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(71) Applicant: JANSSEN PHARMACEUTICA NV

[BE/BE]; Turnhoutseweg 30, 2340 Beerse (BE).

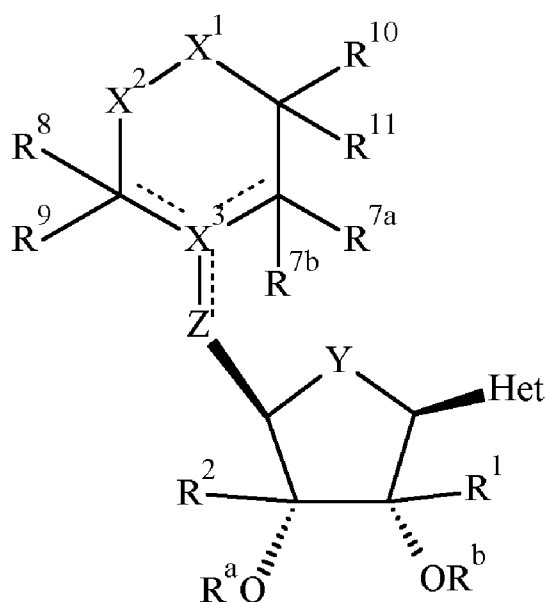
(72) Inventors: BERTHELOT, Didier Jean-Claude; c/o Janssen Pharmaceutica NV, Turnhoutseweg 30, 2340 Beerse (BE). BREHMER, Dirk; c/o Janssen Pharmaceutica NV, Turnhoutseweg 30, 2340 Beerse (BE). BEKE, Lijs; c/o Janssen Pharmaceutica NV, Turnhoutseweg 30, 2340 Beerse (BE). BOECKX, An; c/o Janssen Pharmaceutica NV, Turnhoutseweg 30, 2340 Beerse (BE).

DIELS, Gaston Stanislas Marcella; c/o Janssen Pharmaceutica NV, Turnhoutseweg 30, 2340 Beerse (BE). GILISEN, Ronaldus Arnodus Hendrika Joseph; c/o Janssen Pharmaceutica NV, Turnhoutseweg 30, 2340 Beerse (BE). LAWSON, Edward Charles; c/o Janssen Research & Development, LLC, 920 Route 202, Raritan, New Jersey 08869 (US). PANDE, Vineet; c/o Janssen Pharmaceutica NV, Turnhoutseweg 30, 2340 Beerse (BE). PARADÉ, Marcus Cornelis Bernardus Catharina; c/o Janssen Pharmaceutica NV, Turnhoutseweg 30, 2340 Beerse (BE). SCHEPENS, Wim Bert Griet; c/o Janssen Pharmaceutica NV, Turnhoutseweg 30, 2340 Beerse (BE). SHOOK, Brian Christopher; c/o Janssen Research & Development, LLC, 920 Route 202, Raritan, New Jersey 08869 (US). THURING, Johannes Wilhelmus John F.; c/o Janssen Pharmaceutica NV, Turnhoutseweg 30, 2340 Beerse (BE). VIELLEVOYE, Marcel; c/o Janssen Pharmaceutica NV, Turnhoutseweg 30, 2340 Beerse (BE). SUN, Weimei; c/o Janssen Research & Development, LLC, 920 Route 202, Raritan, New Jersey 08869 (US). WU, Tongfei; c/o Janssen Pharmaceutica NV, Turnhoutseweg 30, 2340 Beerse (BE). MEERPOEL, Lieven; c/o Janssen Pharmaceutica NV, Turnhoutseweg 30, 2340 Beerse (BE).

(74) Agent: LENAERTS, Philip; J&J Patent law department, Turnhoutseweg 30, 2340 Beerse (BE).

[Continued on next page]

(54) Title: SUBSTITUTED NUCLEOSIDE ANALOGUES FOR USE AS PRMT5 INHIBITORS



(I)

(57) Abstract: The present invention relates novel substituted nucleoside analogues of Formula (I) wherein the variables have the meaning defined in the claims. The compounds according to the present invention are useful as PRMT5 inhibitors. The invention further relates to pharmaceutical compositions comprising said compounds as an active ingredient as well as the use of said compounds as a medicament.



(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, 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.

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SUBSTITUTED NUCLEOSIDE ANALOGUES FOR USE AS PRMT5
INHIBITORS

Field of the Invention

- 5 The present invention relates to novel substituted nucleoside analogues useful as PRMT5 inhibitors. The invention further relates to pharmaceutical compositions comprising said compounds as an active ingredient as well as the use of said compounds as a medicament.

Background of the invention

- 10 PRMT5, also described as Hsl7, Jbp1, Skb1, Capsuleen or Dart5, is one of the major methyltransferases responsible for mono- and symmetric dimethylation of arginines. Post-translational arginine methylation on histones and non-histone proteins seems to be crucial for a variety of biological processes, like genome organisation, transcription, differentiation, spliceosome function, signal transduction and regulation of cell-cycle
15 progression, stem cells and T-cell fate [Stopa, N. et al., Cell Mol Life Sci, 2015. **72**(11): p. 2041-59] [Geoghegan, V. et al., Nat Commun, 2015. **6**: p. 6758]. Metazoan PRMT5 forms a functional complex with the methylosome protein 50 (MEP50) also named as Wdr77, androgen receptor coactivator p44 and Valois. Both, elevated PRMT5-MEP50 protein level and cytoplasmic accumulation are implicated in cancer tumorigenesis and
20 have recently been correlated with poor clinical outcome [Shilo, K. et al., Diagn Pathol, 2013. **8**: p. 201]. Cellular rescue experiments that addressed both the catalytic and scaffold function of the PRMT5-MEP50 complex, beside comprehensive enzymological studies have substantiate the oncogenic link between protein level, localisation and enzymatic function [Gu, Z. et al., Biochem J, 2012. **446**(2): p. 235-41] [Di Lorenzo, A.
25 et al., FEBS Lett, 2011. **585**(13): p. 2024-31] [Chan-Penebre, E. et al., Nat Chem Biol, 2015. **11**(6): p. 432-7]. This correlation turns PRMT5 into an essential small molecule drug target against cancer and other diseases [Stopa, N. et al., Cell Mol Life Sci, 2015. **72**(11): p. 2041-59].

- PRMT5 is a member of the type II PRMT subfamily that utilises S-adenosylmethionine
30 (SAM) to generate symmetric dimethylated arginine on histones and non-histone protein substrates and S-adenosylhomocysteine (SAH). The crystal structure of the human hetero-octameric complex (PRMT5)₄(MEP50)₄ co-crystalised with SAH and a histone H4 peptide substrate illustrated the mechanism of methylation and substrate recognition [Antonyamy, S. et al., Proc Natl Acad Sci U S A, 2012. **109**(44): p. 17960-5]. The
35 regulation of PRMT5 activity occurs through a vast number of different binding partners, post-translational modification cross talk, miRNAs and subcellular localisation.

Methylation of histones H2A and H4 on Arg3 and histone H3 on Arg8 regulate chromatin organisation for specific repression of gene transcripts that are involved in differentiation, transformation, cell-cycle progression and tumour suppression [Karkhanis, V. et al., Trends Biochem Sci, 2011. **36**(12): p. 633-41]. Furthermore, PRMT5-mediated methylation of histone H4 on Arg3 might recruit the DNA-methyltransferase DNMT3A to couple histone and DNA methylation for long-term gene silencing [Zhao, Q. et al., Nat Struct Mol Biol, 2009. **16**(3): p. 304-11].

Non-histone methylation can occur either in the cytoplasm or nucleus dependent on the cellular localisation of PRMT5. The methylation of the Sm proteins D1 and D3, which are required for the assembly of the nuclear spliceosome, takes place in the cytoplasm as part of the PRMT5 containing "methylosome" [Friesen, W.J. et al., Mol Cell Biol, 2001. **21**(24): p. 8289-300]. Further evidence for PRMT5 involved in splicing has been provided by the conditional PRMT5 knockout in mouse neural stem cells. Cells that lack PRMT5 showed a selective retention of introns and skipping of exons with weak 5' donor sites [Bezzi, M. et al., Genes Dev, 2013. **27**(17): p. 1903-16].

In addition to a role in splicing, PRMT5 influences key pathways involved in cell fate and homeostasis by direct methylation of key signalling nodules like p53 [Jansson, M. et al., Nat Cell Biol, 2008. **10**(12): p. 1431-9], EGFR [Hsu, J.M. et al., Nat Cell Biol, 2011. **13**(2): p. 174-81], CRAF [Andreu-Perez, P. et al., Sci Signal, 2011. **4**(190): p. ra58], PI3K/AKT [Wei, T.Y. et al., Cell Signal, 2014. **26**(12): p. 2940-50], NFκB [Wei, H. et al., Proc Natl Acad Sci U S A, 2013. **110**(33): p. 13516-21].

Since PRMT5 is one of the major sym-Arg methyltransferases and involved in a multitude of cellular processes, an increased protein expression appears to be an important factor in its tumorigenicity. Interestingly, the translation of PRMT5 in mantle cell lymphoma (MCL) seems to be regulated by miRNAs. Although MCL cells show less mRNA and a slower transcription rate of PRMT5 than normal B lymphocytes, the PRMT5 level and the methylation of H3R8 and H4R3 are significantly increased [Pal, S. et al., EMBO J, 2007. **26**(15): p. 3558-69]. Re-expression of miRNAs that binds the 3'UTR region of PRMT5 decreases PRMT5 protein level [Wang, L. et al., Mol Cell Biol, 2008. **28**(20): p. 6262-77]. Strikingly, a prmt5 antisense RNA has been found within the human prmt5 gene that supports the hypothesis of a specific translational regulation rather than high mRNA expression level [Stopa, N. et al., Cell Mol Life Sci, 2015. **72**(11): p. 2041-59].

Although PRMT5 is considered as a clinical relevant target, very few selective PRMT5 inhibitors have been published, yet. Very recently, a novel sub-nanomolar potent PRMT5 inhibitor (EPZ015666) with anti-tumour activity in multiple MCL xenograft models has

been described to be the first chemical probe suitable for further validation of PRMT5's biology and role in cancer [Chan-Penebre, E. et al., Nat Chem Biol, 2015. **11**(6): p. 432-7].

Further development of specific small molecule inhibitors of PRMT5 may lead to novel
5 chemotherapeutic approaches for cancer.

WO2014100695A1 discloses compounds useful for inhibiting PRMT5 activity;
Methods of using the compounds for treating PRMT5-mediated disorders are also
described.

WO2014100730A1 discloses PRMT5 inhibitors containing a dihydro- or
10 tetrahydroisoquinoline and uses thereof.

Devkota, K. et al., ACS Med Chem Lett, 2014. **5**: p. 293-297, describes the synthesis of
a series of analogues of the natural product sinefungin and the ability of these
analogues to inhibit EHMT1 and EHMT2.

WO2003070739 discloses partial and full agonists of A1 adenosine receptors, their
15 preparation, and their therapeutic use.

WO2012082436 discloses compounds and compositions as modulators of histone
methyltransferases, and for treating diseases influenced by modulation of histone
methyltransferase activity.

WO2012075500 discloses 7-deazapurine modulators of histone methyltransferase, and
20 methods of use thereof.

WO2016135582 and US20160244475 describe substituted nucleoside derivatives
useful as anticancer agents.

WO2014100719 discloses PRMT5 inhibitors and uses thereof.

WO03074083 discloses combination therapies that selectively kill methylthioadenosine
25 phosphorylase deficient cells. Analogs of MTA are described herein as anti-toxicity
agents.

Kung, P.-P. et al., Bioorg Med Chem Lett, 2005. **15**: p. 2829-2833, describes the
design, synthesis, and biological evaluation of novel human 5'-deoxy-5'-
methylthioadenosine phosphorylase (MTAP) substrates.

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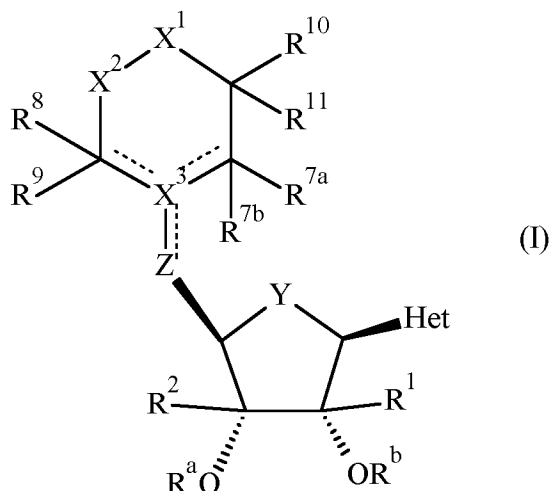
There is thus a strong need for novel PRMT5 inhibitors thereby opening new avenues
for the treatment or prevention of cancer, such as e.g. mantle cell lymphoma. It is
accordingly an object of the present invention to provide such compounds.

Summary of the invention

35 It has been found that the compounds of the present invention are useful as PRMT5
inhibitors. The compounds according to the invention and compositions thereof, may

be useful for the treatment or prevention, in particular for the treatment, of diseases such as a blood disorder, metabolic disorders, autoimmune disorders, cancer, inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, pancreatitis, multiorgan failure, kidney diseases, platelet aggregation, sperm motility, transplantation rejection, graft rejection, lung injuries, and the like.

The present invention concerns novel compounds of Formula (I):



wherein

- 10 R^1 represents hydrogen or CH_3 ;
- R^2 represents hydrogen;
- R^a represents hydrogen or $-\text{C}(=\text{O})-\text{C}_{1-4}\text{alkyl}$;
- R^b represents hydrogen or $-\text{C}(=\text{O})-\text{C}_{1-4}\text{alkyl}$;
- Y represents $-\text{O}-$, $-\text{CH}_2-$ or $-\text{CF}_2-$;
- 15 R^{7a} represents hydrogen;
- R^{7b} represents hydrogen, or $\text{C}_{1-4}\text{alkyl}$ optionally substituted with one or more halo atoms;
- X^1 represents a covalent bond or $-\text{O}-$;
- X^2 represents a covalent bond, $-\text{CH}_2-$, $-\text{CF}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CF}_2\text{CH}_2-$, or $-\text{CH}_2\text{CF}_2-$;
- 20 provided that X^2 represents a covalent bond, $-\text{CH}_2-$ or $-\text{CF}_2-$, when X^1 represents $-\text{O}-$;
- X^3 represents N or CH; or in case one of the dotted lines represents an additional bond, X^3 represents C;
- R^8 and R^{10} each independently are selected from the group consisting of hydrogen; halo; and $\text{C}_{1-6}\text{alkyl}$ optionally substituted with one or more halo atoms;
- 25 R^9 and R^{11} each independently are selected from the group consisting of hydrogen; halo; $-\text{NH}_2$; and $\text{C}_{1-6}\text{alkyl}$ optionally substituted with one $-\text{NR}^{9a}\text{R}^{9b}$;

- or R⁸ and R⁹ are linked together to form together with the common carbon atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing one or two N-atoms and optionally one oxygen atom; wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or more ring carbon atoms with one or more substituents each independently selected from the group consisting of halo, and C₁₋₆alkyl optionally substituted with one or more halo atoms; and wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or two ring N-atoms with a substituent selected from the group consisting of C₁₋₆alkyl; Het^{1a}; C₃₋₆cycloalkyl; -C₁₋₄alkyl-C(=O)-NR^{5a}R^{5b}; C₁₋₄alkyl substituted with one or more halo atoms; and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OC₁₋₄alkyl, cyano, C₃₋₆cycloalkyl, Ar^{1a}, -O-Ar^{1a}, Het^{2a} and -O-Het^{2c};
- or R¹⁰ and R¹¹ are linked together to form together with the common carbon atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing one or two N-atoms and optionally one oxygen atom; wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or more ring carbon atoms with one or more substituents each independently selected from the group consisting of halo, and C₁₋₆alkyl optionally substituted with one or more halo atoms; and wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or two ring N-atoms with a substituent selected from the group consisting of C₁₋₆alkyl; Het^{1b}; C₃₋₆cycloalkyl; -C₁₋₄alkyl-C(=O)-NR^{6a}R^{6b}; C₁₋₄alkyl substituted with one or more halo atoms; and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OC₁₋₄alkyl, cyano, C₃₋₆cycloalkyl, Ar^{1b}, -O-Ar^{1b}, Het^{2b} and -O-Het^{2d};
- Z represents -CH₂-, -C(=O)-, or -CH(C₁₋₄alkyl)-; and in case X³ represents C, Z can also represent =CH-;
- the dotted lines attached to X³ are optional bonds that may be present when X³ represents a carbon atom, provided that maximum one of the dotted lines represents an optional bond;
- in case one of the dotted lines attached to X³ represents an additional bond, X³ represents C, and (i) R^{7a} is absent or (ii) R⁸ is absent or (iii) Z represents =CH-;
- R^{9a} and R^{9b} each independently are selected from the group consisting of hydrogen and C₁₋₄alkyl; or R^{9a} and R^{9b} are linked together to form together with the common nitrogen atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocyclyl which optionally contains one oxygen atom;

R^{5a} and R^{5b} each independently are selected from the group consisting of hydrogen and C₁₋₄alkyl;

Het^{1a} and Het^{1b} are attached to the remainder of the molecule of Formula (I) through any available ring carbon atom;

- 5 Het^{1a} and Het^{1b} each independently represent a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N;

- Ar^{1a} and Ar^{1b} each independently represent phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo; cyano; and C₁₋₄alkyl optionally substituted with one or more halo atoms;

- 10 Het^{2a} and Het^{2b} each independently represent a 4-, 5-, 6- or 7-membered monocyclic aromatic or non-aromatic heterocyclyl containing at least one heteroatom each independently selected from O, S, S(=O)_p and N; or a fused 8-, 9-, 10- or 11-membered bicyclic aromatic or non-aromatic heterocyclyl containing at least one heteroatom each
15 independently selected from O, S, S(=O)_p and N; said monocyclic heterocyclyl or said fused bicyclic heterocyclyl optionally being substituted with one or more substituents each independently selected from the group consisting of halo, cyano, and C₁₋₄alkyl optionally substituted with one or more halo atoms;

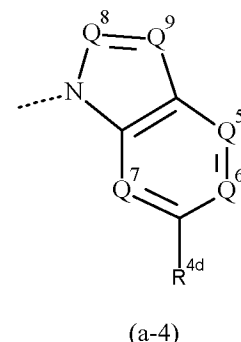
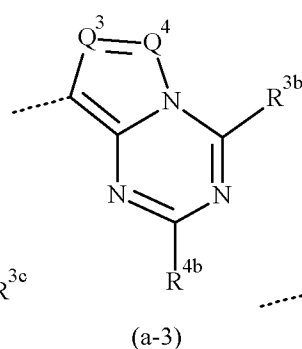
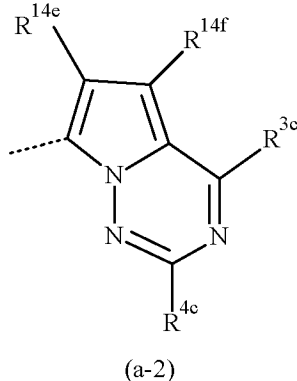
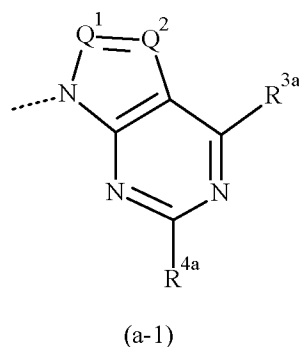
- Het^{2c} and Het^{2d} are attached to the remainder of the molecule of Formula (I) through
20 any available ring carbon atom;

- Het^{2c} and Het^{2d} each independently represent a 4-, 5-, 6- or 7-membered monocyclic aromatic or non-aromatic heterocyclyl containing at least one heteroatom each independently selected from O, S, S(=O)_p and N; or a fused 8-, 9-, 10- or 11-membered bicyclic aromatic or non-aromatic heterocyclyl containing at least one heteroatom each
25 independently selected from O, S, S(=O)_p and N; said monocyclic heterocyclyl or said fused bicyclic heterocyclyl optionally being substituted with one or more substituents each independently selected from the group consisting of halo, cyano, and C₁₋₄alkyl optionally substituted with one or more halo atoms;

- R^{6a} and R^{6b} each independently are selected from the group consisting of hydrogen and
30 C₁₋₄alkyl;

p represents 1 or 2;

Het represents a bicyclic aromatic heterocyclic ring system selected from the group consisting of (a-1), (a-2), (a-3) and (a-4):



R^{3a} , R^{3b} , R^{3c} and R^{3d} each independently are selected from the group consisting of hydrogen, halo, $-NR^{12a}R^{12b}$, C_{1-4} alkyl, and $-O-C_{1-4}$ alkyl;

R^{12a} and R^{12b} each independently are selected from the group consisting of hydrogen;

- 5 C_{3-6} cycloalkyl; C_{1-4} alkyl; and C_{1-4} alkyl substituted with one phenyl which is optionally substituted with one or more substituents selected from the group consisting of halo, cyano, $-OC_{1-4}$ alkyl, $-OH$, and C_{1-4} alkyl optionally substituted with one or more halo atoms;

R^{4a} , R^{4b} , R^{4c} , R^{4d} , R^{4e} and R^{4f} each independently are selected from the group

- 10 consisting of hydrogen, halo, $-NR^{13a}R^{13b}$, and C_{1-4} alkyl;

R^{13a} and R^{13b} each independently are selected from the group consisting of hydrogen and C_{1-4} alkyl;

Q^1 represents N or CR^{14a} ;

Q^2 represents N or CR^{14b} ;

- 15 Q^3 represents N or CR^{14c} ;

Q^4 represents N or CR^{14d} ;

provided that maximum one of Q^3 and Q^4 represents N;

Q^8 represents N or CR^{14g} ;

Q^9 represents N or CR^{14h} ;

- 20 Q^{10} represents N or CR^{14i} ;

Q^{11} represents N or CR^{14j} ;

Q^5 represents CR^{3d} ; Q^6 represents N; and Q^7 represents CR^{4f} ; or

Q^5 represents CR^{3d} ; Q^6 represents CR^{4e} ; and Q^7 represents N; or

Q^5 represents N; Q^6 represents CR^{4e} ; and Q^7 represents CR^{4f} ; or

- 25 Q^5 represents N; Q^6 represents CR^{4e} ; and Q^7 represents N; or

Q^5 represents N; Q^6 represents N; and Q^7 represents CR^{4f} ; or

Q^5 represents N; Q^6 represents N; and Q^7 represents N;

R^{14a} , R^{14b} , R^{14c} , R^{14d} , R^{14e} , R^{14f} , R^{14g} , R^{14h} , R^{14i} , and R^{14j} each independently are selected from the group consisting of hydrogen; halogen; C_{1-4} alkyl; $-NR^{15a}R^{15b}$; and C_{1-4} alkyl substituted with one or more halo atoms;

- 5 R^{15a} and R^{15b} each independently are selected from the group consisting of hydrogen and C_{1-4} alkyl;

provided that R^{10} and R^{11} may not be linked together when R^8 and R^9 are linked together;

and wherein at least one of R^8 , R^9 , R^{10} and R^{11} contains a nitrogen atom;

- 10 and pharmaceutically acceptable addition salts, and solvates thereof.

The present invention also concerns methods for the preparation of compounds of the present invention and pharmaceutical compositions comprising them.

- 15 The compounds of the present invention were found to inhibit PRMT5 per se or can undergo metabolism to a (more) active form in vivo (prodrugs), and therefore may be useful in the treatment or prevention, in particular in the treatment, of diseases such as a blood disorder, metabolic disorders, autoimmune disorders, cancer, inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, pancreatitis, multiorgan failure, kidney diseases, platelet aggregation, sperm motility, transplantation rejection, graft rejection, lung injuries, and the like.

- 20 In view of the aforementioned pharmacology of the compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, it follows that they may be suitable for use as a medicament.

- 25 In particular the compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, may be suitable in the treatment or prevention, in particular in the treatment, of any one of the diseases or conditions mentioned hereinbefore or hereinafter, in particular cancer.

- 30 The present invention also concerns the use of compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, for the manufacture of a medicament for the inhibition of PRMT5, for the treatment or prevention of any one of the diseases or conditions mentioned hereinbefore or hereinafter, in particular cancer.

The present invention will now be further described. In the following passages, different aspects of the invention are defined in more detail. Each aspect so defined may be combined with any other aspect or aspects unless clearly indicated to the contrary. In particular, any feature indicated as being preferred or advantageous may be

combined with any other feature or features indicated as being preferred or advantageous.

Detailed description

When describing the compounds of the invention, the terms used are to be construed in accordance with the following definitions, unless a context dictates otherwise.

When any variable occurs more than one time in any constituent or in any formula (e.g. Formula (I)), its definition in each occurrence is independent of its definition at every other occurrence.

Whenever the term “substituted” is used in the present invention, it is meant, unless otherwise is indicated or is clear from the context, to indicate that one or more hydrogens, in particular from 1 to 3 hydrogens, preferably 1 or 2 hydrogens, more preferably 1 hydrogen, on the atom or radical indicated in the expression using “substituted” are replaced with a selection from the indicated group, provided that the normal valency is not exceeded, and that the substitution results in a chemically stable compound, i.e. a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into a therapeutic agent.

When two or more substituents are present on a moiety they may, unless otherwise is indicated or is clear from the context, replace hydrogens on the same atom or they may replace hydrogen atoms on different atoms in the moiety.

The expression “at least one” in particular means “one, two or three”, more in particular “one or two”, even more in particular “one”.

Het^{2a} and Het^{2b} may be attached to the remainder of the molecule of formula (I) through any available ring carbon or heteroatom as appropriate, if not otherwise specified. Thus, for example, when the heterocyclyl is imidazolyl, it may be 1-imidazolyl, 2-imidazolyl, 4-imidazolyl and the like.

It will be clear for the skilled person that, unless otherwise is indicated or is clear from the context, a substituent on a 4-, 5-, 6- or 7-membered monocyclic aromatic or non-aromatic heterocyclyl containing at least one heteroatom each independently selected from O, S, S(=O)_p and N (as in the definition of Het^{2a}, Het^{2b}, Het^{2c} and Het^{2d}), may replace any hydrogen atom on a ring carbon atom or where possible on a ring nitrogen atom (in which case a hydrogen on a nitrogen atom may be replaced by a substituent).

The prefix “C_{x-y}” (where x and y are integers) as used herein refers to the number of carbon atoms in a given group. Thus, a C₁₋₄alkyl group contains from 1 to 4 carbon atoms, a C₁₋₃alkyl group contains from 1 to 3 carbon atoms and so on.

The term "halo" as a group or part of a group is generic for fluoro, chloro, bromo, iodo unless otherwise is indicated or is clear from the context.

The term "C₁₋₄alkyl" as a group or part of a group refers to a hydrocarbyl radical of Formula C_nH_{2n+1} wherein n is a number ranging from 1 to 4. C₁₋₄alkyl groups comprise from 1 to 4 carbon atoms, preferably from 1 to 3 carbon atoms, more preferably 1 to 2 carbon atoms. C₁₋₄alkyl groups may be linear or branched and may be substituted as indicated herein. When a subscript is used herein following a carbon atom, the subscript refers to the number of carbon atoms that the named group may contain. C₁₋₄alkyl includes all linear, or branched alkyl groups with between 1 and 4 carbon atoms, and thus includes methyl, ethyl, *n*-propyl, *i*-propyl, 2-methyl-ethyl, butyl and its isomers (e.g. *n*-butyl, *isobutyl* and *tert*-butyl), and the like.

Similar, the term 'C₁₋₆alkyl' as used herein as a group or part of a group represents a straight or branched chain saturated hydrocarbon radical having from 1 to 6 carbon atoms such as the groups defined for C₁₋₄alkyl and *n*-pentyl, *n*-hexyl, 2-methylbutyl and the like.

In case Z is =CH-, it is intended that the double bond is attached to X³ being C.

Whenever substituents are represented by chemical structure, "---" represents the bond of attachment to the remainder of the molecule of Formula (I). Lines drawn from substituents into ring systems indicate that the bond may be attached to any of the suitable ring atoms.

Non-limiting examples of Het^{1a} and Het^{1b} are carbon-linked oxetanyl (e.g. 3-oxetanyl), piperidinyl, tetrahydrofuranyl, pyrrolidinyl, thiolanyl, piperazinyl, tetrahydropyranyl and the like.

Non-limiting examples of Het^{2c} and Het^{2d} are carbon-linked oxetanyl (e.g. 3-oxetanyl), piperidinyl, tetrahydrofuranyl, pyrrolidinyl, thiolanyl, piperazinyl, tetrahydropyranyl, pyridinyl, furanyl, pyrazinyl, thiazolyl, benzimidazolyl and the like; each of which may optionally be substituted, where possible, on carbon and/or nitrogen atoms according to any of the embodiments.

Non-limiting examples of Het^{2a} and Het^{2b} are carbon- or nitrogen-linked oxetanyl, piperidinyl, tetrahydrofuranyl, pyrrolidinyl, thiolanyl, piperazinyl, tetrahydropyranyl, pyridinyl, furanyl, pyrazinyl, thiazolyl, benzimidazolyl and the like; each of which may optionally be substituted, where possible, on carbon and/or nitrogen atoms according to any of the embodiments.

Non-limiting examples of R⁸ and R⁹, or R¹⁰ and R¹¹, taken together to form a 4-, 5-, 6- or 7-membered saturated heterocyclyl, are piperidinyl, azetidyl, pyrrolidinyl,

morpholinyl, hexahydro-1H-azepinyl; each of which may optionally be substituted, where possible, on carbon and/or nitrogen atoms according to any of the embodiments.

The term "subject" as used herein, refers to an animal, preferably a mammal (e.g. cat, dog, primate or human), more preferably a human, who is or has been the object of
5 treatment, observation or experiment.

The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medicinal doctor or other clinician, which includes alleviation or reversal
10 of the symptoms of the disease or disorder being treated.

The term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

The term "treatment", as used herein, is intended to refer to all processes wherein there may be a slowing, interrupting, arresting or stopping of the progression of a disease, but
15 does not necessarily indicate a total elimination of all symptoms.

The term "compounds of the (present) invention" as used herein, is meant to include the compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof.

20 Some of the compounds of Formula (I) may also exist in their tautomeric form. The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible *via* a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions *via* migration of a proton, such as keto-enol and imine-enamine isomerisations. Valence tautomers include
25 interconversions by reorganisation of some of the bonding electrons.

Such forms in so far as they may exist, although not explicitly indicated in the above Formula (I), are intended to be included within the scope of the present invention.

As used herein, any chemical formula with bonds shown only as solid lines and not as solid wedged or hashed wedged bonds, or otherwise indicated as having a particular
30 configuration (e.g. *R*, *S*) around one or more atoms, contemplates each possible stereoisomer, or mixture of two or more stereoisomers. Where the stereochemistry of any particular chiral atom is not specified in the structures shown herein, then all stereoisomers are contemplated and included as the compounds of the invention, either as a pure stereoisomer or as a mixture of two or more stereoisomers.

Hereinbefore and hereinafter, the term “compound of Formula (I)” is meant to include the stereoisomers thereof and the tautomeric forms thereof. However where stereochemistry, as mentioned in the previous paragraph, is specified by bonds which are shown as solid wedged or hashed wedged bonds, or are otherwise indicated as
5 having a particular configuration (e.g. *R*, *S*), then that stereoisomer is so specified and defined. It will be clear this also applies to subgroups of Formula (I).

It follows that a single compound may, where possible, exist in both stereoisomeric and tautomeric form.

10 The terms “stereoisomers”, “stereoisomeric forms” or “stereochemically isomeric forms” hereinbefore or hereinafter are used interchangeably.

Enantiomers are stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a racemate or racemic mixture.

Atropisomers (or atropoisomers) are stereoisomers which have a particular spatial configuration, resulting from a restricted rotation about a single bond, due to large
15 steric hindrance. All atropisomeric forms of the compounds of Formula (I) are intended to be included within the scope of the present invention.

Diastereomers (or diastereoisomers) are stereoisomers that are not enantiomers, i.e. they are not related as mirror images.

Anomers are diastereoisomers of cyclic forms of sugars or similar molecules differing
20 in the configuration at the anomeric carbon (C-1 atom of an aldose or the C-2 atom of a 2-ketose). The cyclic forms of carbohydrates can exist in two forms, α - and β - based on the position of the substituent at the anomeric center. Anomers are designated α if the configuration at the anomeric carbon is the same as that at the reference asymmetric carbon in a Fischer projection. If the configuration differs the anomer is designated β .
25 For example, α -D-glucopyranose and β -D-glucopyranose, the two cyclic forms of glucose, are anomers.

If a compound contains a double bond, the substituents may be in the E or the Z configuration. Substituents on bivalent cyclic (partially) saturated radicals may have either the cis- or trans-configuration; for example if a compound contains a
30 disubstituted cycloalkyl group, the substituents may be in the cis or trans configuration. Therefore, the invention includes enantiomers, atropisomers, diastereomers, racemates, E isomers, Z isomers, cis isomers, trans isomers and mixtures thereof, whenever chemically possible.

The meaning of all those terms, i.e. enantiomers, atropisomers, diastereomers, racemates, E isomers, Z isomers, cis isomers, trans isomers and mixtures thereof are known to the skilled person.

The absolute configuration is specified according to the Cahn-Ingold-Prelog system.

- 5 The configuration at an asymmetric atom is specified by either R or S. Resolved stereoisomers whose absolute configuration is not known can be designated by (+) or (-) depending on the direction in which they rotate plane polarized light. For instance, resolved enantiomers whose absolute configuration is not known can be designated by (+) or (-) depending on the direction in which they rotate plane polarized light.
- 10 When a specific stereoisomer is identified, this means that said stereoisomer is substantially free, i.e. associated with less than 50%, preferably less than 20%, more preferably less than 10%, even more preferably less than 5%, in particular less than 2% and most preferably less than 1%, of the other stereoisomers. Thus, when a compound of Formula (I) is for instance specified as (R), this means that the compound is
- 15 substantially free of the (S) isomer; when a compound of Formula (I) is for instance specified as E, this means that the compound is substantially free of the Z isomer; when a compound of Formula (I) is for instance specified as cis, this means that the compound is substantially free of the trans isomer.

- For therapeutic use, salts of the compounds of Formula (I) and solvates thereof, are
- 20 those wherein the counterion is pharmaceutically acceptable. However, salts of acids and bases which are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether pharmaceutically acceptable or not are included within the ambit of the present invention.

- 25 Pharmaceutically-acceptable salts include acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form with one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. *in vacuo*, by
- 30 freeze-drying or by filtration). Salts may also be prepared by exchanging a counter-ion of a compound of the invention in the form of a salt with another counter-ion, for example using a suitable ion exchange resin.

- The pharmaceutically acceptable addition salts as mentioned hereinabove or hereinafter are meant to comprise the therapeutically active non-toxic acid and base addition salt
- 35 forms which the compounds of Formula (I) and solvates thereof, are able to form.

Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclamic, salicylic, p-aminosalicylic, pamoic and the like acids.

Conversely said salt forms can be converted by treatment with an appropriate base into the free base form.

The compounds of Formula (I) and solvates thereof containing an acidic proton may also be converted into their non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases.

Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. primary, secondary and tertiary aliphatic and aromatic amines such as methylamine, ethylamine, propylamine, isopropylamine, the four butylamine isomers, dimethylamine, diethylamine, diethanolamine, dipropylamine, diisopropylamine, di-n-butylamine, pyrrolidine, piperidine, morpholine, trimethylamine, triethylamine, tripropylamine, quinuclidine, pyridine, quinoline and isoquinoline; the benzathine, N-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like. Conversely the salt form can be converted by treatment with acid into the free acid form.

For the purposes of this invention prodrugs are also included within the scope of the invention.

The term “prodrug” of a relevant compound of the invention includes any compound that, following oral or parenteral administration, in particular oral administration, is metabolised *in vivo* to a form that compound in an experimentally-detectable amount, and within a predetermined time (e.g. within a dosing interval of between 6 and 24 hours (i.e. once to four times daily)). For the avoidance of doubt, the term “parenteral” administration includes all forms of administration other than oral administration, in particular intravenous (IV), intramuscular (IM), and subcutaneous (SC) injection.

Prodrugs may be prepared by modifying functional groups present on the compound in such a way that the modifications are cleaved, *in vivo* when such prodrug is administered to a mammalian subject. The modifications typically are achieved by synthesising the parent compound with a prodrug substituent. In general, prodrugs include compounds of the invention wherein a hydroxyl, amino, sulfhydryl, carboxy or carbonyl group in a compound of the invention is bonded to any group that may be

cleaved *in vivo* to regenerate the free hydroxyl, amino, sulfhydryl, carboxy or carbonyl group, respectively; in particular wherein a hydroxyl group in a compound of the invention is bonded to any group (e.g. $\text{-C(=O)-C}_{1-4}\text{alkyl}$) that may be cleaved *in vivo* to regenerate the free hydroxyl. Within the context of this invention, prodrugs in

- 5 particular are compounds of Formula (I) or subgroups thereof wherein R^a and/or R^b represent $\text{-C(=O)-C}_{1-4}\text{alkyl}$.

Examples of prodrugs include, but are not limited to, esters and carbamates of hydroxy functional groups, esters groups of carboxyl functional groups, N-acyl derivatives and N-Mannich bases. General information on prodrugs may be found e.g. in Bundegaard,
10 H. "Design of Prodrugs" p. 1-92, Elsevier, New York-Oxford (1985).

The term solvate comprises the hydrates and solvent addition forms which the compounds of Formula (I) are able to form, as well as pharmaceutically acceptable addition salts thereof. Examples of such forms are e.g. hydrates, alcoholates and the like.

- 15 The compounds of the invention as prepared in the processes described below may be synthesized in the form of mixtures of enantiomers, in particular racemic mixtures of enantiomers, that can be separated from one another following art-known resolution procedures. A manner of separating the enantiomeric forms of the compounds of Formula (I), and pharmaceutically acceptable addition salts, and solvates thereof,
20 involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound would be synthesized by stereospecific methods of preparation. These
25 methods will advantageously employ enantiomerically pure starting materials.

The present invention also embraces isotopically-labeled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature (or the most abundant one
30 found in nature).

- All isotopes and isotopic mixtures of any particular atom or element as specified herein are contemplated within the scope of the compounds of the invention, either naturally occurring or synthetically produced, either with natural abundance or in an isotopically enriched form. Exemplary isotopes that can be incorporated into compounds of the
35 invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine and iodine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}O , ^{17}O , ^{18}O , ^{32}P , ^{33}P ,

^{35}S , ^{18}F , ^{36}Cl , ^{122}I , ^{123}I , ^{125}I , ^{131}I , ^{75}Br , ^{76}Br , ^{77}Br and ^{82}Br . Preferably, the radioactive isotope is selected from the group of ^2H , ^3H , ^{11}C and ^{18}F . More preferably, the radioactive isotope is ^2H . In particular, deuterated compounds are intended to be included within the scope of the present invention.

- 5 Certain isotopically-labeled compounds of the present invention (e.g., those labeled with ^3H and ^{14}C) are useful in compound and for substrate tissue distribution assays. Tritiated (^3H) and carbon-14 (^{14}C) isotopes are useful for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^2H may afford certain therapeutic advantages resulting from greater metabolic stability
- 10 (e.g., increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Positron emitting isotopes such as ^{15}O , ^{13}N , ^{11}C and ^{18}F are useful for positron emission tomography (PET) studies to examine substrate receptor occupancy.

- 15 In an embodiment, the present invention concerns novel compounds of Formula (I), wherein
 - R^1 represents hydrogen or CH_3 ;
 - R^2 represents hydrogen;
 - R^a represents hydrogen or $-\text{C}(=\text{O})-\text{C}_{1-4}\text{alkyl}$;
 - 20 R^b represents hydrogen or $-\text{C}(=\text{O})-\text{C}_{1-4}\text{alkyl}$;
 - Y represents $-\text{O}-$, $-\text{CH}_2-$ or $-\text{CF}_2-$;
 - R^{7a} represents hydrogen;
 - R^{7b} represents hydrogen, or $\text{C}_{1-4}\text{alkyl}$ optionally substituted with one or more halo atoms;
- 25 X^1 represents a covalent bond or $-\text{O}-$;
- X^2 represents a covalent bond, $-\text{CH}_2-$, $-\text{CF}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CF}_2\text{CH}_2-$, or $-\text{CH}_2\text{CF}_2-$;
- provided that X^2 represents a covalent bond, $-\text{CH}_2-$ or $-\text{CF}_2-$, when X^1 represents $-\text{O}-$;
- X^3 represents N or CH; or in case one of the dotted lines represents an additional bond, X^3 represents C;

- 30 R^8 and R^{10} each independently are selected from the group consisting of hydrogen; halo; and $\text{C}_{1-6}\text{alkyl}$ optionally substituted with one or more halo atoms;
- R^9 and R^{11} each independently are selected from the group consisting of hydrogen; halo; $-\text{NH}_2$; and $\text{C}_{1-6}\text{alkyl}$ optionally substituted with one $-\text{NR}^{9a}\text{R}^{9b}$;
- or R^8 and R^9 are linked together to form together with the common carbon atom to
- 35 which they are attached a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing one or two N-atoms and optionally one oxygen atom; wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or more ring carbon

- atoms with one or more substituents each independently selected from the group consisting of halo, and C₁₋₆alkyl optionally substituted with one or more halo atoms; and wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or two ring N-atoms with a substituent selected from the group consisting of C₁₋₆alkyl; Het^{1a}; C₃₋₆cycloalkyl; -C₁₋₄alkyl-C(=O)-NR^{5a}R^{5b}; C₁₋₄alkyl substituted with one or more halo atoms; and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OC₁₋₄alkyl, cyano, C₃₋₆cycloalkyl, Ar^{1a}, -O-Ar^{1a}, Het^{2a} and -O-Het^{2c};
- or R¹⁰ and R¹¹ are linked together to form together with the common carbon atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing one or two N-atoms and optionally one oxygen atom; wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or more ring carbon atoms with one or more substituents each independently selected from the group consisting of halo, and C₁₋₆alkyl optionally substituted with one or more halo atoms; and wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or two ring N-atoms with a substituent selected from the group consisting of C₁₋₆alkyl; Het^{1b}; C₃₋₆cycloalkyl; -C₁₋₄alkyl-C(=O)-NR^{6a}R^{6b}; C₁₋₄alkyl substituted with one or more halo atoms; and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OC₁₋₄alkyl, cyano, C₃₋₆cycloalkyl, Ar^{1b}, -O-Ar^{1b}, Het^{2b} and -O-Het^{2d};
- Z represents -CH₂-, -C(=O)-, or -CH(C₁₋₄alkyl)-; and in case X³ represents C, Z can also represent =CH-;
- the dotted lines attached to X³ are optional bonds that may be present when X³ represents a carbon atom, provided that maximum one of the dotted lines represents an optional bond;
- in case one of the dotted lines attached to X³ represents an additional bond, X³ represents C, and (i) R^{7a} is absent or (ii) R⁸ is absent or (iii) Z represents =CH-;
- R^{9a} and R^{9b} each independently are selected from the group consisting of hydrogen and C₁₋₄alkyl; or R^{9a} and R^{9b} are linked together to form together with the common nitrogen atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocyclyl which optionally contains one oxygen atom;
- R^{5a} and R^{5b} each independently are selected from the group consisting of hydrogen and C₁₋₄alkyl;
- Het^{1a} and Het^{1b} are attached to the remainder of the molecule of Formula (I) through any available ring carbon atom;
- Het^{1a} and Het^{1b} each independently represent a 4-, 5-, 6- or 7-membered saturated

heterocyclyl, containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N;

Ar^{1a} and Ar^{1b} each independently represent phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo;

5 cyano; and C₁₋₄alkyl optionally substituted with one or more halo atoms;

Het^{2a} and Het^{2b} each independently represent a 4-, 5-, 6- or 7-membered monocyclic aromatic or non-aromatic heterocyclyl containing at least one heteroatom each independently selected from O, S, S(=O)_p and N; or a fused 8-, 9-, 10- or 11-membered bicyclic aromatic or non-aromatic heterocyclyl containing at least one heteroatom each
10 independently selected from O, S, S(=O)_p and N; said monocyclic heterocyclyl or said fused bicyclic heterocyclyl optionally being substituted with one or more substituents each independently selected from the group consisting of halo, cyano, and C₁₋₄alkyl optionally substituted with one or more halo atoms;

Het^{2c} and Het^{2d} are attached to the remainder of the molecule of Formula (I) through
15 any available ring carbon atom;

Het^{2c} and Het^{2d} each independently represent a 4-, 5-, 6- or 7-membered monocyclic aromatic or non-aromatic heterocyclyl containing at least one heteroatom each independently selected from O, S, S(=O)_p and N; or a fused 8-, 9-, 10- or 11-membered bicyclic aromatic or non-aromatic heterocyclyl containing at least one heteroatom each
20 independently selected from O, S, S(=O)_p and N; said monocyclic heterocyclyl or said fused bicyclic heterocyclyl optionally being substituted with one or more substituents each independently selected from the group consisting of halo, cyano, and C₁₋₄alkyl optionally substituted with one or more halo atoms;

R^{6a} and R^{6b} each independently are selected from the group consisting of hydrogen and
25 C₁₋₄alkyl;

p represents 1 or 2;

Het represents a bicyclic aromatic heterocyclic ring system selected from the group consisting of (a-1), (a-2) and (a-3);

R^{3a}, R^{3b} and R^{3c} each independently are selected from the group consisting of
30 hydrogen, halo, -NR^{12a}R^{12b}, C₁₋₄alkyl, and -O-C₁₋₄alkyl;

R^{12a} and R^{12b} each independently are selected from the group consisting of hydrogen; C₃₋₆cycloalkyl; C₁₋₄alkyl; and C₁₋₄alkyl substituted with one phenyl which is optionally substituted with one or more substituents selected from the group consisting of halo, cyano, -OC₁₋₄alkyl, -OH, and C₁₋₄alkyl optionally substituted with one or more halo
35 atoms;

- R^{4a} , R^{4b} and R^{4c} each independently are selected from the group consisting of hydrogen, halo, $-NR^{13a}R^{13b}$, and C_{1-4} alkyl;
 R^{13a} and R^{13b} each independently are selected from the group consisting of hydrogen and C_{1-4} alkyl;
- 5 Q^1 represents N or CR^{14a} ;
 Q^2 represents N or CR^{14b} ;
 Q^3 represents N or CR^{14c} ;
 Q^4 represents N or CR^{14d} ;
provided that maximum one of Q^3 and Q^4 represents N;
- 10 R^{14a} , R^{14b} , R^{14c} , R^{14d} , R^{14e} and R^{14f} each independently are selected from the group consisting of hydrogen; halogen; C_{1-4} alkyl; $-NR^{15a}R^{15b}$, and C_{1-4} alkyl substituted with one or more halo atoms;
 R^{15a} and R^{15b} each independently are selected from the group consisting of hydrogen and C_{1-4} alkyl;
- 15 provided that R^{10} and R^{11} may not be linked together when R^8 and R^9 are linked together;
and wherein at least one of R^8 , R^9 , R^{10} and R^{11} contains a nitrogen atom;
and pharmaceutically acceptable addition salts, and solvates thereof.
- 20 In an embodiment, the present invention concerns novel compounds of Formula (I), wherein
 R^1 represents hydrogen or CH_3 ;
 R^2 represents hydrogen;
 R^a represents hydrogen;
- 25 R^b represents hydrogen;
Y represents $-O-$, $-CH_2-$ or $-CF_2-$;
 R^{7a} represents hydrogen;
 R^{7b} represents hydrogen, or C_{1-4} alkyl optionally substituted with one or more halo atoms;
- 30 X^1 represents a covalent bond or $-O-$;
 X^2 represents a covalent bond, $-CH_2-$, $-CF_2-$, $-CH_2CH_2-$, $-CF_2CH_2-$, or $-CH_2CF_2-$;
provided that X^2 represents a covalent bond, $-CH_2-$ or $-CF_2-$, when X^1 represents $-O-$;
 X^3 represents N or CH; or in case one of the dotted lines represents an additional bond, X^3 represents C;
- 35 R^8 and R^{10} each independently are selected from the group consisting of hydrogen; halo; and C_{1-6} alkyl optionally substituted with one or more halo atoms;

- R⁹ and R¹¹ each independently are selected from the group consisting of hydrogen; halo; -NH₂; and C₁₋₆alkyl optionally substituted with one -NR^{9a}R^{9b};
 or R⁸ and R⁹ are linked together to form together with the common carbon atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing
 5 one or two N-atoms and optionally one oxygen atom; wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or more ring carbon atoms with one or more substituents each independently selected from the group consisting of halo, and C₁₋₆alkyl optionally substituted with one or more halo atoms; and wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally
 10 substituted on one or two ring N-atoms with a substituent selected from the group consisting of C₁₋₆alkyl; Het^{1a}; C₃₋₆cycloalkyl; -C₁₋₄alkyl-C(=O)-NR^{5a}R^{5b}; C₁₋₄alkyl substituted with one or more halo atoms; and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OC₁₋₄alkyl, cyano, C₃₋₆cycloalkyl, Ar^{1a}, -O-Ar^{1a}, Het^{2a} and -O-Het^{2c};
 15 or R¹⁰ and R¹¹ are linked together to form together with the common carbon atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing one or two N-atoms and optionally one oxygen atom; wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or more ring carbon atoms with one or more substituents each independently selected from the group
 20 consisting of halo, and C₁₋₆alkyl optionally substituted with one or more halo atoms; and wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or two ring N-atoms with a substituent selected from the group consisting of C₁₋₆alkyl; Het^{1b}; C₃₋₆cycloalkyl; -C₁₋₄alkyl-C(=O)-NR^{6a}R^{6b}; C₁₋₄alkyl substituted with one or more halo atoms; and C₁₋₄alkyl substituted with one substituent
 25 selected from the group consisting of -OC₁₋₄alkyl, cyano, C₃₋₆cycloalkyl, Ar^{1b}, -O-Ar^{1b}, Het^{2b} and -O-Het^{2d};
 Z represents -CH₂-, -C(=O)-, or -CH(C₁₋₄alkyl)-; and in case X³ represents C, Z can also represent =CH-;
 the dotted lines attached to X³ are optional bonds that may be present when X³
 30 represents a carbon atom, provided that maximum one of the dotted lines represents an optional bond;
 in case one of the dotted lines attached to X³ represents an additional bond, X³ represents C, and (i) R^{7a} is absent or (ii) R⁸ is absent or (iii) Z represents =CH-;
 R^{9a} and R^{9b} each independently are selected from the group consisting of hydrogen and
 35 C₁₋₄alkyl; or R^{9a} and R^{9b} are linked together to form together with the common nitrogen atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocyclyl which optionally contains one oxygen atom;

R^{5a} and R^{5b} each independently are selected from the group consisting of hydrogen and C₁₋₄alkyl;

Het^{1a} and Het^{1b} are attached to the remainder of the molecule of Formula (I) through any available ring carbon atom;

- 5 Het^{1a} and Het^{1b} each independently represent a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N;

- Ar^{1a} and Ar^{1b} each independently represent phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo; cyano; and C₁₋₄alkyl optionally substituted with one or more halo atoms;

- Het^{2a} and Het^{2b} each independently represent a 4-, 5-, 6- or 7-membered monocyclic aromatic or non-aromatic heterocyclyl containing at least one heteroatom each independently selected from O, S, S(=O)_p and N; or a fused 8-, 9-, 10- or 11-membered bicyclic aromatic or non-aromatic heterocyclyl containing at least one heteroatom each independently selected from O, S, S(=O)_p and N; said monocyclic heterocyclyl or said fused bicyclic heterocyclyl optionally being substituted with one or more substituents each independently selected from the group consisting of halo, cyano, and C₁₋₄alkyl optionally substituted with one or more halo atoms;

- Het^{2c} and Het^{2d} are attached to the remainder of the molecule of Formula (I) through any available ring carbon atom;

- Het^{2c} and Het^{2d} each independently represent a 4-, 5-, 6- or 7-membered monocyclic aromatic or non-aromatic heterocyclyl containing at least one heteroatom each independently selected from O, S, S(=O)_p and N; or a fused 8-, 9-, 10- or 11-membered bicyclic aromatic or non-aromatic heterocyclyl containing at least one heteroatom each independently selected from O, S, S(=O)_p and N; said monocyclic heterocyclyl or said fused bicyclic heterocyclyl optionally being substituted with one or more substituents each independently selected from the group consisting of halo, cyano, and C₁₋₄alkyl optionally substituted with one or more halo atoms;

- R^{6a} and R^{6b} each independently are selected from the group consisting of hydrogen and C₁₋₄alkyl;

p represents 1 or 2;

Het represents a bicyclic aromatic heterocyclic ring system selected from the group consisting of (a-1), (a-2) and (a-3);

- R^{3a}, R^{3b} and R^{3c} each independently are selected from the group consisting of hydrogen, halo, -NR^{12a}R^{12b}, C₁₋₄alkyl, and -O-C₁₋₄alkyl;

- R^{12a} and R^{12b} each independently are selected from the group consisting of hydrogen; C₃₋₆cycloalkyl; C₁₋₄alkyl; and C₁₋₄alkyl substituted with one phenyl which is optionally substituted with one or more substituents selected from the group consisting of halo, cyano, -OC₁₋₄alkyl, -OH, and C₁₋₄alkyl optionally substituted with one or more halo atoms;
- 5 R^{4a}, R^{4b} and R^{4c} each independently are selected from the group consisting of hydrogen, halo, -NR^{13a}R^{13b}, and C₁₋₄alkyl;
- R^{13a} and R^{13b} each independently are selected from the group consisting of hydrogen and C₁₋₄alkyl;
- 10 Q¹ represents N or CR^{14a};
 Q² represents N or CR^{14b};
 Q³ represents N or CR^{14c};
 Q⁴ represents N or CR^{14d};
 provided that maximum one of Q³ and Q⁴ represents N;
- 15 R^{14a}, R^{14b}, R^{14c}, R^{14d}, R^{14e} and R^{14f} each independently are selected from the group consisting of hydrogen; halogen; C₁₋₄alkyl; -NR^{15a}R^{15b}, and C₁₋₄alkyl substituted with one or more halo atoms;
- R^{15a} and R^{15b} each independently are selected from the group consisting of hydrogen and C₁₋₄alkyl;
- 20 provided that R¹⁰ and R¹¹ may not be linked together when R⁸ and R⁹ are linked together;
 and wherein at least one of R⁸, R⁹, R¹⁰ and R¹¹ contains a nitrogen atom;
 and pharmaceutically acceptable addition salts, and solvates thereof.
- 25 In an embodiment, the present invention concerns novel compounds of Formula (I), wherein
- R¹ represents hydrogen or CH₃;
 R² represents hydrogen;
 R^a represents -C(=O)-C₁₋₄alkyl;
- 30 R^b represents -C(=O)-C₁₋₄alkyl;
 Y represents -O-, -CH₂- or -CF₂-;
 R^{7a} represents hydrogen;
 R^{7b} represents hydrogen, or C₁₋₄alkyl optionally substituted with one or more halo atoms;
- 35 X¹ represents a covalent bond or -O-;
 X² represents a covalent bond, -CH₂-, -CF₂-, -CH₂CH₂-, -CF₂CH₂-, or -CH₂CF₂-;

provided that X^2 represents a covalent bond, $-CH_2-$ or $-CF_2-$, when X^1 represents $-O-$; X^3 represents N or CH; or in case one of the dotted lines represents an additional bond, X^3 represents C;

- R^8 and R^{10} each independently are selected from the group consisting of hydrogen; halo; and C_{1-6} alkyl optionally substituted with one or more halo atoms;
- 5 R^9 and R^{11} each independently are selected from the group consisting of hydrogen; halo; $-NH_2$; and C_{1-6} alkyl optionally substituted with one $-NR^{9a}R^{9b}$;
- or R^8 and R^9 are linked together to form together with the common carbon atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing
- 10 one or two N-atoms and optionally one oxygen atom; wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or more ring carbon atoms with one or more substituents each independently selected from the group consisting of halo, and C_{1-6} alkyl optionally substituted with one or more halo atoms; and wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally
- 15 substituted on one or two ring N-atoms with a substituent selected from the group consisting of C_{1-6} alkyl; Het^{1a} ; C_{3-6} cycloalkyl; $-C_{1-4}alkyl-C(=O)-NR^{5a}R^{5b}$; $C_{1-4}alkyl$ substituted with one or more halo atoms; and $C_{1-4}alkyl$ substituted with one substituent selected from the group consisting of $-OC_{1-4}alkyl$, cyano, C_{3-6} cycloalkyl, Ar^{1a} , $-O-Ar^{1a}$, Het^{2a} and $-O-Het^{2c}$;
- 20 or R^{10} and R^{11} are linked together to form together with the common carbon atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing one or two N-atoms and optionally one oxygen atom; wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or more ring carbon atoms with one or more substituents each independently selected from the group
- 25 consisting of halo, and C_{1-6} alkyl optionally substituted with one or more halo atoms; and wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or two ring N-atoms with a substituent selected from the group consisting of C_{1-6} alkyl; Het^{1b} ; C_{3-6} cycloalkyl; $-C_{1-4}alkyl-C(=O)-NR^{6a}R^{6b}$; $C_{1-4}alkyl$ substituted with one or more halo atoms; and $C_{1-4}alkyl$ substituted with one substituent
- 30 selected from the group consisting of $-OC_{1-4}alkyl$, cyano, C_{3-6} cycloalkyl, Ar^{1b} , $-O-Ar^{1b}$, Het^{2b} and $-O-Het^{2d}$;
- Z represents $-CH_2-$, $-C(=O)-$, or $-CH(C_{1-4}alkyl)-$; and in case X^3 represents C, Z can also represent $=CH-$;
- the dotted lines attached to X^3 are optional bonds that may be present when X^3
- 35 represents a carbon atom, provided that maximum one of the dotted lines represents an optional bond;

in case one of the dotted lines attached to X^3 represents an additional bond, X^3 represents C, and (i) R^{7a} is absent or (ii) R^8 is absent or (iii) Z represents $=CH-$;

R^{9a} and R^{9b} each independently are selected from the group consisting of hydrogen and C_{1-4} alkyl; or R^{9a} and R^{9b} are linked together to form together with the common nitrogen
5 atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocyclyl which optionally contains one oxygen atom;

R^{5a} and R^{5b} each independently are selected from the group consisting of hydrogen and C_{1-4} alkyl;

Het^{1a} and Het^{1b} are attached to the remainder of the molecule of Formula (I) through
10 any available ring carbon atom;

Het^{1a} and Het^{1b} each independently represent a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing one or two heteroatoms each independently selected from O, S, $S(=O)_p$ and N;

Ar^{1a} and Ar^{1b} each independently represent phenyl optionally substituted with one or
15 more substituents each independently selected from the group consisting of halo; cyano; and C_{1-4} alkyl optionally substituted with one or more halo atoms;

Het^{2a} and Het^{2b} each independently represent a 4-, 5-, 6- or 7-membered monocyclic aromatic or non-aromatic heterocyclyl containing at least one heteroatom each independently selected from O, S, $S(=O)_p$ and N; or a fused 8-, 9-, 10- or 11-membered
20 bicyclic aromatic or non-aromatic heterocyclyl containing at least one heteroatom each independently selected from O, S, $S(=O)_p$ and N; said monocyclic heterocyclyl or said fused bicyclic heterocyclyl optionally being substituted with one or more substituents each independently selected from the group consisting of halo, cyano, and C_{1-4} alkyl optionally substituted with one or more halo atoms;

Het^{2c} and Het^{2d} are attached to the remainder of the molecule of Formula (I) through
25 any available ring carbon atom;

Het^{2c} and Het^{2d} each independently represent a 4-, 5-, 6- or 7-membered monocyclic aromatic or non-aromatic heterocyclyl containing at least one heteroatom each independently selected from O, S, $S(=O)_p$ and N; or a fused 8-, 9-, 10- or 11-membered
30 bicyclic aromatic or non-aromatic heterocyclyl containing at least one heteroatom each independently selected from O, S, $S(=O)_p$ and N; said monocyclic heterocyclyl or said fused bicyclic heterocyclyl optionally being substituted with one or more substituents each independently selected from the group consisting of halo, cyano, and C_{1-4} alkyl optionally substituted with one or more halo atoms;

R^{6a} and R^{6b} each independently are selected from the group consisting of hydrogen and C₁₋₄alkyl;

p represents 1 or 2;

Het represents a bicyclic aromatic heterocyclic ring system selected from the group consisting of (a-1), (a-2) and (a-3);

R^{3a}, R^{3b} and R^{3c} each independently are selected from the group consisting of hydrogen, halo, -NR^{12a}R^{12b}, C₁₋₄alkyl, and -O-C₁₋₄alkyl;

R^{12a} and R^{12b} each independently are selected from the group consisting of hydrogen; C₃₋₆cycloalkyl; C₁₋₄alkyl; and C₁₋₄alkyl substituted with one phenyl which is optionally substituted with one or more substituents selected from the group consisting of halo, cyano, -OC₁₋₄alkyl, -OH, and C₁₋₄alkyl optionally substituted with one or more halo atoms;

R^{4a}, R^{4b} and R^{4c} each independently are selected from the group consisting of hydrogen, halo, -NR^{13a}R^{13b}, and C₁₋₄alkyl;

R^{13a} and R^{13b} each independently are selected from the group consisting of hydrogen and C₁₋₄alkyl;

Q¹ represents N or CR^{14a};

Q² represents N or CR^{14b};

Q³ represents N or CR^{14c};

Q⁴ represents N or CR^{14d};

provided that maximum one of Q³ and Q⁴ represents N;

R^{14a}, R^{14b}, R^{14c}, R^{14d}, R^{14e} and R^{14f} each independently are selected from the group consisting of hydrogen; halogen; C₁₋₄alkyl; -NR^{15a}R^{15b}, and C₁₋₄alkyl substituted with one or more halo atoms;

R^{15a} and R^{15b} each independently are selected from the group consisting of hydrogen and C₁₋₄alkyl;

provided that R¹⁰ and R¹¹ may not be linked together when R⁸ and R⁹ are linked together;

and wherein at least one of R⁸, R⁹, R¹⁰ and R¹¹ contains a nitrogen atom;

and pharmaceutically acceptable addition salts, and solvates thereof.

In an embodiment, the present invention concerns novel compounds of Formula (I), wherein

R¹ represents hydrogen or CH₃; in particular hydrogen;

R² represents hydrogen;

R^a represents hydrogen or -C(=O)-C₁₋₄alkyl;

R^b represents hydrogen or -C(=O)-C₁₋₄alkyl;

Y represents -O- or -CH₂-;

R^{7a} represents hydrogen;

R^{7b} represents hydrogen, or C₁₋₄alkyl optionally substituted with one or more halo

5 atoms;

X¹ represents a covalent bond or -O-;

X² represents a covalent bond, -CH₂-, -CF₂CH₂-, or -CH₂CF₂-;

provided that X² represents a covalent bond or -CH₂-, when X¹ represents -O-;

X³ represents N; or in case one of the dotted lines represents an additional bond, X³

10 represents C;

R⁸ and R¹⁰ each independently are selected from the group consisting of hydrogen;

halo; and C₁₋₆alkyl optionally substituted with one or more halo atoms;

R⁹ and R¹¹ each independently are selected from the group consisting of hydrogen;

halo; -NH₂; and C₁₋₆alkyl optionally substituted with one -NR^{9a}R^{9b};

15 or R⁸ and R⁹ are linked together to form together with the common carbon atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing one or two N-atoms; wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or two ring N-atoms with a substituent selected from the group consisting of C₁₋₆alkyl; Het^{1a}; C₃₋₆cycloalkyl; -C₁₋₄alkyl-C(=O)-NR^{5a}R^{5b}; C₁₋
20 4alkyl substituted with one or more halo atoms; and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OC₁₋₄alkyl, cyano, C₃₋₆cycloalkyl, Ar^{1a}, -O-Ar^{1a}, and Het^{2a};

or R¹⁰ and R¹¹ are linked together to form together with the common carbon atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing
25 one or two N-atoms and optionally one oxygen atom; wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or more ring carbon atoms with one or more halo substituents; and wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or two ring N-atoms with a substituent selected from the group consisting of C₁₋₆alkyl; and C₁₋₄alkyl substituted
30 with one Ar^{1b};

Z represents -CH₂- or -C(=O)-; and in case X³ represents C, Z can also represent =CH-; the dotted lines attached to X³ are optional bonds that may be present when X³ represents a carbon atom, provided that maximum one of the dotted lines represents an optional bond;

35 in case one of the dotted lines attached to X³ represents an additional bond, X³ represents C, and (i) R^{7a} is absent or (ii) R⁸ is absent or (iii) Z represents =CH-;

R^{9a} and R^{9b} each independently are selected from the group consisting of hydrogen and C_{1-4} alkyl; or R^{9a} and R^{9b} are linked together to form together with the common nitrogen atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocyclyl which optionally contains one oxygen atom;

- 5 R^{5a} and R^{5b} each independently are selected from the group consisting of hydrogen and C_{1-4} alkyl;

Het^{1a} is attached to the remainder of the molecule of Formula (I) through any available ring carbon atom;

- Het^{1a} represents a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing one or
10 two heteroatoms each independently selected from O;

Ar^{1a} and Ar^{1b} each independently represent phenyl optionally substituted with one or more halo substituents;

- Het^{2a} represents a 4-, 5-, 6- or 7-membered monocyclic aromatic or non-aromatic heterocyclyl containing at least one heteroatom each independently selected from O, S,
15 S(=O)_p and N; or a fused 8-, 9-, 10- or 11-membered bicyclic aromatic or non-aromatic heterocyclyl containing at least one heteroatom each independently selected from O, S, S(=O)_p and N; said monocyclic heterocyclyl or said fused bicyclic heterocyclyl optionally being substituted with one or more C_{1-4} alkyl substituents;

p represents 1 or 2;

- 20 Het represents a bicyclic aromatic heterocyclic ring system selected from the group consisting of (a-1), (a-2) and (a-3);

R^{3a} , R^{3b} and R^{3c} each independently are selected from the group consisting of hydrogen, halo, and $-NR^{12a}R^{12b}$;

- R^{12a} and R^{12b} each independently are selected from the group consisting of hydrogen;
25 C_{3-6} cycloalkyl; C_{1-4} alkyl; and C_{1-4} alkyl substituted with one phenyl which is optionally substituted with one or more halo substituents;

R^{4a} , R^{4b} and R^{4c} each independently are selected from the group consisting of hydrogen and C_{1-4} alkyl;

Q¹ represents CR^{14a};

- 30 Q² represents N or CR^{14b};

Q³ represents CR^{14c};

Q⁴ represents N;

R^{14a} , R^{14b} , R^{14c} , R^{14e} and R^{14f} each independently are selected from the group consisting of hydrogen and halogen;

provided that R¹⁰ and R¹¹ may not be linked together when R⁸ and R⁹ are linked together;

and wherein at least one of R⁸, R⁹, R¹⁰ and R¹¹ contains a nitrogen atom;

and pharmaceutically acceptable addition salts, and solvates thereof.

5

In an embodiment, the present invention concerns novel compounds of Formula (I), wherein

R¹ represents hydrogen or CH₃; in particular hydrogen;

R² represents hydrogen;

10 R^a represents hydrogen or -C(=O)-C₁₋₄alkyl;

R^b represents hydrogen or -C(=O)-C₁₋₄alkyl;

Y represents -O- or -CH₂-;

R^{7a} represents hydrogen;

15 R^{7b} represents hydrogen, or C₁₋₄alkyl optionally substituted with one or more halo atoms;

X¹ represents a covalent bond or -O-;

X² represents a covalent bond, -CH₂-, -CF₂CH₂-, or -CH₂CF₂-;

provided that X² represents a covalent bond or -CH₂-, when X¹ represents -O-;

20 X³ represents N; or in case one of the dotted lines represents an additional bond, X³ represents C;

R⁸ and R¹⁰ each independently are selected from the group consisting of hydrogen; halo; and C₁₋₆alkyl optionally substituted with one or more halo atoms;

R⁹ and R¹¹ each independently are selected from the group consisting of hydrogen; halo; -NH₂; and C₁₋₆alkyl optionally substituted with one -NR^{9a}R^{9b};

25 or R⁸ and R⁹ are linked together to form together with the common carbon atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing one or two N-atoms; wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or two ring N-atoms with a substituent selected from the group consisting of C₁₋₆alkyl; Het^{1a}; C₃₋₆cycloalkyl; -C₁₋₄alkyl-C(=O)-NR^{5a}R^{5b}; C₁₋₄alkyl substituted with one or more halo atoms; and C₁₋₄alkyl substituted with one
30 substituent selected from the group consisting of -OC₁₋₄alkyl, cyano, C₃₋₆cycloalkyl, Ar^{1a}, -O-Ar^{1a}, and Het^{2a};

or R¹⁰ and R¹¹ are linked together to form together with the common carbon atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing
35 one or two N-atoms and optionally one oxygen atom; wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or more ring carbon

atoms with one or more halo substituents; and wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or two ring N-atoms with a substituent selected from the group consisting of C₁₋₆alkyl; and C₁₋₄alkyl substituted with one Ar^{1b};

- 5 Z represents -CH₂- or -C(=O)-; and in case X³ represents C, Z can also represent =CH-; the dotted lines attached to X³ are optional bonds that may be present when X³ represents a carbon atom, provided that maximum one of the dotted lines represents an optional bond;

- 10 in case one of the dotted lines attached to X³ represents an additional bond, X³ represents C, and (i) R^{7a} is absent or (ii) R⁸ is absent or (iii) Z represents =CH-;

R^{9a} and R^{9b} each independently are selected from the group consisting of hydrogen and C₁₋₄alkyl; or R^{9a} and R^{9b} are linked together to form together with the common nitrogen atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocyclyl which optionally contains one oxygen atom;

- 15 R^{5a} and R^{5b} each independently are selected from the group consisting of hydrogen and C₁₋₄alkyl;

Het^{1a} is attached to the remainder of the molecule of Formula (I) through any available ring carbon atom;

- 20 Het^{1a} represents a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing one or two heteroatoms each independently selected from O;

Ar^{1a} and Ar^{1b} each independently represent phenyl optionally substituted with one or more halo substituents;

- 25 Het^{2a} represents a 4-, 5-, 6- or 7-membered monocyclic aromatic or non-aromatic heterocyclyl containing at least one heteroatom each independently selected from O, S, S(=O)_p and N; or a fused 8-, 9-, 10- or 11-membered bicyclic aromatic or non-aromatic heterocyclyl containing at least one heteroatom each independently selected from O, S, S(=O)_p and N; said monocyclic heterocyclyl or said fused bicyclic heterocyclyl optionally being substituted with one or more C₁₋₄alkyl substituents;

p represents 1 or 2;

- 30 Het represents a bicyclic aromatic heterocyclic ring system selected from the group consisting of (a-1), (a-2), (a-3) and (a-4);

R^{3a}, R^{3b}, R^{3c} and R^{3d} each independently are selected from the group consisting of hydrogen, halo, and -NR^{12a}R^{12b};

R^{12a} and R^{12b} each independently are selected from the group consisting of hydrogen;

C₃₋₆cycloalkyl; C₁₋₄alkyl; and C₁₋₄alkyl substituted with one phenyl which is optionally substituted with one or more halo substituents;

R^{4a}, R^{4b}, R^{4c} and R^{4d} each independently are selected from the group consisting of hydrogen and C₁₋₄alkyl;

5 R^{4f} represent hydrogen;

Q¹ represents CR^{14a};

Q² represents N or CR^{14b};

Q³ represents CR^{14c};

Q⁴ represents N;

10 Q⁸ represents CR^{14g};

Q⁹ represents CR^{14h};

Q⁵ represents CR^{3d}, Q⁶ represents N; and Q⁷ represents CR^{4f};

R^{14a}, R^{14b}, R^{14c}, R^{14e} and R^{14f} each independently are selected from the group consisting of hydrogen and halogen;

15 R^{14g} and R^{14h} represent hydrogen;

provided that R¹⁰ and R¹¹ may not be linked together when R⁸ and R⁹ are linked together;

and wherein at least one of R⁸, R⁹, R¹⁰ and R¹¹ contains a nitrogen atom;

and pharmaceutically acceptable addition salts, and solvates thereof.

20

Another embodiment of the present invention relates to those compounds of Formula (I), and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein one or more of the following restrictions apply:

25 (i) R¹ represents hydrogen;

(ii) Y represents -O- or -CH₂-;

(iii) X² represents a covalent bond, -CH₂-, -CF₂CH₂-, or -CH₂CF₂-;

provided that X² represents a covalent bond or -CH₂-, when X¹ represents -O-;

(iv) X³ represents N; or in case one of the dotted lines represents an additional bond, X³

30 represents C;

(v) R⁸ and R¹⁰ each independently are selected from the group consisting of hydrogen; halo; and C₁₋₆alkyl optionally substituted with one or more halo atoms;

R⁹ and R¹¹ each independently are selected from the group consisting of hydrogen; halo; -NH₂; and C₁₋₆alkyl optionally substituted with one -NR^{9a}R^{9b};

35 or R⁸ and R⁹ are linked together to form together with the common carbon atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing

- one or two N-atoms; wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or two ring N-atoms with a substituent selected from the group consisting of C₁₋₆alkyl; Het^{1a}; C₃₋₆cycloalkyl; -C₁₋₄alkyl-C(=O)-NR^{5a}R^{5b}; C₁₋₄alkyl substituted with one or more halo atoms; and C₁₋₄alkyl substituted with one
- 5 substituent selected from the group consisting of -OC₁₋₄alkyl, cyano, C₃₋₆cycloalkyl, Ar^{1a}, -O-Ar^{1a}, and Het^{2a};
- or R¹⁰ and R¹¹ are linked together to form together with the common carbon atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing one or two N-atoms and optionally one oxygen atom; wherein said 4-, 5-, 6- or 7-
- 10 membered saturated heterocyclyl is optionally substituted on one or more ring carbon atoms with one or more halo substituents; and wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or two ring N-atoms with a substituent selected from the group consisting of C₁₋₆alkyl; and C₁₋₄alkyl substituted with one Ar^{1b};
- 15 (vi) Z represents -CH₂- or -C(=O)-; and in case X³ represents C, Z can also represent =CH-;
- the dotted lines attached to X³ are optional bonds that may be present when X³ represents a carbon atom, provided that maximum one of the dotted lines represents an optional bond;
- 20 in case one of the dotted lines attached to X³ represents an additional bond, X³ represents C, and (i) R^{7a} is absent or (ii) R⁸ is absent or (iii) Z represents =CH-;
- (vii) Het^{1a} is attached to the remainder of the molecule of Formula (I) through any available ring carbon atom;
- Het^{1a} represents a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing one or
- 25 two heteroatoms each independently selected from O;
- (viii) Ar^{1a} and Ar^{1b} each independently represent phenyl optionally substituted with one or more halo substituents;
- (ix) Het^{2a} represents a 4-, 5-, 6- or 7-membered monocyclic aromatic or non-aromatic heterocyclyl containing at least one heteroatom each independently selected from O, S,
- 30 S(=O)_p and N; or a fused 8-, 9-, 10- or 11-membered bicyclic aromatic or non-aromatic heterocyclyl containing at least one heteroatom each independently selected from O, S, S(=O)_p and N; said monocyclic heterocyclyl or said fused bicyclic heterocyclyl optionally being substituted with one or more C₁₋₄alkyl substituents;
- (x) R^{3a}, R^{3b} and R^{3c} each independently are selected from the group consisting of
- 35 hydrogen, halo, and -NR^{12a}R^{12b};
- (xi) R^{12a} and R^{12b} each independently are selected from the group consisting of

hydrogen; C₃₋₆cycloalkyl; C₁₋₄alkyl; and C₁₋₄alkyl substituted with one phenyl which is optionally substituted with one or more halo substituents;

(xii) R^{4a}, R^{4b} and R^{4c} each independently are selected from the group consisting of hydrogen and C₁₋₄alkyl;

5 (xiii) Q¹ represents CR^{14a};

(xiv) Q² represents N or CR^{14b};

(xv) Q³ represents CR^{14c};

(xvi) Q⁴ represents N;

10 (xvii) R^{14a}, R^{14b}, R^{14c}, R^{14e} and R^{14f} each independently are selected from the group consisting of hydrogen and halogen.

In an embodiment, the present invention concerns novel compounds of Formula (I), wherein

R¹ represents hydrogen; R² represents hydrogen;

15 R^a represents hydrogen or -C(=O)-C₁₋₄alkyl;

R^b represents hydrogen or -C(=O)-C₁₋₄alkyl;

Y represents -O- or -CH₂-;

R^{7a} represents hydrogen;

R^{7b} represents hydrogen;

20 X¹ represents a covalent bond or -O-;

X² represents a covalent bond or -CH₂-;

X³ represents N; or in case one of the dotted lines represents an additional bond, X³ represents C;

25 R⁸ and R¹⁰ each independently are selected from the group consisting of hydrogen and halo;

R⁹ and R¹¹ each independently are selected from the group consisting of hydrogen and halo;

30 or R⁸ and R⁹ are linked together to form together with the common carbon atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing one N-atom; wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one ring N-atom with C₁₋₆alkyl;

35 or R¹⁰ and R¹¹ are linked together to form together with the common carbon atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing one N-atom; wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one ring N-atom with C₁₋₆alkyl;

provided that R¹⁰ and R¹¹, or R⁸ and R⁹ are linked together;

Z represents $-\text{CH}_2-$; and in case X^3 represents C, Z can also represent $=\text{CH}-$; the dotted lines attached to X^3 are optional bonds that may be present when X^3 represents a carbon atom, provided that maximum one of the dotted lines represents an optional bond;

- 5 in case one of the dotted lines attached to X^3 represents an additional bond, X^3 represents C, and (i) R^{7a} is absent or (ii) R^8 is absent or (iii) Z represents $=\text{CH}-$;

Het represents a bicyclic aromatic heterocyclic ring system selected from the group consisting of (a-1) and (a-2);

R^{3a} and R^{3c} represent NH_2 ;

- 10 R^{4a} and R^{4c} represent hydrogen;

Q^1 represents CR^{14a} ;

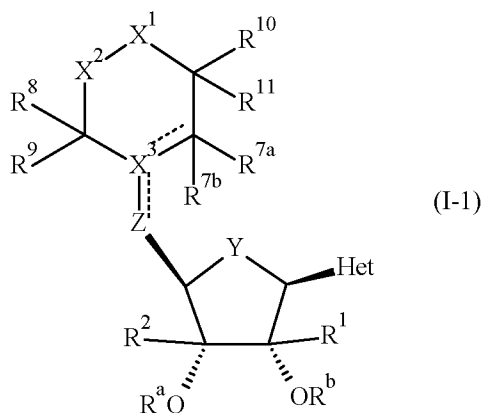
Q^2 represents CR^{14b} ;

R^{14a} , R^{14b} , R^{14e} and R^{14f} each independently are selected from the group consisting of hydrogen and halogen;

- 15 and pharmaceutically acceptable addition salts, and solvates thereof.

In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein the compounds of

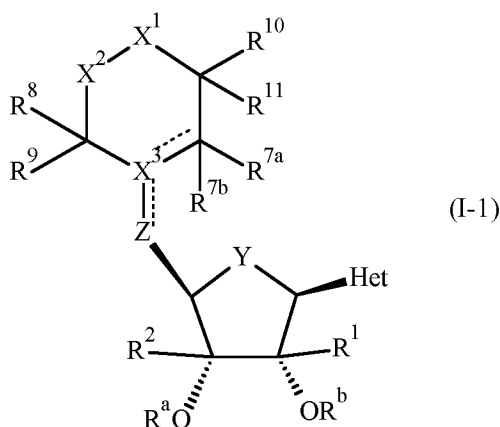
- 20 Formula (I) are restricted to the compounds of Formula (I-1):



wherein all variables are defined as for compounds of Formula (I) or any subgroup thereof as mentioned in any of the other embodiments.

- 25 In an embodiment, the present invention concerns novel compounds of Formula (I-1)

-34-



, wherein

- R^1 represents hydrogen; R^2 represents hydrogen;
 R^a represents hydrogen or $-C(=O)-C_{1-4}\text{alkyl}$;
 R^b represents hydrogen or $-C(=O)-C_{1-4}\text{alkyl}$;
 5 Y represents $-O-$ or $-CH_2-$;
 R^{7a} represents hydrogen;
 R^{7b} represents hydrogen;
 X^1 represents a covalent bond or $-O-$;
 X^2 represents a covalent bond or $-CH_2-$;
 10 X^3 represents N; or in case one of the dotted lines represents an additional bond, X^3 represents C;
 R^{10} represents hydrogen or halo;
 R^{11} represents hydrogen or halo;
 R^8 and R^9 are linked together to form together with the common carbon atom to which
 15 they are attached a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing one N-atom; wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one ring N-atom with $C_{1-6}\text{alkyl}$;
 Z represents $-CH_2-$; and in case X^3 represents C, Z can also represent $=CH-$;
 the dotted lines attached to X^3 are optional bonds that may be present when X^3
 20 represents a carbon atom, provided that maximum one of the dotted lines represents an optional bond;
 in case one of the dotted lines attached to X^3 represents an additional bond, X^3 represents C, and (i) R^{7a} is absent or (iii) Z represents $=CH-$;
 Het represents a bicyclic aromatic heterocyclic ring system selected from the group
 25 consisting of (a-1);
 R^{3a} represents NH_2 ; R^{4a} represents hydrogen;
 Q^1 represents CR^{14a} ; Q^2 represents CR^{14b} ;

R^{14a} and R^{14b} each independently are selected from the group consisting of hydrogen and halogen; in particular R^{14a} represents hydrogen; and pharmaceutically acceptable addition salts, and solvates thereof.

- 5 Another embodiment of the present invention relates to those compounds of Formula (I), and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein one or more of the following restrictions apply:
- (i) R¹ represents hydrogen;
- 10 (ii) Y represents -O- or -CH₂-;
- (iii) R^{7b} represents hydrogen;
- (iv) X² represents a covalent bond or -CH₂-;
- (v) X³ represents N; or in case one of the dotted lines represents an additional bond, X³ represents C;
- 15 (vi) R⁸ and R¹⁰ each independently are selected from the group consisting of hydrogen and halo;
- R⁹ and R¹¹ each independently are selected from the group consisting of hydrogen and halo;
- or R⁸ and R⁹ are linked together to form together with the common carbon atom to
- 20 which they are attached a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing one N-atom; wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one ring N-atom with C₁₋₆alkyl;
- or R¹⁰ and R¹¹ are linked together to form together with the common carbon atom to
- 25 which they are attached a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing one N-atom; wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one ring N-atom with C₁₋₆alkyl;
- (vii) Z represents -CH₂-; and in case X³ represents C, Z can also represent =CH-; the dotted lines attached to X³ are optional bonds that may be present when X³ represents a carbon atom, provided that maximum one of the dotted lines represents an
- 30 optional bond;
- in case one of the dotted lines attached to X³ represents an additional bond, X³ represents C, and (i) R^{7a} is absent or (ii) R⁸ is absent or (iii) Z represents =CH-;
- (viii) Het represents a bicyclic aromatic heterocyclic ring system selected from the group consisting of (a-1) and (a-2);
- 35 (ix) R^{3a} and R^{3c} represent NH₂;
- (x) R^{4a} and R^{4c} represent hydrogen;

(xi) Q^1 represents CR^{14a} ;

(xii) Q^2 represents CR^{14b} ;

(xiii) R^{14a} , R^{14b} , R^{14e} and R^{14f} each independently are selected from the group consisting of hydrogen and halogen.

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In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein

R^a and R^b represent hydrogen.

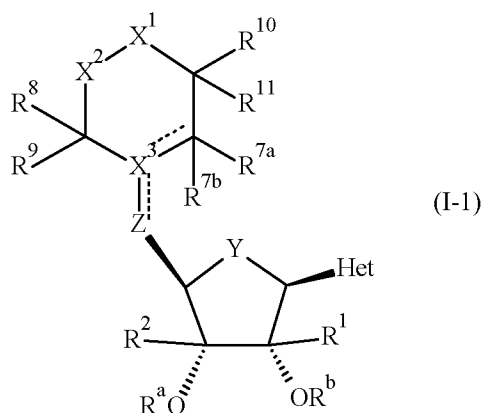
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In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein

R^a represents $-C(=O)-C_{1-4}alkyl$; R^b represents $-C(=O)-C_{1-4}alkyl$.

15

In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein the compounds of Formula (I) are restricted to the compounds of Formula (I-1)



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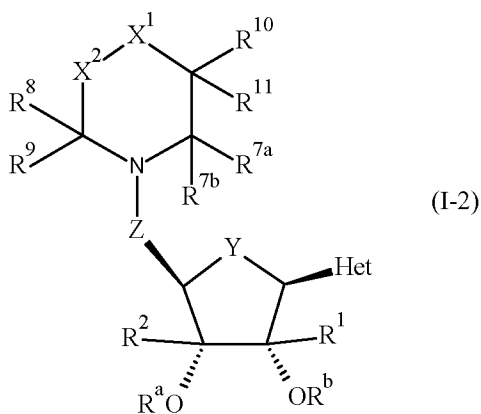
, wherein R^8 and R^9 are always linked together.

In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein the compounds of

25

Formula (I) are restricted to the compounds of Formula (I-1), wherein Het represents a bicyclic aromatic heterocyclic ring system selected from the group consisting of (a-1), and wherein R^8 and R^9 are always linked together.

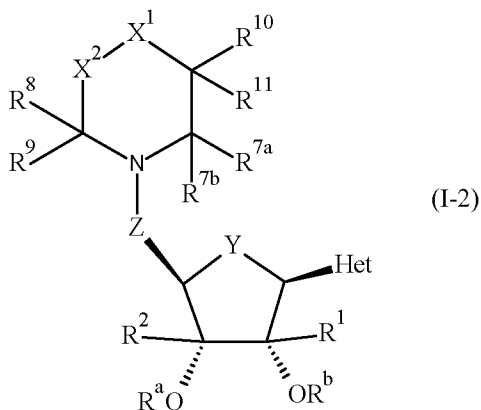
In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein the compounds of Formula (I) are restricted to the compounds of Formula (I-2):



5

wherein all variables are defined as for compounds of Formula (I) or any subgroup thereof as mentioned in any of the other embodiments.

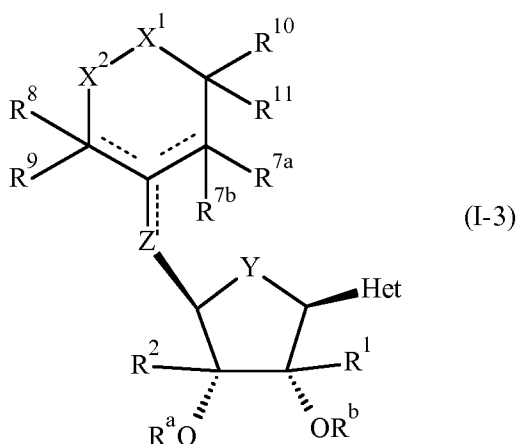
10 In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein the compounds of Formula (I) are restricted to the compounds of Formula (I-2)



, wherein R⁸ and R⁹ are always linked together.

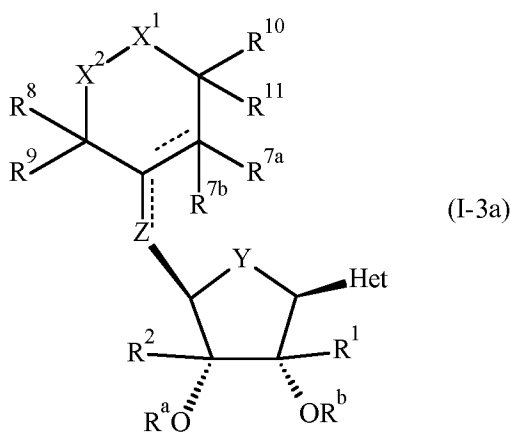
15 In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R⁸ and R⁹ are always linked together.

In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein the compounds of Formula (I) are restricted to the compounds of Formula (I-3)



5 wherein all variables are defined as for compounds of Formula (I) or any subgroup thereof as mentioned in any of the other embodiments.

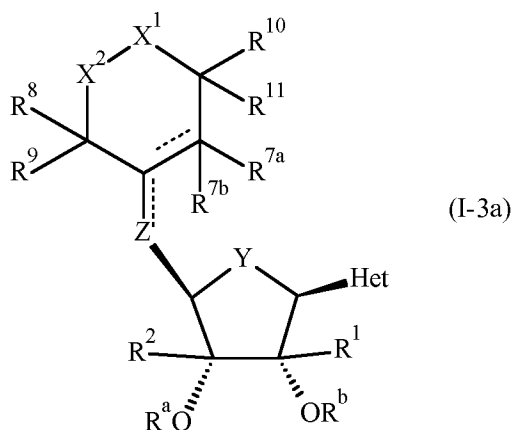
In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein the compounds of Formula (I) are restricted to the compounds of Formula (I-3a)



wherein all variables are defined as for compounds of Formula (I) or any subgroup thereof as mentioned in any of the other
15 embodiments.

In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup

thereof as mentioned in any of the other embodiments, wherein the compounds of Formula (I) are restricted to the compounds of Formula (I-3a)

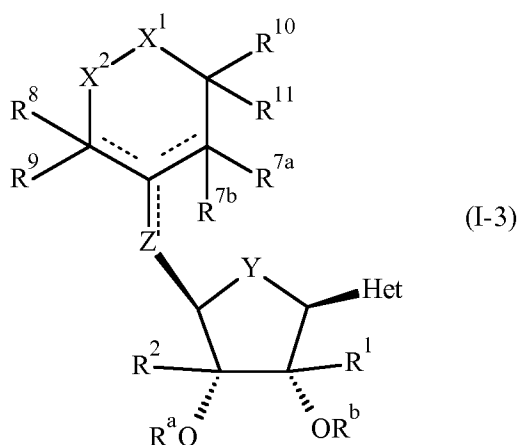


, wherein R⁸ and R⁹ are always linked

together.

5

In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein the compounds of Formula (I) are restricted to the compounds of Formula (I-3)



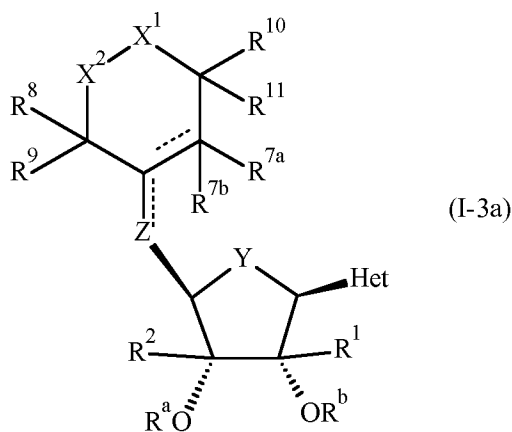
10

, and wherein at least one of the dotted lines

represents an additional bond.

15

In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein the compounds of Formula (I) are restricted to the compounds of Formula (I-3a)



, wherein R⁸ and R⁹ are always linked together, and wherein at least one of the dotted lines represents an additional bond.

5 All variables in the structures of Formula (I-1), (I-2), (I-3) or (I-3a), may be defined as defined for the compounds of Formula (I) or any subgroup thereof as mentioned in any of the other embodiments.

10 In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein at least one of the dotted lines, where possible, represent an additional bond.

15 In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein X³ represents N.

In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein X³ represents C or CH.

20 In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R¹⁰ and R¹¹, or R⁸ and R⁹ are linked together.

25 In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het represents a bicyclic aromatic heterocyclic ring system selected from the group consisting of (a-1),

and wherein R⁸ and R⁹ are always linked together.

In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het represents a bicyclic aromatic heterocyclic ring system selected from the group consisting of (a-1), and wherein R¹⁰ and R¹¹, or R⁸ and R⁹ are linked together.

In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R⁸ and R¹⁰ each independently are selected from the group consisting of hydrogen; halo; and C₁₋₆alkyl optionally substituted with one or more halo atoms; R⁹ and R¹¹ each independently are selected from the group consisting of hydrogen; halo; -NH₂; and C₁₋₆alkyl optionally substituted with one -NR^{9a}R^{9b}; or R⁸ and R⁹ are linked together to form together with the common carbon atom to which they are attached a 5-, 6- or 7-membered saturated heterocyclyl, containing one or two N-atoms and optionally one oxygen atom; wherein said 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or more ring carbon atoms with one or more substituents each independently selected from the group consisting of halo, and C₁₋₆alkyl optionally substituted with one or more halo atoms; and wherein said 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or two ring N-atoms with a substituent selected from the group consisting of C₁₋₆alkyl; Het^{1a}; C₃₋₆cycloalkyl; -C₁₋₄alkyl-C(=O)-NR^{5a}R^{5b}; C₁₋₄alkyl substituted with one or more halo atoms; and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OC₁₋₄alkyl, cyano, C₃₋₆cycloalkyl, Ar^{1a}, -O-Ar^{1a}, Het^{2a} and -O-Het^{2c}; or R¹⁰ and R¹¹ are linked together to form together with the common carbon atom to which they are attached a 5-, 6- or 7-membered saturated heterocyclyl, containing one or two N-atoms and optionally one oxygen atom; wherein said 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or more ring carbon atoms with one or more substituents each independently selected from the group consisting of halo, and C₁₋₆alkyl optionally substituted with one or more halo atoms; and wherein said 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or two ring N-atoms with a substituent selected from the group consisting of C₁₋₆alkyl; Het^{1b}; C₃₋₆cycloalkyl; -C₁₋₄alkyl-C(=O)-NR^{6a}R^{6b}; C₁₋₄alkyl substituted with one or more halo atoms; and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OC₁₋₄alkyl, cyano, C₃₋₆cycloalkyl, Ar^{1b}, -O-Ar^{1b}, Het^{2b} and -O-Het^{2d}.

In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein

- 5 X^2 is other than a covalent bond;
 R^8 and R^{10} each independently are selected from the group consisting of hydrogen; halo; and C_{1-6} alkyl optionally substituted with one or more halo atoms;
 R^9 and R^{11} each independently are selected from the group consisting of hydrogen; halo; $-NH_2$; and C_{1-6} alkyl optionally substituted with one $-NR^{9a}R^{9b}$;
- 10 or R^8 and R^9 are linked together to form together with the common carbon atom to which they are attached a 5-, 6- or 7-membered saturated heterocyclyl, containing one or two N-atoms and optionally one oxygen atom; wherein said 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or more ring carbon atoms with one or more substituents each independently selected from the group consisting of halo,
- 15 and C_{1-6} alkyl optionally substituted with one or more halo atoms; and wherein said 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or two ring N-atoms with a substituent selected from the group consisting of C_{1-6} alkyl; Het^{1a}; C_{3-6} cycloalkyl; $-C_{1-4}$ alkyl-C(=O)- $NR^{5a}R^{5b}$; C_{1-4} alkyl substituted with one or more halo atoms; and C_{1-4} alkyl substituted with one substituent selected from the group consisting
- 20 of $-OC_{1-4}$ alkyl, cyano, C_{3-6} cycloalkyl, Ar^{1a}, $-O-Ar^{1a}$, Het^{2a} and $-O-Het^{2c}$;
- or R^{10} and R^{11} are linked together to form together with the common carbon atom to which they are attached a 5-, 6- or 7-membered saturated heterocyclyl, containing one or two N-atoms and optionally one oxygen atom; wherein said 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or more ring carbon atoms with
- 25 one or more substituents each independently selected from the group consisting of halo, and C_{1-6} alkyl optionally substituted with one or more halo atoms; and wherein said 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or two ring N-atoms with a substituent selected from the group consisting of C_{1-6} alkyl; Het^{1b}; C_{3-6} cycloalkyl; $-C_{1-4}$ alkyl-C(=O)- $NR^{6a}R^{6b}$; C_{1-4} alkyl substituted with one or more halo
- 30 atoms; and C_{1-4} alkyl substituted with one substituent selected from the group consisting of $-OC_{1-4}$ alkyl, cyano, C_{3-6} cycloalkyl, Ar^{1b}, $-O-Ar^{1b}$, Het^{2b} and $-O-Het^{2d}$.

- In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
- 35 X^1 is a covalent bond;

- X² is other than a covalent bond;
 R⁸ and R¹⁰ each independently are selected from the group consisting of hydrogen;
 halo; and C₁₋₆alkyl optionally substituted with one or more halo atoms;
 R⁹ and R¹¹ each independently are selected from the group consisting of hydrogen;
 5 halo; -NH₂; and C₁₋₆alkyl optionally substituted with one -NR^{9a}R^{9b};
 or R⁸ and R⁹ are linked together to form together with the common carbon atom to
 which they are attached a 5-, 6- or 7-membered saturated heterocyclyl, containing one
 or two N-atoms and optionally one oxygen atom; wherein said 5-, 6- or 7-membered
 saturated heterocyclyl is optionally substituted on one or more ring carbon atoms with
 10 one or more substituents each independently selected from the group consisting of halo,
 and C₁₋₆alkyl optionally substituted with one or more halo atoms; and wherein said 5-,
 6- or 7-membered saturated heterocyclyl is optionally substituted on one or two ring N-
 atoms with a substituent selected from the group consisting of C₁₋₆alkyl; Het^{1a}; C₃₋₆
 cycloalkyl; -C₁₋₄alkyl-C(=O)-NR^{5a}R^{5b}; C₁₋₄alkyl substituted with one or more halo
 15 atoms; and C₁₋₄alkyl substituted with one substituent selected from the group consisting
 of -OC₁₋₄alkyl, cyano, C₃₋₆cycloalkyl, Ar^{1a}, -O-Ar^{1a}, Het^{2a} and -O-Het^{2c};
 or R¹⁰ and R¹¹ are linked together to form together with the common carbon atom to
 which they are attached a 5-, 6- or 7-membered saturated heterocyclyl, containing one
 or two N-atoms and optionally one oxygen atom; wherein said 5-, 6- or 7-membered
 20 saturated heterocyclyl is optionally substituted on one or more ring carbon atoms with
 one or more substituents each independently selected from the group consisting of halo,
 and C₁₋₆alkyl optionally substituted with one or more halo atoms; and wherein said 5-,
 6- or 7-membered saturated heterocyclyl is optionally substituted on one or two ring N-
 atoms with a substituent selected from the group consisting of C₁₋₆alkyl; Het^{1b}; C₃₋₆
 25 cycloalkyl; -C₁₋₄alkyl-C(=O)-NR^{6a}R^{6b}; C₁₋₄alkyl substituted with one or more halo
 atoms; and C₁₋₄alkyl substituted with one substituent selected from the group consisting
 of -OC₁₋₄alkyl, cyano, C₃₋₆cycloalkyl, Ar^{1b}, -O-Ar^{1b}, Het^{2b} and -O-Het^{2d}.

- In an embodiment, the present invention relates to those compounds of Formula (I) and
 30 pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup
 thereof as mentioned in any of the other embodiments, wherein

- X¹ is a covalent bond;
 X² is other than a covalent bond;
 R⁸ and R¹⁰ each independently are selected from the group consisting of hydrogen;
 35 halo; and C₁₋₆alkyl optionally substituted with one or more halo atoms;
 R⁹ and R¹¹ each independently are selected from the group consisting of hydrogen;
 halo; -NH₂; and C₁₋₆alkyl optionally substituted with one -NR^{9a}R^{9b};

or R⁸ and R⁹ are linked together to form together with the common carbon atom to which they are attached a 5-, 6- or 7-membered saturated heterocyclyl, containing one or two N-atoms and optionally one oxygen atom; wherein said 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or more ring carbon atoms with one or more substituents each independently selected from the group consisting of halo, and C₁₋₆alkyl optionally substituted with one or more halo atoms; and wherein said 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or two ring N-atoms with a substituent selected from the group consisting of C₁₋₆alkyl; Het^{1a}; C₃₋₆cycloalkyl; -C₁₋₄alkyl-C(=O)-NR^{5a}R^{5b}; C₁₋₄alkyl substituted with one or more halo atoms; and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OC₁₋₄alkyl, cyano, C₃₋₆cycloalkyl, Ar^{1a}, -O-Ar^{1a}, Het^{2a} and -O-Het^{2c};

or R¹⁰ and R¹¹ are linked together to form together with the common carbon atom to which they are attached a 5-, 6- or 7-membered saturated heterocyclyl, containing one or two N-atoms and optionally one oxygen atom; wherein said 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or more ring carbon atoms with one or more substituents each independently selected from the group consisting of halo, and C₁₋₆alkyl optionally substituted with one or more halo atoms; and wherein said 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or two ring N-atoms with a substituent selected from the group consisting of C₁₋₆alkyl; Het^{1b}; C₃₋₆cycloalkyl; -C₁₋₄alkyl-C(=O)-NR^{6a}R^{6b}; C₁₋₄alkyl substituted with one or more halo atoms; and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OC₁₋₄alkyl, cyano, C₃₋₆cycloalkyl, Ar^{1b}, -O-Ar^{1b}, Het^{2b} and -O-Het^{2d};

Het represents (a-1).

In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein

X¹ is a covalent bond;

X² is other than a covalent bond;

R⁸ and R⁹ are linked together to form together with the common carbon atom to which they are attached a 5-, 6- or 7-membered saturated heterocyclyl, containing one or two N-atoms and optionally one oxygen atom; wherein said 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or more ring carbon atoms with one or more substituents each independently selected from the group consisting of halo, and C₁₋₆alkyl optionally substituted with one or more halo atoms; and wherein said 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or two ring N-atoms with a substituent selected from the group consisting of C₁₋₆alkyl; Het^{1a}; C₃₋

cycloalkyl; -C₁₋₄alkyl-C(=O)-NR^{5a}R^{5b}; C₁₋₄alkyl substituted with one or more halo atoms; and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OC₁₋₄alkyl, cyano, C₃₋₆cycloalkyl, Ar^{1a}, -O-Ar^{1a}, Het^{2a} and -O-Het^{2c};

R¹⁰ is selected from the group consisting of hydrogen; halo; and C₁₋₆alkyl optionally

5 substituted with one or more halo atoms;

R¹¹ is selected from the group consisting of hydrogen; halo; -NH₂; and C₁₋₆alkyl optionally substituted with one -NR^{9a}R^{9b};

Het represents (a-1).

10 In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein X¹ represents a covalent bond.

15 In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein all 4-, 5-, 6- or 7-membered saturated heterocyclyls are restricted to 5-, 6- or 7-membered saturated heterocyclyls, each of which may be optionally substituted according to any of the
20 other embodiments; X¹ represents a covalent bond; and Het represents (a-1).

In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Y represents -CH₂- or
25 -CF₂-; in particular wherein Y represents -CH₂-.

In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein maximum one of Q¹
30 and Q² represents N.

In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Q¹ represents CR^{14a};
35 and Q² represents CR^{14b}; in particular wherein Q¹ represents CH; and Q² represents CH.

In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het represents (a-1); Q¹ represents CR^{14a}, and Q² represents CR^{14b}; in particular wherein Q¹ represents CH; and
5 Q² represents CH.

In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
10 R¹ and R² represent hydrogen; and Y represents –O–.

In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
15 R^a and R^b represent hydrogen; and Y represents –O–.

In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
20 R^a and R^b represent hydrogen; R¹ and R² represent hydrogen; and Y represents –O–.

In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het represents a
25 bicyclic aromatic heterocyclic ring system selected from the group consisting of (a-1) and (a-2).

In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup
30 thereof as mentioned in any of the other embodiments, wherein Het represents a bicyclic aromatic heterocyclic ring system of Formula (a-1).

In an embodiment, the present invention relates to any one of the compounds of Formula (I-1), (I-2), (I-3) or (I-3a), wherein Het represents a bicyclic aromatic
35 heterocyclic ring system selected from the group consisting of (a-1) and (a-2), in particular wherein Het represents a bicyclic aromatic heterocyclic ring system of Formula (a-1).

In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein

- 5 Het represents a bicyclic aromatic heterocyclic ring system selected from the group consisting of (a-1), (a-2), (a-3) and (a-4);
 R^{3a} , R^{3b} , R^{3c} and R^{3d} each independently are selected from the group consisting of hydrogen, halo, and $-NR^{12a}R^{12b}$;
 R^{12a} and R^{12b} each independently are selected from the group consisting of hydrogen;
- 10 C_{3-6} cycloalkyl; C_{1-4} alkyl; and C_{1-4} alkyl substituted with one phenyl which is optionally substituted with one or more halo substituents;
 R^{4a} , R^{4b} , R^{4c} and R^{4d} each independently are selected from the group consisting of hydrogen and C_{1-4} alkyl;
 R^{4f} represent hydrogen;
- 15 Q^1 represents CR^{14a} ;
 Q^2 represents N or CR^{14b} ;
 Q^3 represents CR^{14c} ;
 Q^4 represents N;
 Q^8 represents CR^{14g} ;
- 20 Q^9 represents CR^{14h} ;
 Q^5 represents CR^{3d} , Q^6 represents N; and Q^7 represents CR^{4f} ;
 R^{14a} , R^{14b} , R^{14c} , R^{14e} and R^{14f} each independently are selected from the group consisting of hydrogen and halogen;
 R^{14g} and R^{14h} represent hydrogen.

25

In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
 R^1 and R^2 represent hydrogen.

30

In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein

- 35 R^1 and R^2 represent hydrogen; Y represents $-O-$; and Het represents a bicyclic aromatic heterocyclic ring system of Formula (a-1).

In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^a and R^b represent hydrogen; Y represents –O–; and Het represents a bicyclic aromatic
5 heterocyclic ring system of Formula (a-1).

In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
10 R^a and R^b represent hydrogen; R¹ and R² represent hydrogen; Y represents –O–; and Het represents a bicyclic aromatic heterocyclic ring system of Formula (a-1).

In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup
15 thereof as mentioned in any of the other embodiments, wherein
R^{3a}, R^{3c}, R^{3b} represent hydrogen; and
R^{4a}, R^{4c}, R^{4b} represent hydrogen, halo, or C₁₋₄alkyl; in particular R^{4a}, R^{4c}, R^{4b} represent halo, or C₁₋₄alkyl.

20 In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^{3a}, R^{3c}, R^{3b} represent hydrogen, halo, –NR^{12a}R^{12b}, or –O-C₁₋₄alkyl; in particular R^{3a},
R^{3c}, R^{3b} represent halo, –NR^{12a}R^{12b}, or –O-C₁₋₄alkyl;
25 R^{4a}, R^{4c}, R^{4b} represent hydrogen.

In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
30 R^{3a}, R^{3c}, R^{3b} represent hydrogen, when R^{4a}, R^{4c}, R^{4b} are different from hydrogen.

In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
35 R^{4a}, R^{4c}, R^{4b} represent hydrogen, when R^{3a}, R^{3c}, R^{3b} are different from hydrogen.

In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R^{7a} and R^{7b} represent hydrogen.

5

In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het represents (a-1); R^{3a} represents $-NR^{12a}R^{12b}$; and R^{12a} and R^{12b} represent hydrogen.

10

In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R^{3a} , R^{3b} and R^{3c} represent other than halo.

15 In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R^{3a} , R^{3b} and R^{3c} represent $-NH_2$.

20 In an embodiment, the present invention relates to those compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^{2a} , Het^{2b} , Het^{2c} and Het^{2d} are aromatic.

25 In an embodiment, the present invention relates to a subgroup of Formula (I) as defined in the general reaction schemes.

In an embodiment the compound of Formula (I) is selected from the group consisting of compounds 19, 29, 74, 94, 95a, 95b, 101, 107, 108, 166, 167, 178, 179, 181, 206 and 207.

30 In an embodiment the compound of Formula (I) is selected from the group consisting of compounds 19, 29, 74, 94, 95a, 95b, 101, 107, 108, 166, 167, 178, 179, 181, 206 and 207, and pharmaceutically acceptable addition salts, the free bases, and solvates thereof.

In an embodiment the compound of Formula (I) is selected from the group consisting of any of the exemplified compounds,

35

and the free bases, the pharmaceutically acceptable addition salts, and the solvates thereof.

All possible combinations of the above-indicated embodiments are considered to be embraced within the scope of this invention.

5

Methods for the Preparation

In this section, as in all other sections unless the context indicates otherwise, references to formula (I) also include all other sub-groups and examples thereof as defined herein.

10 The general preparation of some typical examples of the compounds of Formula (I) is described hereunder and in the specific examples, and are generally prepared from starting materials which are either commercially available or prepared by standard synthetic processes commonly used by those skilled in the art. The following schemes are only meant to represent examples of the invention and are in no way meant to be a limit of the invention.

15 Alternatively, compounds of the present invention may also be prepared by analogous reaction protocols as described in the general schemes below, combined with standard synthetic processes commonly used by those skilled in the art of organic chemistry.

20 The skilled person will realize that in the reactions described in the Schemes, it may be necessary to protect reactive functional groups, for example hydroxy, amino, or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups can be used in accordance with standard practice. This is illustrated in the specific examples.

25 The skilled person will realize that in the reactions described in the Schemes, it may be advisable or necessary to perform the reaction under an inert atmosphere, such as for example under N₂-gas atmosphere, for example when NaH is used in the reaction.

It will be apparent for the skilled person that it may be necessary to cool the reaction mixture before reaction work-up (refers to the series of manipulations required to isolate and purify the product(s) of a chemical reaction such as for example quenching, column chromatography, extraction).

30 The skilled person will realize that heating the reaction mixture under stirring may enhance the reaction outcome. In some reactions microwave heating may be used instead of conventional heating to shorten the overall reaction time.

The skilled person will realize that another sequence of the chemical reactions shown in the Schemes below, may also result in the desired compound of formula (I).

The skilled person will realize that intermediates and final compounds shown in the schemes below may be further functionalized according to methods well-known by the person skilled in the art. For example, a primary or secondary amine group may be reductively alkylated by reaction with an aldehyde or a keton in the presence of a suitable
5 reducing reagent such as for example sodium triacetoxyborohydride ($\text{NaBH}(\text{AcO})_3$) together with a suitable solvent such as for example DCM at a suitable temperature such as for example room temperature; or alternatively in the presence of NaBH_3CN together with a suitable solvent such as for example MeOH at a suitable temperature such as for example between room temperature and 50°C .

10 The skilled person will understand that analogous chemistry as described in Schemes 1 to 6, may also be applied to make compounds of Formula (I) wherein Het represents a bicyclic aromatic heterocyclic ring system (a-4). Some typical examples are illustrated in the specific examples. In addition, this information may be combined with standard synthetic processes commonly used by those skilled in the art of organic chemistry to
15 obtain more compounds of Formula (I) wherein Het represents (a-4).

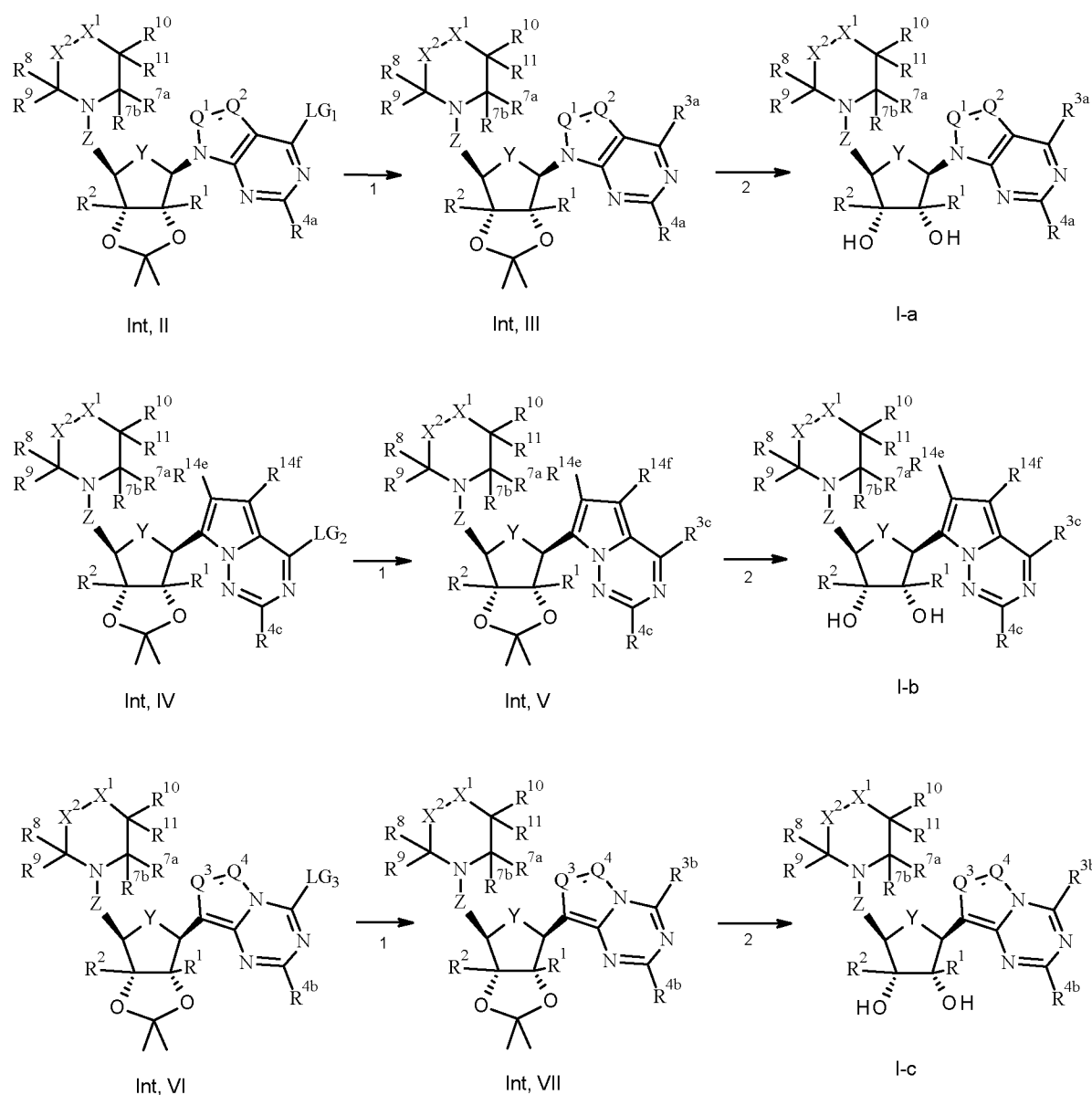
The skilled person will realize that more Compounds of formula (I) can be prepared by using similar synthetic protocols as described in the Schemes below.

In case one of the starting materials is available as a salt form, the skilled person will realize that it may be necessary to first treat the salt with a base, such as for example
20 N,N-diisopropylethylamine (DIPEA).

All variables are defined as mentioned hereabove unless otherwise is indicated or is clear from the context.

In general, compounds of formula (I) wherein X^3 represents N, wherein R^a and R^b are hydrogen, and wherein Het is as shown in the scheme below, can be prepared according
25 to Scheme 1:

Scheme 1:



In scheme 1, 'LG₁' is defined as a leaving group such as halogen; 'LG₂' is defined as leaving group such as halogen or -SCH₃; 'LG₃' is defined as leaving group such as halogen or -SCH₃. All other variables in Scheme 1 are defined according to the scope of the present invention.

In scheme 1, the following reaction conditions typically apply:

1: Different sets of reaction conditions dependent on the definition of R^{3a}, R^{3b} or R^{3c}:

1a: When R^{3a}, R^{3b} or R^{3c} is halogen, step 1 can be skipped.

1b: When R^{3a}, R^{3b} or R^{3c} is NR^{12a}R^{12b}, in the presence of a suitable amine of formula HNR^{12a}R^{12b}, with a suitable solvent such as for example, H₂O, methanol (MeOH), or

ethanol (EtOH), at a suitable temperature such as for example between 100-130 °C typically under microwave conditions or using an autoclave vessel for heating.

5 **1c:** When R^{3a}, R^{3b} or R^{3c} is -O-C₁₋₄alkyl, in the presence of a suitable HO-C₁₋₄alkyl, with a suitable base such as for example NaH, potassium tert-butoxide (tBuOK) in a suitable solvent such as for example tetrahydrofuran (THF) at a suitable temperature. Alternatively in the presence of the suitable HO-C₁₋₄alkyl as solvent with a suitable acid such as for example HCl.

10 **1d:** When R^{3a}, R^{3b} or R^{3c} is hydrogen, under hydrogenation conditions: H₂-gas atmosphere in the presence of a catalyst such as for example Raney Ni, Pd/C (for example 5 wt % or 10 wt %) or Pt/C (for example 5 wt %) in a suitable solvent such as for example methanol (MeOH), ethanol (EtOH) or THF.

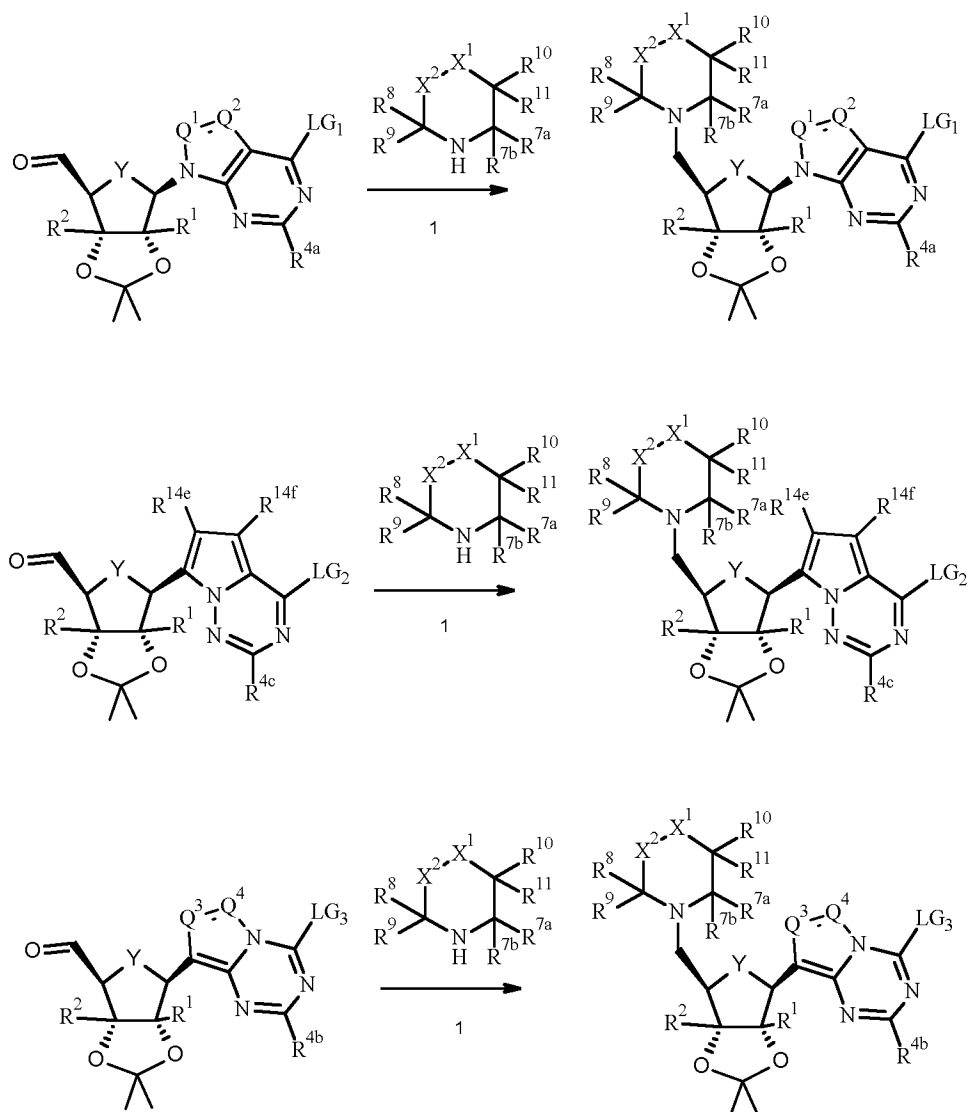
15 **1e:** When R^{3a}, R^{3b} or R^{3c} is C₁₋₄alkyl, in the presence of a suitable boronic acid or ester such as for example methylboronic acid, with a suitable catalyst such as for example 1,1'-bis(diphenylphosphino)ferrocene, and with with a suitable base such as for example K₃PO₄ in a in a suitable solvent or solvent mixture such as for example dioxane/H₂O typically in a 5 to 1 ratio at a suitable temperature such as for example between 80-100 °C.

20 **2:** in the presence of a suitable acid, such as for example 4M HCl in dioxane or 4M HCl in MeOH, with a suitable solvent such as for example MeOH at a suitable temperature such as for example room temperature; or alternatively in the presence of a suitable acid such as for example trifluoroacetic acid (TFA) in dichloromethane (DCM) at a suitable temperature, or acetic acid in THF and water at a suitable temperature such as for example room temperature.

25 The starting materials in scheme 1 are commercially available or can be prepared by standard means obvious to those skilled in the art or as described in following general schemes.

30 In general, intermediates of Formula II, IV and VI wherein Z represents -CH₂- can be prepared according to Scheme 2a. All other variables in Scheme 2a are defined according to the scope of the present invention.

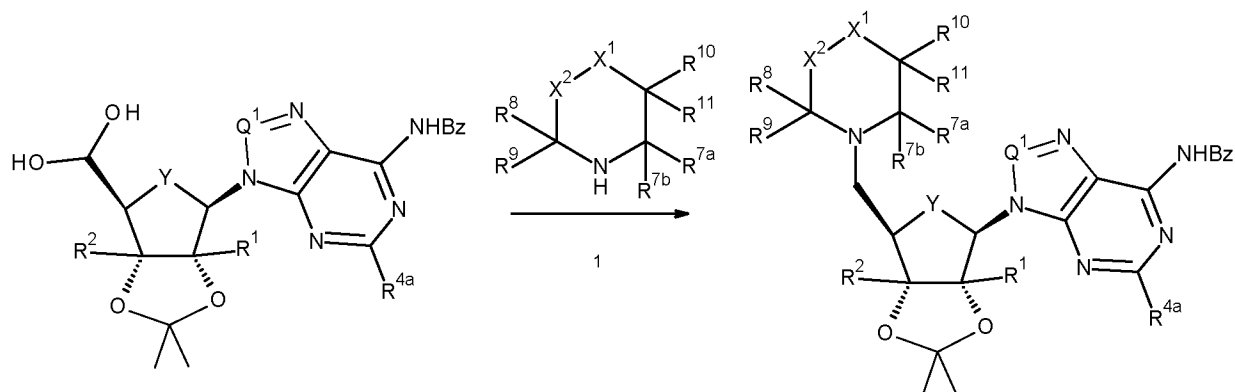
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In scheme 2a, the following reaction conditions apply:

- 1: in the presence of a suitable reduction reagent such as for example sodium triacetoxyborohydride ($\text{NaBH}(\text{AcO})_3$) together with a suitable solvent such as for example DCM at a suitable temperature such as for example room temperature; or alternatively NaBH_3CN together with a suitable solvent such as for example MeOH at a suitable temperature such as for example between room temperature and 50°C .

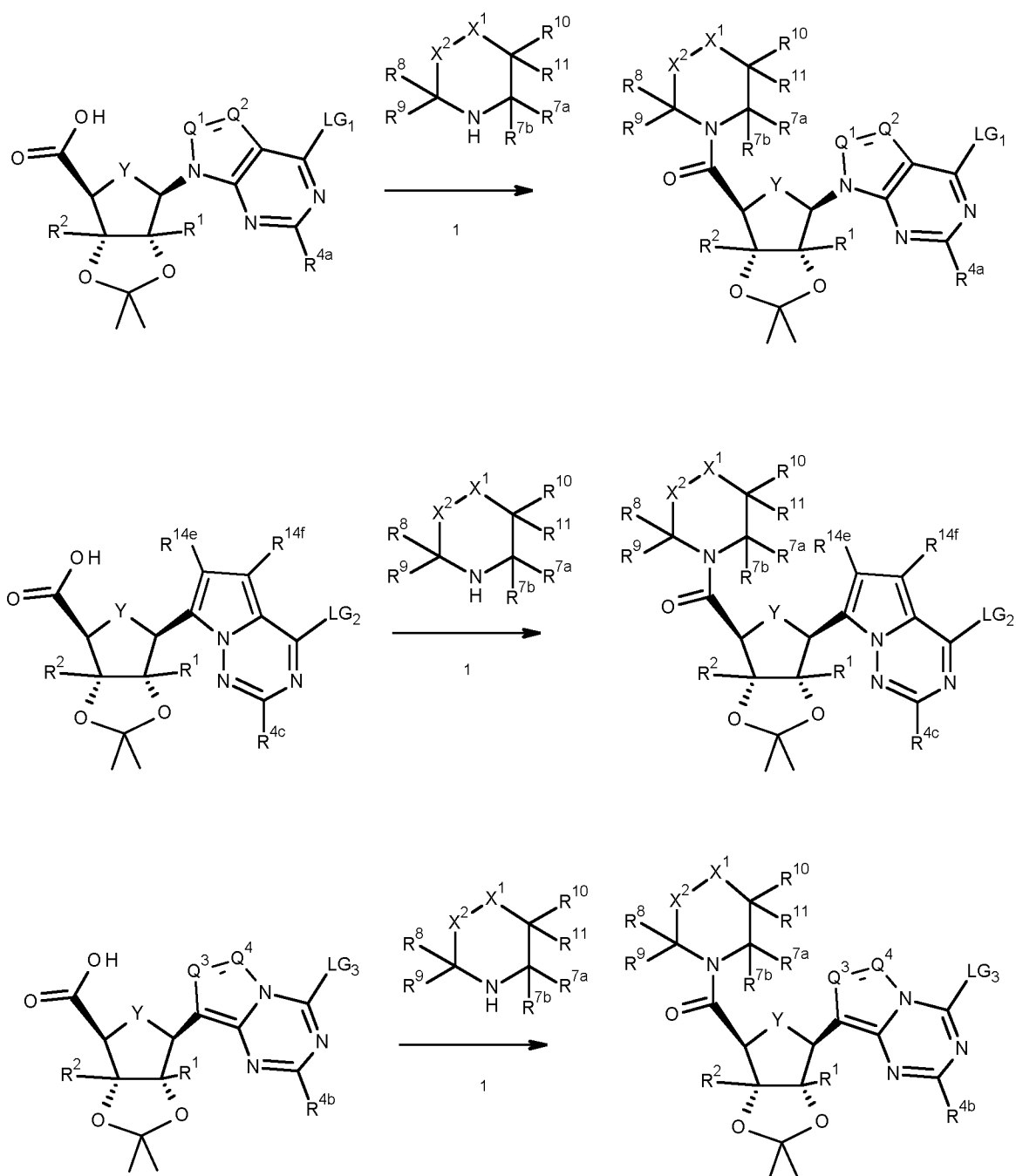
- Alternatively, intermediates of Formula II wherein Z represents $-\text{CH}_2-$, R^{3a} represents NHBz (Bz is benzoyl) and Het is as shown in the scheme below, can be prepared according to scheme 2b. All other variables in Scheme 2b are defined according to the scope of the present invention.



In scheme 2b, the following reaction conditions apply:

- 5 **1:** in the presence of a suitable reduction reagent such as for example sodium triacetoxyborohydride ($\text{NaBH}(\text{AcO})_3$) together with a suitable solvent such as for example DCM at a suitable temperature such as for example room temperature; or alternatively, NaBH_3CN together with a suitable solvent such as for example MeOH at a suitable temperature such as for example between room temperature and 50°C .
- 10 In general, intermediates of Formula II, IV and VI wherein Z represents $-\text{C}(=\text{O})-$ can be prepared according to scheme 3. All other variables in Scheme 3 are defined as before or according to the scope of the present invention.

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In scheme 3, the following reaction conditions apply:

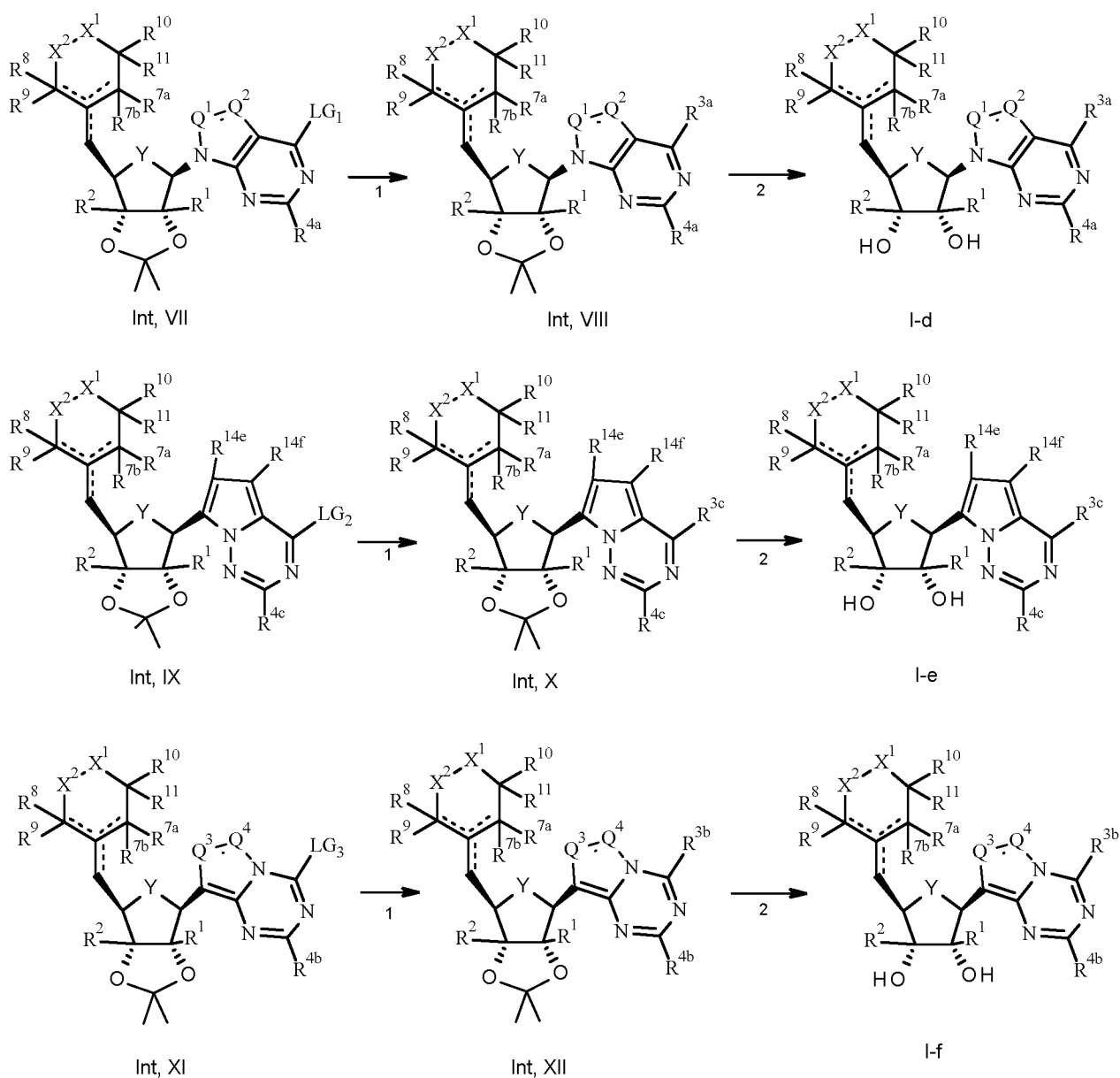
- 1: in the presence of a suitable coupling reagent such as for example 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) together with a suitable solvent such as for example DMF and a suitable base such as DIPEA at a suitable temperature such as for example room temperature.

In general, compounds of Formula (I) wherein X^3 represents C or CH; and Z represents =CH- or -CH₂- can be prepared according to Scheme 4.

The skilled person will realize that compounds wherein X^3 represents C or CH; and Z represents -C(=O)- or -CH(C₁₋₄alkyl)- can also be prepared by an analogous reaction

- 5 protocol as described in Scheme 4, starting from the corresponding starting materials which are commercially available, can be prepared by standard means obvious to those skilled in the art, or which may be prepared by an analogous reaction protocol as described in Scheme 5a (for Z represents -CH(C₁₋₄alkyl)-) or by the reaction protocol as described in Scheme 5b (for Z represents -C(=O)-).

10



In scheme 4, 'LG₁' is defined as a leaving group such as halogen; 'LG₂' is defined as leaving group such as halogen or -SCH₃; 'LG₃' is defined as leaving group such as halogen or -SCH₃. All other variables in Scheme 4 are defined according to the scope of the present invention.

5 In scheme 4, the following reaction conditions typically apply:

1: Different sets of reaction conditions dependent on the definition of R^{3a}, R^{3b} or R^{3c}:

1a: When R^{3a}, R^{3b} or R^{3c} is halogen, step 4 can be skipped.

1b: When R^{3a}, R^{3b} or R^{3c} is NR^{12a}R^{12b}, in the presence of a suitable amine of formula HNR^{12a}R^{12b}, with a suitable solvent such as for example, H₂O, methanol (MeOH), or
10 ethanol (EtOH), at a suitable temperature such as for example between 100-130 °C typically under microwave conditions or using an autoclave vessel for heating.

1c: When R^{3a}, R^{3b} or R^{3c} is -O-C₁₋₄alkyl, in the presence of a suitable HO-C₁₋₄alkyl, with a suitable base such as for example NaH, potassium tert-butoxide (tBuOK) in a suitable solvent such as for example tetrahydrofuran (THF) at a suitable temperature.
15 Alternatively in the presence of the suitable HO-C₁₋₄alkyl as solvent with a suitable acid such as for example HCl.

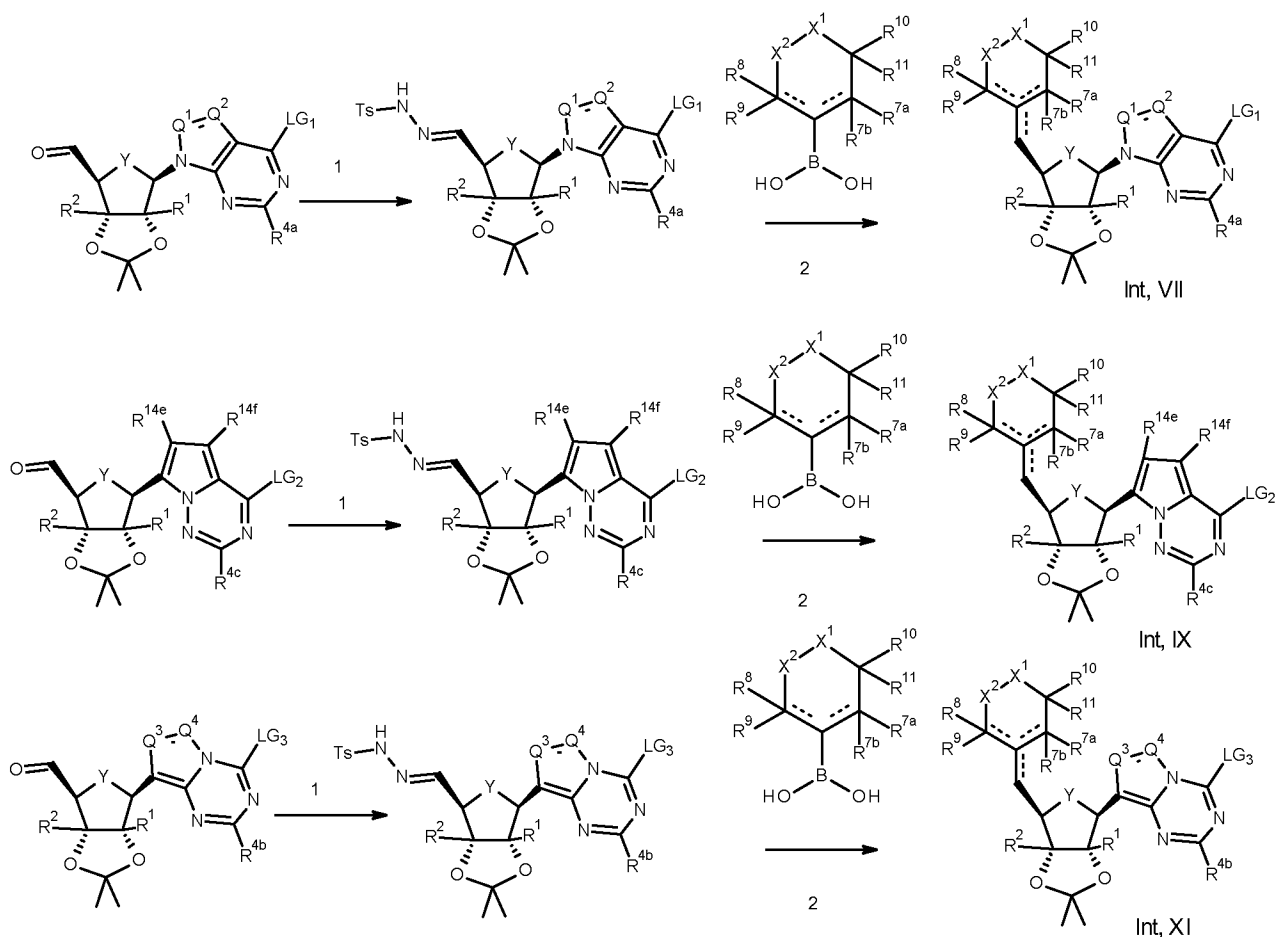
1d: When R^{3a}, R^{3b} or R^{3c} is hydrogen, under hydrogenation conditions: H₂-gas atmosphere in the presence of a catalyst such as for example Raney Ni, Pd/C (for example 5 wt % or 10 wt %) or Pt/C (for example 5 wt %) in a suitable solvent such as for example
20 methanol (MeOH), ethanol (EtOH) or THF.

1e: When R^{3a}, R^{3b} or R^{3c} is C₁₋₄alkyl, in the presence of a suitable boronic acid or ester such as for example methylboronic acid, with a suitable catalyst such as for example 1,1'-bis(diphenylphosphino)ferrocene, and with with a suitable base such as for example K₃PO₄ in a in a suitable solvent or solvent mixture such as for example dioxane/H₂O
25 typically in a 5 to 1 ratio at a suitable temperature such as for example between 80-100 °C.

2: in the presence of a suitable acid, such as for example 4M HCl in dioxane or 4M HCl in MeOH, with a suitable solvent such as for example MeOH at a suitable temperature such as for example room temperature; or alternatively in the presence of a suitable acid
30 such as for example trifluoroacetic acid (TFA) in dichloromethane (DCM) at a suitable temperature, or acetic acid in THF and water at a suitable temperature such as for example room temperature.

The starting materials in scheme 4 are commercially available or can be prepared by standard means obvious to those skilled in the art or as described in following general

scheme 5a. The skilled person will realize that an analogous reaction protocol can be used to prepare the corresponding intermediates wherein Z represents $-\text{CH}(\text{C}_{1-4}\text{alkyl})-$.



In scheme 5a the following reaction conditions apply:

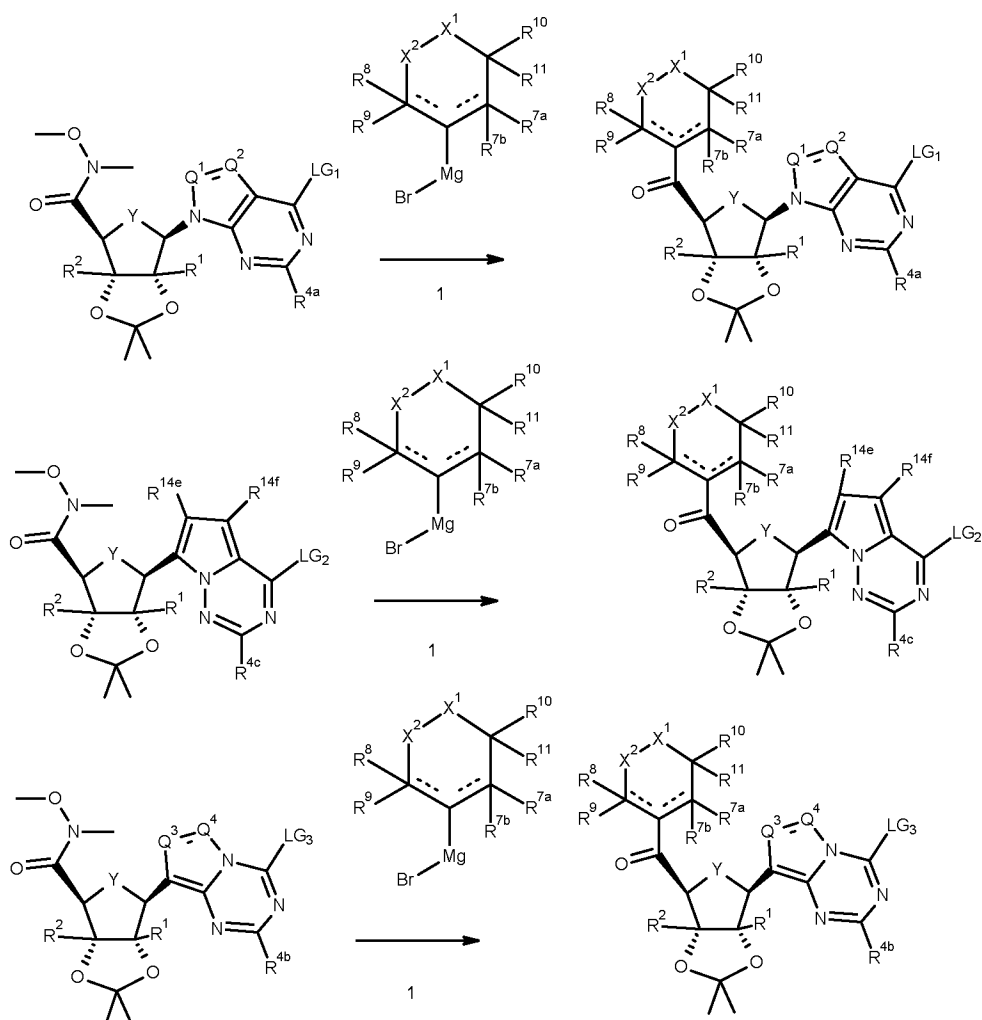
5 **1:** in the presence of *p*-toluenesulfone hydrazide together with a suitable solvent such as MeOH at a suitable temperature such as for example room temperature.

2: in the presence of a suitable boronic acid together with a suitable solvent such as 1,4 dioxane and a suitable base such as K_2CO_3 at a suitable temperature such as for example 110°C .

10

In general, intermediates of Formula VII-a, IX-a and XI-a, wherein X^3 represents C or CH; and Z represents $-\text{C}(=\text{O})-$ can be prepared according to Scheme 5b wherein the other variables are defined as before or according to the scope. The skilled person will realize that the intermediates of Formula VII-a, IX-a and XI-a can be further reacted in an analogous reaction protocol as described in Scheme 4 to obtain the corresponding final compounds.

15



In scheme 5b, the following reaction conditions apply:

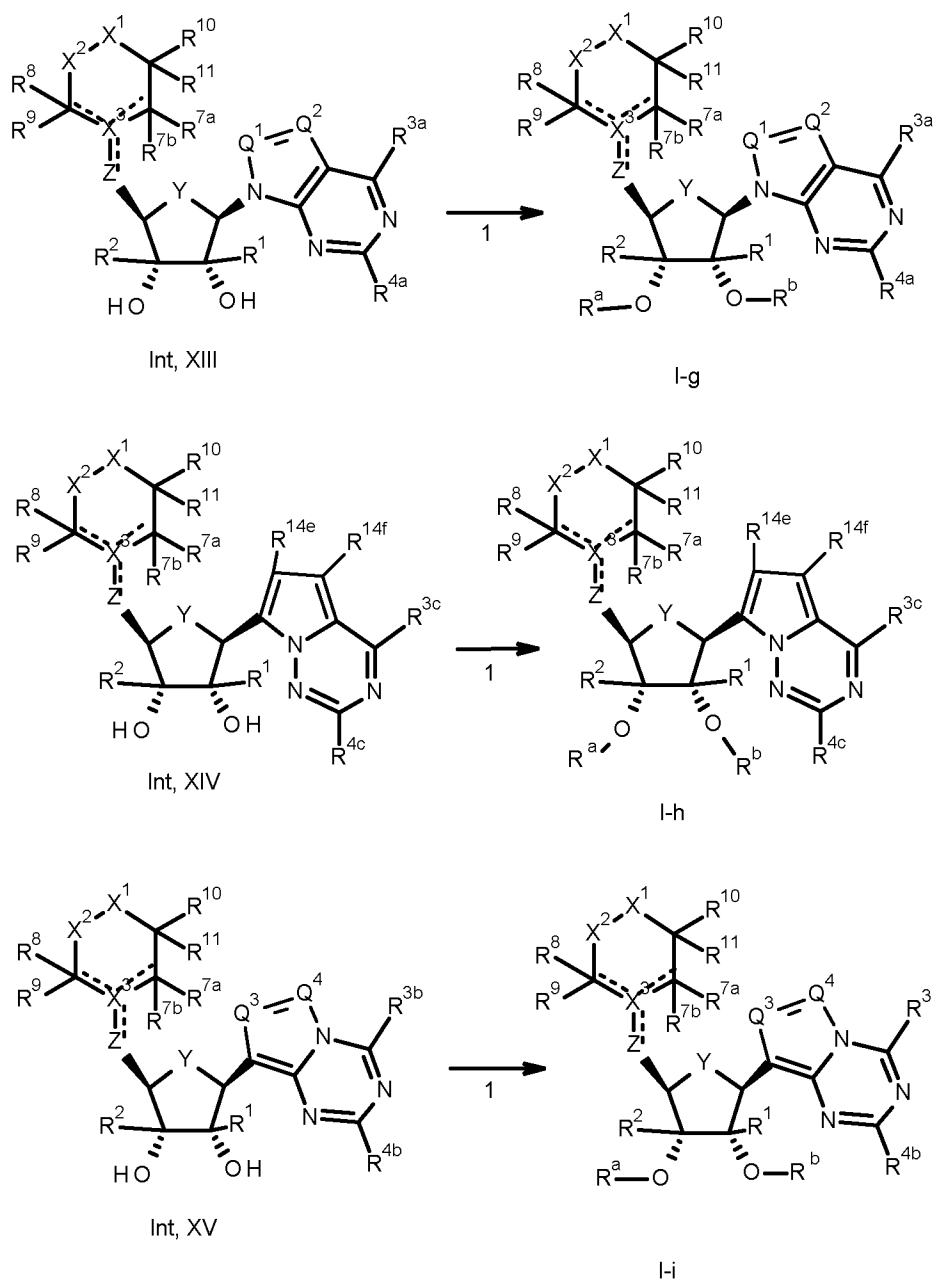
1: in the presence of a suitable solvent such as for example THF and a suitable temperature such as for example -40°C.

5

In general, compounds of formula (I) wherein R^a and/or R^b represents -C(=O)-C₁₋₄alkyl and R^{3a}, R^{3b} and R^{3c} each independently represent hydrogen, halo NR^{12a}R^{12b}, C₁₋₄alkyl, or -O-C₁₋₄alkyl can be prepared according to Scheme 6. All other variables in Scheme 6 are defined according to the scope of the present invention.

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In scheme 6, following reaction conditions apply

- 1a. When R^{3a} , R^{3b} or R^{3c} represents hydrogen, halo, C_{1-4} alkyl, $-O-C_{1-4}$ alkyl, or $NR^{12a}R^{12b}$ with R^{12a} and R^{12b} both being C_{3-6} cycloalkyl or optionally substituted C_{1-4} alkyl: in the presence of a suitable anhydride such as isobutyric anhydride or acetic anhydride in a suitable solvent such as pyridine at a suitable temperature such as for example 50°C .
- 5 1b. When R^{3a} , R^{3b} or R^{3c} represents $NR^{12a}R^{12b}$ with R^{12a} or R^{12b} is hydrogen: in the presence of a suitable anhydride such as isobutyric anhydride or acetic anhydride in a suitable solvent such as pyridine at a suitable temperature such as for example 50°C and

in a next step in the presence of a suitable solvent such as MeOH at a suitable temperature such as 130°C.

5 In all these preparations, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, crystallization, trituration and chromatography.

10 The chirally pure forms of the compounds of Formula (I) form a preferred group of compounds. It is therefore that the chirally pure forms of the intermediates and their salt forms are particularly useful in the preparation of chirally pure compounds of Formula (I). Also enantiomeric mixtures of the intermediates are useful in the preparation of compounds of Formula (I) with the corresponding configuration.

Pharmacology

It has been found that the compounds of the present invention inhibit PRMT5 activity.

15 It is therefore anticipated that the compounds according to the present invention or pharmaceutical compositions thereof may be useful for treating or preventing, in particular treating, of diseases such as a blood disorder, metabolic disorders, autoimmune disorders, cancer, inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, pancreatitis, multiorgan failure, kidney diseases, platelet
20 aggregation, sperm motility, transplantation rejection, graft rejection, lung injuries and the like.

In particular the compounds according to the present invention or pharmaceutical compositions thereof may be useful for treating or preventing, in particular treating, of diseases such as allergy, asthma, hematopoietic cancer, lung cancer, prostate cancer,
25 melanoma, metabolic disorder, diabetes, obesity, blood disorder, sickle cell anemia, and the like.

The compounds according to the present invention or pharmaceutical compositions thereof may be useful for treating or preventing, in particular treating, of diseases such as a proliferative disorder, such as an autoimmune disease, cancer, a benign neoplasm,
30 or an inflammatory disease.

The compounds according to the present invention or pharmaceutical compositions thereof may be useful for treating or preventing, in particular treating, of diseases such as a metabolic disorder comprising diabetes, obesity; a proliferative disorder comprising cancer, hematopoietic cancer, lung cancer, prostate cancer, melanoma, or
35 pancreatic cancer; blood disorder; hemoglobinopathy; sickle cell anemia; β -

thalassemia, an inflammatory disease, and autoimmune disease e.g. rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, diarrhea, gastroesophageal reflux disease, and the like.

In some embodiments, the inhibition of PRMT5 by a provided compound may be
5 useful in treating or preventing, in particular treating, the following non-limiting list of cancers: breast cancer, lung cancer, esophageal cancer, bladder cancer, hematopoietic cancer, lymphoma, medulloblastoma, rectum adenocarcinoma, colon adenocarcinoma, gastric cancer, pancreatic cancer, liver cancer, adenoid cystic carcinoma, lung
10 adenocarcinoma, head and neck squamous cell carcinoma, brain tumors, hepatocellular carcinoma, renal cell carcinoma, melanoma, oligodendroglioma, ovarian clear cell carcinoma, and ovarian serous cystadenoma.

Examples of metabolic disorders which may be treated or prevented, in particular treated, include, but are not limited to, diabetes or obesity.

Examples of blood disorders which may be treated or prevented, in particular treated,
15 include, but are not limited to, hemoglobinopathy, such as sickle cell disease or β -thalassemia.

Examples of cancers which may be treated or prevented, in particular treated, include, but are not limited to, acoustic neuroma, adenocarcinoma, adrenal gland cancer, anal cancer, angiosarcoma (e.g., lymphangio sarcoma, lymphangioendothelio sarcoma,
20 hemangio sarcoma), appendix cancer, benign monoclonal gammopathy, biliary cancer (e.g., cholangiocarcinoma), bladder cancer, breast cancer (e.g., adenocarcinoma of the breast, papillary carcinoma of the breast, mammary cancer, medullary carcinoma of the breast), brain cancer (e.g., meningioma; glioma, e.g., astrocytoma, oligodendroglioma; medulloblastoma), bronchus cancer, carcinoid tumor, cervical cancer (e.g., cervical
25 adenocarcinoma), chordoma, choriocarcinoma, craniopharyngioma, colorectal cancer (e.g., colon cancer, rectal cancer, colorectal adenocarcinoma), epithelial carcinoma, ependymoma, endothelio sarcoma (e.g., Kaposi's sarcoma, multiple idiopathic hemorrhagic sarcoma), endometrial cancer (e.g., uterine cancer, uterine sarcoma), esophageal cancer (e.g., adenocarcinoma of the esophagus, Barrett's adenocarcinoma),
30 Ewing sarcoma, eye cancer (e.g., intraocular melanoma, retinoblastoma), familial hypereosinophilia, gall bladder cancer, gastric cancer (e.g., stomach adenocarcinoma), gastrointestinal stromal tumor (GIST), head and neck cancer (e.g., head and neck squamous cell carcinoma, oral cancer (e.g., oral squamous cell carcinoma (OSCC), throat cancer (e.g., pharyngeal cancer, laryngeal cancer, nasopharyngeal cancer,
35 oropharyngeal cancer)), hematopoietic cancers (e.g., leukemia such as acute

lymphocytic leukemia (ALL) (e.g., B-cell ALL, T-cell ALL), acute myelocytic leukemia (AML) (e.g., B-cell AML, T-cell AML), chronic myelocytic leukemia (CML) (e.g., B-cell CML, T-cell CML), and chronic lymphocytic leukemia (CLL) (e.g., B-cell CLL, T-cell CLL); lymphoma such as Hodgkin lymphoma (HL) (e.g., B-cell HL, T-cell HL) and non-Hodgkin lymphoma (NHL) (e.g., B-cell NHL such as diffuse large cell lymphoma (DLCL) (e.g., diffuse large B-cell lymphoma (DLBCL)), follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), marginal zone B-cell lymphomas (e.g., mucosa-associated lymphoid tissue (MALT) lymphomas, nodal marginal zone B-cell lymphoma, splenic marginal zone B-cell lymphoma), primary mediastinal B-cell lymphoma, Burkitt lymphoma, lymphoplasmacytic lymphoma (i.e., "Waldenstrom's macro globulinemia"), immunoblastic large cell lymphoma, hairy cell leukemia (HCL), precursor B-lymphoblastic lymphoma and primary central nervous system (CNS) lymphoma; and T-cell NHL such as precursor T-lymphoblastic lymphoma/leukemia, peripheral T-cell lymphoma (PTCL) (e.g., cutaneous T-cell lymphoma (CTCL) (e.g., mycosis fungoides, Sezary syndrome), angioimmunoblastic T-cell lymphoma, extranodal natural killer T-cell lymphoma, enteropathy type T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, anaplastic large cell lymphoma); a mixture of one or more leukemia/lymphoma as described above; and multiple myeloma (MM)), heavy chain disease (e.g., alpha chain disease, gamma chain disease, mu chain disease), hemangioblastoma, inflammatory myofibroblastic tumors, immunocytic amyloidosis, kidney cancer (e.g., nephroblastoma a.k.a. Wilms' tumor, renal cell carcinoma), liver cancer (e.g., hepatocellular cancer (HCC), malignant hepatoma), lung cancer (e.g., bronchogenic carcinoma, non-small cell lung cancer (NSCLC), squamous lung cancer (SLC), adenocarcinoma of the lung, Lewis lung carcinoma, lung neuroendocrine tumors: typical carcinoid, atypical carcinoid, small cell lung cancer (SCLC), and large cell neuroendocrine carcinoma), leiomyosarcoma (LMS), mastocytosis (e.g., systemic mastocytosis), myelodysplastic syndromes (MDS), mesothelioma, myeloproliferative disorder (MPD) (e.g., polycythemia Vera (PV), essential thrombocytosis (ET), agnogenic myeloid metaplasia (AMM) a.k.a. myelofibrosis (MF), chronic idiopathic myelofibrosis, chronic myelocytic leukemia (CML), chronic neutrophilic leukemia (CNL), hypereosinophilic syndrome (HES)), neuroblastoma, neurofibroma (e.g., neurofibromatosis (NF) type 1 or type 2, schwannomatosis), neuroendocrine cancer (e.g., gastroenteropancreatic neuroendocrine tumor (GEP-NET), carcinoid tumor), osteosarcoma, ovarian cancer (e.g., cystadenocarcinoma, ovarian embryonal carcinoma, ovarian adenocarcinoma), papillary adenocarcinoma, pancreatic cancer (e.g., pancreatic adenocarcinoma,

intraductal papillary mucinous neoplasm (IPMN), Islet cell tumors), penile cancer (e.g., Paget's disease of the penis and scrotum), pinealoma, primitive neuroectodermal tumor (PNT), prostate cancer (e.g., prostate adenocarcinoma), rectal cancer, rhabdomyosarcoma, salivary gland cancer, skin cancer (e.g., squamous cell carcinoma (SCC), keratoacanthoma (KA), melanoma, basal cell carcinoma (BCC)), small bowel cancer (e.g., appendix cancer), soft tissue sarcoma (e.g., malignant fibrous histiocytoma (MFH), liposarcoma, malignant peripheral nerve sheath tumor (MPNST), chondrosarcoma, fibrosarcoma, myxosarcoma), sebaceous gland carcinoma, sweat gland carcinoma, synovioma, testicular cancer (e.g., seminoma, testicular embryonal carcinoma), thyroid cancer (e.g., papillary carcinoma of the thyroid, papillary thyroid carcinoma (PTC), medullary thyroid cancer), urethral cancer, vaginal cancer, and vulvar cancer (e.g., Paget's disease of the vulva).

Examples of neurodegenerative diseases which may be treated or prevented, in particular treated, include, but are not limited to, motor neurone disease, progressive supranuclear palsy, corticobasal degeneration, Pick's disease, Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy, and cerebellar degeneration.

Examples of cardiovascular diseases which may be treated or prevented, in particular treated, include, but are not limited to, cardiac hypertrophy, restenosis, atherosclerosis, and glomerulonephritis.

Examples of inflammatory diseases which may be treated or prevented, in particular treated, include, but are not limited to, inflammation associated with acne, anemia (e.g., aplastic anemia, haemolytic autoimmune anaemia), rhinitis, asthma, arteritis (e.g., polyarteritis, temporal arteritis, periarteritis nodosa, Takayasu's arteritis), arthritis (e.g., crystalline arthritis, osteoarthritis, psoriatic arthritis, gouty arthritis, reactive arthritis, rheumatoid arthritis and Reiter's arthritis), upper respiratory tract disease, ankylosing spondylitis, amylosis, amyotrophic lateral sclerosis, autoimmune diseases, allergies or allergic reactions, atherosclerosis, bronchitis, bursitis, chronic prostatitis, conjunctivitis, Chagas disease, chronic obstructive pulmonary disease, diverticulitis, dermatomyositis, diabetes (e.g., type I diabetes mellitus, type 2 diabetes mellitus), a skin condition (e.g., psoriasis, eczema, eczema hypersensitivity reactions, burns, dermatitis, pruritus (itch)), endometriosis, Guillain-Barre syndrome, infection, ischaemic heart disease, Kawasaki disease, glomerulonephritis, gingivitis, hypersensitivity, headaches (e.g., migraine headaches, tension headaches), ileus (e.g., postoperative ileus and ileus during sepsis), idiopathic thrombocytopenic purpura, interstitial cystitis (painful bladder syndrome),

gastrointestinal disorder (e.g., selected from peptic ulcers, regional enteritis, diverticulitis, gastrointestinal bleeding, eosinophilic gastrointestinal disorders (e.g., eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic colitis), gastritis, diarrhea, gastroesophageal reflux disease (GORD, or its synonym

5 GERD), inflammatory bowel disease (IBD) (e.g., Crohn's disease, ulcerative colitis, collagenous colitis, lymphocytic colitis, ischaemic colitis, diversion colitis, Behcet's syndrome, indeterminate colitis) and inflammatory bowel syndrome (IBS)), lupus, morphea, myasthenia gravis, myocardial ischemia, multiple sclerosis, nephrotic syndrome, pemphigus vulgaris, pernicious anaemia, peptic ulcers, polymyositis,

10 primary biliary cirrhosis, neuroinflammation associated with brain disorders (e.g., Parkinson's disease, Huntington's disease, and Alzheimer's disease), prostatitis, chronic inflammation associated with cranial radiation injury, pelvic inflammatory disease, reperfusion injury, regional enteritis, rheumatic fever, systemic lupus erythematosus, scleroderma, scleroderma, sarcoidosis, spondyloarthropathies, Sjogren's syndrome,

15 thyroiditis, transplantation rejection, tendonitis, trauma or injury (e.g., frostbite, chemical irritants, toxins, scarring, burns, physical injury), vasculitis, vitiligo and Wegener's granulomatosis.

In particular the inflammatory disease is an acute inflammatory disease (e.g., for example, inflammation resulting from infection). In particular the inflammatory disease

20 is a chronic inflammatory disease (e.g., conditions resulting from asthma, arthritis and inflammatory bowel disease). The compounds may also be useful in treating inflammation associated with trauma and non-inflammatory myalgia. The compounds may also be useful in treating inflammation associated with cancer.

Examples of autoimmune diseases which may be treated or prevented, in particular

25 treated, include, but are not limited to, arthritis (including rheumatoid arthritis, spondyloarthropathies, gouty arthritis, degenerative joint diseases such as osteoarthritis, systemic lupus erythematosus, Sjogren's syndrome, ankylosing spondylitis, undifferentiated spondylitis, Behcet's disease, haemolytic autoimmune anaemias, amyotrophic lateral sclerosis, amylosis, multiple sclerosis, acute painful shoulder,

30 psoriatic, and juvenile arthritis), asthma, atherosclerosis, osteoporosis, bronchitis, tendonitis, bursitis, skin condition (e.g., psoriasis, eczema, eczema hypersensitivity reactions, burns, dermatitis, pruritus (itch)), enuresis, eosinophilic disease, gastrointestinal disorder (e.g., selected from peptic ulcers, regional enteritis, diverticulitis, gastrointestinal bleeding, eosinophilic gastrointestinal disorders (e.g.,

35 eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic colitis), gastritis, diarrhea, gastroesophageal reflux disease (GORD, or its synonym

GERD), inflammatory bowel disease (IBD) (e.g., Crohn's disease, ulcerative colitis, collagenous colitis, lymphocytic colitis, ischaemic colitis, diversion colitis, Behcet's syndrome, indeterminate colitis) and inflammatory bowel syndrome (IBS)), and disorders ameliorated by a gastroprokinetic agent (e.g., ileus, postoperative ileus and
5 ileus during sepsis; gastroesophageal reflux disease (GORD, or its synonym GERD); eosinophilic esophagitis, gastroparesis such as diabetic gastroparesis; food intolerances and food allergies and other functional bowel disorders, such as non-ulcerative dyspepsia (NUD) and non-cardiac chest pain (NCCP, including costo-chondritis)).

In a particular embodiment, a provided compound may be useful in somatic cell
10 reprogramming, such as reprogramming somatic cells into stem cells. In a particular embodiment, a provided compound may be useful in germ cell development, and are thus envisioned useful in the areas of reproductive technology and regenerative medicine.

Other diseases which may be treated or prevented, in particular treated, include, but are
15 not limited to, ischemic injury associated myocardial infarctions, immunological diseases, stroke, arrhythmia, toxin-induced or alcohol related liver diseases, aspirin-sensitive rhinosinusitis, cystic fibrosis, cancer pain, and haematological diseases, for example chronic anemia and aplastic anemia.

The compounds of the present invention may also have therapeutic applications in
20 sensitising tumour cells for radiotherapy and chemotherapy.

Hence the compounds of the present invention may be used as "radiosensitizer" and/or "chemosensitizer" or can be given in combination with another "radiosensitizer" and/or "chemosensitizer".

The term "radiosensitizer", as used herein, is defined as a molecule, preferably a low
25 molecular weight molecule, administered to animals in therapeutically effective amounts to increase the sensitivity of the cells to ionizing radiation and/or to promote the treatment of diseases which are treatable with ionizing radiation.

The term "chemosensitizer", as used herein, is defined as a molecule, preferably a low
30 molecular weight molecule, administered to animals in therapeutically effective amounts to increase the sensitivity of cells to chemotherapy and/or promote the treatment of diseases which are treatable with chemotherapeutics.

Several mechanisms for the mode of action of radiosensitizers have been suggested in the literature including: hypoxic cell radiosensitizers (e.g., 2- nitroimidazole compounds, and benzotriazine dioxide compounds) mimicking oxygen or alternatively

behave like bioreductive agents under hypoxia; non-hypoxic cell radiosensitizers (e.g., halogenated pyrimidines) can be analogues of DNA bases and preferentially incorporate into the DNA of cancer cells and thereby promote the radiation-induced breaking of DNA molecules and/or prevent the normal DNA repair mechanisms; and various other potential mechanisms of action have been hypothesized for radiosensitizers in the treatment of disease.

Many cancer treatment protocols currently employ radiosensitizers in conjunction with radiation of x-rays. Examples of x-ray activated radiosensitizers include, but are not limited to, the following: metronidazole, misonidazole, desmethylmisonidazole, pimonidazole, etanidazole, nimorazole, mitomycin C, RSU 1069, SR 4233, EO9, RB 6145, nicotinamide, 5-bromodeoxyuridine (BUdR), 5-iododeoxyuridine (IUdR), bromodeoxycytidine, fluorodeoxyuridine (FudR), hydroxyurea, cisplatin, and therapeutically effective analogs and derivatives of the same.

Photodynamic therapy (PDT) of cancers employs visible light as the radiation activator of the sensitizing agent. Examples of photodynamic radiosensitizers include the following, but are not limited to: hematoporphyrin derivatives, Photofrin, benzoporphyrin derivatives, tin etioporphyrin, pheoborbide-a, bacteriochlorophyll-a, naphthalocyanines, phthalocyanines, zinc phthalocyanine, and therapeutically effective analogs and derivatives of the same.

Radiosensitizers may be administered in conjunction with a therapeutically effective amount of one or more other compounds, including but not limited to: compounds which promote the incorporation of radiosensitizers to the target cells; compounds which control the flow of therapeutics, nutrients, and/or oxygen to the target cells; chemotherapeutic agents which act on the tumour with or without additional radiation; or other therapeutically effective compounds for treating cancer or other diseases.

Chemosensitizers may be administered in conjunction with a therapeutically effective amount of one or more other compounds, including but not limited to: compounds which promote the incorporation of chemosensitizers to the target cells; compounds which control the flow of therapeutics, nutrients, and/or oxygen to the target cells; chemotherapeutic agents which act on the tumour or other therapeutically effective compounds for treating cancer or other disease. Calcium antagonists, for example verapamil, are found useful in combination with antineoplastic agents to establish chemosensitivity in tumor cells resistant to accepted chemotherapeutic agents and to potentiate the efficacy of such compounds in drug-sensitive malignancies.

The compounds of the present invention might also reduce the risk of cancer recurrence.

The invention relates to compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, for use as a medicament.

The invention relates to compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, for use in the inhibition of PRMT5 activity.

- 5 The compounds of the present invention can be "anti-cancer agents", which term also encompasses "anti-tumor cell growth agents" and "anti-neoplastic agents".

The invention relates to compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, for use in the treatment of diseases mentioned above.

- 10 The invention relates to compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, for the treatment or prevention, in particular for the treatment, of said diseases.

The invention relates to compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, for the treatment or prevention, in particular in the

- 15 treatment, of PRMT5 mediated diseases or conditions.

The invention relates to compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, for the manufacture of a medicament.

The invention relates to compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, for the manufacture of a medicament for the

- 20 inhibition of PRMT5.

The invention relates to compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, for the manufacture of a medicament for the treatment or prevention, in particular for the treatment, of any one of the disease conditions mentioned hereinbefore.

- 25 The invention relates to compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, for the manufacture of a medicament for the treatment of any one of the disease conditions mentioned hereinbefore.

The invention relates to compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, can be administered to mammals, preferably

- 30 humans, for the treatment or prevention of any one of the diseases mentioned hereinbefore.

In view of the utility of the compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, there is provided a method of treating warm-blooded animals, including humans, suffering from or a method of preventing warm-

blooded animals, including humans, to suffer from any one of the diseases mentioned hereinbefore.

Said methods comprise the administration, i.e. the systemic or topical administration, preferably oral administration, of an effective amount of a compound of Formula (I) or
5 a pharmaceutically acceptable addition salt, or a solvate thereof, to warm-blooded animals, including humans.

Those of skill in the treatment of such diseases could determine the effective therapeutic daily amount from the test results presented hereinafter. An effective therapeutic daily amount would be from about 0.005 mg /kg to 50 mg/kg, in particular
10 0.01 mg/kg to 50 mg/kg body weight, more in particular from 0.01 mg/kg to 25 mg/kg body weight, preferably from about 0.01 mg/kg to about 15 mg/kg, more preferably from about 0.01 mg/kg to about 10 mg/kg, even more preferably from about 0.01 mg/kg to about 1 mg/kg, most preferably from about 0.05 mg/kg to about 1 mg/kg body weight. A particular effective therapeutic daily amount might be from about 0.01 to
15 1.00 g twice a day (BID), more in particular 0.30 to 0.85 g BID; even more in particular 0.40 g BID. The amount of a compound according to the present invention, also referred to here as the active ingredient, which is required to achieve a therapeutically effect will of course, vary on case-by-case basis, for example with the particular compound, the route of administration, the age and condition of the recipient, and the
20 particular disorder or disease being treated.

A method of treatment may also include administering the active ingredient on a regimen of between one and four intakes per day. In these methods of treatment the compounds according to the invention are preferably formulated prior to administration. As described herein below, suitable pharmaceutical formulations are
25 prepared by known procedures using well known and readily available ingredients.

The compounds of the present invention, that can be suitable to treat or prevent cancer or cancer-related conditions, may be administered alone or in combination with one or more additional therapeutic agents. Combination therapy includes administration of a single pharmaceutical dosage formulation which contains a compound of Formula (I), a
30 pharmaceutically acceptable addition salt, or a solvate thereof, and one or more additional therapeutic agents, as well as administration of the compound of Formula (I), a pharmaceutically acceptable addition salt, or a solvate thereof, and each additional therapeutic agents in its own separate pharmaceutical dosage formulation. For example, a compound of Formula (I), a pharmaceutically acceptable addition salt, or a solvate
35 thereof, and a therapeutic agent may be administered to the patient together in a single

oral dosage composition such as a tablet or capsule, or each agent may be administered in separate oral dosage formulations.

While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical composition.

- 5 Accordingly, the present invention further provides a pharmaceutical composition and, as active ingredient, a therapeutically effective amount of a compound of Formula (I), a pharmaceutically acceptable addition salt, or a solvate thereof.

- 10 Accordingly, the present invention further provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound of Formula (I), a pharmaceutically acceptable addition salt, or a solvate thereof.

The carrier or diluent must be “acceptable” in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipients thereof.

- 15 For ease of administration, the subject compounds may be formulated into various pharmaceutical forms for administration purposes. The compounds according to the invention, in particular the compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, or any subgroup or combination thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for
20 systemically administering drugs.

- To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These
25 pharmaceutical compositions are desirable in unitary dosage form suitable, in particular, for administration orally, rectally, percutaneously, by parenteral injection or by inhalation. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions,
30 syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the
35 carrier will usually comprise sterile water, at least in large part, though other

ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable solutions containing a compound of Formula (I), a pharmaceutically acceptable addition salt, or a solvate thereof, may be formulated in an oil for prolonged action. Appropriate oils for this purpose are, for example, peanut oil, sesame oil, cottonseed oil, corn oil, soybean oil, synthetic glycerol esters of long chain fatty acids and mixtures of these and other oils. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment. Acid or base addition salts of compounds of Formula (I) due to their increased water solubility over the corresponding base or acid form, are more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, suppositories, injectable solutions or suspensions and the like, and segregated multiples thereof.

In order to enhance the solubility and/or the stability of the compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, in pharmaceutical compositions, it can be advantageous to employ α -, β - or γ -cyclodextrins or their derivatives, in particular hydroxyalkyl substituted cyclodextrins, e.g. 2-hydroxypropyl- β -cyclodextrin or sulfobutyl- β -cyclodextrin. Also co-solvents such as alcohols may improve the solubility and/or the stability of the compounds according to the invention in pharmaceutical compositions.

Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 % by weight, more preferably from 0.1 to 70 % by weight, even more preferably from 0.1 to 50 % by weight of the compound of Formula (I), a pharmaceutically acceptable addition salt, or a solvate thereof, and from 1 to 5 99.95 % by weight, more preferably from 30 to 99.9 % by weight, even more preferably from 50 to 99.9 % by weight of a pharmaceutically acceptable carrier, all percentages being based on the total weight of the composition.

As another aspect of the present invention, a combination of a compound of the present invention with another anticancer agent is envisaged, especially for use as a medicine, 10 more specifically for use in the treatment of cancer or related diseases.

For the treatment of the above conditions, the compounds of the invention may be advantageously employed in combination with antibody based immune cell redirection, for example T-cell/neutrophil redirection. This can be achieved for example by the use of bispecific monoclonal antibodies or artificial T-cell receptors.

15 For the treatment of the above conditions, the compounds of the invention may be advantageously employed in combination with one or more other medicinal agents, more particularly, with other anti-cancer agents or adjuvants in cancer therapy. Examples of anti-cancer agents or adjuvants (supporting agents in the therapy) include but are not limited to:

- 20 - platinum coordination compounds for example cisplatin optionally combined with amifostine, carboplatin or oxaliplatin;
- taxane compounds for example paclitaxel, paclitaxel protein bound particles (AbraxaneTM) or docetaxel;
- topoisomerase I inhibitors such as camptothecin compounds for example 25 irinotecan, SN-38, topotecan, topotecan hcl;
- topoisomerase II inhibitors such as anti-tumour epipodophyllotoxins or podophyllotoxin derivatives for example etoposide, etoposide phosphate or teniposide;
- anti-tumour vinca alkaloids for example vinblastine, vincristine or vinorelbine;
- 30 - anti-tumour nucleoside derivatives for example 5-fluorouracil, leucovorin, gemcitabine, gemcitabine hcl, capecitabine, cladribine, fludarabine, nelarabine;
- alkylating agents such as nitrogen mustard or nitrosourea for example cyclophosphamide, chlorambucil, carmustine, thiotepa, mephalan (melphalan), lomustine, altretamine, busulfan, dacarbazine, estramustine, ifosfamide
- 35 optionally in combination with mesna, pipobroman, procarbazine, streptozocin, temozolomide, uracil;

- anti-tumour anthracycline derivatives for example daunorubicin, doxorubicin optionally in combination with dexrazoxane, doxil, idarubicin, mitoxantrone, epirubicin, epirubicin hcl, valrubicin;
- molecules that target the IGF-1 receptor for example picropodophilin;
- 5 - tetracarcin derivatives for example tetrocarcin A;
- glucocorticoids for example prednisone;
- antibodies for example trastuzumab (HER2 antibody), rituximab (CD20 antibody), gemtuzumab, gemtuzumab ozogamicin, cetuximab, pertuzumab, bevacizumab, alemtuzumab, eculizumab, ibritumomab tiuxetan, nofetumomab,
- 10 panitumumab, tositumomab, CNTO 328;
- estrogen receptor antagonists or selective estrogen receptor modulators or inhibitors of estrogen synthesis for example tamoxifen, fulvestrant, toremifene, droloxifene, faslodex, raloxifene or letrozole;
- aromatase inhibitors such as exemestane, anastrozole, letrozole, testolactone and
- 15 vorozole;
- differentiating agents such as retinoids, vitamin D or retinoic acid and retinoic acid metabolism blocking agents (RAMBA) for example accutane;
- DNA methyl transferase inhibitors for example azacytidine or decitabine;
- antifolates for example premetrexed disodium;
- 20 - antibiotics for example antinomycin D, bleomycin, mitomycin C, dactinomycin, carminomycin, daunomycin, levamisole, plicamycin, mithramycin;
- antimetabolites for example clofarabine, aminopterin, cytosine arabinoside or methotrexate, azacitidine, cytarabine, floxuridine, pentostatin, thioguanine;
- apoptosis inducing agents and antiangiogenic agents such as Bcl-2 inhibitors for
- 25 example YC 137, BH 312, ABT 737, gossypol, HA 14-1, TW 37 or decanoic acid;
- tubuline-binding agents for example combrestatin, colchicines or nocodazole;
- kinase inhibitors (e.g. EGFR (epithelial growth factor receptor) inhibitors, MTKI (multi target kinase inhibitors), mTOR inhibitors) for example
- 30 flavoperidol, imatinib mesylate, erlotinib, gefitinib, dasatinib, lapatinib, lapatinib ditosylate, sorafenib, sunitinib, sunitinib maleate, temsirolimus;
- farnesyltransferase inhibitors for example tipifarnib;
- histone deacetylase (HDAC) inhibitors for example sodium butyrate, suberoylanilide hydroxamic acid (SAHA), depsipeptide (FR 901228), NVP-
- 35 LAQ824, R306465, JNJ-26481585, trichostatin A, vorinostat;
- Inhibitors of the ubiquitin-proteasome pathway for example PS-341, MLN .41 or bortezomib;

-75-

- Yondelis;
- Telomerase inhibitors for example telomestatin;
- Matrix metalloproteinase inhibitors for example batimastat, marimastat, prinostat or metastat.
- 5 - Recombinant interleukins for example aldesleukin, denileukin diftitox, interferon alfa 2a, interferon alfa 2b, peginterferon alfa 2b
- MAPK inhibitors
- Retinoids for example alitretinoin, bexarotene, tretinoin
- Arsenic trioxide
- 10 - Asparaginase
- Steroids for example dromostanolone propionate, megestrol acetate, nandrolone (decanoate, phenpropionate), dexamethasone
- Gonadotropin releasing hormone agonists or antagonists for example abarelix, goserelin acetate, histrelin acetate, leuprolide acetate
- 15 - Thalidomide, lenalidomide
- Mercaptopurine, mitotane, pamidronate, pegademase, pegaspargase, rasburicase
- BH3 mimetics for example ABT-737
- MEK inhibitors for example PD98059, AZD6244, CI-1040
- colony-stimulating factor analogs for example filgrastim, pegfilgrastim,
- 20 sargramostim; erythropoietin or analogues thereof (e.g. darbepoetin alfa); interleukin 11; oprelvekin; zoledronate, zoledronic acid; fentanyl; bisphosphonate; palifermin
- a steroidal cytochrome P450 17alpha-hydroxylase-17,20-lyase inhibitor (CYP17), e.g. abiraterone, abiraterone acetate
- 25 - Glycolysis inhibitors, such as 2-deoxyglucose
- mTOR inhibitors such as rapamycins and rapalogs, and mTOR kinase inhibitors
- PI3K inhibitors and dual mTOR/PI3K inhibitors
- autophagy inhibitors, such as chloroquine and hydroxy-chloroquine
- antibodies that re-activate the immune response to tumors, for example
- 30 nivolumab (anti-PD-1), lambrolizumab (anti-PD-1), ipilimumab (anti-CTLA4), and MPDL3280A (anti-PD-L1).

The present invention further relates to a product containing as first active ingredient a compound according to the invention and as further active ingredient one or more

35 anticancer agents, as a combined preparation for simultaneous, separate or sequential use in the treatment of patients suffering from cancer.

The one or more other medicinal agents and the compound according to the present invention may be administered simultaneously (e.g. in separate or unitary compositions) or sequentially in either order. In the latter case, the two or more compounds will be administered within a period and in an amount and manner that is
5 sufficient to ensure that an advantageous or synergistic effect is achieved. It will be appreciated that the preferred method and order of administration and the respective dosage amounts and regimes for each component of the combination will depend on the particular other medicinal agent and compound of the present invention being
10 administered, their route of administration, the particular tumour being treated and the particular host being treated. The optimum method and order of administration and the dosage amounts and regime can be readily determined by those skilled in the art using conventional methods and in view of the information set out herein.

The weight ratio of the compound according to the present invention and the one or more other anticancer agent(s) when given as a combination may be determined by the
15 person skilled in the art. Said ratio and the exact dosage and frequency of administration depends on the particular compound according to the invention and the other anticancer agent(s) used, the particular condition being treated, the severity of the condition being treated, the age, weight, gender, diet, time of administration and general physical condition of the particular patient, the mode of administration as well as other
20 medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that the effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. A particular weight ratio for the present compound of Formula (I) and another anticancer agent may range
25 from 1/10 to 10/1, more in particular from 1/5 to 5/1, even more in particular from 1/3 to 3/1.

The platinum coordination compound is advantageously administered in a dosage of 1 to 500mg per square meter (mg/m^2) of body surface area, for example 50 to 400 mg/m^2 ,
30 particularly for cisplatin in a dosage of about 75 mg/m^2 and for carboplatin in about 300 mg/m^2 per course of treatment.

The taxane compound is advantageously administered in a dosage of 50 to 400 mg per square meter (mg/m^2) of body surface area, for example 75 to 250 mg/m^2 , particularly
35 for paclitaxel in a dosage of about 175 to 250 mg/m^2 and for docetaxel in about 75 to 150 mg/m^2 per course of treatment.

The camptothecin compound is advantageously administered in a dosage of 0.1 to 400 mg per square meter (mg/m^2) of body surface area, for example 1 to 300 mg/m^2 , particularly for irinotecan in a dosage of about 100 to 350 mg/m^2 and for topotecan in about 1 to 2 mg/m^2 per course of treatment.

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The anti-tumour podophyllotoxin derivative is advantageously administered in a dosage of 30 to 300 mg per square meter (mg/m^2) of body surface area, for example 50 to 250 mg/m^2 , particularly for etoposide in a dosage of about 35 to 100 mg/m^2 and for teniposide in about 50 to 250 mg/m^2 per course of treatment.

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The anti-tumour vinca alkaloid is advantageously administered in a dosage of 2 to 30 mg per square meter (mg/m^2) of body surface area, particularly for vinblastine in a dosage of about 3 to 12 mg/m^2 , for vincristine in a dosage of about 1 to 2 mg/m^2 , and for vinorelbine in dosage of about 10 to 30 mg/m^2 per course of treatment.

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The anti-tumour nucleoside derivative is advantageously administered in a dosage of 200 to 2500 mg per square meter (mg/m^2) of body surface area, for example 700 to 1500 mg/m^2 , particularly for 5-FU in a dosage of 200 to 500 mg/m^2 , for gemcitabine in a dosage of about 800 to 1200 mg/m^2 and for capecitabine in about 1000 to

20 2500 mg/m^2 per course of treatment.

The alkylating agents such as nitrogen mustard or nitrosourea is advantageously administered in a dosage of 100 to 500 mg per square meter (mg/m^2) of body surface area, for example 120 to 200 mg/m^2 , particularly for cyclophosphamide in a dosage of about 100 to 500 mg/m^2 , for chlorambucil in a dosage of about 0.1 to 0.2 mg/kg, for carmustine in a dosage of about 150 to 200 mg/m^2 , and for lomustine in a dosage of about 100 to 150 mg/m^2 per course of treatment.

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The anti-tumour anthracycline derivative is advantageously administered in a dosage of 10 to 75 mg per square meter (mg/m^2) of body surface area, for example 15 to 60 mg/m^2 , particularly for doxorubicin in a dosage of about 40 to 75 mg/m^2 , for daunorubicin in a dosage of about 25 to 45 mg/m^2 , and for idarubicin in a dosage of about 10 to 15 mg/m^2 per course of treatment.

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The antiestrogen agent is advantageously administered in a dosage of about 1 to 100 mg daily depending on the particular agent and the condition being treated. Tamoxifen is advantageously administered orally in a dosage of 5 to 50 mg, preferably 10 to 20 mg

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- twice a day, continuing the therapy for sufficient time to achieve and maintain a therapeutic effect. Toremifene is advantageously administered orally in a dosage of about 60 mg once a day, continuing the therapy for sufficient time to achieve and maintain a therapeutic effect. Anastrozole is advantageously administered orally in a dosage of about 1mg once a day. Droloxifene is advantageously administered orally in a dosage of about 20-100 mg once a day. Raloxifene is advantageously administered orally in a dosage of about 60 mg once a day. Exemestane is advantageously administered orally in a dosage of about 25 mg once a day.
- Antibodies are advantageously administered in a dosage of about 1 to 5 mg per square meter (mg/m^2) of body surface area, or as known in the art, if different. Trastuzumab is advantageously administered in a dosage of 1 to 5 mg per square meter (mg/m^2) of body surface area, particularly 2 to $4\text{mg}/\text{m}^2$ per course of treatment. These dosages may be administered for example once, twice or more per course of treatment, which may be repeated for example every 7, 14, 21 or 28 days.

The following examples illustrate the present invention. Stereocenters for which no specific stereochemistry is indicated were obtained as mixtures of R and S.

The skilled person will realize that typically after a column purification, the desired fractions were collected and the solvent was evaporated to obtain the desired compound or intermediate.

Examples

- Hereinafter, the term "rt" or "r.t." means room temperature; "Me" means methyl; "MeOH" means MeOH; "Et" means ethyl; "EtOH" means ethanol; "HMPA" means hexamethylphosphorous triamide; "TosOH" means 4-methylbenzenesulfonic acid; "NaBH(AcO)₃" or "NaBH(OAc)₃" means sodium triacetoxyborohydride; "EtOAc" means ethyl acetate; "Et₃N" means triethylamine; "DCM" means dichloromethane; "q.s." means quantum sufficit; "Int." Means intermediate; "ACN" means acetonitrile; "DMF" means *N,N*-dimethyl formamide; "THF" means tetrahydrofuran; "iPrOH" means 2-propanol; "LC" means liquid chromatography; "LCMS" means Liquid Chromatography/Mass spectrometry; "(prep) HPLC" means (preparative) high-performance liquid chromatography; "TFA" means trifluoroacetic acid; "m.p." means melting point; "RP" means reversed phase; "min" means minute(s); "h" means hour(s); "PE" means petroleum ether; "CV" means column volume(s); "Celite®" means diatomaceous earth; "DMSO" means dimethyl sulfoxide; "SFC" means Supercritical Fluid Chromatography; "DIPEA" means *N,N*-diisopropylethylamine; "PPh₃" means

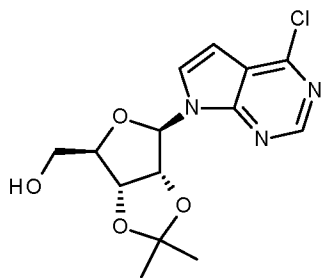
triphenylphosphine; "Et₂O" means diethyl ether; "Pd/C" means palladium on carbon; "Pt/C" means platina on carbon; "TBAF" means tetrabutylammonium fluoride; "psi" means pound-force per square inch; "eq." means equivalent(s); "AcOH" means acetic acid; "Dess-Martin periodinane" means 1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one; "Ph₃PCH₃Br" means methyltriphenylphosphonium bromide; "Bn" means benzyl; "Bz" means benzoyl; "p-TSA" means 4-methylbenzenesulfonic acid; "BF₃.Et₂O" means Boron Trifluoride-Ethyl Ether Complex; "MTBE" means Methyl tert-butyl ether; "Ac₂O" means acetic anhydride; "Co." means final compound; "R_f" means retention factor; "NH₄Ac" means ammonium acetate; "PPTS" means pyridinium p-toluenesulfonate; "LiHMDS" means lithium hexamethyldisilazane; "HOAc" means acetic acid; "MeCN" means methyl cyanide; "Boc" or "BOC" means tert-butoxycarbonyl; "atm" means atmosphere; "DIPE" means diisopropyl ether; "HBTU" means 1-[bis(dimethylamino)methylene]-1H-benzotriazol-1-ium 3-oxide hexafluorophosphate; "TMSCl" means trimethylsilyl chloride; "BINAP" means [1,1'-binaphthalene]-2,2'-diylbis[diphenylphosphine] (racemic); "Pd₂(dba)₃" means tris(dibenzylideneacetone)dipalladium; "t-BuONa" means sodium tert-butoxide; "KOAc" means potassium acetate; "TEMPO" means 2,2,6,6-tetramethyl-1-piperidinyloxy; "TsOH.H₂O" means p-toluenesulfonic acid monohydrate; "Ts" or "Tos" means tosyl (p-toluenesulfonyl); "Tf" means trifluoromethanesulfonyl (triflyl); and "TLC" means thin layer chromatography.

The typical concentration of ammonia in MeOH used in the reactions below, is 7 N.

A. Preparation of intermediates

Example A1

25 Preparation of *intermediate 1*

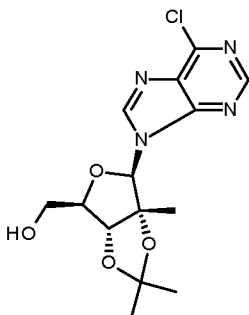


To a mixture of 6-chloro-7-deazapurine-beta-D-ribose (25.0 g, 87.5 mmol) in acetone (330 mL) was added 2,2-dimethoxypropane (18.2 g, 175 mmol) and TosOH (1.51 g, 8.75 mmol) in one portion at 25°C under N₂. The mixture was stirred at 60°C for 2 hours. The mixture was cooled to 25°C. The reaction was quenched by adding saturated NaHCO₃

(100 mL) slowly and then extracted with ethyl acetate (5 times 125 mL). The combined organic phases were washed with saturated brine (120 mL), dried with anhydrous MgSO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (gradient elution: DCM/Ethyl acetate from 1:0 to 2:1) to afford crude *intermediate 1* (38.0 g) as light yellow gum.

Below intermediates were prepared by an analogous reaction protocol as was used for the preparation of *intermediate 1* using the appropriate starting materials:

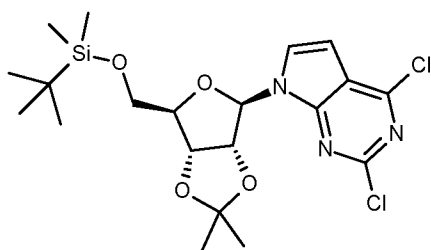
intermediate 4, starting from 6-chloro-9-(2-C-methyl-β-D-ribofuranosyl)-9H-Purine,



10 **Intermediate 4**

Example A2

Preparation of *intermediate 3*



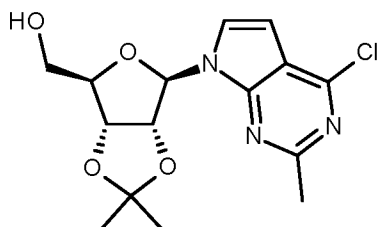
To a solution of 5-O-tert-butyldimethylsilyl-2,3-O-isopropylidene-D-ribofuranose (= *intermediate 2* = **commercial**) (79.8 mmol) in CCl₄ (12.8 mL, 133 mmol) and toluene (200 mL) was added dropwise HMPA (16.32 g, 100 mmol) at -50°C over 30 minutes. After the mixture was stirred at -50°C for 2 hours, the reaction mixture was quickly washed with ice cold brine (30 mL), dried over anhydrous Na₂SO₄ and added immediately to a heavily stirred mixture of powdered KOH (6.5 g, 117 mmol), 2,4-dichloro-7H-pyrrolopyrimidine (10.0 g, 53 mmol), tris(3,6-dioxahexyl)amine (8.27 mL, 26.6 mmol) and toluene (200 mL). The mixture was stirred at r.t. for 48 hours. Then the solvent was concentrated. The residue was treated with 250 mL NH₄Cl solution and

extracted with ethyl acetate (two times 300 ml). The organic layers were combined and dried with Na₂SO₄, filtered and the filtrate was concentrated in vacuum. The residue was purified by column chromatography over silica gel (gradient elution: petroleum ether/ethyl acetate from 25:1 to 15:1). The product fractions were collected and the solvent was evaporated to give the desired **intermediate 3** (6.50 g, 21% yield).

Below intermediates were prepared by an analogous reaction protocol as was used for the preparation of **intermediate 3** using the appropriate starting materials (Table 1).

Table 1:

Int.	Structure	Starting materials
5		Intermediate 2 and 4-chloro-2-methyl-7H-pyrrolo[2,3-d]pyrimidine
6		Intermediate 2 and 4-Chloro-5-fluoro-7H-pyrrolo[2,3-d]-pyrimidine
7		Intermediate 2 and 4-chloro-1H-pyrrolo[3,2-c]pyridine
8		Intermediate 2 and 4-chloro-5-iodo-7H-pyrrolo[2,3-d]-pyrimidine

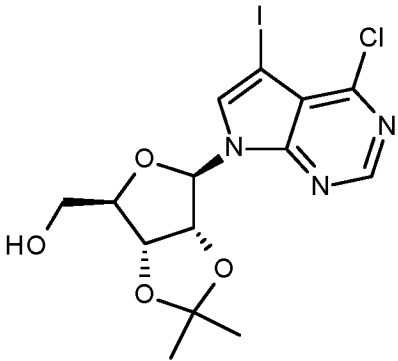
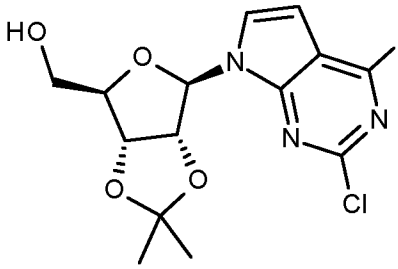
Preparation of *intermediate 9*

To a solution of *intermediate 5* (9.50 g, 20.9 mmol) in THF (82 mL) was added 1M TBAF solution in THF (41.8 mL, 41.8 mmol) at room temperature. The reaction mixture was stirred at room temperature for 3 hours. The mixture was evaporated to dryness. The residue was taken up into water and extracted with DCM (two times 150 ml). The organic layers were dried (Na₂SO₄), filtered and the filtrate was concentrated. The residue was purified by column chromatography over silica gel (gradient elution: petroleum ether/ethyl acetate from 10/1 to 4/1) to give the desired *intermediate 9* (3.68 g, 51% yield).

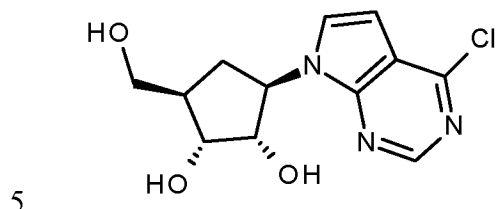
Below intermediate was prepared by an analogous reaction protocol as was used for the preparation of *intermediate 9* using the appropriate starting materials (Table 2).

Table 2:

<i>Int.</i>	Structure	Starting material
<i>10</i>		<i>Intermediate 6</i>
<i>11</i>		<i>Intermediate 7</i>

<i>Int.</i>	Structure	Starting material
12		<i>Intermediate 8</i>
15		<i>intermediate 3</i>

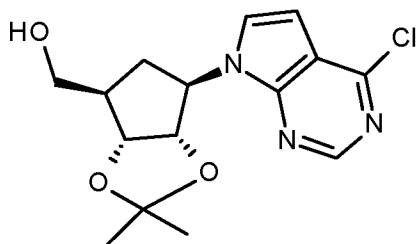
Example A4

Preparation of *intermediate 13*

To a mixture of 4,6-dichloro-5-(2,2-diethoxyethyl)pyrimidine (14.0 g, 52.8 mmol) and (1R,2S,3R,5R)-3-amino-5-(hydroxymethyl)cyclopentane-1,2-diol hydrochloride (10.7 g, 58.1 mmol) in propan-2-ol/H₂O (208 mL, 7:1), was added Et₃N (13.4 g, 132 mmol) in one portion at 25°C under N₂. The mixture was stirred at 90 °C for 23 hours. The mixture was cooled to 50°C and 4M HCl (24 mL, 106 mmol) was added slowly. The reaction mixture was then stirred at 50°C for 2 hours. The reaction mixture was cooled to 25°C and NaHCO₃ (14 g, 100 mmol) was added slowly. Ethyl acetate (230 mL) was added, followed by the addition of a half-saturated NaHCO₃ solution. The organic phase was isolated and the aqueous phase was extracted with ethyl acetate (two times 230 mL). The combined organic phase was dried with anhydrous MgSO₄, filtered and concentrated to

afford **intermediate 13** as yellow solid (17.40 g, quantitative yield in 2 steps). The crude product was directly used as such in the next reaction step without further purification.

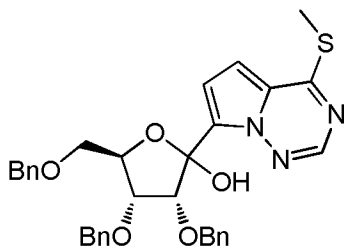
Preparation of **intermediate 14**



- 5 To a mixture of **intermediate 13** (17.4 g, 52.7 mmol) in acetone (250 mL) was added 2,2-dimethoxypropane (11.0 g, 105 mmol) and TsOH.H₂O (908 mg, 5.27 mmol) in one portion at 25°C under N₂. The mixture was stirred at 60°C for 2 hours. The mixture was cooled to 25°C and the solution was concentrated, quenched by saturated NaHCO₃ (100 mL) slowly and then extracted with ethyl acetate (three times 100 mL). The combined
10 organic phase was washed with saturated brine (100 mL), dried with anhydrous MgSO₄, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (gradient elution: DCM/Ethyl acetate from 1/0 to 2/1) to afford **intermediate 14** as light yellow gum (15.50 g, 89% yield).

15 Example A5

Preparation of **intermediate 18**

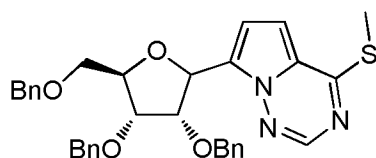


Two batches of the reaction described below were carried out in parallel.

- An oven-dried flask was charged with 7-bromo-4-(methylthio)pyrrolo[2,1-f][1,2,4]triazine (45.0 g, 184.3 mmol) and dry THF (1.20 L) under N₂. The yellow
20 solution was cooled to -78°C and a yellow suspension was formed. n-BuLi (2.5 M, 79.63 mL, 1.1 eq) was added drop wise to the reaction mixture over period of 25 minutes at -78°C. The reaction mixture was stirred at -78°C for 1 hour and a yellow-brown solution was formed. A pre-cooled solution of D-Lyxonic acid, 2,3,5-tris-O-(phenylmethyl)-, γ-lactone (84.0 g, 201 mmol (= **intermediate 17** = commercial) 1.09
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eq) in dry THF (800 mL) in another flask (-78°C) was added to the solution under N₂. The resulting red-brown solution was stirred at -78°C for 1.5 h. The reaction was quenched by addition of a saturated NH₄Cl aqueous solution (300 mL) at -78°C, and subsequently the mixture was warmed to 10°C. The mixture was extracted with ethyl acetate (3 times 500 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The combined residues of the two reactions were load on silica gel then purified by column chromatography (SiO₂, gradient elution: Petroleum ether/Ethyl acetate from 10/1 to 3:1) to afford **intermediate 18** (148.50 g, 242 mmol, 65.6% yield) as an orange gum.

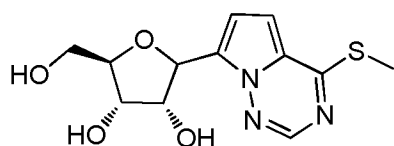
10 Preparation of **intermediate 19**



Two batches of the reaction described below were carried out in parallel.

To a stirred solution of **intermediate 18** (74.0 g, 126.8 mmol, 1.0 eq) and triethylsilane (59.9 g, 514.7 mmol, 4.1 eq) in DCM (1.80 L) was added BF₃.Et₂O (90.9 g, 640.2 mmol, 5.1 eq) dropwise between -30 and -20°C.. The resulting orange solution was stirred between -30 and -20°C for 4.5 hours. The reaction mixture was carefully poured into a saturated NaHCO₃ aqueous solution (2.5 L) with vigorous stirring (gas evolution). The mixture was stirred for 2 hours. The organic layer was separated and the aqueous phase was extracted with DCM (200 mL x3). The combined organic layers were washed with brine (500 mL x2), dried over MgSO₄, filtered and concentrated under reduced pressure. The combined residues of the two reactions were purified by column chromatography (silica gel, petroleum ether/ ethyl acetate = 12:1 to 8:1), affording **intermediate 19** as a light yellow gum (125.7 g, 83 % yield) (mixture of anomers α/β).

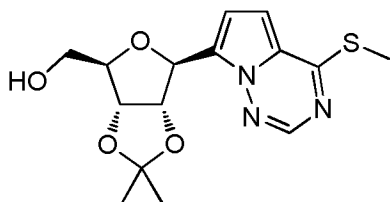
Preparation of **intermediate 20**



1M BCl₃ in CH₂Cl₂ (860 mL, 860 mmol) was added dropwise at -78°C to a stirred solution of **intermediate 19** (75.0 g, 132.1 mmol) in DCM (1.20 L) dropwise over period of 2.5 hours under N₂. The mixture was stirred at -78°C for 1 hour. The reaction mixture was slowly warmed to -40°C. The reaction mixture was poured into MeOH (2.5 L, 20°C) with stirring. The resulting red solution was stirred for 3 hours. Water (250 mL) was added into the mixture and left at 20°C for 16 hours. The solution was portion wise

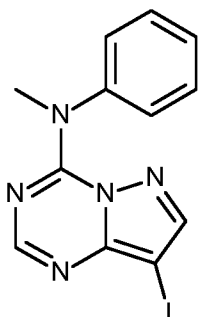
poured onto solid NaHCO_3 (500 g) carefully with vigorous stirring (gas evolution, the color of mixture was turned from orange-red to yellow). The resulting suspension was filtered and the filtrate was concentrated under reduced pressure. The residue was dispensed in $i\text{PrOH}/\text{CH}_2\text{Cl}_2$ (1:3, 1 L) then filtered (to remove some inorganic salt) and the filtrate was concentrated under reduced pressure. The residue was triturated with petroleum ether (500 mL x3) to afford crude **intermediate 20** (40.2 g, crude) (mixture of anomers α/β) as an orange solid, which used in the next reaction step without further purification.

10 Preparation of **intermediate 21**



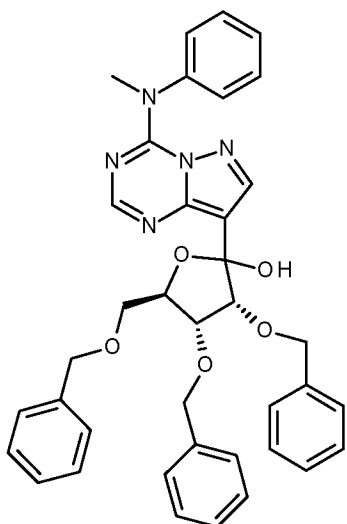
To a suspension of **intermediate 20** (40.2 g, crude) and 2,2-dimethoxypropane (34 mL, 277.2 mmol) in acetone (600 mL) was added $\text{TsOH}\cdot\text{H}_2\text{O}$ (5.92 g, 31.1 mmol, 0.23 eq) at 25°C (pH = 2). The resulting mixture was heated at 60°C for 2 hours. After being cooled to 25°C, the reaction mixture was concentrated under reduced pressure. The residue was partitioned between ethyl acetate (500 mL) and saturated aqueous NaHCO_3 solution (500 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (three times 200 mL). The combined organic layers were washed with brine (100 mL), dried over MgSO_4 , filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, CH_2Cl_2 /Ethyl acetate = 10/1 to 6/1). The fractions containing **intermediate 21** were combined and concentrated under reduced pressure. The residue (28 g, about 80% purity) was purified again by column chromatography (silica gel, Petroleum ether/Ethyl acetate = 20/1 to 4/1). The desired fractions were combined and concentrated under reduced pressure. The residue was diluted with CH_2Cl_2 (15 mL) then petroleum ether/ethyl acetate (4:1, 200 mL) was added. The mixture was concentrated to about 150 mL and solids were precipitated. The slurry was diluted with petroleum ether to about 400 mL and stirred for 16 hours at 20 °C. The mixture was filtered and the solid was rinsed with petroleum ether/ethyl acetate (20/1, 100 mL). The solids were collected and dried under high vacuum to afford pure **intermediate 21** as white solid (18.6 g, yield: 41.7% for 2 steps) (pure β anomer).

Example A6

Preparation of *intermediate 22*

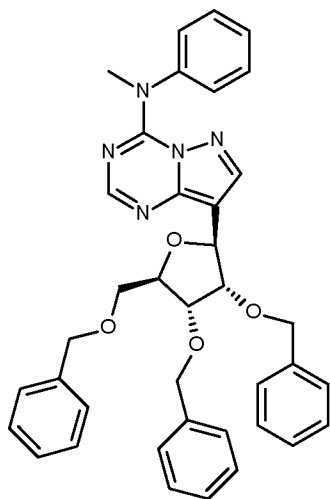
A solution of compound 8-iodo-3H-pyrazolo [1,5-a] [1,3,5] triazin-4-one (2000 mg, 7.6 mmol), phosphorus oxychloride (15mL, 160.3 mmol) and N, N-dimethylaminopyridine (2798 mg, 22.9 mmol) was heated at reflux for 2 hours. The volatile compounds were removed by evaporation. Then the mixture was dried under reduced pressure for 1 hour. The residue was dissolved in dry CH₂Cl₂ and cooled in an ice bath before the dropwise addition of N-methylaniline (3315 μ L, 30.5 mmol, followed by trimethylamine (6.4 mL, 45.8 mmol). The solution was stirred at room temperature for 1 hour. Water was added and the aqueous layer was extracted with CH₂Cl₂. The organic layers were combined and washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. EtOAc was added to the brown solid, which was filtered off, washed with a few quantities of EtOAc, and dried under vacuum overnight to afford the *intermediate 22* (1542 mg, 4.39 mmol, 57.5% yield) as a white solid.

Example A7

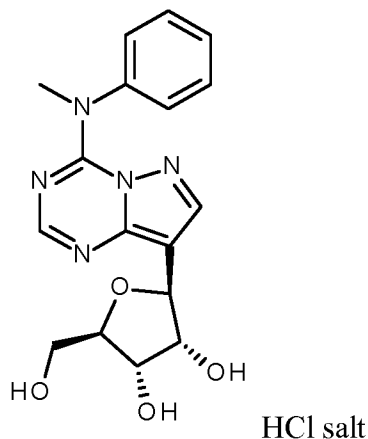
Preparation of *intermediate 23*

Intermediate 22 (1400 mg, 4 mmol) was dissolved in 50 mL dry THF (dried on sodium) and cooled to -78°C under N₂. Isopropyl magnesium chloride (3.4 mL, 4.4 mmol, 1.3M) was added drop wise to the reaction flask and the mixture was stirred for 30 min. D-Lyxonic acid, 2,3,5-tris-*O*-(phenylmethyl)-, γ -lactone (= **intermediate 17** = *commercial*) was dissolved in 20 mL of dry THF and dropwise added to the reaction mixture and the reaction mixture was further stirred at -78°C. After two hours the reaction mixture was allowed to warm to room temperature and was stirred for another 2 hours. The reaction mixture was quenched with saturated aqueous NH₄Cl and the mixture was diluted with EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with water and brine, dried (MgSO₄) and concentrated under reduced pressure. The crude product was purified by column chromatography (heptane/EtOAc: 8/2 to 1/1) to give **intermediate 23** (170 mg, 0.26 mmol, 6.6% yield)

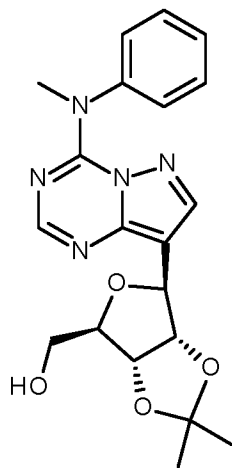
15 Preparation of **intermediate 24**



Et₃SiH (2262.8 μ L, 14.17 mmol) was added in one portion to a stirred solution of **intermediate 23** (2280 mg, 3.54 mmol) in dry CH₂Cl₂ (34 mL) on an ice bath (0°C) under an atmosphere of nitrogen. After 5 min, boron trifluoride etherate (2234 μ L, 17.7 mmol) was added over 1 min by syringe. The resulting mixture was stirred overnight. The reaction mixture was poured into saturated Na₂CO₃ and extracted with CH₂Cl₂. The organic layer was dried with MgSO₄, and concentrated under vacuum. The crude product was purified by column chromatography (heptane/EtOAc: 8/2 to 1/1 to give **intermediate 24** (1810 mg, 2.88 mmol, 81.4% yield).

Preparation of *intermediate 25*

- BCl₃ (1M in DCM, 20.4 mL, 20.4 mmol) was added to a solution of *intermediate 24* (1600 mg, 2.55 mmol) and pentamethylbenzene (1889 mg, 12.7 mmol) in DCM at -78°C. The reaction mixture was stirred for 2 hours after which the reaction was quenched with MeOH and subsequently concentrated in vacuo. The solid was triturated with heptane 3 times and dried in vacuo to give *intermediate 25* (1100 mg, 2.79 mmol) as the HCl salt, which was used as such without further purification.

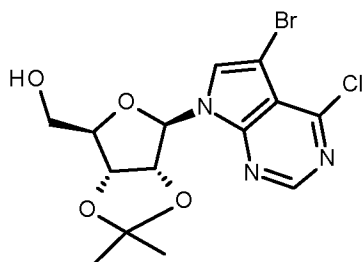
10 Preparation of *intermediate 26*

- Dimethoxypropane (1417 μ L, 11.4 mmol) was added to a mixture of *intermediate 25* (900 mg, 2.28 mmol) and p-TSA (434.7 mg, 2.28 mmol) in acetone, the reaction mixture was stirred at room temperature for 4 hours. Sat. NaHCO₃ was added and the mixture was extracted with EtOAc. The combined organic layers were washed with water and brine, dried with MgSO₄ and concentrated. The residue was purified by silicagel column

chromatography (heptane/ethyl acetate: 20/80 to 50/50) to give *intermediate 26* (648 mg, 1.63 mmol, 71.3% yield).

Example A8

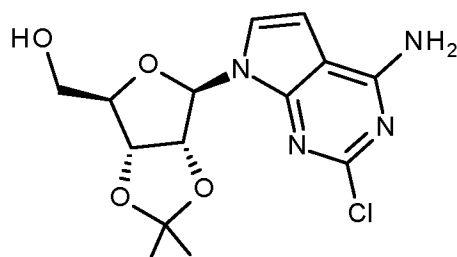
5 Preparation of *intermediate 27*



To a stirred solution of *intermediate 1* (5.39 g, 16.55 mmol) in DMF (25 mL) at room temperature was added portion wise N-bromo succinimide (2.95 g, 16.55 mmol). The mixture was stirred at room temperature for 1 hour. The reaction mixture was poured
10 into water and extracted with ethyl acetate. The combined organic phases were washed with water, dried, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (DCM/MeOH: 99/1) to afford *intermediate 27* (1.8 g, 4.45 mmol, 26.8% yield)

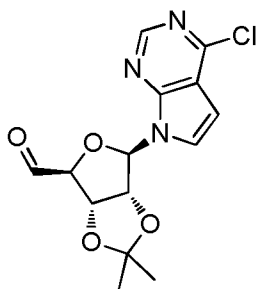
15 Example A9

Preparation of *intermediate 28*



To a solution of *intermediate 15* (1.8 g, 5 mmol) in 1,4-dioxane (30 mL) was added NH₃.H₂O (30 mL). The reaction mixture was heated to 80°C for 12 hours in a sealed
20 tube. The mixture was cooled to room temperature and the solvent was evaporated in vacuum affording *intermediate 28* (1.8 g, 98% yield) as yellow oil.

Example A10

Preparation of *intermediate 29*

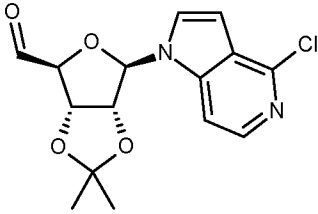
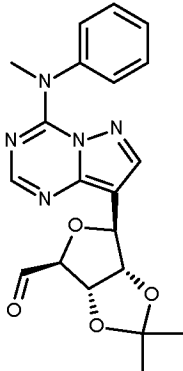
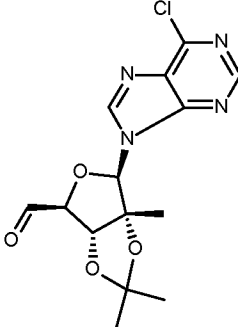
To a mixture of *intermediate 1* (2.00 g, 6.18 mmol) in DCM (40 mL) was added Dess-
 5 Martin periodinane (5.24 g, 12.36 mmol) in one portion at 0°C under N₂. The mixture
 was stirred at 0°C for 3 hours. To the mixture was added Na₂S₂O₃ (4 g) in saturated
 NaHCO₃ (20 mL) and the mixture was stirred for 10 min. The aqueous phase was
 extracted with DCM (three times 20 mL). The combined organic phases were washed
 with saturated brine (two times 20 mL), dried with anhydrous MgSO₄, filtered and
 10 concentrated in vacuum to afford *intermediate 29* (1.80 g, crude) as light yellow gum.
 The crude product was directly used for the next reaction step without further
 purification.

Below intermediates were prepared by an analogous reaction protocol as was used for
 the preparation of *intermediate 29* using the appropriate starting materials (Table 3).

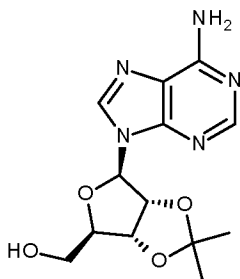
15 Table 3:

Intermediate	structure	Starting material
<i>30</i>		<i>6-chloro-9-beta-d-(2,3-isopropylidene)ribofuranosylpurine</i>
<i>31</i>		<i>intermediate 10</i>

Intermediate	structure	Starting material
32		<i>intermediate 27</i>
33		<i>Intermediate 12</i>
34		<i>intermediate 15</i>
35		<i>intermediate 9</i>
36		<i>intermediate 14</i>
37		<i>intermediate 21</i>
38		<i>Intermediate 28</i>

Intermediate	structure	Starting material
39		<i>Intermediate 7</i>
40		<i>Intermediate 26</i>
41		<i>Intermediate 4</i>

Example A11

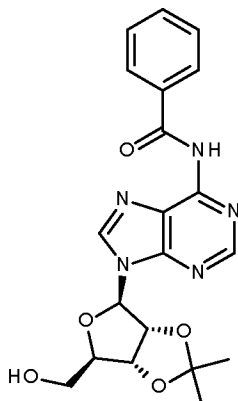
Preparation of *intermediate 42*

- 5 A solution of adenosine (20 g, 74.8 mmol) and p-toluenesulfonic acid monohydrate (14.8 g, 77.9 mmol) in acetone (786 mL) was stirred for 30 min at r.t. and then triethyl orthoformate anhydrous (57 mL, 342.8 mmol) was added. After 2 days volatiles were evaporated and the residue was partitioned in NaHCO₃ aq. and CH₂Cl₂. The solid was filtered and was washed with water and ether to give 20.2 g of *intermediate 42*. The

filtrate was evaporated and the residue was partitioned in NaHCO_3 ac and CH_2Cl_2 . The separated organic layer was washed with brine, dried over MgSO_4 and evaporated. The yellow solid was washed with ether to give another 1.89 g of *intermediate 42*. In total 22.1 g of *intermediate 42* (22.1 g, 69.7 mmol, 93% yield) is formed and isolated.

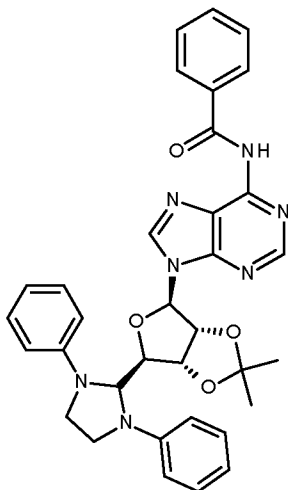
5

Preparation of *intermediate 43*

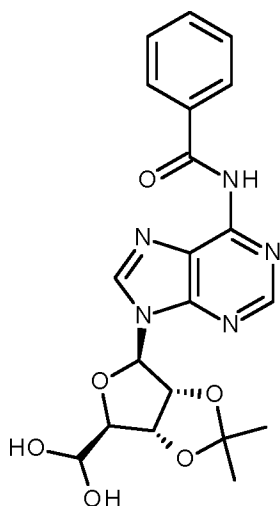


A solution of *intermediate 42* (26 g, 84.6 mmol) in pyridine (436 mL) was cooled on an ice bath under nitrogen atmosphere and chlorotrimethylsilane (54.1 mL, 423 mmol) was added over 10 min. The reaction mixture was stirred at room temperature for 2 hours. Then the solution was cooled again on an ice bath and benzoyl chloride (12.8 mL, 110 mmol) was added slowly. The reaction mixture was stirred at room temperature overnight. An extra amount of Benzoyl chloride (7 mL) was added and the mixture was stirred at room temperature overnight. The mixture was cooled to 0°C and diluted with water (100 mL). After 10 min, a NH_3 -solution in water (50 ml) was added and the mixture was stirred overnight at room temperature. An additional amount of ammonia (10 mL) was added and the reaction mixture was stirred overnight. The solvents were evaporated. The residue was dissolved in CH_2Cl_2 (100 mL), washed in successively with 1M HCl (2 times 100 mL), saturated NaHCO_3 (100 mL), H_2O (100 mL) and brine (100 mL), dried over MgSO_4 and evaporated yielding a yellow solid. The solid was purified by column chromatography (silica; DCM/MeOH from 100:0 to 0:100). The desired fractions were collected and concentrated in vacuo to give *intermediate 43* (25.91 g, 62.3 mmol 74% yield).

20

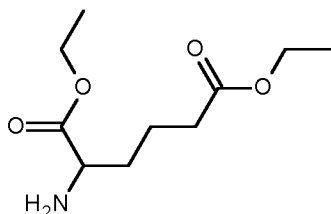
Preparation of *intermediate 44*

A solution of *intermediate 43* (48.53 g, 0.12 mol) and N,N'-dicyclohexylcarbodiimide (72.8 g, 0.35 mol) in DMSO anhydrous (266 mL) was stirred with ice cooling while
5 dichloroacetic acid (4.87 mL, 0.06 mol) was added dropwise. The mixture was stirred at r.t. for 90 min until the reaction was completed. A solution of oxalic acid (21.2 g, 0.24 mol) in MeOH (117.7 mL) was slowly added, and after 30 min at r.t. the mixture was filtered and the crystalline residue of dicyclohexylureum was washed with cold MeOH. N,N'-diphenylethylenediamine (28.8 g, 0.14 mol) was added to the combined filtrate and
10 washings and the resulting solution was stored at room temperature for 1 hour. Water was then added to slight turbidity and the solid was filtered. The filtrate was partitioned between water and chloroform and the organic phase was washed twice with water, dried over MgSO₄ and evaporated. The solid and the residue of organic phase were recrystallized in ethanol to give *intermediate 44* (34.79g, 47.8 mmol, 40% yield).

15 Preparation of *intermediate 45*

- Dowex 50WX4 (CAS: 69011-20-7) (26 g) was added to a solution of *intermediate 44* (13.05 g, 21.6 mmol) in THF (520 mL) and water (520 mL). The suspension was stirred at room temperature for 5 hours. The resin was removed by filtration and washed with THF (4 times 36 mL). The combined filtrates were evaporated to half its volume and the
- 5 resulting white solid was filtered, washed with water and dried in vacuo giving *intermediate 45* (5.90 g, 12.7 mmol, 64% yield)

Example A12

Preparation of *intermediate 46*

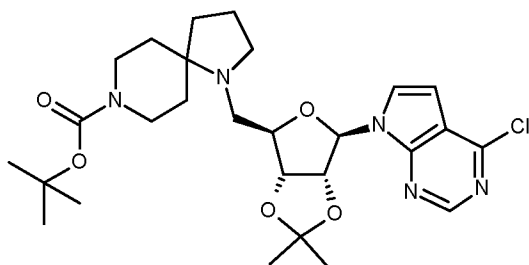
- 10 SOCl₂ (11.25 mL, 1.64g/mL, 155 mmol) was added dropwise to a stirred suspension of dl-2-aminoadipic acid (10 g, 62.1 mmol) in EtOH (200 mL) at 0°C. After addition the reaction mixture was stirred at room temperature for 2 days. The solvents were evaporated to give *intermediate 46* (17.1 g 78.7 mmol), which was used as such without further purification.
- 15 Below intermediates were prepared by an analogous reaction protocol as was used for the preparation of *intermediate 46* using the appropriate starting materials (Table 4).

Table 4

Intermediate	Structure	Starting materials
47		5,5-difluoro-2-piperidinecarboxylic acid

Example A13

- 20 Preparation of *intermediate 48*



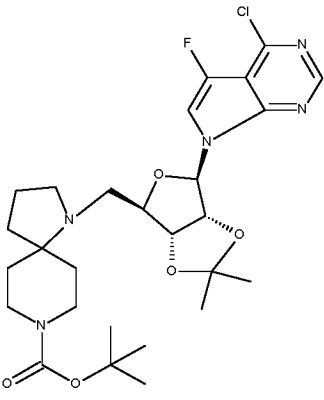
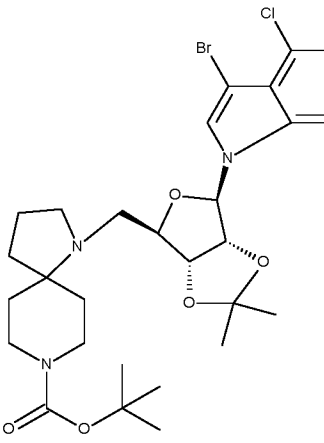
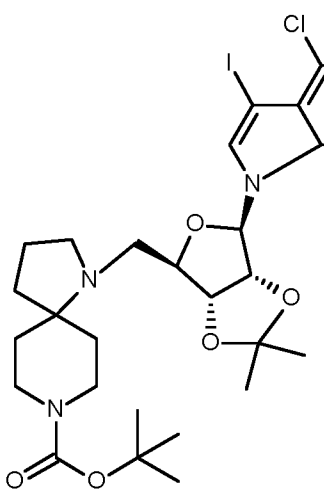
Sodium triacetoxyborohydride (163.8 g, 772.7 mmol) was added to a stirred solution of 1,8-diazospiro[4.5]decane-8-carboxylic acid tert-butyl ester (65 g, 270.4 mmol) and acetic acid (15.5 mL, 270.4 mmol) in DCM (3000 mL). Then a solution of *intermediate* 29 (125.1 g, 386.3 mmol) in DCM (2500 mL) was added dropwise to the reaction mixture at room temperature. After addition the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was filtered over a pad of Celite. The pad was washed with DCM (3x). The solvents of the filtrate were evaporated. The residue was dissolved in DCM, washed two times with a saturated aqueous NaHCO₃ solution, washed with brine, dried with MgSO₄, filtered and the solvents of the filtrate evaporated yielding *intermediate* 48 (188.1 g, 236.8 mmol, 61% yield).

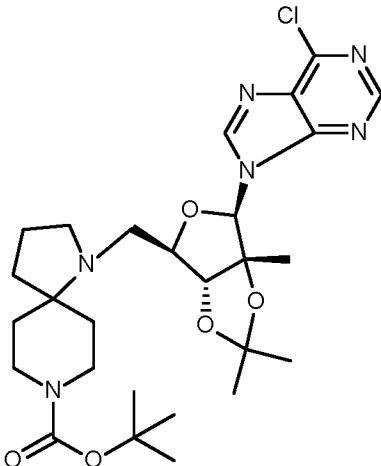
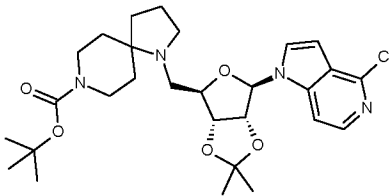
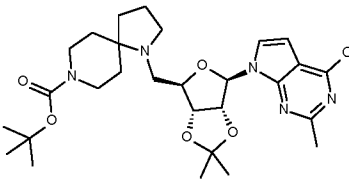
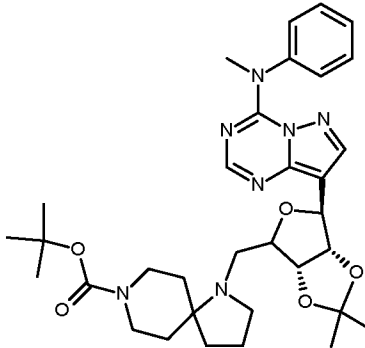
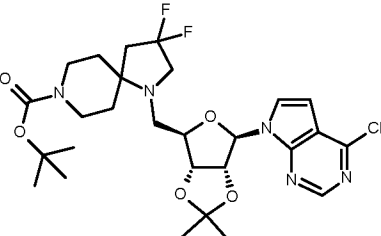
Alternatively also sodium cyanoborohydride in MeOH instead of triacetoxyborohydride in DCM can be used to perform the reaction.

Below intermediates were prepared by an analogous reaction protocol as was used for the preparation of *intermediate* 48 using the appropriate starting materials (Table 5).

Table 5

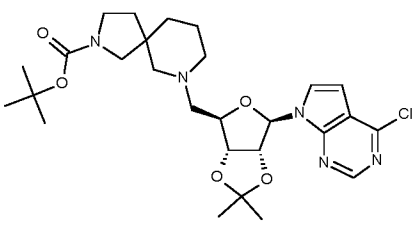
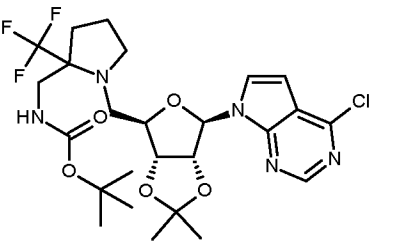
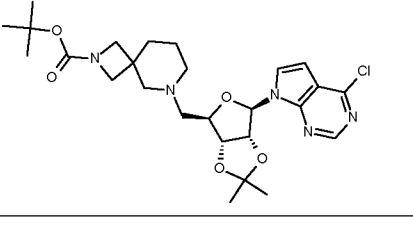
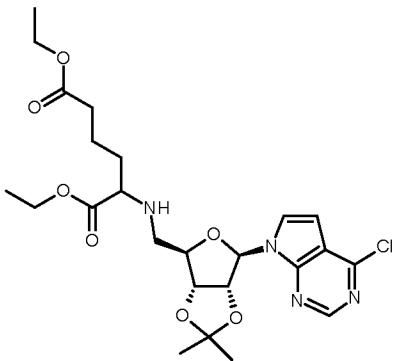
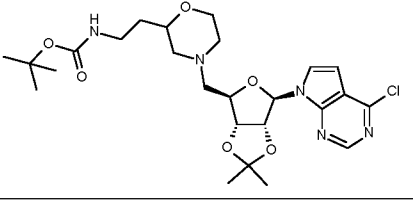
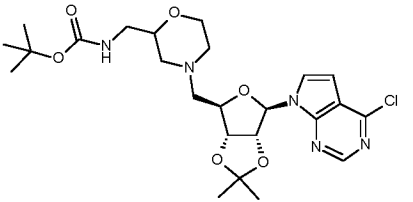
Inter-mediate	Structure	Starting materials and conditions
49		a) <i>Intermediate</i> 30 b) NaBH(OAc) ₃ in DCM c) 1,8-diazospiro[4.5] decane-8-carboxylic acid tert-butyl ester
50		a) <i>Intermediate</i> 30 b) NaBH(OAc) ₃ in DCM c) 1,8-diazospiro[4.5] decane-8-carboxylic acid tert-butyl ester

Inter- mediate	Structure	Starting materials and conditions
52		<i>a) Intermediate 31</i> <i>b) NaBH₃CN in MeOH</i> <i>c) 1,8-diazospiro [4.5]decane-8-carboxylic acid tert-butyl ester</i>
53		<i>a) Intermediate 32</i> <i>b) NaBH₃CN in MeOH</i> <i>c) 1,8-diazospiro [4.5]decane-8-carboxylic acid tert-butyl ester</i>
54		<i>a) Intermediate 33</i> <i>b) NaBH₃CN in MeOH</i> <i>c) 1,8-diazospiro [4.5]decane-8-carboxylic acid tert-butyl ester</i>

Inter- mediate	Structure	Starting materials and conditions
55		a) <i>Intermediate 41</i> b) <i>NaBH₃CN in MeOH</i> c) <i>1,8-diazospiro [4.5]decane-8-carboxylic acid tert-butyl ester</i>
56		a) <i>Intermediate 39</i> b) <i>NaBH₃CN in MeOH</i> c) <i>1,8-diazospiro [4.5]decane-8-carboxylic acid tert-butyl ester</i>
57		a) <i>Intermediate 35</i> b) <i>NaBH₃CN in MeOH</i> c) <i>1,8-diazospiro [4.5]decane-8-carboxylic acid tert-butyl ester</i>
58		a) <i>Intermediate 40</i> b) <i>NaBH(OAc)₃ in DCM</i> c) <i>1,8-diazospiro [4.5]decane-8-carboxylic acid tert-butyl ester</i>
59		a) <i>Intermediate 29</i> b) <i>NaBH(OAc)₃ in DCM</i> c) <i>3,3-difluoro-1,8-diazospiro[4.5]decane-8-carboxylic acid tert-butyl ester</i>

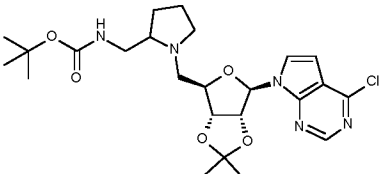
Inter- mediate	Structure	Starting materials and conditions
60		a) <i>Intermediate 29</i> b) <i>NaBH(OAc)₃ in DCM</i> c) <i>8-methyl-1,8-diazaspiro[4.5]decane</i>
61		a) <i>Intermediate 38</i> b) <i>NaBH₃CN in MeOH</i> c) <i>8-methyl-1,8-diazaspiro[4.5]decane</i>
62		a) <i>Intermediate 34</i> b) <i>NaBH₃CN in MeOH</i> c) <i>8-methyl-1,8-diazaspiro[4.5]decane</i>
63		a) <i>Intermediate 39</i> b) <i>NaBH₃CN in MeOH</i> c) <i>8-methyl-1,8-diazaspiro[4.5]decane</i>
64		a) <i>Intermediate 35</i> b) <i>NaBH₃CN in MeOH</i> c) <i>8-methyl-1,8-diazaspiro[4.5]decane</i>
65		a) <i>Intermediate 29</i> b) <i>NaBH(OAc)₃ in DCM</i> c) <i>tert-butyl 5oxa-2,8-diazaspiro[3.5]nonane-2-carboxylate</i>

Inter- mediate	Structure	Starting materials and conditions
66		a) <i>Intermediate 29</i> b) <i>NaBH₃CN in MeOH</i> c) <i>tert-butyl 1-oxa-4,8-diazaspiro[5.5]undecane-8-carboxylate</i>
67		a) <i>Intermediate 29</i> b) <i>NaBH(OAc)₃ in DCM</i> c) <i>tert-butyl 1-oxa-4,8-diazaspiro[5.5]undecane-4-carboxylate</i>
68		a) <i>Intermediate 29</i> b) <i>NaBH(OAc)₃ in DCM</i> c) <i>tert-butyl 1,8-diazaspiro[5.5]undecane-1-carboxylate</i>
69		a) <i>Intermediate 29</i> b) <i>NaBH(OAc)₃ in DCM</i> c) <i>tert-butyl 4-oxa-1,8-diazaspiro[5.5]undecane-1-carboxylate</i>
70		a) <i>Intermediate 29</i> b) <i>NaBH₃CN in MeOH</i> c) <i>tert-butyl 10,10-difluoro-2,7-diazaspiro[4.5]decane-7-carboxylate</i>
71		a) <i>Intermediate 29</i> b) <i>NaBH(OAc)₃ in DCM</i> c) <i>tert-butyl 1,7-diazaspiro[4.5]decane-1-carboxylate</i>

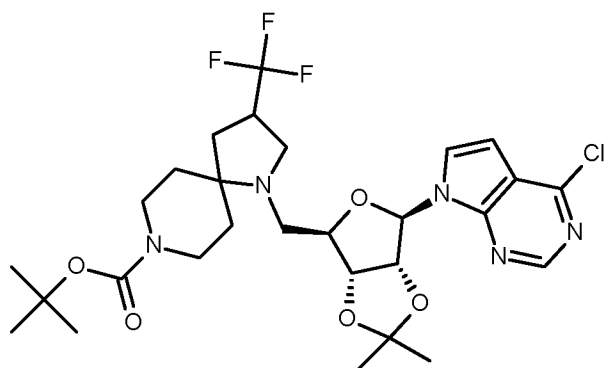
Inter- mediate	Structure	Starting materials and conditions
72		a) <i>Intermediate 29</i> b) <i>NaBH(OAc)₃ in DCM</i> c) <i>tert-butyl 2,7-diazaspiro[4.5]decane-2-carboxylate</i>
73		a) <i>Intermediate 29</i> b) <i>NaBH₃CN in MeOH</i> c) <i>tert-butyl {[2-(trifluoromethyl)pyrrolidin-2-yl]methyl} carbamate</i>
74		a) <i>Intermediate 29</i> b) <i>NaBH(OAc)₃ in DCM</i> c) <i>tert-butyl 2,6-diazaspiro[3.5]nonane-2-carboxylate</i>
75		a) <i>Intermediate 29</i> b) <i>NaBH(OAc)₃ in DCM</i> c) <i>Intermediate 46</i>
76		a) <i>Intermediate 29</i> b) <i>NaBH(OAc)₃ in DCM</i> c) <i>tert-butyl (2-morpholin-2-ylethyl)carbamate</i>
77		a) <i>Intermediate 29</i> b) <i>NaBH(OAc)₃ in DCM</i> c) <i>tert-butyl morpholin-2-ylmethylcarbamate</i>

Inter- mediate	Structure	Starting materials and conditions
78		a) <i>Intermediate 29</i> b) <i>NaBH(OAc)₃ in DCM</i> c) <i>(S)-tert-butyl (morpholin-3-ylmethyl)carbamate</i>
79		a) <i>Intermediate 29</i> b) <i>NaBH(OAc)₃ in DCM</i> c) <i>(R)-tert-butyl (morpholin-3-ylmethyl)carbamate</i>
80		a) <i>Intermediate 29</i> b) <i>NaBH(OAc)₃ in DCM</i> c) <i>Intermediate 47</i>
81		a) <i>intermediate 29</i> b) <i>NaBH(OAc)₃ in DCM</i> c) <i>3-N-boc-aminomethyl piperidine</i>
82		a) <i>Intermediate 29</i> b) <i>NaBH(OAc)₃ in DCM</i> c) <i>2-(boc-aminomethyl)-piperidine</i>
83		a) <i>Intermediate 29</i> b) <i>NaBH(OAc)₃ in DCM</i> c) <i>3-boc-aminopiperidine</i>
84		a) <i>Intermediate 29</i> b) <i>NaBH(OAc)₃ in DCM</i> c) <i>(S)-2-(boc-aminomethyl)-4,4-difluoropyrrolidine</i>

Inter- mediate	Structure	Starting materials and conditions
85		a) <i>Intermediate 29</i> b) $\text{NaBH}(\text{OAc})_3$ in DCM c) 3-(tert-butoxycarbonylamino)pyrrolidine
86		a) <i>Intermediate 29</i> b) $\text{NaBH}(\text{OAc})_3$ in DCM c) tert-butyl 2-(pyrrolidine-3-yl)ethylcarbamate
87		a) <i>Intermediate 29</i> b) $\text{NaBH}(\text{OAc})_3$ in DCM c) (R)-2-(boc-aminomethyl)-4,4-difluoropyrrolidine
88		a) <i>Intermediate 29</i> b) $\text{NaBH}(\text{OAc})_3$ in DCM c) 3-boc-aminomethyl pyrrolidine
89		a) <i>Intermediate 29</i> b) $\text{NaBH}(\text{OAc})_3$ in DCM c) tert-butyl {2-[(2S)-pyrrolidin-2-yl]ethyl} carbamate
90a		a) <i>Intermediate 30</i> b) $\text{NaBH}(\text{OAc})_3$ in DCM c) tert-butyl {2-[(2R)-pyrrolidin-2-yl]ethyl} carbamate
90b		d) <i>Intermediate 30</i> e) $\text{NaBH}(\text{OAc})_3$ in DCM f) tert-butyl {2-[(2S)-pyrrolidin-2-yl]ethyl} carbamate

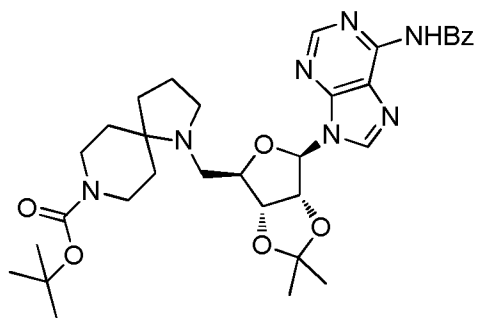
Inter- mediate	Structure	Starting materials and conditions
91		a) <i>Intermediate 29</i> b) <i>NaBH(OAc)₃ in DCM</i> c) <i>2-boc amino methylpyrrolidine</i>

Example A14

Preparation of *intermediate 92*

- 5 TFA (0.56 mL, 7.3 mmol) was added to a stirred solution of N,N'-di-t-boc-3-(trifluoromethyl)-1,8-diazaspiro[4.5]decane (0.5 g, 1.2 mmol) in DCM (20 mL) at room temperature.. The reaction mixture was stirred at room temperature for 18 hours. 50 mL DIPE was added to the reaction mixture. The resulting suspension was stirred for 18 hours at room temperature. The precipitate was filtered off and dried on the air. The residue was stirred in DCM (15 mL) and then AcOH (0.07 mL, 1.2 mmol) and NaBH(OAc)₃ (0.519 g, 2.45 mmol) were added. The reaction mixture was stirred for 10 minutes and then a solution of *intermediate 29* (0.55 g, 1.7 mmol) in DCM (8 mL) was added dropwise. After addition the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was filtered over a pad of Celite. The pad was washed three times with DCM. The solvents of the filtrate were evaporated. The residue was dissolved in DCM, washed two times with a saturated aqueous NaHCO₃ solution, washed with brine, dried with MgSO₄, filtered and the solvents of the filtrate evaporated. The residue was dissolved in DCM and purified over a SiO₂ column, type Grace Reveleris SRC, 12 g, Si 40, on a Armen Spot II Ultimate purification system using DCM and MeOH as eluens in a gradient starting from 100% DCM and ending with 20% MeOH and 80% DCM. The fractions containing product were combined and the solvents were evaporated to give *intermediate 92* (218 mg, 8.7% yield).

Example A15

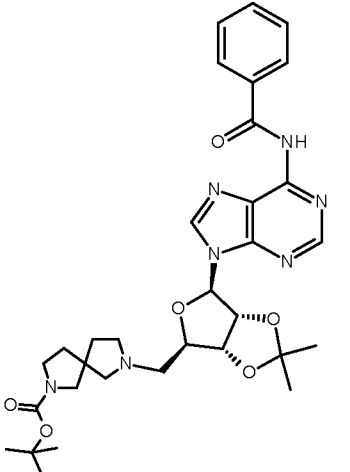
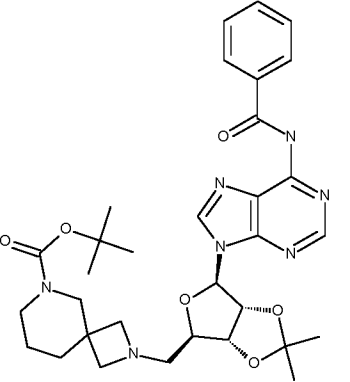
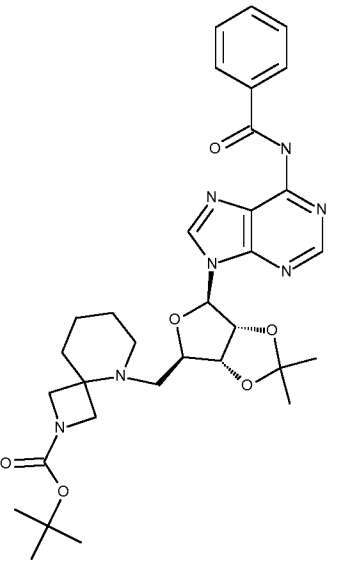
Preparation of *intermediate 93*

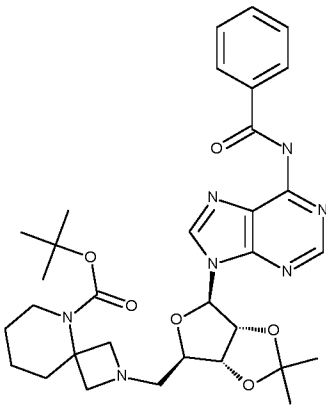
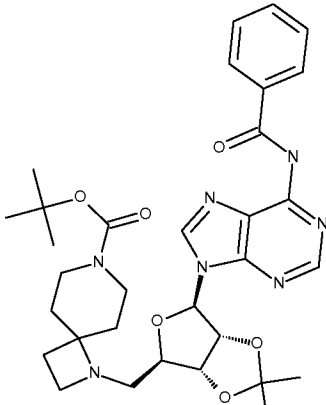
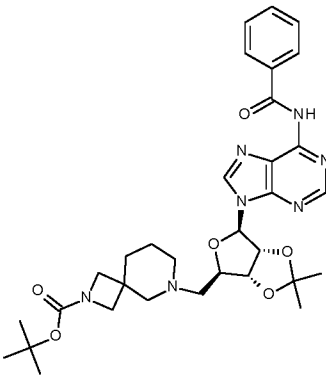
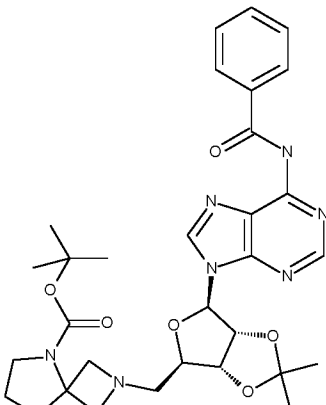
- Intermediate 45** (0.48g, 0.95 mmol) tert-butyl 1,8-diazospiro[4.5]decane-8-carboxylate (0.3g, 1.051 mmol) and sodium acetate (0.0391g, 0.477 mmol) were dissolved in dichloroethane (9 mL) and stirred for 30 min. Then sodium triacetoxyborohydride (0.304g, 1.433 mmol) was added and the solution was stirred overnight at room temperature. The mixture was diluted with DCM (50 mL) and washed with Na₂CO₃ (1M, 50 mL). The organic layer was dried (MgSO₄) and filtered. The solvents were evaporated to dryness to give crude **intermediate 93** (0.824g, 1 mmol, yield: 103%). No further purification was done.

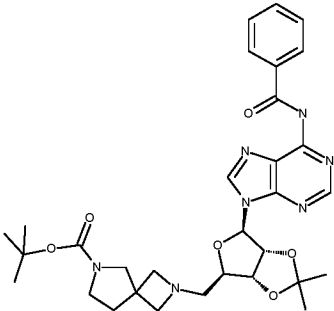
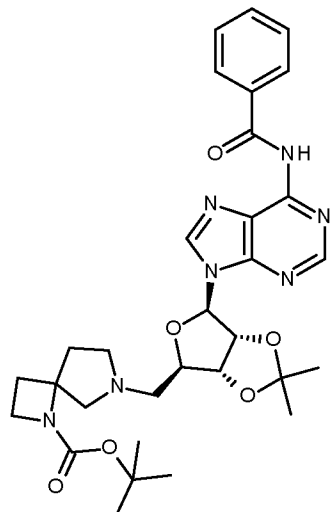
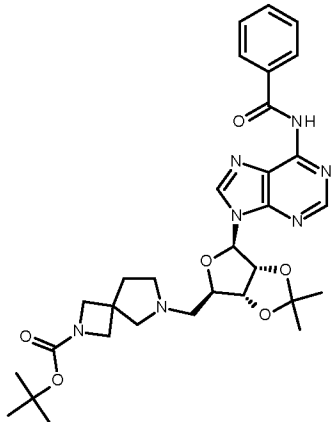
Below intermediates were prepared by an analogous reaction protocol as was used for the preparation of **intermediate 93** using the appropriate starting materials (Table 6).

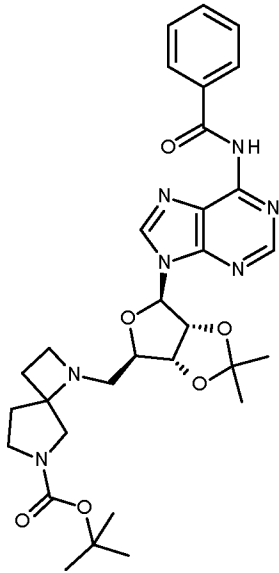
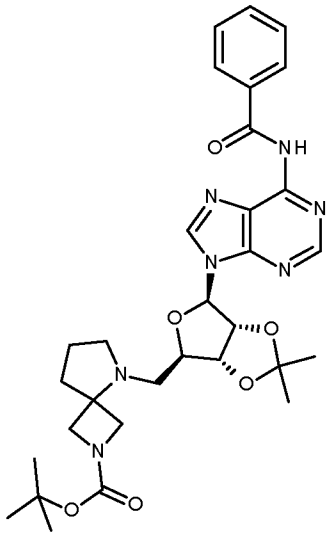
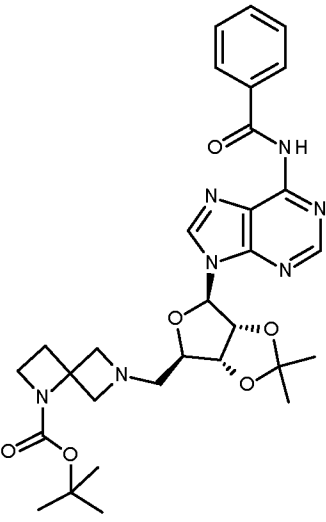
Table 6:

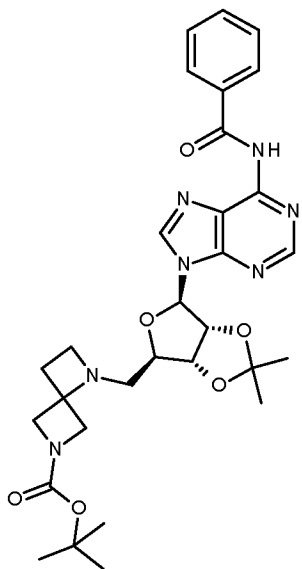
Intermediate	Structure	Starting materials and conditions
94		a) <i>intermediate 45</i> b) <i>tert-Butyl 2,8-diazaspiro[4.5]decane-8-carboxylate</i> c) $\text{NaBH}(\text{OAc})_3$ in DCM
95		a) <i>intermediate 45</i> b) <i>tert-Butyl 1,7-diazaspiro[4.4]nonane-7-carboxylate</i> c) $\text{NaBH}(\text{OAc})_3$ in DCM
96		a) <i>intermediate 45</i> b) <i>tert-Butyl 1,7-diazaspiro[4.4]nonane-1-carboxylate</i> c) $\text{NaBH}(\text{OAc})_3$ in dichloroethane

Intermediate	Structure	Starting materials and conditions
97		a) <i>intermediate 45</i> b) <i>Tert-Butyl 2,7-Diaza-Spiro[4.4]Nonane-2-Carboxylate</i> c) $\text{NaBH}(\text{OAc})_3$ in DCM
98		a) <i>intermediate 45</i> b) <i>tert-Butyl-2,6-diazaspiro[3.5]nonane-6-carboxylate-oxalate</i> c) $\text{NaBH}(\text{OAc})_3$ in dichloroethane
99		a) <i>intermediate 45</i> b) <i>tert-Butyl 2,5-diazaspiro[3.5]nonane-2-carboxylate</i> c) $\text{NaBH}(\text{OAc})_3$ in dichloroethane

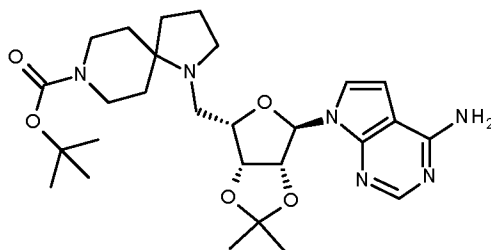
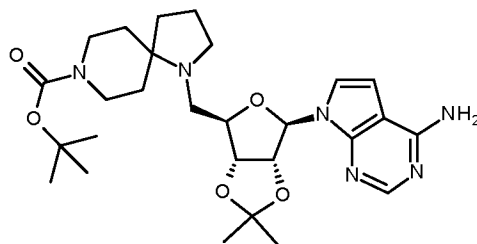
Intermediate	Structure	Starting materials and conditions
100		a) intermediate 45 b) <i>tert</i>-Butyl 2,5-diazaspiro[3.5]nonane-5-carboxylate c) NaBH(OAc)₃ in dichloroethane
101		a) intermediate 45 b) <i>tert</i>-Butyl 1,7-diazaspiro[3.5]nonane-7-carboxylate c) NaBH(OAc)₃ in dichloroethane
102		a) intermediate 45 b) <i>tert</i>-Butyl 2,6-diazaspiro[3.5]nonane-2-carboxylate oxalate c) NaBH(OAc)₃ in dichloroethane
103		a) intermediate 45 b) <i>tert</i>-Butyl 2,5-diazaspiro[3.4]octane-5-carboxylate c) NaBH(OAc)₃ in dichloroethane

Intermediate	Structure	Starting materials and conditions
104		a) <i>intermediate 45</i> b) <i>tert-Butyl 2,6-diazaspiro[3.4]octane-6-carboxylate</i> c) $\text{NaBH}(\text{OAc})_3$ in dichloroethane
105		a) <i>intermediate 45</i> b) <i>tert-Butyl 1,6-diazaspiro[3.4]octane-1-carboxylate</i> c) $\text{NaBH}(\text{OAc})_3$ in dichloroethane
106		a) <i>intermediate 45</i> b) <i>tert-Butyl 2,6-diazaspiro[3.4]octane-2-carboxylate</i> c) $\text{NaBH}(\text{OAc})_3$ in dichloroethane

Intermediate	Structure	Starting materials and conditions
107		a) <i>intermediate 45</i> b) <i>tert-Butyl-1,6-diazaspiro[3.4]octane-6-carboxylate</i> c) $\text{NaBH}(\text{OAc})_3$ in dichloroethane
108		a) <i>intermediate 45</i> b) <i>tert-butyl 2,5-diazaspiro[3.4]octane-2-carboxylate</i> c) $\text{NaBH}(\text{OAc})_3$ in dichloroethane
109		a) <i>intermediate 45</i> b) <i>tert-Butyl 1,6-diazaspiro[3.3]heptane-1-carboxylate</i> c) $\text{NaBH}(\text{OAc})_3$ in dichloroethane

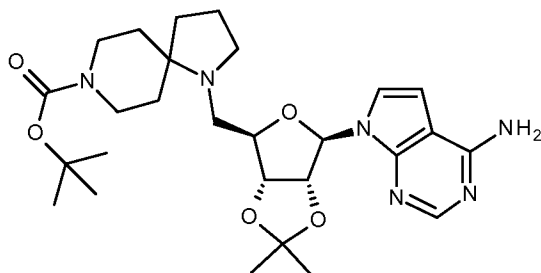
Intermediate	Structure	Starting materials and conditions
110		a) <i>intermediate 45</i> b) <i>tert-Butyl 1,6-diazaspiro[3.3]heptane-6-carboxylate</i> c) $\text{NaBH}(\text{OAc})_3$ in dichloroethane

Example A17

Preparation of *intermediate 113* and *intermediate 114*5 *intermediate 113**intermediate 114*

A solution of crude *intermediate 50* (1.3 g, 2.37 mmol) in NH_3 (0.34 mL, 2.4 mmol, 7M in MeOH) was stirred at 130°C for 4 hours in a Biotage microwave reactor. The solvent was removed and a purification was performed via Prep HPLC (Stationary phase: RP XBridge Prep C18 OBD-10 μm , 30x150mm, Mobile phase: 0.1%TFA solution in water + 5% CH_3CN , CH_3CN) to give *intermediate 113* (90 mg, 0.17 mmol) and *intermediate 114* (300 mg, 0.567 mmol, 24% yield).

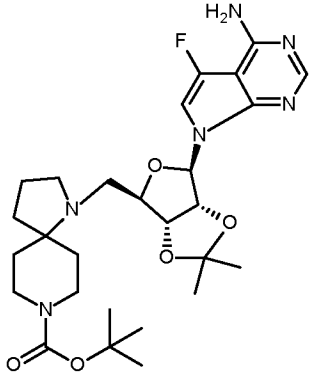
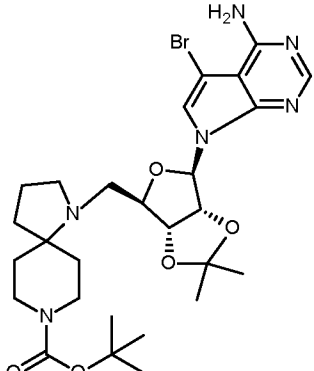
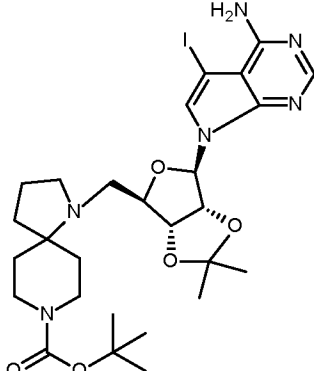
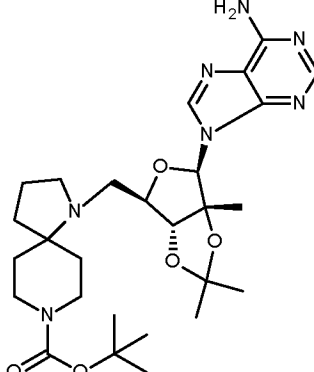
Example A18

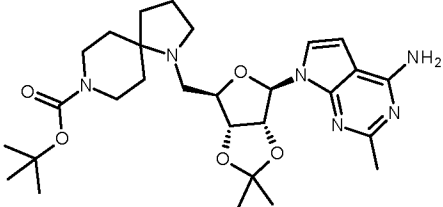
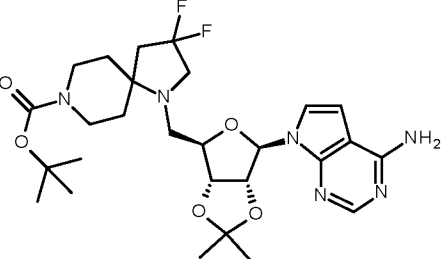
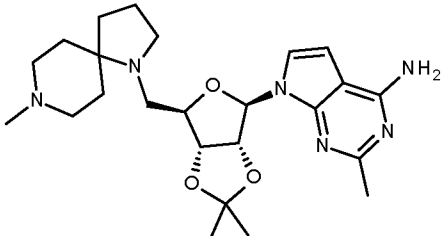
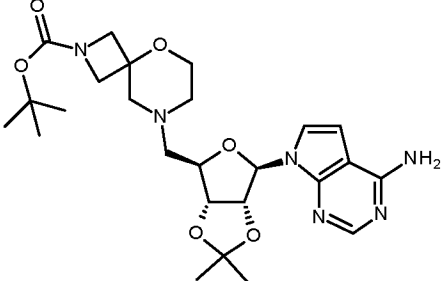
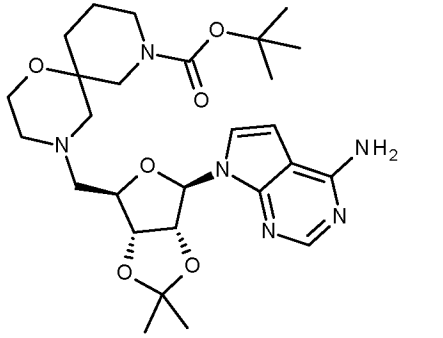
Preparation of *intermediate 114*

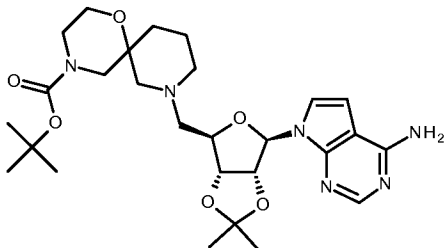
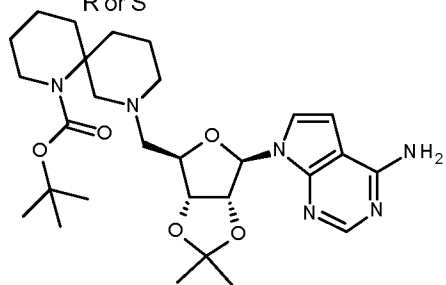
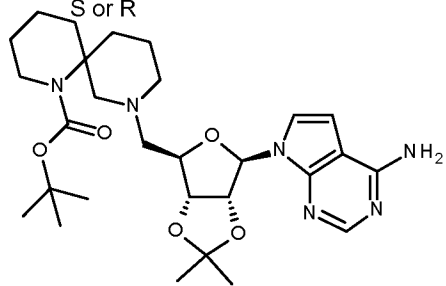
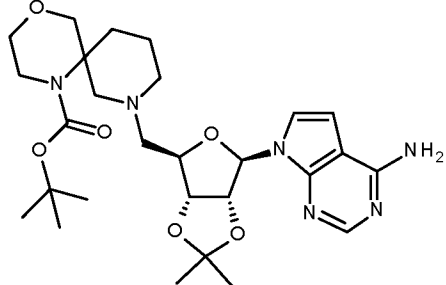
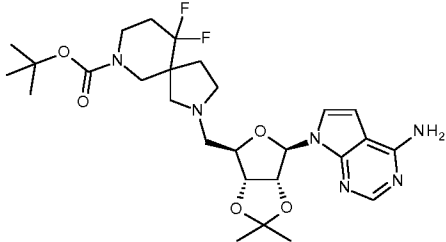
- 5 A solution of *intermediate 48* (52.3 g, 62 mmol) in NH_3 (500 mL, 3500 mmol, 7M in MeOH) was stirred and heated at 130°C for 4 hours in a stainless steel autoclave. The solvents were evaporated. The residue was dissolved in DCM and purified over a SiO_2 column, type Grace Reveleris SRC, 330 g, Si 40, on a Armen Spot II Ultimate purification system using DCM and MeOH as eluents in a gradient starting from 100% DCM and ending with 5% MeOH and 95% DCM. The fractions containing product were combined and the solvents were evaporated yielding the crude *intermediate 114*. A purification was performed via Prep HPLC (Stationary phase: Uptisphere C18 ODB - 10 μm , 200g, 5cm, Mobile phase: 0.25% NH_4HCO_3 solution in water, CH_3CN) yielding pure *intermediate 114* (18.28 g, yield: 55.7%).
- 10
- 15 Below intermediates were prepared by an analogous reaction protocol as was used for the preparation of *intermediate 114* using the appropriate starting materials (Table 7).

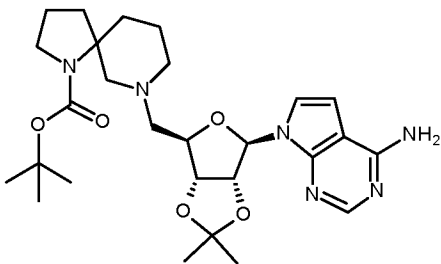
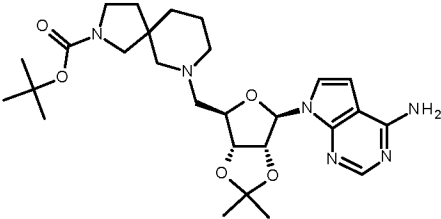
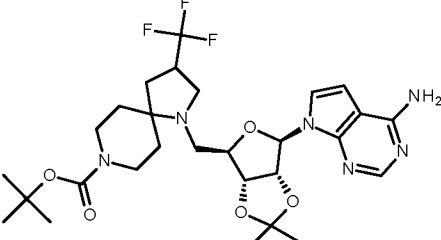
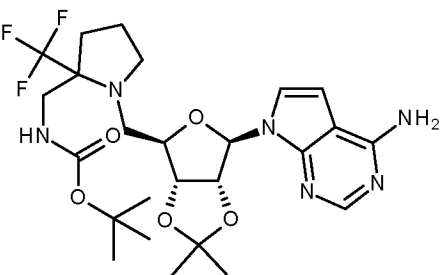
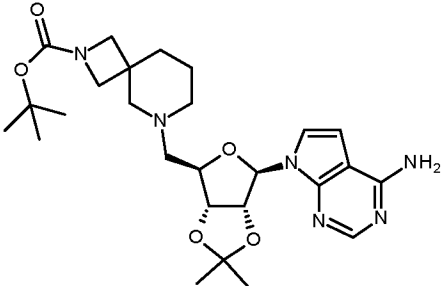
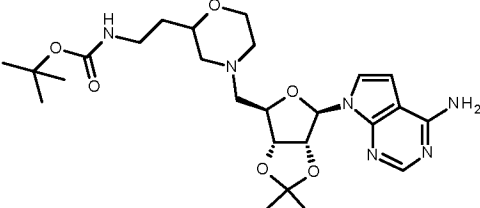
Table 7

Intermediate	Structure	Starting materials and conditions
115		a) <i>intermediate 49</i> b) NH_3 (7M) in MeOH
115		a) <i>Intermediate 50</i> b) NH_3 (7M) in MeOH

Intermediate	Structure	Starting materials and conditions
117		a) <i>Intermediate 52</i> b) <i>NH₃ 28% in H₂O</i>
118		a) <i>Intermediate 53</i> b) <i>NH₃ 28% in H₂O</i>
119		a) <i>Intermediate 54</i> b) <i>NH₃ 28% in H₂O</i>
120		a) <i>Intermediate 55</i> b) <i>NH₄OH in THF</i>

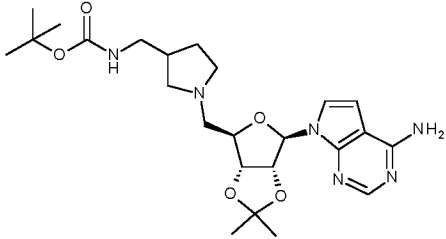
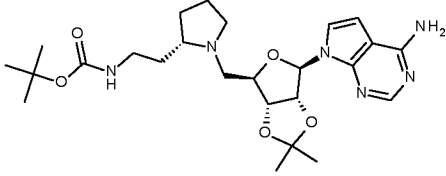
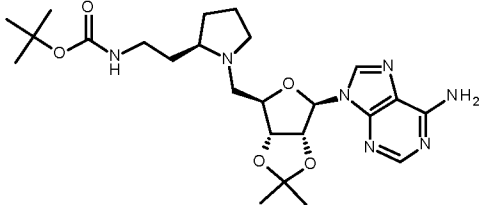
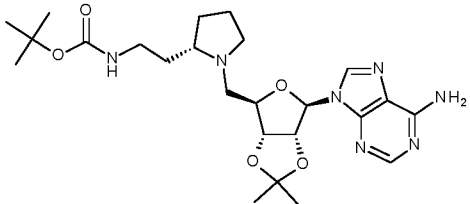
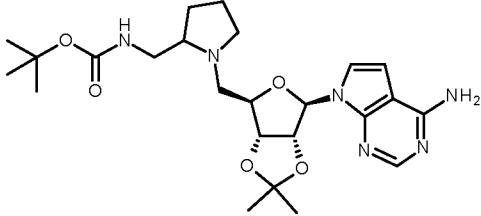
Intermediate	Structure	Starting materials and conditions
121		a) <i>Intermediate 57</i> b) <i>NH₃.H₂O in 1,4 dioxane</i>
122		a) <i>Intermediate 59</i> b) <i>NH₃ in MeOH</i>
123		a) <i>Intermediate 64</i> b) <i>NH₃.H₂O in 1,4 dioxane</i>
124		a) <i>Intermediate 65</i> b) <i>NH₃ in MeOH</i>
125		a) <i>Intermediate 66</i> b) <i>NH₄OH in dioxane</i>

Intermediate	Structure	Starting materials and conditions
126		a) <i>Intermediate 67</i> b) <i>NH₃ (7M) in MeOH</i>
127		a) <i>Intermediate 68</i> b) <i>NH₃ (7M) in MeOH</i>
128		a) <i>Intermediate 68</i> b) <i>NH₃ (7M) in MeOH</i>
129		a) <i>Intermediate 69</i> b) <i>NH₃ (7M) in MeOH</i>
130		a) <i>Intermediate 70</i> b) <i>NH₄OH in dioxane</i>

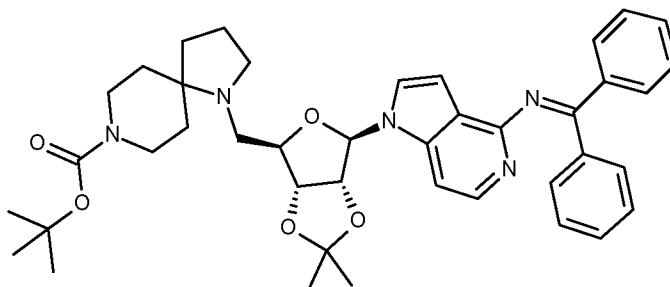
Intermediate	Structure	Starting materials and conditions
131		a) <i>Intermediate 71</i> b) <i>NH₃ in MeOH</i>
132		a) <i>Intermediate 72</i> b) <i>NH₃ in MeOH</i>
133		a) <i>Intermediate 92</i> b) <i>NH₃ in MeOH</i>
134		a) <i>Intermediate 73</i> b) <i>NH₄OH in dioxane</i>
135		a) <i>Intermediate 74</i> b) <i>NH₃ in MeOH</i>
138		a) <i>Intermediate 76</i> b) <i>NH₃ in MeOH</i>

Intermediate	Structure	Starting materials and conditions
139		a) <i>Intermediate 77</i> b) <i>NH₃ in MeOH</i>
140		a) <i>Intermediate 78</i> b) <i>NH₃ in MeOH</i>
141		a) <i>Intermediate 79</i> b) <i>NH₃ in MeOH</i>
142		a) <i>Intermediate 80</i> b) <i>NH₃ in MeOH</i>
143		a) <i>Intermediate 80</i> b) <i>NH₃ in MeOH</i>
144		a) <i>Intermediate 81</i> b) <i>NH₃ in MeOH</i>

Intermediate	Structure	Starting materials and conditions
145		a) <i>Intermediate 82</i> b) <i>NH₃ in MeOH</i>
146		a) <i>Intermediate 83</i> b) <i>NH₃ in MeOH</i>
147		a) <i>Intermediate 84</i> b) <i>NH₃ in MeOH</i>
148		a) <i>Intermediate 85</i> b) <i>NH₃ in MeOH</i>
149		a) <i>Intermediate 86</i> b) <i>NH₃ in MeOH</i>
150		a) <i>Intermediate 87</i> b) <i>NH₃ in MeOH</i>

Intermediate	Structure	Starting materials and conditions
151		a) <i>Intermediate 88</i> b) <i>NH₃ in MeOH</i>
152		a) <i>Intermediate 89</i> b) <i>NH₃ in MeOH</i>
153a		a) <i>Intermediate 90a</i> b) <i>NH₃ in MeOH</i>
153b		c) <i>Intermediate 90b</i> d) <i>NH₃ in MeOH</i>
154		a) <i>Intermediate 91</i> b) <i>NH₃ in MeOH</i>

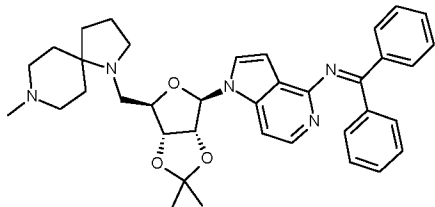
Example A19

Preparation of *intermediate 155*

Intermediate 56 (290 mg, 0.53 mmol), benzophenone imine (144 mg, 0.8 mmol), Pd₂(dba)₃ (48.5 mg, 0.05 mmol), BINAP (33.0 mg, 0.05 mmol) and t-BuONa (101.9 mg, 1.06 mmol) were dissolved in toluene (20 mL). The mixture was stirred at 110°C for 2 hours under N₂, after which it was filtered and the solvent was evaporated. The crude product was purified by preparative HPLC (gradient elution: 0.05% NH₃.H₂O in CH₃CN/0.05% NH₃.H₂O in H₂O). The combined fractions were evaporated to give the desired **intermediate 155** (160 mg, 40% yield).

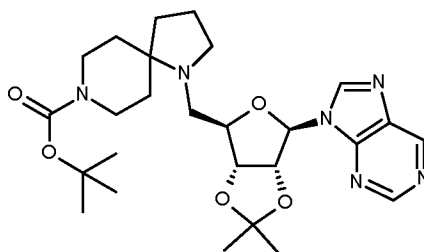
Below intermediates were prepared by an analogous reaction protocol as was used for the preparation of **intermediate 155** using the appropriate starting materials (Table 8).

Table 8

Intermediate	Structure	Starting materials and conditions
156		a) Intermediate 63 b) Benzophenone imine

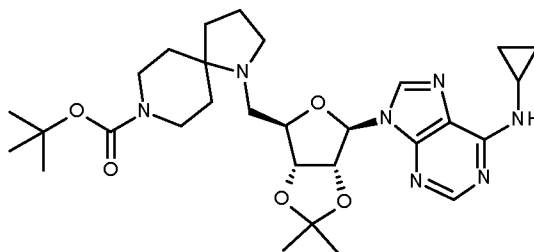
Example A20

Preparation of **intermediate 157**



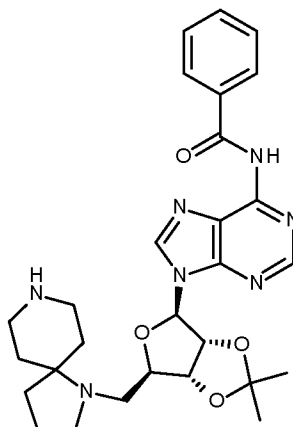
MeOH (50 mL) was gently added to Pd/C 10% (87.7 mg) under nitrogen atmosphere. Thiophene 4% solution in DIPE (0.5 mL) and KOAc (222 mg, 2.26 mmol) were added to the solution. Then **intermediate 49** (620 mg, 1.13 mmol) was added and then the reaction mixture was hydrogenated at room temperature under 1 atm of hydrogen gas until 1 equivalent of hydrogen was absorbed. The catalyst was filtered off over a pad of dicalite and the residue was washed with MeOH. The filtrate was diluted with EtOAc (100 mL) after which NaHCO₃ (50 mL) was added. The organic layer was extracted and washed with water (50 mL), dried over MgSO₄ and concentrated under vacuo to give **intermediate 157** (480 mg, 0.6 mmol, yield: 56%)

Example A21

Preparation of *intermediate 158*

- 5 To a solution of *intermediate 49* (100 mg, 0.13 mmol) in EtOH (5 mL) was added cyclopropylamine (87.1 μ L, 1.26 mmol). Then the vial was sealed and heated for 30 minutes in a microwave at 150°C. The reaction mixture was concentrated under vacuo yielding crude *intermediate 158* (67 mg). No further purification was done.

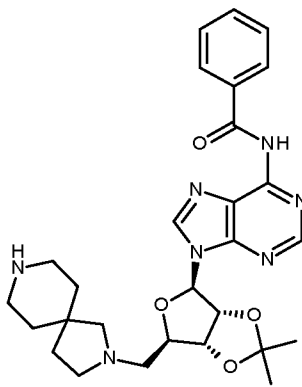
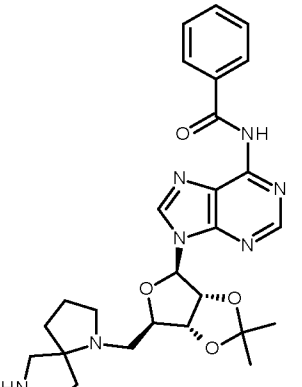
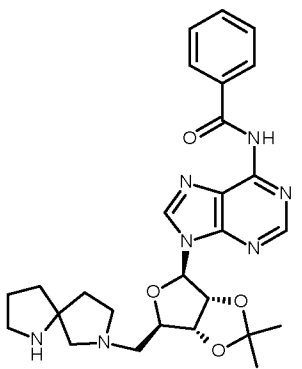
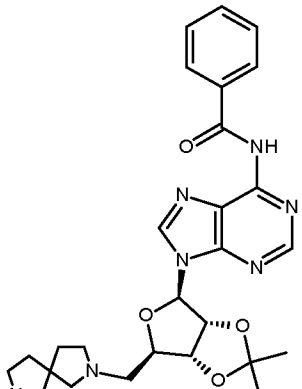
10 Example A22

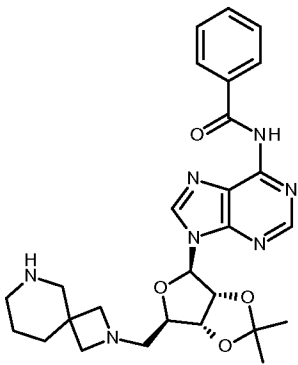
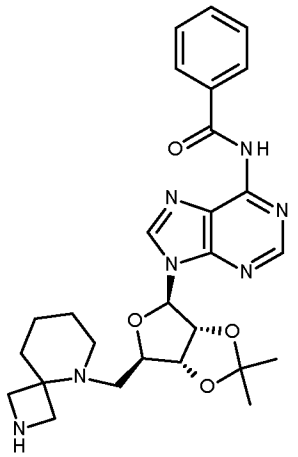
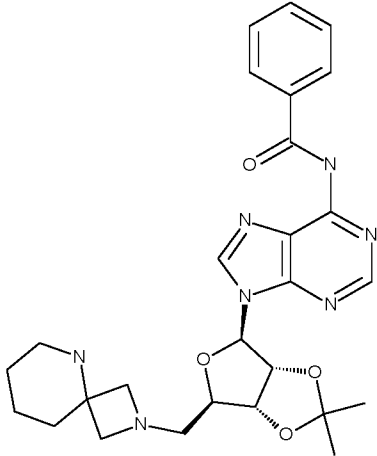
Preparation of *intermediate 159*

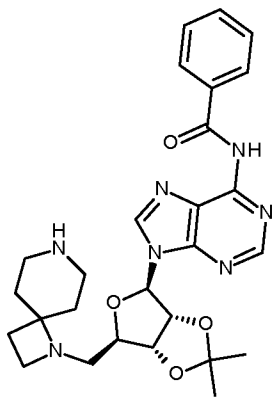
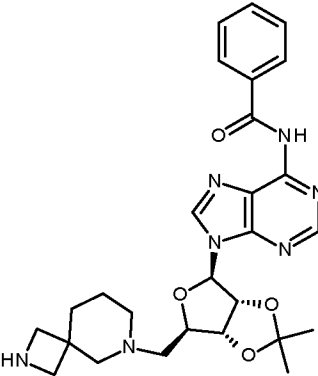
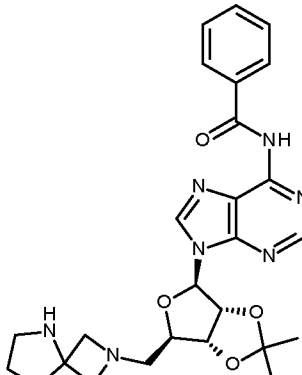
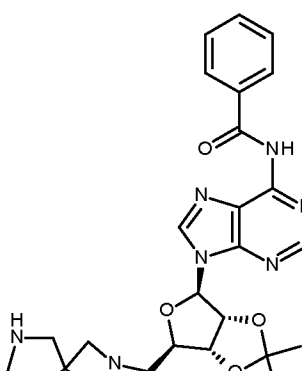
- Intermediate 93* (824 mg, 0.99 mmol) was dissolved in DCM (10 mL) and cooled to 0°C. The suspension was treated with trifluoroacetic acid (5.8 mL) dropwise. The mixture was stirred at room temperature overnight. The mixture was evaporated to dryness yielding crude *intermediate 159* (640 mg, 100% yield) which was used as such without further purification.

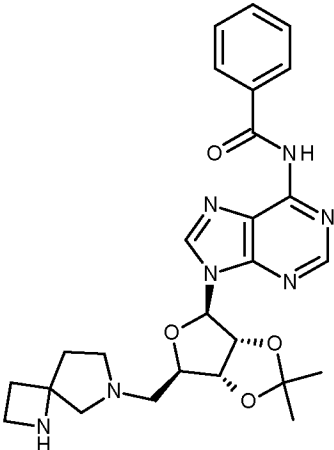
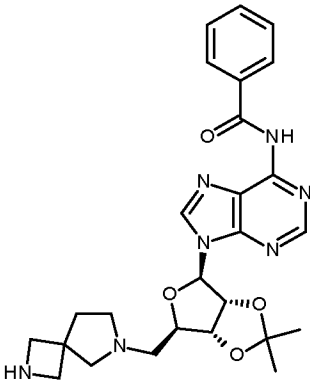
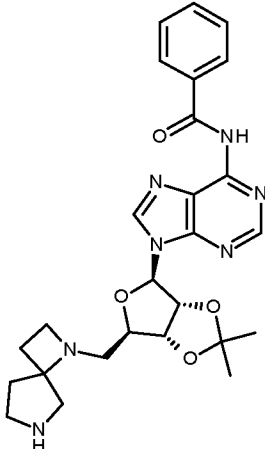
Below intermediates were prepared by an analogous reaction protocol as was used for the preparation of *intermediate 159* using the appropriate starting materials (Table 9).

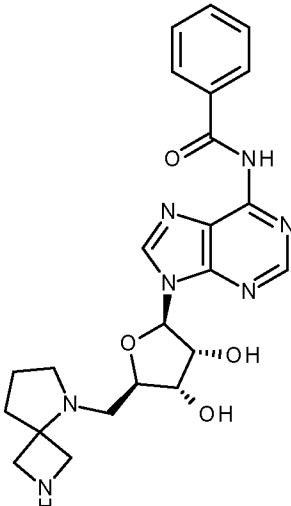
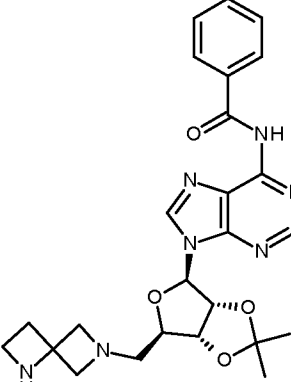
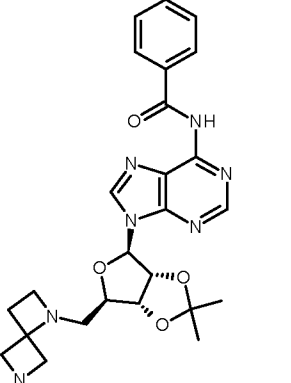
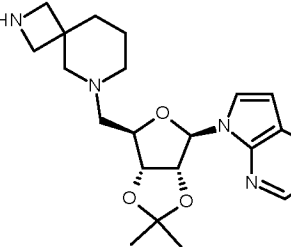
20 Table 9

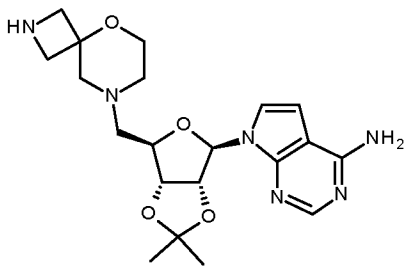
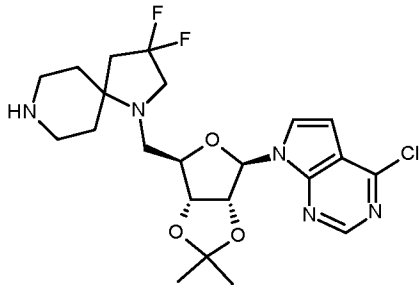
Intermediate	Structure	Starting materials and conditions
160		a) <i>Intermediate 94</i> b) <i>TFA in DCM</i>
161		a) <i>Intermediate 95</i> b) <i>TFA in DCM</i>
162		a) <i>Intermediate 96</i> b) <i>TFA in DCM</i>
163		a) <i>Intermediate 97</i> b) <i>TFA in DCM</i>

Intermediate	Structure	Starting materials and conditions
164		a) <i>Intermediate 98</i> b) <i>TFA in DCM</i>
165		a) <i>Intermediate 99</i> b) <i>TFA in DCM</i>
166		a) <i>Intermediate 100</i> b) <i>TFA in DCM</i>

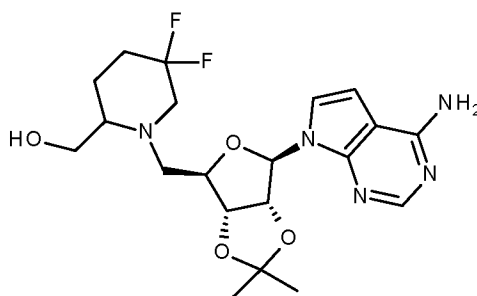
Intermediate	Structure	Starting materials and conditions
167		a) <i>Intermediate 101</i> b) <i>TFA in DCM</i>
168		a) <i>Intermediate 102</i> b) <i>TFA in DCM</i>
169		a) <i>Intermediate 103</i> b) <i>TFA in DCM</i>
170		a) <i>Intermediate 104</i> b) <i>TFA in DCM</i>

Intermediate	Structure	Starting materials and conditions
171		a) <i>Intermediate 105</i> b) <i>TFA in DCM</i>
172		a) <i>Intermediate 106</i> b) <i>TFA in DCM</i>
173		a) <i>Intermediate 107</i> b) <i>TFA in DCM</i>

Intermediate	Structure	Starting materials and conditions
174		a) <i>Intermediate 108</i> b) <i>TFA in DCM/H₂O</i>
175		a) <i>Intermediate 109</i> b) <i>TFA in DCM</i>
176		a) <i>Intermediate 110</i> b) <i>TFA in DCM</i>
177		a) <i>Intermediate 135</i> b) <i>TFA in DCM</i>

Intermediate	Structure	Starting materials and conditions
178		a) <i>Intermediate 124</i> b) <i>TFA in DCM</i>
179		a) <i>Intermediate 59</i> b) <i>TFA in DCM</i>

Example A23

Preparation of *intermediate 180*

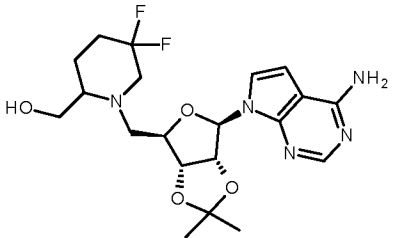
5

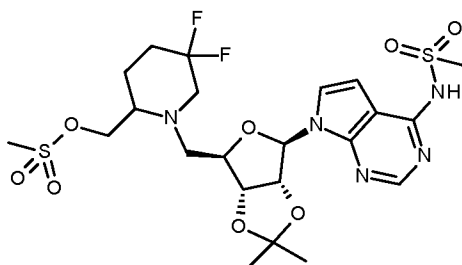
Lithium aluminum hydride (0.765 mL, 0.765 mmol, 1M in THF) was added dropwise to a stirred solution of *intermediate 143* (104 mg, 0.19 mmol) in THF (4 mL, anhydrous) at 0°C and under nitrogen atmosphere. After addition the reaction mixture was stirred at 0°C for 10 minutes. The reaction was cooled to 0°C and then quenched with water.

10 MeOH was added and the resulting suspension was filtered. The residue was washed with MeOH. The combined solvents of the filtrate were evaporated. A purification was performed via Prep HPLC (Stationary phase: RP XBridge Prep C18 OBD-10µm, 30x150mm, Mobile phase: 0.25% NH₄HCO₃ solution in water and CH₃CN to give *intermediate 180* (48 mg, 57% yield)

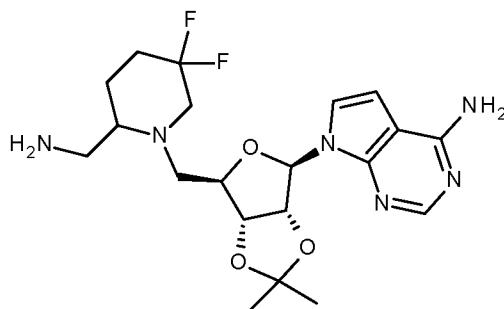
15 Below intermediates were prepared by an analogous reaction protocol as was used for the preparation of *intermediate 180* using the appropriate starting materials (Table 10).

Table 10

Intermediate	Structure	Starting materials and conditions
180		a) <i>Intermediate 142</i> b) <i>Lithium aluminium hydride 1M in THF</i>

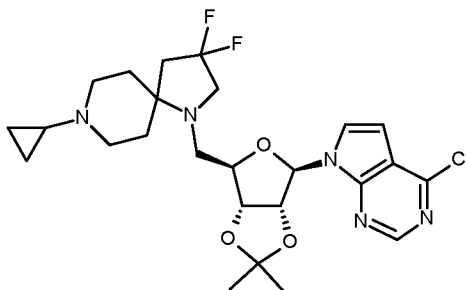
Preparation of *intermediate 181*

- 5 Methanesulfonyl chloride (0.078 mL, 1.0 mmol) was added dropwise to a stirred solution of *intermediate 180* (173 mg, 0.39 mmol) and Et₃N (0.14 mL, 1.0 mmol) in DCM (5 mL) at 0°C. After addition the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was cooled to 0°C and then an additional amount of Et₃N (0.28 mL, 2.0 mmol) was added followed by the addition of methanesulfonyl chloride
- 10 (0.16 mL, 2.0 mmol). The reaction mixture was stirred at 0°C for 1 hour. The reaction was diluted with 5 mL DCM and then quenched with 3 mL water. The organic layer was separated, dried with MgSO₄, filtered and the solvents of the filtrate evaporated to give crude *intermediate 181* (346 mg, 63.6% yield), directly used as such in the next reaction step.

Preparation of *intermediate 182*

Intermediate 181 (346 mg, 0.215 mmol) was dissolved in NH_3 (5 mL, 35 mmol, 7 M in MeOH) in a microwave vial and then stirred and heated at 100°C using microwave irradiation for 2 hour. The solvents were evaporated and the residue was purified with Prep HPLC (Stationary phase: RP XBridge Prep C18 OBD-10 μm , 30x150mm, Mobile phase: 0.25% NH_4HCO_3 solution in water, MeOH) to give **intermediate 182** (39.6 mg, 30% yield).

10 Example A24

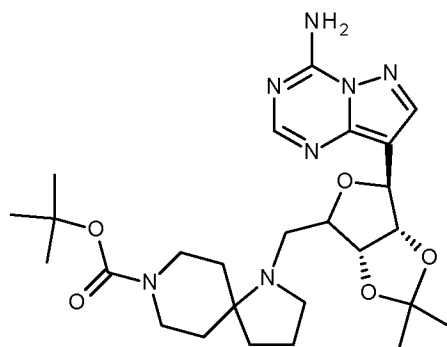
Preparation of *intermediate 186*

To a solution of **intermediate 179** in MeOH (4 mL) was added (1-ethoxycyclopropoxy)trimethylsilane (227 mg, 1.3 mmol) and AcOH (0.025 mL, 0.4 mmol) at room temperature. Then NaBH_3CN (95.4 mg, 1.5 mmol) was added into the reaction mixture. The resulting mixture was stirred at 60°C for 15 hours. The reaction mixture was diluted with MeOH (20 mL) and was filtered through celite. The filtrate was concentrated to dryness after which the residue was purified via silica column chromatography (gradient: DCM/MeOH from 100:0 to 95:5). The desired fractions were collected and concentrated to be dry to give **intermediate 186** (50 mg, 44% yield)

Example A25

Preparation of *intermediate 187*

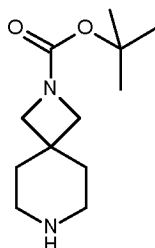
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- A solution of *intermediate 58* (328 mg, 0.53 mmol) and NH₃ 7M in MeOH (3.78 mL, 26.462 mmol) was stirred in EtOH at 110°C for 13 hours after which the reaction mixture was stirred at room temperature overnight. The reaction mixture was evaporated under the reduced pressure and the residue was purified by silica gel column chromatography (DCM/MeOH 100/0 to 96/4, collection at 275 nm) to give *intermediate 187* (200 mg, 71% yield).

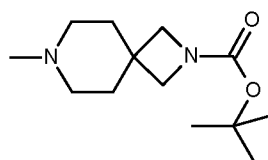
Example A26

10 Preparation of *intermediate 188*



- Pd/C 10% (0.67 g, 0.63 mmol) was added to a solution of tert-Butyl 7-benzyl-2,7-diazaspiro[3.5]nonane-2-carboxylate (2 g, 6.26 mmol) in MeOH (50 mL) under nitrogen atmosphere at 0°C. The reaction was hydrogenated at room temperature under 1 atm hydrogen gas for 4 days. An extra amount of Pd/C 10% (0.67 g, 0.63 mmol) was added and the mixture was stirred overnight The crude was filtered over celite and concentrated in vacuo to give crude *intermediate 188* (1.25 g, 87% yield). No further purification was done.

Preparation of *intermediate 189*



Intermediate 188 (250 mg, 1.1 mmol) and formaldehyde solution 37 wt. % in H₂O (0.09 mL, 1.21 mmol) were dissolved in THF (5 mL) and the mixture was stirred 30 min. Then sodium triacetoxyborohydride (351.2 mg, 1.66 mmol) was added and the solution was stirred at room temperature overnight. The mixture was diluted with DCM (50 mL) and washed with saturated Na₂CO₃ 1M (50 mL). The organic layer was dried over MgSO₄ and filtered. The solvents were evaporated to dryness to give crude **intermediate 189** (0.245 g, 90% yield), which was used as such without further purification.

Preparation of **intermediate 190**



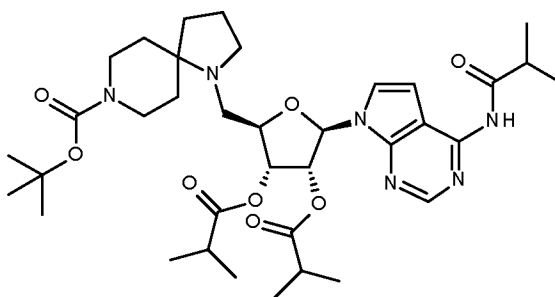
10

Intermediate 189 was dissolved in DCM (15 mL) and cooled to 0°C. The suspension was treated with TFA (3.1 mL) dropwise. The mixture was stirred at room temperature for 3 hours. The solvents were evaporated to dryness and the product was triturated with ether to give crude **intermediate 190** (0.273 g, 100% yield), which was used as such without further purification.

15

Example A27

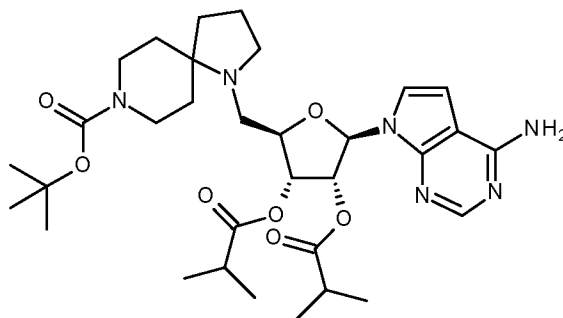
Preparation of **intermediate 324**



Isobutyric anhydride (6.82 mL, 40.9 mmol) was added to a stirred solution of **intermediate 210** (2 g, 4.1 mmol) in pyridine (80 mL) at room temperature. After addition the reaction mixture was stirred at 50°C for 18 hours. The mixture was cooled to room temperature and then diluted with ethylacetate. This mixture was washed three times with water and the organic layer was dried with MgSO₄, filtered and the solvents of the filtrate evaporated. The residue was co-evaporated with toluene to give crude **intermediate 324** (4.11 g, yield: 127%).

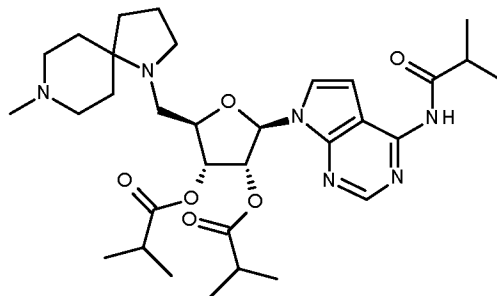
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Preparation of *intermediate 325*

A solution of *intermediate 324* (2.05 g, 2.6 mmol) in MeOH (20 mL) was stirred and heated at 130°C using microwave irradiation for 6 hours. The solvents were evaporated after which a purification was performed via Prep HPLC (Stationary phase: RP XBridge Prep C18 OBD-10µm, 50 x150 mm, Mobile phase: 0.5% NH₄Ac solution in water + 10% CH₃CN, CH₃CN). The organic solvents were evaporated. The product was extracted from the remaining water layer three times with DCM. The combined organic layer was washed with water, washed with brine, dried with MgSO₄, filtered and the solvents of the filtrate evaporated to give *intermediate 325* (0.89 g, yield: 27.0%)

Example A28

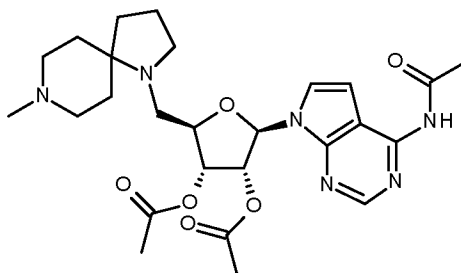
Preparation of *intermediate 327*

Isobutyric anhydride (66.3 mL, 398 mmol) was added to a stirred solution of *compound 168* (18 g, 39.8 mmol) in pyridine (500 mL) at room temperature. After addition the reaction mixture was stirred at 50°C for 6 hours. The solvents were evaporated. The residue was co-evaporated with toluene. The remaining liquid was diluted with ethylacetate. The resulting suspension was filtered over Dicalite. The pad of Dicalite was washed twice with ethyl acetate. The combined filtrates were washed three times with water, once with brine, dried with MgSO₄, filtered and the solvents of the filtrate evaporated. The residue was purified over a SiO₂ column, type Grace Reveleris SRC, 80 g, Si 40, on a Grace Reveleris X2 purification system using dichlormethane and MeOH as eluents in a gradient starting from 100% DCM to 25% MeOH and 75% DCM.

The fractions containing product were combined and the solvents were evaporated yielding 10.5 g crude *intermediate 327*. The combined water layers were extracted again three times with DCM with some MeOH. The combined organic layer was dried (MgSO₄), filtered and the solvents of the filtrate evaporated yielding 6.62 g crude *intermediate 327*. The water layer was evaporated yielding 12.3 g crude *intermediate 327*. The three crude fractions were combined and purified over a SiO₂ column, type Grace Reveleris SRC, 120 g, Si 40, on a Grace Reveleris X2 purification system with a solid sample loader using DCM and MeOH as eluents in a gradient starting from 100% DCM to 25% MeOH and 75% DCM. The fractions containing product were combined and the solvents were evaporated yielding 18.1 g of pure *intermediate 327* (yield: 72.7 %).

Example A29

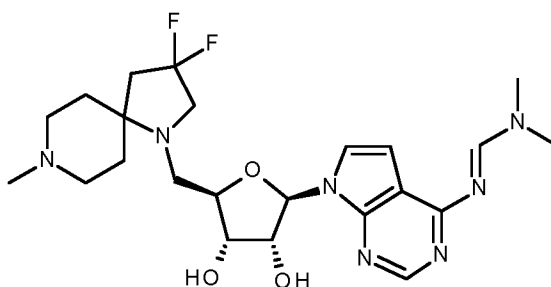
Preparation of *intermediate 329*



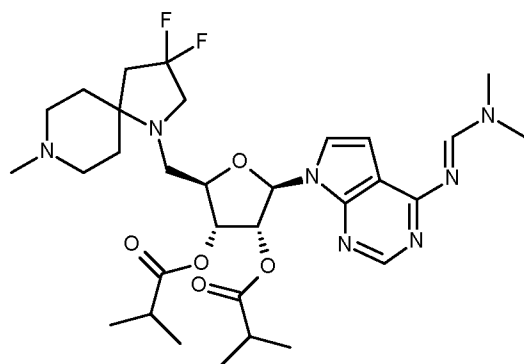
15

Ac₂O (54.8 mL, 579 mmol) was added to a stirred solution of *compound 168* (26.2 g, 57.9 mmol) in pyridine (700 mL) at room temperature. After addition the reaction mixture was stirred at 50°C for 18 hours. The solvents were evaporated. The residue was co-evaporated with toluene and was purified over a SiO₂ column, type Grace Reveleris SRC, 330 g, Si 40, which was neutralized by flushing for 5 column volumes with a solution of 2% Et₃N in DCM and then for 5 column volumes with DCM, on a Grace Reveleris X2 purification system using DCM and MeOH as eluents in a gradient starting from 100% DCM to 100% MeOH. The fractions containing product were combined and the solvents were evaporated. The residue was repurified over a SiO₂ column, type Grace Reveleris SRC, 330 g, Si 40, which was neutralized by flushing for 5 column volumes with a solution of 2% Et₃N in DCM and then for 5 column volumes with DCM, on a Grace Reveleris X2 purification system using DCM and MeOH as eluents in a gradient starting from 100% DCM to 100% MeOH. The fractions containing product were combined and the solvents were evaporated to give *intermediate 329* (29.5 g, yield: 93.5%).

Example A30

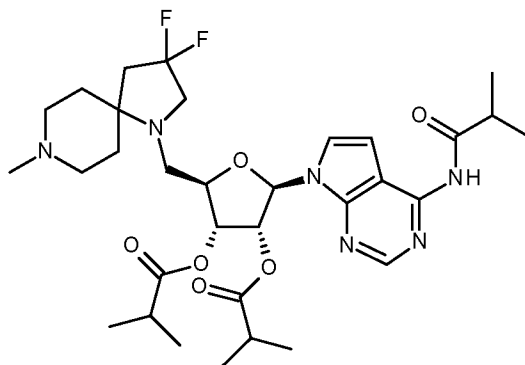
Preparation of *intermediate 332*

- 5 A suspension of **compound 181** (1.14 g, 2.3 mmol) in N, N-dimethylformamide dimethyl acetal (3.8 mL) and DCM (200 mL) and DMF (50 mL) was stirred at room temperature for 18 hours. The reaction mixture was stirred and heated at 50°C allowing the DCM to be evaporated from the reaction mixture under a flow of nitrogen gas. The remaining solution in DMF was stirred and heated at 50°C for 3 hours and then at room temperature
- 10 for 18 hours. The solvents were evaporated. The residue was co-evaporated with toluene yielding **intermediate 332** (1.83 g).

Preparation of *intermediate 333*

- 15 Isobutyric anhydride (1.07 mL, 6.45 mmol) was added to a stirred solution of **intermediate 332** (1.83 g, 2.15 mmol) in pyridine (50 mL) at room temperature. After addition the reaction mixture was stirred at 65°C for 3 days. The solvents were evaporated. The residue was co-evaporated with toluene. The residue was dissolved in EtOAc and washed twice with a saturated aqueous NaHCO₃ solution, washed with water,
- 20 dried with MgSO₄, filtered and the solvents of the filtrate evaporated to give **intermediate 333** (1.10 g)

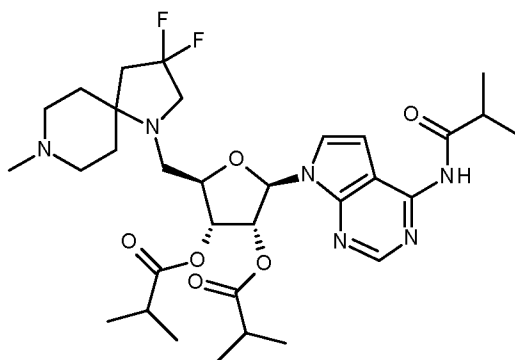
Example A31

Preparation of *intermediate 335*

Isobutyric anhydride (2.4 mL, 14.4 mmol) was added to a stirred solution of **compound 181** (0.68 g, 1.44 mmol) in pyridine (30 mL) at room temperature. After addition the reaction mixture was stirred at room temperature for 18 hours. The solvents were evaporated. The residue was co-evaporated with toluene. The residue was dissolved in DCM and washed twice with water, once with brine, dried with MgSO₄, filtered and the solvents of the filtrate evaporated yielding *intermediate 335* (0.71 g).

10

Example A32

Preparation of *intermediate 335*

Isobutyric anhydride (86.4 mL, 518.7 mmol) was added to a stirred solution of **compound 181** (29.7 g, 51.9 mmol) in pyridine (1 L) at room temperature. After addition the reaction mixture was stirred at 50°C for 18 hours. The solvents were evaporated. The residue was co-evaporated with toluene. The residue was dissolved in DCM and purified over a SiO₂ column, type Grace Reveleris SRC, 330 g, Si 40, on a Armen Spot II Ultimate purification system using DCM and MeOH as eluents in a gradient starting from 100% DCM and ending with 40% MeOH and 60% DCM. The fractions containing product

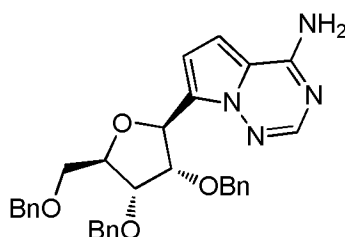
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were combined and the solvents were evaporated to give crude *intermediate 335* (18.1 g, yield: 40.2 %).

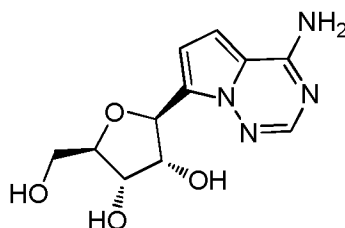
Example A33

5 Preparation of *intermediate 340*



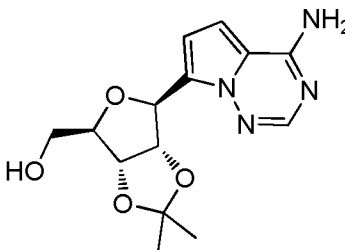
A mixture of *intermediate 19* (10.5 g, 18.5 mmol) in THF (50 mL), iPrOH (50 mL) and NH₄OH (100 mL) were taken into an autoclave. The mixture was stirred at 70 °C for 72h. The reaction was concentrated to dryness. The crude was purified by chromatography on silica gel (0%-70% PE: EtOAc) to give *intermediate 340* (4.30 g, 8.0 mmol, 43.3% yield) as yellow oil.

Preparation of *intermediate 341*



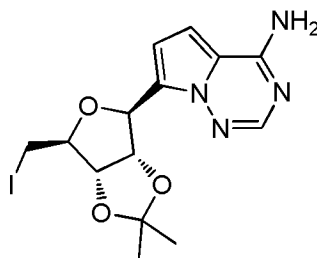
15 To a solution of *intermediate 340* (2.00 g, 3.7 mmol) in acetic acid (100 mL) was added Pd/C (2.0 g, 18.9 mmol). The suspension was stirred under an atmosphere of H₂ (15psi) at 20 °C for 15 h. The reaction was filtered and concentrated to dryness. The crude was added HCl/ MeOH (10 mL) and concentrated to dryness. *Intermediate 341* (900 mg, 2.53 mmol, 67.7% yield) was obtained as a yellow solid.

20 Preparation of *intermediate 342*



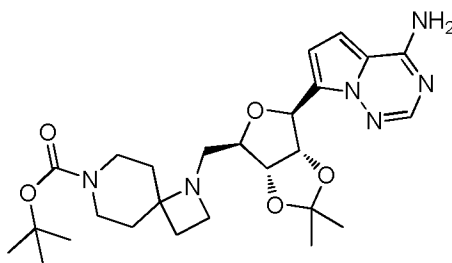
- To a solution of *intermediate 341* (900 mg, 2.97 mmol) in DMF (10 mL) and acetone (10 mL) were added 2,2-dimethoxypropane (3.1 g, 29.7 mmol) and TsOH.H₂O (622 mg, 3.27 mmol). The mixture was stirred at 60 °C for 15 h. NaHCO₃ was added to the mixture and the mixture was extracted with EtOAc (three times 50 mL). The organic layer was washed with brine and dried over MgSO₄. The crude was purified by column (DCM:MeOH 20:1) to obtain *intermediate 342* (400 mg, 1.18 mmol, 39.7 % yield).

Preparation of *intermediate 343*



- To a solution of *intermediate 342* (1.40 g, 4.57 mmol) in THF (30 mL) were added imidazole (622 mg, 9.14 mmol), I₂ (1.51 g, 5.94 mmol) and PPh₃ (1.56 g, 5.94 mmol). The mixture was stirred at 40 °C for 15h. 10% Na₂S₂O₃ was added. The mixture was diluted with EtOAc. The organic layer was washed with brine, dried over MgSO₄ and concentrated to obtain a crude which was purified by column chromatography (DCM: EtOH 20:1) to obtain *intermediate 343* (800 mg, 1.92 mmol, 42.0% yield).

Preparation of *intermediate 344*

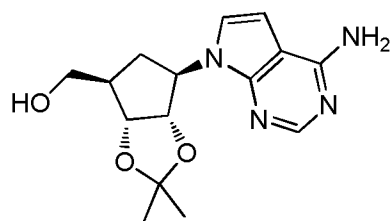


- To a solution of *intermediate 343* (100 mg, 240.2 μmol, 1 eq) in CH₃CN (5 mL) were added tert-butyl 1, 7-diazaspiro[3.5]nonane-7-carboxylate (109 mg, 480.5 μmol, 2 eq) and K₂CO₃ (199 mg, 1.44 mmol, 6 eq). The mixture was stirred at 70 °C for 15h. The mixture was extracted with EtOAc and the organic layer was concentrated to dryness. The crude was purified by TLC (EtOAc), to give *intermediate 344* (40 mg, 54.4 μmol, 22.6% yield).

- Example A34

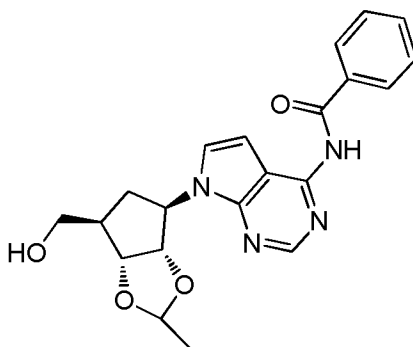
Preparation of *intermediate 345*

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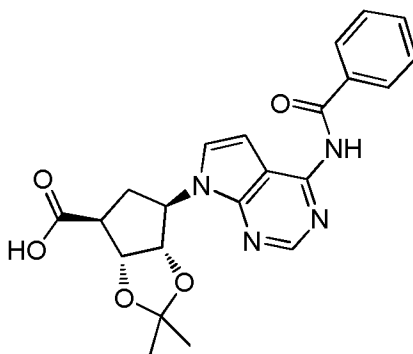


To a mixture of **intermediate 14** (500 mg, 1.54 mmol, 1 eq) in THF (1.0 mL) and propan-2-ol (3.0 mL) was added NH₄OH (4.55 g, 129.8 mmol, 84.3 eq) in one portion at 25°C. The mixture was stirred at 85 °C for 5 days in sealed tube. The mixture was concentrated in vacuum. The residue was purified by silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0-100% Ethyl acetate / DCM, 0~5% 7N NH₃ in MeOH / DCM gradient @ 30 mL/min). **Intermediate 345** (490 mg, 1.53 mmol, 99.3% yield) was obtained as a white solid.

10 Preparation of **intermediate 346**

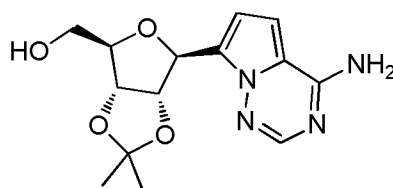


To a mixture of **intermediate 345** (490 mg, 1.61 mmol, 1 eq) in pyridine (10 mL) was added TMSCl (875 mg, 8.0 mmol, 5 eq) in one portion at 25°C. The mixture was stirred at 25 °C for 30 min. Then benzoylchloride (294 mg, 2.1 mmol, 1.3 eq) was added at 25 °C for 4 h. The mixture was cooled to 0 °C and diluted with water (0.33 mL) and after 10 min, NH₄OH (2.97 g, 84.85 mmol, 52.7 eq) was added. The mixture was allowed to 25 °C for 30 min. The mixture was concentrated in vacuum. The residue was purified by silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0-50% Ethyl acetate/DCM gradient @ 30 mL/min). **Intermediate 346** (520 mg, 1.23 mmol, 76.7% yield) was obtained as a white solid.

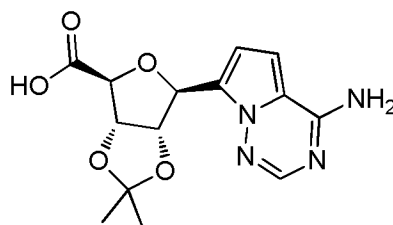
Preparation of *intermediate 347*

To a mixture of *intermediate 346* (400 mg, 979 μ mol, 1 eq) in CH₃CN/ H₂O (1:1) (2.0 mL) was added TEMPO (30.8 mg, 196 μ mol, 0.2 eq) and [acetoxy(phenyl)-iodanyl] acetate (694 mg, 2.15 mmol, 2.2 eq) in one portion at 25°C. The mixture was stirred at 25 °C for 4 h. The mixture was washed by iPr₂O (5mL). The crude product was used into the next step without further purification. *Intermediate 347* (420 mg, crude) was obtained as a light yellow solid.

Example A35

10 Preparation of *intermediate 348*

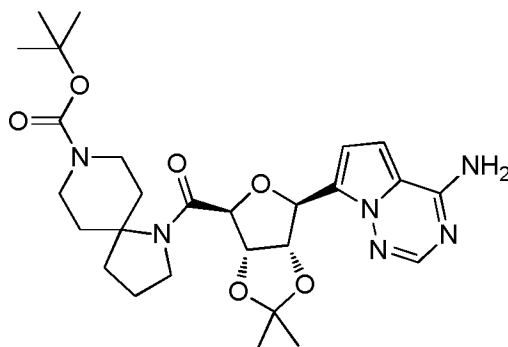
A solution of *intermediate 21* (500 mg, 1.48 mmol, 1 eq) in THF (4.0 mL) and iPrOH (4.0 mL) was taken up into a sealed tube. NH₄OH (7.28 g, 51.9 mmol, 35 eq) was added to the mixture and the resulting suspension was heated at 80 °C for 2.5 days. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~3% MeOH/DCM gradient @ 18 mL/min) to afford *intermediate 348* (442 mg, 1.37 mmol, 92.6% yield) as a white foam solid.

20 Preparation of *intermediate 349*

To a solution of *intermediate 348* (227 mg, 741 μ mol, 1 eq) in CH₃CN (800 μ L) and Water (800 μ L) was added TEMPO (25 mg, 159 μ mol, 0.21 eq) followed by [acetoxy(phenyl)-iodanyl] acetate (478 mg, 1.48 mmol, 2 eq) at 25 °C. The mixture was stirred at 25 °C for 16 hours. MTBE (3 mL) was added into the reaction mixture and stirred for 16 hours. The resulting suspension was filtered and the solid was collected and triturated with MTBE, dried under high vacuum to afford desired *Intermediate 349* (138 mg, 383 μ mol, 51.7% yield) as white solid, which was used as such in the next reaction step without further purification.

10

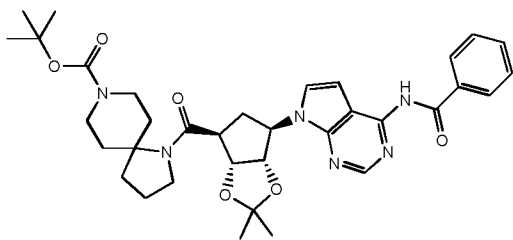
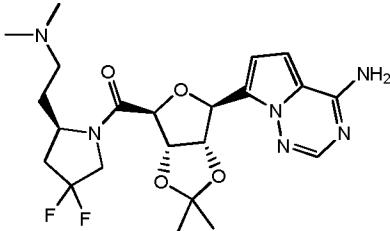
Example A36

Preparation of *intermediate 350*

To a solution of *intermediate 349* (120 mg, 375 μ mol, 1 eq), tert-butyl 1,8-diazaspiro[4.5]decane-8-carboxylate, (110 mg, 458 μ mol, 1.22 eq) and DIPEA (150 mg, 1.16 mmol, 3.1 eq) in DMF (5 mL) was added HBTU (175 mg, 462 μ mol, 1.23 eq) at 20 °C. The mixture was stirred at 25 °C for 16 hours. The reaction mixture was purified by preparative HPLC (Column: Phenomenex Synergi C18 150*30mm, 4 μ m; Mobile phase: from 29% MeCN in water to 59% MeCN in water, 0.1% TFA; Gradient Time: 8 min; Flow Rate: 30 ml/min; Wavelength: 220 nm). The fractions contain desired product were combined and lyophilized to afford *intermediate 350* (180 mg, 260 μ mol, 69.5% yield) as pale yellow solid.

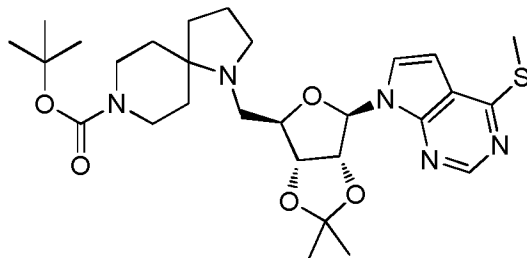
Below intermediates were prepared by an analogous reaction protocol as was used for the preparation of *intermediate 350* using the appropriate starting materials (Table 12).

Table 12:

Int.	Structure	Starting materials
351		Intermediate 347 Tert-butyl 1,8-diazaspiro[4.5]decane-8-carboxylate
352		Intermediate 349 (R)-2-(4,4-difluoropyrrolidin-2-yl)-N,N-dimethylethanamine

Example A37

Method A

Preparation of *intermediate 353*

5

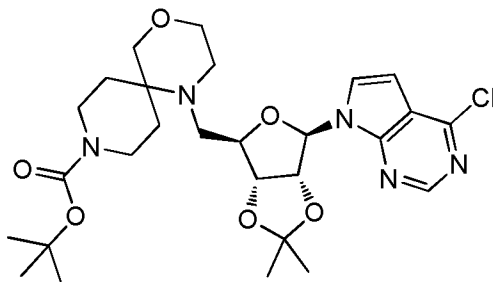
To a stirred solution of tert-butyl 1,8-diazaspiro[4.5]decane-8-carboxylate (110 mg, 458 μmol , 1 eq) in CH_2Cl_2 (8 mL) was added a solution of AcOH (28 mg, 466 μmol , 1.03 eq) in CH_2Cl_2 (1 mL) at 0 °C. $\text{NaBH}(\text{OAc})_3$ (195 mg, 920 μmol , 2 eq) was added to the above solution. A solution of *intermediate 37* (152 mg, 453 μmol , 1 eq) in CH_2Cl_2 (6 mL) was added drop wise to the reaction mixture at 25 °C over a period of 1 hour. The mixture was stirred at 25 °C for further 1.5 hours. The reaction mixture was poured into saturated NaHCO_3 aqueous solution then extracted with CH_2Cl_2 (3 times 25 mL). The combined organic layers were washed with brine (50 mL), dried over MgSO_4 , filtered and concentrated under reduced pressure. The residue was purified by preparative TLC (silica gel, CH_2Cl_2 : EtOAc 3:1) to afford desired *intermediate 353* (199 mg, 352 μmol , 77.7% yield) as yellow gum.

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Method B

Preparation of *intermediate 354*



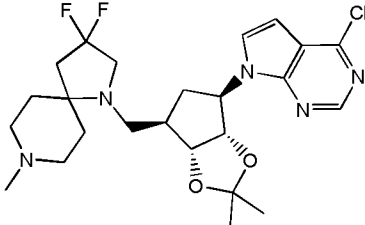
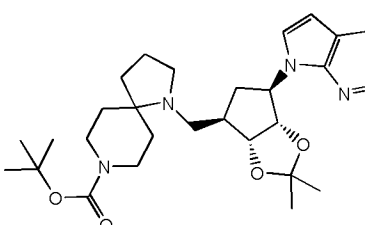
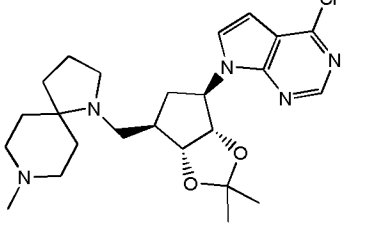
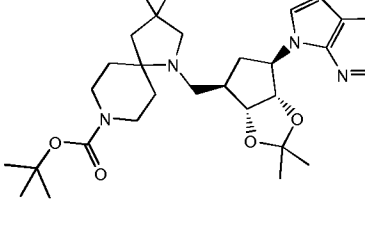
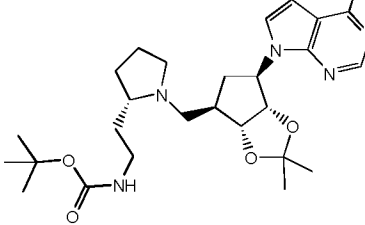
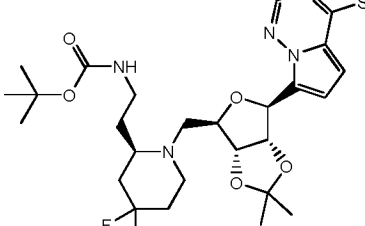
To a mixture of tert-butyl 4-oxa-1,9-diazaspiro[5.5]undecane-9-carboxylate HCl salt (406 mg, 1.39 mmol, 0.9 eq) in CH₂Cl₂ (20 mL) was added Et₃N (140 mg, 1.39 mmol, 0.9 eq) at 0 °C under N₂. The mixture was stirred at 0 °C for 5 min, then warmed to 25 °C. NaBH(OAc)₃ (653 mg, 3.08 mmol, 2 eq) was added in one portion, then *intermediate 29* (500 mg, 1.54 mmol, 1 eq) in DCM (10 mL) was added drop wise very slowly. The mixture was stirred at 25 °C for 16 hours. Saturated NaHCO₃ (20mL) was added and stirred for 10 mins. The aqueous phase was extracted with ethyl acetate (3 times 20 mL). The combined organic phase was washed with saturated brine (two times 20 mL), dried with anhydrous MgSO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 20mm, 100-200 mesh silica gel, CH₂Cl₂/Ethyl acetate=6/1, 2/1) to afford the product, which was further purification by preparative HPLC (Column: Gemini 150*25mm, 5um; Mobile phase: from 50% MeCN in water to 80% MeCN in water, 0.5% NH₃; Gradient Time: 12 min; Flow Rate: 25 ml/min; Wavelength: 220 nm) to afford desired *intermediate 354* (160 mg, 265 μmol, 17.2% yield) as light yellow oil.

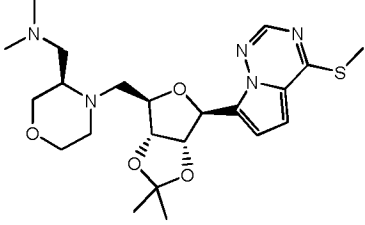
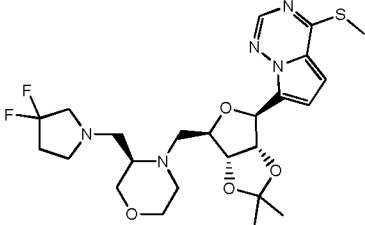
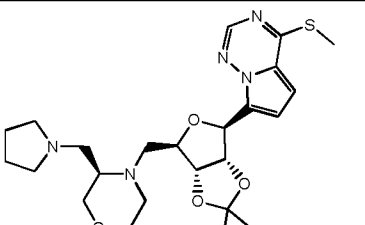
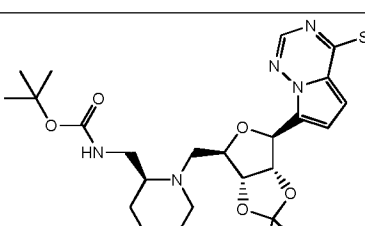
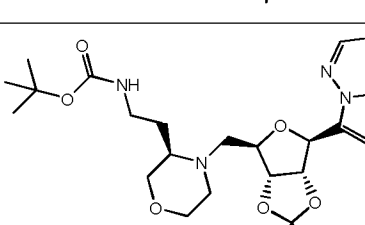
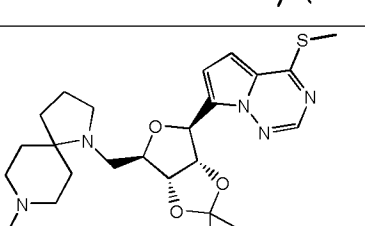
Below intermediates were prepared by an analogous reaction protocol as was used for the preparation of *intermediate 354* or *intermediate 353* using the appropriate starting materials (Table 13).

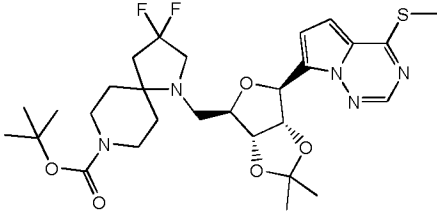
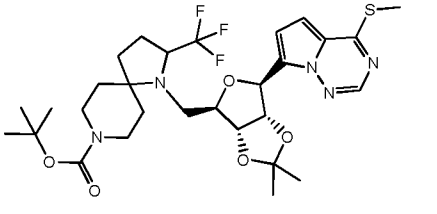
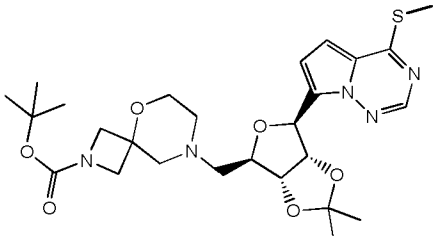
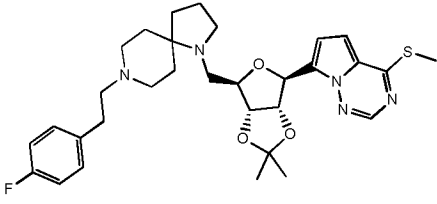
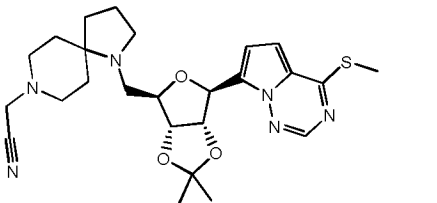
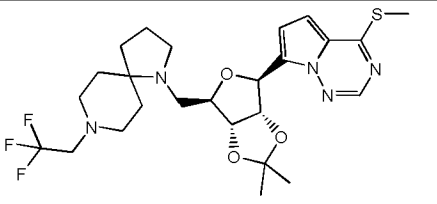
Table 13:

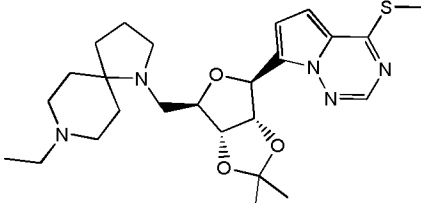
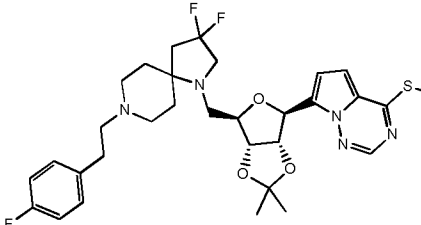
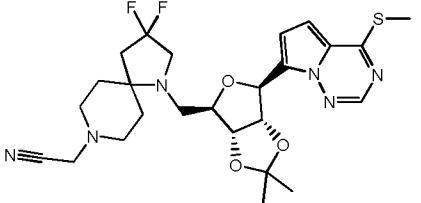
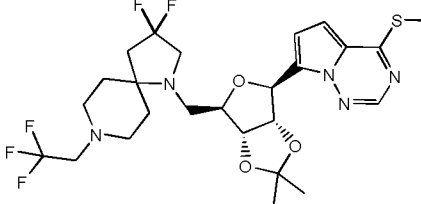
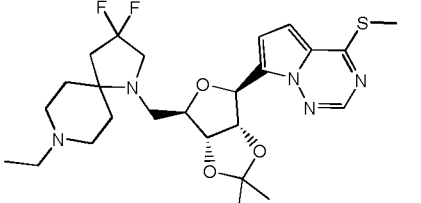
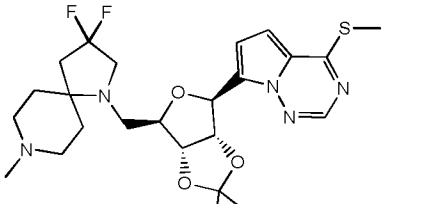
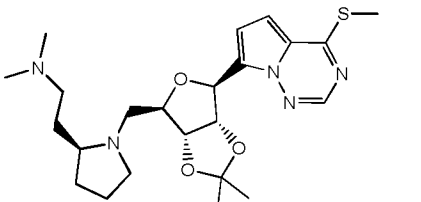
Int.	Structure	starting materials	Method
355		<i>intermediate 29</i> tert-butyl 9-oxa-2,6-diazaspiro[4.5]decane-2-carboxylate	<i>Method A</i>

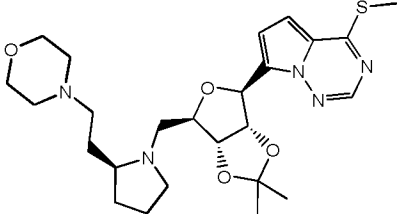
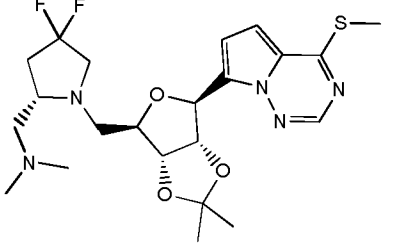
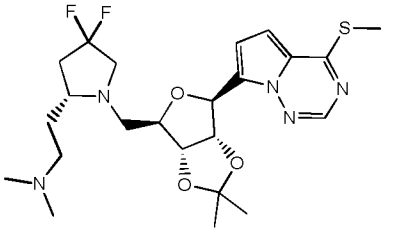
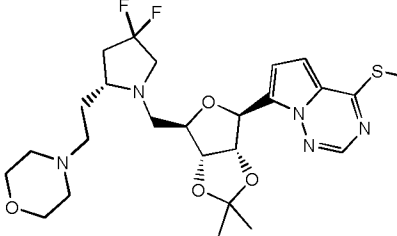
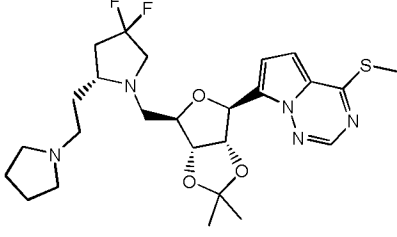
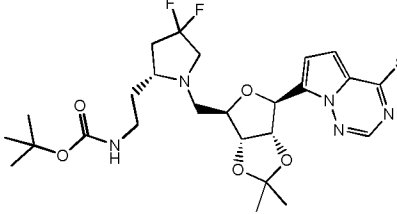
Int.	Structure	starting materials	Method
356		intermediate 29 tert-butyl 1,7- diazaspiro[3.5]nonane-7- carboxylate	<i>Method A</i>
357		intermediate 29 tert-butyl 1,9- diazaspiro[5.5]undecane- 9-carboxylate	<i>Method A</i>
358		intermediate 29 tert-butyl 2,9- diazaspiro[5.5]undecane- 9-carboxylate	<i>Method A</i>
359		intermediate 29 2-trifluoromethyl-1,8- diaza-spiro[4.5]decane- 8-carboxylic acid tert- butyl ester	<i>Method A</i>
360		intermediate 29 tert-butyl 1,8- diazaspiro[4.6]undecane- 8-carboxylate	<i>Method A</i>
361		intermediate 29 tert-butyl 1,7- diazaspiro[4.5]decane-7- carboxylate	<i>Method A</i>
362		intermediate 29 tert-butyl 2,8- diazaspiro[5.5]undecane- 2-carboxylate	<i>Method A</i>

Int.	Structure	starting materials	Method
363		intermediate 36 , 3,3-difluoro-8-methyl- 1,8- diazaspiro[4.5]decane 2hcl salt	<i>Method B</i>
364		intermediate 36 tert-butyl 1,8- diazaspiro[4.5]decane-8- carboxylate	<i>Method A</i>
365		intermediate 36 8-methyl-1,8- diazaspiro[4.5]decane	<i>Method A</i>
366		intermediate 36 tert-butyl 3,3-difluoro- 1,8-diaza- spiro[4.5]decane-8- carboxylate	<i>Method A</i>
367		intermediate 36 (S)-tert-butyl 2-(pyrrolidin- 2-yl)ethylcarbamate	<i>Method A</i>
368		intermediate 37 (R)-tert-butyl (2-(4,4- difluoropiperidin-2- yl)ethyl)carbamate TFA salt	<i>Method B</i>

Int.	Structure	starting materials	Method
369		intermediate 37 (R)-N,N-dimethyl-1-(morpholin-3-yl)methanamine 2hcl salt	<i>Method B</i>
370		intermediate 37 (R)-3-((3,3-difluoropyrrolidin-1-yl)methyl)morpholine	<i>Method A</i>
371		intermediate 37 (R)-3-(pyrrolidin-1-ylmethyl)morpholine	<i>Method A</i>
372		intermediate 37 (R)-tert-butyl (morpholin-3-ylmethyl)carbamate	<i>Method A</i>
373		intermediate 37 (R)-tert-butyl (2-(morpholin-3-yl)ethyl)carbamate	<i>Method A</i>
374		intermediate 37 8-methyl-1,8-diazaspiro[4.5]decane	<i>Method A</i>

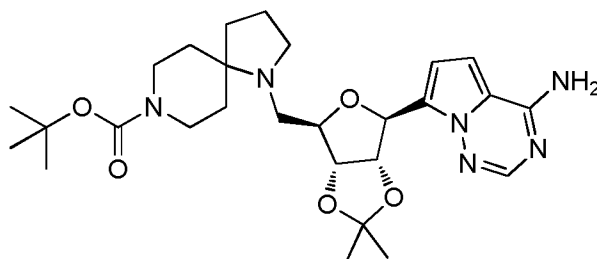
Int.	Structure	starting materials	Method
375		intermediate 37 tert-butyl 3,3-difluoro-1,8-diaza-spiro[4.5]decane-8-carboxylate	<i>Method A</i>
376		intermediate 37 2-trifluoromethyl-1,8-diaza-spiro[4.5]decane-8-carboxylic acid tert-butyl ester,	<i>Method A</i>
377		intermediate 37 tert-butyl 5-oxa-2,8-diazaspiro[3.5]nonane-2-carboxylate	<i>Method A</i>
378		intermediate 37 8-(4-fluorophenethyl)-1,8-diazaspiro[4.5]decane 2HCl salt	<i>Method B</i>
379		intermediate 37 2-(1,8-diazaspiro[4.5]decan-8-yl)acetonitrile 2HCl salt	<i>Method B</i>
380		intermediate 37 8-(2,2,2-trifluoroethyl)-1,8-diazaspiro[4.5]decane, 2HCl salt	<i>Method B</i>

Int.	Structure	starting materials	Method
381		intermediate 37 8-ethyl-1,8-diazaspiro[4.5]decane 2HCl salt	<i>Method B</i>
382		intermediate 37 3,3-difluoro-8-(4-fluorophenethyl)-1,8-diazaspiro[4.5]decane	<i>Method A</i>
383		intermediate 37 2-(3,3-difluoro-1,8-diazaspiro[4.5]decan-8-yl)acetonitrile	<i>Method A</i>
384		intermediate 37 3,3-difluoro-8-(2,2,2-trifluoroethyl)-1,8-diazaspiro[4.5]decane 2HCl salt	<i>Method B</i>
385		intermediate 37 8-ethyl-3,3-difluoro-1,8-diazaspiro[4.5]decane	<i>Method A</i>
386		intermediate 37 3,3-difluoro-8-methyl-1,8-diazaspiro[4.5]decane 2HCl salt	<i>Method B</i>
387		intermediate 37 (S)-N,N-dimethyl-2-(pyrrolidin-2-yl)ethanamine 2hcl salt	<i>Method B</i>

Int.	Structure	starting materials	Method
389		intermediate 37 (S)-4-(2-(pyrrolidin-2-yl)ethyl)morpholine 2HCl salt	<i>Method B</i>
390		intermediate 37 (S)-1-(4,4-difluoropyrrolidin-2-yl)- N,N-dimethylmethanamine 2HCl salt	<i>Method B</i>
391		intermediate 37 (R)-2-(4,4-difluoropyrrolidin-2-yl)- N,N-dimethylethanamine 2HCl salt	<i>Method B</i>
393		intermediate 37 (R)-4-(2-(4,4-difluoropyrrolidin-2-yl)ethyl)morpholine 2HCl salt	<i>Method B</i>
394		intermediate 37 (R)-4,4-difluoro-2-(2-(pyrrolidin-1-yl)ethyl)pyrrolidine 2HCl salt	<i>Method B</i>
395		intermediate 37 (R)-tert-butyl (2-(4,4-difluoropyrrolidin-2-yl)ethyl)carbamate	<i>Method A</i>

Int.	Structure	starting materials	Method
396		intermediate 37 (S)-1-(4,4-difluoropiperidin-2-yl)-N,N-dimethylmethanamine 2HCl salt	<i>Method B</i>
398		intermediate 37 (S)-4,4-difluoro-2-(pyrrolidin-1-ylmethyl)piperidine 2HCl salt	<i>Method B</i>
399		intermediate 37 (S)-tert-butyl ((4,4-difluoropiperidin-2-yl)methyl)carbamate	<i>Method A</i>

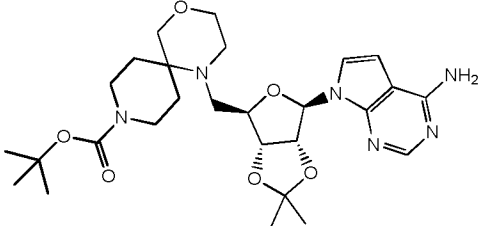
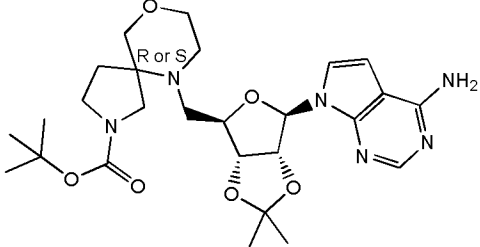
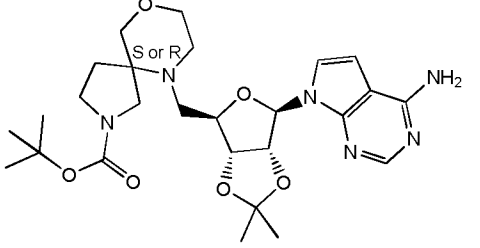
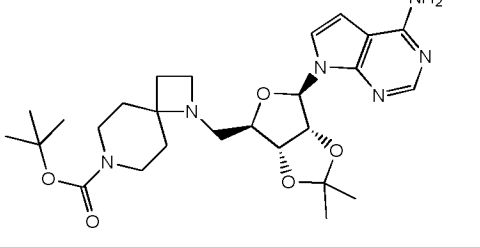
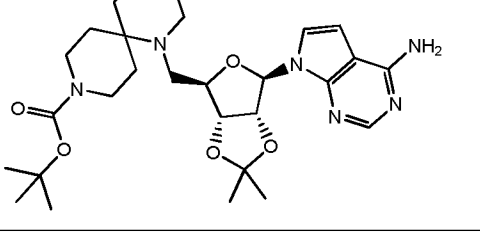
Example A38

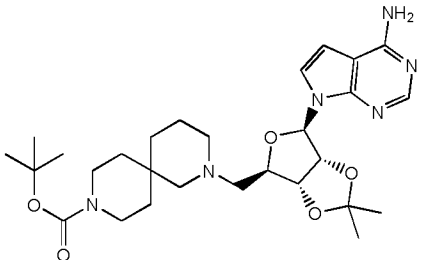
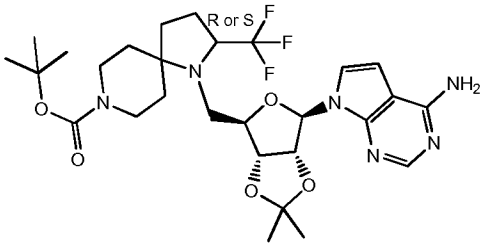
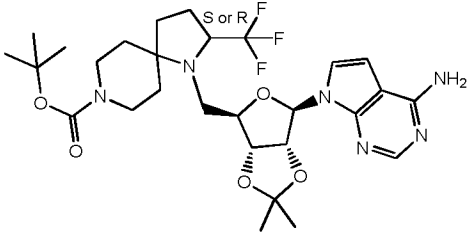
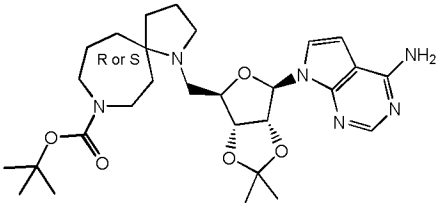
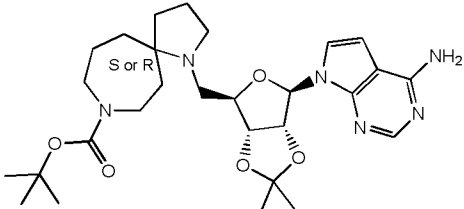
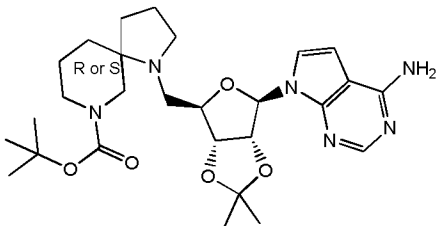
Preparation of *intermediate 400*

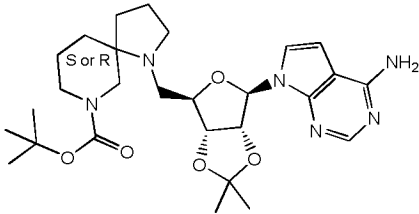
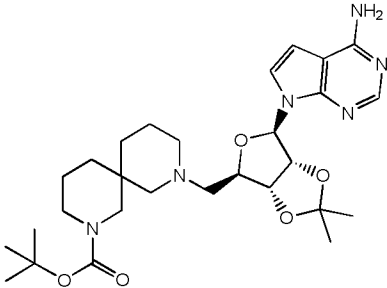
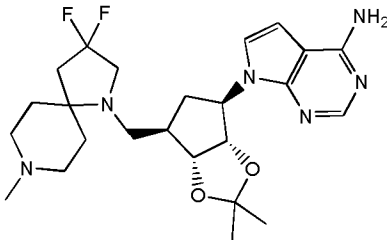
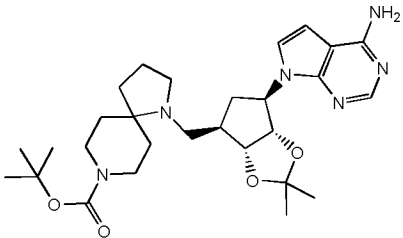
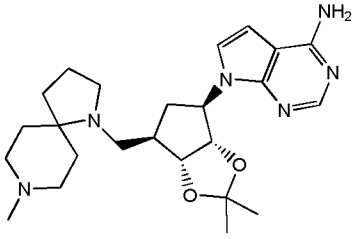
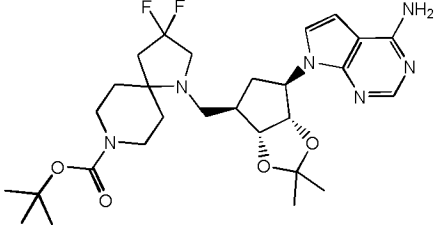
- 5 A solution of *intermediate 353* (199 mg, 355.5 μmol , 1 eq) in THF (1.5 mL) and $i\text{PrOH}$ (2.5 mL) was taken up into a sealed tube. NH_4OH (4.55 g, 32.5 mmol, 91.2 eq) was added to the mixture and the resulting suspension was heated at 80 $^{\circ}\text{C}$ for 3 days. The reaction mixture was concentrated under reduced pressure. The crude was purified by preparative TLC (silica gel, 100% EtOAc) to afford desired *intermediate 400* (150 mg, 272.4 μmol , 76.6% yield) as yellow solid.
- 10

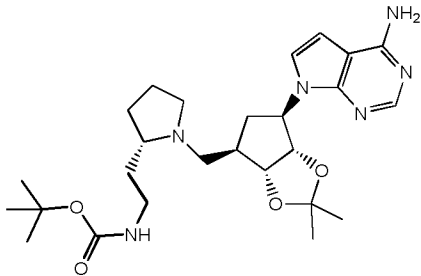
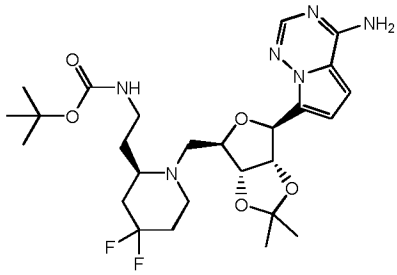
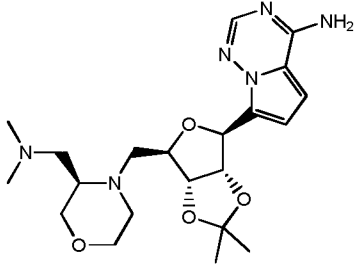
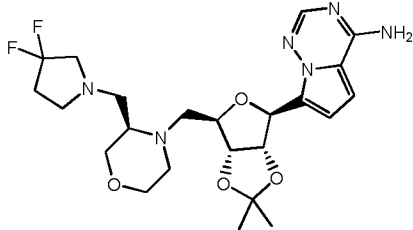
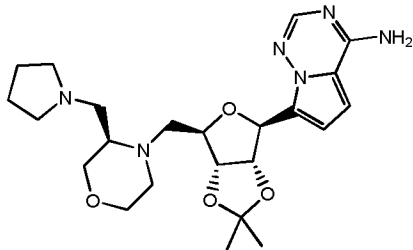
Below intermediates were prepared by an analogous reaction protocol as was used for the preparation of *intermediate 400* using the appropriate starting materials (Table 14).

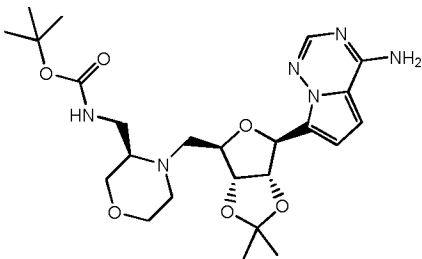
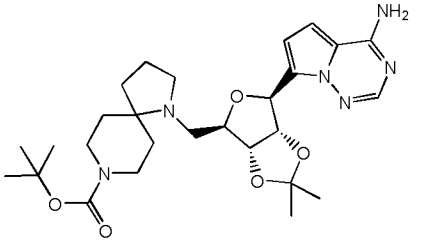
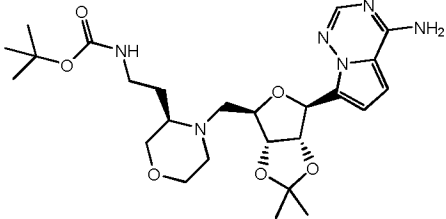
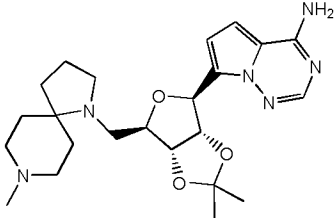
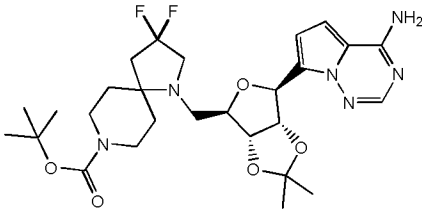
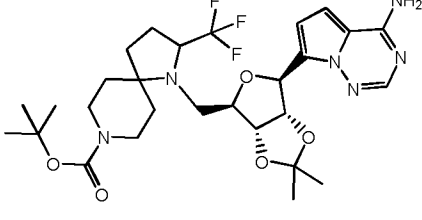
Table 14:

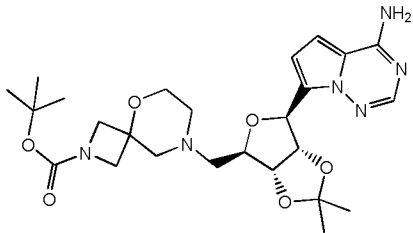
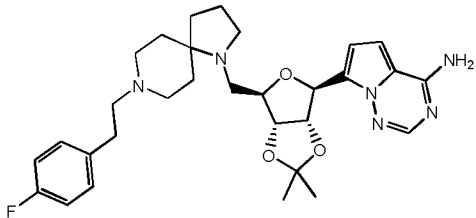
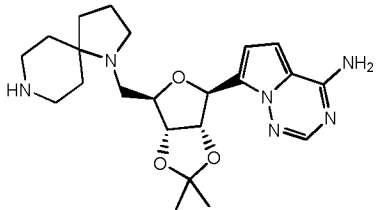
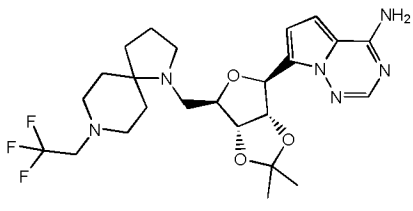
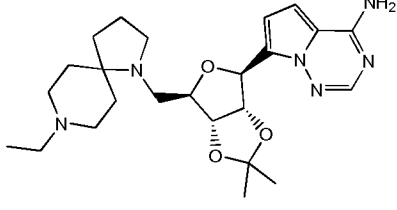
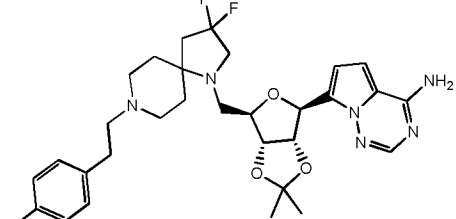
Int.	Structure	Starting materials
401		Intermediate 354
402		Intermediate 355
403		Intermediate 355
404		Intermediate 356
405		Intermediate 357

Int.	Structure	Starting materials
406		Intermediate 358
407		Intermediate 359
408		Intermediate 359
409		Intermediate 360
410		Intermediate 360
411		Intermediate 361

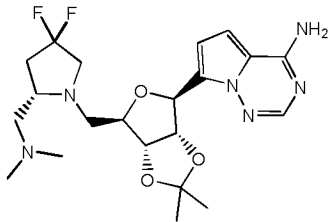
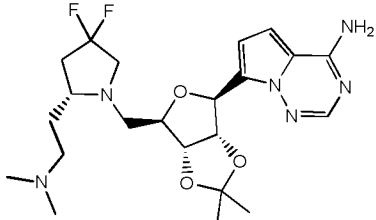
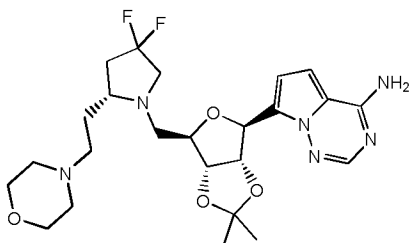
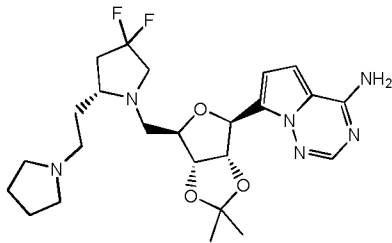
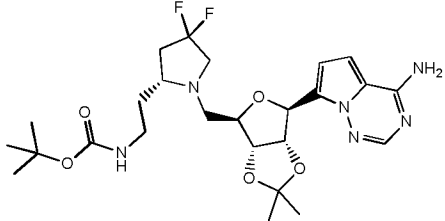
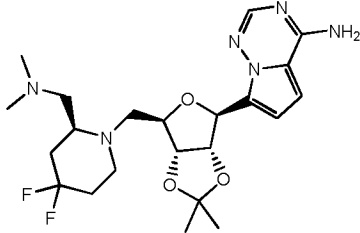
Int.	Structure	Starting materials
412		<i>Intermediate 361</i>
413		<i>Intermediate 362</i>
414		<i>Intermediate 363</i>
415		<i>Intermediate 364</i>
416		<i>Intermediate 365</i>
417		<i>Intermediate 366</i>

Int.	Structure	Starting materials
418		<i>Intermediate 367</i>
419		<i>Intermediate 368</i>
420		<i>Intermediate 369</i>
421		<i>Intermediate 370</i>
422		<i>Intermediate 371</i>

Int.	Structure	Starting materials
423		<i>Intermediate 372</i>
424		<i>Intermediate 353</i>
425		<i>Intermediate 373</i>
426		<i>Intermediate 374</i>
427		<i>Intermediate 375</i>
428		<i>Intermediate 376</i>

Int.	Structure	Starting materials
429		<i>Intermediate 377</i>
430		<i>Intermediate 378</i>
431A		<i>Intermediate 379</i>
432		<i>Intermediate 380</i>
433		<i>Intermediate 381</i>
434		<i>Intermediate 382</i>

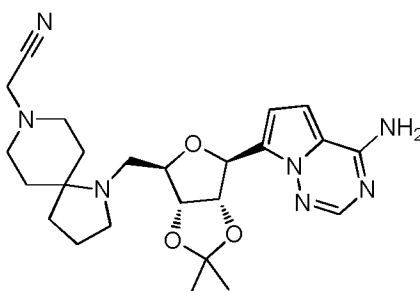
Int.	Structure	Starting materials
435A		<i>Intermediate 383</i>
436		<i>Intermediate 384</i>
437		<i>Intermediate 385</i>
438		<i>Intermediate 386</i>
439		<i>Intermediate 387</i>
441		<i>Intermediate 389</i>

Int.	Structure	Starting materials
442		<i>Intermediate 390</i>
443		<i>Intermediate 391</i>
445		<i>Intermediate 393</i>
446		<i>Intermediate 394</i>
447		<i>Intermediate 395</i>
448		<i>Intermediate 396</i>

Int.	Structure	Starting materials
450		<i>Intermediate 398</i>
451		<i>Intermediate 399</i>

Example A39

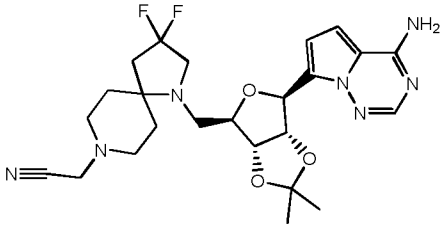
Preparation of *intermediate 452*



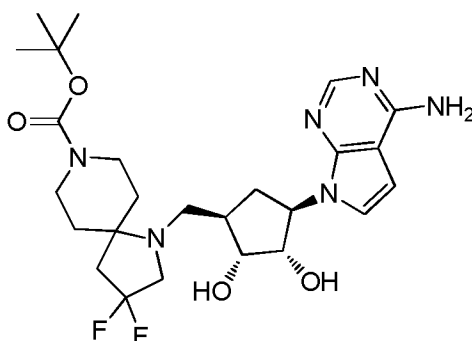
- To a mixture of **Intermediate 431A** (110 mg, 256.7 μmol , 1 eq) in CH_2Cl_2 (20 mL) was added Et_3N (77.9 mg, 770 μmol , 3 eq) and 2-chloroacetonitrile (23.26 mg, 308 μmol , 1.20 eq). The mixture was stirred at 25 $^\circ\text{C}$ for 16h. The mixture was concentrated in vacuum. The residue was purified by preparative HPLC (Column: Gemini 150*25mm, 5 μm ; Mobile phase: from 25% MeCN in water to 45% MeCN in water, 0.5% NH_3 ; Gradient Time: 12 min; Flow Rate: 25 ml/min; Wavelength: 220 nm). **Intermediate 452** (70 mg, 143.1 μmol , 55.7% yield) was obtained as a white solid.

Below intermediates were prepared by an analogous reaction protocol as was used for the preparation of *intermediate 452* using the appropriate starting materials (Table15).

15 Table 15:

Int.	Structure	Starting materials
453		Intermediate 435A

Example A40

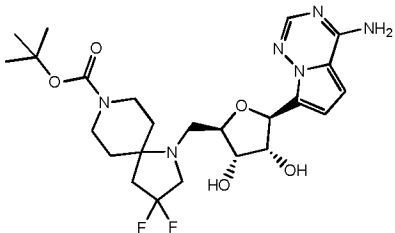
Preparation of *intermediate 454*

- 5 To a mixture of *Intermediate 417* (360 mg, 639.8 μmol , 1 eq) in MeOH (30 mL) was added PPTS (225 mg, 896 μmol , 1.4 eq) in one portion at 25°C. The mixture was stirred at 50 °C for 10 days. The mixture was concentrated in vacuum to afford *Intermediate 454* (450 mg, crude) as a yellow solid, which directly used in next step without further purification.

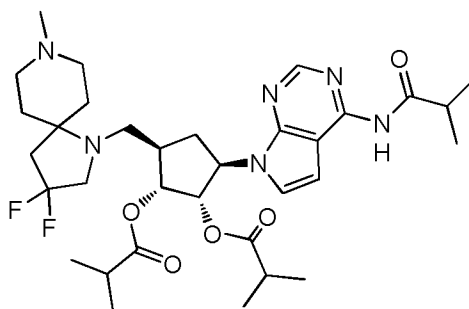
10

Below intermediates were prepared by an analogous reaction protocol as was used for the preparation of *Intermediate 454* using the appropriate starting materials (Table 16).

Table 16:

Int.	Structure	Starting materials
455		Intermediate 427

15 Example A41

Preparation of *intermediate 457*

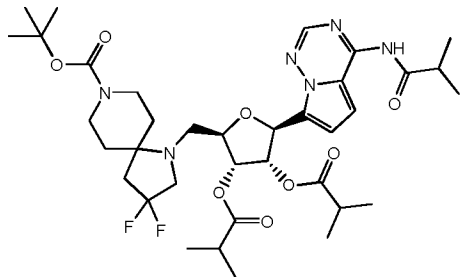
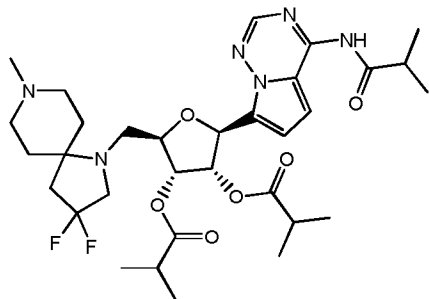
To a mixture of **compound 123** (60 mg, 137.5 μ mol, 1 eq) in pyridine (3 mL) was added isobutyric anhydride (217.5 mg, 1.37 mmol, 10 eq) in one portion at 25°C. The mixture was stirred at 25 °C for 20 h.. The mixture was concentrated in vacuum. The residue was purified by preparative TLC (DCM: MeOH = 10:1 to afford **intermediate 457** (41 mg, 61.2 μ mol, 44.5% yield) as white solid.

Below intermediates were prepared by an analogous reaction protocol as was used for the preparation of **intermediate 457** using the appropriate starting materials (Table 17).

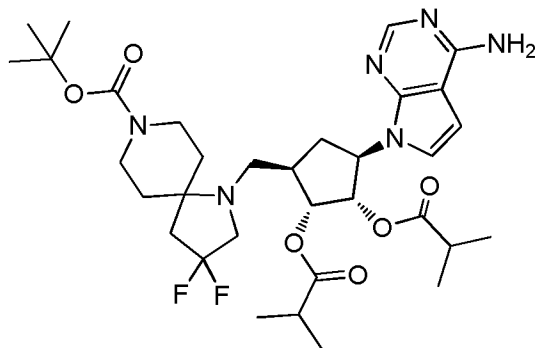
10

Table 17:

Int.	Structure	Starting materials
458		<i>Intermediate 454</i>
459		<i>compound 135</i>

Int.	Structure	Starting materials
461		intermediate 455
462		compound 147

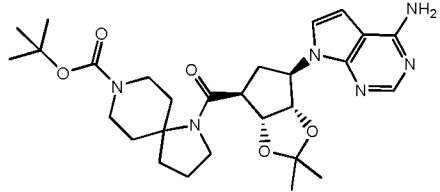
Example A42

Preparation of **intermediate 464**

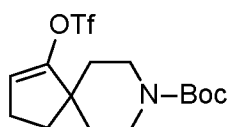
- 5 A mixture of **intermediate 458** (250 mg, 341.1 μmol , 1 eq) in MeOH (500 μL) was stirred at 120°C for 5 h in sealed tube. The mixture was concentrated in vacuum. The crude product was purified by TLC (DCM/Ethyl acetate = 1/2 to afford **intermediate 464** (143 mg, 210.6 μmol , 61.7% yield) as a white solid.

Below final compounds were prepared by an analogous reaction protocol as was used
 10 for the preparation of **intermediate 464** using the appropriate starting materials (Table 18).

Table 18:

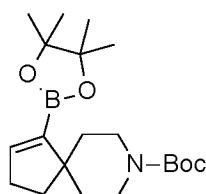
Int.	Structure	Starting materials
465		<i>Intermediate 351</i>

Example A43

Synthesis of *intermediate 525*

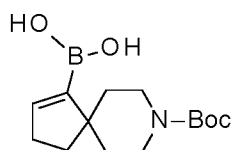
5

A solution of 1M LiHMDS in THF (63 mL, 63 mmol, 2.0 eq) was added dropwise to a solution of 1-oxo-8-Azaspiro[4.5]decane-8-carboxylic acid, 1,1-dimethylethyl ester (8.0 g, 31.6 mmol, 1.0 eq) in anhydrous THF (200 mL) at -78 °C. The reaction mixture was stirred for 2h at -78 °C, then a solution of N,N-bis(trifluoromethylsulfonyl)aniline (22.6 g, 63.0 mmol, 2.0 eq) in anhydrous THF (60 mL) was added dropwise. After complete addition, the cooling bath was replaced with a bath at 0 °C and the reaction was maintained at 0 °C overnight. The reaction was quenched with sat. Na₂CO₃ and then was added diethyl ether, water and brine. The organic phase was separated, washed twice with sat. Na₂CO₃, once with brine, dried over MgSO₄, filtered and concentrated *in vacuo* to afford the crude product. The crude product was purified by normal phase flash chromatography (330g SiO₂) using EtOAc containing 1% Et₃N and Heptane containing 1% Et₃N as eluent (gradient: 0% to 10% EtOAc containing 1% Et₃N; isocratic: 10% EtOAc containing 1% Et₃N), to afford *intermediate 525* as white solid (9.4 g, 24 mmol, yield: 78%)

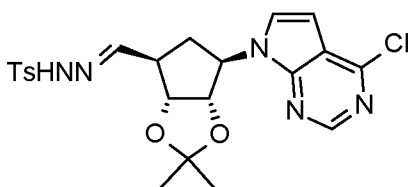
20 Synthesis of *intermediate 526*

A suspension of **intermediate 525** (9.4 g, 25.5 mmol, 1 eq), bis(pinacolato)diboron (6.8 g, 26.9 mmol, 1.1 eq), sodium phenoxide (4.3 g, 36.7 mmol, 1.5 eq), KBr (4.4 g, 36.7 mmol, 1.5 eq) and triphenylphosphine (1.3 g, 4.9 mmol, 0.2 eq) in anhydrous toluene (200 mL) was stirred and flushed with N₂ for 20 min. To the flushed solution was added bis(triphenylphosphine)palladium(II) dichloride (1.7 g, 2.5 mmol, 0.1 eq). The reaction mixture was flushed again for 5 min with N₂ and then heated at 50°C. After stirring for 20 hours, the reaction mixture was filtered over celite and the filter was washed with EtOAc. The filtrate was subsequently washed with water (3x), 1M NaOH solution (2x), and brine (1x), dried over MgSO₄, filtered and concentrated *in vacuo* to afford the crude **intermediate 526** as a dark oil. The crude product was stirred in diisopropyl ether, the precipitate (mainly triphenylphosphine oxide and unknown product) was removed by filtration. The filtrate was concentrated *in vacuo* and the obtained residue purified by normal phase flash chromatography (SiO₂) using EtOAc and heptane as eluent (isocratic: 0% EtOAc gradient: 0% to 12%, to afford **intermediate 526** as white solid product (5.6 g, 15.3 mmol, yield 62%).

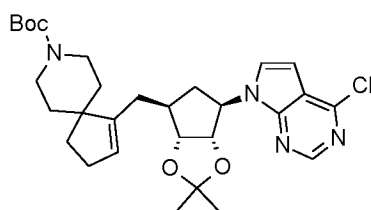
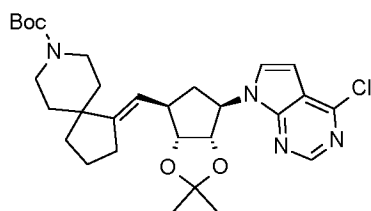
Synthesis of **intermediate 527a**



Boronate ester **intermediate 526** (5.7 g, 15.3 mmol, 1 eq) was dissolved in a mixture of acetone (200 mL) and water (50 mL). To this mixture was then added NH₄OAc (7.1 g, 91.8 mmol, 6.0 eq) and sodium periodate (19.6 g, 91.8 mmol, 6.0 eq), the obtained suspension was stirred for one week at r.t. The reaction mixture was diluted with EtOAc, the remaining precipitate was filtered off. The organic phase was separated, washed three times with brine, dried over MgSO₄, filtered and concentrated *in vacuo* to afford the crude product. The crude product was recrystallized in EtOAc to afford a first batch of **intermediate 527a** as a white solid (1.36 g, 4.8 mmol). The filtrate was concentrated, and the obtained impure product was recrystallized in diisopropyl ether with addition of EtOAc to afford a second batch of **intermediate 527a** as white solid (0.8 g, 2.8 mmol). The impure product was further purified by trituration in diisopropyl ether, this was carried out twice to afford **intermediate 527a** as white solid (0.6 g, 2.1 mmol). The filtrates were concentrated and the remaining impure product was purified by normal phase flash chromatography (SiO₂) using DCM, EtOAc and heptane as eluent (isocratic: 100% DCM), followed by gradient elution: start 70:30 EtOAc: Heptane to 100% EtOAc to afford **intermediate 527a** as solid product (0.7 g, 2.4 mmol). In total 3.4 g of boronic acid **intermediate 527a** (12.2 mmol, yield 79%) was obtained.

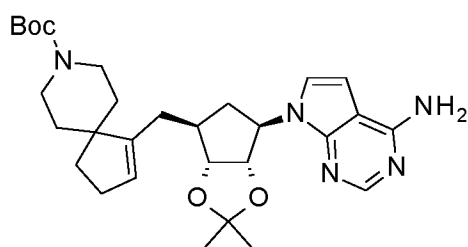
Synthesis of *intermediate 527b*

A solution of *intermediate 14* (3.07 g, 9.5 mmol, 1.0 eq) in anhydrous DCM (45 mL) was added dropwise to a suspension of Dess-Martin periodinane (4.80 g, 11.40 mmol, 1.2 eq) in anhydrous DCM (45 mL) at 0 °C. After the addition, the reaction mixture was allowed to warm to room temperature, stirred for two hours, and then additional Dess-Martin periodinane (0.20 g, 0.48 mmol, 0.05 eq) was added. The reaction mixture was stirred for another half hour, then MeOH (about 50 mL) and *p*-toluenesulfon hydrazide (2.30 g, 12.34 mmol, 1.3 eq) was added. After 2.5 hours stirring, diluted saturated Na₂CO₃/water (50/50) was added, the organic layer was separated and the aqueous layer was extracted once with EtOAc. The organic phases were combined, washed with saturated Na₂CO₃ and brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by normal phase flash chromatography using DCM and MeOH as eluent (SiO₂ column, gradient: 0% MeOH to 1.5% MeOH, isocratic: 1.5% MeOH) to afford *intermediate 527b* as a yellow/white crystal (4.16 g, 8.49 mmol, yield: 89%).

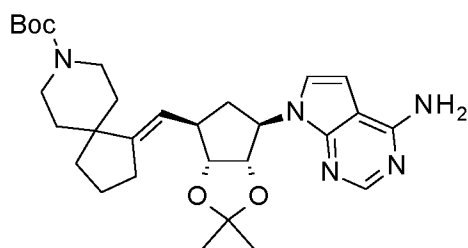
Synthesis of *intermediate 528* and *intermediate 529**intermediate 528**intermediate 529*

A reaction mixture of **intermediate 527b** (5.6 g, 11.4 mmol, 1.0 eq), **intermediate 527a** (3.2 g, 11.4 mmol, 1.0 eq), K₂CO₃ (4.7 g, 34.1 mmol, 3.0 eq) and 1,4-dioxane (60 mL) was heated at 110 °C and stirred for six hours. To the reaction mixture was added EtOAc, then it was washed three times with diluted sat. Na₂CO₃/water (50:50), once
5 with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude mixture was purified with normal phase flash chromatography using heptane and EtOAc as eluent (SiO₂ column, gradient: 20% to 30% EtOAc to afford a mayor fraction of a mixture of 87% **intermediate 528** and 13% **intermediate 529** (2.3 g, yield: 36%) and a minor fraction of pure **intermediate 529** was obtained (246 mg, yield: 4%) .

10 Synthesis of **intermediate 530 and intermediate 531**



intermediate 530



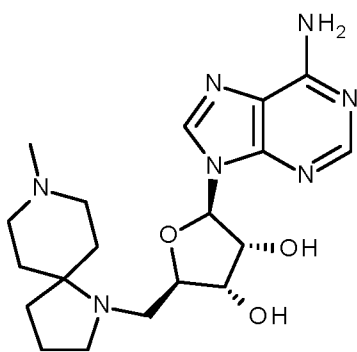
intermediate 531

15 A solution of mixture of **intermediate 528 and intermediate 529** (ratio: 87:13, 2.3 g, 4.3 mmol) in THF (20 mL) and ammonia in water (25% w/t, 20 mL) was stirred in an autoclave at 100 °C until complete conversion (four days). After complete conversion, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in MeOH and the obtained solution was concentrated again to afford the crude mixture of **intermediate**
20 **530 and intermediate 531** which was used in the next step without any purification.

B. Preparation of final compounds

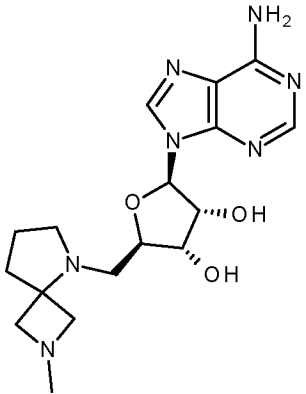
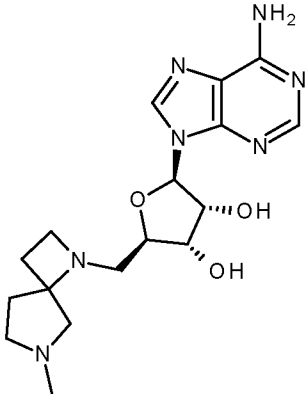
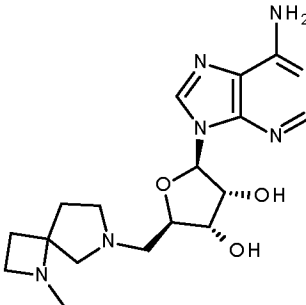
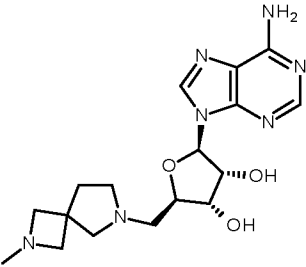
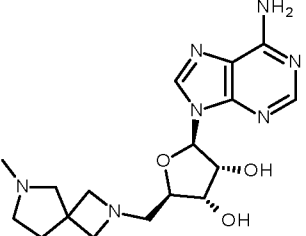
Example B1

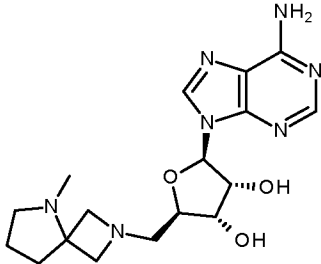
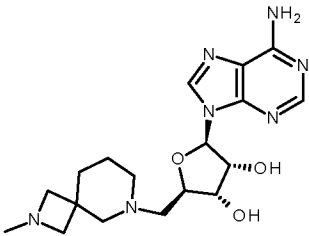
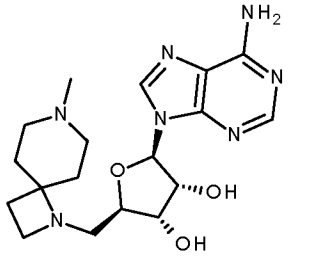
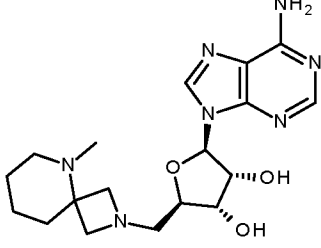
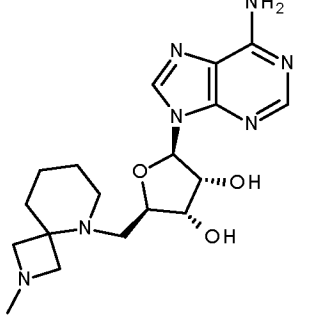
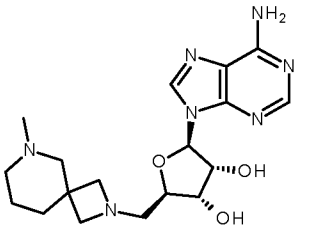
Synthesis of **final compound 1**

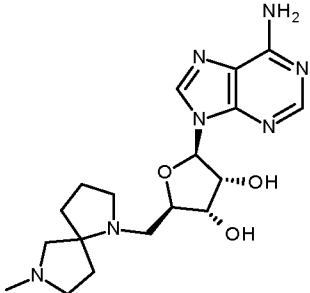
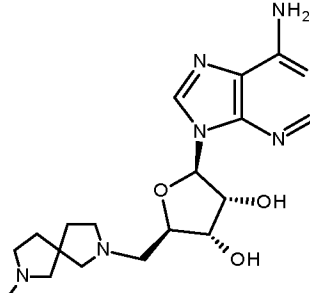
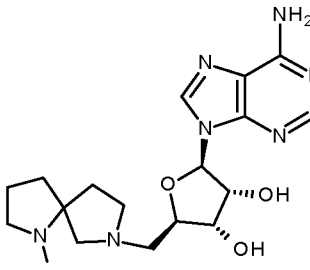
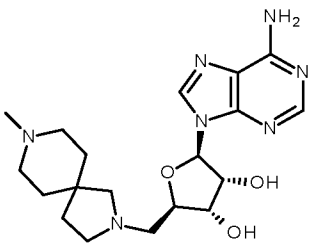
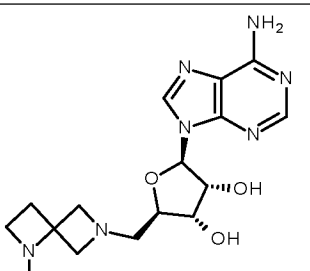


Intermediate 159 (0.18g, 0.278 mmol), formaldehyde solution 37 wt. % in H₂O (0.023 mL, 0.305 mmol) and sodium acetate were dissolved in THF (5 mL) and the mixture was stirred 30 min. Then sodium triacetoxyborohydride (0.088g, 0.42mmol) was added and the solution was stirred at room temperature overnight. The solvents were evaporated to dryness and to the residue in MeOH (3.4 mL) was added ammonia solution 7 N in MeOH (17 mL). The mixture was stirred at room temperature for 4 days. The solvent was evaporated to dryness and the residue was then dissolved in trifluoroacetic acid (16 mL) and water (0.9 mL) and stirred at room temperature overnight. The solvents were evaporated to dryness and the product was purified by reverse phase (Aqueous phase: 25mM NH₄HCO₃ Organic phase: MeCN: 1:1 gradient 95% [Aqueous phase] - 5% [Organic phase] to 63% [Aqueous phase] - 37% [Organic phase] to give **final compound 1** (0.037 gr, yield: 31%).

Below **final compounds** were prepared by an analogous reaction protocol as was used for the preparation of **final compound 1** using the appropriate starting materials (Table 19).

Co.	Structure	Starting materials
2		a) <i>Intermediate 174</i>
3		a) <i>Intermediate 173</i>
4		a) <i>Intermediate 171</i>
5		a) <i>Intermediate 172</i>
6		a) <i>Intermediate 170</i>

Co.	Structure	Starting materials
7		a) <i>Intermediate 169</i>
8		a) <i>Intermediate 168</i>
9		a) <i>Intermediate 167</i>
10		a) <i>Intermediate 166</i>
11		a) <i>Intermediate 165</i>
12		a) <i>Intermediate 164</i>

Co.	Structure	Starting materials
13		a) <i>Intermediate 161</i>
14		a) <i>Intermediate 163</i>
15		a) <i>Intermediate 162</i>
16		a) <i>Intermediate 160</i>
17		a) <i>Intermediate 175</i>

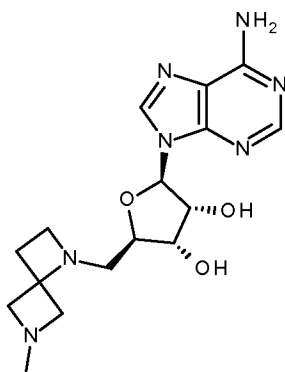
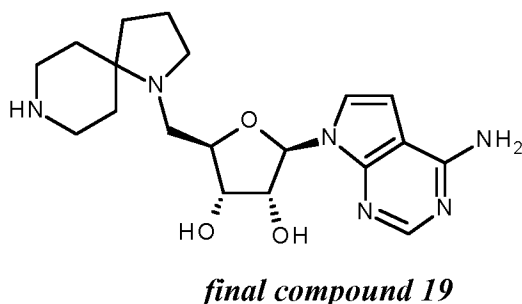
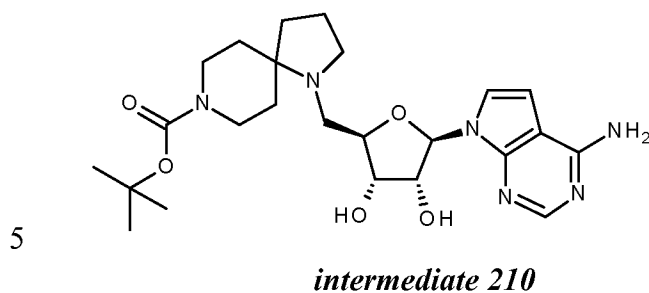
Co.	Structure	Starting materials
18		a) <i>Intermediate 176</i>

Table 19

Example B2

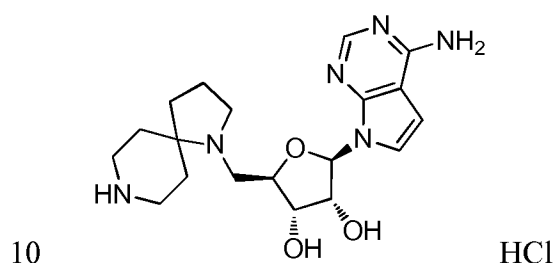
Preparation of *final compound 19* and *intermediate 210*

HCl (104 mL, 416 mmol, 4 M in dioxane) was added to a stirred solution of *intermediate*
 10 *114* (22.7 g, 41.6 mmol) in MeOH (1800 mL) at room temperature. The reaction mixture
 was stirred at room temperature for 18 hours. The reaction mixture was poured out into
 4L DIPE. The resulting suspension was stirred for 10 minutes at room temperature. The
 precipitate was filtered off and washed with DIPE to give *precipitate 1* and *filtrate 1*.
 The *precipitate 1* was dissolved in MeOH and slightly alkalized with a 7N solution of
 15 NH₃ in MeOH. Then the solvents were evaporated yielding 16.51 g of crude *final*
compound 19. A purification was performed via Prep HPLC (Stationary phase:
 Uptisphere C18 ODB - 10μm, 200g, 5cm, Mobile phase: 0.25% NH₄HCO₃ solution in
 water, CH₃CN) to give *final compound 19* (9.18 g, 23.631 mmol, 56.8% yield). The

filtrate 1 was slightly alkalized with a 7N solution of NH₃ in MeOH upon with precipitation occurred. The precipitate was filtered off and the solvents of the filtrate were evaporated yielding 10.7 g of crude *intermediate 210*. A purification was performed via Prep HPLC (Stationary phase: Uptisphere C18 ODB - 10μm, 200g, 5cm, Mobile phase: 0.25% NH₄HCO₃ solution in water, CH₃CN) to give *intermediate 210* (2.11 g, 10.4% yield).

Example B3

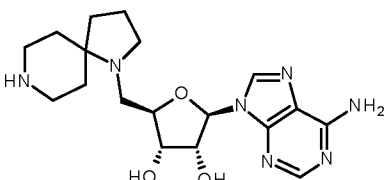
Preparation of *final compound 20*

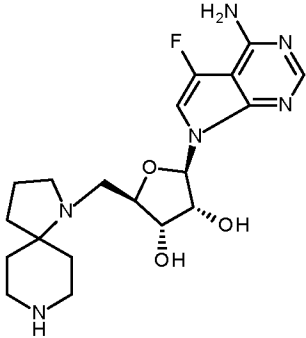
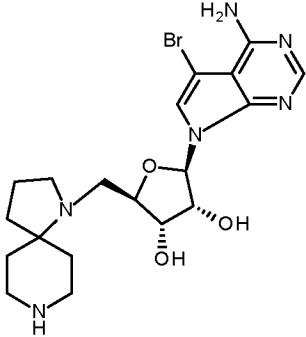
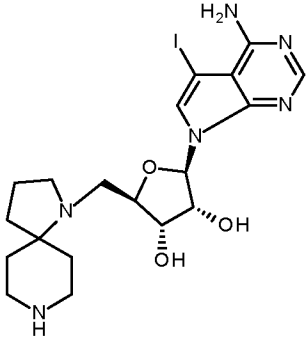
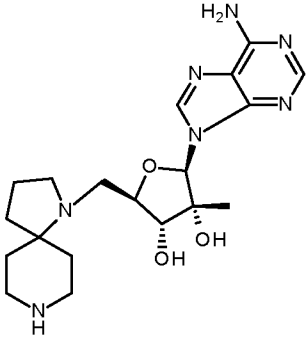
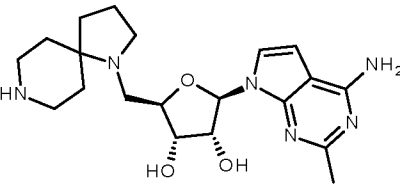


HCl (86.5 mL, 345.8 mmol, 4 M in dioxane) was added to a stirred solution of *intermediate 114* (18.28 g, 34.6 mmol) in MeOH (1500 mL) at room temperature. The reaction mixture was stirred at room temperature. for 5 days. The reaction mixture was poured into 2L DIPE. The resulting suspension was stirred for 10 minutes at room temperature. The solvents were decanted off so that the sticky precipitate remained. This residue was dissolved in MeOH and slightly alkalized with a 7N solution of NH₃ in MeOH. Then the solvents were evaporated yielding *final compound 20* as HCl salt. (17.40 g).

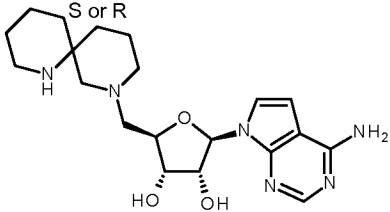
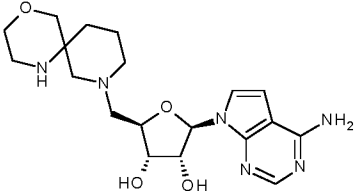
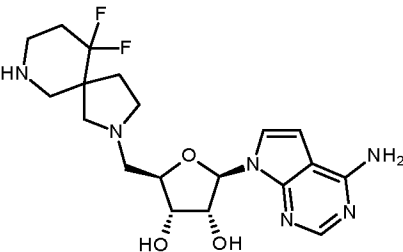
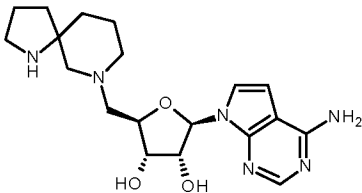
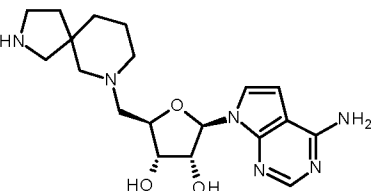
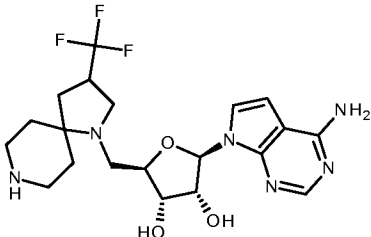
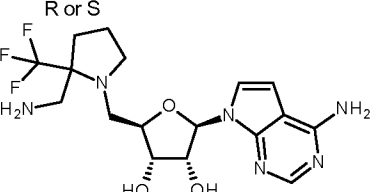
20 Below *final compounds* were prepared by an analogous reaction protocol as was used for the preparation of *final compound 20* using the appropriate starting materials (Table 20).

Table 20

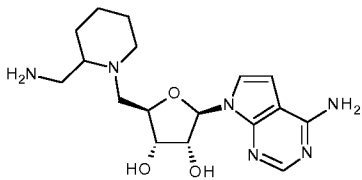
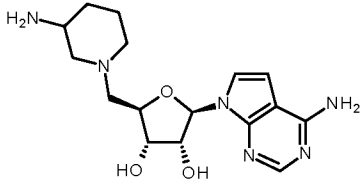
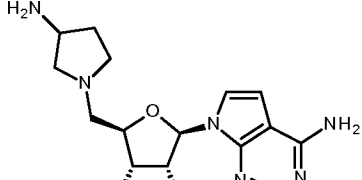
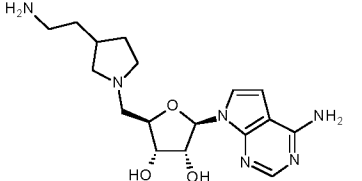
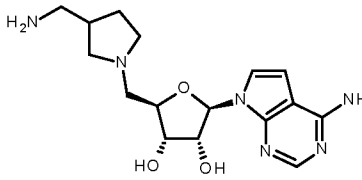
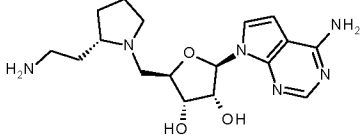
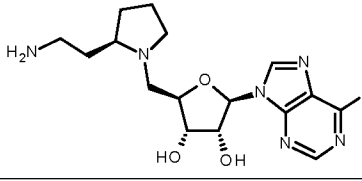
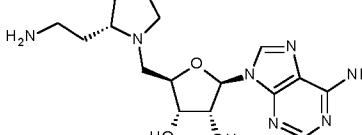
Co.	Structure	Starting materials and conditions
76		a) <i>Intermediate 115</i> b) <i>HCl (4M in dioxane) in MeOH</i>

Co.	Structure	Starting materials and conditions
24		a) <i>Intermediate 117</i> b) <i>HCl (4M in dioxane) in MeOH</i>
25	 HCl salt (eq not determined)	a) <i>Intermediate 118</i> b) <i>HCl (4M in dioxane) in MeOH</i>
26		a) <i>Intermediate 119</i> b) <i>HCl (4M in dioxane) in MeOH</i>
27		a) <i>Intermediate 120</i> b) <i>HCl (4M in dioxane) in MeOH</i>
28		a) <i>Intermediate 121</i> b) <i>HCl in MeOH</i>

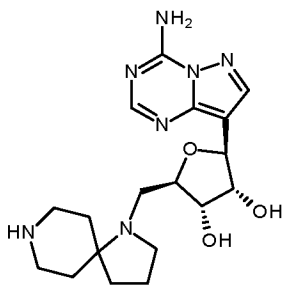
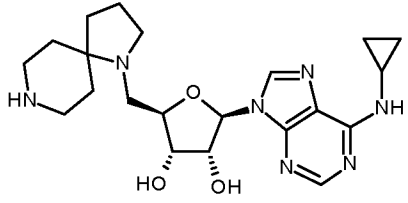
Co.	Structure	Starting materials and conditions
29		a) <i>Intermediate 122</i> b) <i>HCl (4M in dioxane)in MeOH</i>
30		a) <i>Intermediate 123</i> b) <i>HCl in MeOH</i>
31		a) <i>Intermediate 124</i> b) <i>HCl (4M in dioxane)in MeOH</i>
32		a) <i>Intermediate 125</i> b) <i>HCl in MeOH</i>
33		a) <i>Intermediate 126</i> b) <i>HCl (4M in dioxane)in MeOH</i>
34		a) <i>Intermediate 126</i> b) <i>HCl (4M in dioxane)in MeOH</i>
35		a) <i>Intermediate 127</i> b) <i>HCl (4M in dioxane)in MeOH</i>

Co.	Structure	Starting materials and conditions
36		a) <i>Intermediate 128</i> b) <i>HCl (4M in dioxane) in MeOH</i>
37		a) <i>Intermediate 129</i> b) <i>HCl (4M in dioxane) in MeOH</i>
38		a) <i>Intermediate 130</i> b) <i>HCl/MeOH in MeOH</i>
39	 HCl salt (eq not determined)	a) <i>Intermediate 131</i> b) <i>HCl (4M in dioxane) in MeOH</i>
40		a) <i>Intermediate 132</i> b) <i>HCl (4M in dioxane) in MeOH</i>
41		a) <i>Intermediate 133</i> b) <i>HCl (4M in dioxane) in MeOH</i>
42		a) <i>Intermediate 134</i> b) <i>HCl in MeOH</i>

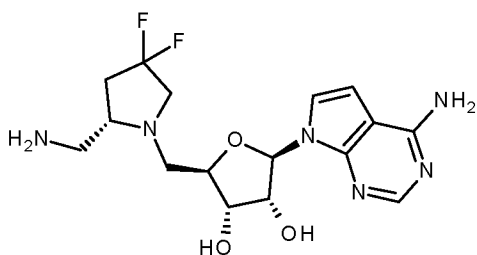
Co.	Structure	Starting materials and conditions
43		a) <i>Intermediate 134</i> b) <i>HCl in MeOH</i>
44		a) <i>Intermediate 134</i> b) <i>HCl in MeOH</i>
45		a) <i>Intermediate 135</i> b) <i>HCl (4M in dioxane)</i>
47		a) <i>Intermediate 138</i> b) <i>HCl (4M in dioxane)in MeOH</i>
48		a) <i>Intermediate 139</i> b) <i>HCl (4M in dioxane)in MeOH</i>
49		a) <i>Intermediate 140</i> b) <i>HCl (4M in dioxane)in MeOH</i>
50		a) <i>Intermediate 182</i> b) <i>HCl (4M in dioxane)in MeOH</i>
51		a) <i>Intermediate 144</i> b) <i>HCl (4M in dioxane)in MeOH</i>

Co.	Structure	Starting materials and conditions
52		a) <i>Intermediate 145</i> b) <i>HCl (4M in dioxane) in MeOH</i>
53		a) <i>Intermediate 146</i> b) <i>HCl (4M in dioxane) in MeOH</i>
54		a) <i>Intermediate 148</i> b) <i>HCl (4M in dioxane) in MeOH</i>
55		a) <i>Intermediate 149</i> b) <i>HCl (4M in dioxane) in MeOH</i>
56		a) <i>Intermediate 151</i> b) <i>HCl (4M in dioxane) in MeOH</i>
57		a) <i>Intermediate 152</i> b) <i>HCl (4M in dioxane) in MeOH</i>
58		a) <i>Intermediate 153a</i> b) <i>HCl (4M in dioxane) in MeOH</i>
59		c) <i>Intermediate 153b</i> d) <i>HCl (4M in dioxane) in MeOH</i>

Co.	Structure	Starting materials and conditions
60		a) <i>Intermediate 154</i> b) <i>HCl (4M in dioxane) in MeOH</i>
61		a) <i>Intermediate 155</i> b) <i>HCl in MeOH</i>
62		a) <i>Intermediate 157</i> b) <i>HCl (4M in dioxane) in MeOH</i>
63		a) <i>Intermediate 59</i> b) <i>TFA in DCM</i>
64		a) <i>Intermediate 48</i> b) <i>HCl (4M in dioxane)</i>
65		a) <i>Intermediate 61</i> b) <i>HCl in MeOH</i>
66		a) <i>Intermediate 156</i> b) <i>HCl in MeOH</i>
67		a) <i>Intermediate 186</i> b) <i>HCl (4M in dioxane) in MeOH</i>

Co.	Structure	Starting materials and conditions
68		a) <i>Intermediate 187</i> b) <i>HCl (4M in dioxane) in MeOH</i>
270		a) <i>Intermediate 158</i> b) <i>HCl (4M in dioxane) in MeOH</i>

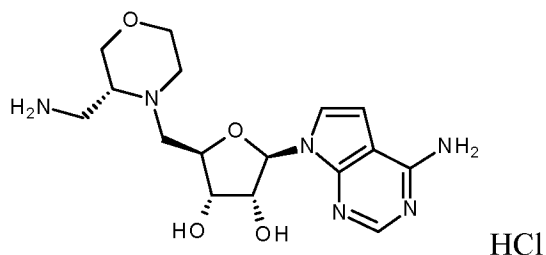
Example B4

Preparation of *final compound 71a and 71b*HCl (**Co. 71a**), free base (**Co. 71b**)

- 5 HCl (5.37 mL, 21.5 mmol, 4 M in dioxane) was added to a stirred solution of *intermediate 147* (1.15 g, 2.15 mmol) in MeOH (90 mL) at room temperature.. The reaction mixture was stirred at room temperature for 3 days after which the mixture was poured out into a beaker with 200 mL DIPE. The resulting suspension was stirred for 10 minutes at room temperature. The solvents were decanted off so that the sticky precipitate remained. This residue was dissolved in MeOH and slightly alkalized with a 7N solution of NH₃ in MeOH. Then the solvents were evaporated to give *final compound 71a* (mono HCl salt) (1.037 g).

- 50 mg was purified with Prep HPLC (Stationary phase: RP XBridge Prep C18 OBD-10μm, 30x150mm, mobile phase: 0.25% NH₄HCO₃ solution in water, MeOH yielding 25.0 mg *final compound 71b* as free base.

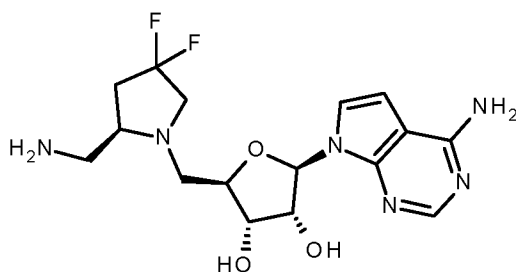
Example B5

Preparation of *final compound 72*

HCl (0.106 mL, 0.4 mmol, 4 M in dioxane) was added to a stirred solution of *intermediate 141* (24 mg, 0.04 mmol) in MeOH (5 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 days. The reaction mixture was diluted with DIPE to 15 mL. The mixture was stirred for 1 hour at room temperature. The solvents were decanted from the formed sticky precipitate. The precipitate was dissolved in 10 mL MeOH and then the solvents were evaporated to give *final compound 72* (15 mg, 0.0374 mmol, 88.4% yield,) as mono HCl salt.

10

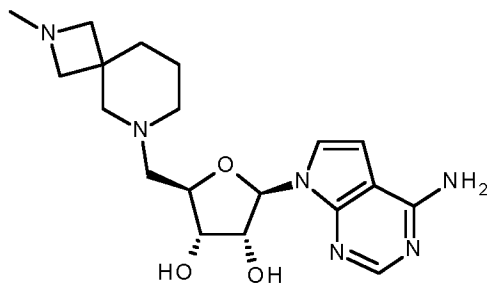
Example B6

Preparation of *final compound 73a and 73b*HCl (**Co. 73a**), free base (**Co. 73b**)

HCl (5.1 mL, 4 M, 20.4 mmol) was added to a stirred solution of *intermediate 150* (1.09 g, 2.04 mmol) in MeOH (85 mL) at room temperature. The reaction mixture was stirred at room temperature for 18 hours after which the mixture was poured out into 200 mL DIPE. The resulting suspension was stirred for 10 minutes at room temperature. The solvents were decanted off so that the sticky precipitate remained. This residue was dissolved in MeOH and the solvents were evaporated to give *final compound 73a* (0.93 g, 103.9% yield,) as mono HCl salt. 50 mg was purified with Prep HPLC (Stationary phase: RP XBridge Prep C18 OBD-10 μ m, 30x150mm, Mobile phase: 0.25% NH₄HCO₃ solution in water and MeOH yielding 29.9 mg *final compound 73b* as free base.

20

Example B7

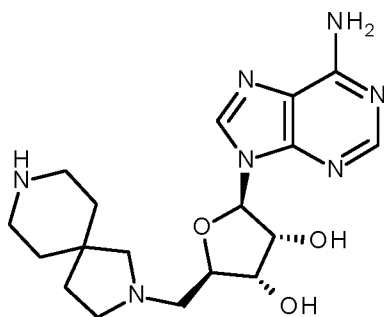
Preparation of *final compound 74*

To a solution of *intermediate 177* (120.6 mg) in MeOH (7.8 mL) was added formaldehyde (0.066 mL) at r.t. The reaction mixture was stirred at room temperature for 15 minutes. Then NaBH₃CN (73.15 mg) was added into the reaction mixture. The reaction mixture was stirred at room temperature for 2 hours. Then the mixture was diluted with water to be 20 mL of mixture of water and MeOH. The reaction mixture was then stirred at room temperature overnight.

A purification was performed via Prep HPLC (Stationary phase: RP SunFire Prep C18 OBD-10μm, 30x150mm, Mobile phase: 0.25% NH₄HCO₃ solution in water, MeOH).

A second purification was performed via Prep SFC (Stationary phase: Chiralpak Diacel AD 20 x 250 mm, Mobile phase: CO₂, MeOH with 0.4% iPrNH₂) yielding 49 mg of *final compound 74*

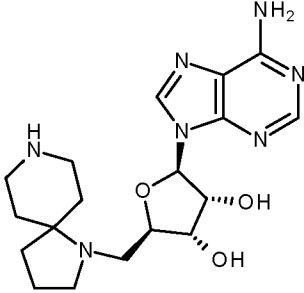
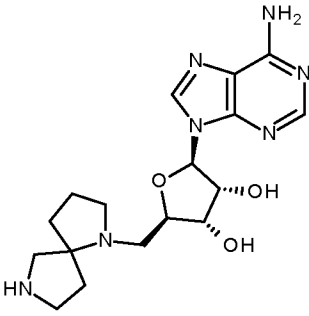
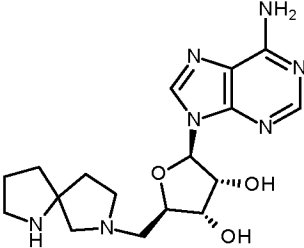
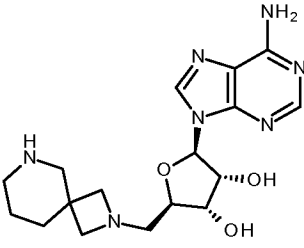
Example B8

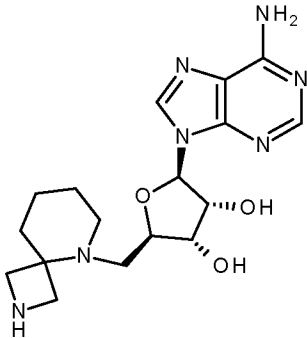
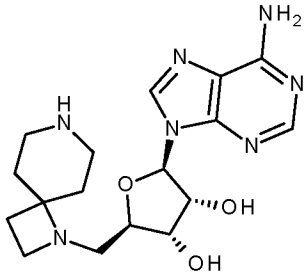
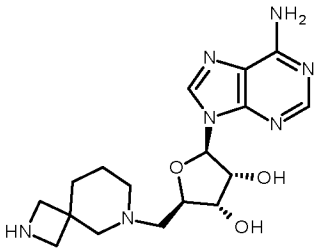
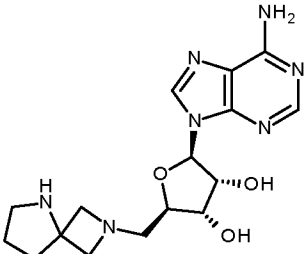
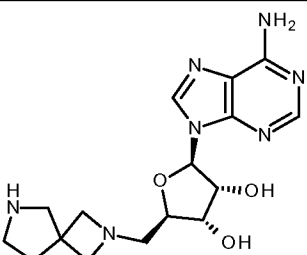
15 Preparation of *final compound 75*

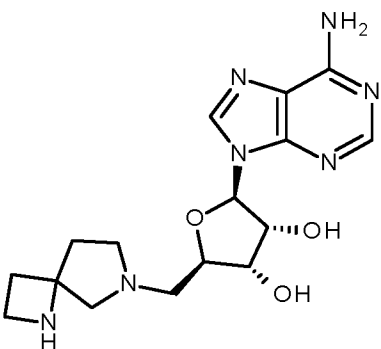
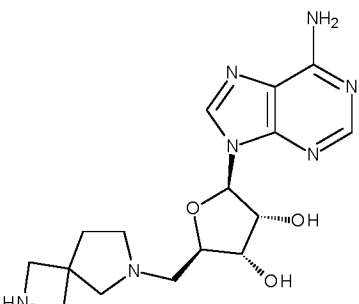
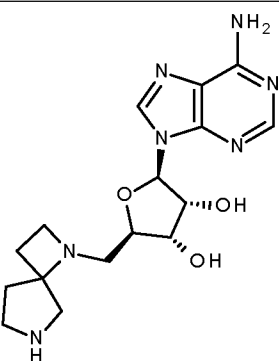
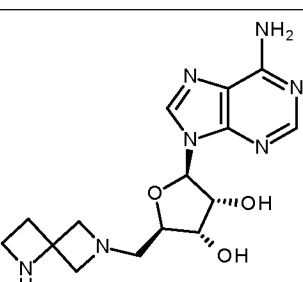
Intermediate 160 (100 mg, 0.154 mmol) was dissolved in MeOH (1.5 mL) and ammonia solution 7 N in MeOH (6 mL) was added. The solution was stirred at room temperature overnight. The solvents were evaporated to dryness and the residue was then dissolved in a mixture of TFA (5 mL) and water (0.3 mL) and stirred at room temperature overnight. The solvents were evaporated to dryness and the product was purified by reverse phase gradient 90% [NH₄OH 0.4% in water] - 10% [MeOH] 54% [NH₄OH 0.4% in water] - 46% [MeOH] to give *final compound 75* (16 mg, yield: 26%).

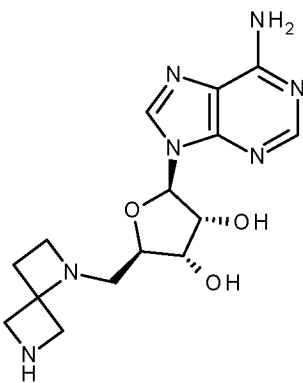
Below intermediates were prepared by an analogous reaction protocol as was used for the preparation of *final compound 75* using the appropriate starting materials (Table 21).

Table 21

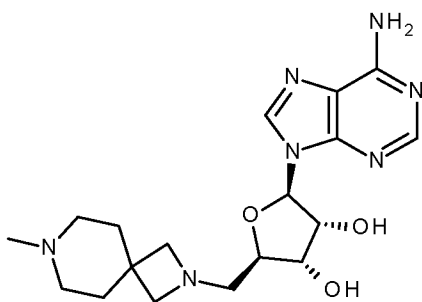
Co.	Structure	Starting materials and conditions
76		<i>a) intermediate 159</i> <i>b) Ammonia solution 7N in MeOH</i> <i>c) TFA in water</i>
77		<i>a) Intermediate 161</i> <i>b) Ammonia solution 7N in MeOH</i> <i>c) TFA in water</i>
78		<i>a) Intermediate 162</i> <i>b) Ammonia solution 7N in MeOH</i> <i>c) TFA in water</i>
79		<i>a) Intermediate 164</i> <i>b) Ammonia solution 7N in MeOH</i> <i>c) TFA in water</i>

Co.	Structure	Starting materials and conditions
80		a) <i>Intermediate 165</i> b) <i>Ammonia solution 7N in MeOH</i> c) <i>TFA in water</i>
81		a) <i>Intermediate 167</i> b) <i>Ammonia solution 7N in MeOH</i> c) <i>TFA in water</i>
82		a) <i>Intermediate 168</i> b) <i>Ammonia solution 7N in MeOH</i> c) <i>TFA in water</i>
83		a) <i>Intermediate 169</i> b) <i>Ammonia solution 7N in MeOH</i> c) <i>TFA in water</i>
84		a) <i>Intermediate 170</i> b) <i>Ammonia solution 7N in MeOH</i> c) <i>TFA in water</i>

Co.	Structure	Starting materials and conditions
85		a) <i>Intermediate 171</i> b) <i>Ammonia solution 7N in MeOH</i> c) <i>TFA in water</i>
86		a) <i>Intermediate 172</i> b) <i>Ammonia solution 7N in MeOH</i> c) <i>TFA in water</i>
87		a) <i>Intermediate 173</i> b) <i>Ammonia solution 7N in MeOH</i> c) <i>TFA in water</i>
88		a) <i>Intermediate 175</i> b) <i>Ammonia solution 7N in MeOH</i> c) <i>TFA in water</i>

Co.	Structure	Starting materials and conditions
89		a) <i>Intermediate 176</i> b) <i>Ammonia solution 7N in MeOH</i> c) <i>TFA in water</i>

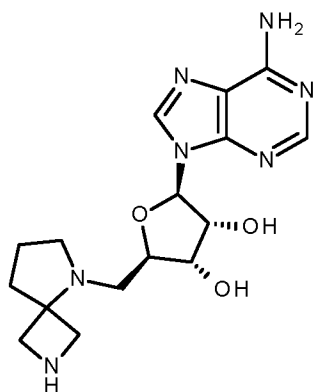
Example B9

Preparation of *final compound 90*

- 5 *Intermediate 45* (396 mg, 0.93 mmol), *intermediate 190* (273 mg, 1.02 mmol) and sodium acetate (79.2 mg, 0.97 mmol) were dissolved in dichloroethane (9 mL) and the mixture was stirred 30 min. Then sodium triacetoxyborohydride (295 mg, 1.39 mmol) was added and the solution was stirred at room temperature overnight. The mixture was diluted with DCM (20 mL) and washed with Na₂CO₃ 1M (20 mL). The organic layer was
- 10 dried over MgSO₄ and filtered. The solvents were evaporated to dryness and to the residue was added an ammonia solution 7 N in MeOH (50 mL). The mixture was stirred at room temperature overnight. The solvents were evaporated to dryness and the residue was then dissolved in water (2.5 mL) and trifluoroacetic acid (47 mL) and stirred at 0°C for 5 h. The solvents were evaporated to dryness and the product was purified by reverse
- 15 phase three times 90% [NH₄OH 0.4% in water] - 10% [MeOH] 54% [NH₄OH 0.4% in water] - 46% [MeOH] The product was triturated in ACN to give *final compound 90* (4 mg, 1% yield).

Example B10

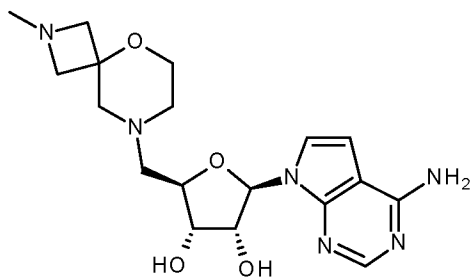
Preparation of *final compound 91*



- Intermediate 174** (45mg, 0.097 mmol) in MeOH (1 mL) was added an ammonia solution 7 N in MeOH (6 mL). The mixture was stirred at room temperature overnight. The solvents were evaporated to dryness and the product was purified by reverse phase 90% [NH₄OH 0.4% in water] - 10% [MeOH] 54% [NH₄OH 0.4% in water] - 46% [MeOH] to give **final compound 91** (6 mg, yield: 16 %).

Example B11

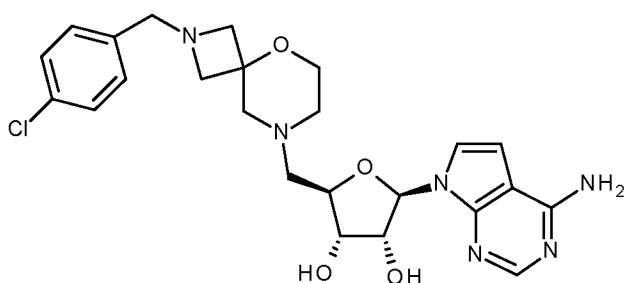
Preparation of **final compound 92**



- To a solution of **intermediate 178** (120.6 mg, 0.29 mmol) in MeOH (5 mL) was added formaldehyde (0.0435 mL, 0.579 mmol 37%) at room temperature and the reaction mixture was stirred for 15 minutes. Then NaBH₃CN (36.4 mg, 0.58 mmol) was added and the reaction mixture was stirred at room temperature for 2 hours. Then molecular sieves were added and the reaction mixture was stirred overnight at room temperature
- The solid was removed by filtration after which HCl in dioxane (0.0724 mL, 0.29 mmol, 4M) was added and the mixture was stirred for another 2 hours. DIPE was used to precipitate the product's salt. The solid was dried and purified by RP-HPLC to give **final compound 92** (52 mg, yield: 46 %).

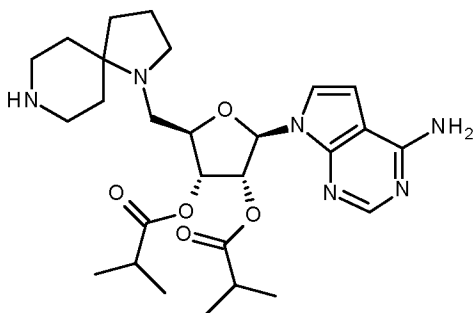
Example B12

Preparation of **final compound 93**



To a solution of **intermediate 178** (120.6 mg, 0.29 mmol) in MeOH (5mL) was added 4-chlorobenzaldehyde (0.041g, 0.29 mmol) at room temperature. The reaction mixture was stirred at room temperature for 15 minutes. Then NaBH₃CN (36.4 mg, 0.58 mmol) was added into the reaction mixture. The reaction mixture was stirred at room temperature for 2 hours. Molecular sieves were added and the reaction mixture was stirred at room temperature overnight. The solid was removed by filtration. 4N HCl in dioxane was added into the reaction mixture after which the mixture was stirred at room temperature for 2 hours. DIPE was used to precipitate the product's salt. The solid was dried and a purification was performed via Prep HPLC (Stationary phase: RP XBridge Prep C18 ODB- 5μm, 30x250mm, Mobile phase: 0.25% NH₄HCO₃ solution in water, CH₃CN) to give **final compound 93** (73 mg, yield: 50.3%).

Preparation of **final compound 94**

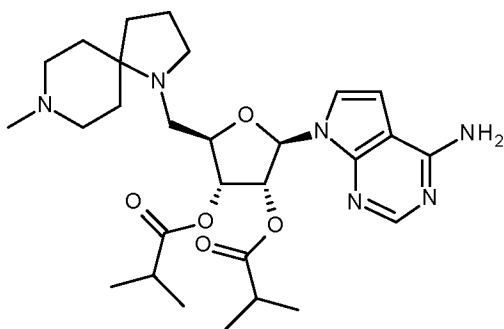


HCl

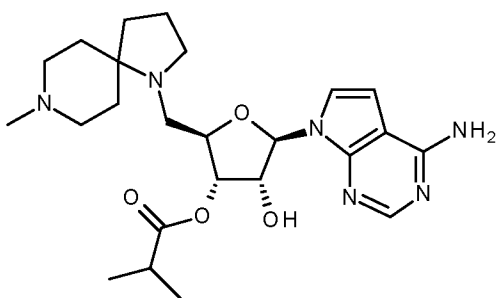
HCl (4M in dioxane) (2.31mL, 4 M, 9.2 mmol) was added to a stirred solution of **intermediate 325** (0.58 g, 0.92 mmol) in MeOH (50 mL) at room temperature. The reaction mixture was stirred at room temperature for 4 days. The reaction mixture was poured out into 60 mL DIPE. The resulting suspension was stirred for 10 minutes at room temperature. The solvents were decanted off so that the sticky precipitate remained. This residue was dissolved in MeOH and then the solvents were evaporated. The residue was dissolved in MeOH and SiO₂-gel was added. The solvents were evaporated and the residue was used in a solid load plunger to be purified over a SiO₂ column, type Grace Reveleris SRC, 12 g, Si 40, on an Armen Spot II Ultimate purification system using

DCM and MeOH as eluents in a gradient starting from 100% DCM and ending with 60% MeOH and 40% DCM. The fractions containing product were combined and the solvents were evaporated yielding **final compound 94** (154 mg, yield: 29.5%) as mono HCl salt.

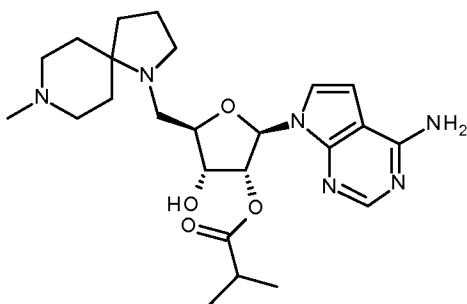
5 Preparation of **final compound 95a, 95b, 96 and 97**



HCl (**Co. 95a**), free base (**Co. 95b**)



final compound 96



10 **final compound 97**

A solution of **intermediate 327** (16.5 g, 26.4 mmol) and isobutyric acid (24.5 mL, 263.9 mmol) in MeOH (250 mL) was stirred and heated at 110°C in a stainless steel autoclave for 4 hours. The solvents were evaporated. The residue was dissolved in DCM and purified over a SiO₂ column, type Grace Reveleris SRC, 120 g, Si 40, on a Grace Reveleris X2 purification system using DCM and MeOH as eluents in a gradient starting from 100% DCM to 40% MeOH and 60% DCM. The fractions containing product were

15

combined and the solvents were evaporated yielding 12.18 g *crude final compound 95a fraction 1* and 1.9 g *crude final compound 96 fraction 1*.

5 The *crude final compound 95a fraction 1* was dissolved in DCM and purified over a SiO₂ column, type Grace Reveleris SRC, 120 g, Si 40, on a Grace Reveleris X2 purification system using DCM and MeOH as eluents in a gradient starting from 100% DCM to 40% MeOH and 60% DCM. The fractions containing product were combined and the solvents were evaporated yielding 4.55 g *crude final compound 95a fraction 2* and 5.43 g *crude final compound 95a fraction 3*.

10 400 mL DIPE was added to fraction *crude final compound 95a fraction 2* which caused a sticky suspension. The mixture was stirred and HCl (6M in iPrOH) (1.4 mL, 6 M, 8.4 mmol) was added. The mixture was stirred at room temperature for 18 hour resulting in a fine solid suspension. The suspension was filtered and the residue was washed with DIPE. The solid material was dried in vacuo at 30°C. The residue was dissolved in DCM and purified over a SiO₂ column, type Grace Reveleris SRC, 40 g, Si 40, on a Grace
15 Reveleris X2 purification system using DCM and MeOH as eluents in a gradient starting from 100% DCM to 40% MeOH and 60% DCM. The fractions containing product were combined and the solvents were evaporated yielding 2.24 g of *pure final compound 95a fraction 1 as mono HCl salt*.

20 400 mL DIPE was added to fraction *crude final compound 95a fraction 3* resulting in a fine solid suspension. The mixture was stirred at room temperature for 18 hours. The suspension was filtered and the residue was washed with DIPE. The solid material was dried in vacuo at 30°C yielding 2.85 g *final compound 95a fraction 2 as monoHCl salt*.

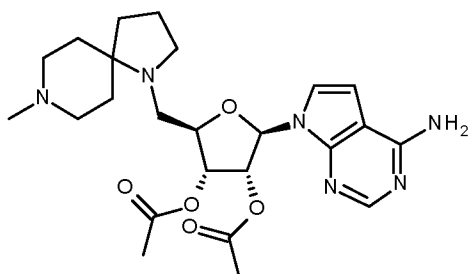
The solvents of the filtrate of *final compound 95a fraction 2* were evaporated. The residue was co-evaporated with DIPE. The solid material was dried in vacuo at 30°C
25 yielding 2.22 g *final compound 95b fraction 3 as free base*.

Fraction *crude final compound 96 fraction 1* was dissolved in DCM and purified over a SiO₂ column, type Grace Reveleris SRC, 80 g, Si 40, on a Grace Reveleris X2 purification system using DCM and MeOH as eluents in a gradient starting from 100% DCM to 40% MeOH and 60% DCM. The fractions containing product were combined
30 and the solvents were evaporated yielding 0.46 g. *A mixture of 70 % final compound 96 as a free base and 30% final compound 97 as a free base*.

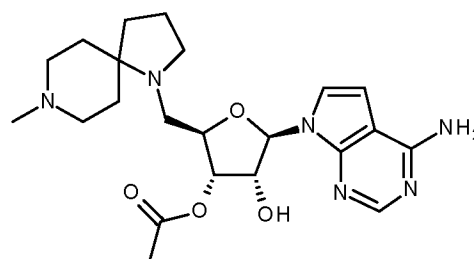
Example B13

Preparation of *final compound 98, 99 and 100*

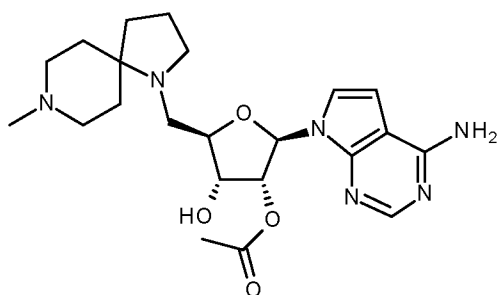
-190-



HCl

Final compound 98

HCl

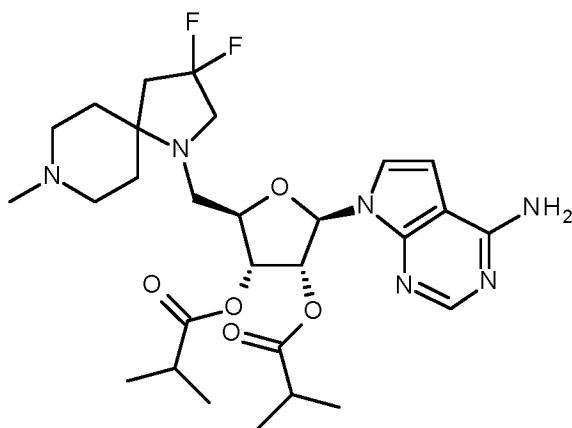
Final compound 99

HCl

Final compound 100

- 5 A solution of *intermediate 329* (27 g, 49.5 mmol) and isobutyric acid (45.9 mL, 495 mmol) in MeOH (450 mL) was stirred and heated in a stainless steel autoclave at 90°C for 4 hour. The solvents were evaporated. The residue was triturated in 400 mL DIPE. HCl (6M in iPrOH) (19.8 mL, 6 M, 119 mmol) was added and the mixture was stirred at room temperature for 18 hours which resulted in a suspension together with some sticky material. This mixture was filtered and washed with DIPE. The residue was combined with the remaining sticky material in the flask, dissolved in DCM and purified over a SiO₂ column, type Grace Reveleris SRC, 330 g, Si 40, on a Armen Spot II Ultimate purification system using DCM and MeOH as eluens in a gradient starting from 100% DCM and ending with 20% MeOH and 80% DCM. The fractions containing product were combined and the solvents were evaporated yielding 0.936 g of *final compounds 98 as mono HCl salt* and 1.97 g of *crude mixture of final compounds 99 and 100*. The *crude mixture of final compounds 99 and 100* were dissolved in DCM and purified over a SiO₂ column, type Grace Reveleris SRC, 80 g, Si 40, on a Armen Spot II Ultimate purification system using DCM and MeOH as eluens in a gradient starting from 100% DCM for 5 CV's and ending with 20% MeOH and 80% DCM over 15 CV's. The fractions containing product were combined and the solvents were evaporated yielding 1.41 g of a mixture of **65 % final compound 99 and 35% final compound 100 as mono HCl salt**.

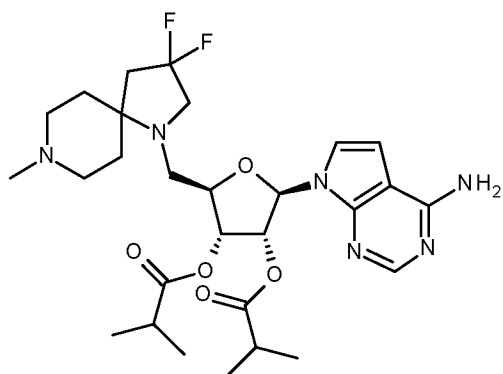
Example B14

Preparation of *final compound 101*

- Ammonium fluoride (0.64 g, 17.4 mmol) was added to a stirred solution of *intermediate* 333 (1.1 g, 1.74 mmol) in MeOH, anhydrous (50 mL) and molecular sieve (2.5 g). The reaction mixture was stirred and refluxed for 5 hours. The reaction mixture was allowed to cool down to room temperature and was then diluted with 50 mL MeOH and 25 mL DCM. The resulting suspension was filtered over a pad of Celite. The pad was washed two times with DCM. The combined solvents of the filtrate were evaporated. The residue was purified with Prep HPLC (Stationary phase: RP XBridge Prep C18 OBD-10 μ m, 30x150 mm, Mobile phase: 0.25% NH₄HCO₃ solution in water, CH₃CN) after which it was again purified with Prep HPLC (Stationary phase: RP XBridge Prep C18 OBD-10 μ m, 30x150mm, Mobile phase: 0.25% NH₄HCO₃ solution in water, CH₃CN) . The residue was again not pure and was purified for a third time with Prep HPLC (Stationary phase: RP XBridge Prep C18 OBD-10 μ m, 30x150mm, Mobile phase: 0.5% NH₄OAc solution in water + 10% CH₃CN, CH₃CN) to give *final compound 101* (1.8 mg, 0.00308 mmol, yield: 0.18%)

Example B15

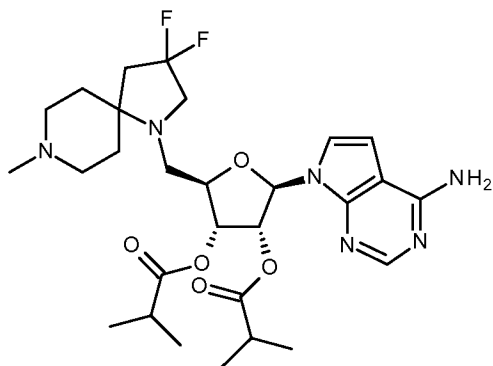
- Preparation of *final compound 101*



A solution of *intermediate 335* (0.71 g, 1.0 mmol) in MeOH (10 mL) was stirred and heated at 110°C using microwave irradiation for 19 hours. The solvents were evaporated after which the residue was dissolved in DCM and purified over a SiO₂ column, type Grace Reveleris SRC, 12 g, Si 40, on a Grace Reveleris X2 purification system using DCM and MeOH as eluents in a gradient starting from 100% DCM to 15% MeOH and 85% DCM. The fractions containing product were combined and the solvents were evaporated to give *final compound 101* (0.34 g).

10 Example B16

Preparation of *final compound 103*



2 HCl

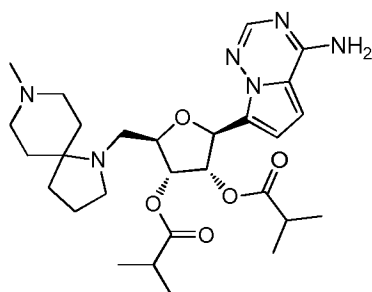
A solution of *intermediate 335* (17.9 g, 20.6 mmol) and SOCl₂ (1.5 mL, 20.6 mmol) in MeOH (260 mL) was stirred and heated at 110°C in a sealed stainless steel autoclave for 5 hours. The solvents were evaporated and the residue was dissolved in DCM with some MeOH and purified over a SiO₂ column, type Grace Reveleris SRC, 330 g, Si 40, on a Armen Spot II Ultimate purification system using DCM and MeOH as eluents in a gradient starting with 100% DCM and going to 40% MeOH and 60% DCM. The fractions containing product were combined and the solvents were evaporated yielding 9.77 g *crude final compound 103 fraction 1*. *Crude final compound 103 fraction 1* was dissolved in DCM with some MeOH and purified over a SiO₂ column, type Grace

Reveleris SRC, 120 g, Si 40, on a Armen Spot II Ultimate purification system using DCM and MeOH as eluents in a gradient starting with 100% DCM and going to 40% MeOH and 60% DCM. The fractions containing product were combined and the solvents were evaporated yielding 7.22 g of a light brown solid. This residue was recrystallized in ACN yielding a white precipitate which was filtered off, washed with ACN and then dried in vacuo at 40°C yielding 3.57 g ***pure final compound 103 fraction1 as bis HCl salt.***

The solvents of the filtrate of ***pure final compound 103 fraction1*** were evaporated. The residue was triturated in DIPE. The precipitate was filtered off and dried on the air yielding 2.75 g ***crude final compound 103 fraction2. Crude final compound 103 fraction 2*** was dissolved in ACN. Water was added and 1 equivalent of NaHCO₃ (0.35 g, 4.2 mmol). The residue was stirred at room temperature. for 25 minutes. DCM was added and the product was extracted from the mixture. The organic layer was separated, dried with MgSO₄, filtered and the solvents of the filtrate evaporated. The residue was triturated in DIPE. The precipitate was filtered off. The solvents of the filtrate were evaporated yielding 1.90 g of ***crude final compound 103 fraction 3. Crude final compound 103 fraction 3*** was dissolved in a mixture of 200 mL DIPE and 5 mL ACN. A solution of 1.64 mL 2M HCl (3.28 mmol) in diethylether was added. Immediately a white precipitate was formed. The mixture was stirred at room temperature for 30 minutes. The precipitate was filtered off and washed with DIPE. The remaining residue was recrystallized in ACN yielding a white precipitate which was filtered off, washed with cold ACN and then dried in vacuo at 40°C yielding 1.24 g of ***pure final compound 103 fraction2 as bis HCl salt.*** The filtrate of ***pure final compound 103 fraction2*** was evaporated, dissolved in DCM and washed three times with a saturated aqueous NaHCO₃ solution to obtain the product as free base after separation of the organic layer, drying with MgSO₄ and evaporating off the solvents. The residue was dissolved in a mixture of 200 mL DIPE and 25 mL ACN and then acidified with 1 equivalent of HCl using a 2M solution of HCl in Et₂O. The formed white precipitate was filtered off, washed with DIPE and dried. The resulting solid material was recrystallized in 40 mL ACN. The precipitate was filtered off and dried in vacuo at 45°C yielding 196.2 mg ***pure final compound 103 fraction3 as bis HCl salt.***

Example B17

Preparation of ***final compound 104***

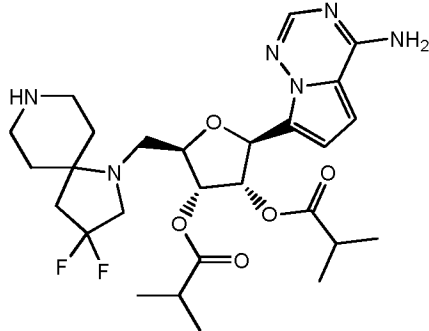


A mixture of **intermediate 459** (177 mg, 289 μmol , 1 eq) in MeOH (5 mL) was heated at 110 °C for 3 hours. The mixture was concentrated under reduced pressure. The residue was purified by preparative HPLC (Column: Gemini 150*25mm, 5 μm ; Mobile phase: 5 from 45% MeCN in water to 65% MeCN in water, 0.5% NH_3 ; Gradient Time: 12 min; Flow Rate: 25 ml/min; Wavelength: 220 nm). The fractions containing desired product were combined and lyophilized to afford **final compound 104** (78 mg, 140.9 μmol , 48.8 % yield) as a white solid.

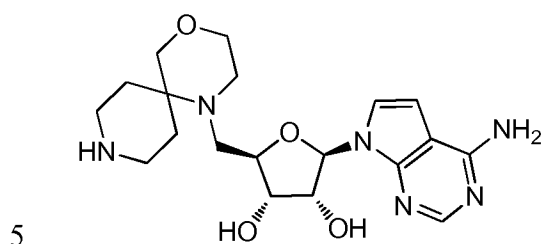
10 Below **final compounds** were prepared by an analogous reaction protocol as was used for the preparation of **final compound 104** using the appropriate starting materials (Table 22).

Table 22

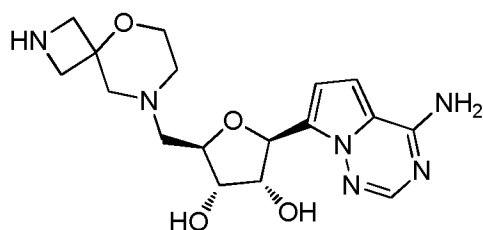
Co.	Structure	Starting materials
105		Intermediate 462
106		Intermediate 457

Co.	Structure	Starting materials
107		<i>Intermediate 461</i>

Example B18

Method APreparation of *final compound 108*

To a solution of *intermediate 401* (100 mg, 183.6 μmol , 1 eq) in MeOH (2 mL) was added HCl/dioxane (2 mL) and the mixture was stirred at 25 °C for 16 h. The solvent was removed and the residue was dissolved in MeOH (5 mL) and the basified to pH = 8 by 25% aqueous ammonia. The crude was purified by preparative HPLC (Column: Gemini 150*25mm, 5 μm ; Mobile phase: from 5% MeCN in water to 30% MeCN in water, 0.5% NH_3 ; Gradient Time: 12 min; Flow Rate: 25 ml/min; Wavelength: 220 nm). The fractions contain desired product were combined and lyophilized to give *final compound 108* (41.14 mg, 100.9 μmol , 54.9% yield) as a white solid.

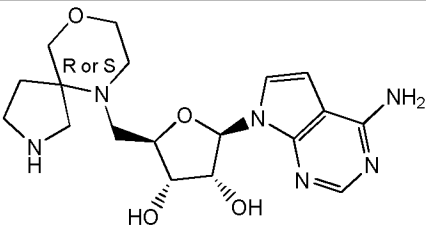
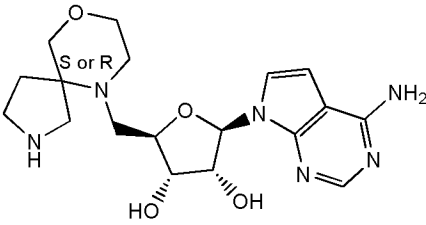
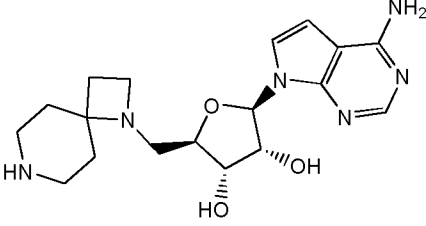
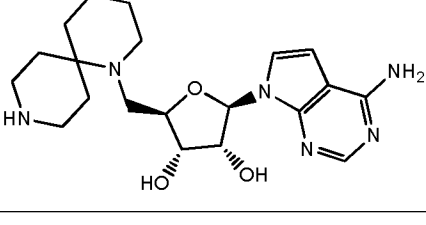
Method B15 Preparation of *final compound 109*

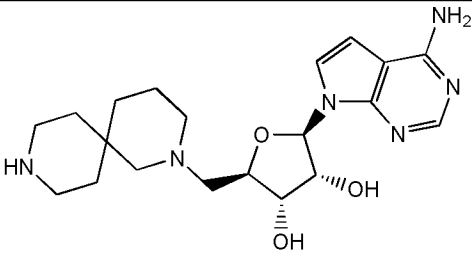
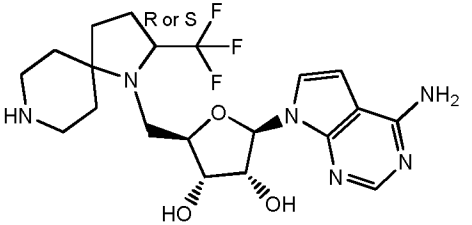
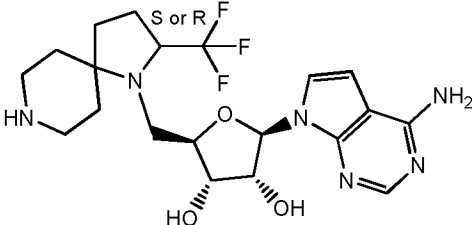
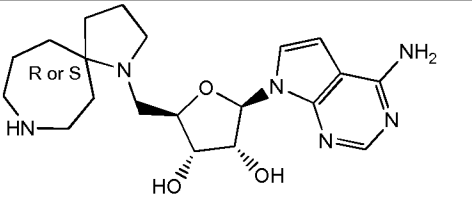
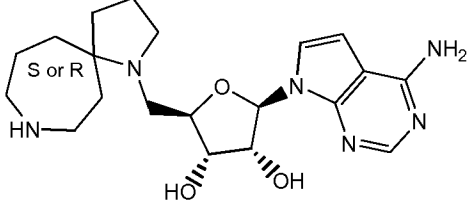
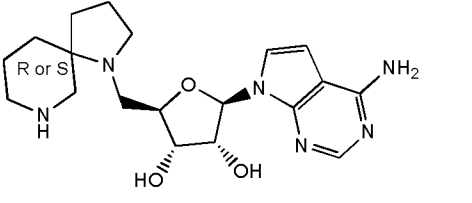
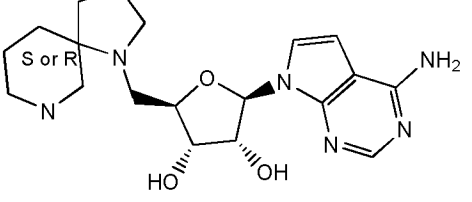
To a stirred solution of *Intermediate 429* (142 mg, 275 μmol , 1 eq) in CH_2Cl_2 (6 mL) was added TFA (1.5 mL) at 25 °C. The mixture was stirred at 25 °C for 16 hours. The

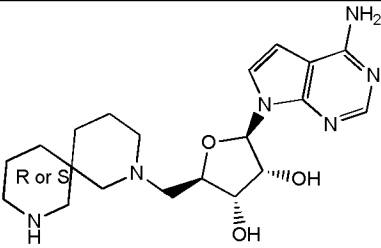
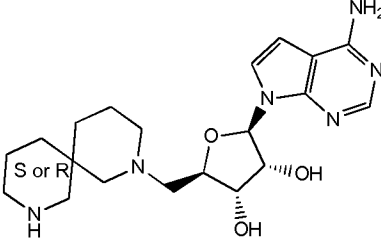
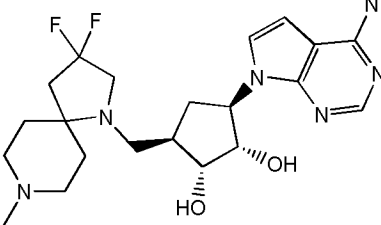
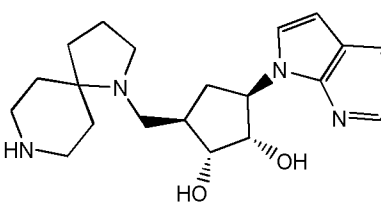
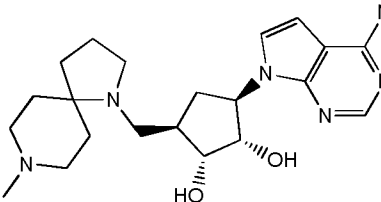
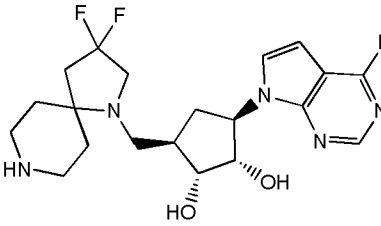
- reaction mixture was concentrated under reduced pressure. The solvent was removed and the residue was dissolved in MeOH (5 mL) and the basified to pH = 8 by 25% aqueous ammonia. The crude was purified by preparative HPLC (Column: Gemini 150*25mm, 5μm; Mobile phase: from 5% MeCN in water to 25% MeCN in water, 0.5% NH₃; Gradient Time: 12 min; Flow Rate: 25 ml/min; Wavelength: 220 nm). The fractions containing desired product were combined and lyophilized to afford **final compound 109** (58 mg, 147.92 μmol, 53.8% yield) as a white solid.

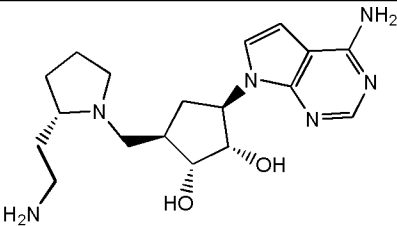
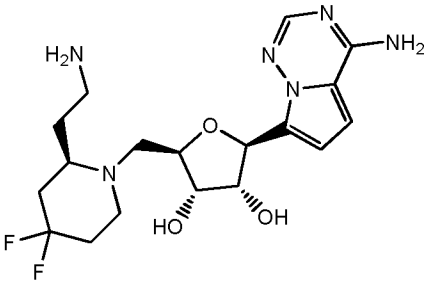
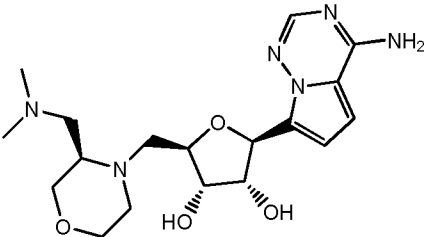
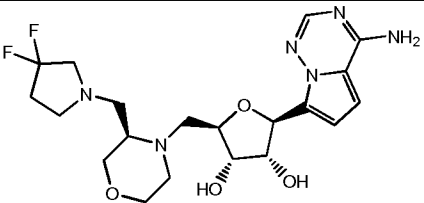
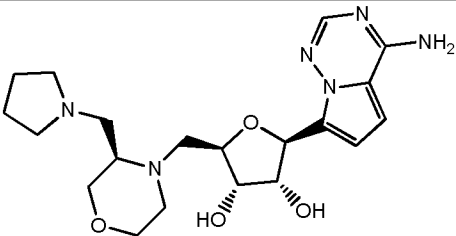
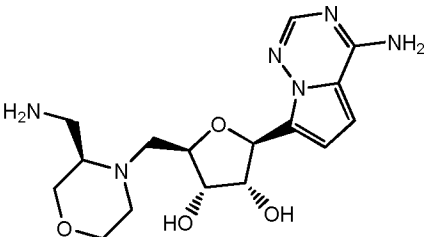
- Below **final compounds** were prepared by an analogous reaction protocol as was used for the preparation of **final compound 108** or **final final compound 109** using the appropriate starting materials (Table 23).

Table 23:

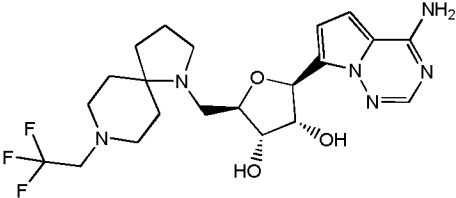
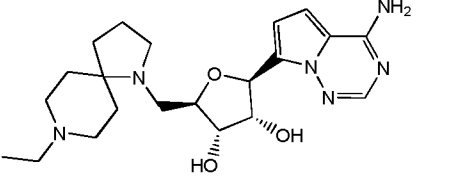
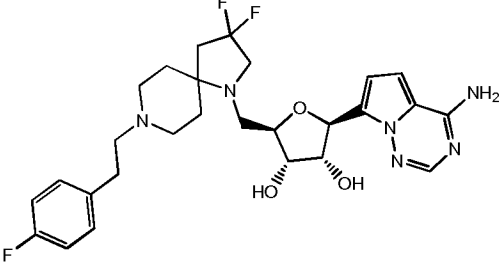
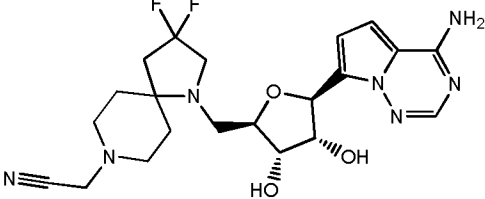
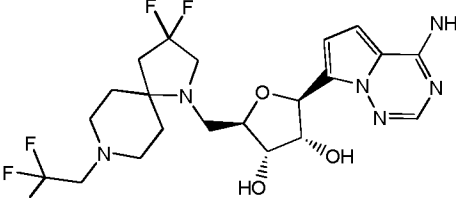
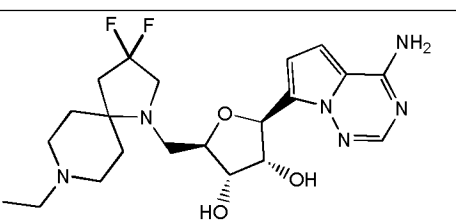
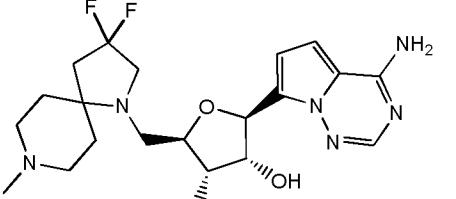
Co.	Structure	Starting materials	Method
110		Intermediate 402	<i>Method A</i>
111		Intermediate 403	<i>Method A</i>
112		Intermediate 404	<i>Method B</i>
113		Intermediate 405	<i>Method A</i>

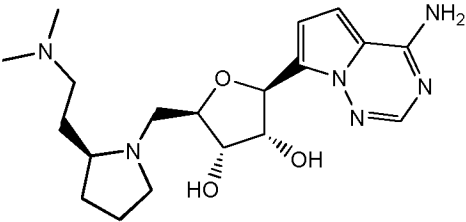
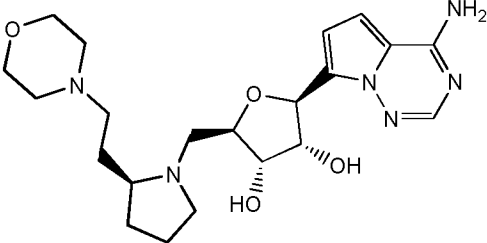
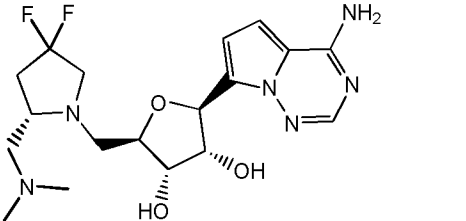
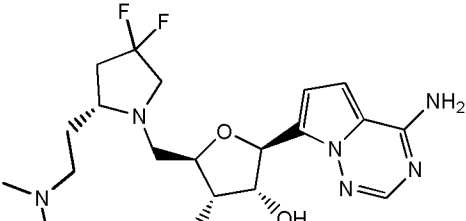
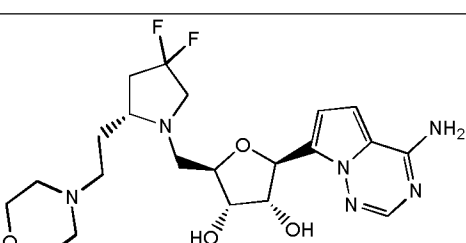
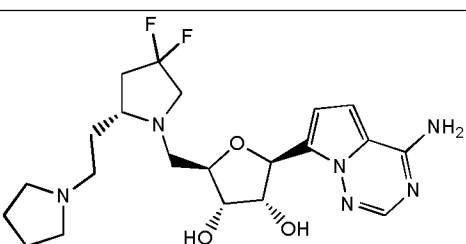
Co.	Structure	Starting materials	Method
114		<i>Intermediate 406</i>	<i>Method A</i>
115		<i>Intermediate 407</i>	<i>Method A</i>
116		<i>Intermediate 408</i>	<i>Method A</i>
117		<i>Intermediate 409</i>	<i>Method A</i>
118		<i>Intermediate 410</i>	<i>Method A</i>
119		<i>Intermediate 411</i>	<i>Method A</i>
120		<i>Intermediate 412</i>	<i>Method A</i>

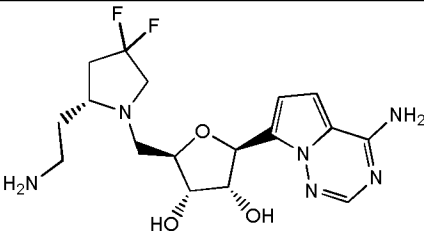
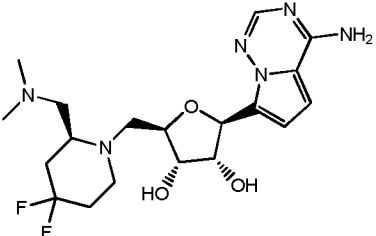
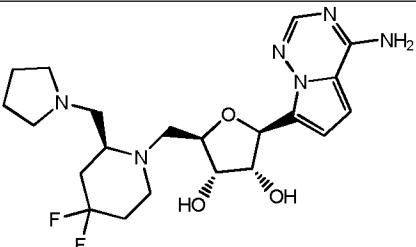
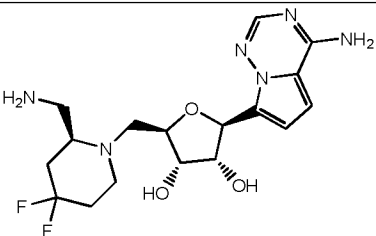
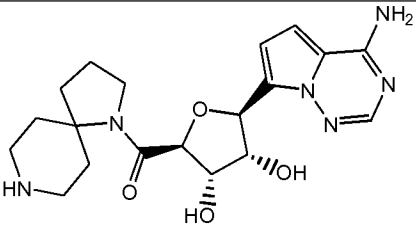
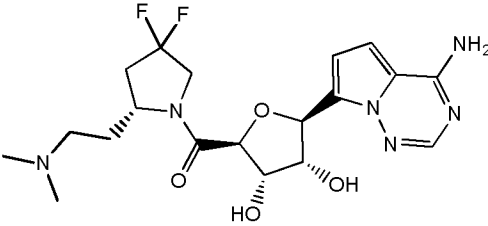
Co.	Structure	Starting materials	Method
121		<i>Intermediate 413</i>	<i>Method A</i>
122		<i>Intermediate 413</i>	<i>Method A</i>
123		<i>Intermediate 414</i>	<i>Method A</i>
124		<i>Intermediate 415</i>	<i>Method A</i>
125		<i>Intermediate 416</i>	<i>Method A</i>
126		<i>Intermediate 417</i>	<i>Method A</i>

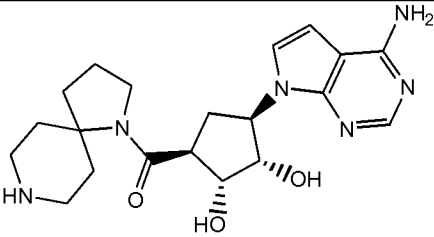
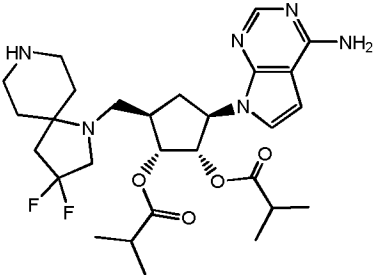
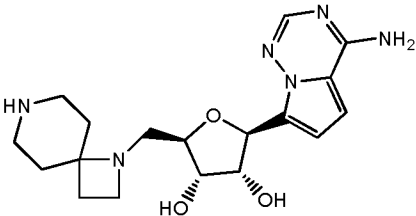
Co.	Structure	Starting materials	Method
127		<i>Intermediate 418</i>	<i>Method A</i>
128		<i>Intermediate 419</i>	<i>Method A</i>
129		<i>Intermediate 420</i>	<i>Method A</i>
130		<i>Intermediate 421</i>	<i>Method A</i>
131		<i>Intermediate 422</i>	<i>Method A</i>
132		<i>Intermediate 423</i>	<i>Method A</i>

Co.	Structure	Starting materials	Method
133		Intermediate 424	<i>Method A</i>
134		Intermediate 425	<i>Method A</i>
135		Intermediate 426	<i>Method A</i>
136		Intermediate 427	<i>Method A</i>
137		Intermediate 428	<i>Method A</i>
139		Intermediate 430	<i>Method A</i>
140		Intermediate 431	<i>Method B</i>

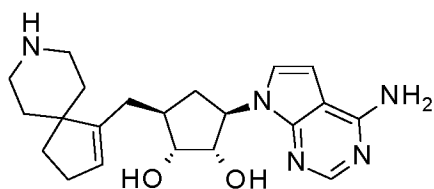
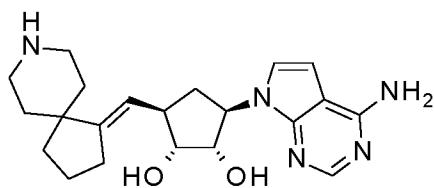
Co.	Structure	Starting materials	Method
141		<i>Intermediate 432</i>	<i>Method A</i>
142		<i>Intermediate 433</i>	<i>Method A</i>
143		<i>Intermediate 434</i>	<i>Method A</i>
144		<i>Intermediate 435</i>	<i>Method B</i>
145		<i>Intermediate 436</i>	<i>Method A</i>
146		<i>Intermediate 437</i>	<i>Method A</i>
147		<i>Intermediate 438</i>	<i>Method A</i>

Co.	Structure	Starting materials	Method
148		Intermediate 439	<i>Method A</i>
150		Intermediate 441	<i>Method A</i>
151		Intermediate 442	<i>Method A</i>
152		Intermediate 443	<i>Method A</i>
154		Intermediate 445	<i>Method A</i>
155		Intermediate 446	<i>Method A</i>

Co.	Structure	Starting materials	Method
156		<i>Intermediate 447</i>	<i>Method A</i>
157		<i>Intermediate 448</i>	<i>Method A</i>
159		<i>Intermediate 450</i>	<i>Method A</i>
160		<i>Intermediate 451</i>	<i>Method A</i>
161		<i>Intermediate 350</i>	<i>Method A</i>
162		<i>Intermediate 352</i>	<i>Method B</i>

Co.	Structure	Starting materials	Method
163		<i>Intermediate 462</i>	<i>Method B</i>
164		<i>Intermediate 461</i>	<i>Method B</i>
165		<i>Intermediate 452</i>	<i>Method A</i>

Example B19

Synthesis of *final compound 166* and *final compound 167*5 *final compound 166**final compound 167*

To a solution of a crude mixture of *intermediate 530* and *intermediate 531* in EtOH (50 mL) was added 1M HCl in water (54 mL, 54 mmol, 12 eq) at room temperature. After stirring overnight, the reaction mixture was heated to 40 °C and additional 1M HCl in

water (23 mL, 23 mmol, 5 eq) was added. The reaction mixture was stirred for 12 hours at 40 °C to afford complete conversion, then neutralised with ammonia in water (25% w/t) and concentrated *in vacuo*. The crude product was triturated in water with few drops of EtOH and the obtained suspension was filtered leaving the product as residue.

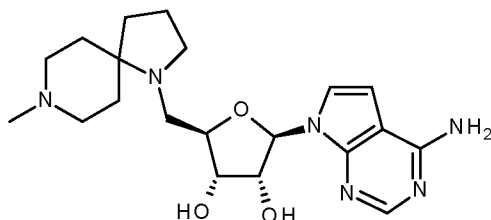
- 5 The filtrate was concentrated *in vacuo* and triturated with again with water and the suspension was filtered. The residues were combined and purified by preparative reversed phase flash chromatography (Stationary phase: Uptisphere C18 ODB - 10µm, 200g, 5cm, Mobile phase: 0.25% NH₄HCO₃ solution in water, CH₃CN) to afford a pure fraction of **final compound 166** (354 mg, 0.92 mmol, yield over two steps: 21%) and a
- 10 fraction of crude **final compound 167**. The crude **final compound 167** was further purified with preparative reversed phase flash chromatography (Stationary phase: RP XBridge Prep C18 ODB- 5µm, 30x250mm, Mobile phase: 0.25% NH₄HCO₃ solution in water, MeOH) to afford **final compound 167** (16 mg, 40 µmol, yield over two steps: 1%).

15

C. Conversions of final compounds

Example C1

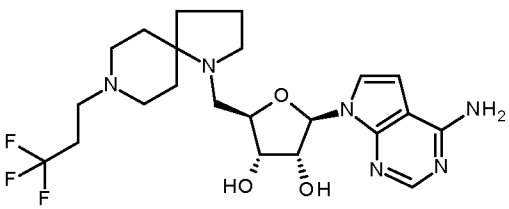
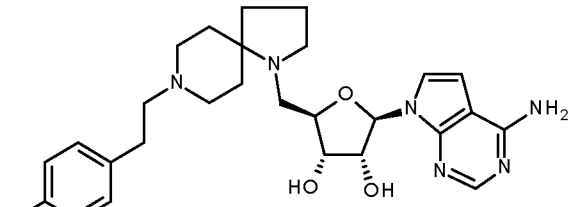
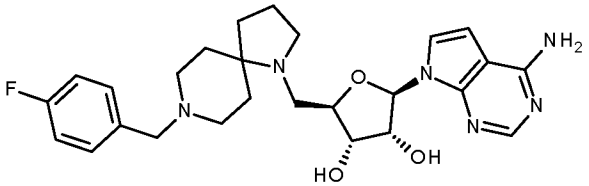
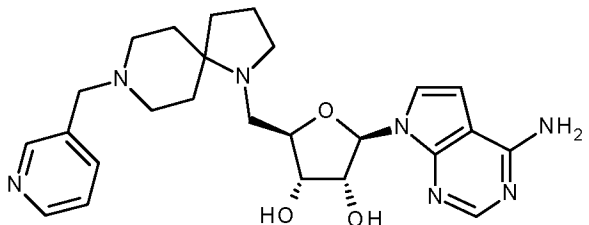
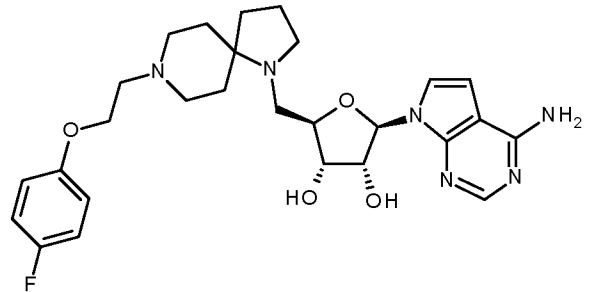
Preparation of **final compound 168**

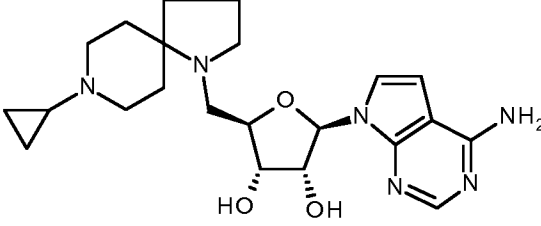
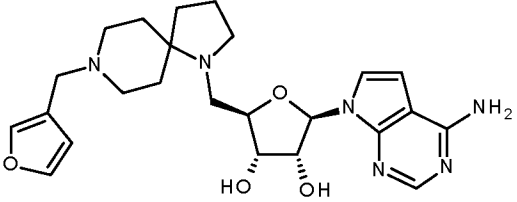
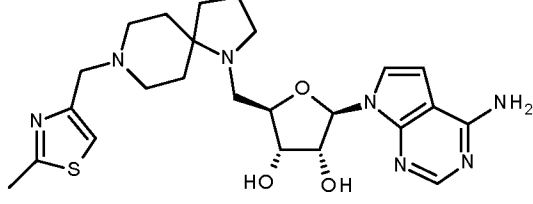
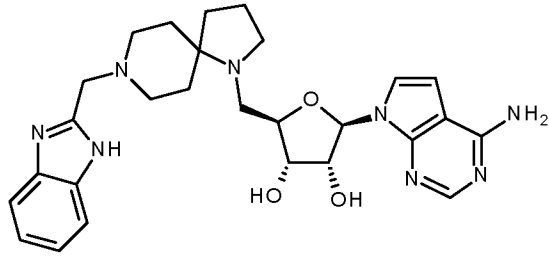
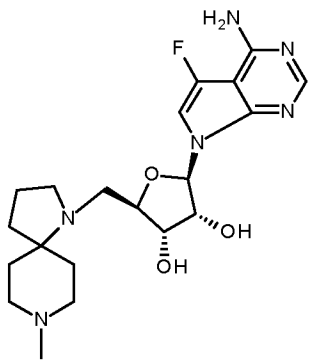


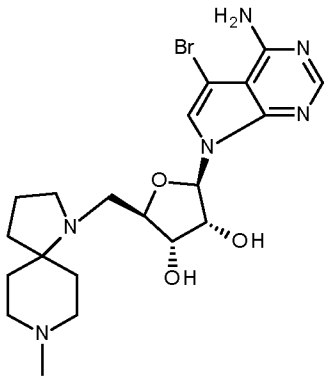
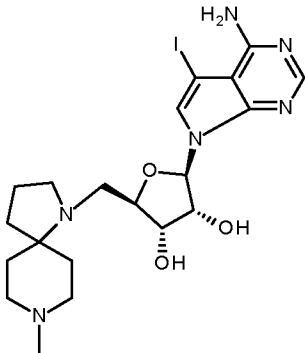
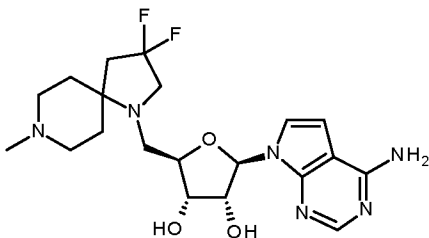
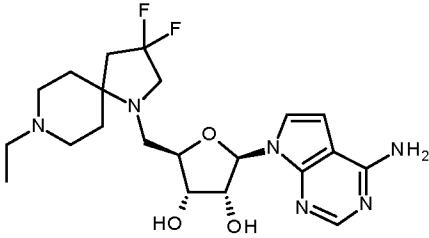
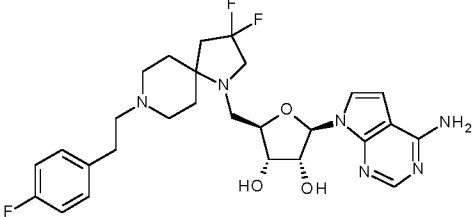
- 20 Sodium cyanoborohydride (17.04 g, 271 mmol) was added to a stirred solution of **compound 19** (60 g, 135.5 mmol) and formaldehyde (14.2 mL, 190 mmol) in MeOH (3000 mL) at room temperature. After addition the reaction mixture was stirred at room temperature for 1 hour. The reaction was quenched by the addition of 10 mL water and 5 mL of a saturated aqueous NaHCO₃ solution and then filtered over a pad of Celite. The
- 25 pad was washed two times with MeOH. The solvents of the filtrate were evaporated and co-evaporated with toluene yielding **final compound 168** (64.4 g, yield: 110.9%).

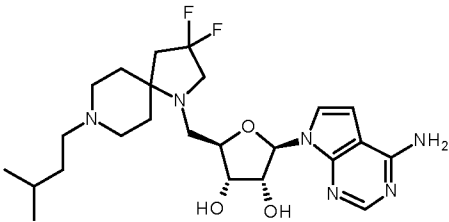
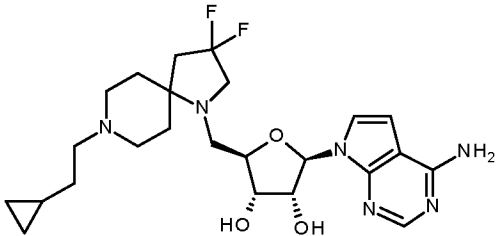
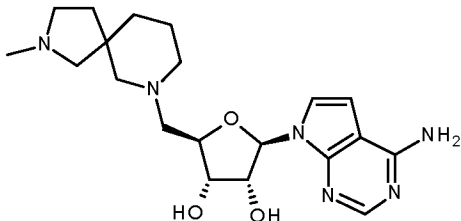
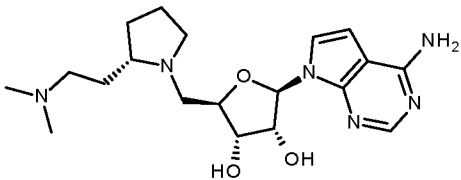
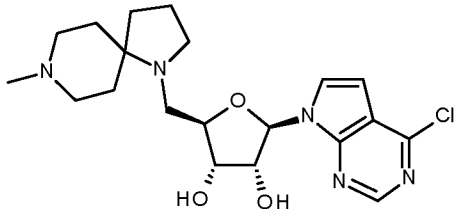
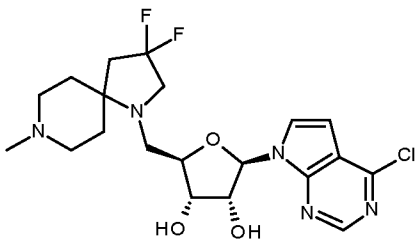
- Below **final compounds** were prepared by an analogous reaction protocol as was used for the preparation of **final compound 168** using the appropriate starting materials (Table
- 30 24).

Table 24

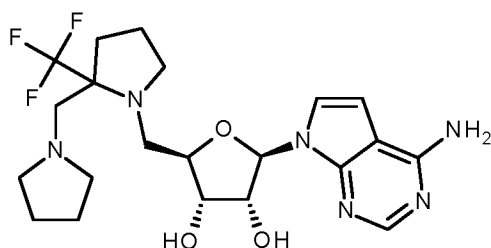
Compound	Structure	Starting materials and methods
169		a) Compound 19 b) 3,3,3-trifluoropropanal c) Acetic acid, NaBH_3CN in MeOH
170		a) Compound 19 b) Benzeneacetaldehyde, 4-fluoro-Acetic acid, c) NaBH_3CN in MeOH
171		a) Compound 19 b) 4-fluorobenzaldehyde c) Acetic acid, NaBH_3CN in MeOH
172		a) Compound 19 b) 3-Pyridinecarboxaldehyde c) Acetic acid, $\text{NaBH}(\text{OAc})_3$, DCM, MeOH
173		a) Compound 19 b) 2-(4-fluorophenoxy)acetaldehyde c) Acetic acid, $\text{NaBH}(\text{OAc})_3$, DCM, MeOH

Compound	Structure	Starting materials and methods
174		a) Compound 19 b) (1-ethoxycyclopropoxy)trimethylsilane c) Acetic acid, NaBH_3CN in MeOH
175		a) Compound 19 b) 3-furaldehyde c) Acetic acid, $\text{NaBH}(\text{OAc})_3$, DCM, MeOH
176		a) Compound 19 b) 4-formyl-2-methylthiazole c) Acetic acid, $\text{NaBH}(\text{OAc})_3$, DCM, MeOH
177		a) Compound 19 b) 1H-benzoimidazole-2-carboxaldehyde c) Acetic acid, $\text{NaBH}(\text{OAc})_3$, DCM, MeOH
178		a) Compound 24 b) paraformaldehyde c) potassium acetate, NaBH_3CN in MeOH

Compound	Structure	Starting materials and methods
179		a) <i>Compound 25</i> b) <i>paraformaldehyde</i> c) <i>potassium acetate, NaBH₃CN in MeOH</i>
180		a) <i>Compound 26</i> b) <i>Paraform</i> c) <i>potassium acetate, NaBH₃CN in MeOH</i>
181		a) <i>Compound 29</i> b) <i>formaldehyde</i> c) <i>NaBH₃CN in MeOH</i>
182		a) <i>Compound 29</i> b) <i>Acetaldehyde</i> c) <i>NaBH₃CN in MeOH</i>
183		a) <i>Compound 29</i> b) <i>(4-fluoro-phenyl)-acetaldehyde</i> c) <i>NaBH₃CN in MeOH</i>

Compound	Structure	Starting materials and methods
184		a) <i>Compound 29</i> b) <i>isovaleraldehyde</i> c) <i>NaBH₃CN in MeOH</i>
185		a) <i>Compound 29</i> b) <i>2-cyclopropylacetaldehyde: 50% (w/w) in toluene</i> c) <i>NaBH₃CN in MeOH</i>
186		a) <i>Compound 40</i> b) <i>formaldehyde</i> c) <i>NaBH₃CN in MeOH</i>
187		a) <i>compound 57</i> b) <i>Formaldehyde</i> c) <i>NaBH₃CN in MeOH</i>
208		a) <i>Compound 64</i> b) <i>Formaldehyde</i> c) <i>NaBH₃CN in MeOH</i>
188		a) <i>compound 63</i> b) <i>Formaldehyde</i> c) <i>NaBH₃CN in MeOH</i>

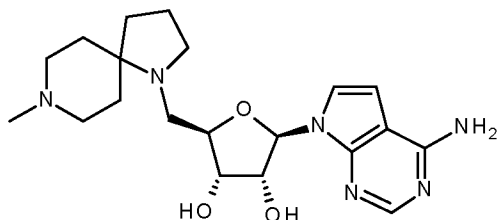
Example C2

Preparation of *final compound 189*

A mixture of **compound 236** (210 mg, 0.46 mmol) 1,4- dibromobutane (119 mg, 0.55 mmol) and K_2CO_3 (317 mg, 2.3 mmol) in 20 ml of ACN was stirred at 66°C for 24 hours. The solid was filtered off, the filtrate was concentrated under reduced pressure. The residue was purified by prep. HPLC, column: Waters Xbridge 150*25 5u, gradient: $CH_3CN/10\text{ mM }NH_4HCO_3$ 20%~50%; Gradient Time: 12 min; FlowRate: 25 ml/min to afford **final compound 189** (14.7 mg, 5% yield) as a white solid.

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Example C3

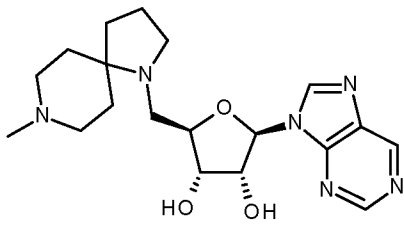
Preparation of *final compound 168*

$Pd/C_{10\%}$ (50 mg, 0.047 mmol) was suspended in MeOH (40 mL) under nitrogen atmosphere. Thiophene 0.4% solution in DIPE (1 mL), **final compound 19** (0.5 g, 1.29 mmol) and paraformaldehyde (0.116 g, 3.86 mmol) were added. The reaction was hydrogenated under hydrogen gas 1 atmosphere at 50 °C. The catalyst was filtered off over a pad of Celite and washed several times with MeOH. The solvents of the filtrate were evaporated to give **final compound 168** (0.52 g, yield: 94.3%).

Below **final compounds** were prepared by an analogous reaction protocol as was used for the preparation of **final compound 168** using the appropriate starting materials (Table 25).

20

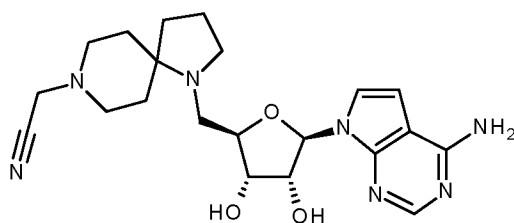
Table 25

Compound	Structure	Starting materials and methods
191		a) <i>compound 62</i> b) <i>formaldehyde</i>

Example C4

Preparation of *final compound 192*

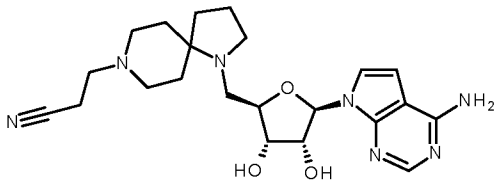
5



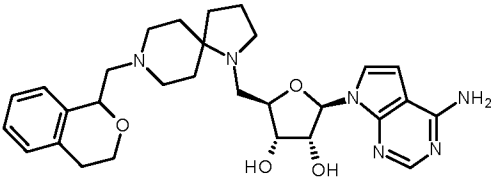
A mixture of *final compound 19* (0.1 g, 0.26 mmol), chloroacetonitrile (0.019 g, 0.26 mmol) and Na₂CO₃ (0.03 g, 0.28 mmol) in ACN (5 mL) was stirred and heated at 80°C for 3 hours. The solvents were evaporated. The residue was dissolved in 20 mL MeOH and then filtered. The filtrate was purified with Prep HPLC (Stationary phase: RP XBridge Prep C18 OBD-10μm, 30x150mm, Mobile phase: 0.25% NH₄HCO₃ solution in water, MeOH) to give *final compound 192* (35 mg, 0.082 mmol, yield: 31.8 %).

Below *final compounds* were prepared by an analogous reaction protocol as was used for the preparation of *final compound 192* using the appropriate starting materials (Table 26).

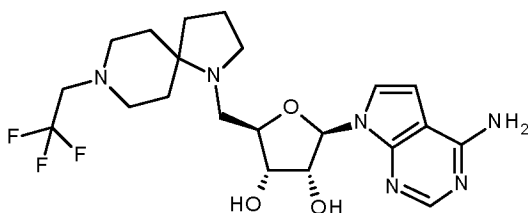
Table 26

Compound	Structure	Starting materials and conditions
193		a) <i>compound 19</i> b) <i>Acrylonitrile</i> c) <i>sodium carbonate, acetonitrile</i>

194		a) compound 19 b) 2-bromoethyl methyl ether c) sodium carbonate, acetonitrile
195		a) compound 19 b) 3-chloro-N-methylpropanamide c) sodium carbonate, acetonitrile
196		a) compound 19 b) 2-iodo-1,1-difluoroethane c) sodium carbonate, acetonitrile
197		a) compound 19 b) 2-chloro-N-methylacetamide c) sodium carbonate, acetonitrile
198		a) compound 19 b) 3-bromooxetane c) sodium carbonate, acetonitrile
199		a) compound 19 b) 3-(bromomethyl)pyridazine hydrobormide c) sodium carbonate, acetonitrile
200		a) compound 19 b) 2-(chloromethyl)thiazole c) sodium carbonate, acetonitrile

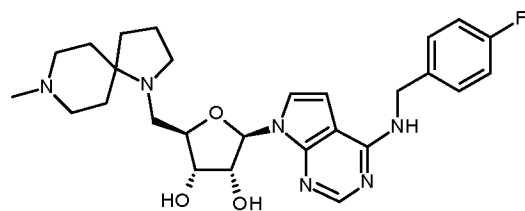
201		a) <i>compound 19</i> b) <i>1-(bromomethyl)-3,4-dihydro-1H-2-benzopyran</i> c) <i>sodium carbonate, acetonitrile</i>
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Example C5

Preparation of *final compound 202*

- 5 2,2,2-trifluoroethyl methanesulfonate (0.46 g, 2.57 mmol) was added to a stirred solution of *compound 19* (125 mg, 0.32 mmol) and Et₃N (0.36 mL, 2.57 mmol) in THF (5 mL) at room temperature. After addition the reaction mixture was stirred at room temperature for 2 days. The solvents were evaporated. The residue was dissolved in 10 mL MeOH and then purified with Prep HPLC (Stationary phase: RP XBridge Prep C18
- 10 OBD-10μm, 30x150mm, Mobile phase: 0.25% NH₄HCO₃ solution in water, MeOH yielding *final compound 202* (1 mg, 0.0021 mmol, yield: 0.65 %).

Example C6

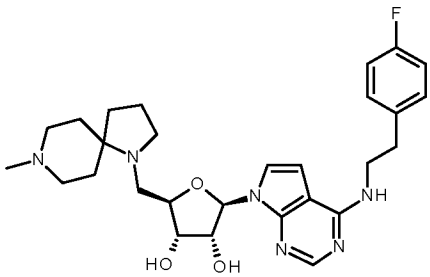
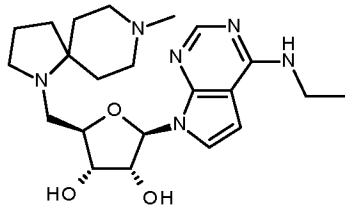
Preparation of *final compound 203*

15

- Compound 208* (100 mg, 0.24 mmol) and 4-fluorobenzylamine (29.7 mg, 0.24 mmol) in EtOH (5 mL) was stirred at 120 °C for 2 h. The reaction mixture was concentrated to dryness. A purification was performed via Prep HPLC (Stationary phase: RP SunFire Prep C18 OBD-10μm, 30x150mm, Mobile phase: 0.25% NH₄HCO₃ solution in water and MeCN) to give *final compound 203* (27 mg, 22% yield).
- 20

Below *final compounds* were prepared by an analogous reaction protocol as was used for the preparation of *final compound 203* using the appropriate starting materials (Table 27).

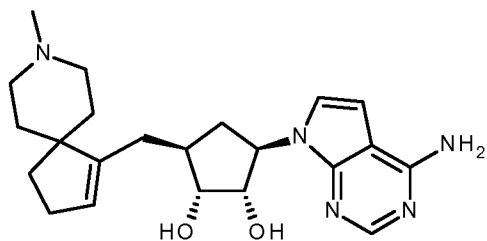
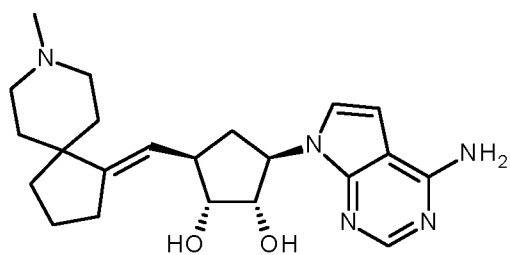
Table 27

Compound	Structure	Starting materials and conditions
204		a) <i>Compound 208</i> b) <i>4-fluorophenethylamine</i>
205		a) <i>Compound 208</i> b) <i>ethylamine</i>

5

Example C7

Synthesis of *final compound 206* and *final compound 207*

*final compound 206**final compound 207*

NaBH(OAc)₃ (432.182 mg, 2.039 mmol) was added to a solution of a mixture of *final*

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compound 166 and final compound 167 (391 mg, 1 mmol), formaldehyde (0.107 mL, 1.43 mmol), AcOH (0.058 mL, 1 mmol) in MeOH (22mL). The solution was stirred at room temperature for 2h. Again NaBH(OAc)₃ (216mg, 1 mmol) was added to the solution and the reaction was stirred overnight. Again NaBH(OAc)₃ (216 mg, 1 mmol) and formaldehyde (0.038 mL, 0.5mmol) were added to the solution and the reaction was stirred overnight. The reaction was quenched with water/sat NaHCO₃ (50/50). The mixture was concentrated *in vacuo*. The residue was purified via Prep HPLC (Stationary phase: RP XBridge Prep C18 OBD-10μm, 50x150mm, Mobile phase: 0.25% NH₄HCO₃ solution in water, CH₃CN) yielding *final compound 206* (220 mg, 54.3%) and *final compound 207* (18.5 mg 4.6%)

Analytical Part

LCMS (Liquid chromatography/Mass spectrometry)

The High Performance Liquid Chromatography (HPLC) measurement was performed using a LC pump, a diode-array (DAD) or a UV detector and a column as specified in the respective methods. If necessary, additional detectors were included (see table of methods below).

Flow from the column was brought to the Mass Spectrometer (MS) which was configured with an atmospheric pressure ion source. It is within the knowledge of the skilled person to set the tune parameters (e.g. scanning range, dwell time...) in order to obtain ions allowing the identification of the compound's nominal monoisotopic molecular weight (MW). Data acquisition was performed with appropriate software.

Compounds are described by their experimental retention times (R_t) and ions. If not specified differently in the table of data, the reported molecular ion corresponds to the [M+H]⁺ (protonated molecule) and/or [M-H]⁻ (deprotonated molecule). In case the compound was not directly ionizable the type of adduct is specified (i.e. [M+NH₄]⁺, [M+HCOO]⁻, etc...). For molecules with multiple isotopic patterns (Br, Cl), the reported value is the one obtained for the lowest isotope mass. All results were obtained with experimental uncertainties that are commonly associated with the method used.

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Hereinafter, "SQD" means Single Quadrupole Detector, "MSD" Mass Selective Detector, "RT" r.t., "BEH" bridged ethylsiloxane/silica hybrid, "DAD" Diode Array Detector, "HSS" High Strength silica., "Q-ToF" Quadrupole Time-of-flight mass spectrometers, "CLND", ChemiLuminescent Nitrogen Detector, "ELSD" Evaporative Light Scanning Detector,

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Table: LCMS Method codes (Flow expressed in mL/min; column temperature (T) in °C; Run time in minutes).

Method code	Instrument	column	mobile phase	gradient	Flow ----- Col T	Run time
1	Waters: Acquity® UPLC® - DAD and SQD	Waters : BEH C18 (1.7µm, 2.1*50mm)	A: 10mM CH ₃ COONH ₄ in 95% H ₂ O + 5% CH ₃ CN B: CH ₃ CN	From 95% A to 5% A in 1.3 min, held for 0.2 min, to 95% A in 0.2 min held for 0.1 min	0.7 ----- 70	1.8
2	Waters: Acquity® UPLC® - DAD and SQD	Waters : BEH C18 (1.7µm, 2.1*50mm)	A: 10mM CH ₃ COONH ₄ in 95% H ₂ O + 5% CH ₃ CN B: CH ₃ CN	From 95% A to 5% A in 1.3 min, held for 0.2 min, to 95% A in 0.2 min held for 0.1 min	0.7 ----- 70	1.8
3	Waters: Acquity® UPLC® - DAD and SQD	Waters : HSS T3 (1.8µm, 2.1*100mm)	A: 10mM CH ₃ COONH ₄ in 95% H ₂ O + 5% CH ₃ CN B: CH ₃ CN	From 100% A to 5% A in 2.10min, to 0% A in 0.90min, to 5% A in 0.5min	0.7 ----- 55	3.5
4	Waters: Acquity® UPLC® - DAD and SQD	Waters : HSS T3 (1.8µm, 2.1*100mm)	A: 0.2% NH ₄ HCO ₃ B: CH ₃ CN	From 96% A to 60% A in 2.10min, to 0% A in 0.4min, hold 0.8 min, to 95% A in 0.2min	0.6 ----- 55	3.5
5	Waters: Acquity® UPLC® - DAD and SQD	BEH C18 column (1.7 µm, 2.1 x 50 mm; Waters Acquity)	A:10 mM ammonium acetate in H ₂ O/acetonitrile 95/5; B: acetonitrile	95 % A and 5 % B to 5 % A and 95 % B in 1.3 minutes and hold for 0.7 minutes	0.8 ----- 55	2
6	Waters: Acquity® UPLC® - DAD and SQD	Waters : HSS T3 (1.8µm, 2.1*100mm)	A: 10mM CH ₃ COONH ₄ in 95% H ₂ O + 5% CH ₃ CN B: CH ₃ CN	From 100% A to 5% A in 2.10min, to 0% A in 0.90min, to 5% A in 0.5min	0.7 ----- 55	3.5

Method code	Instrument	column	mobile phase	gradient	Flow ----- Col T	Run time
7	Agilent: 1100/1200 - DAD and MSD	Waters: Atlantis® HILIC Silica (5µm, 4.6 x150mm)	A: CF ₃ COOH 0.1% in water, B: CF ₃ COOH 0.05% in CH ₃ CN	10% A for 10min.	0.8 ----- 50	10
8	Agilent: 1100/1200 - DAD and MSD	Waters: Atlantis® HILIC Silica (5µm, 4.6 x150mm)	A: CF ₃ COOH 0.1% in water, B: CF ₃ COOH 0.05% in CH ₃ CN	20% A for 10min.	0.8 ----- 50	10
9	Agilent: 1100/1200 - DAD and MSD	Agilent: TC-C18 (5µm, 2.1x50mm)	A: CF ₃ COOH 0.1% in water, B: CF ₃ COOH 0.05% in CH ₃ CN	100% A for 1min, to 40% A in 4min, to 15% A in 2.5min, back to 100% A in 2min.	0.8 ----- 50	10.5
10	Agilent: 1100/1200 - DAD and MSD	Waters: XBridge™ Shield RP18 (5µm, 2.1x50mm)	A: NH ₄ OH 0.05% in water, B: CH ₃ CN	100% A for 1min, to 40% A in 4min, held for 2.5min, back to 100% A in 2min.	0.8 ----- 40	10.5
11	Agilent: 1100-DAD and MSD	YMC: Pack ODS-AQ (3µm, 4.6x50mm)	A: HCOOH 0.1% in water, B: CH ₃ CN	95% A to 5% A in 4.8min, held for 1min, back to 95% A in 0.2min.	2.6 ----- 35	6
12	Agilent 1290 Infinity DAD TOF-LC/MS G6224A	YMC-pack ODS-AQ C18 (50 x 4.6 mm, 3 µm)	A: 0.1% HCOOH in H ₂ O B: CH ₃ CN	ISET 2V1.0 Emulated Agilent Pump G1312A V1.0 From 94.51% A to 5% A in 4.8 min, held for 1.0 min, to 95% A in 0.2 min	2.6 ----- 35	6.0
13	Waters: Acquity® UPLC® - DAD and SQD	Waters : HSS T3 (1.8µm, 2.1*100mm)	A: 10mM CH ₃ COONH ₄ in 95% H ₂ O + 5% CH ₃ CN B: CH ₃ CN	From 100% A to 5% A in 2.10min, to 0% A in 0.90min, to 5% A in 0.5min	0.7 ----- 55	3.5

Table: Co. No. means compound number; Retention time (R_t) in min; n.d. means not determined.

Co. No.	R_t	$[M+H]^+$	LCMS Method
91	0.33	362	11
14	0.25	390	12
2	0.35	376	11
84	0.22	362	11
88	0.24	348	12
89	0.27	348	12
1	0.24	404	11
78	0.24	376	11
13	0.28	390	11
6	0.25	376	12
17	0.24	362	11
76	1.21	390	4
11	0.33	390	11
12	0.22	390	11
3	0.85	376	11
5	0.22	376	11
86	0.26	362	11
75	0.22	390	11
83	0.29	362	11
9	0.23	390	11
79	0.22	376	11
4	0.24	376	11
16	0.23	404	11
7	0.26	376	11
81	0.27	376	12
80	0.33	376	12
82	0.26	376	12
8	0.23	390	11
87	0.26	362	12
18	0.30	362	12
90	0.27	390	11
10	0.28	390	11
58	0.35	364	2
59	1.17	364	4
62	0.87	375	6
19	0.81	389	3
20	0.80	389	3
168	0.39	403	5
74	1.41	389	4
45	1.23	375	4

Co. No.	R_t	$[M+H]^+$	LCMS Method
31	1.11	377	4
92	1.34	391	4
93	1.42	501	3
57	1.27	363	4
29	0.90	425	3
67	0.97	484	5
170	1.42	511	3
174	2.42	429	4
169	1.36	485	3
187	0.79	391	6
171	1.00	497	2
270	0.91	430	6
56	1.02	349	4
191	0.82	389	6
54	0.98	335	4
53	1.15	349	4
48	0.73	365	6
49	1.03	365	4
52	1.38	363	4
60	0.78	349	6
47	0.97	379	4
55	1.08	363	4
51	1.21	363	4
15	0.26	390	11
77	0.27	376	12
201	2.76	535	4
197	1.77	460	4
195	1.70	474	4
193	2.04	442	4
199	1.81	481	4
173	2.77	527	4
177	2.23	519	4
175	2.52	469	4
176	2.35	500	4
172	2.20	480	4
192	1.07	428	3
196	1.20	453	3
200	1.14	486	3
194	0.75	447	3
72	0.78	365	3

Co. No.	R _t	[M+H] ⁺	LCMS Method
27	0.78	404	6
208	1.21	422	3
95b	1.60	543	3
95a	1.60	543	3
203	0.92	511	2
205	2.23	431	4
204	1.56	525	3
114	4.37	403	8
198	1.00	445	3
24	0.83	407	6
179	1.02	481	6
202	0.68	471	5
112	5.09	375	10
28	4.00	403	10
122	2.31	403	7
121	2.30	403	7
133	3.38	389	10
188	1.34	458	3
30	3.58	417	10
63	1.23	444	6
110	2.76	391	10
111	2.74	391	10
108	3.06	405	10
178	0.94	421	3
38	3.40	425	10
181	1.00	439	3
32	3.61	405	10
68	0.78	390	6
127	4.46	361	10
124	3.98	387	10
136	3.61	425	10
135	3.46	403	10
119	3.40	389	10
125	3.61	401	10
120	3.47	389	10
109	2.88	377	10
126	3.99	423	10
101	1.84	579	3
103	1.82	579	6
50	0.99	399	3
66	3.95	402	10
61	4.19	388	10
151	3.24	413	10
104	3.29	543	9

Co. No.	R _t	[M+H] ⁺	LCMS Method
113	4.37	403	10
147	3.59	439	10
156	2.28	399	9
145	4.25	507	10
139	2.62	511	9
154	3.37	469	10
152	2.43	427	9
137	3.60	457	10
71b	0.86	385	3
71a	0.85	385	3
73b	0.84	385	3
73a	0.83	385	3
146	2.57	453	9
143	3.29	547	9
161	3.70	403	10
150	3.32	433	10
65	3.84	437	10
115	2.88	457	9
141	3.91	471	10
142	3.79	417	10
116	2.89	457	9
105	3.98	579	9
107	3.95	565	9
148	0.34	391	1
155	2.52	453	9
118	4.90	403	10
117	4.76	403	10
42	3.46	417	10
43	3.59	417	10
164	3.94	563	9
144	3.52	464	10
140	3.26	428	10
180	0.65	529	1
123	3.75	437	10
162	2.33	441	10
40	0.86	389	6
39	0.40	389	5
98	0.57	487	5
106	3.79	577	9
94	0.79	529	5
37	0.34	405	5
33	1.36	405	4
34	1.36	405	4
129	2.81	393	10

Co. No.	R _t	[M+H] ⁺	LCMS Method
131	3.06	419	10
186	0.43	403	5
182	1.01	453	6
183	1.60	547	6
184	1.39	495	6
185	1.30	493	6
160	3.26	399	10
132	2.58	365	10
130	3.09	455	10
96	0.56	473	5
99	0.42	445	5
157	3.51	427	10
159	4.16	453	10

Co. No.	R _t	[M+H] ⁺	LCMS Method
189	4.15	471	10
35	0.94	403	6
36	0.95	403	6
41	1.07	457	6
163	4.07	401	10
128	3.99	413	10
134	3.19	379	10
166	0.99	384	6
167	1.03	384	3
207	1.01	398	6
206	1.09	398	3
85	0.81	362	6

Melting points

Values are peak values, and are obtained with experimental uncertainties that are commonly associated with this analytical method.

DSC823e

For a number of compounds, melting points were determined with a DSC823e (Mettler-Toledo). Melting points were measured with a temperature gradient of 10°C/minute. Maximum temperature was 300°C.

Co 183: 132.73 °C

Mettler Toledo MP50 apparatus

For a number of compounds, m.p. were determined in open capillary tubes on a Mettler Toledo MP50 apparatus. M.p. were measured with a temperature ranging from 50°C to 300°C, using a gradient of 10 °C/minute. The m.p. value was read from a digital display.

Co. 84: 115.1 °C; Co. 78: 132.4 °C; Co. 13: 121.6 °C; Co. 12: 109.8 °C; Co. 5: 219.8 °C; Co. 1: 140.1 °C; Co. 83: 127.0 °C; Co. 9: 219.0 °C; Co. 79: 172.8 °C; Co. 4: 107.7 °C; Co. 16: 106.0 °C; Co.7: 181.3 °C; Co. 81: 115.8 °C; Co. 80: 102.8 °C; Co. 82: 240.2 °C; Co. 8: 118.9 °C; Co. 77: 223.9 °C

NMR

For a number of compounds, ¹H NMR spectra were recorded on a Bruker DPX-400 spectrometer operating at 400 MHz, on a Bruker DPX-360 operating at 360 MHz, on a Bruker Avance 600 spectrometer operating at 600 MHz. As solvents CHLOROFORM-

d (deuterated chloroform, CDCl₃) or DMSO-*d*₆ (deuterated DMSO, dimethyl-*d*₆ sulfoxide) were used. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS), which was used as internal standard.

- Co. 166: ¹H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.24 (dq, *J*=13.6, 2.3 Hz, 1 H) 1.30 (br dq, *J*=13.6, 2.3 Hz, 1 H) 1.42 (ddd, *J*=12.9, 10.4, 8.5 Hz, 1 H) 1.75 - 1.83 (m, 2 H) 1.83 - 1.90 (m, 2 H) 1.97 (br dd, *J*=15.7, 8.9 Hz, 1 H) 2.11 - 2.17 (m, 1 H) 2.17 - 2.21 (m, 2 H) 2.21 - 2.25 (m, 1 H) 2.25 - 2.30 (m, 1 H) 2.87 (tt, *J*=13.1, 2.9 Hz, 2 H) 3.15 - 3.21 (m, 2 H) 3.69 (br t, *J*=4.5 Hz, 1 H) 4.30 (br t, *J*=6.7 Hz, 1 H) 4.66 (br s, 1 H) 4.79 (dt, *J*=10.3, 8.4 Hz, 1 H) 4.85 (br s, 1 H) 5.46 (t, *J*=1.8 Hz, 1 H) 6.53 (d, *J*=3.5 Hz, 1 H) 6.90 (br s, 2 H) 7.22 (d, *J*=3.5 Hz, 1 H) 8.03 (s, 1 H).
- Co. 167: ¹H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.19 - 1.31 (m, 2 H) 1.35 - 1.49 (m, 2 H) 1.49 - 1.68 (m, 5 H) 2.20 - 2.32 (m, 2 H) 2.35 - 2.41 (m, 1 H) 2.52 - 2.60 (m, 2 H) 2.64 (qd, *J*=8.7, 4.8 Hz, 1 H) 2.79 (br t, *J*=12.9 Hz, 2 H) 3.72 (t, *J*=5.2 Hz, 1 H) 4.20 (dd, *J*=7.3, 5.9 Hz, 1 H) 4.68 (br s, 1 H) 4.78 - 4.88 (m, 2 H) 5.27 (dt, *J*=9.0, 2.5 Hz, 1 H) 6.54 (d, *J*=3.5 Hz, 1 H) 6.90 (br s, 2 H) 7.25 (d, *J*=3.5 Hz, 1 H) 8.03 (s, 1 H).
- Co. 29: ¹H NMR (360 MHz, DMSO-*d*₆) δ ppm 1.31 (br t, *J*=10.6 Hz, 2 H) 1.45 - 1.63 (m, 2 H) 2.10 - 2.32 (m, 2 H) 2.42 (br t, *J*=12.1 Hz, 2 H) 2.61 (dd, *J*=13.7, 5.7 Hz, 1 H) 2.78 - 2.96 (m, 3 H) 3.05 - 3.25 (m, 2 H) 3.84 (q, *J*=5.1 Hz, 1 H) 4.05 (br s, 1 H) 4.35 (br s, 1 H) 5.13 (br s, 1 H) 5.34 (br s, 1 H) 6.03 (d, *J*=5.1 Hz, 1 H) 6.60 (d, *J*=3.7 Hz, 1 H) 7.02 (br s, 2 H) 7.28 (d, *J*=3.7 Hz, 1 H) 8.06 (s, 1 H).
- Co. 95b: ¹H NMR (360 MHz, CHLOROFORM-*d*) δ ppm 1.10 (dd, *J*=15.4, 7.0 Hz, 6 H) 1.20 (dd, *J*=7.0, 1.1 Hz, 6 H) 1.27 - 1.37 (m, 2 H) 1.56 - 1.77 (m, 6 H) 2.00 (br t, *J*=11.2 Hz, 2 H) 2.27 (s, 3 H) 2.46 - 2.67 (m, 2 H) 2.70 - 2.90 (m, 6 H) 4.26 (q, *J*=4.6 Hz, 1 H) 5.13 (s, 2 H) 5.52 (t, *J*=5.3 Hz, 1 H) 5.67 (t, *J*=5.5 Hz, 1 H) 6.39 - 6.47 (m, 2 H) 7.18 (d, *J*=4.0 Hz, 1 H) 8.34 (s, 1 H).
- Co. 94: ¹H NMR (360 MHz, DMSO-*d*₆) δ ppm 0.98 (d, *J*=7.0 Hz, 3 H) 1.03 (d, *J*=7.0 Hz, 3 H) 1.12 (dd, *J*=6.8, 5.7 Hz, 6 H) 1.35 (br d, *J*=13.5 Hz, 2 H) 1.61 - 1.91 (m, 6 H) 2.53 - 2.66 (m, 2 H) 2.67 - 2.92 (m, 6 H) 3.25 (br t, *J*=12.1 Hz, 2 H) 4.14 (q, *J*=5.1 Hz, 1 H) 5.51 (t, *J*=5.3 Hz, 1 H) 5.74 (t, *J*=5.7 Hz, 1 H) 6.21 (d, *J*=5.5 Hz, 1 H) 6.65 (d, *J*=3.7 Hz, 1 H) 7.14 (br s, 2 H) 7.34 (d, *J*=3.7 Hz, 1 H) 8.10 (s, 1 H) 8.91 (br s, 2 H).
- Co. 207: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.14 - 1.39 (m, 2 H) 1.48 - 1.63 (m, 7 H) 1.87 - 2.02 (m, 2 H) 2.15 (s, 3 H) 2.20 - 2.42 (m, 3 H) 2.57 - 2.68 (m, 3 H) 3.71 (t, *J*=5.2 Hz, 1 H) 4.19 (dd, *J*=7.5, 5.7 Hz, 1 H) 4.64 - 4.90 (m, 3 H) 5.23 - 5.32 (m, 1 H) 6.54 (d, *J*=3.5 Hz, 1 H) 6.88 (br s, 2 H) 7.25 (d, *J*=3.5 Hz, 1 H) 8.03 (s, 1 H).
- Co. 19: ¹H NMR (360 MHz, DMSO-*d*₆) δ ppm 1.08 - 1.19 (m, 2 H) 1.39 (td, *J*=12.5, 4.6 Hz, 1 H) 1.46 - 1.73 (m, 5 H) 2.40 - 2.48 (m, 2 H) 2.52 - 2.57 (m, 1 H) 2.61 - 2.72 (m, 1 H) 2.75 - 2.93 (m, 4 H) 3.79 - 3.89 (m, 1 H) 4.03 (t, *J*=4.6 Hz, 1 H) 4.37 (t, *J*=5.3

Hz, 1 H) 5.11 (br s, 1 H) 5.32 (br s, 1 H) 6.04 (d, $J=5.9$ Hz, 1 H) 6.60 (d, $J=3.7$ Hz, 1 H) 7.02 (br s, 2 H) 7.33 (d, $J=3.7$ Hz, 1 H) 8.07 (s, 1 H).

Co. 206: ^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.02 - 1.15 (m, 2 H) 1.32 - 1.43 (m, 1 H) 1.63 - 1.79 (m, 4 H) 1.87 - 2.00 (m, 3 H) 2.05 - 2.31 (m, 8 H) 2.61 - 2.70 (m, 2 H)
5 3.61 - 3.74 (m, 1 H) 4.27 (dd, $J=8.1, 5.5$ Hz, 1 H) 4.41 - 5.00 (m, 3 H) 5.38 (br s, 1 H) 6.53 (d, $J=3.5$ Hz, 1 H) 6.88 (br s, 2 H) 7.24 (d, $J=3.5$ Hz, 1 H) 8.02 (s, 1 H).

Co. 181: ^1H NMR (360 MHz, DMSO- d_6) δ ppm 1.32 (br t, $J=11.2$ Hz, 2 H) 1.59 - 1.81 (m, 2 H) 1.81 - 1.92 (m, 2 H) 1.98 - 2.25 (m, 5 H) 2.58 (dd, $J=13.5, 5.5$ Hz, 1 H) 2.73 (br d, $J=11.3$ Hz, 2 H) 2.85 (dd, $J=13.4, 4.9$ Hz, 1 H) 2.97 - 3.26 (m, 2 H) 3.84 (q, $J=5.1$ Hz, 1 H) 4.04 (t, $J=4.8$ Hz, 1 H) 4.13 (br s, 1 H) 4.36 (t, $J=5.3$ Hz, 1 H) 5.47 (br s, 1 H) 6.03 (d, $J=5.5$ Hz, 1 H) 6.60 (d, $J=3.7$ Hz, 1 H) 7.02 (br s, 2 H) 7.31 (d, $J=3.7$ Hz, 1 H) 8.05 (s, 1 H).
10

Co. 101: ^1H NMR (600 MHz, CHLOROFORM- d) δ ppm 1.09 (d, $J=7.0$ Hz, 3 H) 1.13 (d, $J=7.0$ Hz, 3 H) 1.19 (d, $J=7.0$ Hz, 3 H) 1.20 (d, $J=6.9$ Hz, 3 H) 1.49 - 1.57 (m, 1 H)
15 1.50 - 1.60 (m, 1 H) 1.78 (br s, 1 H) 1.92 (br t, $J=11.2$ Hz, 1 H) 1.99 - 2.08 (m, 2 H) 2.09 - 2.19 (m, 1 H) 2.27 - 2.32 (m, 1 H) 2.33 (s, 3 H) 2.48 - 2.56 (m, 1 H) 2.56 - 2.63 (m, 1 H) 2.76 (dd, $J=14.2, 3.6$ Hz, 1 H) 2.93 (br t, $J=13.6$ Hz, 2 H) 2.98 (dd, $J=14.4, 3.4$ Hz, 1 H) 3.08 (td, $J=15.1, 11.6$ Hz, 1 H) 3.34 - 3.41 (m, 1 H) 4.20 - 4.23 (m, 1 H) 5.21 (s, 2 H) 5.52 (t, $J=5.4$ Hz, 1 H) 5.66 (t, $J=5.9$ Hz, 1 H) 6.43 (d, $J=5.9$ Hz, 1 H)
20 6.45 (d, $J=3.7$ Hz, 1 H) 7.17 (d, $J=3.8$ Hz, 1 H) 8.35 (s, 1 H).

Co. 179: ^1H NMR (360 MHz, DMSO- d_6) δ ppm 1.15 (br t, $J=11.7$ Hz, 2 H) 1.47 - 1.73 (m, 6 H) 1.85 - 1.96 (m, 2 H) 2.15 (s, 3 H) 2.45 - 2.48 (m, 1 H) 2.58 - 2.68 (m, 1 H) 2.72 (br d, $J=10.6$ Hz, 2 H) 2.76 - 2.88 (m, 2 H) 3.86 (dt, $J=6.3, 4.3$ Hz, 1 H) 4.02 (br q, $J=4.0$ Hz, 1 H) 4.34 (q, $J=5.1$ Hz, 1 H) 5.08 (br d, $J=4.4$ Hz, 1 H) 5.32 (d, $J=6.2$ Hz, 1 H) 6.07 (d, $J=5.5$ Hz, 1 H) 6.78 (br s, 2 H) 7.78 (s, 1 H) 8.11 (s, 1 H).
25

Co. 168: ^1H NMR (360 MHz, DMSO- d_6) δ ppm 1.10 - 1.20 (m, 2 H) 1.50 - 1.76 (m, 6 H) 1.87 - 1.98 (m, 2 H) 2.16 (s, 3 H) 2.44 - 2.48 (m, 1 H) 2.59 - 2.86 (m, 5 H) 3.80 - 3.89 (m, 1 H) 3.98 - 4.07 (m, 1 H) 4.37 (t, $J=5.3$ Hz, 1 H) 5.08 (br s, 1 H) 5.27 (br s, 1 H) 6.04 (d, $J=5.9$ Hz, 1 H) 6.60 (d, $J=3.7$ Hz, 1 H) 7.01 (br s, 2 H) 7.35 (d, $J=3.7$ Hz, 1 H) 8.06 (s, 1 H).
30

Co. 108: ^1H NMR (400 MHz, METHANOL- d_4) δ ppm 1.57 - 1.81 (m, 4 H) 2.68 (br t, $J=12.3$ Hz, 2 H) 2.74 - 2.91 (m, 4 H) 2.96 (br d, $J=13.1$ Hz, 2 H) 3.67 (br d, $J=4.8$ Hz, 4 H) 4.00 (q, $J=5.5$ Hz, 1 H) 4.27 (t, $J=5.6$ Hz, 1 H) 4.40 (t, $J=4.8$ Hz, 1 H) 6.15 (d, $J=4.3$ Hz, 1 H) 6.65 (d, $J=3.8$ Hz, 1 H) 7.36 (d, $J=3.8$ Hz, 1 H) 8.09 (s, 1 H).

Co. 74: ^1H NMR (360 MHz, DMSO- d_6) δ ppm 1.31 - 1.53 (m, 4 H) 2.20 (s, 3 H) 2.30 (br s, 2 H) 2.44 (br dd, $J=13.4, 6.4$ Hz, 3 H) 2.64 (dd, $J=13.4, 4.2$ Hz, 1 H) 2.76 (t, $J=6.4$ Hz, 2 H) 2.91 - 2.98 (m, 2 H) 3.87 - 3.98 (m, 1 H) 4.02 (t, $J=5.3$ Hz, 1 H) 4.29 (t,

$J=5.1$ Hz, 1 H) 5.16 (br s, 1 H) 5.34 (br s, 1 H) 6.03 (d, $J=4.8$ Hz, 1 H) 6.60 (d, $J=3.7$ Hz, 1 H) 7.03 (br s, 2 H) 7.30 (d, $J=3.7$ Hz, 1 H) 8.06 (s, 1 H).

EXPERIMENTAL PROCEDURES in vitro assay (assay 1)

5 **Reagents.** PRMT5-MEP50 enzyme was purchased from Charles River (Argentina). The enzyme complex was produced in insect cells (Sf9) infected simultaneously with two baculoviruses. One virus expresses full length human PRMT5 with Flag-tag at N-terminus, the second virus expresses full length MEP50 with His6-TEV cleavage at N-terminus. The protein was affinity purified using anti-Flag (M2) beads eluted with
10 3xFLAG peptide, followed by His-Select eluted with 0.5M imidazole. Eluted protein was then dialysed against tris-buffered saline (TBS) (pH 8.0) containing 20% glycerol and 3mM dithiothreitol (DTT).

Full-length untagged human recombinant histone H2A (residues 1-130, Genbank Accession# NM_021052, MW = 14.1 kDa) expressed in E. coli was purchased from
15 Reaction Biology Corporation, Cat# HMT-11-146. Reagents used for making reaction buffer or stopping reaction were purchased including Tris base (Sigma Cat# T-1503), NaCl (Sigma Cat# RGF-3270), $MgCl_2$ (Sigma Cat # M0250), DTT (Invitrogen Cat# 15508-013) and Formic Acid (Riedel deHaen, Cat# 33015)

High Throughput Mass Spectrometer Assay PRMT5 catalyzes the sequential
20 methylations of the terminal nitrogen atoms on the guanidine groups of arginine residues within proteins using co-substrate S-adenosyl-L-methionine (AdoMet, SAM), forming mono-methyl (MMA), symmetric-dimethyl arginine (sDMA) and S-adenosyl-L-homocysteine (AdoHcy, SAH). The enzyme activity was determined by following the product SAH formation using high throughput mass spectrometry (Agilent
25 Rapidfire 300 System coupled to a Sciex 4000 series QTrap® triple-quad MS/MS). The reaction buffer was 20 mM Tris-HCl, pH 8.5, 50 mM NaCl, 5 mM $MgCl_2$ and 1 mM DTT. The reaction activity was stopped using 1% formic acid (final concentration).

Inhibition Studies. The IC_{50} Studies were performed using eleven point dosing series made for each compound by serially diluted 1:2 in dimethyl sulfoxide (DMSO), with
30 point 12 being a DMSO control. Compounds were first spotted to plates, and followed by addition of 2 μ M SAM and 0.6 μ M H2A (histone H2A) solution mixture. The same volume of enzyme solution was added to initiate the enzymatic reactions. The final concentrations of the reaction are at 1 μ M SAM, 0.3 μ M H2A and 10 nM enzyme. The reaction was incubated at 30 °C for 60 minutes (min) and then quenched by addition of
35 formic acid to a final concentration of 1%. The inhibitions of SAH formation in the presence of compounds were calculated as a percentage of the control relative to the

uninhibited reaction as a function of inhibitor concentration. The data were fit as follows:

$$Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{((\log \text{IC}_{50} - X) * h)})$$

where IC_{50} is the inhibitor concentration (same unit as X) at 50% inhibition and h is the

- 5 Hill slope. Y is percent of inhibition, X is log of compound concentration. Bottom and Top are the plateaus in same units as Y.

EXPERIMENTAL PROCEDURE PD assay (assay 2)

Reagents

- 10 A549 cells (ATCC, Cat # CCL-185) were cultured in Dulbecco's Modified Eagle's Medium (DMEM) (Sigma, Cat #D5796), supplemented with 10% Fetal Calf Serum (FCS) (HyClone™, Cat #SV30160.03), 100 mM Sodium Pyruvate (Sigma, Cat #S8636), 200 mM L-Glutamine (Sigma, Cat #G7513) and 50 mg/mL Gentamycin (Gibco, Cat #15750-037).
- 15 Reagents used for buffers were purchased: Dulbecco's phosphate buffered saline (DPBS) without Ca/Mg (Sigma, Cat #D8537), phosphate buffered saline (PBS) 10X (Roche, Cat #11 666 789 001), Formalin solution 10% (Sigma, HT50-1-128-4L), MeOH 100% (Sigma, Cat #32213-2.5L), Triton X-100 (Acros, Cat #215680010), Bovine Serum Albumin (BSA) (Sigma, Cat #A2153), Alexa fluor 488 goat anti-rabbit
- 20 antibody (Life Technologies, Cat # A11034), HCS CellMask Deep Red Stain (Life Technologies, Cat #H32721), Hoechst Stain (Life Technologies, Cat #33258), Anti-dimethyl-Arginine, sym (SYM10) antibody (Millipore, 07-412).

Immunohistochemistry procedure

- Cells were plated at 400 cells/40μL/well in 384 well black plates μclear bottom (Perkin Elmer) and overnight incubated at 37°C, 5% CO₂. The IC₅₀ Studies were performed using nine point dosing series ranging from 10 μM to 1 pM for each compound. 80 nL of the respective dilution of the compounds was added using the Labcyte POD 810 (Labcyte) reaching a final DMSO concentration of 0.2% in cell culture. After an incubation period of 48h at 37°C and 5% CO₂, cells were fixed in 10% formalin solution for 15 min at r.t. and 20 min in ice-cold MeOH, after which they were washed 3x in DPBS. Subsequently, the cells were blocked for 1 h in blocking buffer (PBS + 1% BSA and 0.5% Triton X-100) and incubated overnight at 4°C with the SYM10 antibody diluted 1/2000 in blocking buffer. The cells were washed 3x with washing buffer (PBS + 0.1% Triton X-100) and incubated with the Alexa fluor 488 goat anti-rabbit antibody diluted 1/200 in blocking buffer for 1 h at r.t.. Subsequently, they were washed 3x with washing buffer and incubated for 30 min at r.t. with PBS containing a 1/5000 dilution of Hoechst Stain and a 1/5000 dilution of the HCS CellMask Deep Red Stain. After a final wash with PBS, the plates were imaged using the 10xW lens of the Opera[®] system (Perkin Elmer Life Sciences) using following settings (values in nm):

laser	Filter camera	Primary dichrome	Detect dichrome
488	540/75	405/488/561/635	510
405	450/50	405/488/561/635	510
635	690/50	405/488/561/635	510

Analyses:

- 20 The inhibition of nuclear symmetric Arginine dimethylation in the presence of compounds (% effect) was calculated as the “median nuclear SYM10 intensity” / “median cytoplasmic SYM10 intensity”, normalized by below equation:

$$normalized = 100 - \frac{raw - lowMedian}{highMedian - lowMedian} * 100$$

- 25 In the above equations, the following variable names are used:

<i>normalized</i>	The normalized feature value
<i>raw</i>	The raw feature value
<i>lowMedian</i>	The median of the raw values of the low control wells
<i>highMedian</i>	The median of the raw values of the high control wells

In the above equations, the following controls were used for normalization:

Low control: minimum level of symmetrically dimethylated Arginines (cells treated with reference compound at 10 μ M).

High control: maximum level of symmetrically dimethylated Arginines (DMSO treated cells).

- 5 IC₅₀ and pIC₅₀ (-logIC₅₀) values were calculated using the appropriate software.

pIC₅₀ values (Co. No. means compound number; n.d. means not determined).

In case several measurements were done on the same compound, all individual measurements are shown in the Table below.

10

Co. No.	pIC ₅₀ Assay 1	pIC ₅₀ Assay 2
1	6.66	5.14
2	6.11	<5
3	5.78	<5
4	5.64	<5
5	5.09	<5
6	<4	n.d.
7	4.18	<5
8	6.81	5.82
9	6.11	<5
10	4.41	<5
10	4.61	<5
11	4.91	<5
12	4.17	<5
13	6.02	<5
14	6.01	<5
15	4.53	<5
16	4.65	<5
17	<4	n.d.
18	5.07	<5
19	7.36	6.93
19	7.94	7.24
24	7.93	~7.17
27	5.87	<5
28	7.58	5.94
29	7.99	~7.22
29	8.12	~7.35
30	6.70	5.76
31	7.40	~5.84
32	5.35	5.04
33	6.62	4.92

Co. No.	pIC ₅₀ Assay 1	pIC ₅₀ Assay 2
34	5.40	<4.7
35	6.98	~5.21
36	5.72	~5.13
37	6.77	5.27
38	5.79	5.41
39	7.17	4.95
40	8.20	6.39
41	5.24	<5
42	7.22	~6.22
43	5.47	<4.7
45	7.08	~6.13
47	6.16	<5
48	6.84	~5.59
49	6.92	~5.29
50	7.35	5.82
51	7.67	6.00
52	7.99	~5.95
53	7.54	6.05
54	5.81	<5
55	6.51	5.21
56	6.73	~5
57	7.95	6.80
58	6.14	~5.16
59	7.35	5.62
60	7.54	5.94
61	6.89	<5
62	6.30	<5
65	7.25	6.02
66	6.22	5.17
67	5.73	~5.21

Co. No.	pIC ₅₀ Assay 1	pIC ₅₀ Assay 2
68	6.64	~5.71
71b	7.29	6.25
72	7.27	~5.45
73b	6.68	5.61
74	7.43	6.43
74	7.45	~6.51
75	4.40	<5
76	7.05	~5.65
76	7.49	n.d.
76	7.61	~5.97
78	5.55	<5
79	4.67	<5
80	5.48	<5
81	6.45	5.09
82	6.90	5.63
83	4.35	<5
84	4.11	<5
86	6.38	<5
87	5.62	<5
88	4.33	<5
89	5.56	<5
90	4.15	<5
91	5.91	<5
92	6.90	~5.86
93	5.52	~5.61
94	<5	~7.3
95b	<4	~7.34
95b	<5	7.05
95a	<5	6.94
95a	<5	6.95
96	6.20	7.69
99	6.76	6.69
101	<5	7.06
101	6.92	7.08
103	<5	6.46
104	<5	5.80
105	<5	5.18
106	<5	4.71
107	<5	6.90
108	7.59	6.69
109	5.65	<5

Co. No.	pIC ₅₀ Assay 1	pIC ₅₀ Assay 2
110	5.91	<5
111	6.76	~5.26
112	7.48	~5.75
113	8.09	6.84
114	7.47	~5.97
115	7.63	~5.78
116	6.82	5.53
117	7.47	6.30
118	7.45	6.29
119	6.81	~5.97
120	5.64	<5
121	5.74	<5
122	7.60	6.18
123	7.65	6.79
124	7.56	6.35
125	6.83	~6.06
126	7.76	7.35
127	7.21	~5.56
128	6.69	<5
129	<5	<4.7
130	<5	<4.7
131	<5	<4.7
132	5.81	<4.7
133	7.54	~5.98
134	6.70	5.05
135	6.21	~5.98
136	7.30	~6.58
137	5.94	<5
139	5.49	5.78
140	6.53	~5.52
141	<5	<5
142	5.71	<5
143	5.14	5.80
144	6.35	~6.03
145	<5	<5
146	5.40	5.33
147	6.73	6.22
148	5.90	<5
150	<5	<5
151	5.26	~5.21
152	5.53	5.39

Co. No.	pIC ₅₀ Assay 1	pIC ₅₀ Assay 2
154	<5	<5
155	5.60	<5
156	7.58	5.98
157	<5	<4.7
159	<5	<4.7
160	5.57	<4.7
161	6.42	5.38
162	5.42	<4.7
163	8.07	6.90
164	<5	~5.19
165	6.06	<5
166	8.73	7.41
166	8.80	7.92
166	9.20	7.87
167	8.50	7.52
167	8.80	7.68
168	7.58	6.69
168	7.76	~6.64
168	8.07	~6.7
169	6.56	6.22
170	7.37	~6.83
171	5.79	~5.39
172	6.51	~6.04
173	6.46	6.11
174	6.30	~5.64
175	6.23	5.85
176	5.95	5.22
177	6.72	6.34
178	7.29	6.92
179	7.50	7.02
180	7.99	6.57

Co. No.	pIC ₅₀ Assay 1	pIC ₅₀ Assay 2
181	7.71	7.18
182	7.81	6.30
183	7.65	~6.62
184	7.17	~5.83
185	7.60	6.23
186	7.87	6.21
187	7.20	5.77
188	6.43	6.15
189	<5	n.d.
191	5.04	<5
192	7.16	7.08
193	6.73	6.33
194	6.37	~5.25
195	6.27	<5
196	5.94	5.49
197	5.19	<5
198	6.36	~5.96
199	6.05	5.73
200	5.32	<5
201	6.34	~4.99
202	5.70	~5.33
203	6.68	6.18
204	6.43	5.86
205	5.79	5.15
206	8.29	7.19
207	8.30	7.28
208	7.12	6.31
270	5.33	<5
270	5.37	<5
270	5.46	<5

Composition examples

- “Active ingredient” (a.i.) as used throughout these examples relates to compounds of Formula (I), and pharmaceutically acceptable addition salts, and solvates thereof; in particular to any one of the exemplified compounds.

Typical examples of recipes for the formulation of the invention are as follows:

1. Tablets

Active ingredient

5 to 50 mg

-229-

	Di-calcium phosphate	20 mg
	Lactose	30 mg
	Talcum	10 mg
	Magnesium stearate	5 mg
5	Potato starch	ad 200 mg

2. *Suspension*

An aqueous suspension is prepared for oral administration so that each milliliter contains 1 to 5 mg of active ingredient, 50 mg of sodium carboxymethyl cellulose, 1 mg of sodium benzoate, 500 mg of sorbitol and water ad 1 ml.

10 3. *Injectable*

A parenteral composition is prepared by stirring 1.5 % (weight/volume) of active ingredient in 0.9 % NaCl solution or in 10 % by volume propylene glycol in water.

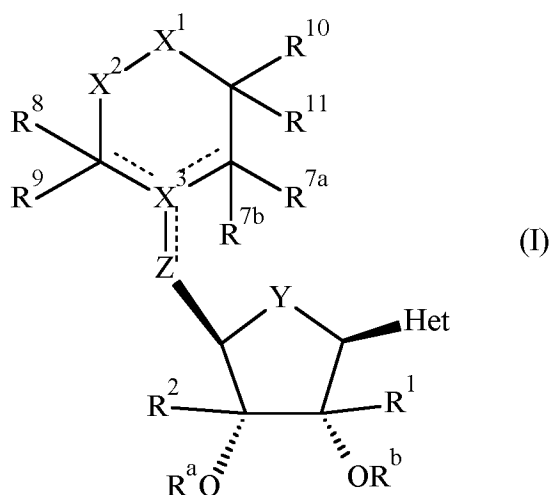
4. *Ointment*

	Active ingredient	5 to 1000 mg
15	Stearyl alcohol	3 g
	Lanoline	5 g
	White petroleum	15 g
	Water	ad 100 g

- 20 In this Example, active ingredient can be replaced with the same amount of any of the compounds according to the present invention, in particular by the same amount of any of the exemplified compounds.

Claims

1. A compound of Formula (I)



5 wherein

R^1 represents hydrogen or CH_3 ;

R^2 represents hydrogen;

R^a represents hydrogen or $-C(=O)-C_{1-4}alkyl$;

R^b represents hydrogen or $-C(=O)-C_{1-4}alkyl$;

10 Y represents $-O-$, $-CH_2-$ or $-CF_2-$;

R^{7a} represents hydrogen;

R^{7b} represents hydrogen, or $C_{1-4}alkyl$ optionally substituted with one or more halo atoms;

X^1 represents a covalent bond or $-O-$;

15 X^2 represents a covalent bond, $-CH_2-$, $-CF_2-$, $-CH_2CH_2-$, $-CF_2CH_2-$, or $-CH_2CF_2-$;

provided that X^2 represents a covalent bond, $-CH_2-$ or $-CF_2-$, when X^1 represents $-O-$;

X^3 represents N or CH; or in case one of the dotted lines represents an additional bond, X^3 represents C;

R^8 and R^{10} each independently are selected from the group consisting of hydrogen;

20 halo; and $C_{1-6}alkyl$ optionally substituted with one or more halo atoms;

R^9 and R^{11} each independently are selected from the group consisting of hydrogen; halo; $-NH_2$; and $C_{1-6}alkyl$ optionally substituted with one $-NR^{9a}R^{9b}$;

or R^8 and R^9 are linked together to form together with the common carbon atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing

25 one or two N-atoms and optionally one oxygen atom; wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or more ring carbon

- atoms with one or more substituents each independently selected from the group consisting of halo, and C₁₋₆alkyl optionally substituted with one or more halo atoms; and wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or two ring N-atoms with a substituent selected from the group consisting of C₁₋₆alkyl; Het^{1a}; C₃₋₆cycloalkyl; -C₁₋₄alkyl-C(=O)-NR^{5a}R^{5b}; C₁₋₄alkyl substituted with one or more halo atoms; and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OC₁₋₄alkyl, cyano, C₃₋₆cycloalkyl, Ar^{1a}, -O-Ar^{1a}, Het^{2a} and -O-Het^{2c};
- or R¹⁰ and R¹¹ are linked together to form together with the common carbon atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing one or two N-atoms and optionally one oxygen atom; wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or more ring carbon atoms with one or more substituents each independently selected from the group consisting of halo, and C₁₋₆alkyl optionally substituted with one or more halo atoms; and wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or two ring N-atoms with a substituent selected from the group consisting of C₁₋₆alkyl; Het^{1b}; C₃₋₆cycloalkyl; -C₁₋₄alkyl-C(=O)-NR^{6a}R^{6b}; C₁₋₄alkyl substituted with one or more halo atoms; and C₁₋₄alkyl substituted with one substituent selected from the group consisting of -OC₁₋₄alkyl, cyano, C₃₋₆cycloalkyl, Ar^{1b}, -O-Ar^{1b}, Het^{2b} and -O-Het^{2d};
- Z represents -CH₂-, -C(=O)-, or -CH(C₁₋₄alkyl)-; and in case X³ represents C, Z can also represent =CH-;
- the dotted lines attached to X³ are optional bonds that may be present when X³ represents a carbon atom, provided that maximum one of the dotted lines represents an optional bond;
- in case one of the dotted lines attached to X³ represents an additional bond, X³ represents C, and (i) R^{7a} is absent or (ii) R⁸ is absent or (iii) Z represents =CH-;
- R^{9a} and R^{9b} each independently are selected from the group consisting of hydrogen and C₁₋₄alkyl; or R^{9a} and R^{9b} are linked together to form together with the common nitrogen atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocyclyl which optionally contains one oxygen atom;
- R^{5a} and R^{5b} each independently are selected from the group consisting of hydrogen and C₁₋₄alkyl;
- Het^{1a} and Het^{1b} are attached to the remainder of the molecule of Formula (I) through any available ring carbon atom;

Het^{1a} and Het^{1b} each independently represent a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing one or two heteroatoms each independently selected from O, S, S(=O)_p and N;

- 5 Ar^{1a} and Ar^{1b} each independently represent phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo; cyano; and C₁₋₄alkyl optionally substituted with one or more halo atoms;

- 10 Het^{2a} and Het^{2b} each independently represent a 4-, 5-, 6- or 7-membered monocyclic aromatic or non-aromatic heterocyclyl containing at least one heteroatom each independently selected from O, S, S(=O)_p and N; or a fused 8-, 9-, 10- or 11-membered bicyclic aromatic or non-aromatic heterocyclyl containing at least one heteroatom each independently selected from O, S, S(=O)_p and N; said monocyclic heterocyclyl or said fused bicyclic heterocyclyl optionally being substituted with one or more substituents each independently selected from the group consisting of halo, cyano, and C₁₋₄alkyl optionally substituted with one or more halo atoms;

- 15 Het^{2c} and Het^{2d} are attached to the remainder of the molecule of Formula (I) through any available ring carbon atom;

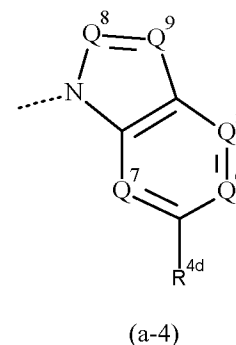
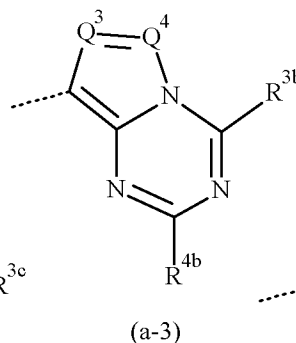
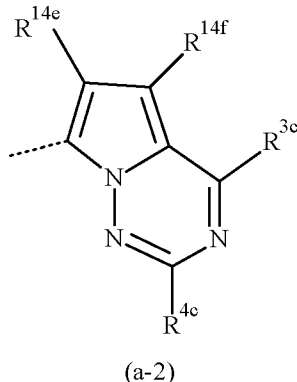
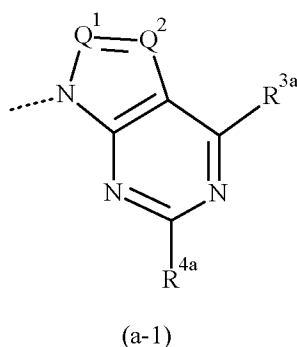
- Het^{2c} and Het^{2d} each independently represent a 4-, 5-, 6- or 7-membered monocyclic aromatic or non-aromatic heterocyclyl containing at least one heteroatom each independently selected from O, S, S(=O)_p and N; or a fused 8-, 9-, 10- or 11-membered bicyclic aromatic or non-aromatic heterocyclyl containing at least one heteroatom each independently selected from O, S, S(=O)_p and N; said monocyclic heterocyclyl or said fused bicyclic heterocyclyl optionally being substituted with one or more substituents each independently selected from the group consisting of halo, cyano, and C₁₋₄alkyl optionally substituted with one or more halo atoms;

- 25 R^{6a} and R^{6b} each independently are selected from the group consisting of hydrogen and C₁₋₄alkyl;

p represents 1 or 2;

Het represents a bicyclic aromatic heterocyclic ring system selected from the group consisting of (a-1), (a-2), (a-3) and (a-4):

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R^{3a} , R^{3b} , R^{3c} and R^{3d} each independently are selected from the group consisting of hydrogen, halo, $-NR^{12a}R^{12b}$, $C_{1-4}alkyl$, and $-O-C_{1-4}alkyl$;

R^{12a} and R^{12b} each independently are selected from the group consisting of hydrogen;

- 5 $C_{3-6}cycloalkyl$; $C_{1-4}alkyl$; and $C_{1-4}alkyl$ substituted with one phenyl which is optionally substituted with one or more substituents selected from the group consisting of halo, cyano, $-OC_{1-4}alkyl$, $-OH$, and $C_{1-4}alkyl$ optionally substituted with one or more halo atoms;

R^{4a} , R^{4b} , R^{4c} , R^{4d} , R^{4e} and R^{4f} each independently are selected from the group

- 10 consisting of hydrogen, halo, $-NR^{13a}R^{13b}$, and $C_{1-4}alkyl$;

R^{13a} and R^{13b} each independently are selected from the group consisting of hydrogen and $C_{1-4}alkyl$;

Q^1 represents N or CR^{14a} ;

Q^2 represents N or CR^{14b} ;

- 15 Q^3 represents N or CR^{14c} ;

Q^4 represents N or CR^{14d} ;

provided that maximum one of Q^3 and Q^4 represents N;

Q^8 represents N or CR^{14g} ;

Q^9 represents N or CR^{14h} ;

- 20 Q^{10} represents N or CR^{14i} ;

Q^{11} represents N or CR^{14j} ;

Q^5 represents CR^{3d} ; Q^6 represents N; and Q^7 represents CR^{4f} ; or

Q^5 represents CR^{3d} ; Q^6 represents CR^{4e} ; and Q^7 represents N; or

Q^5 represents N; Q^6 represents CR^{4e} ; and Q^7 represents CR^{4f} ; or

- 25 Q^5 represents N; Q^6 represents CR^{4e} ; and Q^7 represents N; or

Q^5 represents N; Q^6 represents N; and Q^7 represents CR^{4f} ; or

Q^5 represents N; Q^6 represents N; and Q^7 represents N;

R^{14a} , R^{14b} , R^{14c} , R^{14d} , R^{14e} , R^{14f} , R^{14g} , R^{14h} , R^{14i} , and R^{14j} each independently are selected from the group consisting of hydrogen; halogen; C_{1-4} alkyl; $-NR^{15a}R^{15b}$; and C_{1-4} alkyl substituted with one or more halo atoms;

5 R^{15a} and R^{15b} each independently are selected from the group consisting of hydrogen and C_{1-4} alkyl;

provided that R^{10} and R^{11} may not be linked together when R^8 and R^9 are linked together;

and wherein at least one of R^8 , R^9 , R^{10} and R^{11} contains a nitrogen atom;

10 or a pharmaceutically acceptable addition salt or a solvate thereof.

2. The compound according to claim 1, wherein

Het represents a bicyclic aromatic heterocyclic ring system selected from the group consisting of (a-1), (a-2) and (a-3).

15

3. The compound according to claim 2, wherein

R^1 represents hydrogen;

Y represents $-O-$ or $-CH_2-$;

20 R^{7b} represents hydrogen, or C_{1-4} alkyl optionally substituted with one or more halo atoms;

X^2 represents a covalent bond, $-CH_2-$, $-CF_2CH_2-$, or $-CH_2CF_2-$;

provided that X^2 represents a covalent bond or $-CH_2-$, when X^1 represents $-O-$;

X^3 represents N; or in case one of the dotted lines represents an additional bond, X^3 represents C;

25 R^8 and R^{10} each independently are selected from the group consisting of hydrogen; halo; and C_{1-6} alkyl optionally substituted with one or more halo atoms;

R^9 and R^{11} each independently are selected from the group consisting of hydrogen; halo; $-NH_2$; and C_{1-6} alkyl optionally substituted with one $-NR^{9a}R^{9b}$;

30 or R^8 and R^9 are linked together to form together with the common carbon atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing one or two N-atoms; wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or two ring N-atoms with a substituent selected from the group consisting of C_{1-6} alkyl; Het^{1a} ; C_{3-6} cycloalkyl; $-C_{1-4}$ alkyl- $C(=O)-NR^{5a}R^{5b}$; C_{1-4} alkyl substituted with one or more halo atoms; and C_{1-4} alkyl substituted with one

- substituent selected from the group consisting of $-\text{OC}_{1-4}\text{alkyl}$, cyano, $\text{C}_{3-6}\text{cycloalkyl}$, Ar^{1a} , $-\text{O}-\text{Ar}^{1a}$, and Het^{2a} ;
 or R^{10} and R^{11} are linked together to form together with the common carbon atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing
 5 one or two N-atoms and optionally one oxygen atom; wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or more ring carbon atoms with one or more halo substituents; and wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one or two ring N-atoms with a substituent selected from the group consisting of $\text{C}_{1-6}\text{alkyl}$; and $\text{C}_{1-4}\text{alkyl}$ substituted
 10 with one Ar^{1b} ;
- Z represents $-\text{CH}_2-$ or $-\text{C}(=\text{O})-$; and in case X^3 represents C, Z can also represent $=\text{CH}-$; the dotted lines attached to X^3 are optional bonds that may be present when X^3 represents a carbon atom, provided that maximum one of the dotted lines represents an optional bond;
- 15 in case one of the dotted lines attached to X^3 represents an additional bond, X^3 represents C, and (i) R^{7a} is absent or (ii) R^8 is absent or (iii) Z represents $=\text{CH}-$;
- Het^{1a} is attached to the remainder of the molecule of Formula (I) through any available ring carbon atom;
- Het^{1a} represents a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing one or
 20 two heteroatoms each independently selected from O;
- Ar^{1a} and Ar^{1b} each independently represent phenyl optionally substituted with one or more halo substituents;
- Het^{2a} represents a 4-, 5-, 6- or 7-membered monocyclic aromatic or non-aromatic heterocyclyl containing at least one heteroatom each independently selected from O, S,
 25 $\text{S}(=\text{O})_p$ and N; or a fused 8-, 9-, 10- or 11-membered bicyclic aromatic or non-aromatic heterocyclyl containing at least one heteroatom each independently selected from O, S, $\text{S}(=\text{O})_p$ and N; said monocyclic heterocyclyl or said fused bicyclic heterocyclyl optionally being substituted with one or more $\text{C}_{1-4}\text{alkyl}$ substituents;
- R^{3a} , R^{3b} and R^{3c} each independently are selected from the group consisting of
 30 hydrogen, halo, and $-\text{NR}^{12a}\text{R}^{12b}$;
- R^{12a} and R^{12b} each independently are selected from the group consisting of hydrogen; $\text{C}_{3-6}\text{cycloalkyl}$; $\text{C}_{1-4}\text{alkyl}$; and $\text{C}_{1-4}\text{alkyl}$ substituted with one phenyl which is optionally substituted with one or more halo substituents;
- R^{4a} , R^{4b} and R^{4c} each independently are selected from the group consisting of hydrogen
 35 and $\text{C}_{1-4}\text{alkyl}$;

Q¹ represents CR^{14a};

Q² represents N or CR^{14b};

Q³ represents CR^{14c};

Q⁴ represents N;

- 5 R^{14a}, R^{14b}, R^{14c}, R^{14e} and R^{14f} each independently are selected from the group consisting of hydrogen and halogen;
provided that R¹⁰ and R¹¹ may not be linked together when R⁸ and R⁹ are linked together;
and wherein at least one of R⁸, R⁹, R¹⁰ and R¹¹ contains a nitrogen atom.

10

4. The compound according to claim 2, wherein

R¹ represents hydrogen;

Y represents -O- or -CH₂-;

R^{7b} represents hydrogen;

- 15 X² represents a covalent bond or -CH₂-;

X³ represents N; or in case one of the dotted lines represents an additional bond, X³ represents C;

R⁸ and R¹⁰ each independently are selected from the group consisting of hydrogen and halo;

- 20 R⁹ and R¹¹ each independently are selected from the group consisting of hydrogen and halo;

or R⁸ and R⁹ are linked together to form together with the common carbon atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing one N-atom; wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally

- 25 substituted on one ring N-atom with C₁₋₆alkyl;

or R¹⁰ and R¹¹ are linked together to form together with the common carbon atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocyclyl, containing one N-atom; wherein said 4-, 5-, 6- or 7-membered saturated heterocyclyl is optionally substituted on one ring N-atom with C₁₋₆alkyl;

- 30 provided that R¹⁰ and R¹¹, or R⁸ and R⁹ are linked together;

Z represents -CH₂-; and in case X³ represents C, Z can also represent =CH-;

the dotted lines attached to X³ are optional bonds that may be present when X³ represents a carbon atom, provided that maximum one of the dotted lines represents an optional bond;

in case one of the dotted lines attached to X^3 represents an additional bond, X^3 represents C, and (i) R^{7a} is absent or (ii) R^8 is absent or (iii) Z represents =CH-;

Het represents a bicyclic aromatic heterocyclic ring system selected from the group consisting of (a-1) and (a-2);

- 5 R^{3a} and R^{3c} represent NH_2 ;
 R^{4a} and R^{4c} represent hydrogen;
 Q^1 represents CR^{14a} ;
 Q^2 represents CR^{14b} ;
 R^{14a} , R^{14b} , R^{14c} and R^{14f} each independently are selected from the group consisting of
10 hydrogen and halogen.

5. The compound according to any one of claims 1 to 4, wherein R^a and R^b represent $-C(=O)-C_{1-4}alkyl$.
- 15 6. The compound according to any one of claims 1 to 4, wherein R^a and R^b represent hydrogen.
7. The compound according to any one of claims 1 to 6, wherein R^1 and R^2 represent hydrogen.
- 20 8. The compound according to any one of claims 1 to 7, wherein X^3 represents C or CH.
9. The compound according to any one of claims 1 to 7, wherein X^3 represents N.
- 25 10. The compound according to any one of claims 1 to 9, wherein Het represents a bicyclic aromatic heterocyclic ring system of Formula (a-1).
11. The compound according to claim 10, wherein
30 R^{3a} represents $-NR^{12a}R^{12b}$; and R^{12a} and R^{12b} represent hydrogen.
12. The compound according to any one of claims 1 to 11 wherein R^{10} and R^{11} , or R^8 and R^9 are linked together.

13. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound according to any one of claims 1 to 12.
- 5 14. A compound as defined in any one of claims 1 to 12 for use as a medicament.
15. A compound as defined in any one of claims 1 to 12 for use in the treatment or prevention of a disease or condition selected from a blood disorder, metabolic disorders, autoimmune disorders, cancer, inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, pancreatitis, multiorgan failure, kidney diseases, platelet aggregation, sperm motility, transplantation rejection, graft rejection, and lung injuries.
- 10 16. The compound according to claim 15 wherein the disease or condition is cancer.
- 15

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/054324

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D519/00 C07D473/34 C07D487/04 C07H19/06 C07H19/16
A61K31/519 A61K31/52 A61P29/00 A61P35/00 A61P37/00

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	VUILHORGNE, M. ET AL.: "New synthetic S-adenosyl-homocysteine analogs with oncostatic and antiviral activity", HETEROCYCLES, vol. 11, 1978, pages 495-520, XP009112700, ISSN: 0385-5414	1-3,6,7, 9-11,13, 14
Y	page 497; compound 19	1-11, 13-16
A	----- -/--	12

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

21 April 2017

Date of mailing of the international search report

02/05/2017

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Kiernan, Andrea

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2017/054324

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PRASAD, R.N. ET AL.: "Modification of the 5' position of purine nucleosides. 2. Synthesis and some cardiovascular properties of adenosine-5'-(N-substituted)carboxamides", JOURNAL OF MEDICINAL CHEMISTRY, vol. 23, no. 3, 1980, pages 313-319, XP055020044, ISSN: 0022-2623, DOI: 10.1021/jm00177a021	1-3,6,7, 9-11, 13-15
Y	page 314 - page 315; table I; compounds 45,46	1-11, 13-16
A		12
X	----- MOUKHA-CHAFIQ, O. ET AL.: "Synthesis and General Biological Activity of a Small Adenosine-5'-(Carboxamide and Sulfanilamide) Library", NUCLEOSIDES, NUCLEOTIDES AND NUCLEIC ACIDS, vol. 33, no. 11, 8 October 2014 (2014-10-08), pages 709-729, XP055297353, ISSN: 1525-7770, DOI: 10.1080/15257770.2014.931588	1-3,6,7, 9-11, 13-16
Y	Scheme 1; page 711; compound 13	1-11, 13-16
A		12
X	----- SCHMIDT, R.R. ET AL.: "Synthese 5'-modifizierter Adenosinderivate", CHEMISCHE BERICHTE, vol. 101, no. 2, 1968, pages 590-594, XP055297323, ISSN: 0009-2940, DOI: 10.1002/cber.19681010228	1-3,6,7, 9-11,13, 14
Y	page 591; compound 5	1-11, 13-16
A		12
X	----- US 4 224 438 A (FAULAND ERICH ET AL) 23 September 1980 (1980-09-23)	1-3,6,7, 9-11,13, 14
Y	column 6; claim 12; examples 9(c),(d)	1-11, 13-16
A		12
X	----- US 2003/225205 A1 (EPPLER ROBERT [US] ET AL) 4 December 2003 (2003-12-04)	1-3,6,7, 9-11,13, 14
Y	figures 13G, 13I	1-11, 13-16
A		12
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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2017/054324

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/074083 A1 (PFIZER INC.) 12 September 2003 (2003-09-12) cited in the application	1-3,6,7, 9-11,13, 14
Y	page 79; example 2(B)(9)	1-11,
A	page 80; example 2(B)(10)	13-16 12
Y	----- WO 2012/082436 A2 (EPIZYME, INC.) 21 June 2012 (2012-06-21) cited in the application	1-11, 13-16
A	page 32; claims; figures 7A,7B	12
Y	----- HU, H. ET AL.: "Small Molecule Inhibitors of Protein Arginine Methyltransferases", EXPERT OPINION ON INVESTIGATIONAL DRUGS, vol. 25, no. 3, 16 February 2016 (2016-02-16), pages 335-358, XP055297479, ISSN: 1354-3784, DOI: 10.1517/13543784.2016.1144747	1-11, 13-16
A	abstract page 337; table 1 pages 345-347, paragraph 6.; table 5 page 349; table 7; compound 64	12
Y,P	----- WO 2016/135582 A1 (PFIZER INC.) 1 September 2016 (2016-09-01) cited in the application abstract page 1 pages 258,261; claim 18 -----	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2017/054324

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4224438	A	23-09-1980	NONE
US 2003225205	A1	04-12-2003	NONE
WO 03074083	A1	12-09-2003	AR 038863 A1 02-02-2005 AU 2003206019 A1 16-09-2003 BR 0308222 A 09-02-2005 CA 2477422 A1 12-09-2003 EP 1482977 A1 08-12-2004 KR 20040091089 A 27-10-2004 PA 8568201 A1 12-11-2003 PE 09072003 A1 29-10-2003 TW 200304380 A 01-10-2003 US 2004043959 A1 04-03-2004 UY 27692 A1 31-10-2003 WO 03074083 A1 12-09-2003
WO 2012082436	A2	21-06-2012	AU 2011341441 A1 20-06-2013 CA 2819620 A1 21-06-2012 EP 2646455 A2 09-10-2013 US 2013310333 A1 21-11-2013 US 2016068559 A1 10-03-2016 WO 2012082436 A2 21-06-2012
WO 2016135582	A1	01-09-2016	CA 2921314 A1 24-08-2016 TW 201643176 A 16-12-2016 US 2016244475 A1 25-08-2016 UY 36564 A 30-09-2016 WO 2016135582 A1 01-09-2016