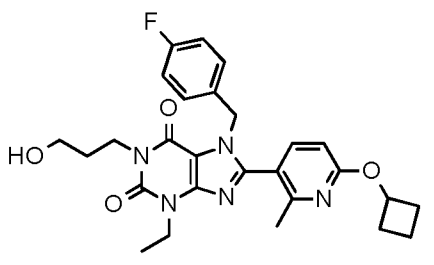
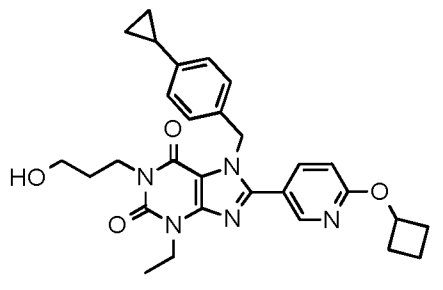
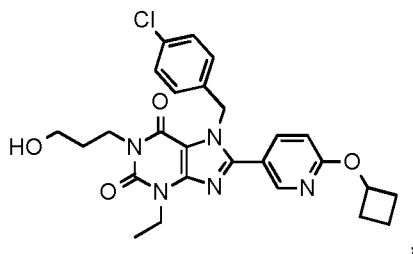


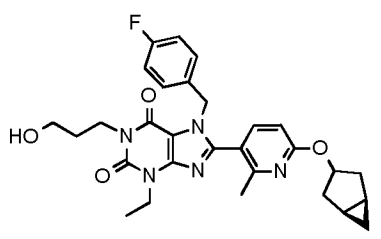
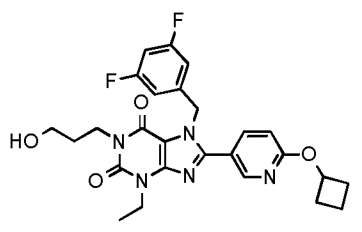
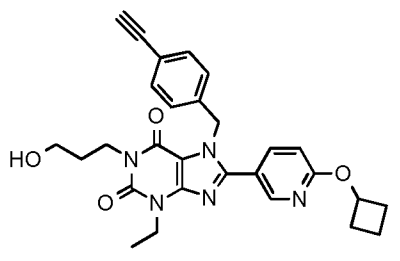
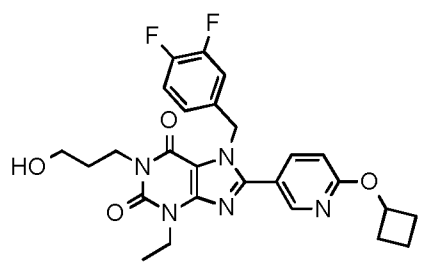
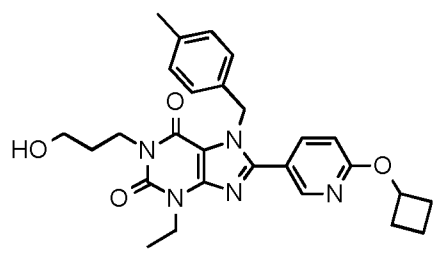
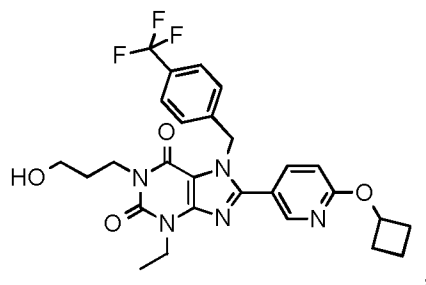


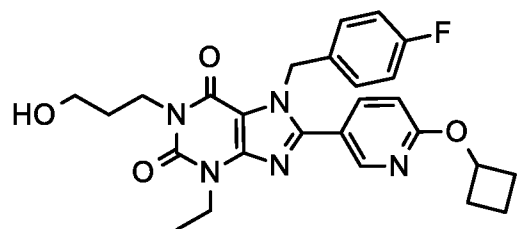
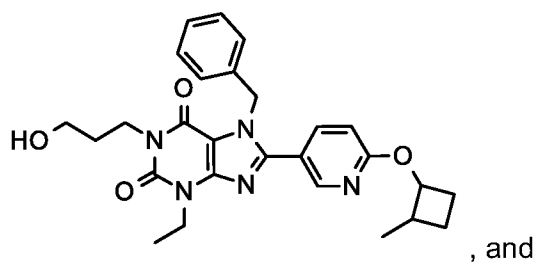
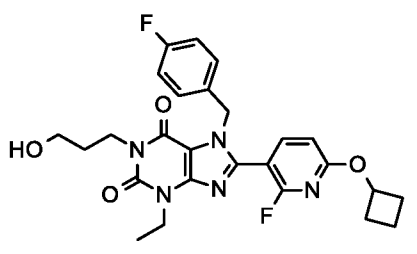
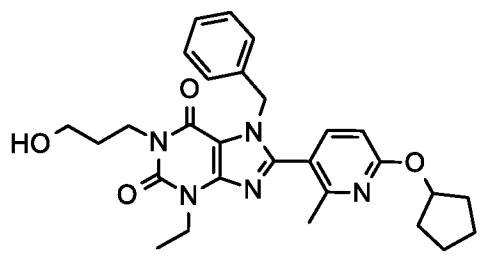
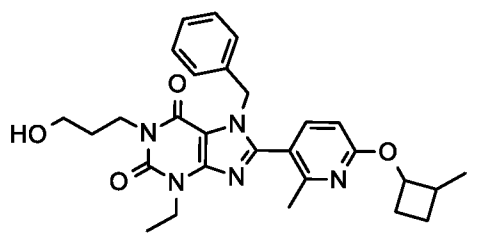












4. A pharmaceutically acceptable salt of the compound according to any one of claims 1-3.
5. A pharmaceutical composition comprising the compound according to any one of claims 1-3 or the pharmaceutically acceptable salt of claim 4.

6. Use of the compound according to any one of claims 1-3 or the pharmaceutically acceptable salt of claim 4 for the manufacture of a medicament for the treatment of a psychiatric, neurological or neurodegenerative condition, wherein the inhibition of the activity of the transient receptor potential cation channel TRPC5 is of therapeutic benefit.
7. The use according to claim 6, wherein the psychiatric, neurological or neurodegenerative condition is selected from the group consisting of diseases associated with dysregulated emotional processing (e.g. borderline personality disorder or depressive disorders like major depression, major depressive disorder, psychiatric depression, dysthymia, and postpartum depression, and bipolar disorders), anxiety and fear-related disorders (e.g. post-traumatic stress disorder, panic disorder, agoraphobia, social phobias, generalized anxiety disorder, panic disorder, social anxiety disorder, obsessive compulsive disorder, and separation anxiety), memory disorders (e.g. Alzheimer's disease, amnesia, aphasia, brain injury, brain tumor, chronic fatigue syndrome, Creutzfeldt-Jakob disease, dissociative amnesia, fugue amnesia, Huntington's disease, learning disorders, sleeping disorders, multiple personality disorder, pain, post-traumatic stress disorder, schizophrenia, sports injuries, stroke, and Wernicke-Korsakoff syndrome), disorders associated with impaired impulse control and addiction as well as Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and other brain disorders caused by trauma or other insults including aging.
8. A method for treating a TRPC5 mediated disorder in a subject, the method comprising administering to the subject an effective amount of the compound of any one of claims 1-3 or the pharmaceutically acceptable salt of claim 4.
9. The method according to claim 8, wherein the TRPC5 mediated disorder is a psychiatric, neurological or neurodegenerative condition.
10. The method according to claim 9, wherein the psychiatric, neurological or neurodegenerative condition is selected from the group consisting of diseases associated with dysregulated emotional processing (e.g. borderline personality disorder or depressive disorders like major depression, major depressive disorder, psychiatric depression, dysthymia, and postpartum depression, and bipolar disorders), anxiety and fear-related disorders (e.g. post-traumatic stress disorder, panic disorder, agoraphobia, social phobias, generalized anxiety disorder, panic disorder, social anxiety disorder, obsessive compulsive disorder, and separation anxiety), memory disorders (e.g. Alzheimer's

disease, amnesia, aphasia, brain injury, brain tumor, chronic fatigue syndrome, Creutzfeldt-Jakob disease, dissociative amnesia, fugue amnesia, Huntington's disease, learning disorders, sleeping disorders, multiple personality disorder, pain, post-traumatic stress disorder, schizophrenia, sports injuries, stroke, and Wernicke-Korsakoff syndrome), disorders associated with impaired impulse control and addiction as well as Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and other brain disorders caused by trauma or other insults including aging.