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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 January 2014 (16.01.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/009509 A1

(51) International Patent Classification:
C07D 487/16 (2006.01) *A61K 31/52* (2006.01)
C07D 498/16 (2006.01) *A61P 31/00* (2006.01)

(21) International Application Number:
PCT/EP2013/064763

(22) International Filing Date:
12 July 2013 (12.07.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
12176330.4 13 July 2012 (13.07.2012) EP

(71) Applicant: **JANSSEN R&D IRELAND** [IE/IE]; Eastgate Village, Eastgate, Little Island, Co Cork (IE).

(72) Inventors: **BONFANTI, Jean-François**; 11 Impasse des Lauriers, F-27430 Andé (FR). **FORTIN, Jérôme Michel Claude**; 22, rue des acacias, F-27460 Igoville (FR). **MULLER, Philippe**; 17 Route d'Herqueville, F-27430 Andé (FR). **DOUBLET, Frédéric Marc Maurice**; 1646, Route de Neufchatel, F-76230 Isneauville (FR). **RABOISSON, Pierre Jean-Marie Bernard**; Rue Jolie 3, B-1331 Rosieres (BE). **ARNOULT, Eric Pierre Alexandre**; 34 domaine de l'île au Moulin, F-27100 Le Vaudreuil (FR).

(74) Agent: **DAELEMANS, Frank**; Turnhoutseweg 30, B-2340 Beerse (BE).

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

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

Declarations under Rule 4.17:

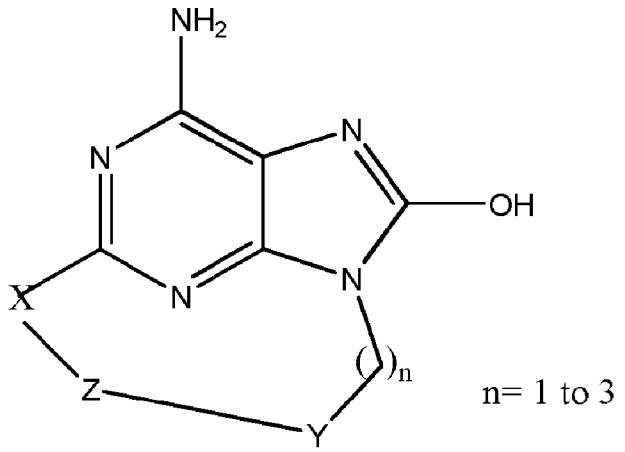
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *of inventorship (Rule 4.17(iv))*

Published:

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

(54) Title: MACROCYCLIC PURINES FOR THE TREATMENT OF VIRAL INFECTIONS



(I)

n= 1 to 3

(57) Abstract: This invention relates macrocyclic purine derivatives having formula (I), processes for their preparation, pharmaceutical compositions, and their use in treating viral infections.

WO 2014/009509 A1

Macrocyclic purines for the treatment of viral infections

This invention relates macrocyclic purine derivatives, processes for their preparation, pharmaceutical compositions, and their use in treating viral infections.

The present invention relates to the use of macrocyclic purine derivatives in the treatment of viral infections, immune or inflammatory disorders, whereby the modulation, or agonism, of toll-like-receptors (TLRs) is involved. Toll-Like Receptors are primary transmembrane proteins characterized by an extracellular leucine rich domain and a cytoplasmic extension that contains a conserved region. The innate immune system can recognize pathogen-associated molecular patterns via these TLRs expressed on the cell surface of certain types of immune cells. Recognition of foreign pathogens activates the production of cytokines and upregulation of co-stimulatory molecules on phagocytes. This leads to the modulation of T cell behaviour.

It has been estimated that most mammalian species have between ten and fifteen types of Toll-like receptors. Thirteen TLRs (named TLR1 to TLR13) have been identified in humans and mice together, and equivalent forms of many of these have been found in other mammalian species. However, equivalents of certain TLR found in humans are not present in all mammals. For example, a gene coding for a protein analogous to TLR10 in humans is present in mice, but appears to have been damaged at some point in the past by a retrovirus. On the other hand, mice express TLRs 11, 12, and 13, none of which are represented in humans. Other mammals may express TLRs which are not found in humans. Other non-mammalian species may have TLRs distinct from mammals, as demonstrated by TLR14, which is found in the Takifugu pufferfish. This may complicate the process of using experimental animals as models of human innate immunity.

For detailed reviews on toll-like receptors see the following journal articles. Hoffmann, J.A., Nature, **426**, p33-38, 2003; Akira, S., Takeda, K., and Kaisho, T., Annual Rev. Immunology, **21**, p335-376, 2003; Ulevitch, R. J., Nature Reviews: Immunology, **4**, p512-520, 2004.

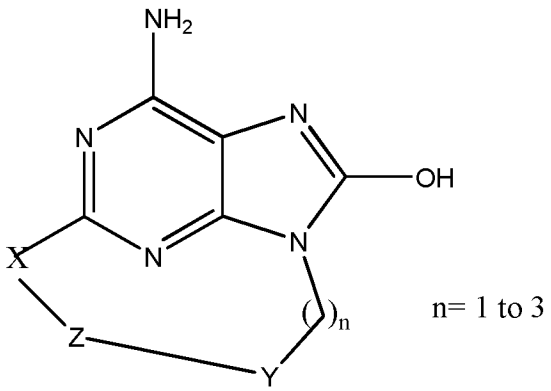
Compounds indicating activity on Toll-Like receptors have been previously described such as purine derivatives in WO 2006/117670, adenine derivatives in WO 98/01448 and WO 99/28321, and pyrimidines in WO 2009/067081.

However, there exists a strong need for novel Toll-Like receptor modulators having preferred selectivity, higher potency, higher metabolic stability, and an improved safety profile compared to the compounds of the prior art.

In the treatment of certain viral infections, regular injections of interferon (IFN-alfa) can be administered, as is the case for hepatitis C virus (HCV). For more information reference Fried et. al. Peginterferon-alfa plus ribavirin for chronic hepatitis C virus infection, *N Engl J Med* 2002; 347: 975-82. Orally available small molecule IFN inducers offer the potential advantages of reduced immunogenicity and convenience of administration. Thus, novel IFN inducers are potentially effective new class of drugs for treating virus infections. For an example in the literature of a small molecule IFN inducer having antiviral effect see De Clercq, E.; Descamps, J.; De Somer, P. *Science* **1978**, *200*, 563-565.

IFN-alfa is also given in combination with other drugs in the treatment of certain types of cancer (refer to Eur. J. Cancer 46, 2849–57, and Cancer Res. **1992**, *52*, 1056 for examples). TLR 7/8 agonists are also of interest as vaccine adjuvants because of their ability to induce pronounced Th1 response (refer to Hum. Vaccines 2010, 6, 1−14, and Hum. Vaccines 2009, 5, 381−394 for examples).

In accordance with the present invention a compound of formula (I) is provided

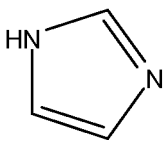


(I)

n= 1 to 3

and pharmaceutically accepted salts thereof, wherein

X is oxygen, nitrogen, sulfur or

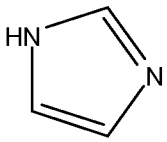


,

Y represents an aromatic ring or heterocyclic ring comprising at least a nitrogen, optionally substituted by one or more substituents independently selected from C_{1-6}alkyl, C_{1-4}alkoxy, trifluoromethyl or halogen,

Z represents C_{1-10} saturated or unsaturated alkyl optionally substituted by an alkyl or alkylhydroxyl;
or Z represents C_{1-6}alkyl -NH-C(O)- C_{1-6}alkyl- or C_{1-6}alkyl -NH-C(O)- C_{1-6}alkyl -O-;
or Z represents C_{1-10}alkyl -O- wherein said alkyl is unsaturated or saturated and can optionally be substituted by an alkyl or alkylhydroxyl ,
or Z represents C_{1-6}alkyl-O-C_{1-6}alkyl- wherein said alkyl is unsaturated or saturated and can optionally be substituted by an alkyl or alkylhydroxyl
or Z represents C_{1-6}alkyl-O-C_{1-6}alkyl-O- wherein said alkyl is unsaturated or saturated and can optionally be substituted by an alkyl or alkylhydroxyl.

Part of the invention is also those compounds of formula (I) wherein
X is O, N-C_{1-4}alkyl, NH, S or



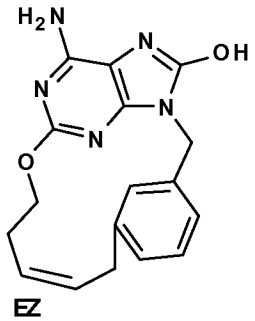
,

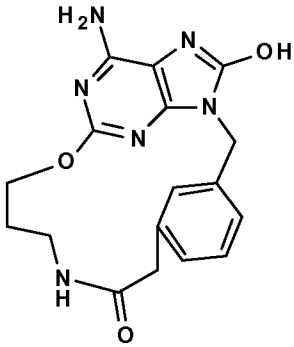
Y represents an aromatic ring or heterocyclic ring comprising at least a nitrogen, optionally substituted by one or more substituents independently selected from C_{1-6}alkyl, C_{1-4}alkoxy, trifluoromethyl, halogen, C(O)NH- C_{1-6}alkyl, NH(CO)-C_{1-6}alkyl, CN, NH-C_{1-6}alkyl, N-(C_{1-6}alkyl)$_2$, C(O)-C_{1-6}alkyl or OH,

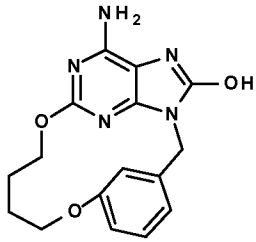
Z represents C_{1-10} saturated or unsaturated alkyl optionally substituted by an alkyl or alkylhydroxyl or OH;
or Z represents C_{1-6}alkyl -NH-C(O)- C_{1-6}alkyl- or C_{1-6}alkyl -NH-C(O)- C_{1-6}alkyl -O-;
or Z represents C_{1-6}alkyl –NCH_3-C(O)- C_{1-6}alkyl- or C_{1-6}alkyl –NCH_3-C(O)- C_{1-6}alkyl -O-;
or Z represents C_{1-6}alkyl –C(O)-NH- C_{1-6}alkyl- or C_{1-6}alkyl –C(O)-NH- C_{1-6}alkyl -O-;
or Z represents C_{1-6}alkyl –C(O)-NCH_3- C_{1-6}alkyl- or C_{1-6}alkyl –C(O)-NCH_3- C_{1-6}alkyl -O-;
or Z represents C_{1-10}alkyl -O- wherein said alkyl is unsaturated or saturated and can optionally be substituted by an alkyl or alkylhydroxyl or OH;
or Z represents C_{1-10}alkyl -NH- wherein said alkyl is unsaturated or saturated and can optionally be substituted by an alkyl or alkylhydroxyl or OH;

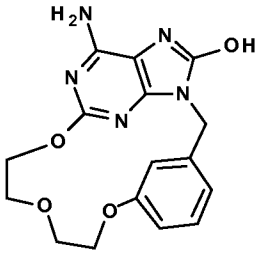
or Z represents C_{1-6}alkyl-O-C_{1-6}alkyl- wherein said alkyl is unsaturated or saturated and can optionally be substituted by an alkyl or alkylhydroxyl or OH;
or Z represents C_{1-6}alkyl-O-C_{1-6}alkyl-O- wherein said alkyl is unsaturated or saturated and can optionally be substituted by an alkyl or alkylhydroxyl or OH.

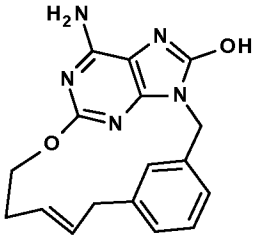
Preferred compounds having one of the following formula's according to the invention were selected from the group of:

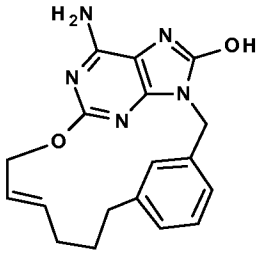


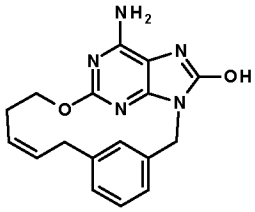
,


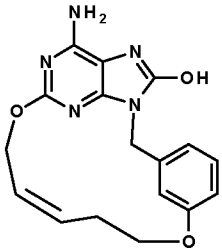
,


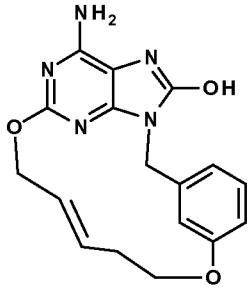
,


,


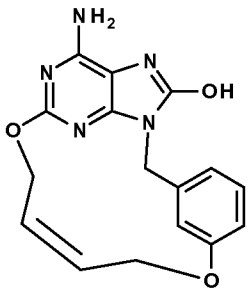
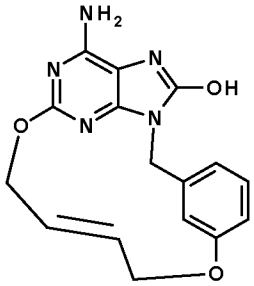
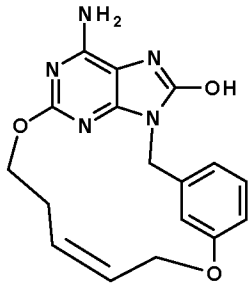
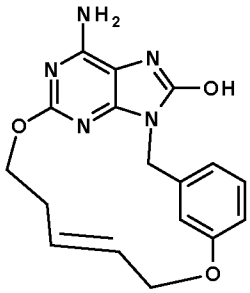
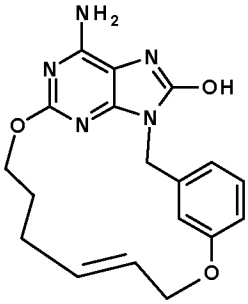
,


,


,


,


,


,

,

,

or

.

Other preferred compounds according to the invention are compounds having the following numbers (as mentioned in the Tables 1 and 2 respectively): 32, 45, 60, 64, 65, 68, 75, 87, 90, 91 and 92.

Part of the invention is also a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof together with one or more pharmaceutically acceptable excipients, diluents or carriers.

Furthermore to the invention belongs a compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof or a pharmaceutical composition above mentioned for use as a medicament.

The invention also relates to a compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof or a pharmaceutical composition above mentioned for use in the treatment of a disorder in which the modulation of TLR7 is involved.

The term “alkyl” refers to a straight-chain or branched-chain mostly saturated (but in specific compounds according to the invention being unsaturated) aliphatic hydrocarbon containing the specified number of carbon atoms.

The term “halogen” refers to fluorine, chlorine, bromine or iodine.

The term “alkoxy” refers to an alkyl (carbon and hydrogen chain) group singular bonded to oxygen like for instance a methoxy group or ethoxy group.

Pharmaceutically acceptable salts of the compounds of formula (I) include the acid addition and base salts thereof. Suitable acid addition salts are formed from acids which form non-toxic salts. Suitable base salts are formed from bases which form non-toxic salts.

The compounds of the invention may also exist in unsolvated and solvated forms. The term “solvate” is used herein to describe a molecular complex comprising the compound of the invention and one or more pharmaceutically acceptable solvent molecules, for example, ethanol.

The term “polymorph” refers to the ability of the compound of the invention to exist in more than one form or crystal structure.

The compounds of the invention can be present in a so-called “tautomer(s)” formation refering to isomers of organic compounds that readily interconvert by a chemical reaction called tautomerization. This reaction results in the formal migration of a hydrogen atom or proton, accompanied by a switch of a single bond and adjacent double bond.

The compounds of the present invention may be administered as crystalline or amorphous products. They may be obtained for example as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. They may be administered alone or in combination with one or more other compounds of the invention or in combination with one or more other drugs. Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term “excipient” is used herein to describe any ingredient other than the compound(s) of the invention. The choice of excipient depends largely on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

The compounds of the present invention or any subgroup thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form, 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 pharmaceutical compositions are desirably in unitary dosage form suitable, for example, for oral, rectal, or percutaneous administration. 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, 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. Also included are solid form preparations that can be converted, shortly before use, to liquid forms. 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. The compounds of the present invention may also be administered via inhalation or insufflation by means of methods and formulations employed in the art for administration via this way. Thus, in general the compounds of the present invention may be administered to the lungs in the form of a solution, a suspension or a dry powder.

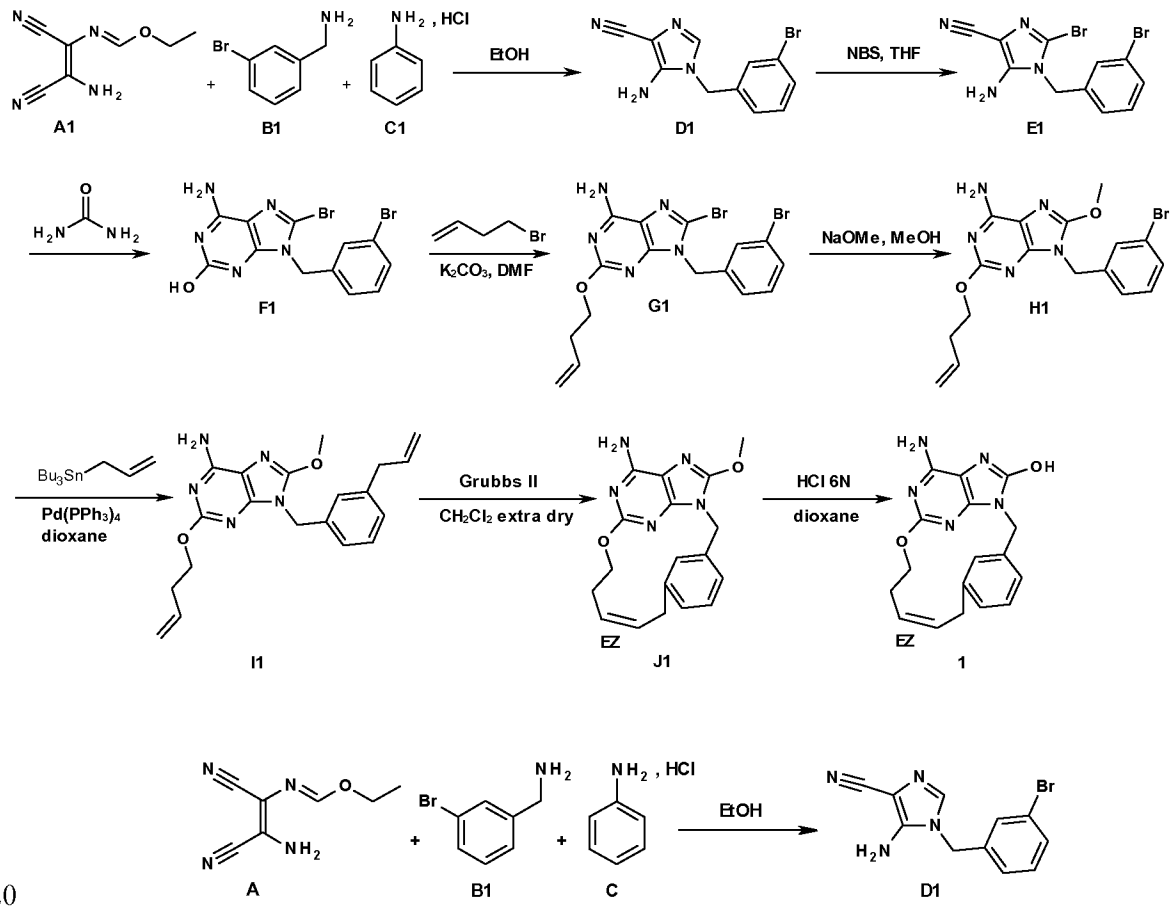
It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity 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.

Those of skill in the treatment of infectious diseases will be able to determine the effective amount from the test results presented hereinafter. In general it is contemplated that an effective daily amount would be from 0.01 mg/kg to 50 mg/kg body weight, more preferably from 0.1 mg/kg to 10 mg/kg body weight. It may be

appropriate to administer the required dose as two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms, for example, containing 1 to 1000 mg, and in particular 5 to 200 mg of active ingredient per unit dosage form.

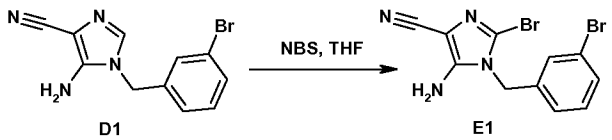
The exact dosage and frequency of administration depends on the particular compound of formula (I) used, the particular condition being treated, the severity of the condition being treated, the age, weight and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that the effective 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. The effective amount ranges mentioned above are therefore only guidelines and are not intended to limit the scope or use of the invention to any extent.

Overall Scheme in the preparation of final products: method 1



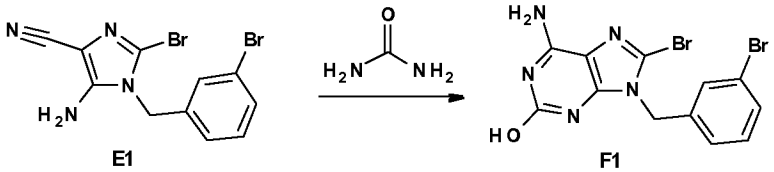
Synthesis of intermediate D1

At 10°C, 3-bromobenzylamine (11.9 g, 63.96 mmol) was added drop wise to a mixture of A1 (10 g, 60.91 mmol) and C1 (125 mg, 0.97 mmol) in EtOH (100 mL). The mixture was stirred at RT overnight. 120 mL of NaOH 1N was added drop wise and the mixture was stirred at RT for 1h. The precipitate was filtered off, washed with a minimum of cold EtOH and dried to give 12.74 g (75% yield) of intermediate D1.



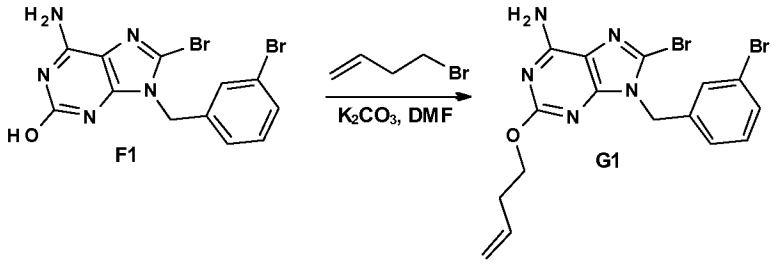
Synthesis of intermediate E1

N-Bromosuccinimide (7.56 g, 42.47 mmol) was added portion wise to a suspension of D1 (10.7 g, 38.61 mmol) in THF (100 mL) keeping the temperature at 15°C, then the reaction mixture was stirred at 15°C for 10 minutes. The mixture was poured into an aqueous solution of $NaHCO_3$ and EtOAc. The layers were decanted and separated. The organic layer was dried over $MgSO_4$, filtered and solvent was evaporated. The crude compound was taken up in CH_3CN, the precipitate was filtered off and dried to give 7.5 g (55% yield) of a part of intermediate E1. The filtrate was evaporated and was purified by chromatography over silica gel (Irregular SiOH 20-45µm; mobile phase (99% CH_2Cl_2, 1% CH_3OH). The pure fractions were collected and concentrated under reduced pressure to give 2.8 g (20% yield) of a second batch of intermediate E1.



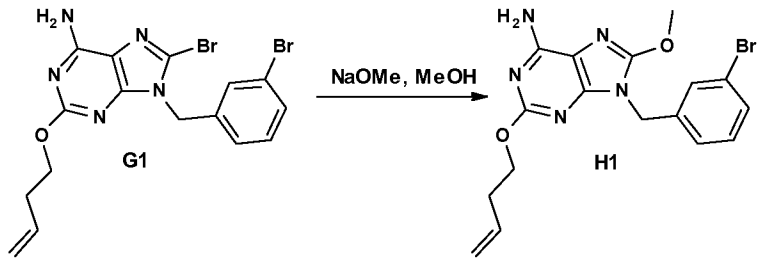
Synthesis of intermediate F1

A mixture of E1 (8.3 g, 23.31 mmol) in urea (14 g, 233.1 mmol) was heated at 160°C for 4h. Urea (14 g, 233.1 mmol) was added again and the mixture was stirred at 160°C for 2h. The mixture was cooled to RT and water was added. The precipitate was triturated and filtered off, washed with water and dried under vacuum at 60°C to give 9.25 g (99% yield) of intermediate F1.



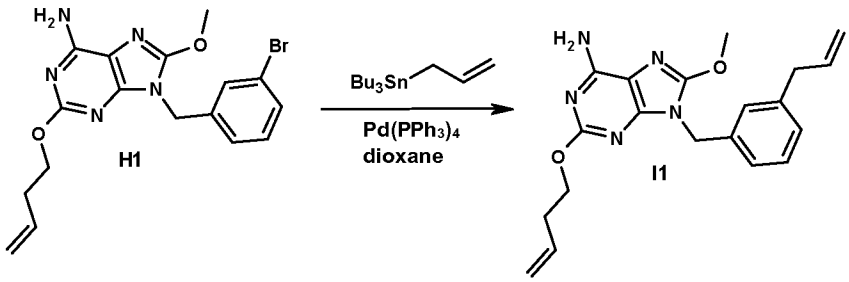
Synthesis of intermediate G1

A mixture of F1 (3 g, 7.52 mmol), 4-Bromo-1-butene (2.29 mL, 22.55 mmol), K_2CO_3 (3.11 g, 22.55 mmol) in dry DMF (40 mL) was stirred at 50°C for 12h. The solvent was evaporated. The residue was taken up in EtOAc. The organic layer was washed with water, dried over $MgSO_4$, filtered and the solvent was evaporated. The crude was purified by flash chromatography over silica gel (15-40µm, 50g, CH_2Cl_2/CH_3OH: 98-2). The pure fractions were collected and evaporated to dryness to give 1.95 g (57% yield) of intermediate G1.



Synthesis of intermediate H1

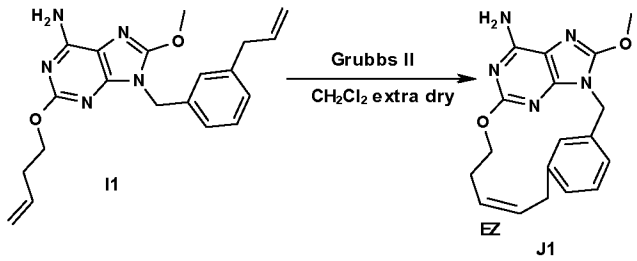
At RT, sodium methoxide (30wt% solution in CH_3OH) (8.4 mL, 45.24 mmol) was added drop wise to a mixture of G1 (4.1 g, 9.05 mmol) in CH_3OH (100 mL). The mixture was stirred at 60°C for 6h. The mixture was poured into water. The aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and the solvent was evaporated to give 3.8 g (100% yield) of intermediate H1. The crude compound was directly used in the next step.



Synthesis of intermediate I1

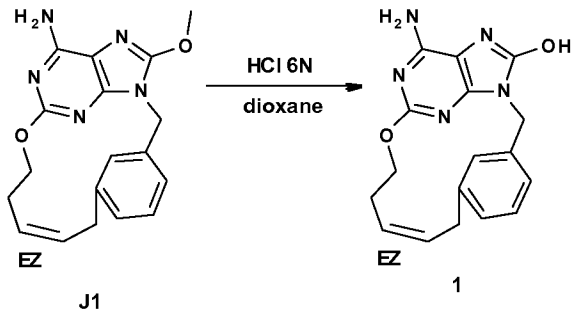
The reaction was performed twice in parallel.

A mixture of H1 (2*1.75 g, 8.66 mmol), allyltri-N-butyltin (2*1.32 mL, 8.66 mmol) and tetrakis(triphenylphosphine)palladium(0) (2*500 mg, 0.87 mmol) in dioxane (2*17.5 mL) was stirred at 140°C for 1h. The mixture was cooled to RT and was poured into a KF water solution (1g/100mL). The mixture was stirred for 10 min at RT. EtOAc was added and the mixture was filtered through a pad of celite®. The celite® was washed with EtOAc. The layers were decanted. The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated. The crude was purified by flash chromatography over silica gel (15-40µm, 120g, $CH_2Cl_2/CH_3OH/NH_4OH$: 98.5/1.5/0.1) The pure fractions were collected and concentrated under reduced pressure to give 1.76 g (56% yield) of intermediate I1.



Synthesis of intermediate J1

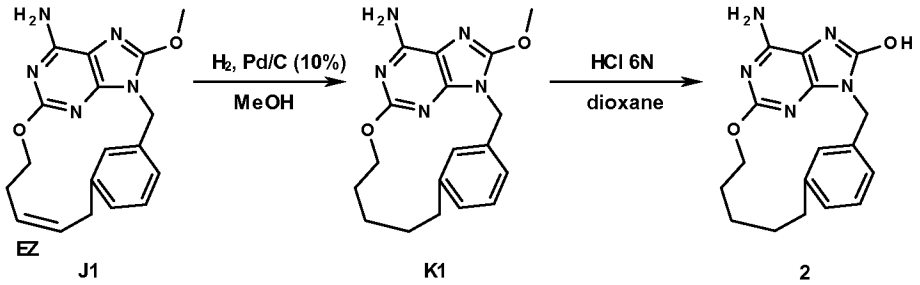
I1 (950 mg, 2.6 mmol) was added to CH_2Cl_2 extra dry (760 mL) and the resulting mixture was degassed by bubbling N_2 through the solution for 30min. Grubbs catalyst 2nd generation (222 mg, 0.26 mmol) was added in one portion and the mixture was stirred under a N_2 flow for 24h. The solvent was evaporated and the crude compound was immediately purified by flash chromatography over silica gel (15-40µm, 10g, $CH_2Cl_2/CH_3OH/NH_4OH$: 98.5/1.5/0.1) The pure fractions were collected and concentrated under reduced pressure to give 280 mg of intermediate I1 and 200 mg (23% yield) of intermediate J1 (as a mixture of two isomers E and Z).



Synthesis of final compound 1

A mixture of J1 (200 mg, 0.59 mmol) in HCl 6N (2 mL) and dioxane (5 mL) was stirred at RT for 16h. The mixture was washed with EtOAc (15mL) then the mixture was basified at 0°C with K_2CO_3 (a precipitate appears) and was extracted many times with EtOAc and CH_3OH. The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated. The residue was recrystallized from CH_3CN, the precipitate was filtered off and dried to give 108 mg (56% yield) of compound 1 (mixture of isomers E/Z 55/45).

Overall Scheme in the preparation of final products: method 2



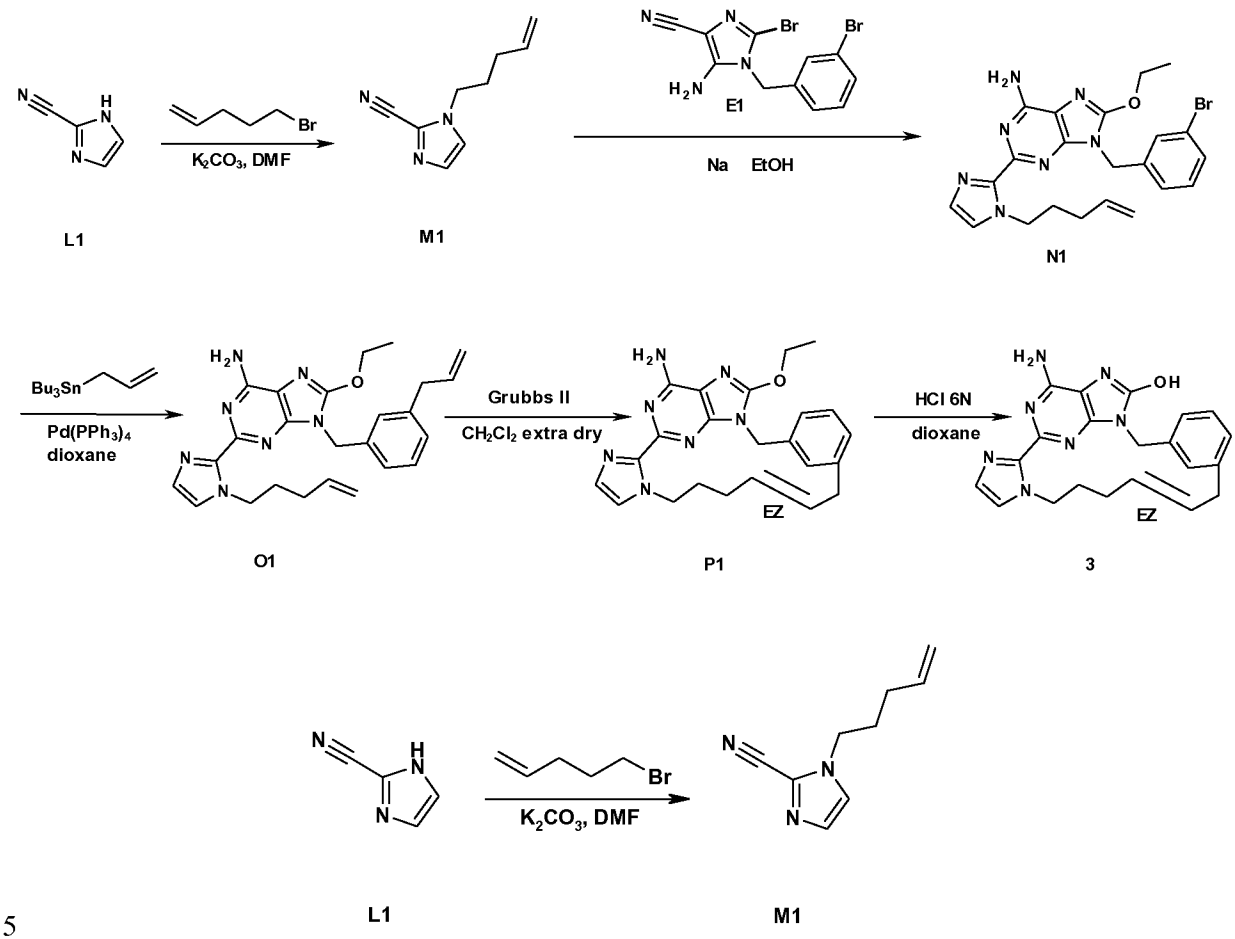
Synthesis of intermediate K1

A mixture of J1 (130 mg, 0.39 mmol), Pd/C (10%) (20 mg, 0.02 mmol) in CH_3OH (30 mL) was hydrogenated under an atmospheric pressure of H_2 for 4h. The catalyst was removed by filtration through celite®. The celite® was washed with CH_3OH. The filtrate was evaporated to give 126 mg (96% yield) of intermediate K1, used as such in the next step.

Synthesis of final compound 2

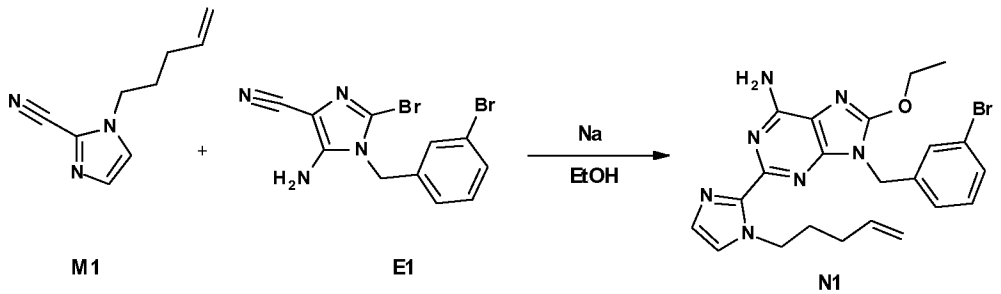
At RT, a mixture of K1 (110 mg, 0.32 mmol) in HCl 6N (1 mL) and dioxane (2 mL) was stirred for 6h. The mixture was poured into ice and was neutralized with NaOH 3N. The precipitate was filtered off, washed with water, EtOH, then with diethylether and dried to give 79 mg (75% yield) of compound 2.

Overall Scheme in the preparation of final products: method 3



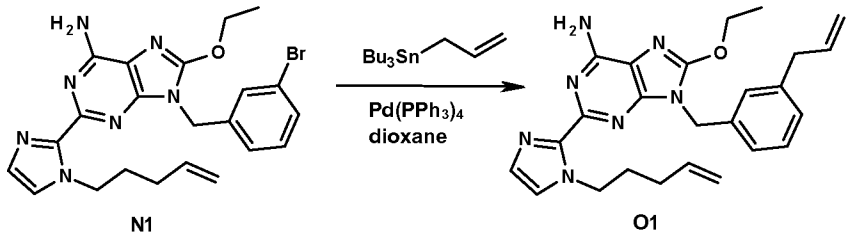
Synthesis of intermediate M1

L1 (3.0 g, 32.23 mmol), 5-Bromo-1-pentene (4.8 g, 32.23 mmol) and K_2CO_3 (5.34 g, 38.67 mmol) in DMF (75 mL) was stirred at 60°C for 12h. The mixture was concentrated under reduced pressure. The residue was taken up in EtOAc. The organic layer was washed with water, dried over $MgSO_4$, filtered and the solvent was evaporated to give 4.6 g (89% yield) of intermediate M1 used as such in the next step.



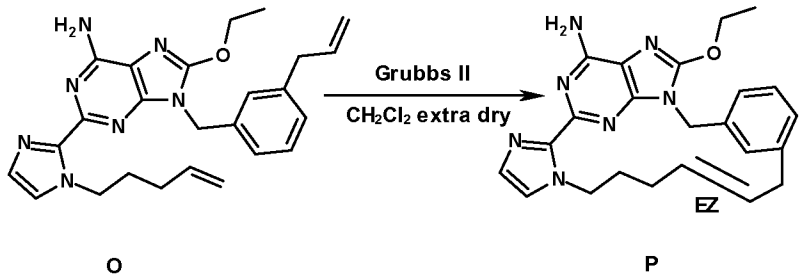
Synthesis of intermediate N1

Under a N_2 flow, sodium (1.42 g, 62.03 mmol) was dissolved into EtOH (80 mL) at RT. M1 (2.0 g, 12.41 mmol), E1 (4.42 g, 12.41 mmol) in EtOH (20 mL) were added drop wise and the resulting mixture was stirred at 90°C for 5h under a N_2 flow. The solvent was evaporated. EtOAc and water were added. The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and the solvent was evaporated. The crude was purified by chromatography over silica gel (Irregular SiOH 20-45µm; mobile phase (0.5% NH_4OH, 94% CH_2Cl_2, 6% CH_3OH). The pure fractions were collected and concentrated under reduced pressure to give 3.15 g (53% yield) of intermediate N1.



Synthesis of intermediate O1

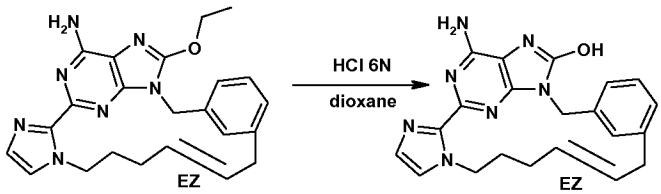
A mixture of N1 (0.50 g, 1.04 mmol), allyltri-N-butyltin (0.32 mL, 1.04 mmol) and tetrakis(triphenylphosphine)palladium(0) (120 mg, 0.10 mmol) in dioxane (4 mL) was stirred at 140°C for 1h. The mixture was cooled to RT and was poured into a KF water solution (5 g/100 mL). The mixture was stirred for 10min at RT. EtOAc was added and the layers were decanted. The organic layer was washed with brine, dried over $MgSO_4$, filtered and the solvent was evaporated. The crude was purified by chromatography over silica gel (Irregular SiOH 15-40µm; mobile phase (0.5% NH_4OH, 95% CH_2Cl_2, 5% CH_3OH). The pure fractions were collected and concentrated under reduced pressure to give 300 mg (65% yield) of intermediate O1.



Synthesis of intermediate P1

O1 (1.80 g, 4.06 mmol) was added to CH_2Cl_2 extra dry (1080 mL) and the resulting mixture was degassed by bubbling N_2 through the solution for 30min. Grubbs catalyst

2nd generation (346 mg, 0.41 mmol) was added in one portion and the mixture was stirred at RT under a N_2 flow for 24h. The mixture was concentrated under reduced pressure. The crude was purified by flash chromatography over silica gel (15-40µm, 120g, $CH_2Cl_2/CH_3OH/NH_4OH$: 96/4/0.5). The pure fractions were collected and concentrated under reduced pressure to give 1.47 g of crude product. The residue was purified by Reverse phase chromatography on (X-Bridge-C18 5µm 30*150mm), mobile phase (Gradient from 80% NH_4HCO_3 0.5% pH10 buffer, 20% CH_3CN to 0% NH_4HCO_3 0.5% pH10 buffer, 100% CH_3CN). The pure fractions were collected and concentrated under reduced pressure to give 83 mg (5% yield) of intermediate P1 (as a mixture of two isomers E and Z) and 800 mg of intermediate O1.

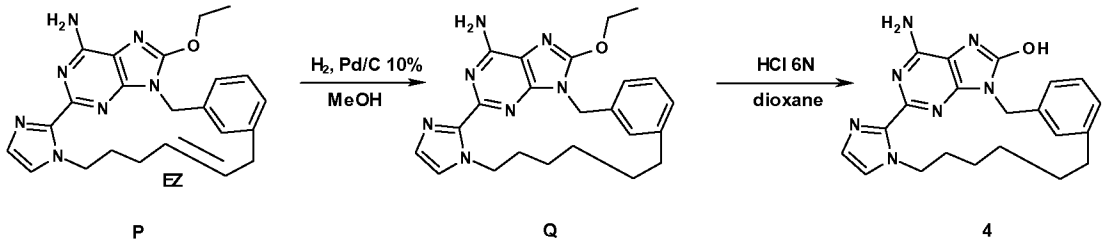


P1 3

Synthesis of final compound 3

P1 (40 mg, 0.10 mmol) in HCl 6N (2 mL) and dioxane (2 mL) was stirred at RT for 18h. At 0°C, the mixture was basified with K_2CO_3 and was extracted with EtOAc and CH_3OH. The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated. The crude was purified by flash chromatography over silica gel (15-40 µm, 12 g, $CH_2Cl_2/CH_3OH/NH_4OH$: 90/10/0.5). The pure fractions were collected and concentrated under reduced pressure to give 23 mg. The compound was taken up in diethylether, the precipitate was filtered off and dried to give 15 mg (40% yield) of compound 3 (as a mixture of two isomers E/Z 70/30).

Overall Scheme in the preparation of final products: method 4



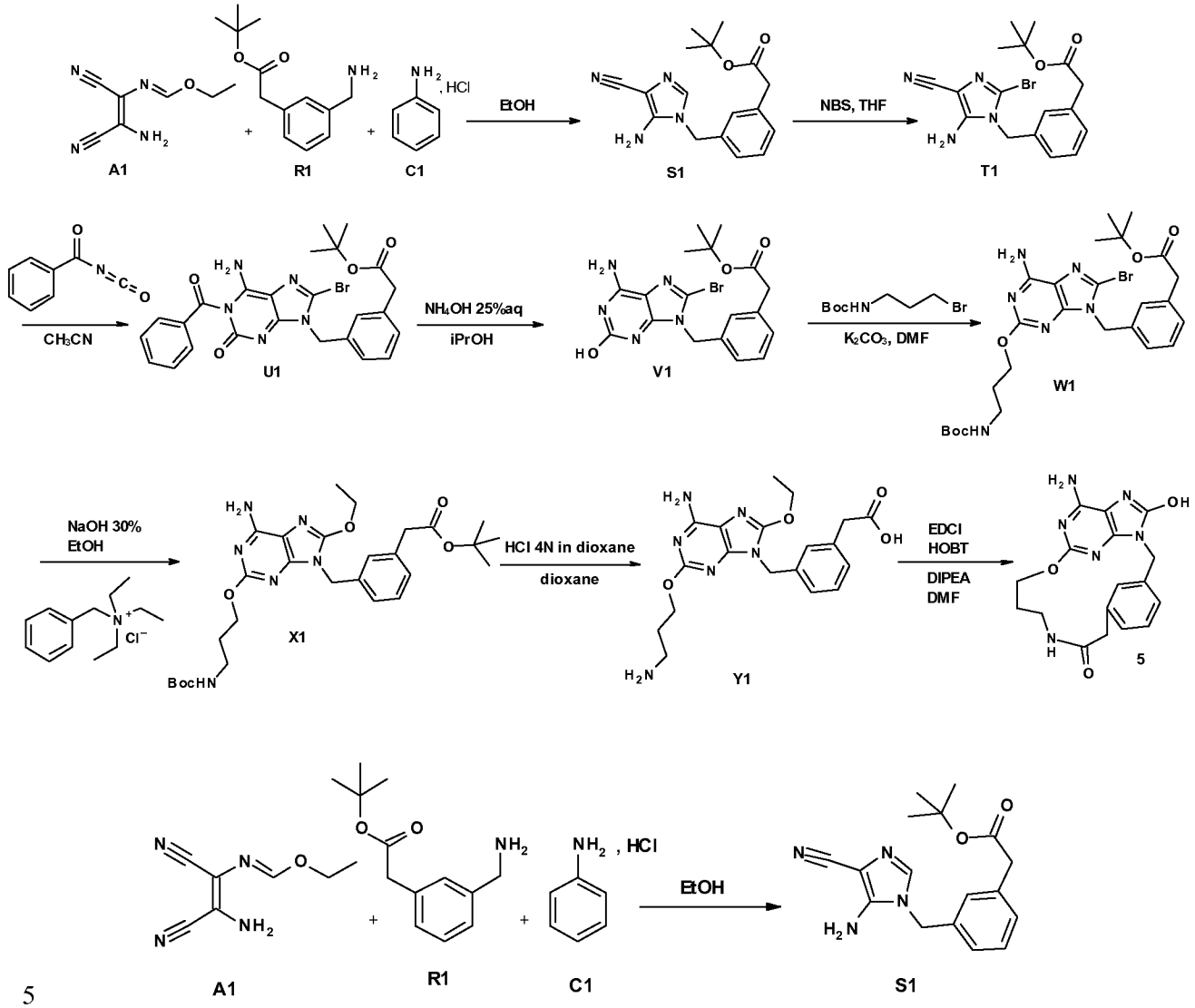
Synthesis of intermediate Q1

A mixture of P1 (70 mg, 0.17 mmol), Pd/C 10% (18 mg, 0.02 mmol) in CH_3OH (5 mL) was hydrogenated under an atmospheric pressure of H_2 for 4h. The catalyst was removed by filtration through a pad of celite®. The celite® was washed with CH_3OH and the filtrate was evaporated. The crude was purified by flash chromatography over silica gel (15-40 µm, 10 g, $CH_2Cl_2/CH_3OH/NH_4OH$: 96/4/0.5). The pure fractions were collected and concentrated under reduced pressure to give 50 mg (71% yield) of intermediate Q1.

Synthesis of final compound 4

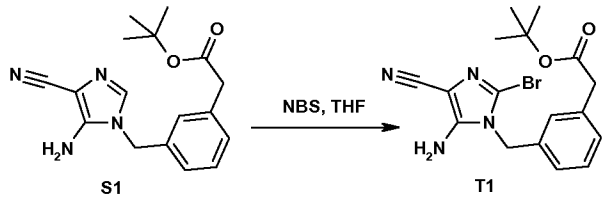
Q1 (50 mg, 0.12 mmol) in HCl 6N (1 mL) and dioxane (1 mL) was stirred at RT for 18h. The precipitate was filtered off, washed with dioxane and dried to give 38 mg (71% yield) of compound 4 (1HCl, $1H_2O$).

Overall Scheme in the preparation of final products: method 5



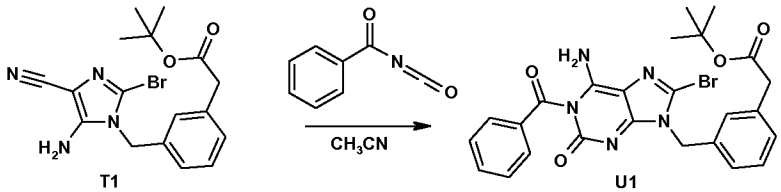
Synthesis of intermediate S1

At 10°C, R1 (7.70 g, 34.79 mmol) in EtOH (30 mL) was added drop wise to a mixture of A1 (5.44 g, 33.14 mmol), C1 (68 mg, 0.53 mmol) in EtOH (25 mL). The mixture was stirred at RT overnight. 60 mL of NaOH 1N was added drop wise and the mixture was stirred at RT for 1h. The mixture was extracted with CH_2Cl_2 (3 times). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and the solvent was evaporated. The crude was purified by chromatography over silica gel (Irregular SiOH 20-45 µm; mobile phase (0.1% NH_4OH, 98% CH_2Cl_2, 2% CH_3OH). The pure fractions were collected and concentrated under reduced pressure to give 5.1 g (49% yield) of intermediate S1.



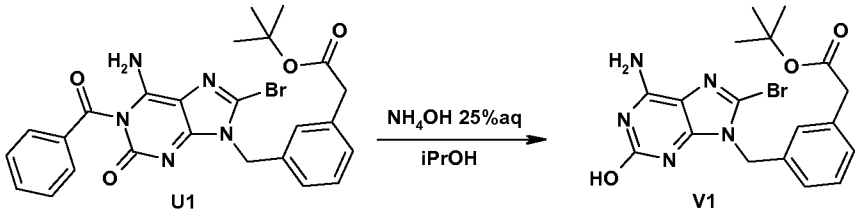
Synthesis of intermediate T1

At 10°C, under a N_2 flow, N-bromosuccinimide (2.90 g, 16.33 mmol) was added portion wise to a mixture of S1 (5.1 g, 16.33 mmol) in THF (100 mL). The mixture was stirred for 10 min at 10°C. The mixture was poured into a solution of $NaHCO_3$ 10% in water and EtOAc. The layers were decanted. The organic layer was dried over $MgSO_4$, filtered and solvent was evaporated. The crude was purified by flash chromatography over silica gel (15-40 µm, 80 g, CH_2Cl_2/CH_3OH 99-1). The pure fractions were collected and concentrated under reduced pressure to give 3.75 g (59% yield) of intermediate T1.



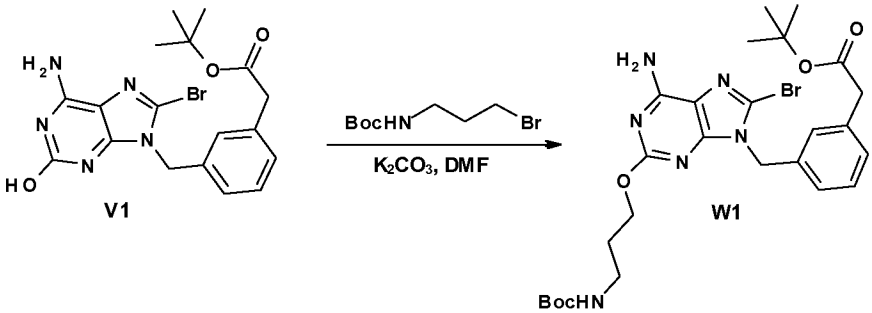
Synthesis of intermediate U1

Benzoyl isocyanate (7.05 g, 47.92 mmol) was added to a mixture of T1 (3.75 g, 9.58 mmol) in CH_3CN (80 mL) under stirring at RT. The mixture was stirred at RT overnight. The solvent was evaporated, the residue was dissolved in 2-propanol/25% aqueous NH_3 1:1 (200 mL) and the resulting solution was stirred at RT for 72h. The solvent was evaporated and the resulting mixture was poured into water, neutralized with diluted HCl and extracted with EtOAc. The layers were filtered through a pad of celite®, the celite® was washed with EtOAc. The filtrate was decanted. The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated. The crude compound was purified by flash chromatography over silica gel (15-40 µm, 80 g , $CH_2Cl_2/CH_3OH/NH_4OH$: 98/2/0.1). The pure fractions were collected and concentrated under reduced pressure to give 1.70 g (33% yield) of intermediate U1.



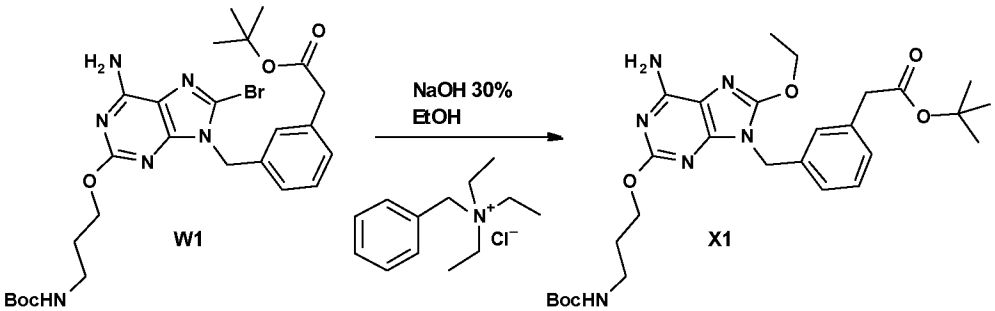
Synthesis of intermediate V1

A mixture of U1 (1.6 g, 2.97 mmol) in NH_4OH 25% (160 mL) and iPrOH (160 mL) was stirred at RT for 72h. iPrOH was evaporated and water was added. The mixture was extracted with EtOAc. A precipitate appeared between the 2 phases. The precipitate was filtered off and dried to give 880 mg (68% yield) of intermediate V1. The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated to give 680 mg of intermediate U1.



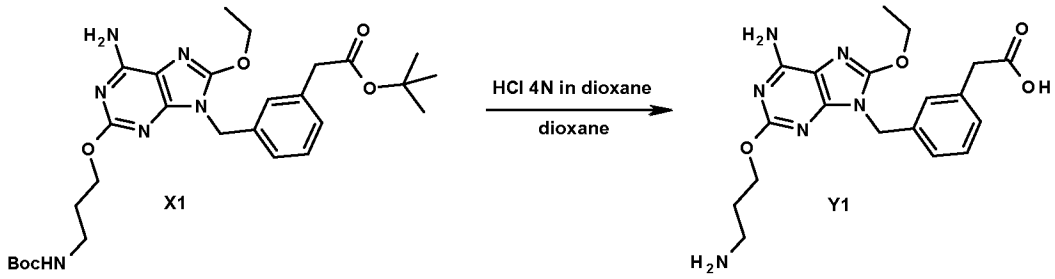
Synthesis of intermediate W1

A mixture of V1 (520 mg, 1.20 mmol), tert-butyl N-(3-bromopropyl)carbamate (570 mg, 2.40 mmol) and K_2CO_3 (496 mg, 3.59 mmol) in DMF (20 mL) was stirred at 80°C for 5h. After cooling down to RT, the mixture was poured into water and was extracted with EtOAc. The organic layer was washed with water, brine, dried over $MgSO_4$, filtered and the solvent was evaporated to give 800 mg (>100% yield) of intermediate W1. The crude compound was used directly in the next step.



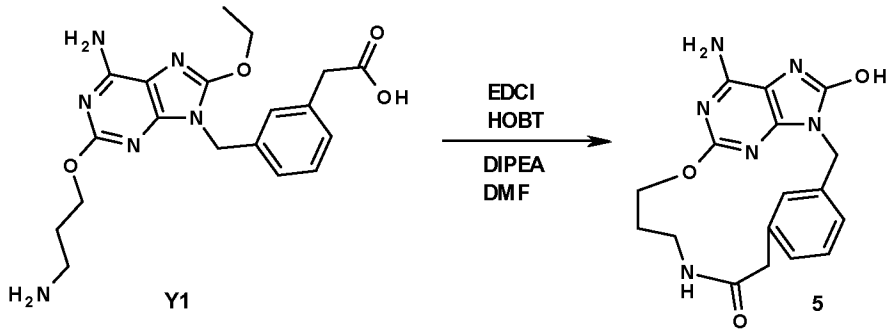
Synthesis of intermediate X1

A mixture of W1 (0.60 g, 1.01 mmol), benzyltriethylammonium chloride (11.5 mg, 0.05 mmol) in NaOH 30% (15 mL) and EtOH (15 mL) was stirred at 60°C for 4h. The mixture was half-concentrated. The pH was adjusted to 5 with HCl 3N. The mixture was extracted with EtOAc (twice). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated to give 500 mg (98% yield) of intermediate X1.



Synthesis of intermediate Y1

At 0°C, HCl 4N in dioxane (1.25 mL, 4.99 mmol) was added drop wise to a mixture of X1 (0.50 g, 1 mmol) in dioxane (2.5 mL). The mixture was stirred at RT for 12h. The mixture was evaporated until dryness to give 450 mg (>100% yield) of intermediate Y1. The crude compound was used without any further purification in the next step.

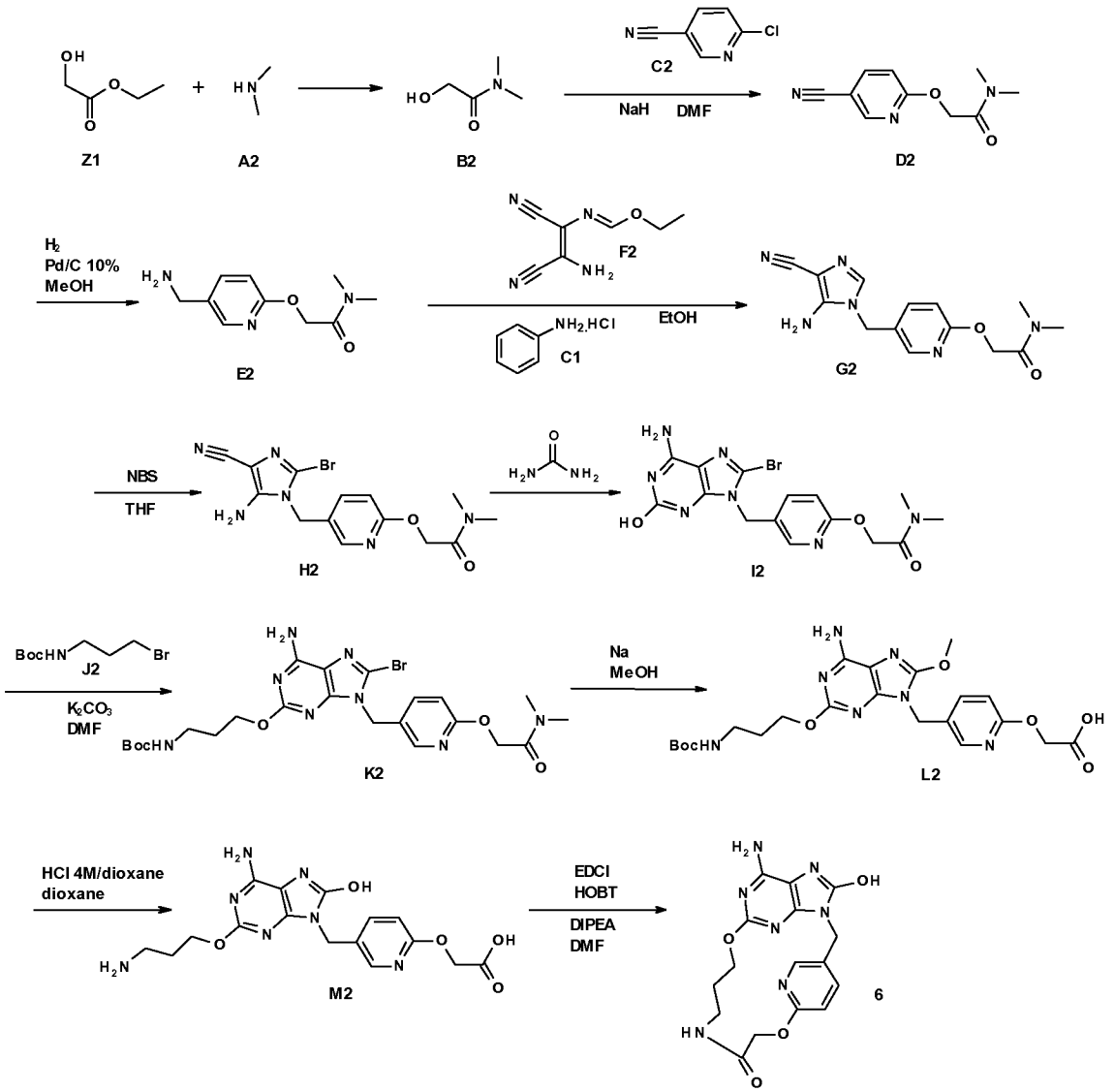


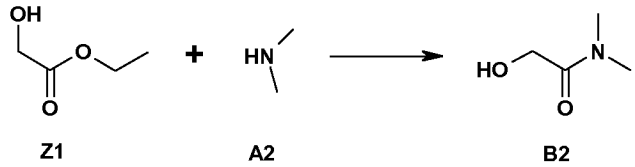
Synthesis of final compound 5

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (520 mg, 2.72 mmol) and 1-hydroxybenzotriazole (367 mg, 2.72 mmol) were slowly added to a mixture of Y1 (370 mg, 0.91 mmol), diisopropylethylamine (0.78 mL, 4.53 mmol) in DMF (270 mL).The mixture was stirred at RT for 24h. The solvent was evaporated until dryness. The residue was taken up in CH_2Cl_2-CH_3OH (90-10) and was washed with water. A precipitate appeared in the decantation funnel. The precipitate was filtered off to give 103 mg. This precipitate was taken up in hot EtOH, stirred at reflux for 1h, cooled to RT and filtered off. The crude was purified by reverse phase on (X-Bridge-

C18 5 µm 30*150 mm), mobile phase (gradient from 75% NH_4HCO_3 0.5% pH10 buffer, 25% CH_3OH to 0% NH_4HCO_3 0.5% pH10 buffer, 100% CH_3OH). The pure fractions were collected and concentrated under reduced pressure to give 8 mg (pure) and 50 mg (crude). The crude was purified by reverse phase on (X-Bridge-C18 5 µm 30*150 mm), mobile phase (gradient from 90% trifluoroacetic acid 0.05%, 10% CH_3OH to 0% trifluoroacetic acid 0.05%, 100% CH_3OH). The pure fractions were collected and concentrated under reduced pressure to give 20 mg. The 2 fractions (8 mg and 20 mg) were combined, taken up in dioxane and CH_3CN and 0.50 mL of HCl 4N in dioxane was added. The mixture was stirred at RT for 2h. The precipitate was filtered off and dried to give 28 mg (7% yield) of compound 5 (HCl salt).

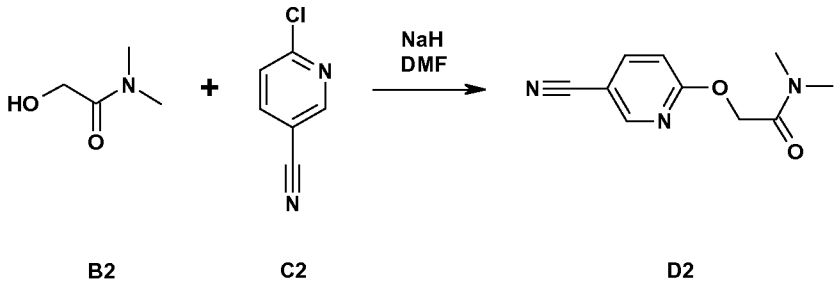
Overall Scheme in the preparation of final products: method 6





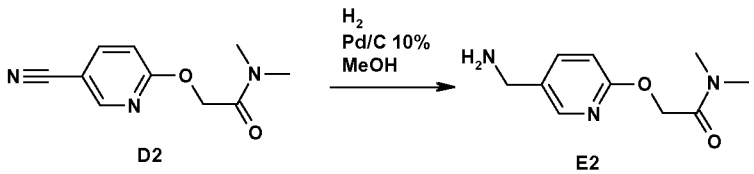
Synthesis of intermediate B2

A solution of ethyl glycolate (10.0 g, 96.06 mmol) in dimethylamine (40% solution in water) (100 mL) was stirred at RT for 16h and concentrated under vacuum. The residue was taken up in EtOH and concentrated again. The cycle was performed 3 times to give 9.75 g (98% yield) of intermediate B2.



Synthesis of intermediate D2

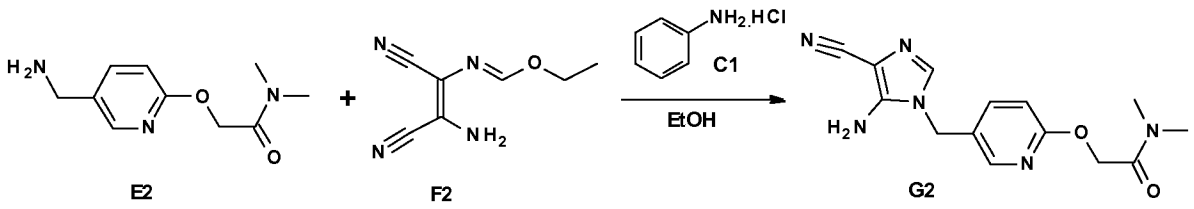
At 0°C under a N_2 flow, NaH (2.16 g, 54.13 mmol) was added to a solution of B2 (4.09 g, 39.69 mmol) in DMF (36 mL) at RT. The mixture was stirred at RT for 30 min and 6-chloroniconitrile C2 (5.0 g, 36.09 mmol) was added (exothermic) and the mixture was stirred at RT for 16h. A 10% aqueous solution of $NaHCO_3$ (150 mL) was added, then brine solution was added. The aqueous layer was extracted with EtOAc (twice). The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated to give 7.0 g (95% yield) of intermediate D2.



Synthesis of intermediate E2

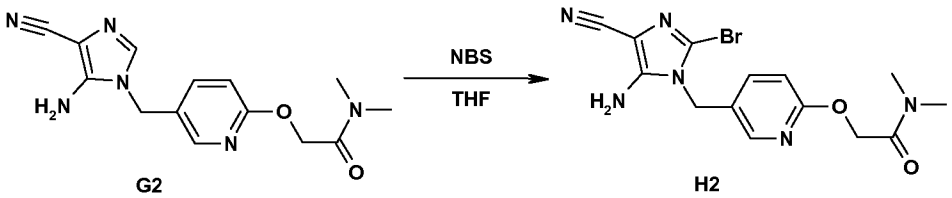
Pd/C 10% (2.0 g) was added to a solution of D2 (7.0 g, 34.11 mmol) in MeOH (140 mL). The reaction mixture was stirred for 16h at RT under H_2 atmosphere (1 atm). Pd/C 10% (1.5 g, 0.04 mmol) was added and the reaction mixture was stirred with the same conditions for 4h. The catalyst was filtered over a pad of celite®. The celite® was washed with CH_3OH and the filtrate was concentrated under vacuum. This fraction was combined with another batch before purification.

The residue was purified by flash chromatography over silica gel (15-40μm, 120 g, $CH_2Cl_2/CH_3OH/NH_4OH$: 92/8/0.5) The pure fractions were collected and concentrated under reduced pressure to give 2.2 g (27% yield) of intermediate E2.



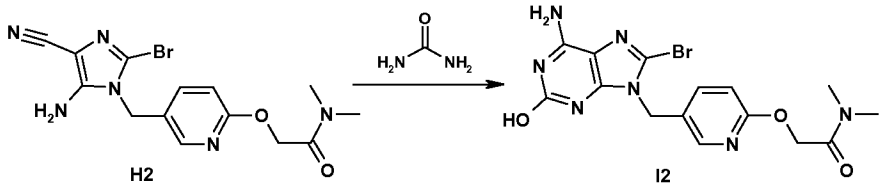
Synthesis of intermediate G2

E2 (2.2 g, 10.51 mmol) in EtOH (10 mL) was added drop wise to a solution of F2 (1.64 g, 10.01 mmol) and aniline hydrochloride (20 mg, 0.16 mmol) in EtOH (10 mL) at 10°C. The reaction mixture was stirred at RT for 20h. An aqueous solution of NaOH 1M (25 mL) was added drop wise to the solution at 10°C and the resulting mixture was stirred at RT for 1h. The precipitate was filtered off, washed with a minimum of cold EtOH and dried under vacuum to give 2.25 g (75% yield) of intermediate G2. G2 was directly used in the next step without further purification.



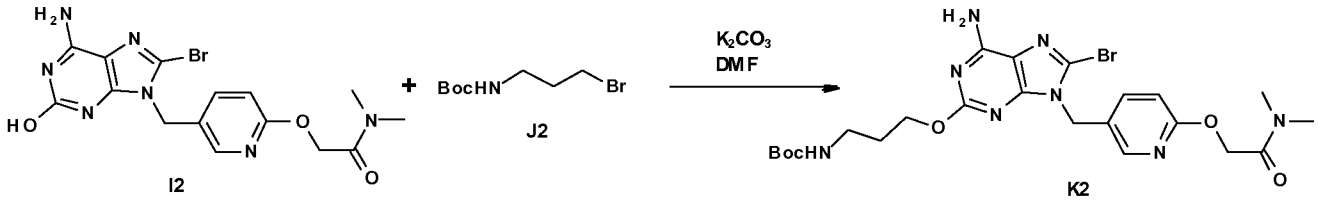
Synthesis of intermediate H2

A solution of N-bromosuccinimide (1.47 g, 8.24 mmol) in THF (50 mL) was added drop wise over 25 min to a solution of G2 (2.25 g, 7.49 mmol) in THF (80 mL) at 0°C. The mixture was stirred at 0°C for 30 min and then at RT for 45 min. The mixture was taken up in CH_2Cl_2, washed with a saturated aqueous solution of $NaHCO_3$, then with brine, dried over $MgSO_4$, filtered and concentrated. The crude compound was crystallized from CH_3CN, the precipitate was filtered off and dried to give 0.79 g (27% yield) of intermediate H2. The filtrate was evaporated and the residue was purified by flash chromatography over silica gel (15-40 μm, 50 g, $CH_2Cl_2/CH_3OH/NH_4OH$: 97/3/0.1). The pure fractions were collected and concentrated to give 0.71 g (25% yield) of intermediate H2.



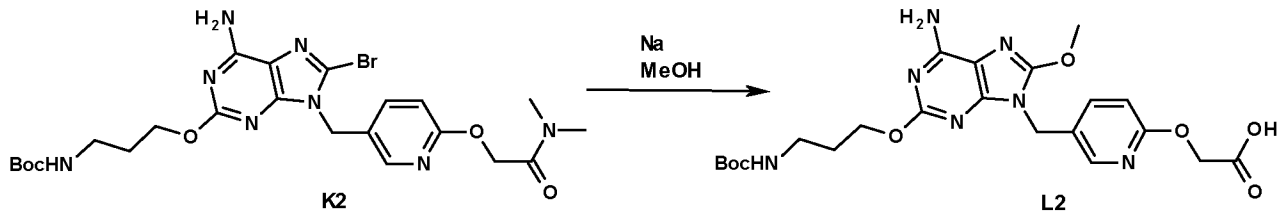
Synthesis of intermediate I2

A mixture of H2 (1.4 g, 3.69 mmol) in urea (13.3 g, 221.51 mmol) was heated at 160°C for 6h. The mixture was cooled to RT and water was added. The precipitate was triturated and filtered off, washed with water and dried under vacuum at 60°C to give 1.05 g (67% yield) of intermediate I2.



Synthesis of intermediate K2

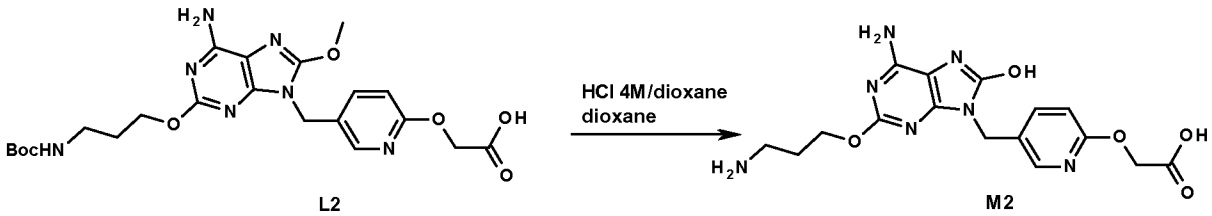
A mixture of I2 (1.23 g, 2.91 mmol), tert-butyl-N-(3-bromopropyl)carbamate J2 (1.04 g, 4.37 mmol), K_2CO_3 (604 mg, 4.37 mmol) in DMF (20 mL) was stirred at 50°C for 12h. The solvent was evaporated. The residue was taken up in EtOAc. The organic layer was washed with water, dried over $MgSO_4$, filtered and the solvent was evaporated. The residue was purified by flash chromatography over silica gel (15-40 µm, 80 g, $CH_2Cl_2/CH_3OH/NH_4OH$: 95/5/0.5). The pure fractions were collected and concentrated to give 0.97 g (57% yield) of intermediate K2.



Synthesis of intermediate L2

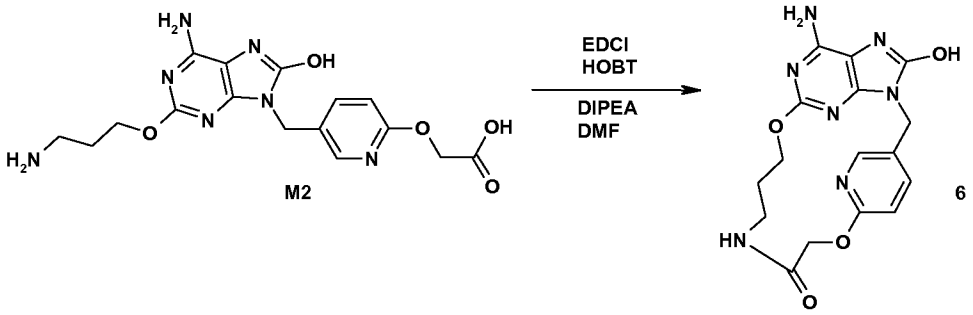
At RT, sodium (446 mg, 19.42 mmol) was added to MeOH (30 mL). The mixture was stirred until sodium was in solution (exothermic). K2 (750 mg, 1.29 mmol) was added and the mixture was stirred at 50°C for 16h under a N_2 flow. Water was added and the pH was adjusted to 5-6. The aqueous layer was extracted with EtOAc. The organic

layer was dried over $MgSO_4$, filtered and the solvent was evaporated to give 0.54 g (83% yield) of intermediate L2.



Synthesis of intermediate M2

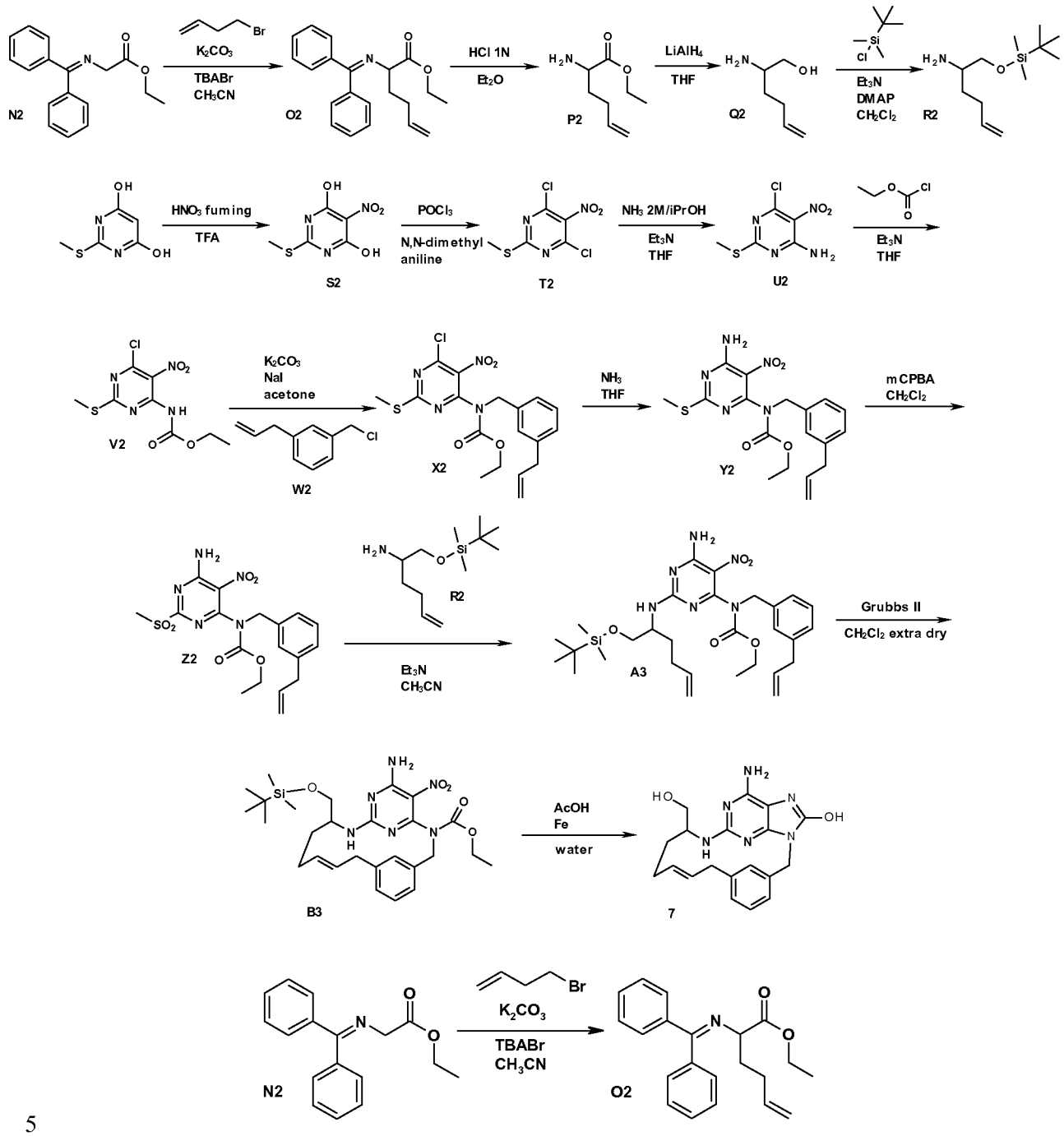
At 0°C, HCl 4M in dioxane (2.68 mL, 10.73 mmol) was added drop wise to a mixture of L2 (0.54 g, 1.07 mmol) in dioxane (20 mL). The mixture was stirred at RT for 12h. The mixture was evaporated until dryness to give 0.74 g (>100% yield). The crude compound was used without any further purification in the next step.



Synthesis of final compound 6

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (675 mg, 3.52 mmol) and hydroxybenzotriazole (476 mg, 3.52 mmol) were slowly added to a mixture of M2 (500 mg, 1.17 mmol), diisopropylethylamine (1.01 mL, 5.87 mmol) in DMF (360 mL). The mixture was stirred at RT for 24h. The solvent was evaporated until dryness. The residue was taken up in water. The precipitate was filtered off, washed with water and dried. The residue was purified by reverse phase chromatography on (X-Bridge-C18 5 µm 30*150 mm), mobile phase (gradient from 90% trifluoroacetic acid 0.05%, 10% MeOH to 0% trifluoroacetic acid 0.05%, 100% MeOH). The pure fractions were collected and concentrated to give 75 mg of compound 6 and 100 mg (crude precipitate). The pure fraction (75 mg) was taken up in dioxane and CH_3CN and 1mL of HCl 4N in dioxane was added. The mixture was stirred at RT for 2h. The precipitate was filtered off and dried to give 57 mg (12% yield) of compound 6 (HCl salt).

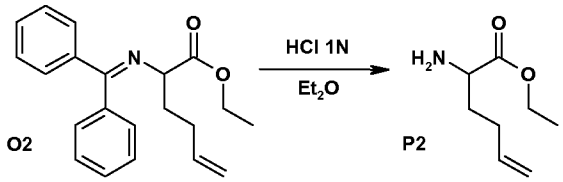
Overall Scheme in the preparation of final products: method 7



Synthesis of intermediate O2

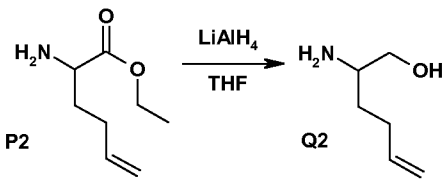
4-Bromo-1-butene (8.6 mL, 84.17 mmol) was added to a mixture of N2 (15 g, 56.11 mmol), K_2CO_3 (23.3 g, 168.33 mmol), tetrabutylammonium bromide (1.81 g, 5.61 mmol) in CH_3CN (75 mL). The resulting mixture was stirred at reflux for 18h. The mixture was cooled to RT. The solvent was evaporated. Water and EtOAc were

added. The layers were decanted. The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated. The residue was purified by flash chromatography over silica gel (15-40 µm, 120 g, Heptane/EtOAc: 93-7). The pure fractions were collected and concentrated to give 14.8 g (82% yield) of intermediate O2.



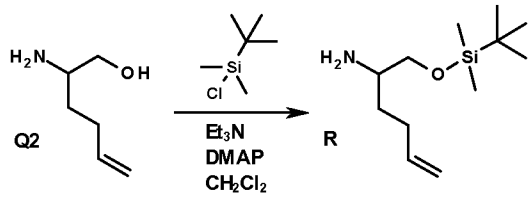
Synthesis of intermediate P2

At 0°C, HCl 1N (120 mL, 119.47 mmol) was added drop wise to a mixture of O2 (19.2 g, 59.74 mmol) in Et_2O (250 mL). The mixture was stirred at 0°C for 30min then stirred vigorously at RT for 12h. The resulting layers were decanted. The aqueous layer was basified until pH 8 with K_2CO_3 (powder) then extracted with Et_2O (3 times). The aqueous layer was saturated with K_2CO_3 then extracted again with CH_2Cl_2 (2 times). The organic layers were combined, dried over $MgSO_4$, filtered and the solvent was evaporated to give 7.9 g (84% yield) of intermediate P2.



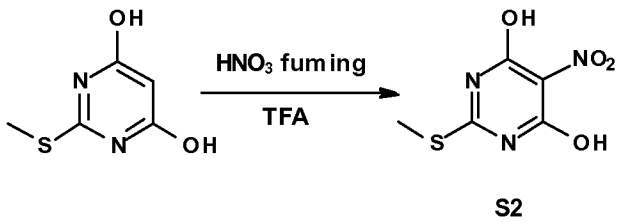
Synthesis of intermediate Q2

Under a N_2 flow, $LiAlH_4$ (4.4 g, 114.50 mmol) was suspended into THF (150 mL) at 10°C. P2 (9 g, 57.25 mmol) in THF (150 mL) was added drop wise. The reaction was allowed to warm to RT and was stirred at RT for 30 min. The reaction was cooled to -10°C and was quenched by the addition of water (5 mL), NaOH 3N (5 mL) and again water (14 mL). The suspension was filtered through a pad of celite®. The celite® was washed with THF and the filtrate was concentrated under vacuum. The residue was taken up in EtOAc, dried over $MgSO_4$, filtered and the solvent was evaporated to give 5.3 g (80 % yield) of intermediate Q2.



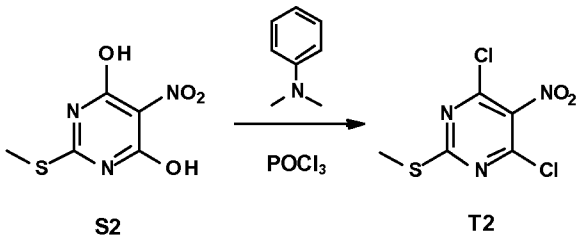
Synthesis of intermediate R2

At 0°C, tert-butyldimethylsilyl chloride (1.31 g, 8.68 mmol) was added to a mixture of Q2 (1.0 g, 8.68 mmol), Et_3N (1.33 mL, 9.55 mmol), 4-dimethylaminopyridine (106 mg, 0.87 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred at RT for 24h. Water was added and the layers were decanted. The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated to give 1.70 g (85% yield) of intermediate R2.



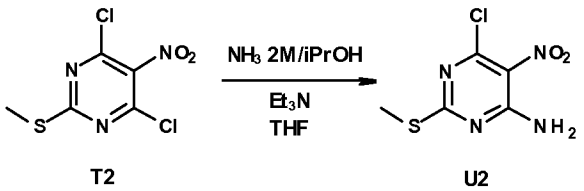
Synthesis of intermediate S2

A solution of 4,6-dihydroxy-2-methylthiopyrimidine (50 g, 316.09 mmol) in trifluoroacetic acid (210 mL) was stirred at RT for 30 min. The mixture was cooled to 5°C then HNO_3 fuming (19.5 mL, 426.73 mmol) was added drop wise at 5°C. The temperature was maintained at 10-15°C during the addition. The ice bath was removed and when the temperature reached 20°C, a violent exothermic event occurred (from 20°C to 45°C in 5 seconds). The mixture was stirred at RT for 16h. The mixture was poured into a mixture of water and ice. The precipitate was filtered off and washed with water. The precipitate was dried under vacuum at 50°C to give 42 g (65% yield) of intermediate S2. This intermediate was directly used in the next step without any further purification.



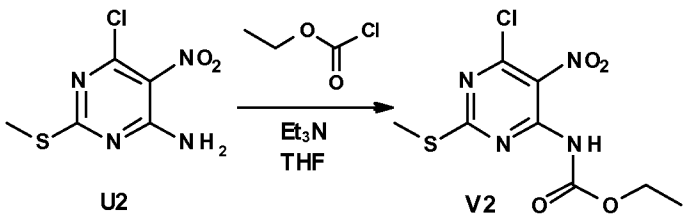
Synthesis of intermediate T2

N,N-dimethylaniline (76.7 mL, 0.61 mol) was added drop wise to $POCl_3$ (93.7 mL, 1.01 mol) at 0°C. S2 (41 g, 201.79 mmol) was added portion wise at 0°C then the mixture was warmed to 100°C for 2h. The solution was concentrated under vacuum and the residual $POCl_3$ was removed by azeotropic evaporation with toluene (3 times). The resulting oil was taken up in a solution of CH_2Cl_2-Heptane (70-30) and was filtered through a glass filter of SiO_2. The filtrate was concentrated and the residue was purified by preparative LC on (Irregular SiOH 20-45 µm 1000 g DAVISIL), mobile phase (80% Heptane, 20% CH_2Cl_2). The pure fractions were collected and concentrated to give 37.8 g (78% yield) of intermediate T2.



Synthesis of intermediate U2

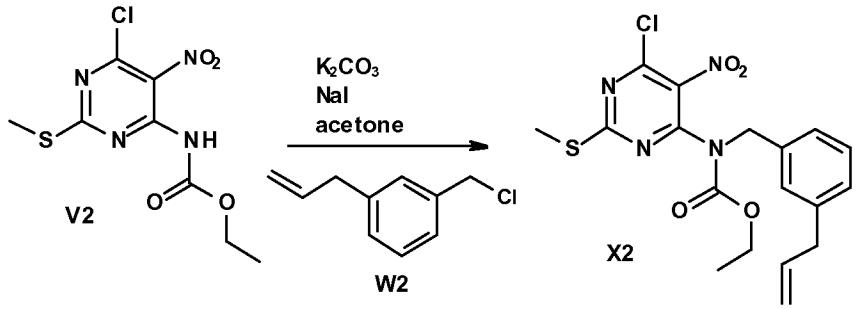
A solution of NH_3 2M in iPrOH (115 mL, 229.31 mmol) was added drop wise to a solution of T2 (36.7 g, 152.87 mmol) and Et_3N (23.4 mL, 168.16 mmol) in THF (360 mL) (the temperature was maintained at RT with an ice-water bath during the addition). The reaction mixture was stirred at RT for 5h. The mixture was evaporated to dryness. Water and EtOAc were added to the residue. The layers were separated and the aqueous layer was extracted with EtOAc (twice). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure to give 34.5 g (100% yield) of intermediate U2.



Synthesis of intermediate V2

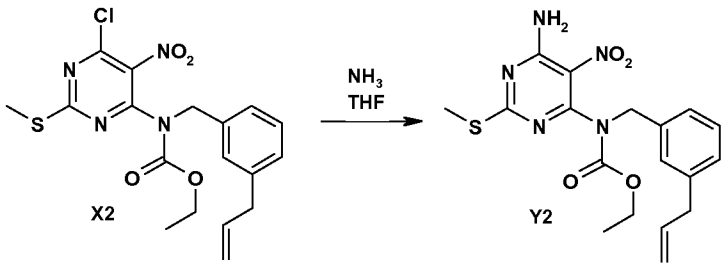
Ethyl chloroformate (13.5 mL, 138.90 mmol) was added to a solution of U2 (39.8 g, 126.27 mmol) and Et_3N (26.5 mL, 189.40 mmol) in THF (1300 mL). The mixture was stirred at RT for 6h and the solvent was partially evaporated under reduced pressure. The residue was taken up in CH_2Cl_2 and water. The layers were separated; the aqueous layer was extracted with CH_2Cl_2 (twice). The combined organic layers were dried over

$MgSO_4$, filtered and the solvent was removed under reduced pressure. The residue was purified by preparative LC on (Irregular SiOH 20-45 µm 1000 g DAVISIL), mobile phase (gradient from 85% heptane, 15% AcOEt to 80% heptane, 20% AcOEt). The pure fractions were collected and concentrated to give 35 g (95% yield) of intermediate V2.



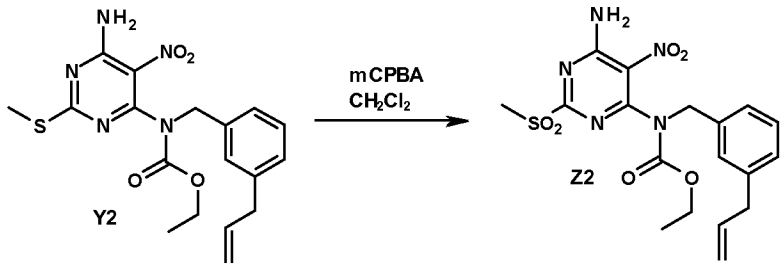
Synthesis of intermediate X2

A mixture of V2 (5.0 g, 17.08 mmol), W2 (2.85 g, 17.08 mmol), K_2CO_3 (3.54 g, 25.6 mmol) and NaI (2.56 g, 17.08 mmol) in acetone (200 mL) were stirred at RT for 48h. The mixture was filtered off and the filtrate was evaporated to dryness. The residue was purified by flash chromatography over silica gel (15-40 µm, 220 g, CH_2Cl_2/heptane 50-50). The pure fractions were collected and concentrated to give 7.4 g (100% yield) of intermediate X2.



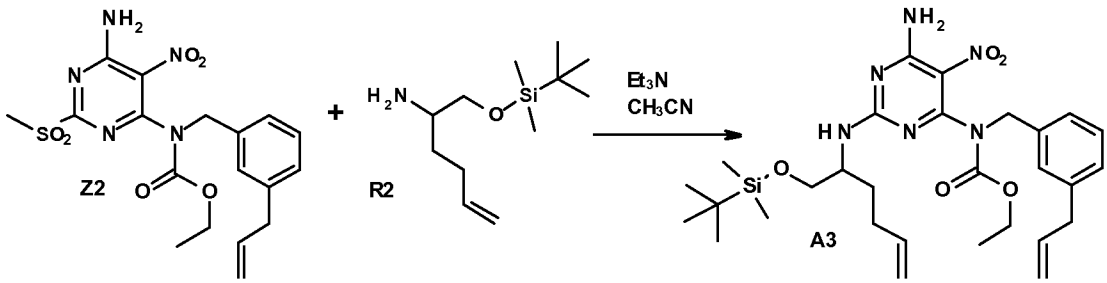
Synthesis of intermediate Y2

A solution of X2 (7.20 g, 17.03 mmol) and NH_3 30% in water (100 mL) in THF (100 mL) was stirred at RT for 2h. Solvent was removed under reduced pressure. The residue was suspended in water and extracted with CH_2Cl_2. The organic layer was washed with water and dried over $MgSO_4$, filtered and the solvent was evaporated under vacuum to give 7.1 g (100% yield) of intermediate Y2 (a yellow oil). This intermediate was directly used in the next step.



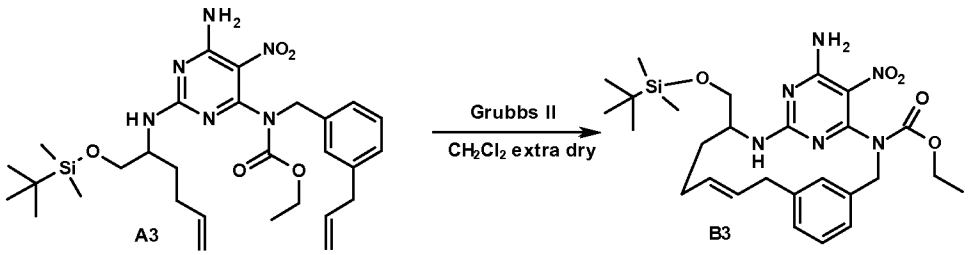
Synthesis of intermediate Z2

3-chloroperoxybenzoic acid (2.44 g, 9.91 mmol) in CH_2Cl_2 (20 mL) was added drop wise to a solution of Y2 (2.0 g, 4.96 mmol) in CH_2Cl_2 (100 mL) at RT. The mixture was stirred at RT for 20h. An aqueous solution of $Na_2S_2O_3$ (5eq) was added to the mixture. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (twice). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to give 2.70 g (>100% yield) of intermediate Z2. This intermediate was directly used in the next step without further purification.



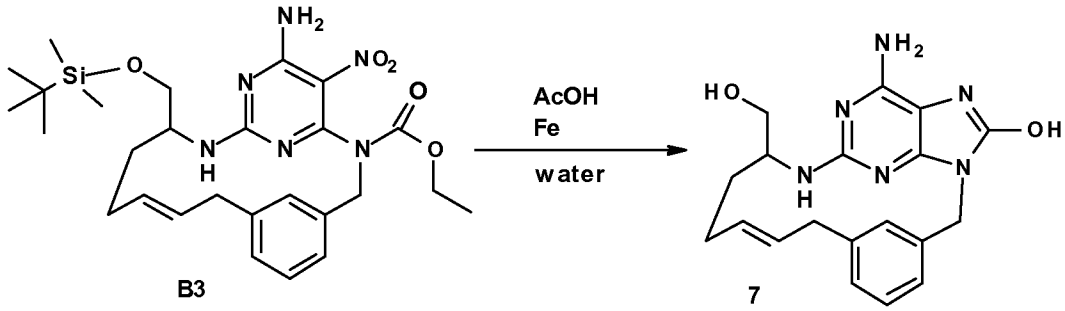
Synthesis of intermediate A3

A mixture of Z2 (2.16 g, 4.96 mmol), R2 (1.70 g, 7.44 mmol) and Et_3N (1.04 mL, 7.44 mmol) in CH_3CN (70 mL) was stirred at RT for 2h. Water was added and the mixture was extracted with EtOAc (twice). The organic layer was washed with brine, dried over $MgSO_4$, filtered and the solvent was evaporated. The residue was purified by flash chromatography over silica gel (15-40 µm, 90 g, CH_2Cl_2/CH_3OH/99.5-0.5). The pure fractions were collected and concentrated to give 1.10 g (38% yield) of intermediate A3.



Synthesis of intermediate B3

A3 (1.05 g, 1.80 mmol) was added to CH_2Cl_2 extra dry (230 mL) and the resulting mixture was degassed by bubbling N_2 through the solution for 30 min. Grubbs catalyst 2nd generation (153 mg, 0.18 mmol) was added in one portion and the mixture was stirred at RT under N_2 flow for 24h. The mixture was concentrated. The residue was purified by preparative LC on (irregular SiOH 15-40 µm 300 g MERCK), mobile phase (80% heptane, 20% AcOEt). The pure fractions were collected and concentrated to give 0.70 g (70% yield) of intermediate B3.



Synthesis of final compound 7

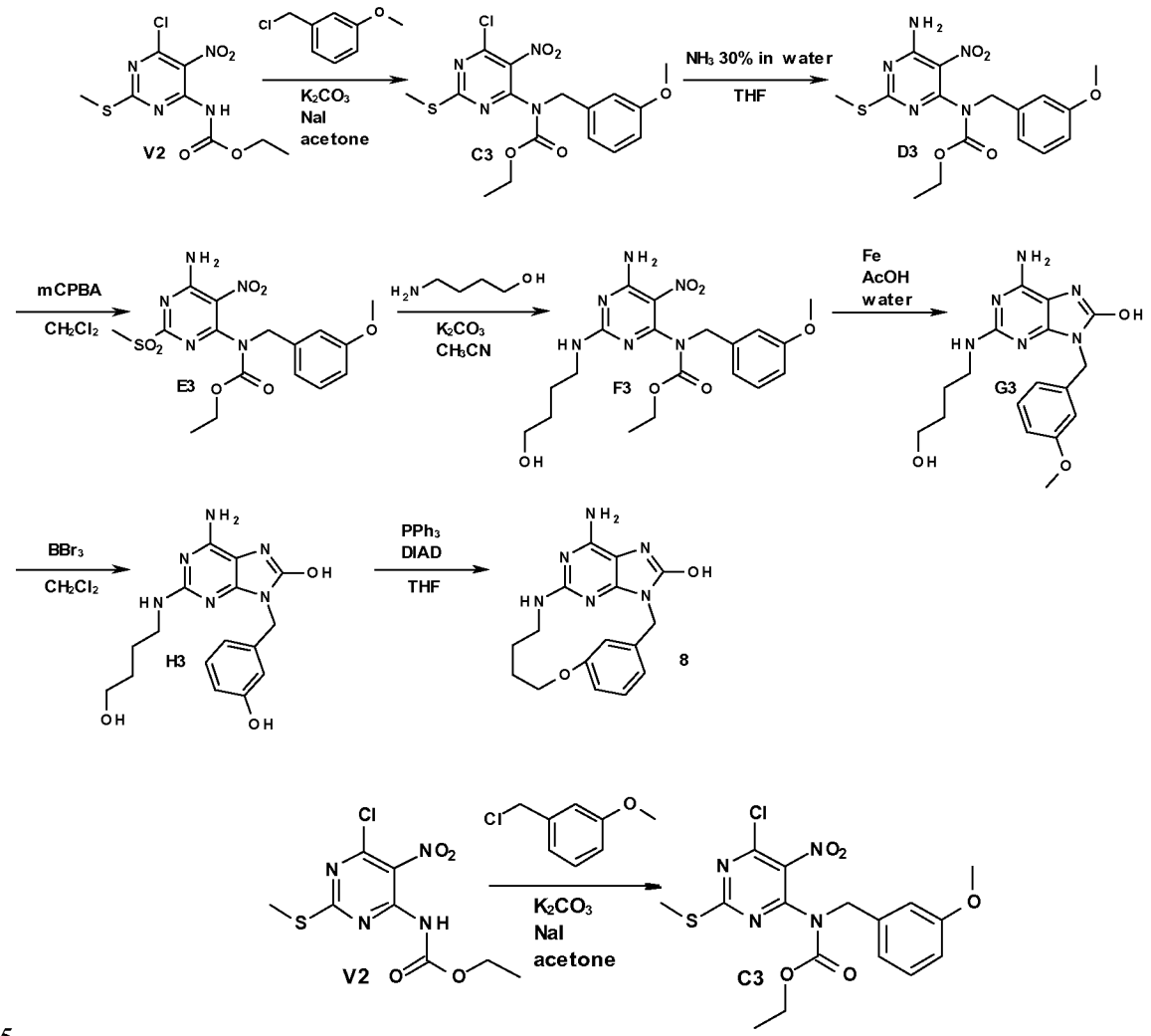
Fe (385 mg, 6.90 mmol) was added to a mixture of B3 (640 mg, 1.15 mmol) in AcOH (6.8 mL) and water (1.36 mL). The mixture was heated at 100°C using one single mode microwave (Biotage Initiator) with a power output ranging from 0 to 400 W for 40 min. The mixture was filtered on a pad of celite® and rinsed with AcOH. The filtrate was concentrated under vacuum and co-evaporated with toluene (twice) to dryness. The residue was taken up in CH_2Cl_2/MeOH/NH_4OH 90-10-0.5. A precipitate was filtered (the precipitate (1.0g) contained expected compound) and the filtrate was evaporated to be purified by chromatography;

The residue (of filtrate) was purified by flash chromatography over silica gel (15-40 µm, 80 g, CH_2Cl_2/CH_3OH/NH_4OH: 90-10-0.5). The pure fractions were collected and evaporated to give 52 mg of fraction 1.

The precipitate previously obtained was purified by chromatography (the compound and SiO_2 were mixed before elution). The residue was purified by flash chromatography over silica gel (15-40 µm, 25 g, CH_2Cl_2/CH_3OH/NH_4OH: 90-10-0.5). The pure fractions were collected and concentrated to give 80 mg of fraction 2.

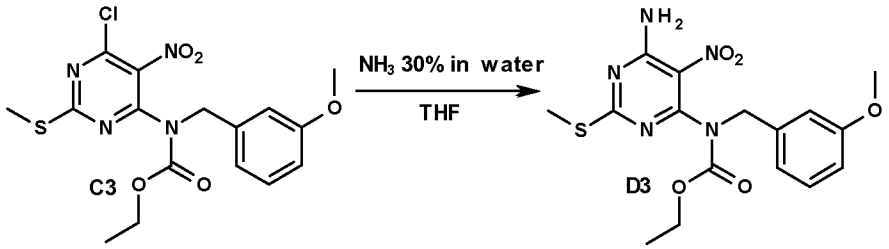
Fraction 1 and fraction2 were combined, and then solidified from CH_3CN to afford 95 mg (23% yield) of compound 7 (E isomer with 3.5% of Z isomer).

Overall Scheme in the preparation of final products: method 8



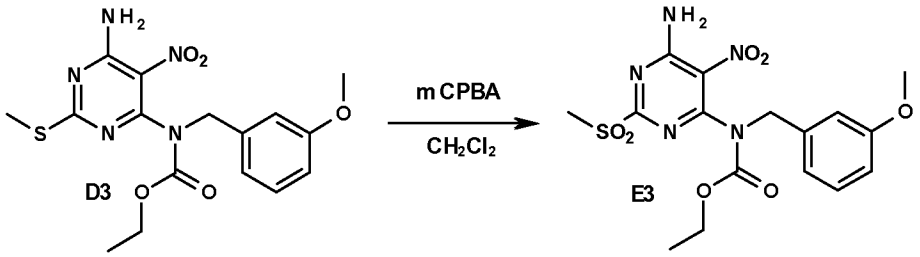
Synthesis of intermediate C3

V2 (1.7 g, 5.8 mmol), 3-methoxybenzyl chloride (0.93 mL, 6.4 mmol), K_2CO_3 (2 g, 14.5 mmol) and sodium iodide (0.87 g, 5.8 mmol) in acetone (60 mL) were stirred at RT for 16h. The solution was filtered off and the filtrate was evaporated under reduced pressure. The crude product was purified by preparative LC (irregular SiOH 15-40 µm, 80 g Merck, mobile phase heptane/CH_2Cl_2 70/30). The pure fractions were collected and concentrated to give 1.4 g (58% yield) of intermediate C3.



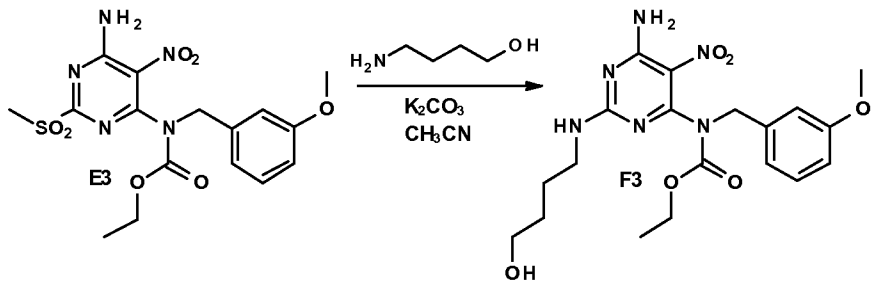
Synthesis of intermediate D3

C3 (1.4 g, 3.4 mmol) was stirred in NH_3 30% in water (30 mL) and THF (30 mL) at RT for 16h. The mixture was concentrated and the residue was dried by azeotropic evaporation with EtOH (twice) to give 1.3 g (97% yield). The crude product was used without further purification in the next step.



Synthesis of intermediate E3

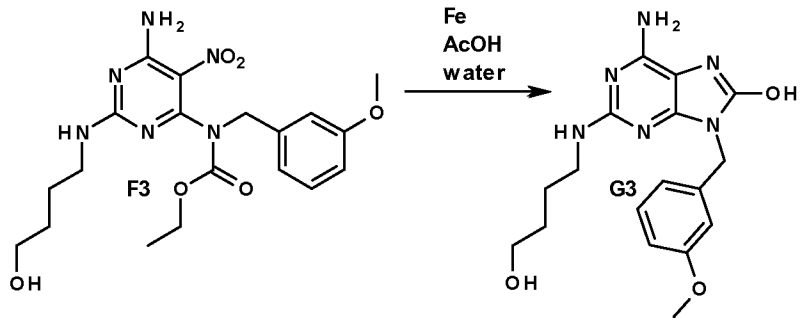
3-chloroperoxybenzoic acid (2.04 g, 8.3 mmol) was added to a solution of D3 (1.3 g, 3.3 mmol) in CH_2Cl_2 (80 mL) at RT. The mixture was stirred at RT for 20h. An aqueous solution of $Na_2S_2O_3$ (2.61 g, 16.52 mmol) was added to the mixture. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (twice). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, filtered and the solvent was evaporated to give 1.4 g (100% yield) of intermediate E3.



Synthesis of intermediate F3

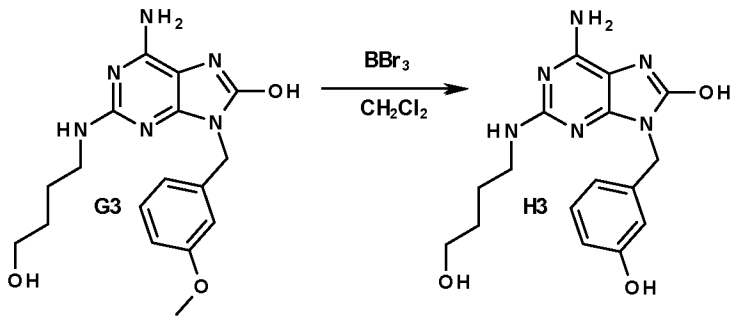
A mixture of E3 (1.4 g, 3.3 mmol), 4-amino-1-butanol (0.45 mL, 3 mmol) and K_2CO_3 (414 mg, 4.9 mmol) in CH_3CN (65 mL) was stirred at 80°C for 1h30. The salts were

filtered and water was added to the filtrate. The mixture was extracted with CH_2Cl_2 (twice). The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated. The crude was purified by preparative LC (irregular SiOH 15-40 µm, 80 g Merck, mobile phase CH_2Cl_2/MeOH/NH_4OH 98/2/0.1). The pure fractions were collected and concentrated to give 1.2 g (84% yield) of intermediate F3.



Synthesis of intermediate G3

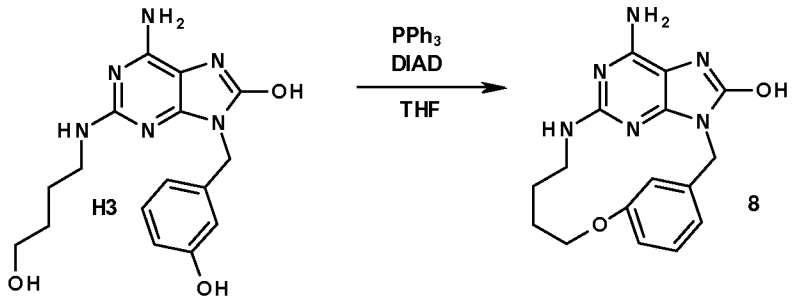
Fe (1.54 g, 27.6 mmol) was added to a mixture of F3 (1.2 g, 2.76 mmol) in AcOH (24 mL) and water (8.6 mL). The mixture was stirred vigorously at RT for 24h. The reaction mixture was concentrated under vacuum and the residue was diluted with EtOAc and water. The mixture was filtered on a pad of celite® and rinsed with EtOAc. The layers were separated and the organic layer was washed with a saturated aqueous solution of $NaHCO_3$ (twice), then brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by chromatography over silica gel column (15-40 µm, 40 g) in CH_2Cl_2/MeOH/NH_4OH (90/10/0.5). The pure fractions were collected and concentrated. This fraction was solidified from CH_3CN/diisopropylether to give 0.70 g (71% yield) of intermediate G3.



Synthesis of intermediate H3

At -60°C, under a N_2 flow, BBr_3 (5.6 mL, 5.6 mmol) was added drop wise to a mixture of G3 (400 mg, 1.1 mmol) in CH_2Cl_2 (40 mL). The mixture was stirred at -60°C for 1h, and then at RT for 12h, under a N_2 flow. 1mL of CH_3OH was added drop wise at 0°C.

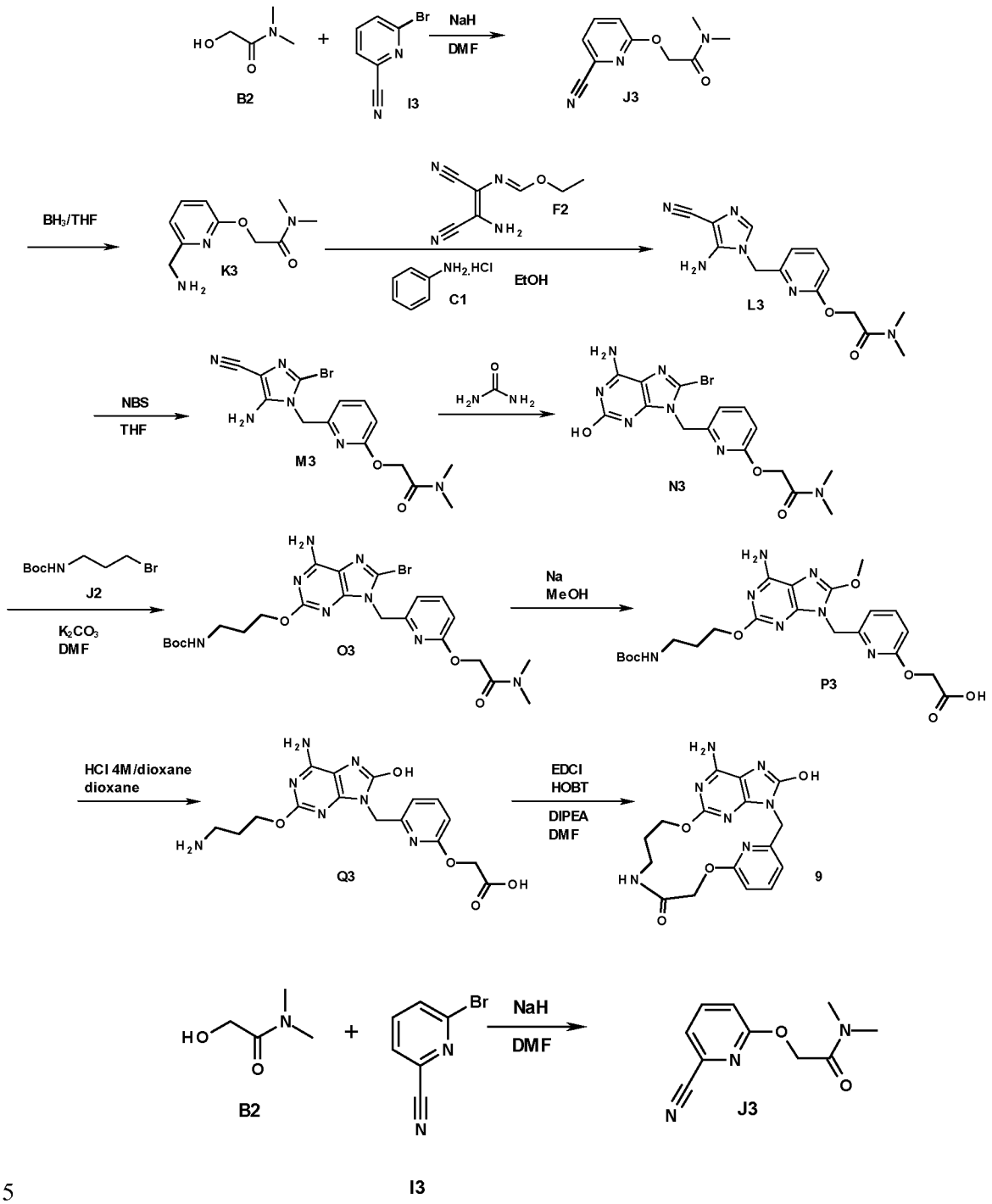
The mixture was then poured into a saturated solution of K_2CO_3 in water. The mixture was extracted with a solution of CH_2Cl_2/MeOH. The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated. The crude compound was purified by chromatography over silica gel column (15-40 µm, 40 g) in CH_2Cl_2/MeOH/NH_4OH (90/10/0.5). The pure fractions were collected and concentrated. The residue was solidified from CH_3CN/diisopropylether to give 265 mg (69% yield) of intermediate H3.



Synthesis of final compound 8

At RT under a N_2 flow, a solution of diisopropylazodicarboxylate (0.27 mL, 1.36 mmol) in THF (5 mL) was slowly added drop wise to a mixture of H3 (235 mg, 0.68 mmol), PPh_3 (358 mg, 1.36 mmol) in THF (50 mL). The mixture was stirred at RT for 6h. The reaction mixture was poured into ice-water and EtOAc was added. The mixture was basified with an aqueous solution of $NaHCO_3$ 10% in water then the organic layer was separated, dried over $MgSO_4$, filtered and solvents were evaporated until dryness. The crude compound was purified by chromatography over silica gel column (15-40 µm, 40 g) in CH_2Cl_2/MeOH/NH_4OH (95/5/0.1). The pure fractions were collected and evaporated. The residue was solidified from CH_3CN/ diisopropylether to give 75 mg (34% yield) of compound 8.

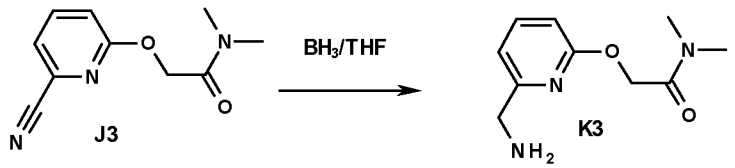
Overall Scheme in the preparation of final products: method 9



Synthesis of intermediate J3

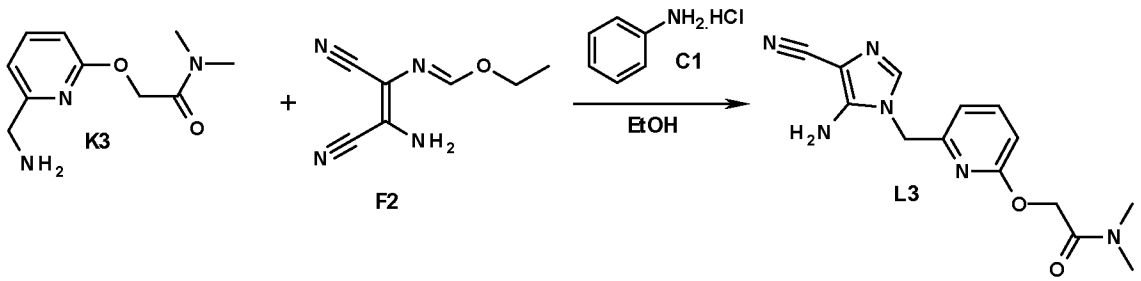
At 0°C under a N_2 flow, NaH (3.28 g, 82 mmol) was added to a solution of B2 (7.32 g, 71 mmol) in DMF (80 mL). The mixture was stirred at RT for 30 min and I3 (10 g, 54.6 mmol) was added (exothermic) and the mixture was stirred at RT for 4h. A 10% aqueous solution of $NaHCO_3$ (150 mL) and then brine (150 mL) were added. The

resulting mixture was extracted with EtOAc (twice). The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated. The residue was taken up in the minimum of AcOEt, the precipitate was filtered off and dried to give intermediate J3 (9.04 g, 81% yield).



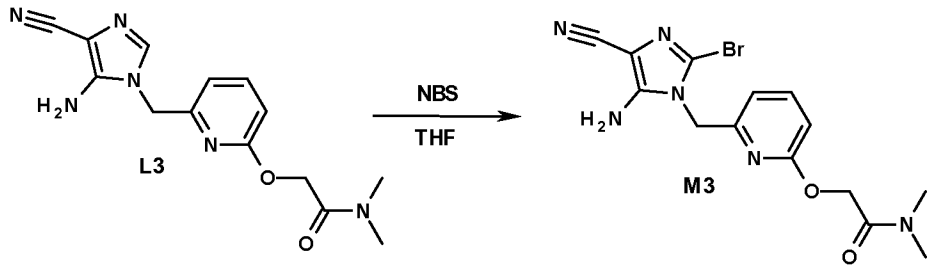
Synthesis of intermediate K3

At 0°C, under a N_2 flow, BH_3/THF (110 mL, 39 mmol) was added drop wise to a solution of J3 (9.0 g, 43.9 mmol) in THF (60 mL). The mixture was stirred at RT for 2h then quenched with HCl 2M and stirred at RT for 12h. The reaction mixture was evaporated until dryness. The residue was taken up in CH_2Cl_2-CH_3OH-NH_4OH 90-10-1. The precipitate was filtered off (minerals) and the filtrate was concentrated. Purification was carried out by flash chromatography over silica gel (15-40 µm, 330 g, CH_2Cl_2/CH_3OH/NH_4OH: 96/4/0.5 to 90/10/0.5). The pure fractions were collected and evaporated to dryness to give intermediate K3 (6.2 g, 73% yield).



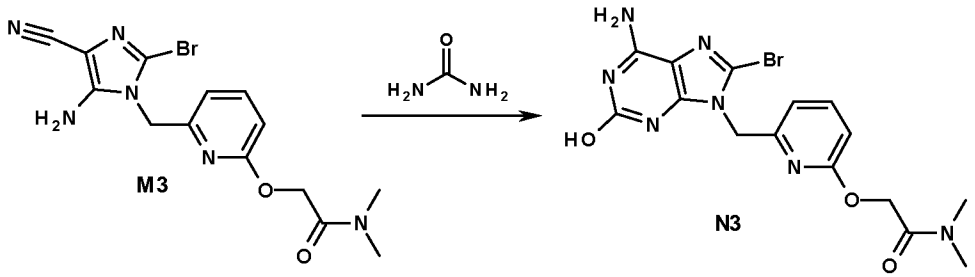
Synthesis of intermediate L3

K3 (6.2 g, 29.5 mmol) in EtOH (30 mL) was added drop wise to a solution of F2 (4.6 g, 28 mmol) and aniline hydrochloride (56 mg, 0.43 mmol) in EtOH (25 mL) at 10°C. The reaction mixture was stirred at RT for 20h. An aqueous solution of NaOH 1M (25 mL) was added drop wise to the solution at 10°C and the resulting mixture was stirred at RT for 1h. The precipitate was filtered off, washed with a minimum of cold EtOH and dried under vacuum. Mother layers were concentrated, a second precipitate was obtained in CH_2Cl_2, filtered and dried under vacuum. The two batches were combined to give intermediate L3 (2.44 g, 29% yield).



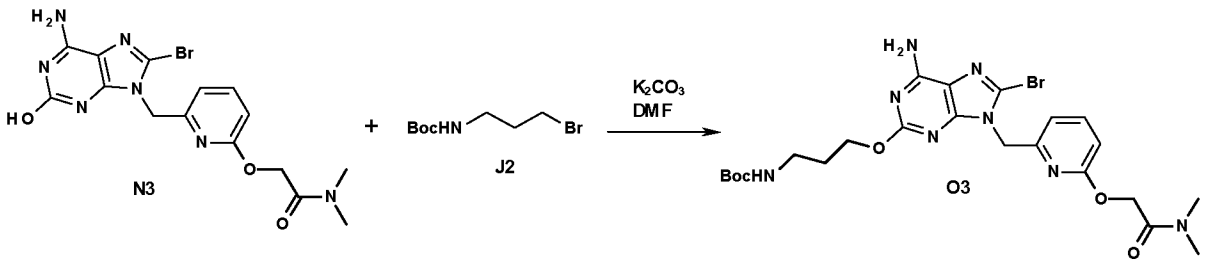
Synthesis of intermediate M3

A solution of NBS (0.326 g, 1.83 mmol) in THF (15 mL) was added drop wise over 25 min to a solution of L3 (0.5 g, 1.67 mmol) in THF (15 mL) at 0°C. The mixture was stirred at 0°C for 30 min and then at RT for 45 min. The mixture was taken up in CH_2Cl_2, washed with a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, filtered and evaporated under vacuum. This crude compound was solidified from CH_3CN. The precipitate was filtered off and dried to give intermediate M3 (216 mg, 34% yield).



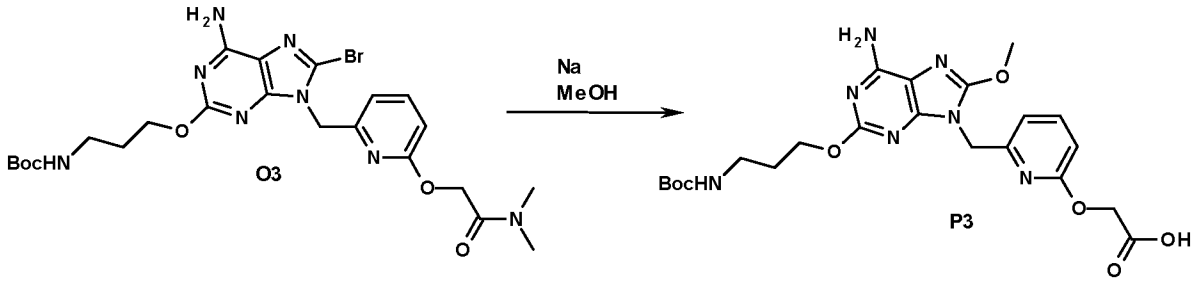
Synthesis of intermediate N3

A mixture of M3 (1.04 g, 2.74 mmol) in urea (4.9 g, 82.28 mmol) was heated at 160°C for 4h. Urea (3 g, 2.64 mmol) was added again and the mixture was stirred at 160°C for 12h. The mixture was cooled to RT and water was added. The precipitate was triturated and filtered off, washed with water and dried under vacuum at 60°C to give intermediate N3. The crude compound was used directly in the next step.



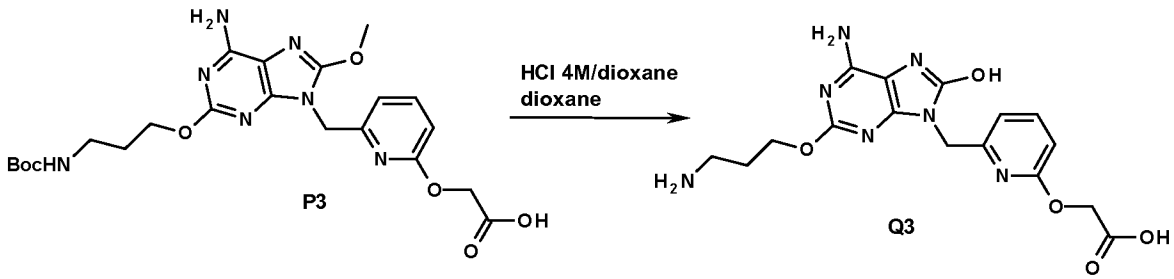
Synthesis of intermediate O3

A mixture of N3 (crude), J2 (1.557 g, 6.54 mmol), K_2CO_3 (904 mg, 6.54 mmol) in DMF (30 mL) was stirred at 50°C for 12h. The solvent was evaporated. The residue was taken up in EtOAc. The organic layer was washed with water, dried over $MgSO_4$, filtered and the solvent was evaporated. The crude compound was purified by preparative LC on (irregular SiOH 15-40 µm 300 g Merck), mobile phase: 0.3% NH_4OH, 97% CH_2Cl_2, 3% MeOH to give intermediate O3 (280 mg, 11% yield).



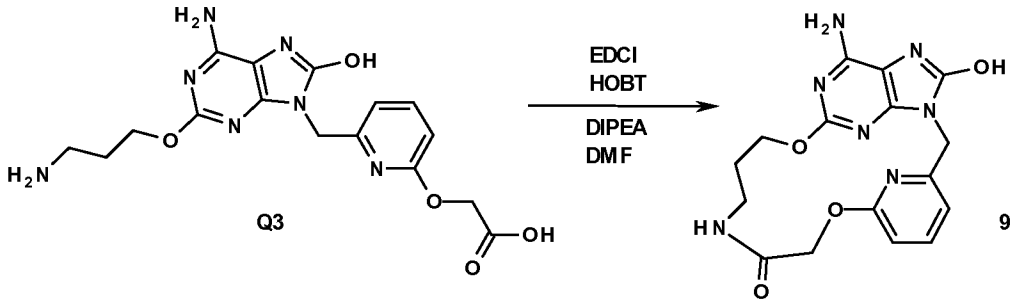
Synthesis of intermediate P3

At RT, Na (167 mg, 7.25 mmol) was added to MeOH (11 mL). The mixture was stirred until Na was in solution (exothermic). O3 (280 mg, 0.48 mmol) was added and the mixture was stirred at 50°C for 16h under a N_2 flow. Water was added and the pH was adjusted (with HCl 1N) to 5-6. The aqueous layer was extracted with EtOAc. The aqueous phase was saturated with K_2CO_3 powder and extracted with AcOEt. The combined organic phases were dried over $MgSO_4$, filtered and solvent was evaporated to give intermediate P3 (140 mg, 58% yield).



Synthesis of intermediate Q3

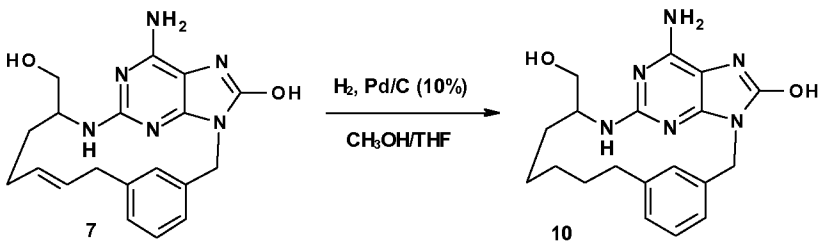
At 0°C, HCl (4M in dioxane) (0.7 mL, 2.78 mmol) was added drop wise to a mixture of P3 (140 mg, 2.78 mmol) in dioxane (5 mL). The mixture was stirred at RT for 12h. The solvent was evaporated until dryness to give intermediate Q3. The crude compound was used in the next step without any further purification.



Synthesis of final compound 9

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (318 mg, 1.66 mmol) and hydroxybenzotriazole (224 mg, 1.66 mmol) were slowly added to a mixture of Q3 (crude), diisopropylethylamine (0.476 mL, 2.76 mmol) in DMF (170 mL). The mixture was stirred at RT for 24h. The solvent was evaporated until dryness. The residue was taken up in water. The precipitate was filtered off, washed with water and dried. The crude compound was purified by reverse phase on (X-Bridge-C18 5µm 30*150mm), mobile phase (Gradient from 90% NH_4HCO_3 0.5%, 10% CH_3CN to 0% NH_4HCO_3 0.5%, 100% CH_3CN) to give final compound 9 (37 mg, 18% yield).

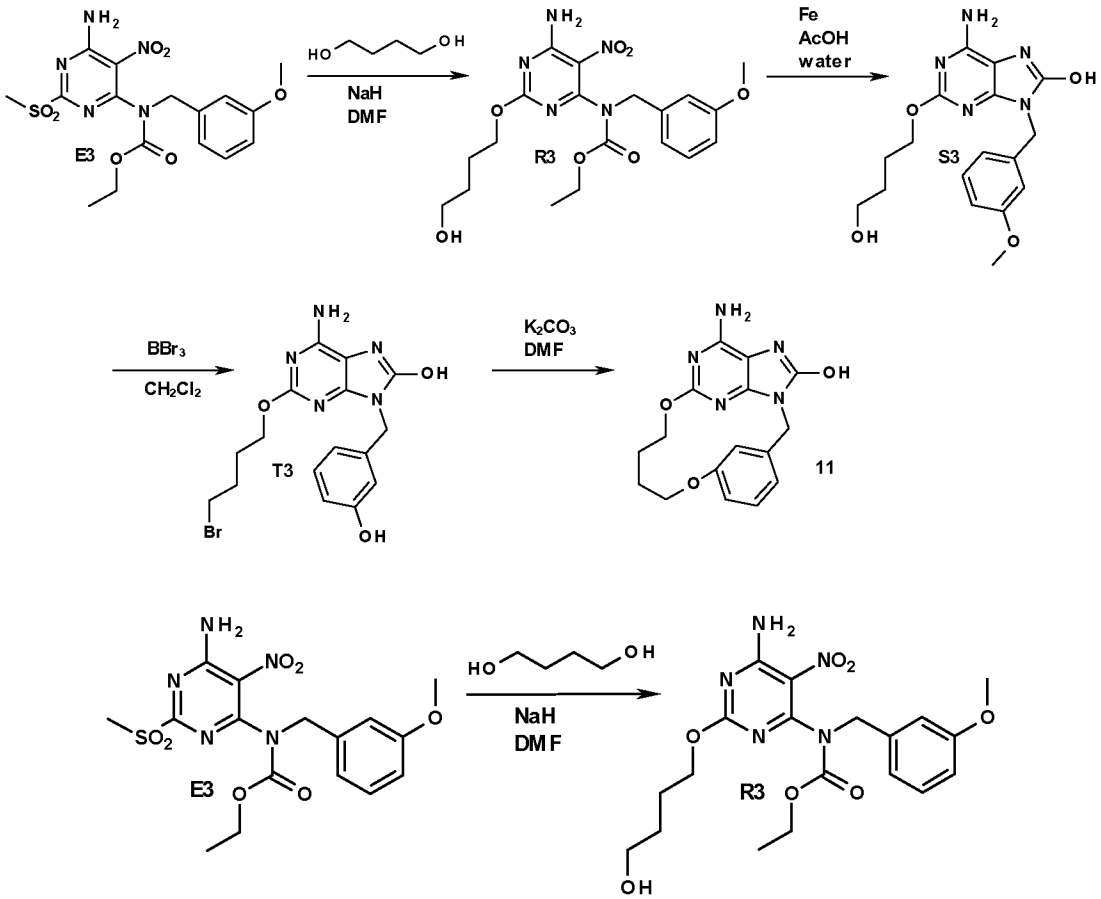
Overall Scheme in the preparation of final products: method 10



Synthesis of final compound 10:

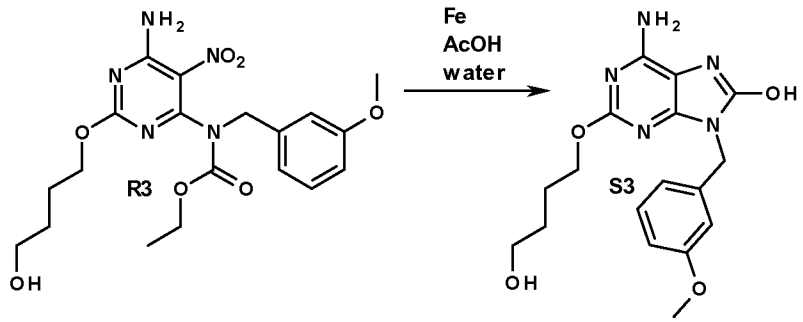
A mixture of compound 7 (100 mg, 0.27 mmol), Pd/C (10%) (14.5 mg, 0.014 mmol) in CH_3OH/THF 50/50 (10 mL) was hydrogenated under an atmospheric pressure of H_2 for 4h. The catalyst was removed by filtration through a filter (chromafil Xtra 0.45µm). The filtrate was concentrated. This fraction was solidified from CH_3CN, the precipitate was filtered off and dried to give final compound 10 (81 mg, 81% yield).

Overall Scheme in the preparation of final products: method 11



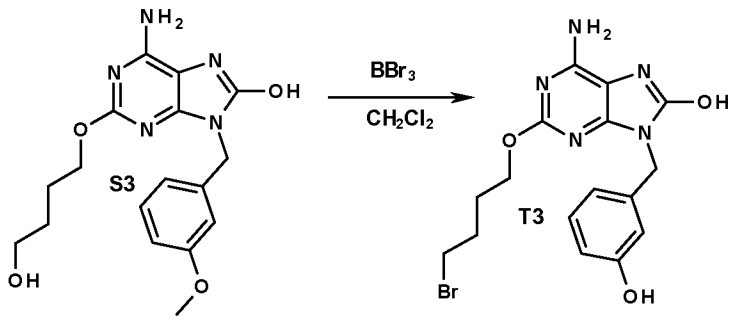
Synthesis of intermediate R3

At 0°C under a N_2 flow, NaH (705 mg, 17.6 mmol) was added to a solution of 1,4-butanediol (3.2 g, 35.26 mmol) in DMF (30 mL). The mixture was stirred for 30 min at RT, then E3 (2.5 g, 5.87 mmol) was added. The mixture was stirred at RT for 1h. Ice was added and the mixture was extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated. Purification was carried out by flash chromatography over silica gel (15-40µm, 80g, $CH_2Cl_2/CH_3OH/NH_4OH$: 97/3/0.1). The pure fractions were collected and evaporated to dryness to give intermediate R3 (1.78 g, 70% yield).



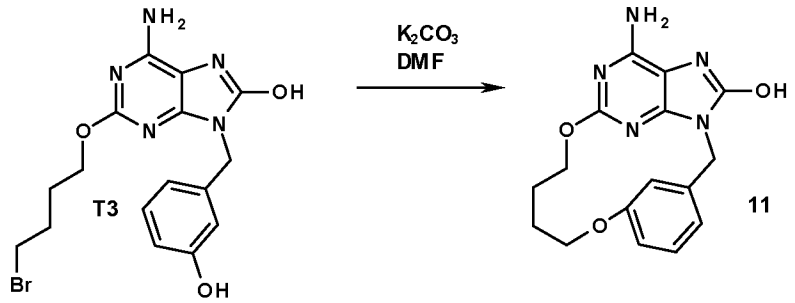
Synthesis of intermediate S3

Iron powder (2.27 g, 40.65 mmol) was added to a mixture of R3 (1.77 g, 4.07 mmol) in AcOH (35 mL) and water (11 mL). The mixture was stirred at 50°C for 8h. The reaction mixture was diluted with water and was basified with K_2CO_3 10% in water. EtOAc and CH_3OH were added and the resulting mixture was filtered through a pad of celite®. The celite® was washed with CH_2Cl_2/CH_3OH (80/20). The filtrate was decanted. The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated. The fraction was taken up in CH_3CN, the precipitate was filtered off and dried to give intermediate S3 (1.2 g, 82% yield).



Synthesis of intermediate T3

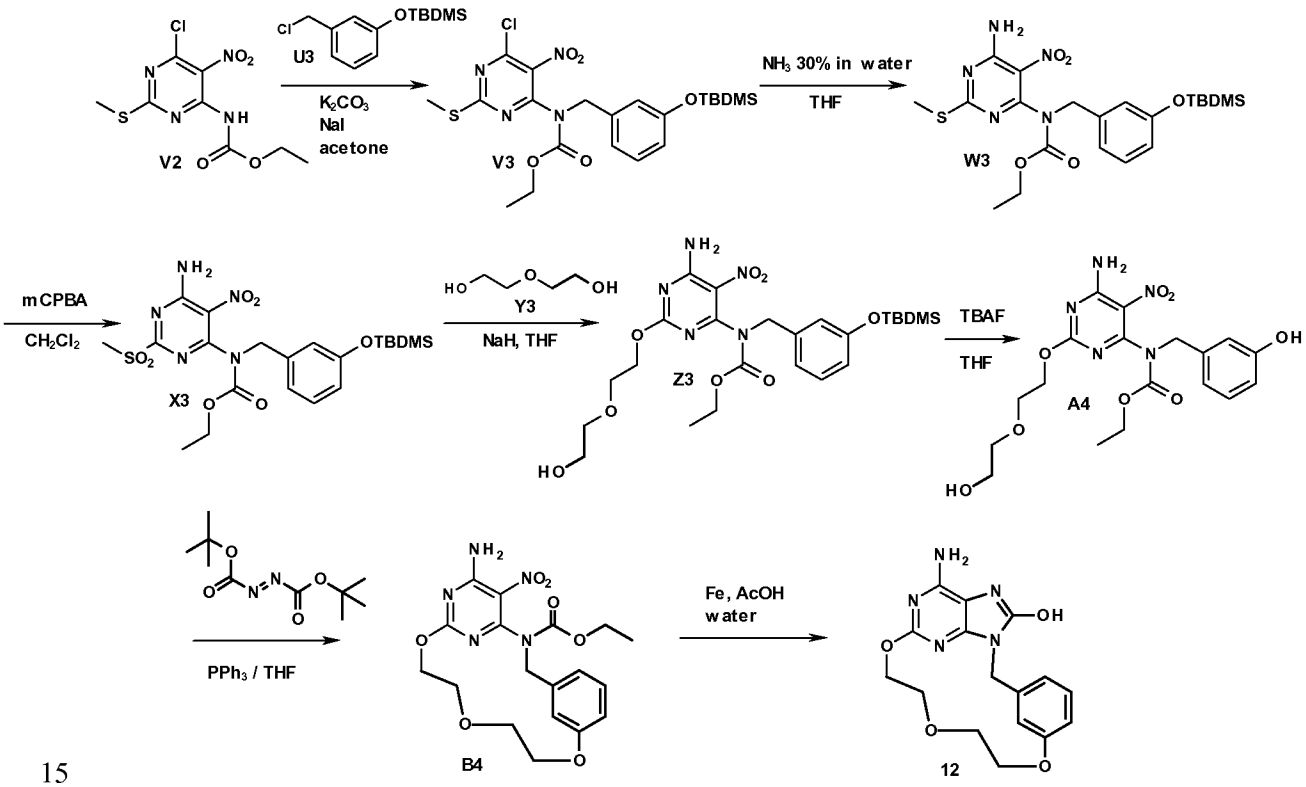
At -60°C under a N_2 flow, BBr_3 (13.6 mL, 13.6 mmol) was added drop wise to a mixture of S3 (980 mg, 2.727mmol) in CH_2Cl_2 (40 mL). The mixture was stirred at -60°C for 1h under a N_2 flow. The mixture was stirred 5h at 0°C. 5 mL of CH_3OH was added drop wise at -60°C. The mixture was then poured into a saturated solution of K_2CO_3. The mixture was extracted with CH_2Cl_2/CH_3OH. The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated to give intermediate T3 (0.55 g, 49% yield), which was directly used in the next step without further purification.

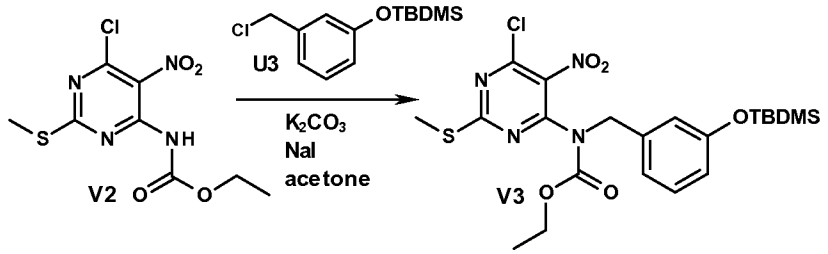


Synthesis of final compound 11

A mixture of T3 (537 mg, 1.32 mmol), K_2CO_3 (182 mg, 1.32 mmol) in DMF (71 mL) was stirred at 80°C for 12h. The crude mixture was filtered off and the filtrate was concentrated under reduced pressure. The residue was taken up in the minimum of DMF and 5 g of SiO_2 35-70µm was added. The resulting suspension was evaporated until dryness and put on the top of a 50 g chromatography column and eluted with a gradient of CH_2Cl_2-CH_3OH-NH_4OH 95-5-0.5 to 90-10-0.5. The fractions containing the expected compounds were combined and concentrated under reduced pressure. The solid was crystallized from CH_3CN, the precipitate was filtered off and dried to give final compound 11 (33 mg, 8% yield).

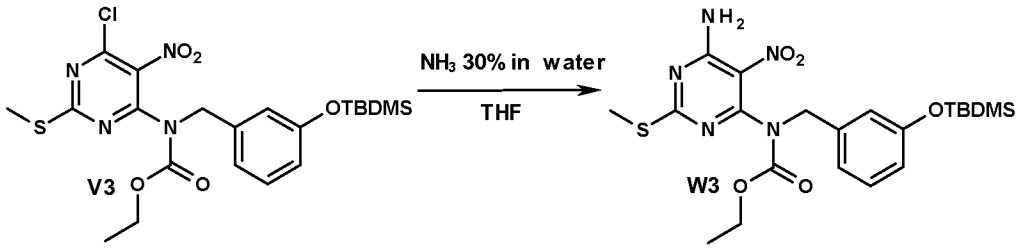
Overall Scheme in the preparation of final products: method 12





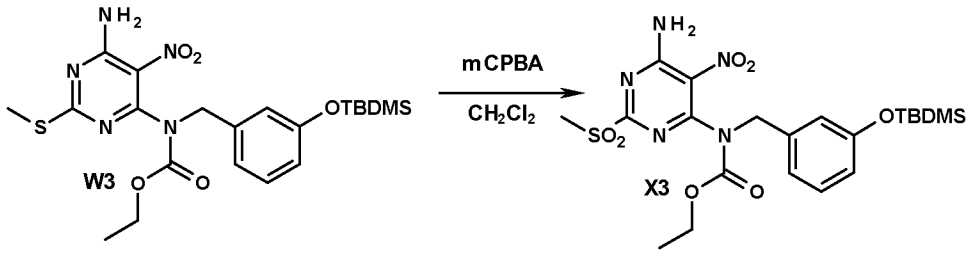
Synthesis of intermediate V3

V2 (1.4 g, 4.8 mmol), U3 (1.44 g, 4.8 mmol), K_2CO_3 (1.65 g, 12 mmol) and NaI (0.72 g, 4.8 mmol) in acetone (60 mL) were stirred at RT for 16h. The solution was filtered off and the filtrate was evaporated under reduced pressure. The crude product was purified by preparative LC (irregular SiOH 15-40 µm, 80 g Merck, mobile phase heptane/CH_2Cl_2 85/15) to give intermediate V3 (2.3 g, 94% yield).



Synthesis of intermediate W3

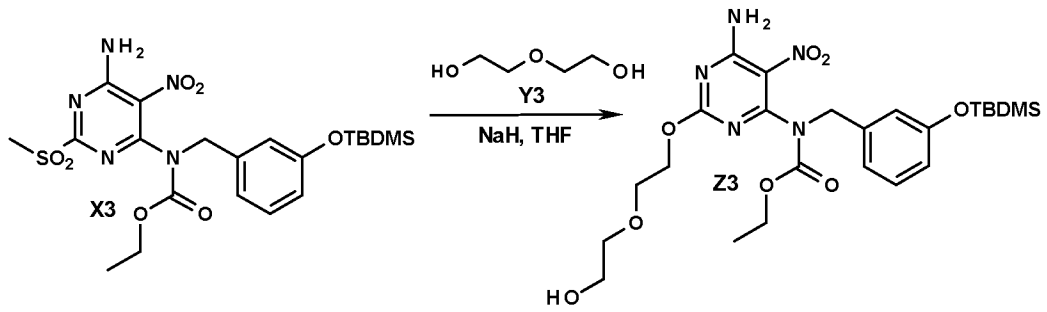
V3 (2.3 g, 4.5 mmol) was stirred in NH_3 (30% in water) (40 mL) and THF (40 mL) at RT for 16h. The mixture was concentrated under vacuum and the residue was dried by azeotropic evaporation of EtOH (twice). The crude product was purified by preparative LC (irregular SiOH 15-40 µm, 40 g Merck, mobile phase heptane/AcOEt 85/15) to give intermediate W3 (1.25 g, 56% yield).



Synthesis of intermediate X3

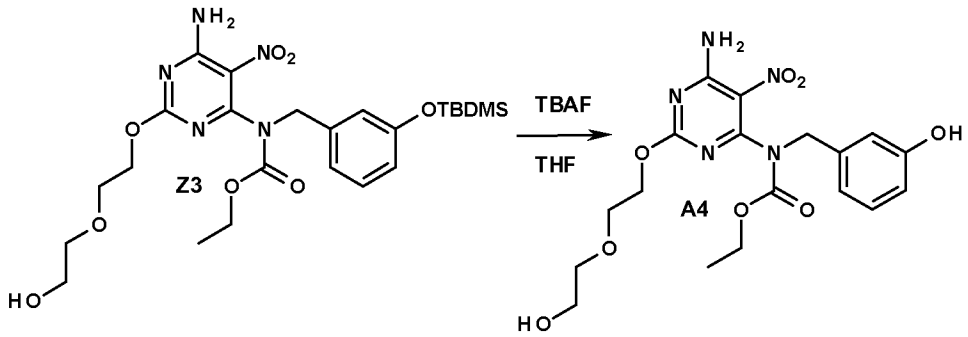
3-chloroperoxybenzoic acid (2.04 g, 8.2 mmol) was added to a solution of W3 (1.3 g, 3.3 mmol) in CH_2Cl_2 (70 mL) at RT. The mixture was stirred at RT for 20h. An aqueous solution of $Na_2S_2O_3$ (5 eq) was added to the mixture. The two layers were

separated and the aqueous layer was extracted with CH_2Cl_2 (twice). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was used directly in the next step without any further purification.



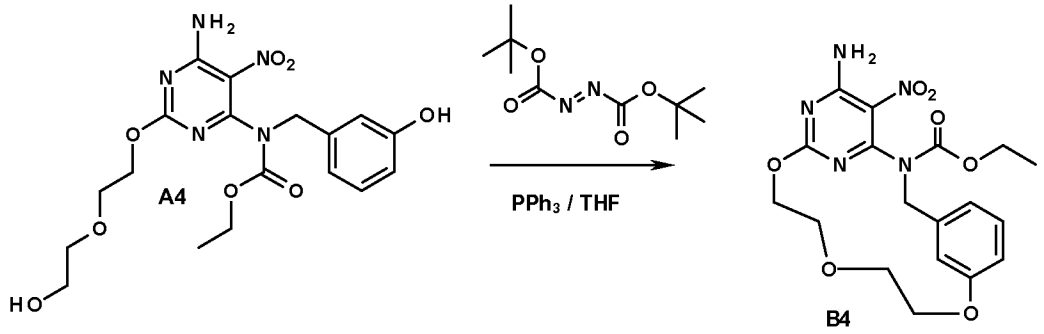
Synthesis of intermediate Z3

At 0°C under a N_2 flow, NaH (457 mg, 11.4 mmol) was added to a solution of Y3 (2.1 ml, 22.8 mmol) in THF (100 mL). The mixture was stirred for 30 min at RT, then X3 (2 g, 3.8 mmol) in solution into 20 ml of THF was added at 0°C. The mixture was stirred at 5°C for 15 min. Ice was added and the mixture was extracted with EtOAc. The crude compound was purified by chromatography over silicagel (15-40µm, 80g) in CH_2Cl_2/MeOH/NH_4OH (98/2/0.1) to give intermediate Z3 (1 g, 48% yield).



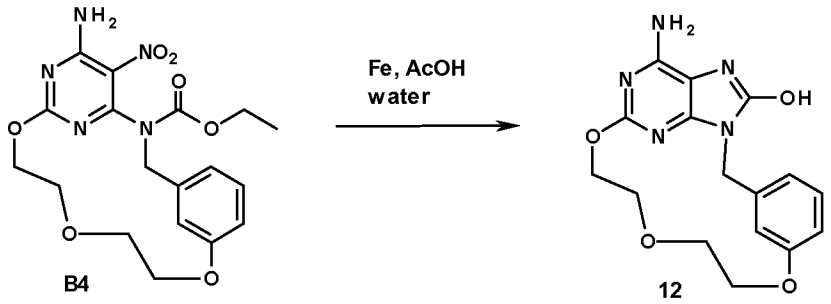
Synthesis of intermediate A4

Tetrabutylammonium fluoride (0.653 mL, 0.65 mmol) was added drop wise to a solution of Z3 (0.3 g, 0.544 mmol) in THF (10 mL) at RT. The reaction was stirred at RT for 3h. The mixture was diluted with EtOAc and poured into water. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered and the solvent was evaporated to give intermediate A4 (220 mg, 92% yield).



Synthesis of intermediate B4

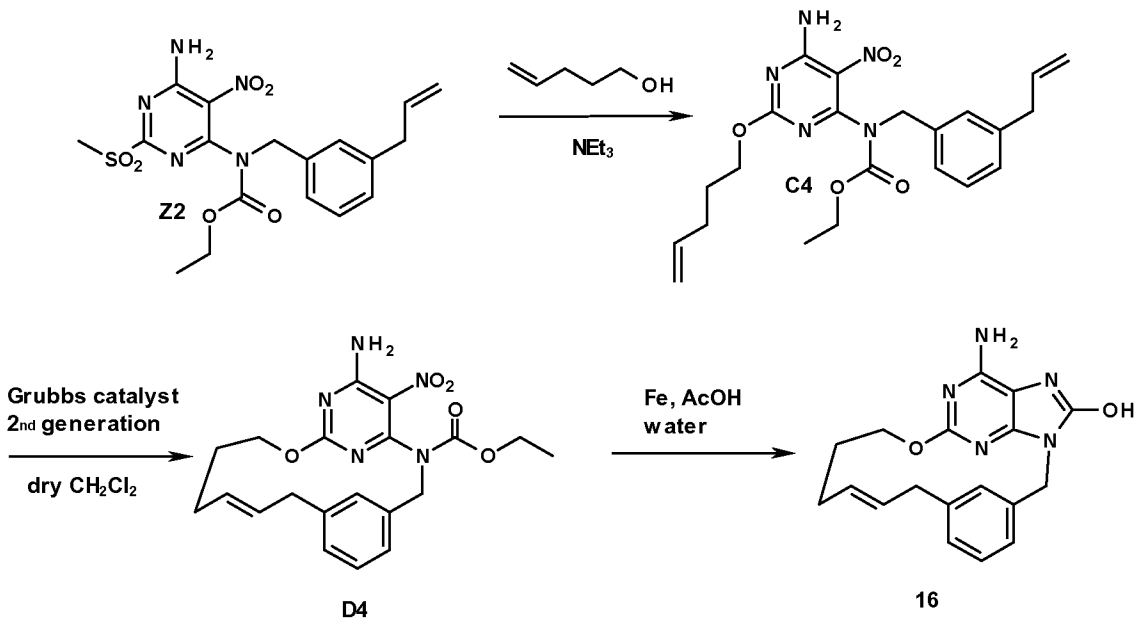
At RT under a N_2 flow, a solution of di-tert-butyl azodicarboxylate (0.72 ml, 3.2 mmol) in THF (10 mL) was slowly added drop wise to a mixture of A4 (0.7 g, 1.6 mmol) and PPh_3 (0.84 g, 3.2 mmol) in THF (120 mL). The mixture was stirred at RT for 12h. The reaction mixture was poured into ice-water and EtOAc was added. The mixture was basified with an aqueous 10% solution of $NaHCO_3$, then the organic layer was separated, dried over $MgSO_4$, filtered and solvents were evaporated until dryness to give intermediate B4 (60 mg, 9% yield).

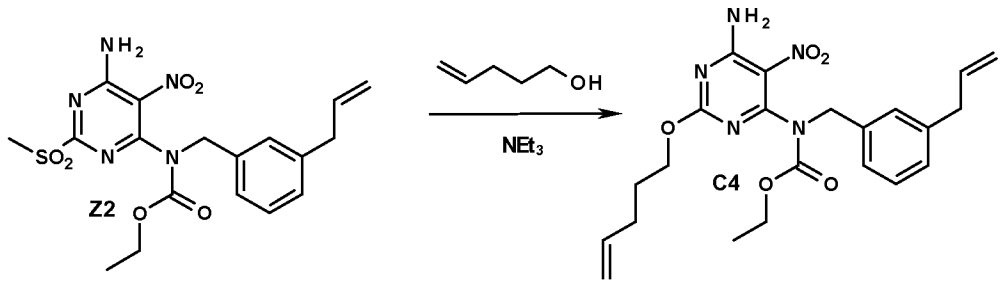


Synthesis of final compound 12

Iron powder (80 mg, 1.43 mmol) was added to a mixture of B4 (60 mg, 0.143 mmol) in AcOH (1.3 mL) and water (0.5 mL). The mixture was stirred vigorously at RT for 6h. The reaction mixture was concentrated under vacuum and the residue was diluted with CH_2Cl_2/MeOH 90/10 and water. The aqueous layer was saturated with K_2CO_3 and extracted with CH_2Cl_2/MeOH 90/10. The organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The crude compound was purified by chromatography over silicagel (15-40µm, 40 g) in CH_2Cl_2/MeOH/NH_4OH (90/10/0.5). Crystallization from CH_3CN/Diisopropylether gave final compound 12 (14 mg, 29% yield).

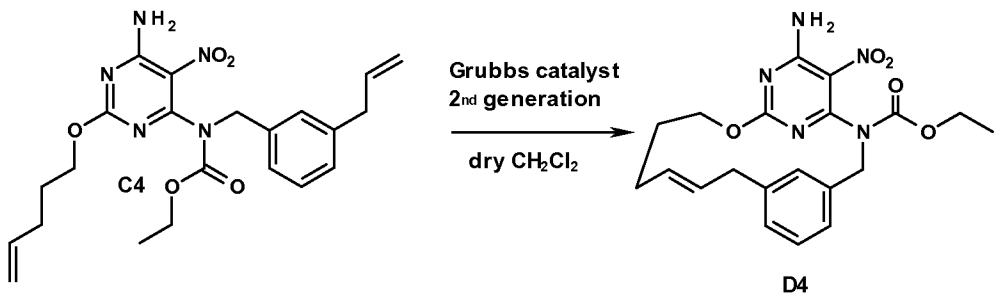
Overall Scheme in the preparation of final products: method 13





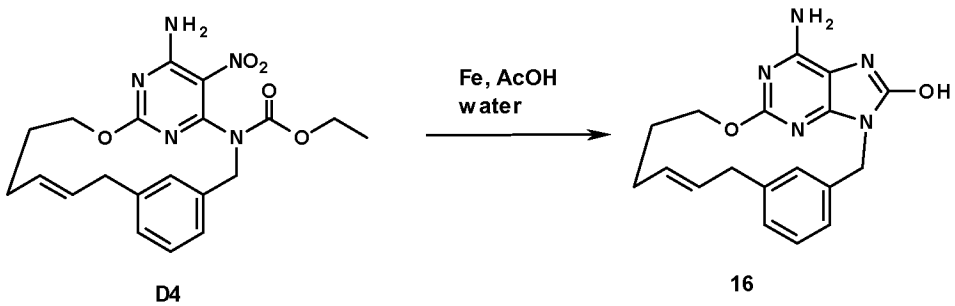
Synthesis of intermediate C4

A solution of Z2 (2.12 g, 4.87 mmol) and NEt_3 (677 µL, 4.87 mmol) in 4-penten-1-ol (75 mL) was stirred at RT for 48 h. The solvent was removed under vacuum. The crude compound was purified by preparative LC (irregular SiOH 15-40 µm, 90 g Merck, mobile phase gradient: heptane/CH_2Cl_2 50/50 to 0/100) to give intermediate C4 (1.6 g, 66% yield) as a yellow oil.



Synthesis of intermediate D4

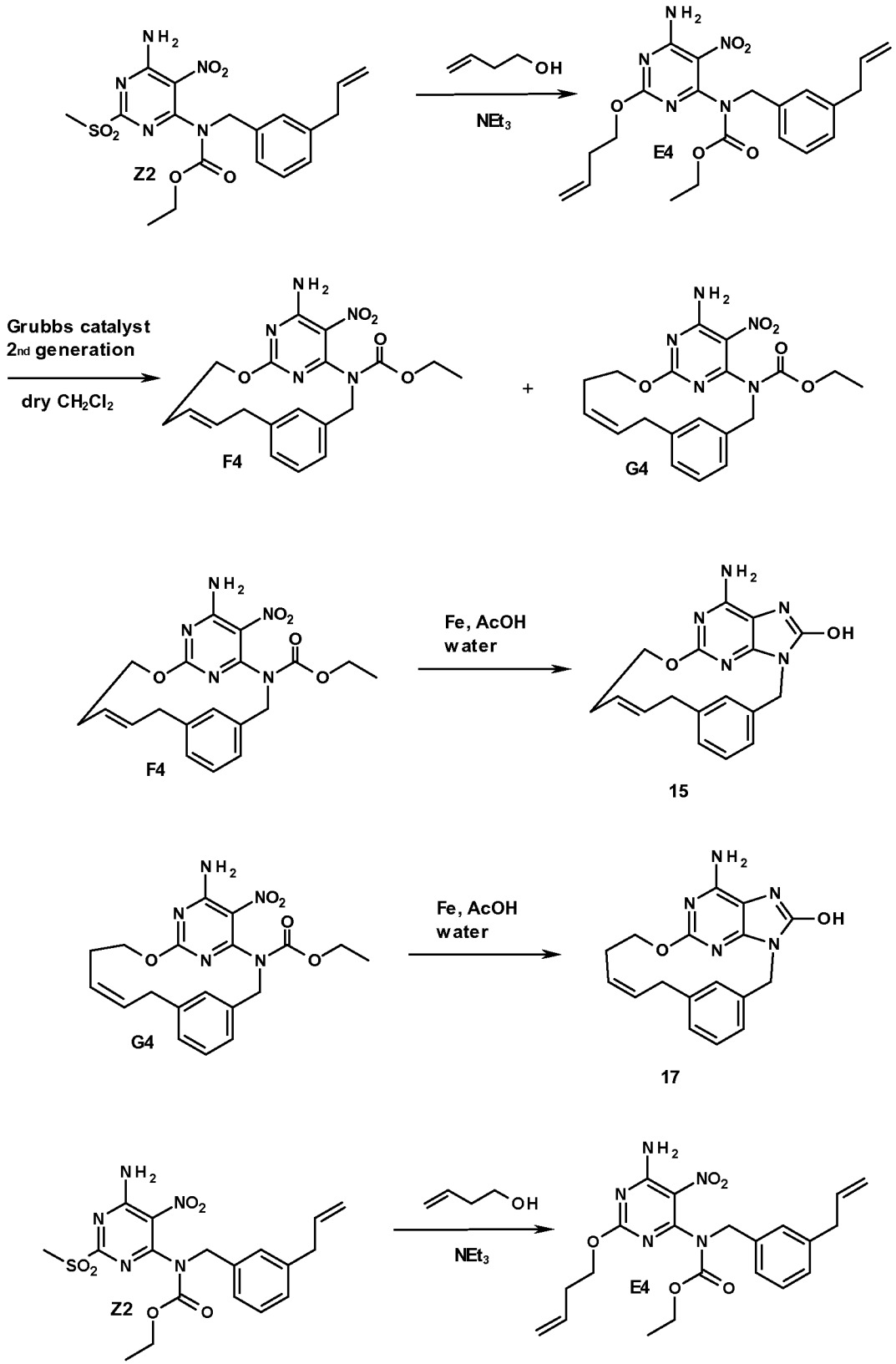
Grubbs catalyst 2nd generation (41 mg, 48.47 mmol) was added to a degassed solution of C4 (208 mg, 0.47 mmol) in CH_2Cl_2 (150 mL) at RT. The solution was stirred at RT for 2 h. SiliaBond® DMT (Ru scavenger from Silicycle®) (298 mg, 0.388 mmol) was added and the mixture was stirred at RT for 6 h and the solution was filtered off over celite®. The filtrate was concentrated under vacuum. The crude compound was purified by preparative LC (irregular SiOH 15-40 µm, 90 g Merck, mobile phase gradient: from heptane/AcOEt 100/0 to 70/30). The fractions containing the expected product were collected and partially evaporated and the precipitate was filtered off to give 736 mg of intermediate D4 (73% yield, containing 6% of Z isomer). 297 mg of this batch was purified by preparative LC (Stability Silica 5µm 150x30.0mm, mobile phase gradient: from Heptane/AcOEt 85/15 to 0/100) to give 195 mg of intermediate D4 as a white solid (pure isomer E). Purity of isomer E was checked by analytical reversed phase chromatography (Column Nucleodur Sphinx 150X4.6mm, mobile phase: Gradient from 70% MeOH, 30% HCOOH 0.1% to 100% MeOH). This batch of pure E isomer was used in the next step.



Synthesis of final compound 16

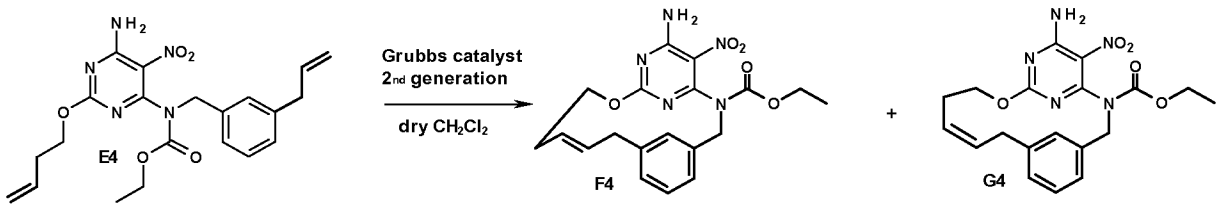
Iron powder (158 mg, 2.83 mmol) was added to a solution of D4 (195 mg, 0.47 mmol) in AcOH (8 mL) and water (741 µL). The mixture was heated at 100°C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 1h. The mixture was filtered on a pad of celite® and rinsed with DMF (250 mL). The filtrate was concentrated under vacuum and the residue was triturated in CH_2Cl_2/MeOH (80:20). The precipitate was filtered off, rinsed with CH_2Cl_2/MeOH (80:20). The resulting yellow solid was solubilized in DMF and filtered on a pad of celite®. The filtrate was concentrated under vacuum and the residue was triturated in CH_2Cl_2/MeOH (90:10). The precipitate was filtered off to give final compound 16 as a white solid (17 mg, 10% yield).

Overall Scheme in the preparation of final products: method 14



Synthesis of intermediate E4

A solution of Z2 (3.8 g, 5.06 mmol) and NEt_3 (844 µL, 6.07 mmol) in 3-buten-1-ol (68 mL) was stirred at RT for 20h, then stirred at 30°C for 1h. The solvent was removed under vacuum to give 5 g of yellow oil. The crude was purified by preparative LC (Irregular SiOH 15-40 µm, 120 g Grace, mobile phase gradient: Heptane/CH_2Cl_2 from 50/50 to 10/90). The fractions containing the expected product were combined and the solvent was removed under vacuum to give 2.2 g of intermediate E4 as a yellow oil.



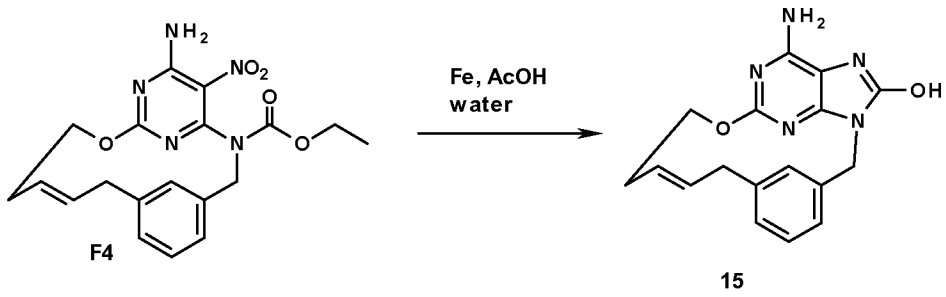
Synthesis of intermediates F4 and G4:

E4 (1.34 g, 3.14 mmol) was added to dry CH_2Cl_2 (1 L) and the resulting mixture was degassed by N_2 bubbling through the solution for 30 min. Grubbs catalyst 2nd generation (134 mg, 0.157 mmol) was added in one portion and the mixture was stirred at RT under N_2 atmosphere for 16 h. SiliaBond® DMT (0.965 g, 1.25 mmol) was added and the mixture was stirred at RT for 16 h and the solution was filtered over celite®. The filtrate was evaporated under vacuum to give 1.89 g of brown solid. The crude was purified by preparative LC (Irregular SiOH 15-40 µm, 50 g Merck, mobile phase gradient: Heptane/AcOEt from 100/0 to 80/20). The fractions containing the expected product were partialy evaporated (AcOEt), the product was precipitated and filtered off to give 162 mg of intermediate F4 (13% yield, E isomer) as a yellow solid. The other fractions containing the expected products were combined and the solvent was removed under vacuum to give 244 mg of white solid (mixture of F4 (E isomer) and G4 (Z isomer)).

The same reaction was carried out in parallel starting from 895 mg of E4. From this reaction, a batch of 110 mg of F4 was isolated (13% yield, isomer E). A second batch of 184 mg was obtained (mixture of F4 (E isomer) and G4 (Z isomer)).

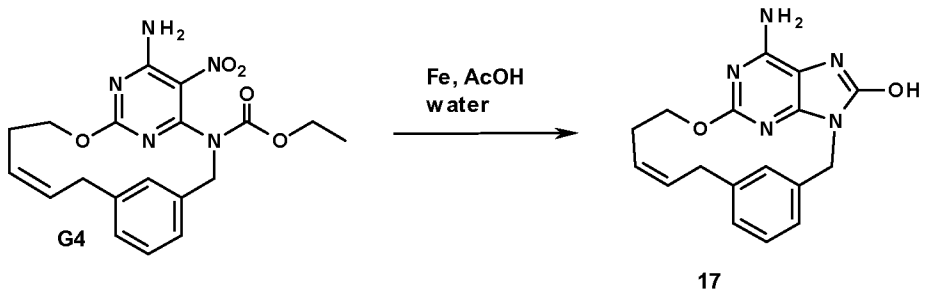
The two batches containing a mixture of E and Z isomers were combined (428 mg) and were purified by preparative LC (Stability Silica 5µm 150x30.0mm, mobile phase gradient: from CH_2Cl_2/MeOH 100/0 to 98/2) to give 175 mg of F4 (14% yield, isomer E) as a yellow solid and 130 mg of G4 (10% yield, isomer Z) as a white solid.

In total, 447 mg of intermediate F4 (E isomer) and 130 mg of intermediate G4 (Z isomer) were obtained.



Synthesis of final compound 15:

Iron (93 mg, 1.67 mmol) was added to a solution of F4 (111 mg, 0.278 mmol) in acetic acid (5 mL) and distilled water (330 µL). The mixture was heated at 100°C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 1 h. The mixture was concentrated under vacuum and triturated in $AcOH/H_2O$ (50:50). The precipitate was filtered off to give a grey solid, which was solubilized in DMF and filtered on a pad of celite®. The filtrate was concentrated under reduced pressure to give a white-brown solid. This solid was triturated in $AcOH/H_2O$ (50:50); the precipitate was filtered off to give 40 mg of final compound 15 (45% yield) as a white solid.

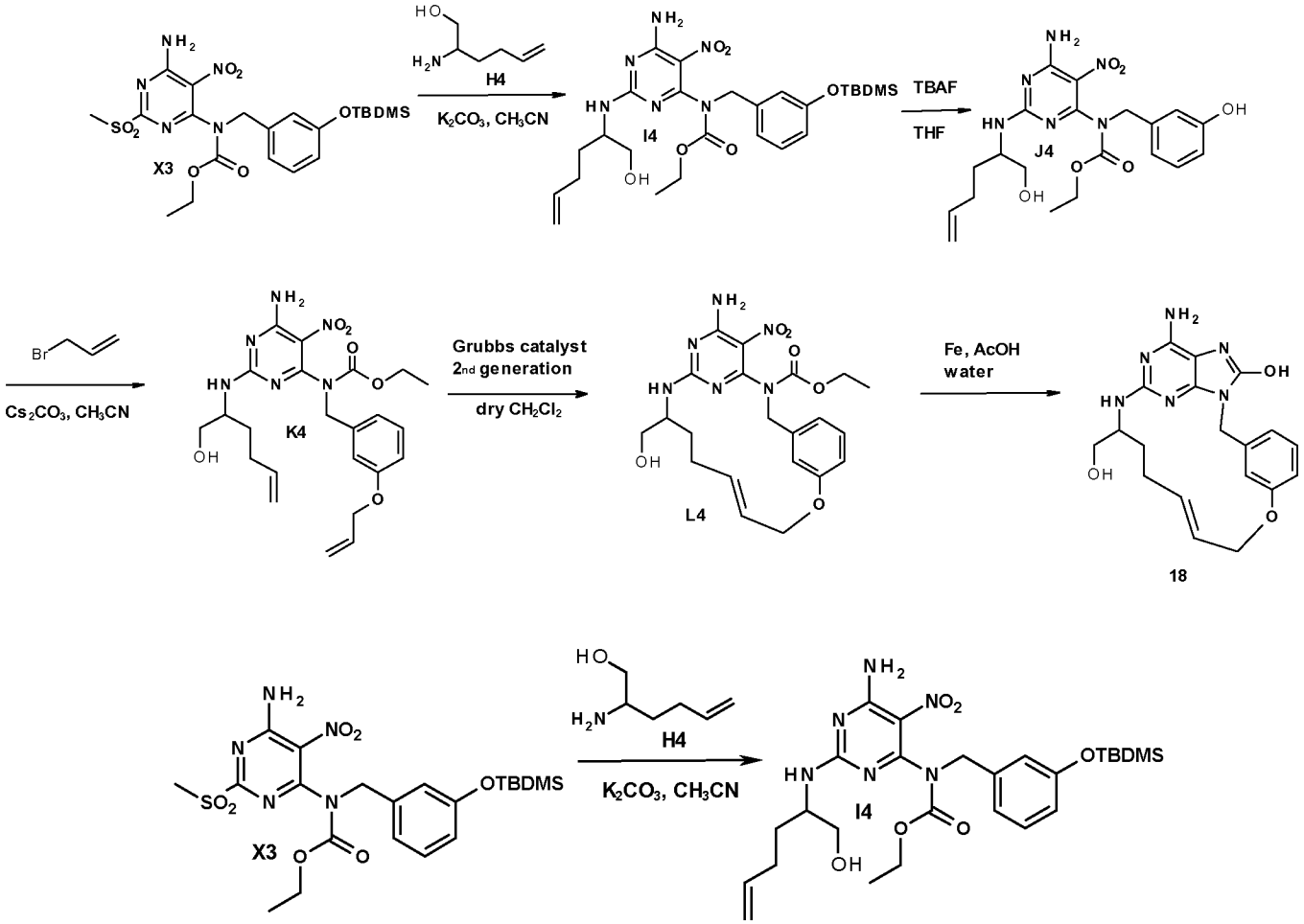


Synthesis of final compound 17:

Iron (109 mg, 1.95 mmol) was added to a solution of G4 (130 mg, 0.325 mmol) in acetic acid (6 mL) and distilled water (390 µL). The mixture was heated at 100°C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 1 h 30. The mixture was concentrated under vacuum and triturated in a solution of $AcOH/H_2O$ (50:50). The precipitate was filtered off to give a grey solid, which was triturated in $AcOH/H_2O$ (50:50); the precipitate was filtered off and solubilized in DMF. The mixture was filtered on a pad of celite® and the filtrate was concentrated under vacuum to give a white solid. This solid was triturated in a cold

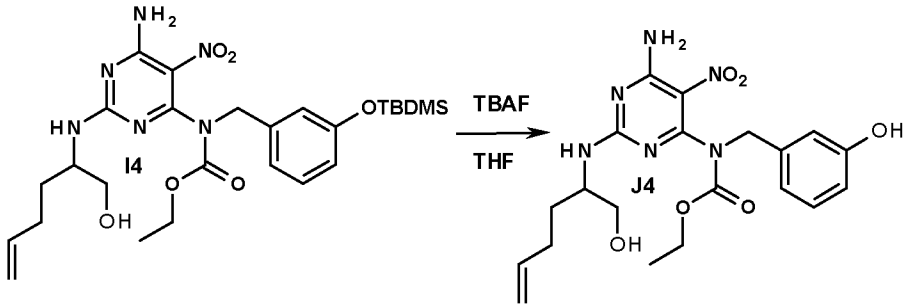
solution of AcOH/H_2O (50:50); the precipitate was filtered off to give 18 mg of final compound 17 (17% yield) as a white solid.

Overall Scheme in the preparation of final products: method 15



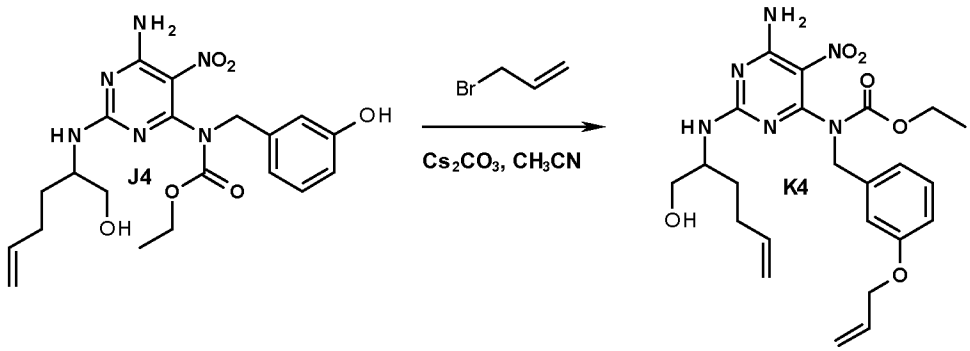
Synthesis of intermediate I4:

A mixture of X3 (4 g, 7.61 mmol), H4 (1.1 g, 9.13 mmol) and K_2CO_3 (1.3 g, 9.13 mmol) in CH_3CN (120 mL) was stirred at 80°C for 1.5 h. Water was added and the mixture was extracted with EtOAc (twice). The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude was purified by chromatography over silica gel (15-40 µm; 120 g) in CH_2Cl_2/MeOH/NH_4OH 98/2/0.1 to give 2.7 g (63% yield) of intermediate I4.



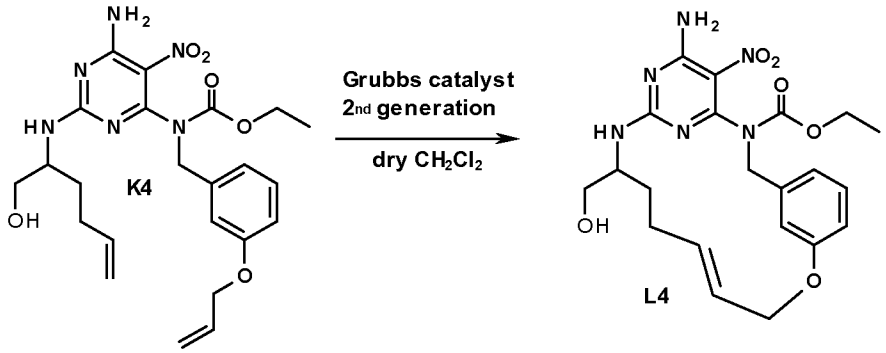
Synthesis of intermediate J4:

Tetrabutylammonium fluoride (5.6 mL, 5.56 mmol) was added drop wise to a solution of I4 (2.6 g, 4.64 mmol) in THF (125 mL) at room temperature. The reaction was stirred at room temperature for 3 hours. The mixture was diluted with EtOAc and poured into water. The organic layer was washed with brine, dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude was purified by preparative LC (irregular SiOH 15-40 µm, 80 g Grace, mobile phase: CH_2Cl_2/MeOH/NH_4OH 96/4/0.1) to give 1.82 g of intermediate J4. The crude compound was used in the next step.



Synthesis of intermediate K4:

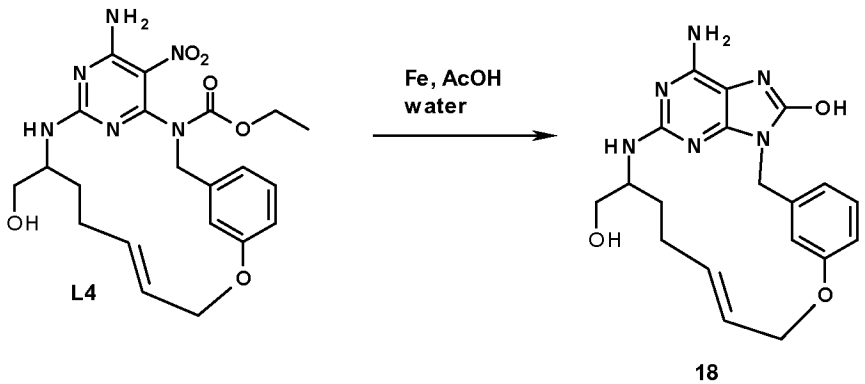
A mixture of J4 (1.82 g, 4.08 mmol), Cs_2CO_3 (1.47 g, 4.49 mmol), allyl bromide (0.39 mL, 4.49 mmol) in CH_3CN (60 ml) was stirred at RT for 5h and then at 50°C for 1h. The reaction mixture was poured into ice-water and EtOAc was added. The mixture was basified with an aqueous solution of $NaHCO_3$ 10% in water. The organic layer was separated, dried over $MgSO_4$, filtered and the solvents were evaporated until dryness to give 1.94 g of intermediate K4. The crude compound was used directly in the next step.



Synthesis of intermediate L4:

Grubbs catalyst 2nd generation (100 mg, 0.117 mmol) was added to a degassed solution of K4 (570 mg, 1.17 mmol) in CH_2Cl_2 (225 mL) at RT. The solution was stirred at RT for 36 h.

SiliaBond® DMT (1.8 g) was added to the reaction mixture, which was stirred at RT 18 hours. The mixture was filtered through a pad of celite®. The celite® was washed with CH_2Cl_2. The filtrate was evaporated under reduced pressure. Purification was carried out by flash chromatography over silica gel (15-40 µm, 40 g, $CH_2Cl_2/CH_3OH/NH_4OH$ 97.5/2.5/0.1). The pure fractions were collected and evaporated to dryness. The dry solid was purified again by achiral SFC on (AMINO 6µm 150x21.2mm), mobile phase (80% CO_2, 20% MeOH) to give 182 mg (34% yield) of intermediate L4 (E isomer).

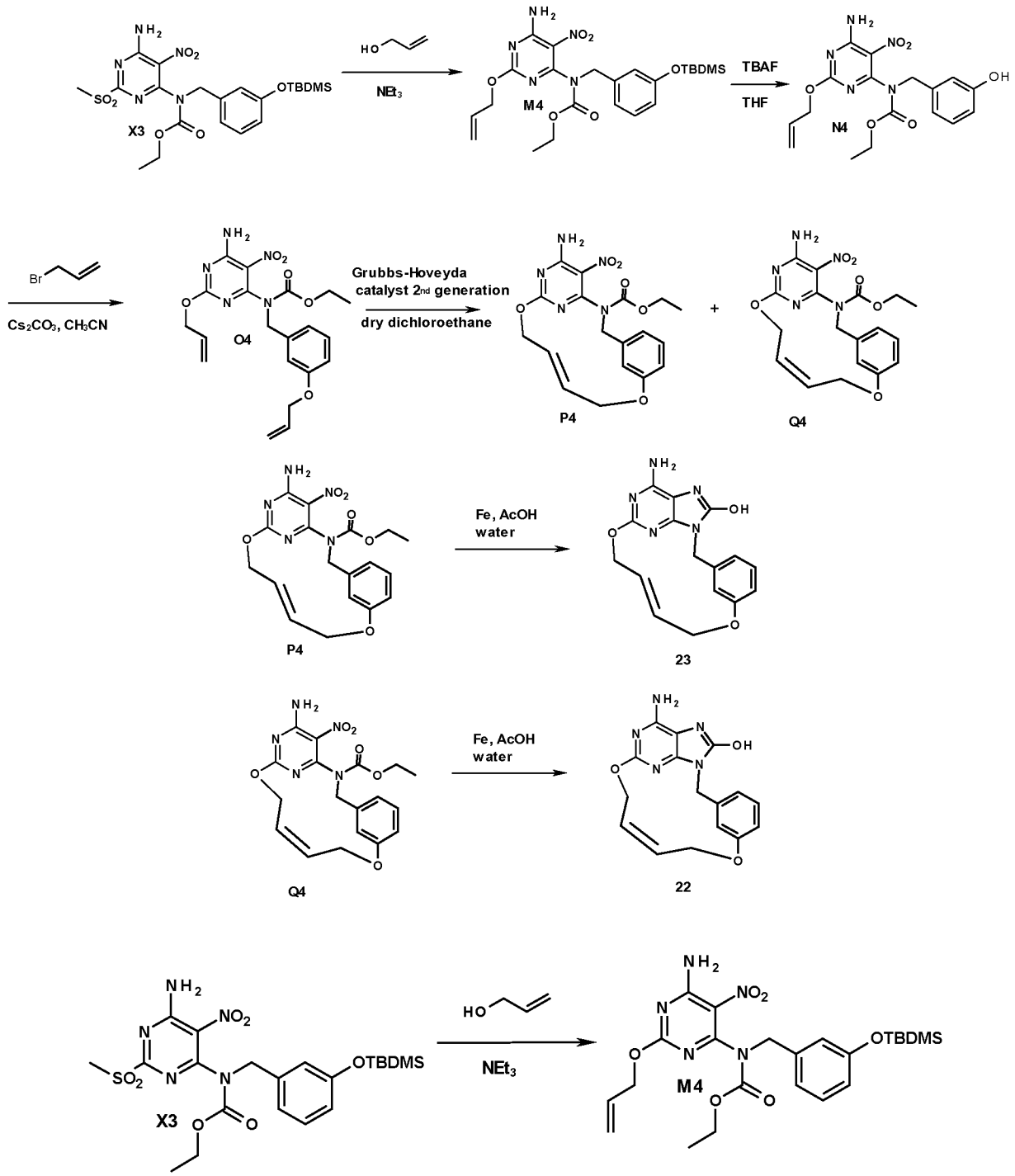


Synthesis of final compound 18:

Iron (200 mg, 3.58 mmol) was added to a mixture of L4 (182 mg, 0.40 mmol) in acetic acid (4.3 mL) and distilled water (0.85 mL). The mixture was stirred at RT for 12h. 6.5 mL of acetic acid were added and the mixture was stirred at 50°C for 3h, and then at 80°C for 2h.

The crude was purified by Reverse phase on (X-Bridge-C18 5µm 30*150mm), mobile phase (Gradient from 90% formic acid 0.1%, 10% CH_3CN to 0% formic acid 0.1%, 100% CH_3CN) to give 44 mg (29% yield) of final compound 18.

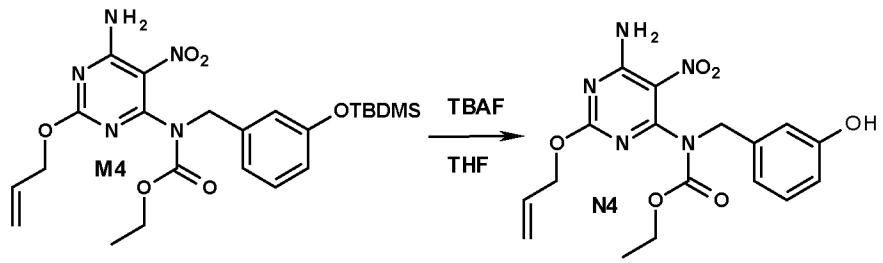
Overall Scheme in the preparation of final products: method 16



Synthesis of intermediate M4:

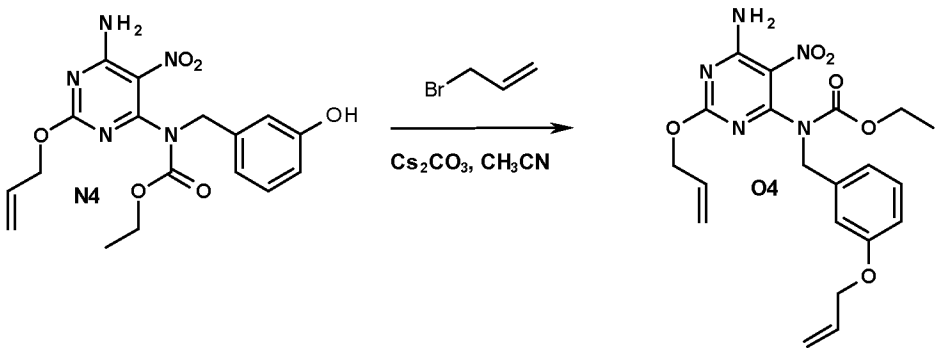
A solution of X3 (1.4 g, 2.66 mmol) and NEt_3 (0.44 mL, 0.46 mmol) in allylic alcohol (14 mL) was stirred at 80°C for 1h. CH_2Cl_2 and H_2O were added and the mixture was decanted. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by preparative LC (irregular SiOH 15-40 µm,

80 g Merck, mobile phase heptane/AcOEt 85/15) to give 500 mg (37% yield) of intermediate M4.



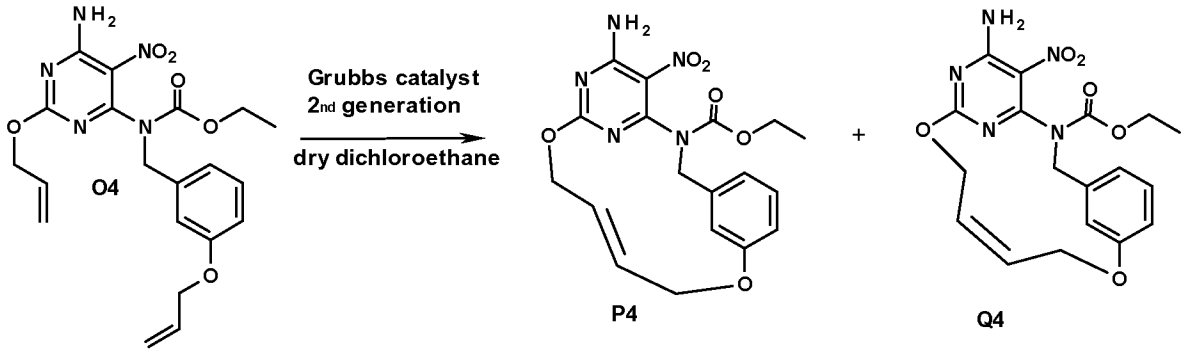
Synthesis of intermediate N4:

Tetrabutylammonium fluoride (4.5 mL, 4.5 mmol) was added drop wise to a solution of M4 (1.9 g, 3.77 mmol) in THF (90 mL) at room temperature. The reaction was stirred at room temperature for 3 hours. The reaction mixture was diluted with EtOAc and poured into water. The organic layer was washed with brine and dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by preparative LC (irregular SiOH 15-40 µm, 40 g Merck, mobile phase heptane/AcOEt 70/30) to give 900 mg (61% yield) of intermediate N4.



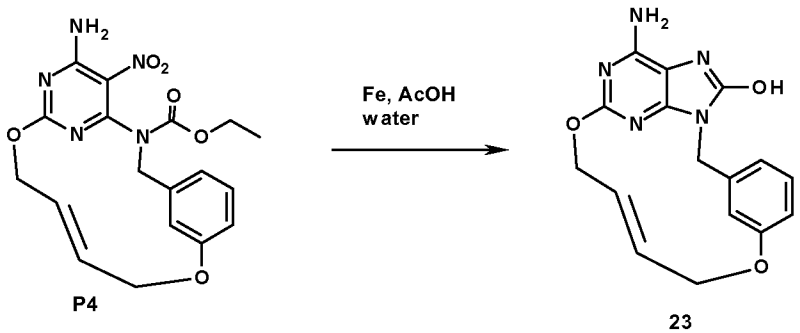
Synthesis of intermediate O4:

A mixture of N4 (2.5 g, 6.42 mmol), Cs_2CO_3 (3.14 g, 9.63 mmol), allyl bromide (0.83 mL, 9.63 mmol) in CH_3CN (100 mL) was stirred at 70°C for 1h. The reaction mixture was poured into ice-water and EtOAc was added. The mixture was basified with an aqueous saturated solution of $NaHCO_3$. The organic layer was then separated, dried over $MgSO_4$, filtered and the solvents were evaporated until dryness. The crude compound was purified by chromatography over silicagel (15-40 µm, 80 g) in heptane/AcOEt 80/20 to give 1.47 g (53% yield) of intermediate O4.



Synthesis of intermediates P4 and Q4:

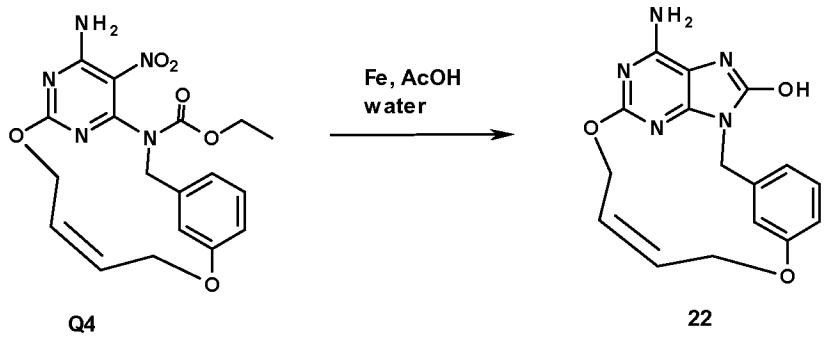
A solution of O4 (400 mg, 0.93 mol) and cholorocyclohexylborane 1 M solution in hexane (186 µL, 0.19 mmol) in dry dichloroethane (220 mL) was stirred at 80°C and under N_2 atmosphere for 1 h. 0.033 eq of Grubbs-Hoveyda catalyst 2nd generation (20 mg, 0.031 mmol) was added and the mixture was stirred in a sealed tube at 120°C for 1 h. The tube was then opened, 0.033 eq of Grubbs-Hoveyda catalyst 2nd generation (20mg, 0.031 mmol) was added and the mixture was stirred in the sealed tube at 120°C for 1 h. The tube was then opened, 0.033 eq of Grubbs-Hoveyda catalyst 2nd generation (20mg, 0.031 mmol) was added and the mixture was stirred in the sealed tube at 120°C for 2 h. SiliaBond® DMT (1.43g, 0.745 mmol) was added to the mixture, which was stirred at RT for 12h. The mixture was filtered through a pad of celite® and concentrated under reduced pressure. The crude product was purified first by preparative LC (irregular SiOH 15-40 µm, 40 g Merck, mobile phase heptane/AcOEt 80/20) and then by achiral SFC on (Amino 6µm 150x21.2mm), mobile phase (83% CO_2, 17% MeOH) to give 55 mg (15%) of intermediate P4 (isomer E) and 80 mg (21% yield) of intermediate Q4 (isomer Z).



Synthesis of final compound 23:

Iron (264 mg, 4.73 mmol) was added to a mixture of P4 (190 mg, 0.47 mmol) in acetic acid (10 mL) and distilled water (2 mL). The mixture was stirred vigorously at 50°C for 5h. The reaction mixture was concentrated under vacuum and the residue was diluted with CH_2Cl_2/MeOH 90/10 and water. The mixture was saturated with K_2CO_3, extracted

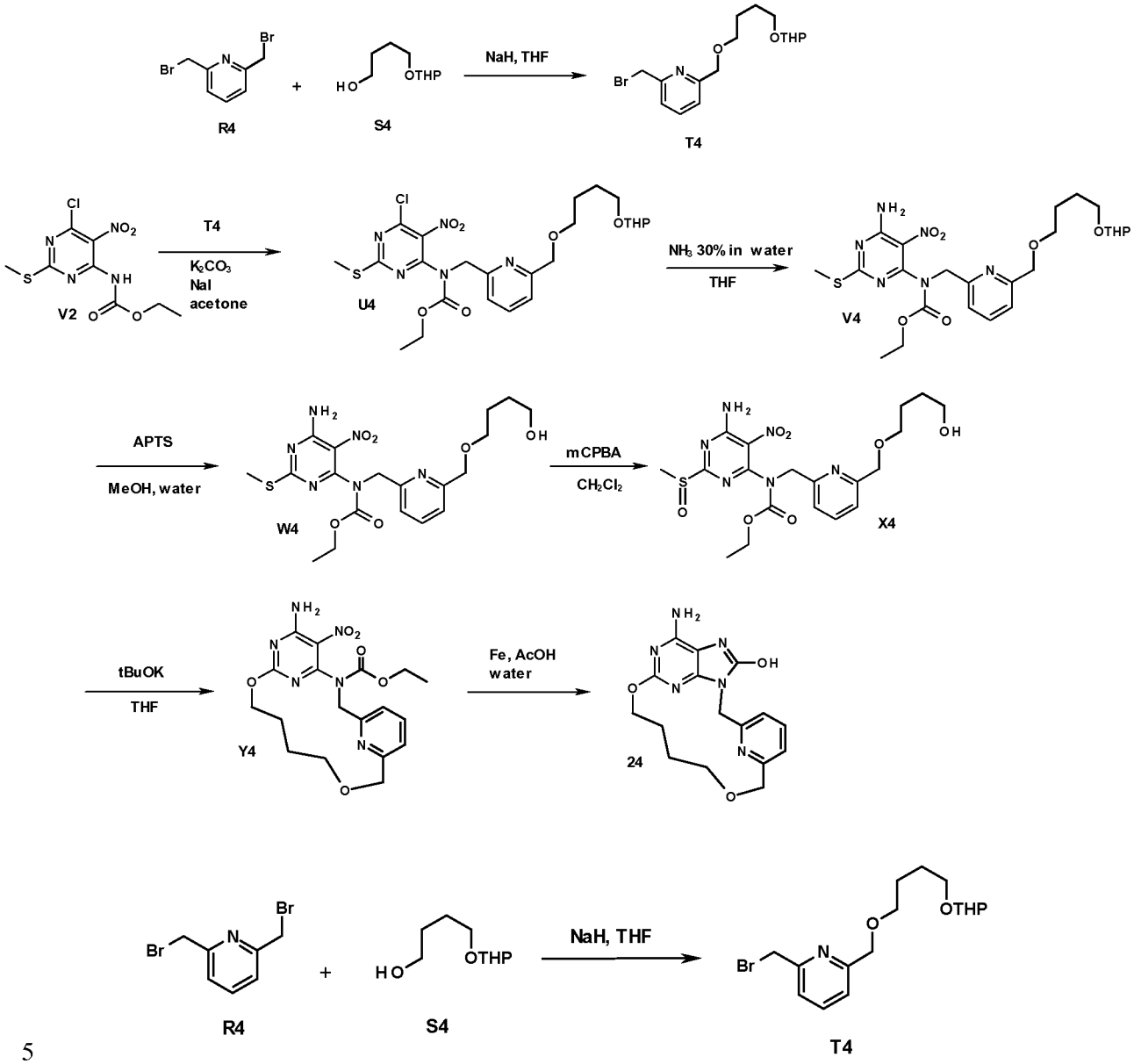
with CH_2Cl_2/MeOH 90/10. The organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The crude compound was purified by chromatography over silicagel (15-40 µm, 40 g) in CH_2Cl_2/MeOH/NH_4OH(90/10/0.5) to give 40 mg (26% yield) of final compound 23.



Synthesis of final compound 22:

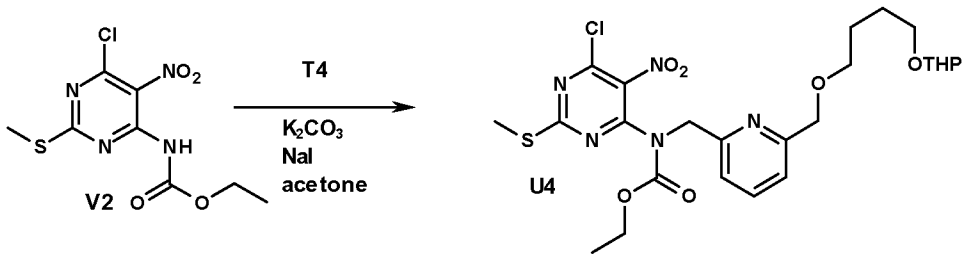
Iron (334 mg, 5.98 mmol) was added to a mixture of Q4 (240 mg, 0.6 mmol) in acetic acid (12 mL) and water (2.5 mL). The mixture was stirred vigorously at 50°C for 5h. The reaction mixture was concentrated under vacuum and the residue was diluted with CH_2Cl_2/MeOH 90/10 and water. The mixture was saturated with K_2CO_3, extracted with CH_2Cl_2/MeOH 90/10. The organics layer were dried over $MgSO_4$, filtered and concentrated under vacuum. The crude compound was purified by chromatography over silicagel (15-40 µm, 40 g) in CH_2Cl_2/MeOH/NH_4OH (90/10/0.5) to give 70 mg (36% yield) of final compound 22.

Overall Scheme in the preparation of final products: method 17



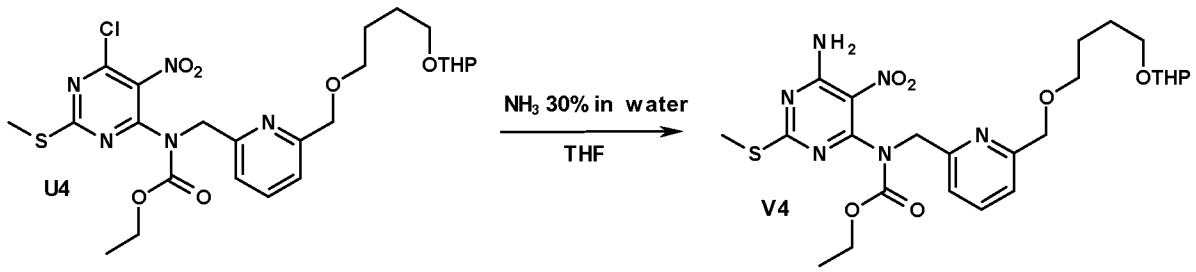
Synthesis of intermediate T4:

At 0°C, NaH (695 mg, 17.36 mmol) was added portion wise to S4 (1.52 g, 8.68 mmol) in THF (70 mL). The mixture was stirred at 0°C for 30 min and then added drop wise at 0°C to R4 (4.6 g, 17.36 mmol) in THF (45 mL). The reaction was stirred at RT overnight. A very little quantity of ice was added and expected compound was extracted with AcOEt. The solvent was evaporated under reduced pressure. The crude product was purified by chromatography over silica gel (15-40 µm; 220 g) in heptane/AcOEt 80/20 to 60/40 to give 1.44 g (23% yield) of intermediate T4.



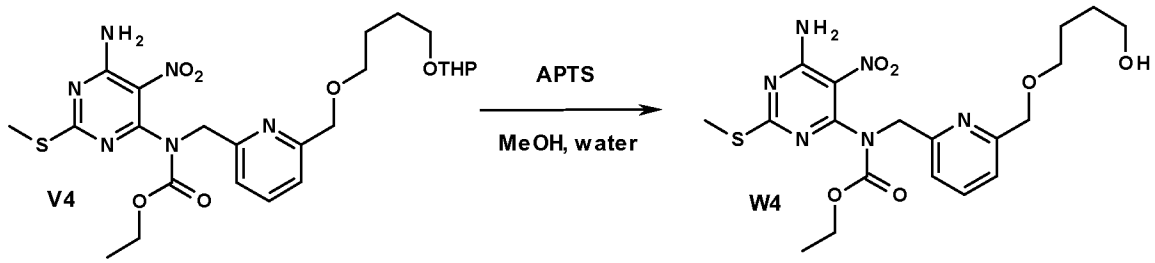
Synthesis of intermediate U4:

A mixture of V2 (1 g, 3.42 mmol), T4 (1.35 g, 3.76 mmol), K_2CO_3 (1.18 g, 8.54 mmol) and NaI (512 mg, 3.42 mmol) in acetone (25 mL) was stirred at RT overnight. The precipitate was filtered off, washed with acetone and the filtrate was concentrated under reduced pressure. The crude product was purified by chromatography over silica gel column (15-41 µm; 40 g) in heptane/AcOEt 80/20 to give 1.4 g (72% yield) of intermediate U4.



Synthesis of intermediate V4:

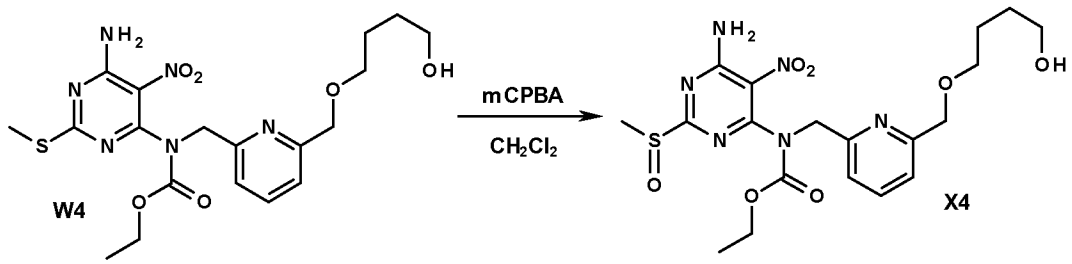
U4 (1.5 g, 2.63 mmol) was stirred in NH_3 30% in water (30 mL) and THF (30 mL) at RT for 2h. The mixture was concentrated under vacuum and the residue was dried by azeotropic distillation with EtOH (twice). The crude product (1.3 g, 89% yield) was used without further purification in the next step.



Synthesis of intermediate W4:

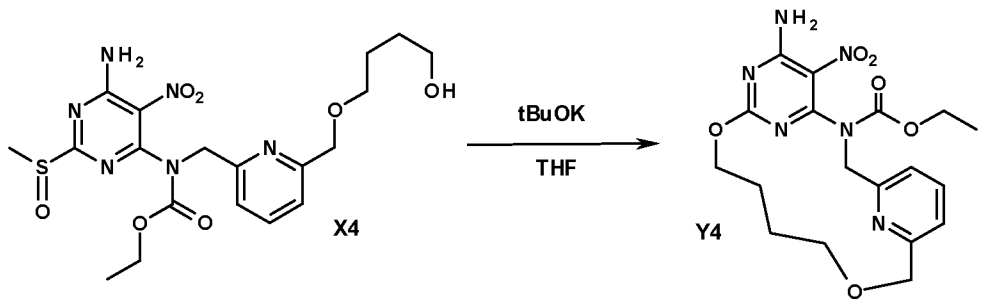
At RT, *para*-toluene sulfonic acid monohydrate (81 mg, 0.47 mmol) was added to a mixture of V4 (2.60 g, 4.72 mmol) in MeOH (26 mL) and water (2.60 mL). The

mixture was stirred at RT overnight and then at 60°C for 12h. The reaction mixture was diluted with EtOAc and was basified with K_2CO_3 10% in water. The organic layer was separated, dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure to give 2 g (90% yield) of intermediate W4.



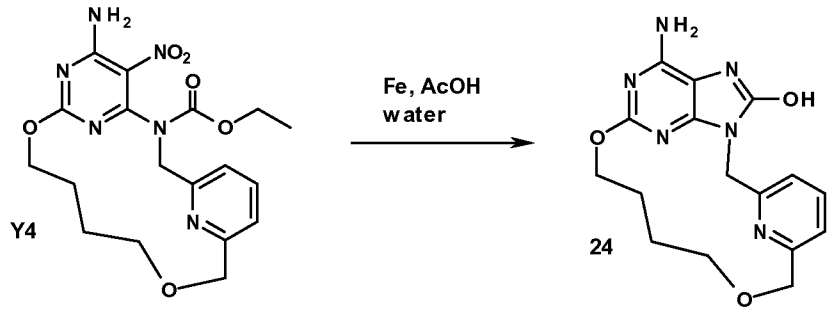
Synthesis of intermediate X4:

Meta-chloroperoxybenzoic acid (951 mg, 3.86 mmol) in CH_2Cl_2 (40 mL) was added drop wise to a solution of W4 (1.80 g, 3.86 mmol) in CH_2Cl_2 (10 mL) at RT. The mixture was stirred at RT for 6h. An aqueous solution of $Na_2S_2O_3$ (2 eq) was added to the mixture. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (twice). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification was carried out by flash chromatography over silica gel (15-40 µm, 80 g, CH_2Cl_2/CH_3OH: 95/5. The pure fractions were collected and evaporated to dryness to give 1.4 g (75% yield) of intermediate X4.



Synthesis of intermediate Y4:

At 0°C, under a N_2 flow, tBuOK (577 mg, 5.14 mmol) was added to a mixture of X4 (1.24 g, 2.57 mmol) in THF (418 mL). The mixture was stirred at 80°C overnight. Water was added and the mixture was extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated. Purification was carried out by flash chromatography over silica gel (15-40µm, 50g, CH_2Cl_2/CH_3OH 98/2). The pure fractions were collected and evaporated to dryness to give 85 mg (7% yield) of intermediate Y4.

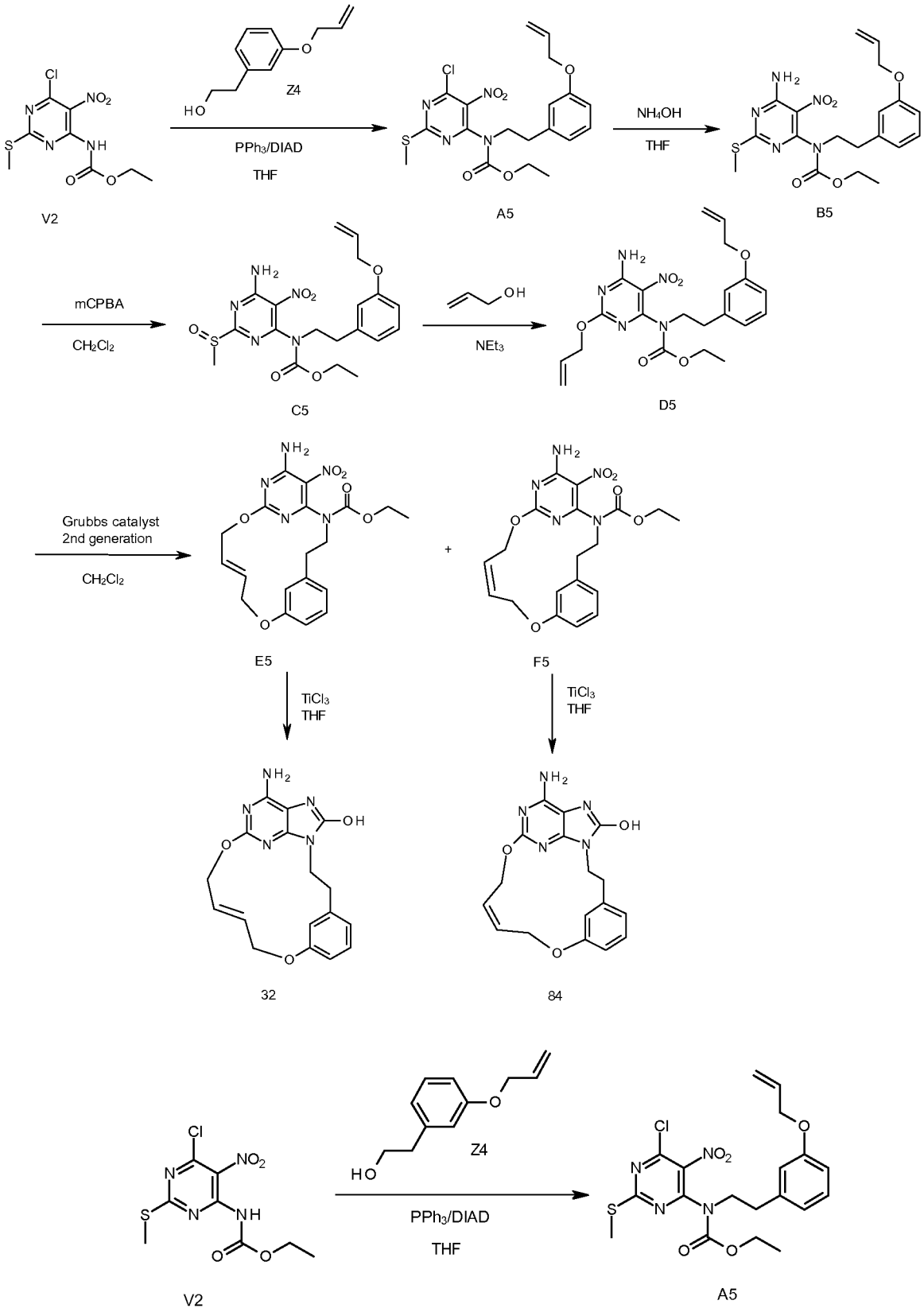


Synthesis of final compound 24:

Iron (68 mg, 1.22 mmol) was added to a mixture of Y4 (85 mg, 0.21 mmol) in acetic acid (2.2 mL) and water (0.24 mL). The mixture was stirred at 50°C for 3h. The mixture was filtered, washed with AcOH and the filtrate was concentrated under reduced pressure. The crude compound was taken up in DMF and 2 g of SiO_2 63-200 µm was added. The resulting suspension was evaporated until dryness and put on a top on a 25 g purification cartridge.

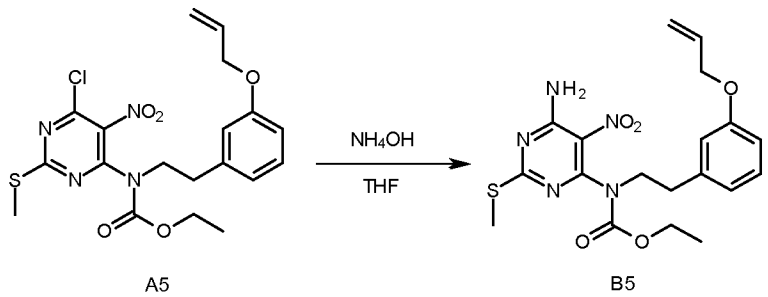
Purification was carried out by flash chromatography over silica gel (15-40 µm, 25 g, $CH_2Cl_2/CH_3OH/NH_4OH$: 95/5/0.5). The pure fractions were collected and evaporated to dryness to give 31 mg. The compound was solidified from CH_3CN, the precipitate was filtered off and dried to give 22 mg (32% yield) of final compound 24.

Overall Scheme in the preparation of final products: method 18



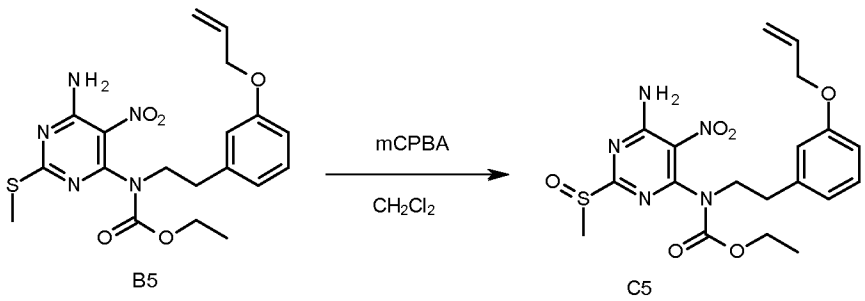
Synthesis of intermediate A5:

At 0°C, diisopropylazodicarboxylate (20.4 mL; 102.5 mmol) was added drop wise to a mixture of V2 (20 g; 68.33 mmol), Z4 (12.2 g; 68.33 mmol) and PPh_3 (27 g; 102.5 mmol) in THF (500 mL). The mixture was stirred at RT for 12h. EtOAc and water were added. The layers were decanted. The organic layer was washed with water, dried over $MgSO_4$, filtered and the solvent was evaporated. The crude compound was purified by flash chromatography over silica gel (15-40 µm, 330 g, CH_2Cl_2/Heptane 70/30). The pure fractions were collected and evaporated to dryness to give 12 g (39% yield) of intermediate A5.



Synthesis of intermediate B5:

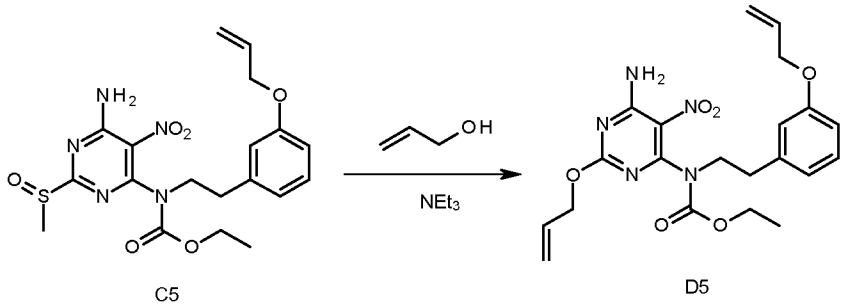
A mixture of A5 (5.4 g; 11.92 mmol) in NH3 30% in water (100 mL) and THF (100 mL) was stirred at RT for 1.3 h. The mixture was concentrated. The residue was taken up with toluene and concentrated (the process was repeated twice) to give 5.15 g of intermediate B5.



Synthesis of intermediate C5:

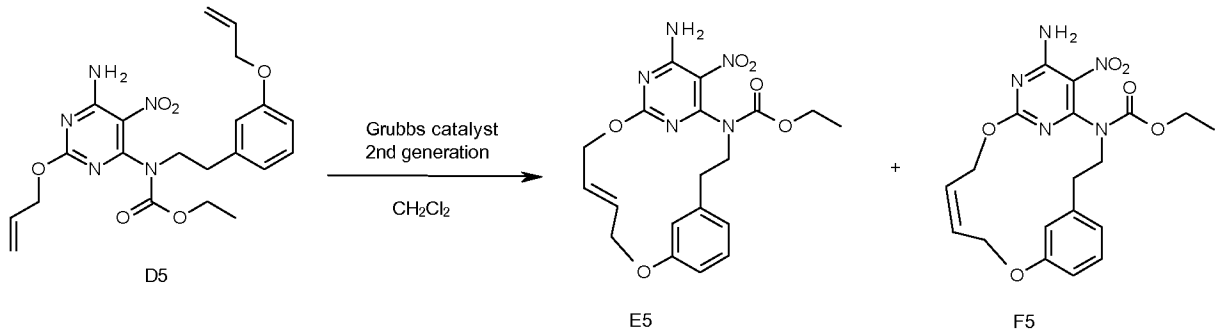
At 0°C, 3-chloroperbenzoic acid (2.93 g; 11.86 mmol) in CH_2Cl_2 (20 mL) was added to a mixture of B5 (5.14 g; 11.86 mmol) in CH_2Cl_2 (100 mL). The mixture was stirred at RT for 3h. An aqueous solution of $Na_2S_2O_3$ (2 eq) was added to the mixture. 2 layers were separated and the aqueous layer was extracted with CH_2Cl_2 (twice). The

combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to give 6.7 g of intermediate C5 (containing sulfone analog) which was directly used in the next step.



Synthesis of intermediate D5:

A mixture of C5 (5.6 g; 12.46 mmol), NEt_3 (2.6 mL; 18.69 mmol) in allyl alcohol (47.6 mL) was stirred at 100°C for 30 min. The mixture was concentrated and the crude compound was purified by flash chromatography over silica gel (15-40 µm, 330 g, Heptane/AcOEt 80/20). The pure fractions were collected and evaporated to dryness to give 3.45 g of intermediate D5 (62% yield).

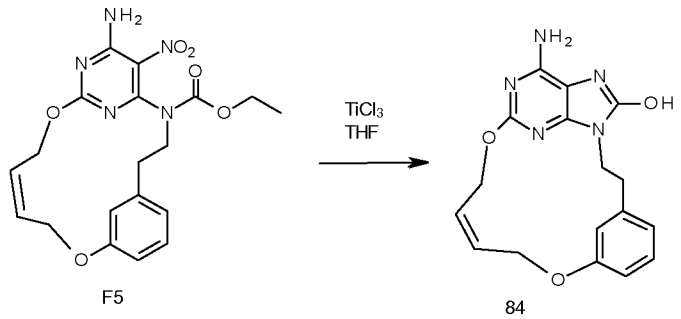


Synthesis of intermediates E5 and F5:

Experiment was performed in 4 batches of 2 g of D5.

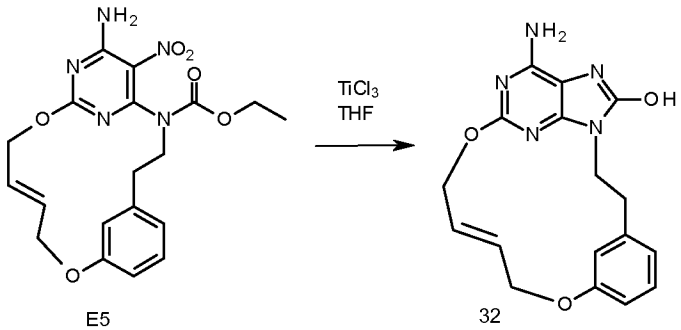
Grubbs catalyst 2nd generation (1.54 g; 1.80 mmol) was added in 3 times (3*514 mg) (at t = 0, t = 12 h, t = 24 h) to a mixture of D5 (8 g; 18.04 mmol) in CH_2Cl_2 extra dry (3470 mL). The mixture was stirred at RT for 36 h. SiliaBond® DMT (24 g; 14.43 mmol) was added then the mixture was stirred 24 h at RT. The solid was filtered off and the solvent was evaporated to give 8.2 g. Purification was carried out by flash chromatography over silica gel (15-40 µm, 330 g, CH_2Cl_2/MeOH 99.5/0.5) The pure fractions were collected and evaporated to dryness to give 4.55 g of a mixture of E5 and F5 after filtration and drying of a solid in CH_2Cl_2/Diisopropylether. The two isomers were separated by achiral SFC (Stationary phase: Chiralpak IA 5 µm 250*20

mm), Mobile phase: 70% CO_2, 30% MeOH) to give 4.07 g of intermediate E5 (isomer E, 54% yield) and 187 mg of intermediate F5 (isomer Z, 2.5% yield).



Synthesis of final compound 84:

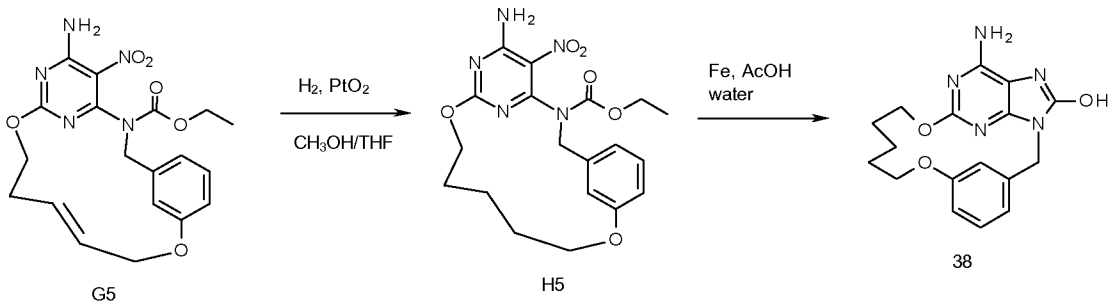
At RT, $TiCl_3$ (5.5 mL; 6.45 mmol) was added drop wise to a mixture of F5 (134 mg; 0.32 mmol) in THF (20 mL). The mixture was stirred at RT overnight. At 0°C, the mixture was basified with K_2CO_3 powder. The resulting muddy mixture was filtered through a pad of celite® and the celite® was washed with a solution of AcOEt/CH_3OH 8/2. The filtrate was dried over $MgSO_4$, filtered and the solvent was evaporated to give 182 mg of a crude compound. MeOH was added, a solid appeared, it was filtered and dried under vacuum at 90°C to 66 mg of final compound 84 (60% yield).



Synthesis of final compound 32:

At RT, $TiCl_3$ (60 mL; 69.811 mmol) was added drop wise to a mixture of E5 (1.45 g; 3.49 mmol) in THF (130 mL). The mixture was stirred at RT overnight. At 0°C, the mixture was basified with K_2CO_3 powder. The resulting muddy mixture was filtered through a pad of celite® and the celite® was washed with a solution of AcOEt/CH_3OH 8/2. The filtrate was partially evaporated to give 1.1 g of crude compound after filtration of a white solid and drying under vacuum. The crude compound was purified by preparative LC (Stationary phase: dry loading 220 g + 10 g 15-40 µm Grace), Mobile phase: 0.5% NH_4OH, 97% CH_2Cl_2, 3% MeOH to 0.5% NH_4OH, 90% CH_2Cl_2, 10% MeOH) to give 730 mg of final compound 32 after evaporation of solvent and drying under vacuum (62% yield).

Overall Scheme in the preparation of final products: method 19



Synthesis of intermediate H5:

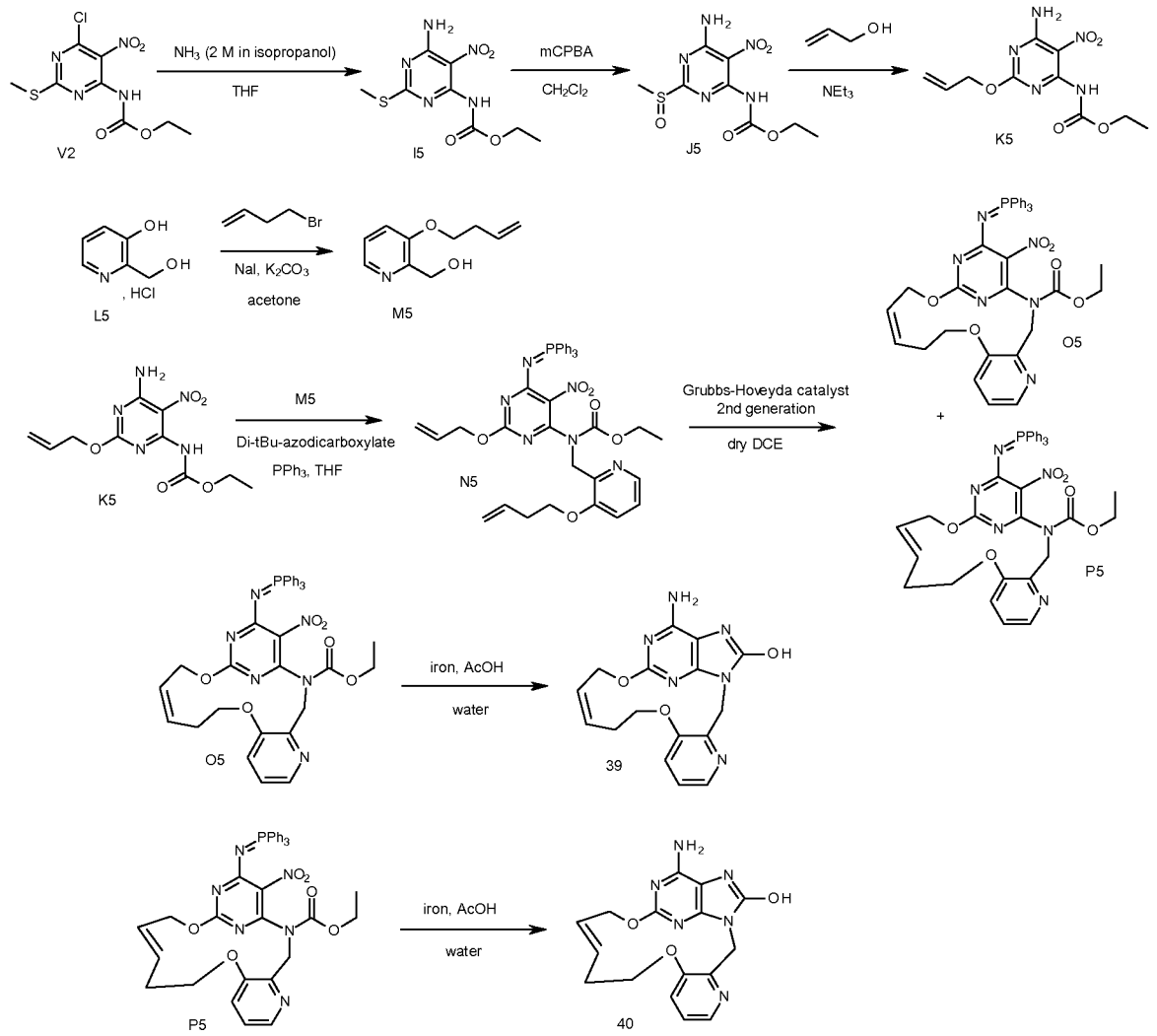
Intermediate G5 was synthesized using the procedure described for intermediate P4.

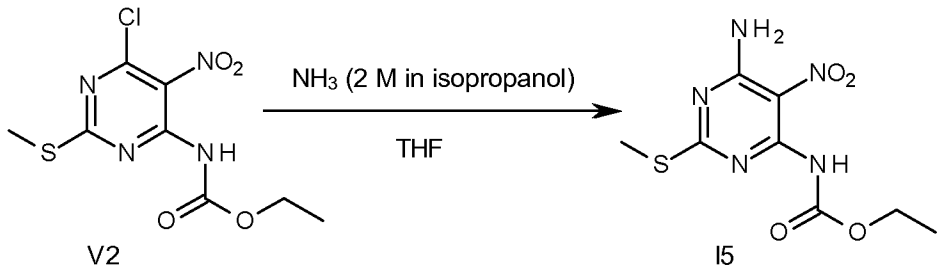
A mixture of G5 (250 mg, 0.60 mmol), PtO_2 (25 mg) in CH_3OH/THF (50/50) (20 mL) was hydrogenated under an atmospheric pressure of H_2 for 30 mn. The catalyst was removed by filtration. The filtrate was concentrated under reduced pressure. The crude compound was purified by preparative LC on (irregular 15-40 µm 30 g Merck), mobile phase (80% Heptane, 20% AcOEt). >The resulting compound was further purified by achiral SFC on (2-Ethylpyridine 6µm 150x30mm), mobile phase (70% CO_2, 30% CH_3OH) to give 113 mg of intermediate H5 (45% yield).

Synthesis of final compound 38:

Iron (147 mg; 2.63 mmol) was added to a mixture of H5 (110 mg; 0.26 mmol) in acetic acid (7m L) and water (1.5 mL). The mixture was stirred vigorously at RT for 6 h at 50°C. The reaction mixture was concentrated in vacuo and the residue was taken up by a mixture of DMF/THF, filtered through a pad of celite® and evaporated. The crude product was diluted with acetic acid/water, a precipitate was filtered off, washed with CH_3OH and dried to give 55 mg of final compound 38 (61% yield).

Overall Scheme in the preparation of final products: method 20





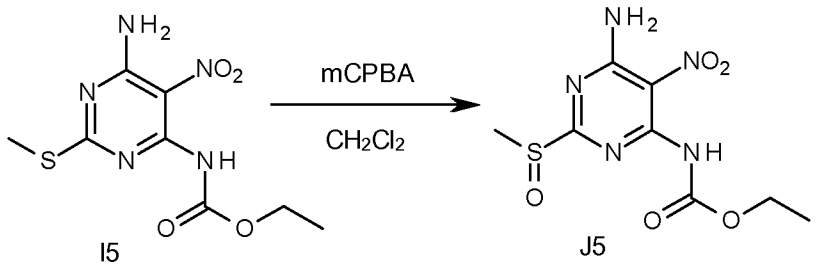
Synthesis of intermediate I5:

The reaction was done in 2 batches of 15 g of V2.

Here is the protocol for one batch of 15 g:

NH_3 (2M in isopropanol) (51 mL; 102 mmol) was added to a solution of V2 (15 g; 51.2 mmol) in THF (250 mL) at RT for 2 h. The two batches were mixed. The suspension

was concentrated to dryness. The solid was dissolved in CH_2Cl_2. The organic layer was washed with water (once), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to give 28.5 g of intermediate I5 (100% yield) as a white solid.

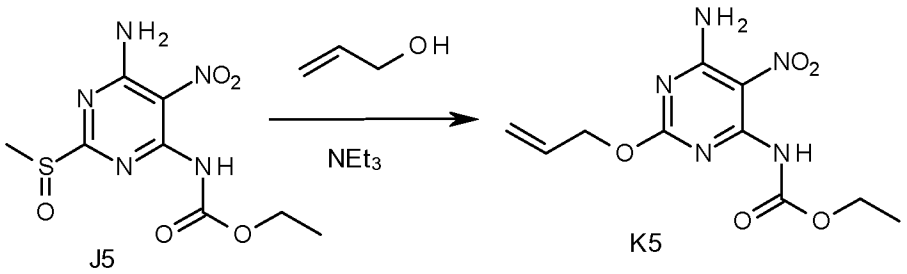


Synthesis of intermediate J5:

The reaction was done in 2 batches of 14 g of I5.

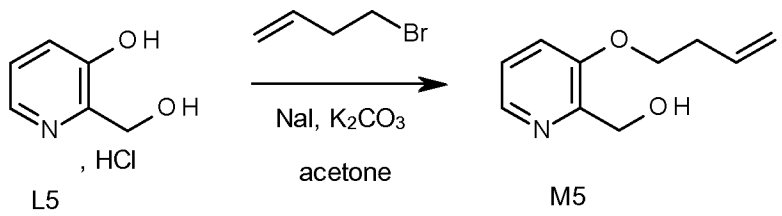
Here is the protocol for one batch of 14 g:

A solution of meta-chloroperbenzoic acid (9.58 g; 40.0 mmol) in CH_2Cl_2 (500 mL) was added drop wise to a solution of I5 (14 g; 33.3 mmol) in CH_2Cl_2 (2 L) at RT. The mixture was stirred at RT for 16 h. The solution was filtered to give 18 g of fraction 1. A 10% aqueous solution of $Na_2S_2O_3$ and a saturated aqueous solution of $NaHCO_3$ were added to the filtrate. The layers were separated and the organic layer was dried over $MgSO_4$, filtered and the solvent was removed in vacuo to give 14 g of intermediate J5 as a yellow solid. The crude compound was used directly in the next reaction step.



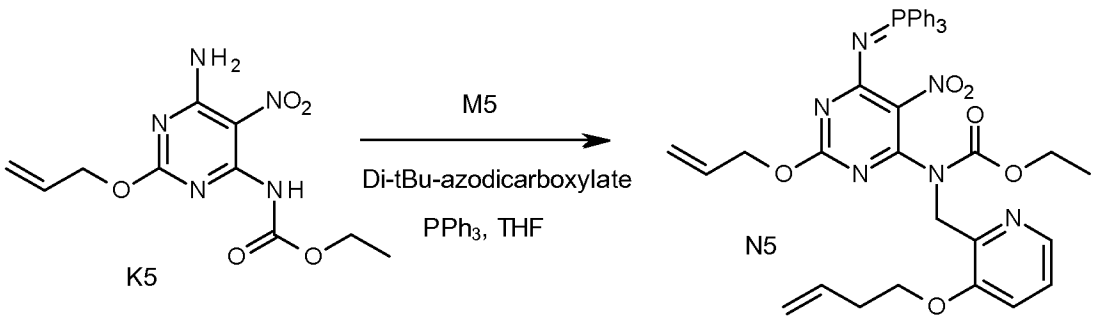
Synthesis of intermediate K5:

A solution of J5 (6 g; 20.7 mmol) and NEt_3 (3.2 mL; 22.8 mmol) in allyl alcohol (120 mL) was stirred at RT for 16 h. The solvent was removed in vacuo to give a yellow solid. The crude compound was purified by preparative LC (Irregular SiOH 15-40 µm, 120 g Grace, mobile phase gradient: from CH_2Cl_2/EtOAc, 100/0 to 85/15) to give 4 g of intermediate K5 as a pale yellow solid (68% yield).



Synthesis of intermediate M5:

To a suspension of L5 (5.2 g; 32.2 mmol) and K_2CO_3 (11.1 g; 80.5 mmol) in acetone (250 mL) was added 4-bromo-1-butene (4.1 mL; 40.2 mmol), and the mixture was heated at 60°C during 16 h. 4-bromo-1-butene (4.1 mL; 40.2 mmol) and NaI (0.965 g; 6.43 mmol) were added, and the mixture was heated at 60°C during 5 days, during which successive additions of 4-bromo-1-butene (2x4.1 mL; 80.4 mmol), K_2CO_3 (2x2.22 g; 32.2 mmol), and NaI (3.86 g; 25.7 mmol) were performed in order to achieve complete conversion, as observed by TLC. The mixture was filtered and the filtrate was concentrated in vacuo to give a brown oil. The crude compound was purified by preparative LC on (Irregular SiOH 20-45 µm, 450 g Matrex), mobile phase (0.7% NH_4OH, 85% Heptane, 15% iPrOH) to afford 3.6 g of intermediate M5 as an orange oil (62% yield).



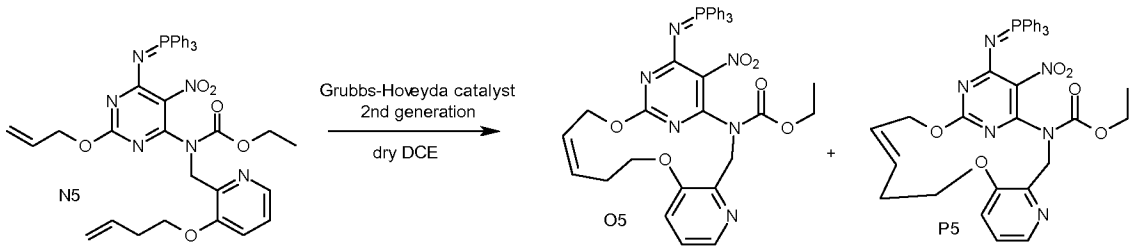
Synthesis of intermediate N5:

The reaction was performed in 3 batches.

Typical procedure for one batch:

Under nitrogen, a solution of K5 (667 mg; 2.35 mmol), M5 (633 mg; 3.53 mmol), PPh_3 (926 mg; 3.53 mmol) and di-tert-butylazodicarboxylate (813 mg; 3.53 mmol) in dry THF (20 mL) was heated at 130°C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 1 h.

The 3 batches were combined and evaporated under vacuum to give 9.8 g of a brown oil. The crude compound was purified by preparative LC on (Irregular SiOH 20-45 µm 450 g Matrex), mobile phase (Gradient from 60% Heptane, 40% AcOEt to 50% Heptane, 50% AcOEt) to afford 1.1 g of intermediate N5 (22% yield) as a yellow solid.

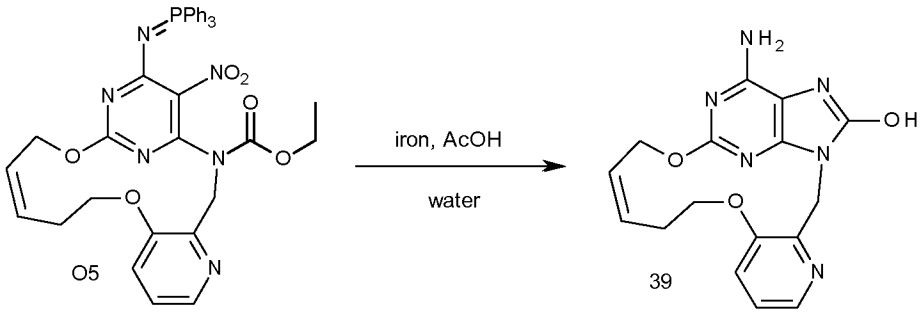


Synthesis of intermediates O5 and P5:

A solution of N5 (950 mg; 1.35 mmol) and chlorodicyclohexylborane (1 M in hexane) (270 µL; 270 µmol) in dry dichloroethane (452 mL) was stirred at 80°C for 1 h. Grubbs-Hoveyda catalyst 2nd generation (35 mg; 56.2 µmol) was added and the mixture was stirred at 120°C for 1 h then more catalyst (35 mg; 56.2 µmol) was added. The mixture was stirred at 120°C for 24 h. Grubbs-Hoveyda catalyst 2nd generation (57 mg; 90.9 mmol) was added again and the mixture was stirred at 120°C for 6 h. SiliaBond® DMT (3.11 g; 1.62 mmol) was added and the mixture was stirred at RT for 24 h, then the dark solid was filtered off and the filtrate was evaporated in vacuo. The crude compound was purified by preparative LC (irregular SiOH 15-40 µm, Merck 90 g; mobile phase gradient: from heptane/iPrOH 90/10 to 65/35) to give 0.12 g of intermediate O5 (13% yield), 0.47 g of a mixture of intermediates O5 and P5 (52% yield) and 28 mg of intermediate P5 (3% yield).

The mixture of intermediates O5 and P5 was further purified by preparative LC (Stability silica 5 µm 150x30.0 mm, mobile phase gradient: from heptane/AcOEt 85/15 to 0/100) to give 120 mg of intermediate O5 and 224 mg of intermediate P5.

global yield : 54% (E-isomer O5: 28%, Z-isomer P5: 26%).

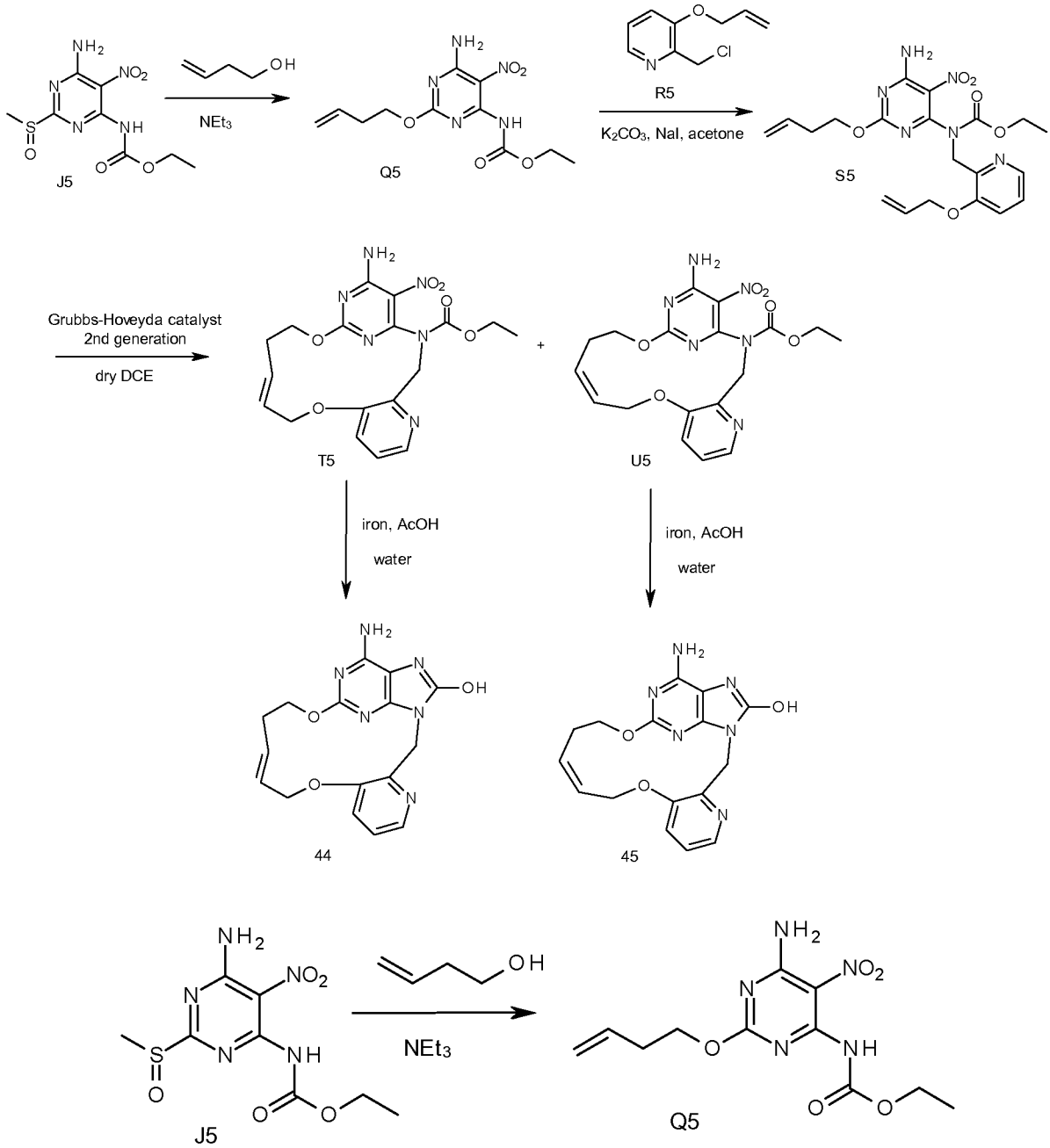


Synthesis of final compound 39:

A mixture of O5 (240 mg; 0.355 mmol) and iron (119 mg; 2.13 mmol) in acetic acid (4.3 mL) and water (0.4 mL) were heated at 100°C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 1 h. The

solvent was removed in vacuo and the residue was taken up with DMF. The mixture was filtered over celite® and the filtrate was evaporated in vacuo to give fraction 1. SiliaBond® imidazole (Fe scavenger from Silicycle®) (3.67 g; 4.25 mmol) was added to fraction 1 in DMF (50 mL). The mixture was stirred at RT for 16 h and filtered over celite® and the filtrate was evaporated in vacuo to give 100 mg of fraction 2. Fraction 2 was purified by preparative LC (irregular SiOH 15-40 µm, 25 g Merck, dry loading, mobile phase gradient: from CH_2Cl_2/MeOH/NH_3aq 95/5/0.5 to 85/15/1.5) to give 9 mg of final compound 39 as a white solid (7% yield).

Overall Scheme in the preparation of final products: method 21

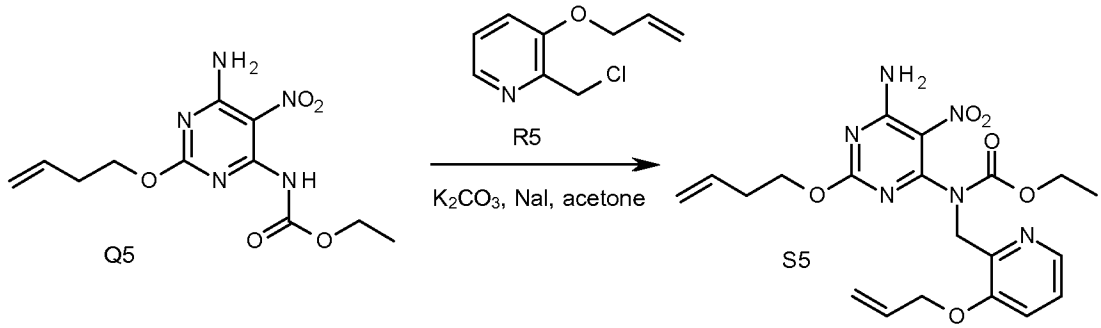


Synthesis of intermediate Q5:

The reaction was done in 3 batches of 20 g of intermediate J5.

Here is the protocol for one batch of 20 g:

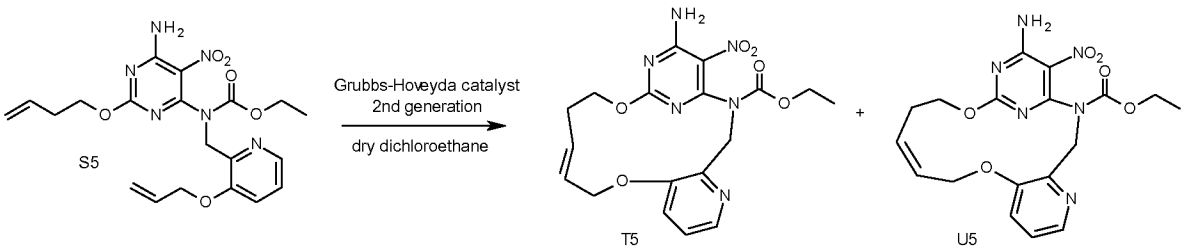
A solution of J5 (20 g; 69.1 mmol) and NEt_3 (11.5 mL; 83.0 mmol) in 3-buten-1-ol (500 mL) was stirred at RT for 16 h. The solvent was removed in vacuo to give a yellow solid. The combined 3 reactions were purified by preparative LC (Irregular SiOH 15-40 µm, 750 g Grace, mobile phase gradient: CH_2Cl_2/EtOAc from 100/0 to 80/20). The fractions containing product were combined and the solvent was removed in vacuo to give 39 g of intermediate Q5 (63% yield).



Synthesis of intermediate S5:

Q5 (12.8 g; 43.2 mmol), R5 (16.1 g; 77.8 mmol), K_2CO_3 (14.9 g; 108 mmol) and NaI (6.48 g; 43.2 mmol) in acetone (690 mL) were stirred at RT for 1 h and then the mixture was heated at 75°C for 16 h. The mixture was cooled to RT and was filtered through a pad of celite®. The filtrate was evaporated in vacuo to give fraction 1. Fraction 1 was combined with another batch (reaction with 67.46 mmol of Q5) to be purified by preparative LC (2 serial chromatography, irregular SiOH, 15-40 µm, 220 g Grace, liquid injection, mobile phase gradient: from CH_2Cl_2/EtOAc 100/0 to 50/50) to give 1.97 g of fraction 2 as a brown solid and 10.7 g of fraction 3 as a brown solid.

The two fractions were taken up and diluted with CH_2Cl_2. Heptane was added and the mixture was partially evaporated in vacuo to give a pale brown precipitate which was filtered off to give 11.26 g of intermediate S5 as an off-white solid (59% yield).

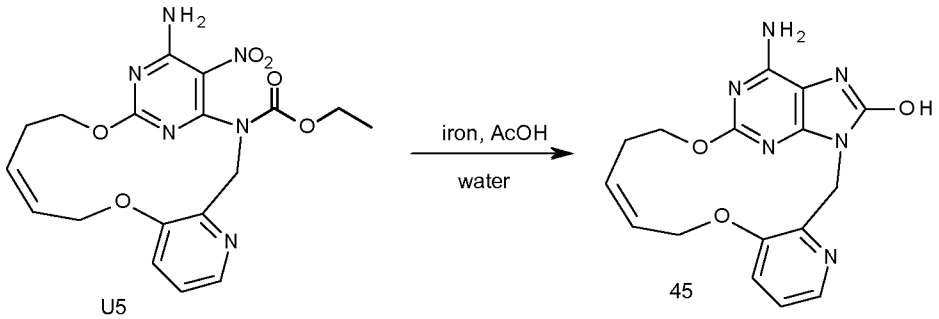


Synthesis of intermediates T5 and U5:

This reaction was performed in 2 batches using respectively 2.75 g and 1.51 g of intermediate S5.

Typical procedure for 1 batch:

A solution of S5 (1.51 g; 3.40 mmol) and chlorodicyclohexylborane (1M in hexane) (0.679 mL; 0.679 mmol) in dry dichloroethane (908 mL) degassed by N_2 bubbling for 15 min was stirred at 80°C under N_2 atmosphere for 1 h. Grubbs-Hoveyda catalyst 2nd generation (213 mg; 0.340 mmol) was added and the mixture was stirred at 80°C for 1 h. SiliaBond® DMT (4.45 g; 2.72 mmol) was added and the resulting mixture was stirred at RT for 20 h. The 2 batches were combined and filtered through a pad of celite®. The filtrate was evaporated in vacuo to give 4.2 g of a brown solid. The solid was purified by preparative LC (regular SiOH, 30 µm, 200 g Interchim, mobile phase gradient: from CH_2Cl_2/AcOEt 100/0 to 25/75) to give 2.5 g of fraction 1 and 1.3 g of of intermediate T5 (32%, E isomer). Fraction 1 was taken-up with CH_2Cl_2 then heptane was added. CH_2Cl_2 was partially evaporated in vacuo and the resulting precipitate was filtered and dried under vacuum to give 1.52 g of intermediate U5 (38% yield, Z isomer).



Synthesis of final compound 45:

This reaction was performed in 5 batches using respectively 0.5 g, 3 times 1 g, and two times 1.45 g of intermediate U5.

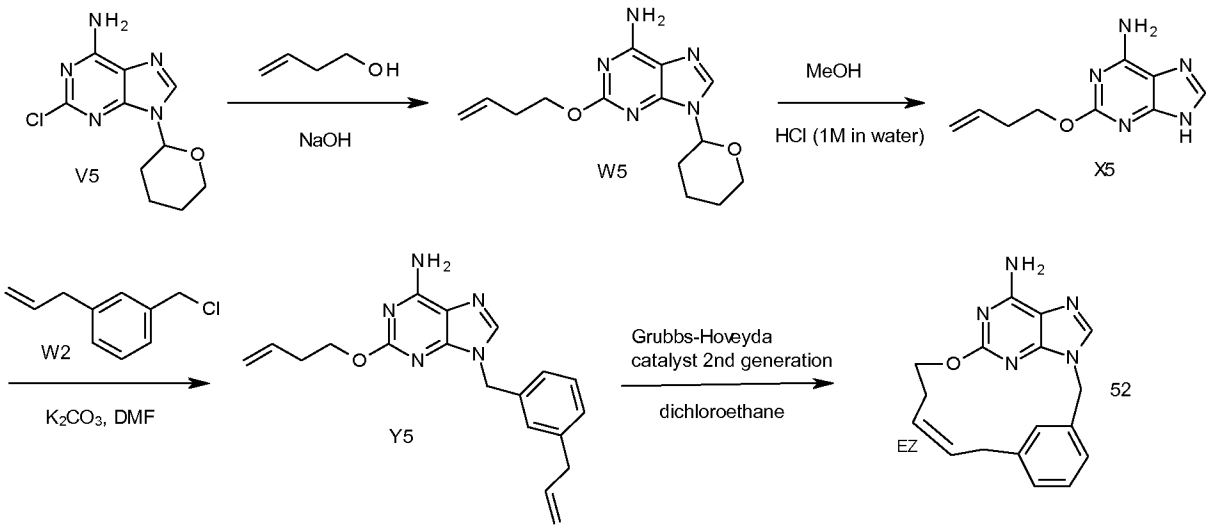
Here is the procedure for 2 batches of 1.45 g:

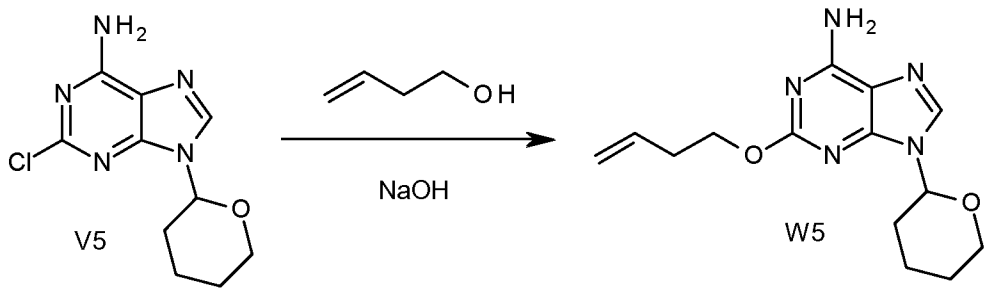
Under N_2 atmosphere, U5 (1.45 g; 3.48 mmol) was added portion wise to a solution of acetic acid (193 mL) and water (19 mL) heated at 70°C. After complete dissolution, iron (1.17 g; 20.9 mmol) was added in one portion and the mixture was stirred at 70°C for 4 h. The 2 batches were combined and filtered hot through a pad of celite® and the celite® was rinsed with hot acetic acid. The resulting filtrate was concentrated to give a brown residue which was taken up with MeOH, sonicated and heated to give a yellow precipitate which was filtered off to give fraction 1 as a yellow solid. Fraction 1 was taken up with acetic acid (30 mL) and sonicated until partial dissolution. Water was

added (700 mL) and the resulting mixture was sonicated for 1 h, cooled to 0°C (ice bath) to give a precipitate which was filtered off (glass frit n°5) to give an off-white solid. The solid was taken up with MeOH, mixed with 3 other batches (obtained with 0.5 g and 2 times 1 g of U5). The resulting mixture was sonicated, heated and cooled to 0°C (ice bath) and the resulting solid was filtered off (glass frit n°4) to give 3.5 g of fraction 2 as an off-white solid. Fraction 2 was mixed with the last batch (obtained with 1 g of U5), DMSO (280 mL) was added and the mixture was heated at 100°C until complete dissolution. The resulting solution was filtered off and the filtrate was added to water (1.7 L). The resulting precipitate was stirred at RT for 16 h. The precipitate was filtered off to give 4.1 g of fraction 3 as an off-white solid.

Fraction 3 was taken up with EtOH and was sonicated at 45°C for 2 h. The resulting mixture was directly filtered off (glass frit n°4) to give 3.63 g of fraction 4 as an off-white solid. Fraction 4 was taken up with MeOH (180 mL) and the mixture was stirred at 60°C for 1 h. The mixture was filtered hot to give 3.47 g of final compound 45 as an off-white solid (54% yield).

Overall Scheme in the preparation of final products: method 22



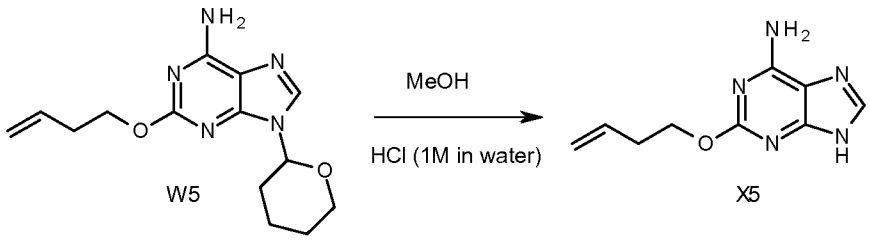


Synthesis of intermediate W5:

This reaction was performed in 3 batches using respectively 0.2 g, 1.5 g, and 4 g of intermediate V5.

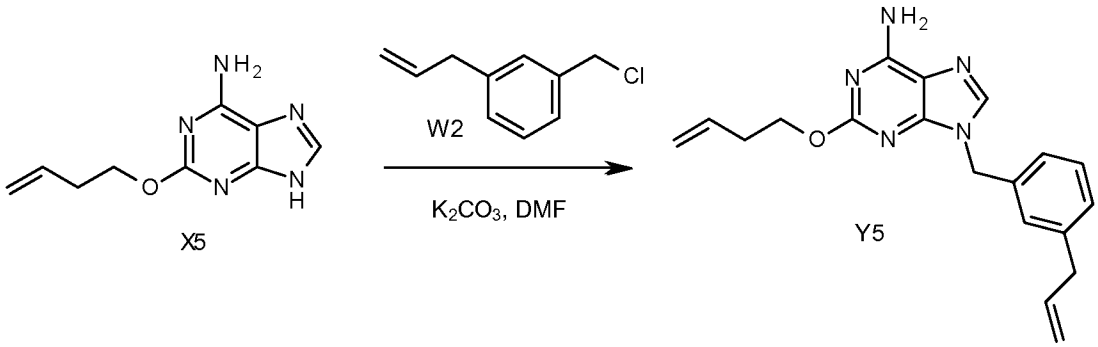
Here is the procedure for the 4 g batch:

V5 (4 g; 15.8 mmol), NaOH (2.52 g; 63.1 mmol) and 3-buten-1-ol (100 mL) were stirred at 90°C for 24 h. The solvent was removed under reduced pressure to give fraction 1 as a brown oil. Fraction 1 was combined with the two other batches to give fraction 2. Fraction 2 was purified by preparative LC (Irregular SiOH 15-40 µm, 80 g Grace, dry loading, mobile phase gradient: CH_2Cl_2/MeOH/NH_3aq from 97/3/0.03 to 80/20/2) to give 3.88 g of intermediate W5 as an orange solid (60% yield).



Synthesis of intermediate X5:

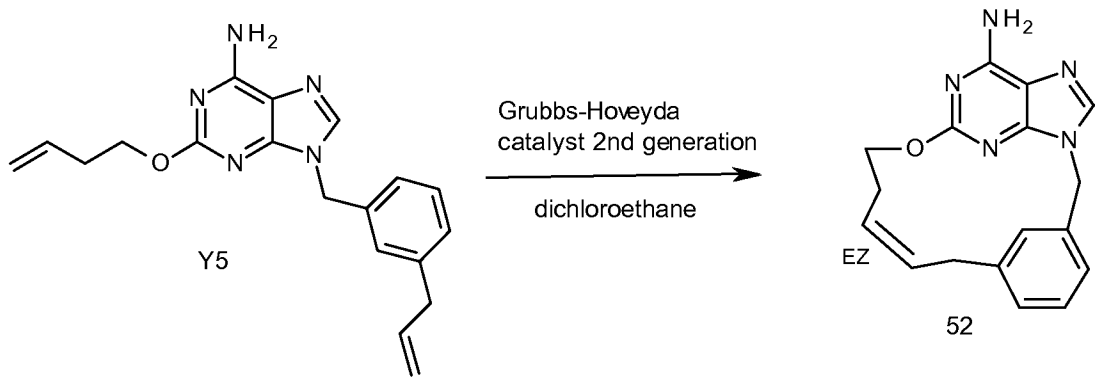
HCl (1 M in water) (2 mL) was added to a stirred solution of W5 (3.88 g; 13.4 mmol) in MeOH (160 mL) at RT. The resulting mixture was stirred at 60°C for 4 h. Then HCl (3 M in water) (2 mL) was added and the mixture was stirred at 60°C for 64 h. The reaction mixture was concentrated in vacuo, the resulting residue was taken up with CH_2Cl_2, filtered off and dried under reduced pressure to give 2.72 g of intermediate X5 as a pale brown solid (84% yield). The compound was used directly in the next reaction step.



Synthesis of intermediate Y5:

W2 (2.34 g; 14.0 mmol) was added to a stirred solution of X5 (2.62 g; 12.8 mmol) and K_2CO_3 (3.9 g; 28.1 mmol) in DMF (40 mL). The mixture was stirred at RT for 1 h and then at 70°C for 3 h. The reaction mixture was cooled to RT, diluted with MeOH and

filtered on a pad of celite®. The resulting filtrate was concentrated in vacuo to give fraction 1. Fraction 1 was purified by preparative LC (Irregular SiOH 15-40 µm, 80 g Grace, dry loading, mobile phase gradient: CH_2Cl_2/MeOH/NH_3aq from 100/0/0 to 80/20/2) to give 4.6 g of an orange solid. The solid was purified by preparative LC (Irregular SiOH 15-40 µm, 80 g Grace, dry loading, mobile phase gradient: Heptane/CH_2Cl_2/MeOH from 100/0/0 to 0/90/10) to give 3 g of intermediate Y5 a pale orange solid. The compound was used as such in the next reaction step.



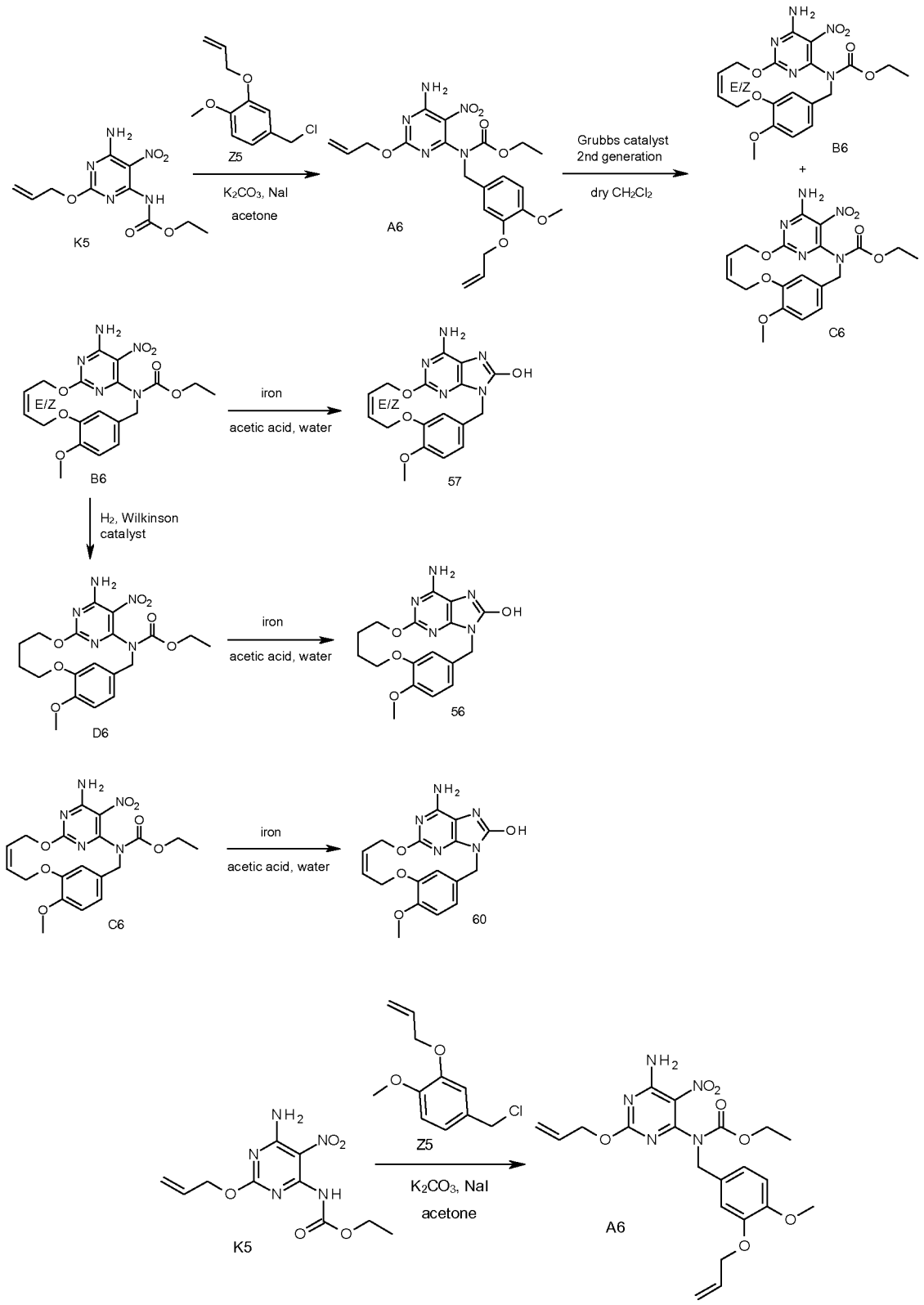
Synthesis of final compound 52:

The reaction was performed in 2 batches of 250 mg of intermediate Y5.

Herein is reported the procedure for one batch of 250 mg:

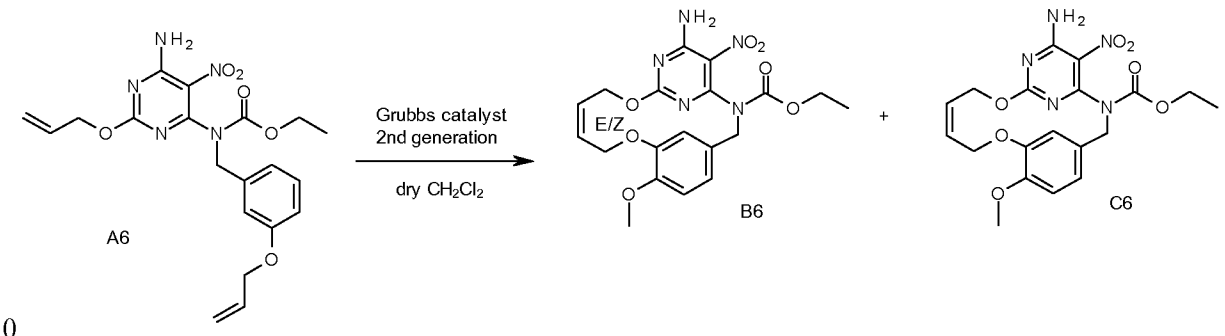
In a schlenk flask, Y5 (250 mg; 0.745 mmol) was dissolved in dry dichloroethane (250 mL) and the solution was degassed by N_2 bubbling through the solution for 20 min. Chlorodicyclohexylborane (1 M in hexane) (150 µL; 150 µmol) was added and the resulting solution was stirred at 70°C for 1 h. Grubbs-Hoveyda catalyst 2nd generation (23 mg; 37.3 µmol) was added and the mixture was stirred at 120°C for 16 h. Catalyst (23 mg; 37.3 µmol) was added again and the mixture was stirred at 120°C for 4 h. Catalyst (9 mg; 14.9 µmol) was added again and the mixture was stirred at 120°C for 3 h. SiliaBond® DMT (1.19 g; 0.716 mmol) was added and the mixture was stirred at RT for 16 h. The two batches were mixed and filtered through a pad of celite®. The resulting filtrate was concentrated to give a brown residue. The residue was purified by preparative LC (Irregular SiOH 15-40 µm, 40 g Merck, dry loading, mobile phase gradient: CH_2Cl_2/MeOH/NH_3aq from 100/0/0 to 80/20/0.2) to give 155 mg of final compound 52 as an off-white solid (E/Z mixture, 34% yield).

Overall Scheme in the preparation of final products: method 23



Synthesis of intermediate A6:

K5 (3.0 g; 10.6 mmol), Z5 (2.5 g; 11.7 mmol), K_2CO_3 (2.93 g; 21.2 mmol) and NaI (1.6 g; 10.6 mmol) in acetone (150 mL) were stirred at 75°C for 16 h. The solution was filtered and the filtrate was evaporated under reduced pressure to give fraction 1. Fraction 1 was purified by preparative LC (Irregular SiOH 15-40 µm, 90 g Merck, mobile phase gradient: from Heptane/CH_2Cl_2/EtOAc 100/0/0 to 0/90/10). The fractions containing product were combined and the solvent was removed in vacuo to give 4.4 g of intermediate A6 (90% yield) as a yellow solid.



Synthesis of intermediates B6 and C6:

The reaction was performed in 2 batches of 1.5 g and one batch of 1.2 g of intermediate A6.

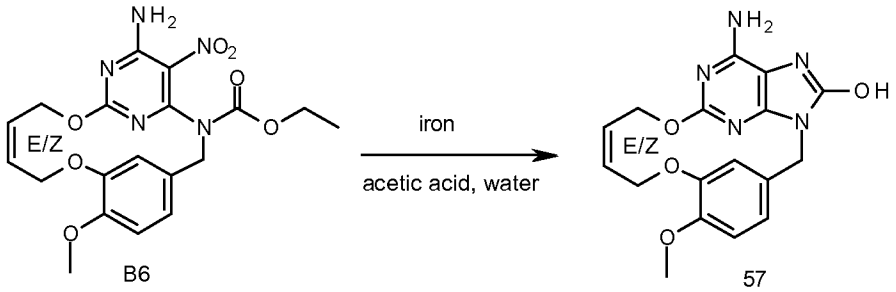
Herein is reported the procedure for one batch of 1.5 g:

A6 (1.5 g; 3.27 mmol) was added to dry CH_2Cl_2 (900 mL) and the resulting mixture was degassed by N_2 bubbling through the solution for 30 min. Grubbs catalyst 2nd generation (92 mg; 108 µmol) was added in one portion and the mixture was stirred at RT under N_2 atmosphere for 2 h. Catalyst (92 mg; 108 µmol) was added again in one portion and the mixture was stirred at RT under N_2 atmosphere for 16 h. Catalyst (92 mg; 108 µmol) was added again in one portion and the mixture was stirred at RT under N_2 atmosphere for 48 h.

The 3 batches were mixed, SiliaBond® DMT (12 g; 7.31 mmol) was added and the mixture was stirred at RT for 16 h. The reaction mixture was filtered through a pad of celite® and the filtrate was evaporated in vacuo to give fraction 1 as a brown solid. Fraction 1 was purified by preparative LC (Irregular SiOH 15-40 µm, 70 g Merck, mobile phase gradient: CH_2Cl_2/EtOAc from 100/0 to 80/20). The fractions containing product were combined and the solvent was removed in vacuo to give fraction 2 and fraction 3. Fraction 2 was solubilized in hot EtOH/Acetone. The mixture was left to cool down to RT. Then the precipitate was filtered off, washed (3 times) with 20 mL of EtOH and dried in vacuo to give 800 mg of intermediate B6 (E/Z mixture) as a yellow solid.

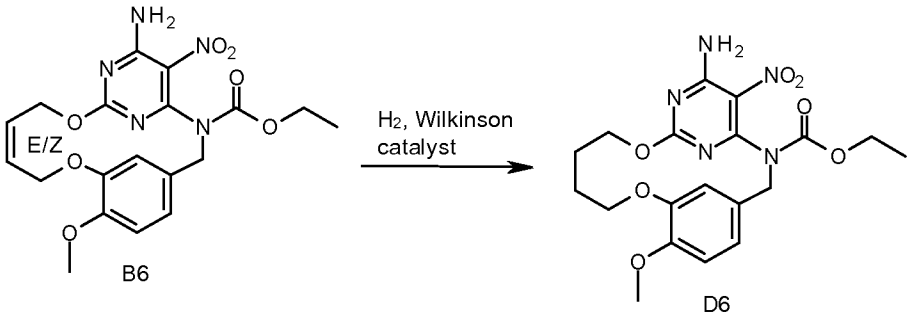
Fraction 3 was solubilized in hot EtOH/Acetone. The mixture was allowed to cool down to RT. Then the precipitate was filtered off, washed (3 times) with 15 mL of EtOH and dried in vacuo to give 300 mg of intermediate B6 (E/Z mixture) as a yellow solid.

Part of intermediate B6 (100 mg) was purified by achiral SFC (Stationary phase: AMINO 6µm 150x21.2 mm, Mobile phase: CO_2/MeOH; 75/25) to give 78 mg of intermediate C6 (E isomer) as a yellow solid.



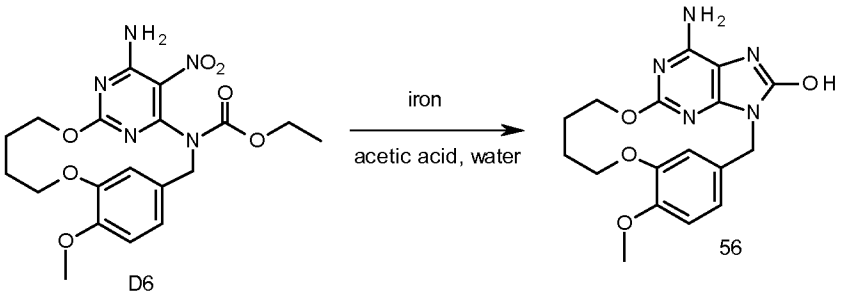
Synthesis of final compound 57:

A mixture of B6 (150 mg; 348 µmol) and iron (117 mg; 2.09 mmol) in acetic acid (10 mL) and water (1 mL) was stirred at 80°C for 2 h. The mixture was filtered through a pad of celite® and the filtrate was evaporated in vacuo to give fraction 1. Fraction 1 was taken up with DMF. SiliaBond® imidazole (3.6 g; 4.17 mmol) was added and the reaction was stirred at RT for 16 h. The solution was filtered through a pad of celite®. The filtrate was evaporated in vacuo. The residue was taken up with acetic acid and water (30:70). The precipitate was filtered and dried under vacuum to give fraction 2. Fraction 2 was taken up with MeOH. The precipitate was filtered and dried under vacuum to give fraction 3. Fraction 3 was filtered through a pad of silica gel (mobile phase: DMF), the fractions containing product were combined and the solvent was removed in vacuo to give fraction 4. Fraction 4 was taken up with DMF. SiliaBond® imidazole (3.6 g; 4.17 mmol) was added and stirred at RT for 16 h. The solution was filtered through a pad of celite®. The filtrate was evaporated in vacuo to give fraction 5. Fraction 5 was taken up with acetic acid and water (70:30). The precipitate was filtered and dried under vacuum to give fraction 6. Fraction 6 was purified by preparative LC (Irregular SiOH 15-40 µm, 10 g Merck, mobile phase gradient: CH_2Cl_2/MeOH/NH_3aq from 97/3/0.1 to 80/20/3). The fractions containing product were combined and the solvent was removed in vacuo to give 35 mg of fraction 7 as a white solid. Fraction 7 was taken up with water. The precipitate was filtered, washed (twice) with EtOH and Et_2O, dried under vacuum to give 26 mg of final compound 57 as a white solid (21% yield).



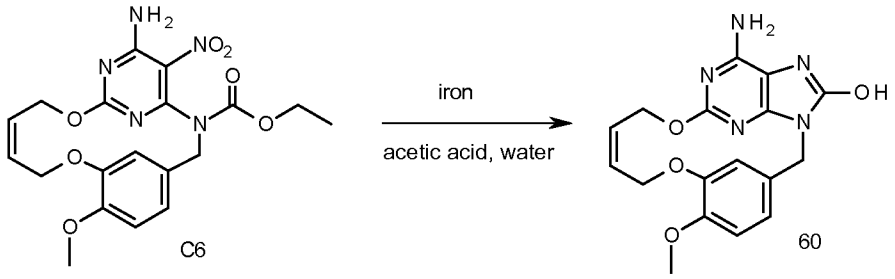
Synthesis of intermediate D6:

A mixture of B6 (300 mg; 695 µmol), Wilkinson's catalyst (64 mg; 69.5 µmol) in THF/MeOH (50/50) (60 mL) was hydrogenated under 7 bars pressure at RT for 20 h. The mixture was filtered through a pad of celite® and the filtrate was evaporated in vacuo to give a brown solid. The crude compound was purified by preparative LC (Irregular SiOH 15-40 µm, 25 g Merck, mobile phase gradient: CH_2Cl_2/EtOAc from 100/0 to 80/20). The fractions containing product were combined and the solvent was removed in vacuo to give 305 mg of intermediate D (quantitative yield) as a yellow solid.



Synthesis of final compound 56:

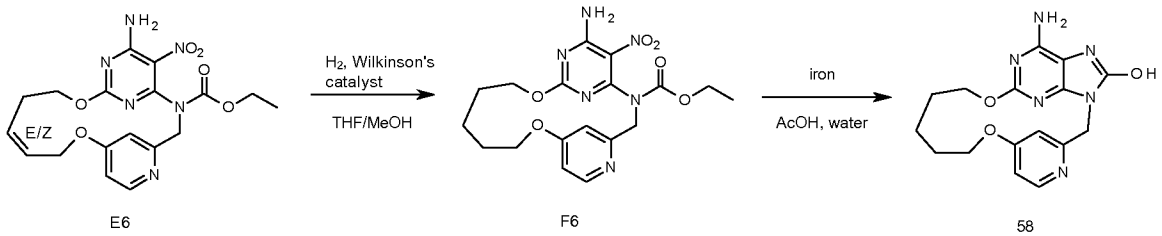
A mixture of D6 (250 mg; 577 µmol) and iron (193 mg; 3.46 mmol) in acetic acid (30 mL) and water (3 mL) was stirred at 120°C for 6 h, then 2 h at 140°C. The mixture was evaporated in vacuo to give fraction 1. Fraction 1 was taken up with DMF and filtered through a pad of celite® and the filtrate was evaporated in vacuo to give Fraction 2. Fraction 2 was taken up with AcOH and water (30:70). The solution was extracted with CH_2Cl_2/MeOH (9:1) (twice). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to give fraction 3. Fraction 3 was purified by preparative LC (Irregular SiOH 15-40 µm, 12 g Grace, mobile phase gradient: CH_2Cl_2/MeOH/NH_3aq from 97/3/0.1 to 80/20/3). The fractions containing product were combined and the solvent was removed in vacuo to give 90 mg of final compound 56 (44% yield) as a white solid.



Synthesis of final compound 60:

A mixture of C6 (70 mg; 162 µmol) and iron (54 mg; 974 µmol) in acetic acid (10 mL) and water (1 mL) was stirred at 120°C for 5 h. The mixture was evaporated in vacuo to give fraction 1. Fraction 1 was taken up with DMF and filtered through a pad of celite® and the filtrate was evaporated in vacuo to give fraction 2. Fraction 2 was taken up with AcOH and water (30:70). The precipitate was filtered, washed (twice) with EtOH then Et_2O and dried under vacuum to give 46 mg of final compound 60 (80% yield) as a white solid.

Overall Scheme in the preparation of final products: method 24



Synthesis of intermediate E6:

Intermediate E6 (mixture of E and Z isomers, 90 mg, 17% yield) was synthesized using the procedure described for intermediates T5 and U5.

Synthesis of intermediate F6:

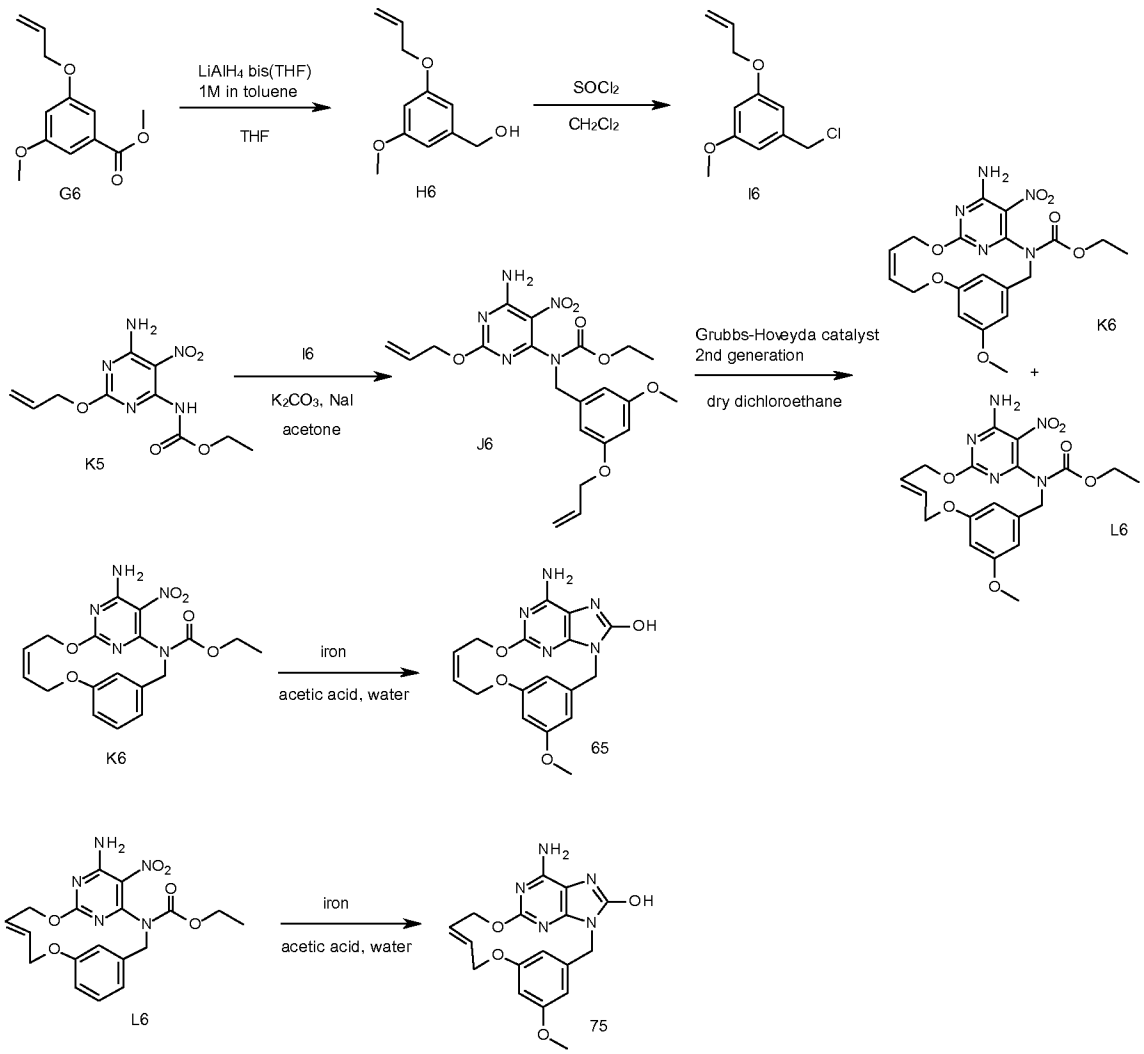
A solution of E6 (90 mg; 216 µmol) and Wilkinson's catalyst (20 mg; 21.6 µmol) in THF (7 mL) and MeOH (7 mL) was degassed by N_2 bubbling for 10 min. The mixture was hydrogenated under 5 bars pressure at RT for 16 h. The mixture was degassed by N_2 bubbling for 10 min and Wilkinson's catalyst (40 mg; 43.2 µmol) was added. The mixture was hydrogenated under 10 bars pressure at RT for 16 h. The mixture was degassed by N_2 bubbling for 10 min and Wilkinson's catalyst (20 mg; 21.6 µmol) was added. The mixture was hydrogenated under 10 bars pressure at RT for 16 h. The mixture was filtered over celite® and the filtrate was concentrated in vacuo to give 140 mg of a green oil. The crude compound was purified by preparative LC (Irregular SiOH

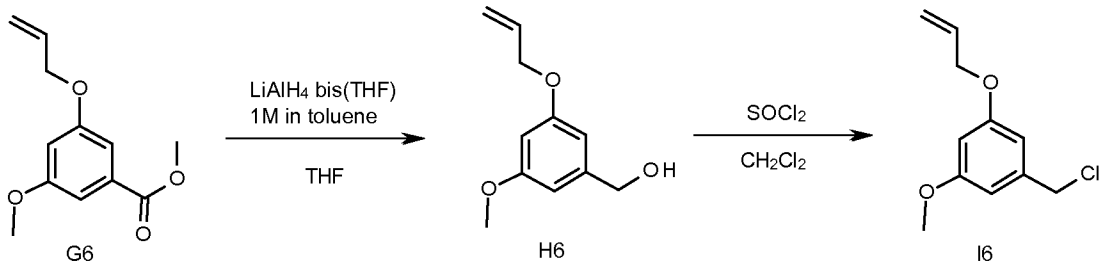
15-40 µm, 4 g Grace, mobile phase gradient: from CH_2Cl_2/EtOAc 100/0 to 80/20). The fractions containing product were combined and the solvent was removed in vacuo to give 60 mg of intermediate F6 (66% yield) as a yellow oil.

Synthesis of final compound 58:

A mixture of F6 (76 mg; 0.182 mmol) and iron (81 mg; 1.45 mmol) in acetic acid (4.2 mL) and water (0.21 mL) was stirred at 80°C for 6 h, then 100 °C for 16 h. The mixture was filtered through celite® and the filtrate was evaporated in vacuo. The crude compound was purified by preparative LC (irregular SiOH 15-40 µm, 25 g Merck, dry loading, mobile phase gradient: from CH_2Cl_2/MeOH/NH_3aq 97/3/0.3 to 85/15/1.5) to give 21 mg of final compound 58 (34% yield).

Overall Scheme in the preparation of final products: method 25

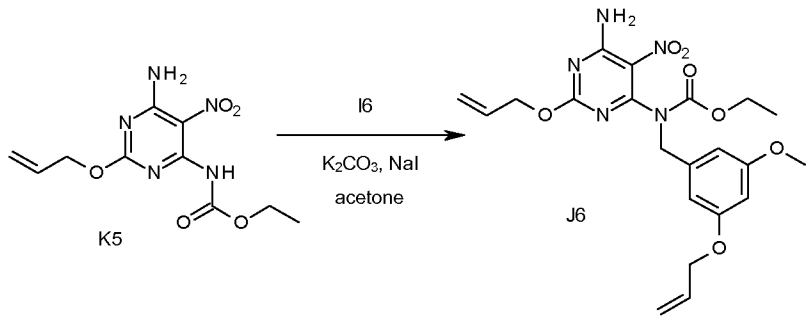




Synthesis of intermediate I6:

To a solution of G6 (21.11 g; 95.0 mmol) in THF (500 mL) at 0°C was added drop wise lithium aluminium hydride bis(THF) (1M in toluene) (190 mmol; 190 mL). The solution was stirred for 1h30 at 0°C, and then at RT for 1h30. The mixture was cooled to 0°C and was quenched by cautious drop wise addition of 7.5 mL of water, then 7.5 mL of aqueous NaOH (5%) and finally 15 mL of water. After 30 minute of further stirring, the mixture was filtered through a pad of celite®. The celite® was washed with EtOAc, the filtrate was evaporated under vacuum to afford 19.64 g (99% yield) of intermediate H6 as a clear yellow oil.

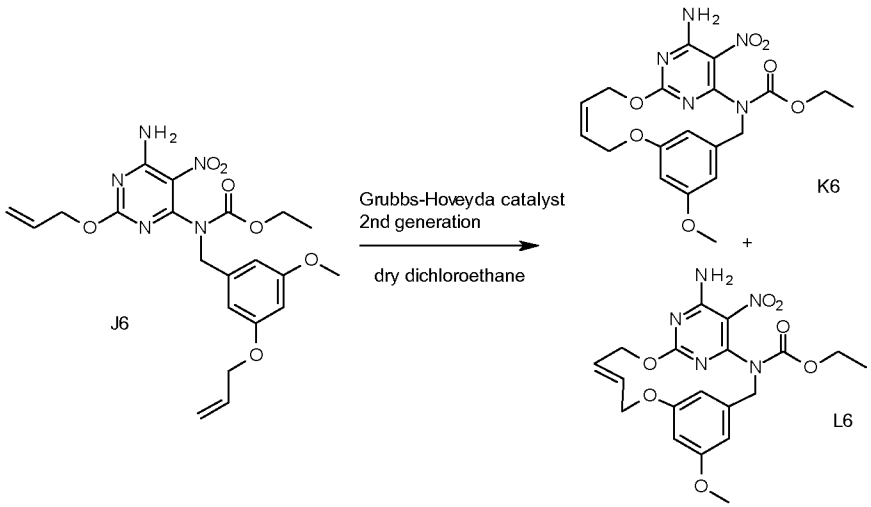
$SOCl_2$ (73 mL; 1.01 mol) was added drop wise to a mixture of H6 (19.6 g; 101 mmol) in CH_2Cl_2 (450 mL) at 0°C. The mixture was stirred at RT for 3 h. The solvent was evaporated and the residue was dried by azeotropic distillation with toluene (twice) to give 23.6 g of a brown oil. The brown oil was dissolved in CH_2Cl_2, washed with 2 x 100 mL of aqueous NaOH 5%, dried over $MgSO_4$, filtered, and evaporated under vacuum to afford 20.5 g of a brown oil. The crude was purified by preparative LC (Stationary phase: Irregular SiOH 20-45µm 450g Matrex), Mobile phase: Gradient from 50% Heptane, 50% CH_2Cl_2 to 0% Heptane, 100% CH_2Cl_2) to afford intermediate I6 (4.77 g; 22% yield) as a yellow oil.



Synthesis of intermediate J6:

I6 (2.7 g; 12.7 mmol) was added to a solution of K5 (3 g; 10.6 mmol), K_2CO_3 (2.93 g; 21.2 mmol) and NaI (1.59 g; 10.6 mmol) in acetone (180 mL) was stirred at 70°C for 16 h. The reaction was combined with another batch (from 200 mg of K5). The mixture

was filtered and the filtrate was concentrated in vacuo to give a yellow solid. The solid was taken up in CH_2Cl_2. The precipitate was filtered and the filtrate was concentrated in vacuo to give 4.14 g of a yellow oil. The crude was purified by preparative LC (Irregular SiOH 15-40 µm, 120 g Grace, mobile phase gradient: from Heptane/EtOAc 100/0/ to 50/50). The fractions containing product were combined and the solvent was removed in vacuo to give 3.83 g of a yellow oil, which was re-purified by preparative LC (Irregular SiOH 15-40 µm, 80 g Grace, mobile phase gradient: from CH_2Cl_2/EtOAc 100/0 to 95/5). The fractions containing product were combined and the solvent was removed in vacuo to give 2.3 g (44% yield) of intermediate J6 as a yellow oil.



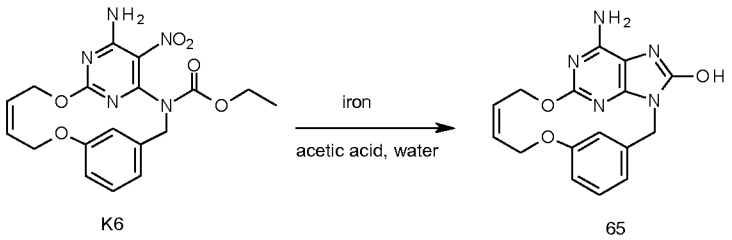
Synthesis of intermediates K6 and L6:

The reaction was performed in 2 batches.

Typical procedure for one batch:

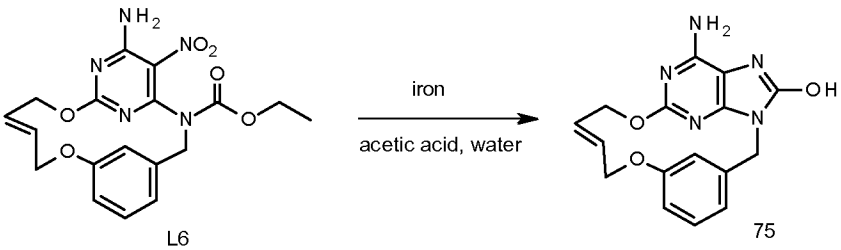
A solution of J6 (940 mg; 2.05 mmol) and chlorodicyclohexylborane (1M in hexane) (409 µL; 409 µmol) in dry dichloroethane (564 mL) was stirred at 80°C and under N_2 atmosphere for 1 h. Grubbs-Hoveyda catalyst 2nd generation (85 mg; 136 µmol) was added and the mixture was stirred at 120°C for 1 h. More catalyst (85 mg; 136 µmol) was added and the mixture was stirred at 120°C for 1 h. More catalyst (85 mg; 136 µmol) was added again and the mixture was stirred at 120°C for 16 h. The 2 batches were combined, SiliaBond® diamine (Ru scavenger from Silicycle®) (2.48 g; 3.97 mmol) was added and the mixture was stirred at RT for 16 h. The mixture was filtered and the filtrate was concentrated in vacuo to give 1.75 g of a black oil. This batch was combined with another one (0.48 mmol scale) to give 2.03 g of a black oil. The black oil was purified by preparative LC (Irregular SiOH 15-40 µm, 50 g Merck, mobile phase gradient: from CH_2Cl_2/EtOAc 100/0 to 98/2). The fractions containing product were combined and the solvent was removed in vacuo to give 70 mg of fraction 1 (intermediate K6, Z isomer), 160 mg of fraction 2 (mixture of intermediates K6 and L6

(75/25)) and 116 mg of fraction 3 (mixture of intermediates K6 and L6 (94/6)). Fraction 2 was purified by achiral SFC (Stationary phase: AMINO 6 µm 150x21.2 mm, mobile phase: 85% CO_2, 15% MeOH) to give 45 mg of intermediate L6 (4% yield, E isomer) as a yellow oil and 176 mg of intermediate K6 (16% yield, Z isomer) as a white solid (Global Yield: 27%).



Synthesis of final compound 65:

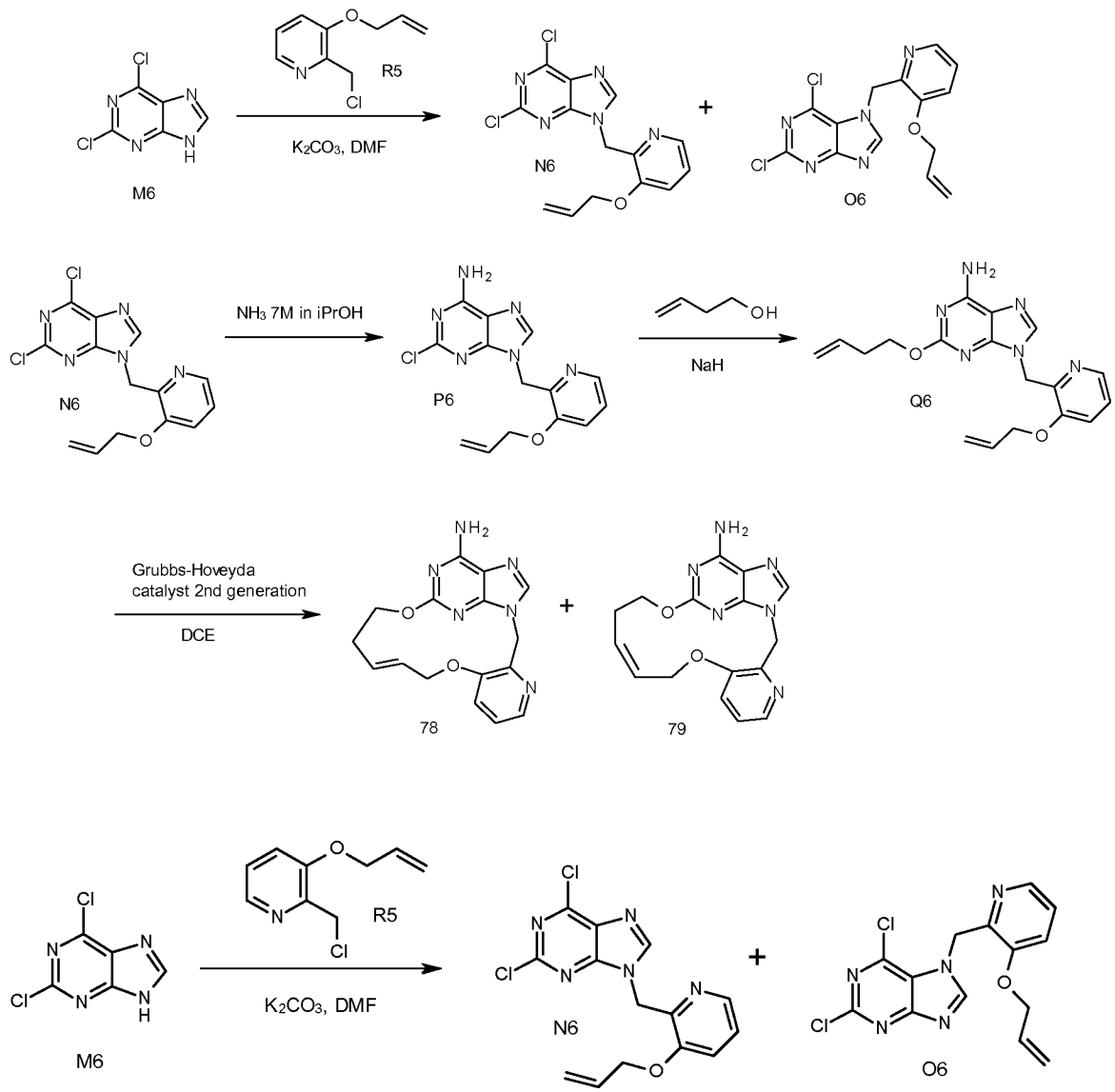
Iron (182 mg; 3.26 mmol) was added to a solution of K6 (176 mg; 0.408 mmol) in acetic acid (10 mL) and water (480 µL). The mixture was stirred at 70°C for 1 h and was then concentrated in vacuo until dryness. DMF was added, the mixture was heated and filtered hot through celite® and the celite® was rinsed with DMF. SiliaBond® imidazole (5.63 g; 26.6 mmol) was added to the filtrate and the mixture was stirred at RT for 16 h. The mixture was filtered through celite®, the celite® was rinsed with DMF and the filtrate was concentrated in vacuo. The residue was taken up with acetic acid (1 mL) then water was added and the mixture was cooled to 0°C, leading to precipitation. The precipitate was filtered to give an off-white solid. The solid was taken up in EtOH and heated at 80°C. The mixture was allowed to cool down to RT and the precipitate was filtered to give 50 mg of a white solid. The solid was dried in vacuo overnight and then solubilized in hot DMF and SiliaBond® imidazole (2 g; 2.32 mmol) was added. The mixture was stirred at RT for 16 h. The mixture was filtered through celite®, the celite® was rinsed with DMF and the filtrate was concentrated in vacuo to give 44 mg of final compound 65 (30% yield) as a white solid.



Synthesis of final compound 75:

Final compound 75 (11 mg, 30% yield) was obtained using the procedure described for final compound 65, starting from 45 mg of intermediate L6.

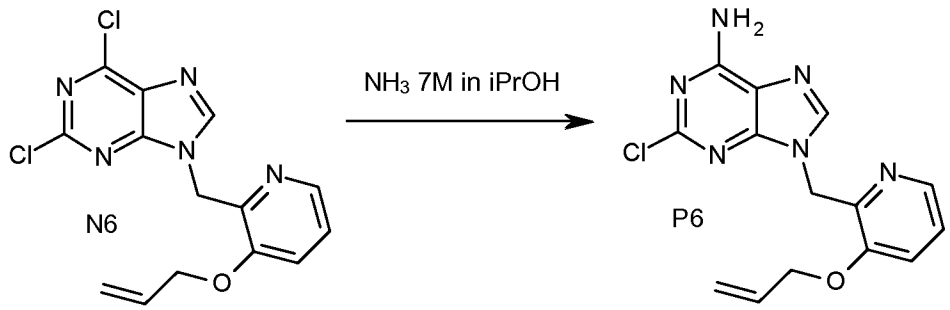
Overall Scheme in the preparation of final products: method 26



Synthesis of intermediates N6 and O6:

R5 (8.7 g; 47.6 mmol) in DMF (50 mL) was added drop wise over 1 h to a mixture of M6 (5 g; 26.5 mmol) and K_2CO_3 (14.6 g; 106 mmol) in DMF (50 mL) at RT and under N_2 atmosphere. The mixture was stirred at RT for 72 h. The mixture was evaporated and water/EtOAc were added. The layers were separated and the aqueous layer was

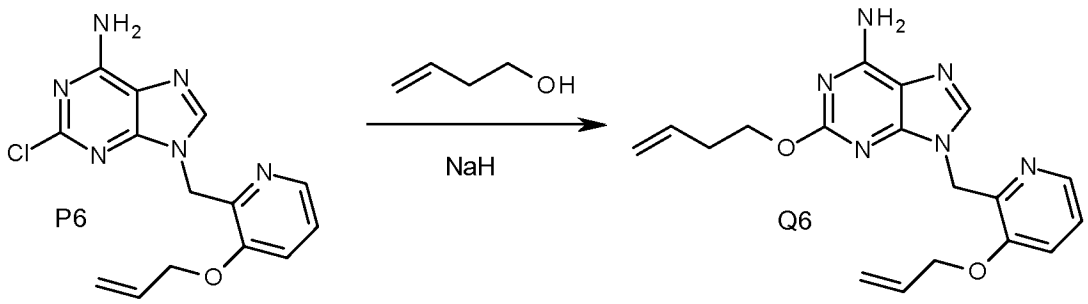
extracted with EtOAc (twice). The combined organic layers were washed with water (twice), dried over $MgSO_4$, filtered and dried in vacuo to give a brown solid. The solid was purified together with another batch (1 mmole scale) by preparative LC (Irregular SiOH 15-40 µm, 150 g Merck, mobile phase gradient: from CH_2Cl_2/EtOAC 100/0 to 90/10). The fractions containing product were combined and the solvent was removed in vacuo to give 2.11 g of intermediate N6 (24% yield) as an orange solid and 2.64 g of a second fraction (mixture of N6 and O6 (83/17).



Synthesis of intermediate P6:

The reaction was performed in Autoclave.

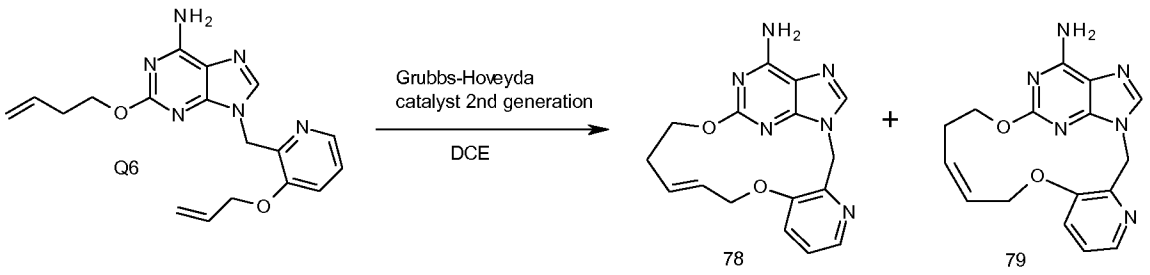
A solution of N6 (1.9 g; 5.65 mmol) in NH_3 (7M in isopropanol) (40 mL) was stirred at 120°C for 16 h. The mixture was cooled down to RT and the precipitate was filtered off. The precipitate was washed with Et_2O and dried in vacuo to give 1.42 g of intermediate P6 (79% yield) as a brown solid.



Synthesis of intermediate Q6:

A solution of P6 (1.42 g; 4.48 mmol) and NaH (60% in oil) (412 mg; 10.3 mmol) in 3-buten-1-ol (29 mL) was stirred at 90°C for 16 h. The solvent was removed in vacuo to give a brown solid. The solid was purified by preparative LC (Irregular SiOH 15-40 µm, 50 g Merck, mobile phase: CH_2Cl_2/MeOH 95/5). The fractions containing product were combined and the solvent was removed in vacuo to give 1.26 g of a brown solid.

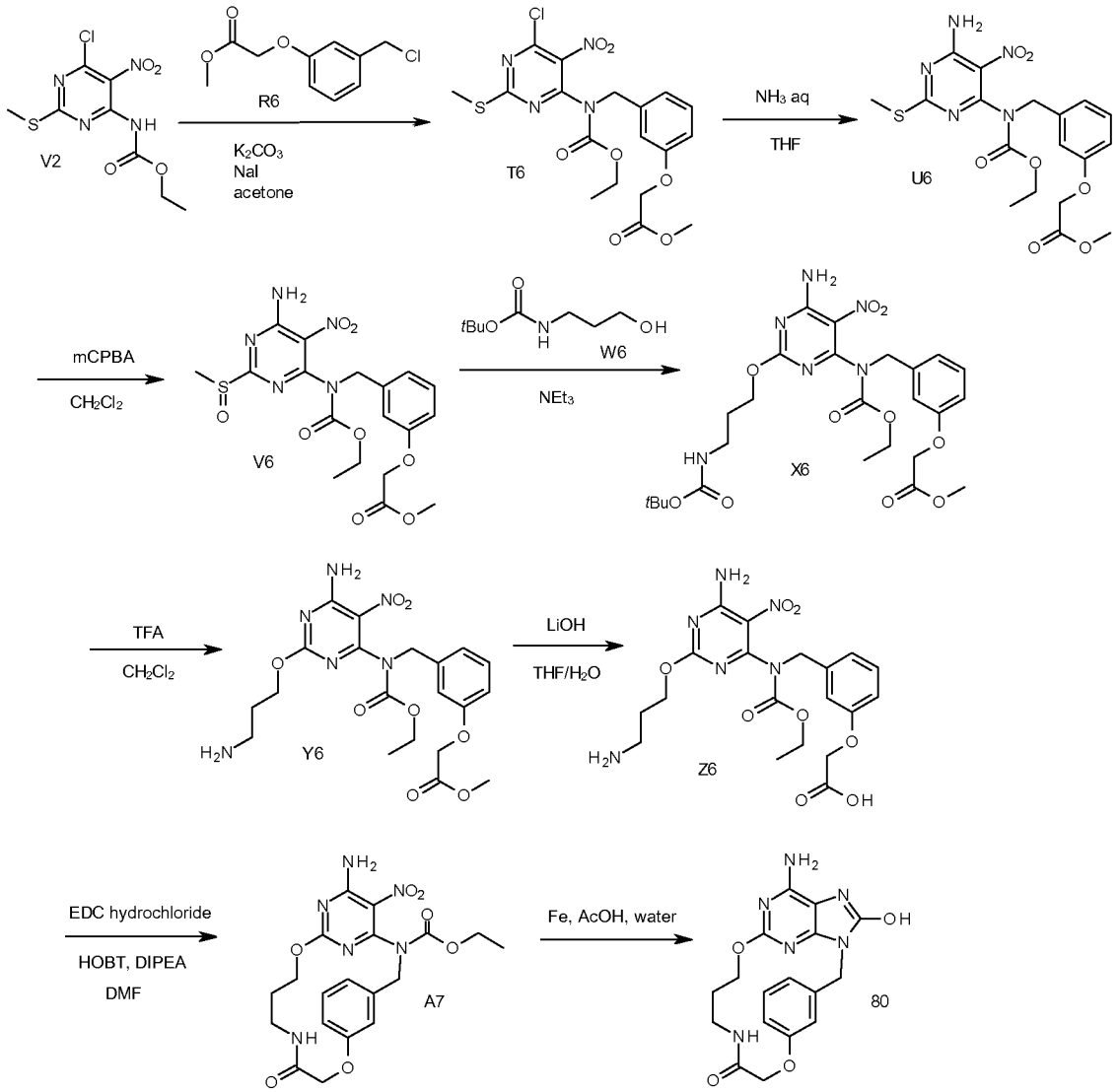
The solid was taken up in Et_2O leading to precipitation, the precipitate was filtered and dried in vacuo to give 920 mg of intermediate Q6 (58% yield) as a white solid.

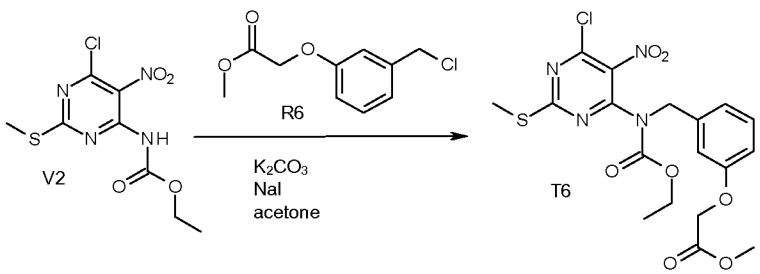


Synthesis of final compounds 78 and 79:

A solution of Q6 (460 mg; 1.31 mmol) and chlorodicyclohexylborane (1M in hexane) (261 µL; 261 µmol) in dichloroethane (430 mL) was stirred at 80°C under N_2 atmosphere for 1 h. Grubbs-Hoveyda catalyst 2nd generation (82 mg; 131 µmol) was added and the mixture was stirred in sealed tube at 120°C for 8 h. chlorodicyclohexylborane (1M in hexane) (261 µL; 261 µmol) was added and the mixture was stirred at 80°C under N_2 atmosphere for 1 h. Grubbs-Hoveyda catalyst 2nd generation (82 mg; 131 µmol) was added and the mixture was stirred at 120°C for 2 h. SiliaBond® DMT (3.48 g; 2.08 mmol) was added and the mixture was stirred at RT for 16 h. The mixture was filtered through celite® and the filtrate was evaporated in vacuo to give 640 mg of a black solid. The solid was purified together with another batch (1.3 mmole scale) by preparative LC (Irregular SiOH 15-40 µm, 40 g Grace, mobile phase gradient: from CH_2Cl_2/MeOH 100/0 to 90/10). The fractions containing product were combined and the solvent was removed in vacuo to give 463 mg of a brown solid. The solid was purified by achiral SFC (Stationary phase: AMINO 6 µm 150x21.2 mm, mobile phase: 82% CO_2, 18% MeOH(0.3% $iPrNH_2$)) to give 36 mg of final compound 78 (E isomer, 4% yield) as a white solid and a precipitate. This precipitate was purified by preparative LC (Stationary phase: Spherical bare silica 5 µm 150x30.0 mm, mobile phase gradient: from Heptane/EtOAc/MeOH (10% NH_3) 71/28/1 to 0/80/20) to give 10 mg of final compound 79 (Z isomer, 1% yield) as a white solid.

Overall Scheme in the preparation of final products: method 27

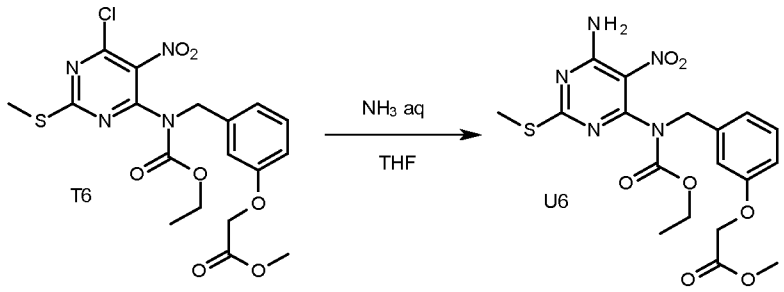




Synthesis of intermediate T6:

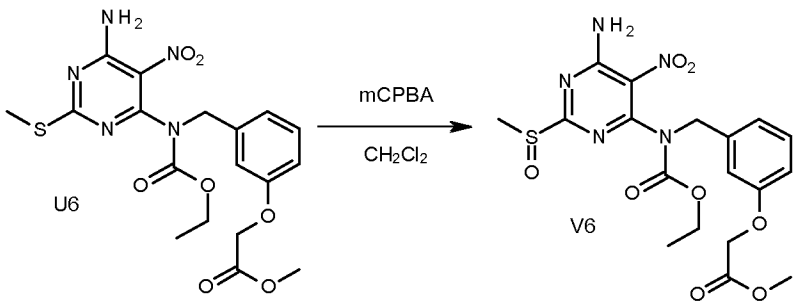
A mixture of V2 (7.04 g; 24.04 mmol), R6 (5.16 g; 24.04 mmol), K_2CO_3 (4.98 g; 36.06 mmol) and NaI (3.6 g; 24.04 mmol) in acetone (240 mL) were stirred at RT for 24 h. The precipitate was filtered off, rinsed with acetone. The filtrate was evaporated to give

18.7 g. The crude compound was dissolved into CH_2Cl_2. The precipitate was eliminated by filtration and the filtrate was concentrated in vacuo. The crude compound was purified by preparative LC (Stationary phase: Irregular SiOH 20-45 µm 450 g Matrex), mobile phase: 75% heptane, 25% AcOEt) to yield 7.4 g of intermediate T6 (65% yield).



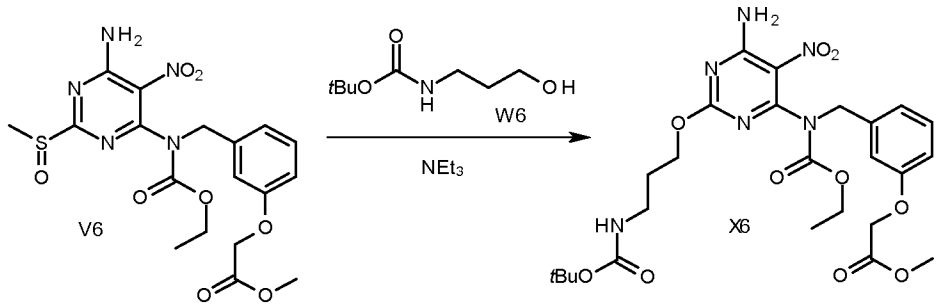
Synthesis of intermediate U6:

A mixture of T6 (7.25 g, 15.396mmol) in aqueous solution of NH_3 (30%) (110 mL) and THF (110 mL) was stirred at RT for 1 h. The mixture was concentrated. The residue was taken up with toluene and concentrated (the process was repeated twice). The residue was taken up with CH_2Cl_2, dried over $MgSO_4$, filtered and the solvent was evaporated to give 7.5 g of intermediate U6. The crude compound was used directly in the next reaction step.



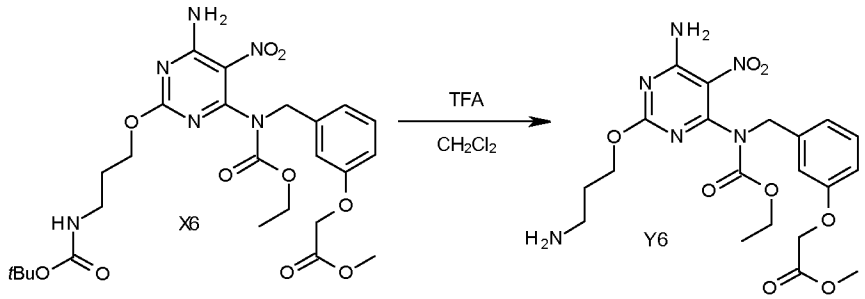
Synthesis of intermediate V6:

At 0°C, *m*eta-chloroperoxybenzoic acid (1.36 g, 5.54 mmol) in CH_2Cl_2 (25 mL) was added to a mixture of U6 (2.5 g, 5.54 mmol) in CH_2Cl_2 (25 mL). The mixture was stirred at RT for 3 h. An aqueous solution of $Na_2S_2O_3$ (2 eq) was added to the mixture. 2 layers were separated and the aqueous layer was extracted with CH_2Cl_2 (twice). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to afford 4.0 g of intermediate V6 as a yellow oil which was directly used in the next step.



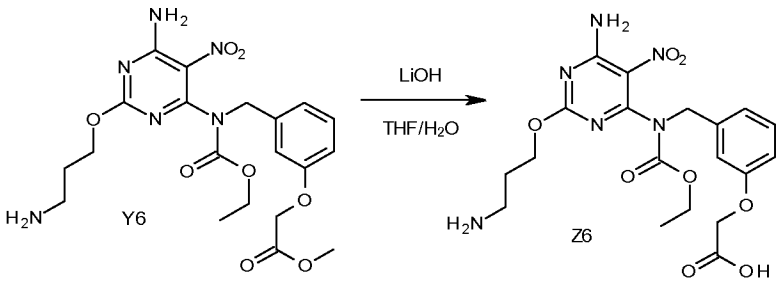
Synthesis of intermediate X6:

A mixture of V6 (2.58 g, 5.52 mmol) and NEt_3 (1.53 mL, 11.04 mmol) in W6 (28 mL) was stirred at 100°C for 2.5 h. Water was added and the mixture was extracted with CH_2Cl_2. The organic layer was washed with HCl 0.5N (6 times), dried over $MgSO_4$, filtered and the solvent was evaporated. The crude was purified by preparative LC (Stationary phase: Irregular SiOH 20-45 µm 450 g Matrex), mobile phase: 98% CH_2Cl_2, 2% iPrOH) to yield 1.3 g of intermediate X6 (41% yield).



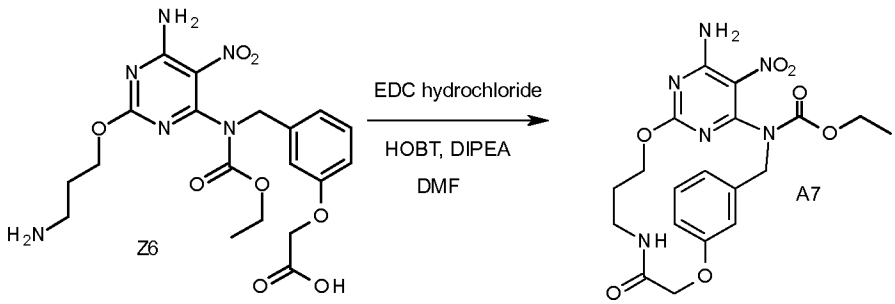
Synthesis of intermediate Y6:

At 0°C, TFA (1.72 mL, 22.47 mmol) was added drop wise to a mixture of X6 (1.30 g, 2.25 mmol) in CH_2Cl_2 (25 mL). The mixture was stirred at RT for 12 h. At 0°C, water was added. The mixture was basified with K_2CO_3 10% in water and was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated to give 1.1 g of intermediate Y6, which was directly used in the next step.



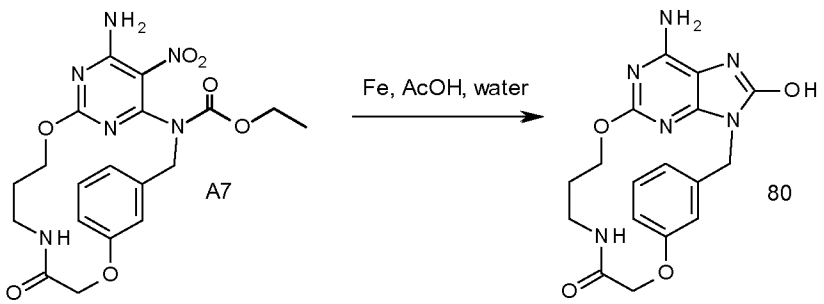
Synthesis of intermediate Z6:

At 0°C, LiOH monohydrate (289 mg, 6.89 mmol) was added to a mixture of Y6 (1.1 g, 2.3 mmol) in THF/water (50/50) (10 mL). The mixture was stirred at RT for 12 h. At 0°C, water was added and the mixture was acidified with HCl 3N until pH 2-3. The mixture was extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated to yield 0.85 g of intermediate Z6 (80% yield).



Synthesis of intermediate A7:

1-Ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride (941 mg, 4.91 mmol) and hydroxybenzotriazole (663 mg, 4.91 mmol) were slowly added to a mixture of Z6 (760 mg, 1.64 mmol), diisopropylethylamine (1.41 mL, 8.18 mmol) in DMF (380 mL). The mixture was stirred at RT for 24 h. The solvent was evaporated until dryness. The residue was taken up with CH_2Cl_2 and was washed with water, then with brine. The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated. Purification was carried out by flash chromatography over silica gel (15-40 µm, 40 g, $CH_2Cl_2/CH_3OH/NH_4OH$: 99/1/0.1). The pure fractions were collected and evaporated to dryness to yield 0.61 g of intermediate A7 (84% yield).

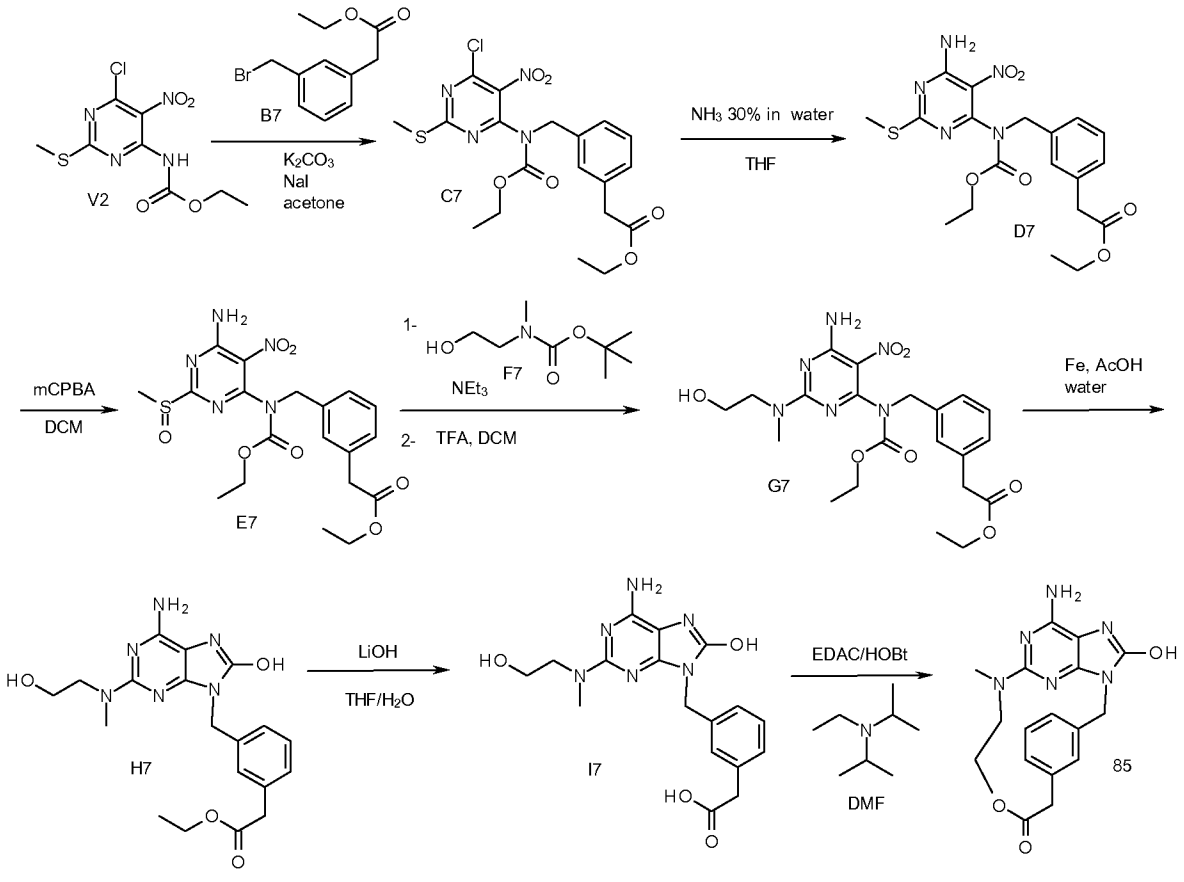


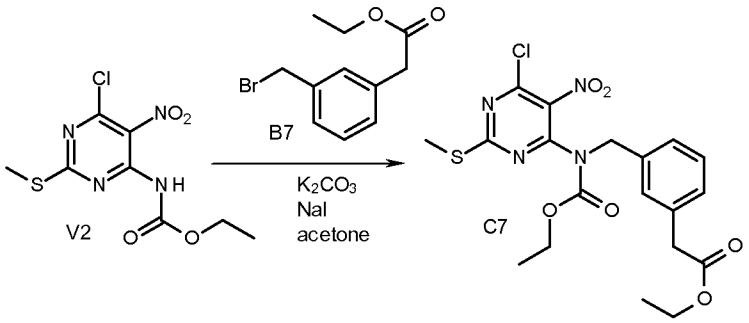
Synthesis of final compound 80:

Iron (1.4 g; 25.09 mmol) was added to a mixture of A7 (560 mg; 1.25 mmol) in acetic acid (14.4 mL) and water (1.47 mL). The mixture was stirred at 50°C for 6 h. The

mixture was filtered through celite®, washed with acetic acid then the filtrate was concentrated under reduced pressure. The crude compound was dissolved into DMF with 4 g of SiO_2 60-200 µm and the resulting suspension was evaporated until dryness and put on the top of a 25 g column chromatography. Purification was carried out by flash chromatography over silica gel (15-40 µm, 25 g, $CH_2Cl_2/CH_3OH/NH_4OH$: 95/5/0.5). The pure fractions were collected and evaporated to dryness and then taken up with CH_3OH. The resulting precipitate was filtered off and dried to give 152 mg final compound 80 as the free base (33% yield). The hydrochloride salt was prepared with 10 eq of HCl 4N in dioxane, which was added to the suspension of the compound in CH_3OH. The precipitate was stirred for 1 h, filtered then dried under vacuum to yield 109 mg final compound 80 as an HCl salt.

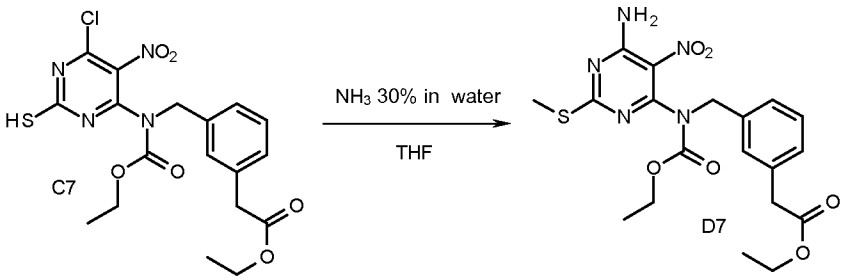
Overall Scheme in the preparation of final products: method 28





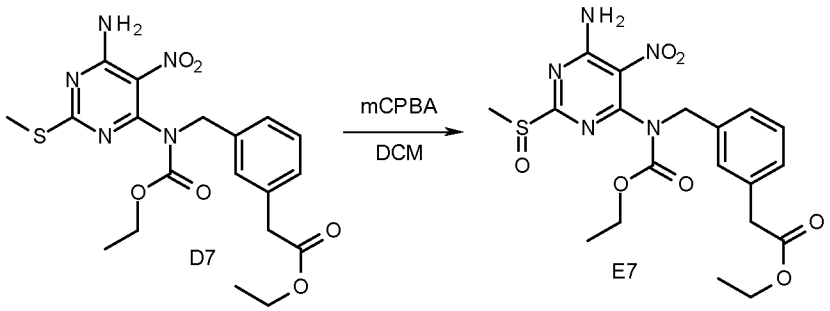
Synthesis of intermediate C7:

A mixture of V2 (7.5 g; 25.6 mmol), B7 (7.25 g; 28.2 mmol), K_2CO_3 (8.85g; 64 mmol) and NaI (3.85 g; 25.6 mmol) in acetone (220 mL) was stirred at RT for 16 h. The mixture was filtered through a pad of celite® and the filtrate was evaporated in vacuo to give a yellow oil. The crude was purified by preparative LC (Irregular SiOH 15-40 µm, 120 g Merck, mobile phase gradient: CH_2Cl_2/Heptane 70/30). The fractions containing product were combined and the solvent was removed in vacuo. The product was crystallized from diisopropylether to give 11.4 g of intermediate C7 (95% yield).



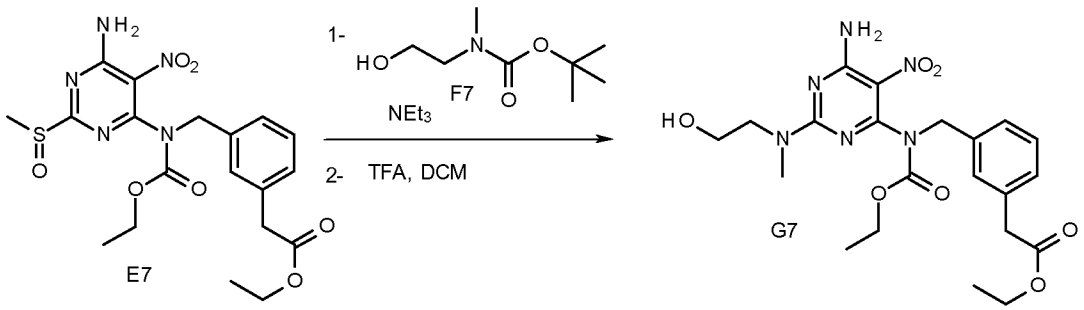
Synthesis of intermediate D7:

A solution of C7 (11.3 g; 24.1 mmol) and NH_3 (30% in H_2O) (170 mL) in THF (170 mL) was stirred at RT overnight. The mixture of solvents was removed in vacuo and the residue was taken up by CH_2Cl_2, decanted, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was taken up with diisopropylether and the precipitate was filtered off and air-dried to give 10.5 g of intermediate D7 (97% yield).



Synthesis of intermediate E7:

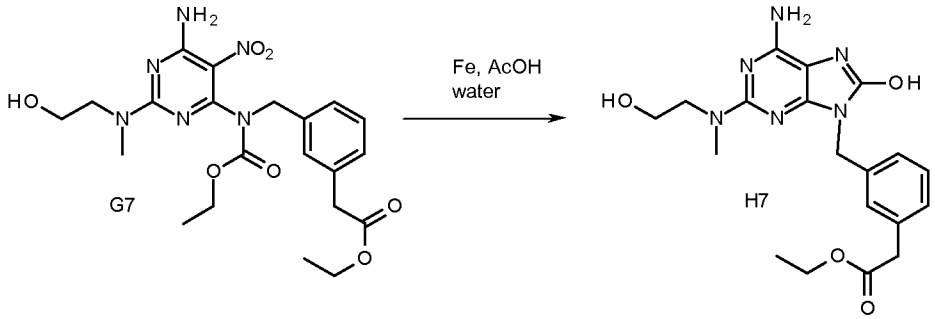
Metachloroperbenzoic acid (6.33 g; 26 mmol) was added portion wise to a solution of D7 (10.5 g; 23.3 mmol) in CH_2Cl_2 (300 mL) at RT. The mixture was stirred at RT for 16 h. A 10% aqueous solution of $Na_2S_2O_3$ (4 eq) and an aqueous solution of $NaHCO_3$ were added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (twice). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under vacuum to give 10.8 g of intermediate E7 (99% yield).



Synthesis of intermediate G7:

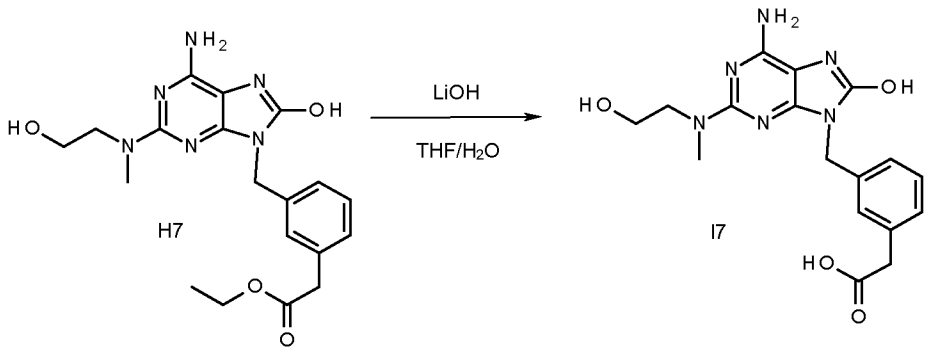
E7 (3.5 g; 7.54 mmol) was added portion wise to a solution of NEt_3 (1.15 mL; 8.3 mmol) and F7 (13.2g; 75.3 mmol) and the resulting mixture was stirred at RT for 16 h. Water and CH_2Cl_2 were added , the organic layer was decanted, dried over $MgSO_4$ and concentrated. The crude product was purified by preparative LC (irregular SiOH 15-40 µm, 40 g merck, ($MeOH/CH_2Cl_2$, 0.5/99.5) to afford intermediate G7a (3.6 g).

To a solution of G7a (3.6 g; 6.2 mmol) in CH_2Cl_2 (120 mL) was added trifluoroacetic acid (9.5 mL; 41.6 mmol) at RT. The reaction mixture was stirred at RT for 12 h. The reaction mixture was diluted with CH_2Cl_2 and was treated with a saturated aqueous solution of $NaHCO_3$. The layers were separated and the organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by preparative LC (irregular SiOH 15-40 µm, 40 g Grace, dry loading, mobile phase gradient: from $CH_2Cl_2/MeOH/NH_4OH$ 98/2/0.1) to give 1.7 g of intermediate G7 (57% yield).



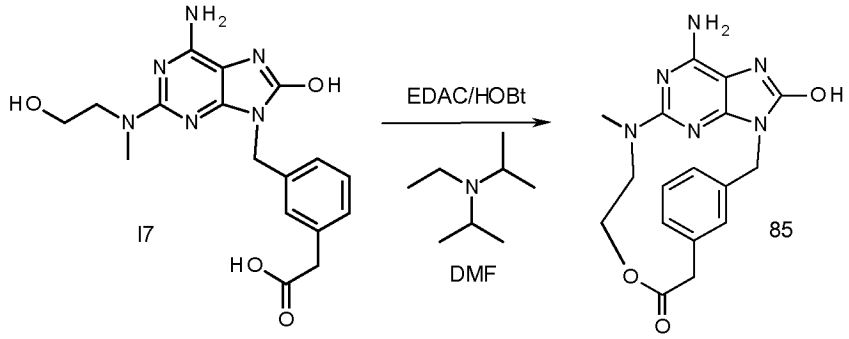
Synthesis of intermediate H7:

Iron (2.8 g; 50.3 mmol) was added to a mixture of G7 (4 g; 8.4 mmol) in acetic acid (12 mL) and water (3 mL).The mixture was stirred vigorously at 50°C for 5h. The reaction mixture was diluted with CH_2Cl_2, filtered through a pad of celite® and the filtrate was concentrated under vacuum .The crude compound was taken up with a mixture of CH_2Cl_2/MeOH (90/10) and a precipitate was filtered of. The filtrate was purified by preparative LC (irregular SiOH 15-40 µm, 80 g Grace, mobile phase CH_2Cl_2/MeOH 98/2). The product was crystallized from diisopropylether to give 2.1 g of intermediate H7 (62.5% yield).



Synthesis of intermediate I7:

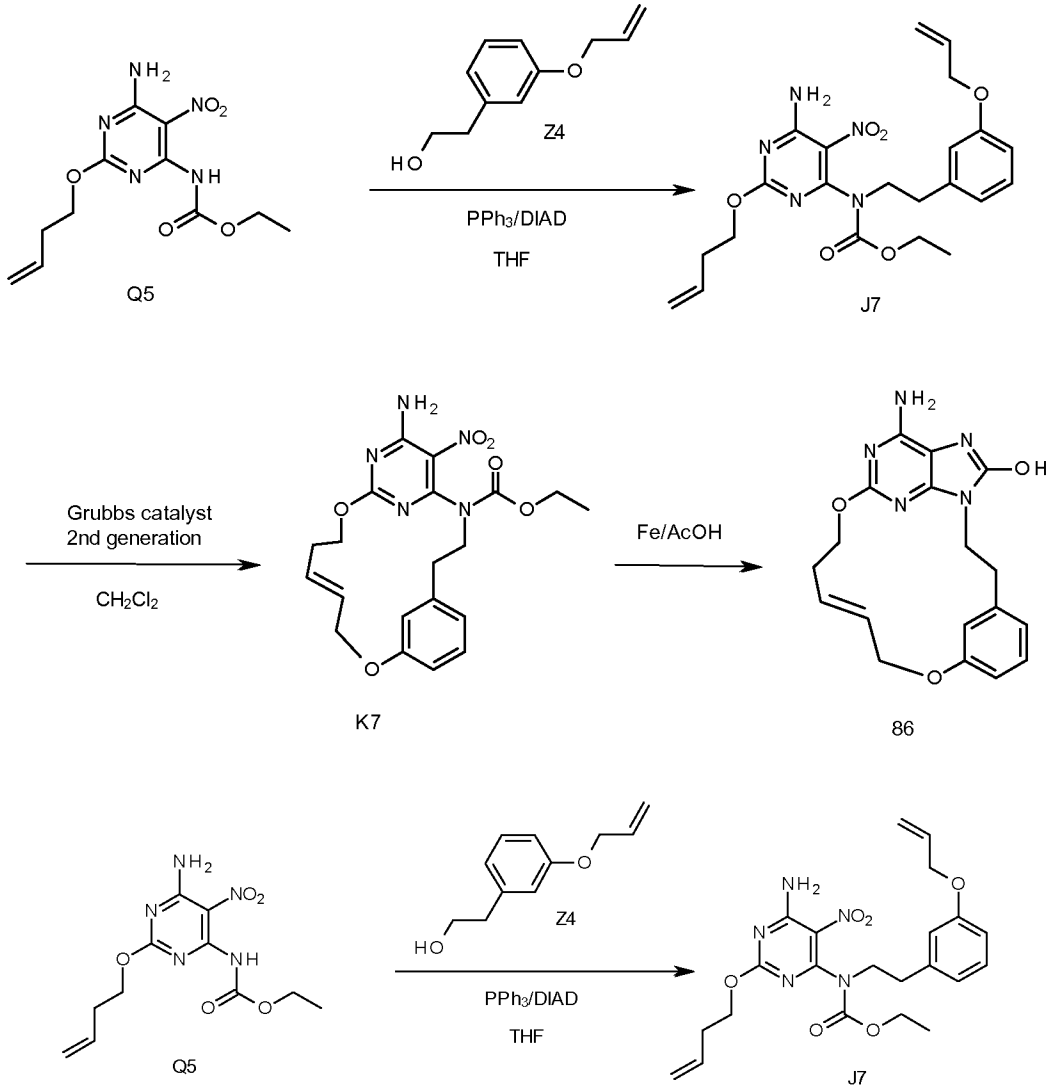
At 0°C, LiOH monohydrate (157 mg, 3.75 mmol) was added to a mixture of H7 (0.5 g, 1.25mmol) in THF/H_2O (50/50) (10 mL). The mixture was stirred at RT for 12h. At 0°C, water was added and the mixture was acidified with HCl 3N until pH 2-3. The mixture was extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated to give 460 mg of intermediate I7 (99% yield). The crude compound was used directly in the next reaction step.



Synthesis of final compound 85:

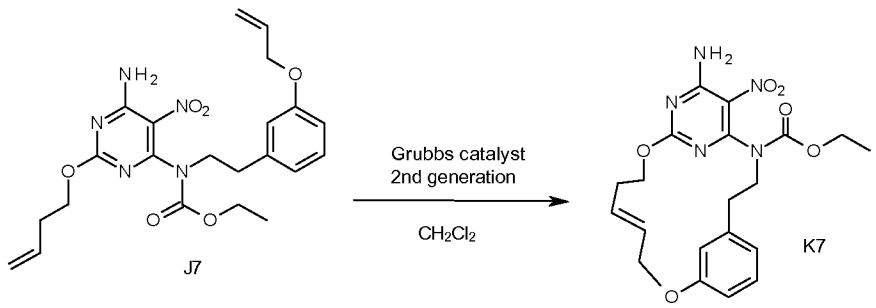
3-Dimethylaminopropyl)-3-ethylcarbodiimide (1 g, 1.5.3 mmol) and 1-hydroxybenzotriazole (720 mg, 5.3 mmol) were slowly added to a mixture of I7 (660 mg, 1.77 mmol), diisopropylethylamine (1.5 mL, 8.86 mmol) in DMF (400 mL). The mixture was stirred at RT for 24h. The solvent was evaporated until dryness. The residue was taken up with CH_2Cl_2 and was washed with water, then with brine. The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated. Purification was carried out by flash chromatography over silica gel (15-40 µm, 80 g, $CH_2Cl_2/CH_3OH/NH_4OH$: 95/5/0.5). The pure fractions were collected and evaporated to dryness to give 47 mg of final compound 85 (7.5% yield).

Overall Scheme in the preparation of final products: method 29



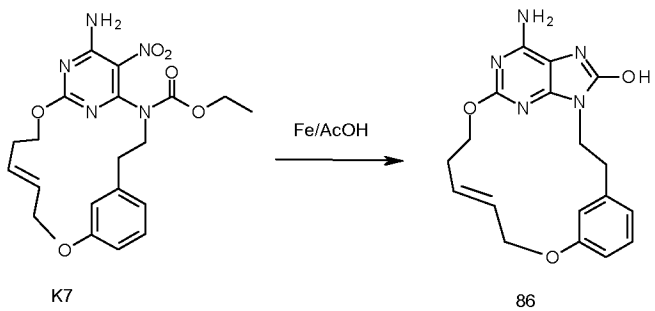
Synthesis of intermediate J7:

At 0°C, diisopropylazodicarboxylate (0.9 mL; 4.541 mmol) was added drop wise to a mixture of Q5 (0.9 g; 3.028 mmol), Z4 (0.54 g; 3.028 mmol) and PPh_3 (1.19 g; 4.541 mmol) in THF (45 mL). The mixture was stirred at RT for 2h. EtOAc and water were added. The layers were decanted. The organic layer was washed with water, dried over $MgSO_4$, filtered and the solvent was evaporated. The crude compound was purified by flash chromatography over silica gel (15-40 µm, 120 g, Heptane-EtOAc 85-15 to 70/30). The pure fractions were collected and evaporated to dryness to give intermediate J7 after crystallization with diisopropylether (520 mg, 38% yield).



Synthesis of intermediate K7:

Grubbs catalyst 2nd generation (91 mg; 0.107 mmol) was added to a mixture of J7 (0.488 g; 1.067 mmol) in CH_2Cl_2 (205 mL). The mixture was stirred at RT for 7h. After 7 hours SiliaBond® DMT (1.42 g; 0.853 mmol) was added and the mixture was stirred at RT overnight. The reaction was filtered through a pad of celite®, washed with CH_2Cl_2 and the solvent was evaporated. The crude was purified together with another batch (0.12 mmole scale) by flash chromatography over silica gel (15-40 µm, 40 g, CH_2Cl_2/MeOH 99.75/0.25). The pure fractions were collected and evaporated to dryness to give fraction 1; which was then purified by achiral SFC (Stationary phase: Chiralpak IA 5 µm 250*20 mm), Mobile phase: 70% CO_2, 30% MeOH) to give 240 mg of intermediate K7 (E isomer, 52% yield).

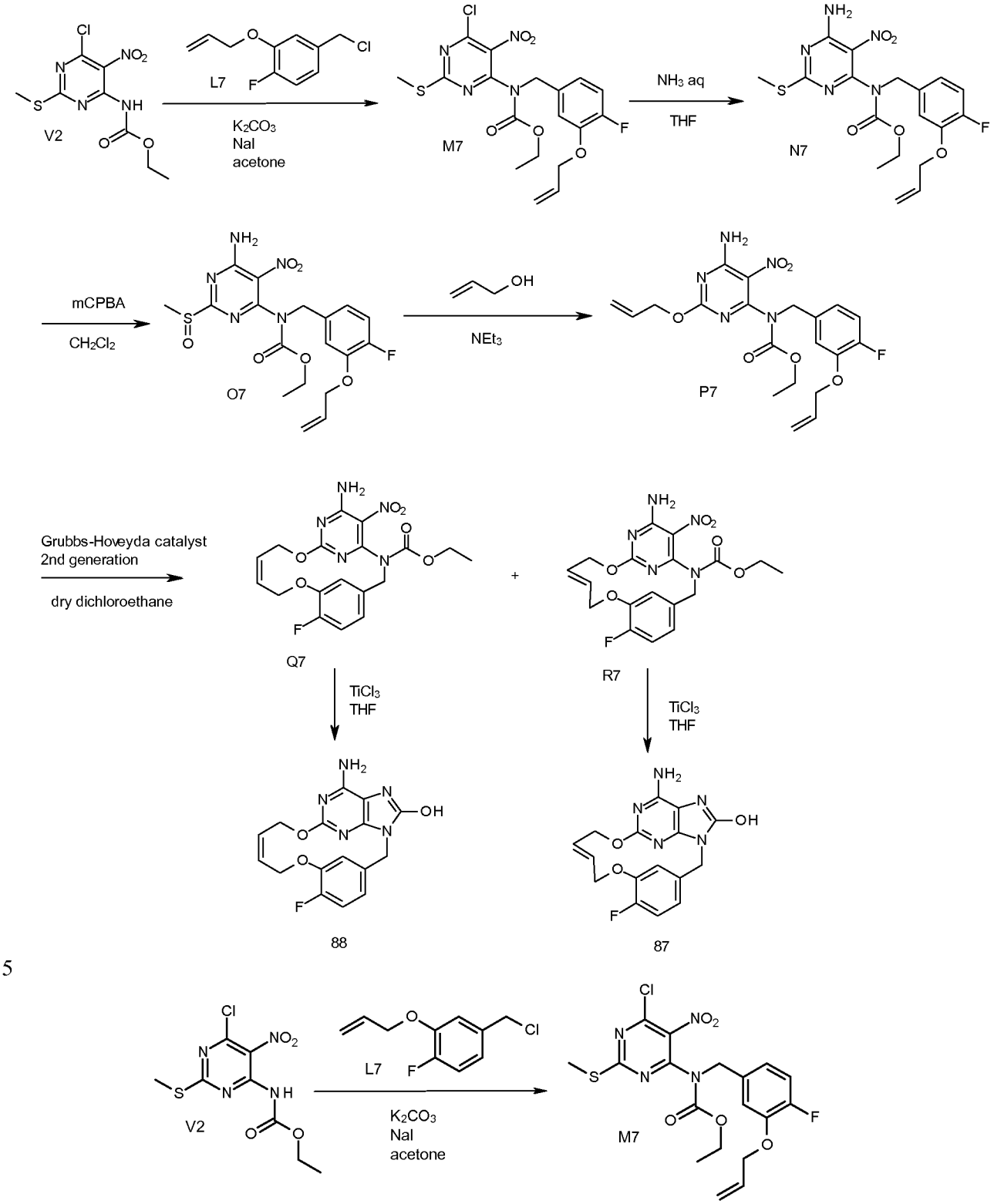


Synthesis of final compound 86:

Iron (0.52 g; 9.315 mmol) was added to a mixture of K7 (0.2 g; 0.466 mmol) in acetic acid (5.4 mL) and water (550 µL). The mixture was stirred at 50°C for 5h. The mixture was filtered through celite®, washed with AcOH, and then the filtrate was concentrated. The crude compound was dissolved into DMF with 5 g of SiO_2 60-200 µm and the resulting suspension was evaporated until dryness and put on the top of a 25 g column chromatography. Purification was carried out by flash chromatography over silica gel (15-40 µm, 25 g, $CH_2Cl_2/CH_3OH/NH_4OH$: 95/5/0.5 to 90/10/0.5). The pure fractions were collected and evaporated to dryness. This batch was crystallized from CH_3OH, the

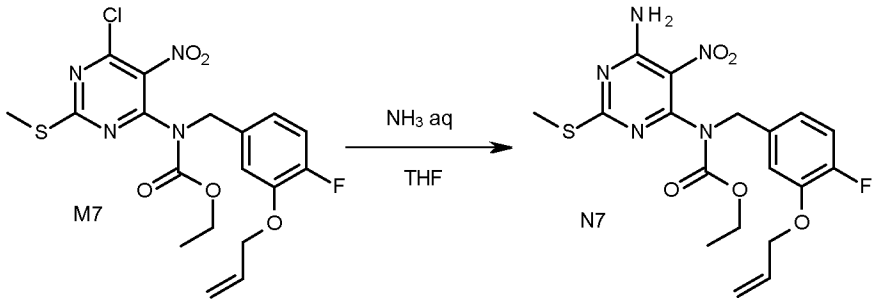
precipitate was filtered off, dried under vacuum at 90°C to give final compound 86 (68 mg, 41% yield).

Overall Scheme in the preparation of final products: method 30



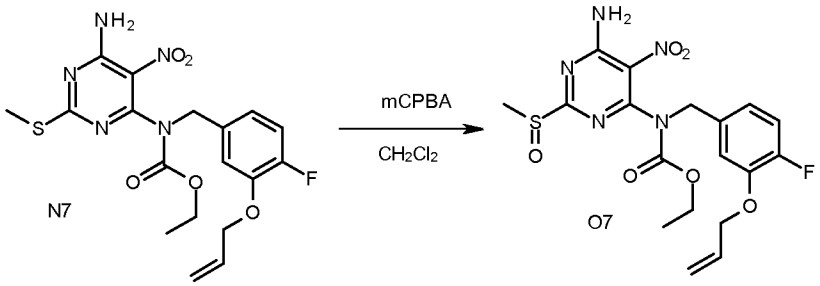
Synthesis of intermediate M7:

A mixture of V2 (10.0 g; 34.16 mmol), L7 (6.85 g; 34.16 mmol), NaI (5.12 g; 34.16 mmol) and K_2CO_3 (7.08 g; 51.24 mmol) in acetone (370 mL) were stirred at RT for 24h. The precipitate was filtered off, rinsed with acetone. The filtrate was concentrated under reduced pressure. The crude compound was taken up with CH_2Cl_2, the precipitate (residual intermediate V2) was filtered off, washed with the minimum of CH_2Cl_2 and the filtrate was concentrated to give 16.8 g of intermediate M7, which was directly used in the next step.



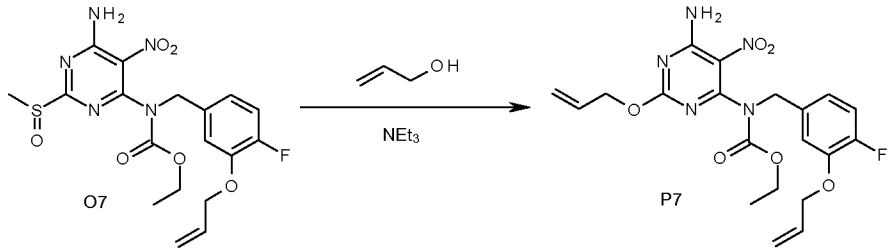
Synthesis of intermediate N7:

A mixture of M7 (16.8 g, 36.77 mmol) in NH_3 in water (30%) (100 mL) and THF (100 mL) was stirred at RT for 1h. The mixture was diluted with water and was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and the solvent was evaporated to give 15.7 g of intermediate N7 (98% yield).



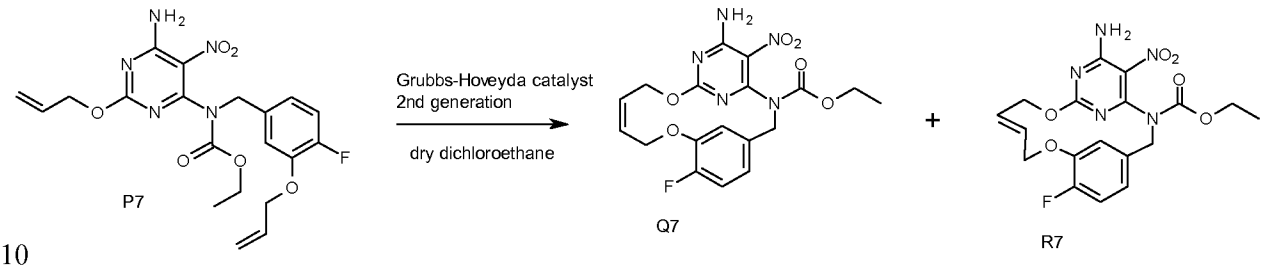
Synthesis of intermediate O7:

At 0°C, 3-chloroperoxybenzoic acid (8.8 g, 35.66 mmol) in CH_2Cl_2 (100 mL) was added to a mixture of N7 (15.6 g, 35.66 mmol) in CH_2Cl_2 (100 mL). The mixture was stirred at RT for 3h. An aqueous solution of $Na_2S_2O_3$ (2 eq) was added to the mixture. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (twice). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to afford 16 g of intermediate O7 as a yellow oil (99% yield).



Synthesis of intermediate P7:

A mixture of O7 (8.0 g, 17.642 mmol) in allyl alcohol (90 mL) and NEt_3 (4.9 mL, 35.285 mmol) was stirred at 90°C for 1h. The mixture was evaporated until dryness and purified by flash chromatography over silica gel (15-40 µm, 120 g, $CH_2Cl_2/CH_3OH/NH_4OH$: 99.5/0.5). The pure fractions were collected and evaporated to dryness to give 6.3 g of intermediate P7 (80% yield).

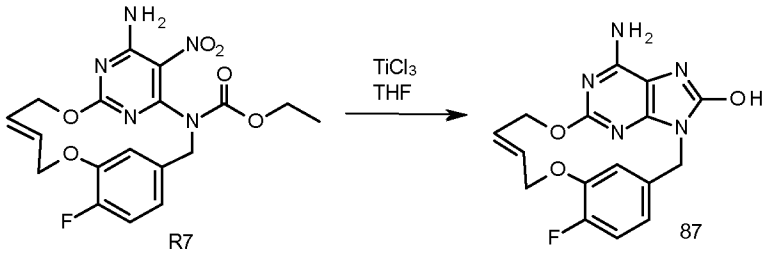


Synthesis of intermediates Q7 and R7:

The solvent was degassed by bubbling N_2 through. Reaction was split into 2 equal portions of 750 mg of P7:

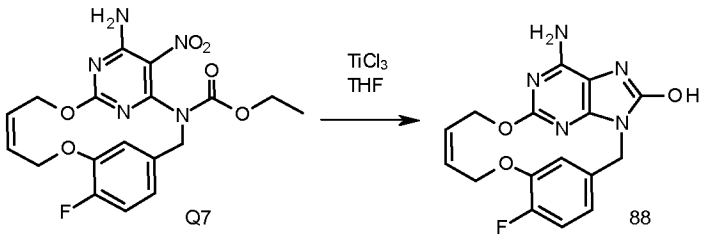
A solution of P7 (750 mg; 1.676 mol) and chlorodicyclohexylborane (1M in hexane) (335 µL; 0.335 µmol) in dry dichloroethane (330 mL) was stirred at 80°C and under N_2 atmosphere for 1 h. 0.033 eq of Grubbs-Hoveyda catalyst 2nd generation (35 mg; 56µmol) was added and the mixture was stirred in sealed tube at 120°C for 1 h. Then the tube was opened, 0.033eq of catalyst (35 mg; 56 µmol) was added again and the mixture was stirred in sealed tube at 120°C for 1 h (sequence repeated two times). SiliaBond® DMT (1.72 g; 0.894 mmol) was added to the mixture, which was stirred at RT overnight. The mixture was filtered through a pad of celite®, the celite® was washed with CH_2Cl_2 and the filtrate was evaporated. The compound was taken up with CH_2Cl_2, the precipitate was filtered off (0.82 g, fraction 1). The filtrate was purified by flash chromatography over silica gel (15-40 µm, 80 g, $CH_2Cl_2/CH_3OH/NH_4OH$: 99.5/0.5/0.5). The pure fractions were collected and evaporated to dryness (0.11 g, fraction 2). Fractions 1 and 2 were combined (0.93 g) and were purified by achiral SFC (Stationary phase: AMINO 6µm 150x21.2mm), Mobile phase: 80% CO_2, 20% MeOH)

to give 0.25 g of intermediate R7 (18% yield, isomer E) and 0.566 g of intermediate Q7 (40% yield, isomer Z).



Synthesis of final compound 87:

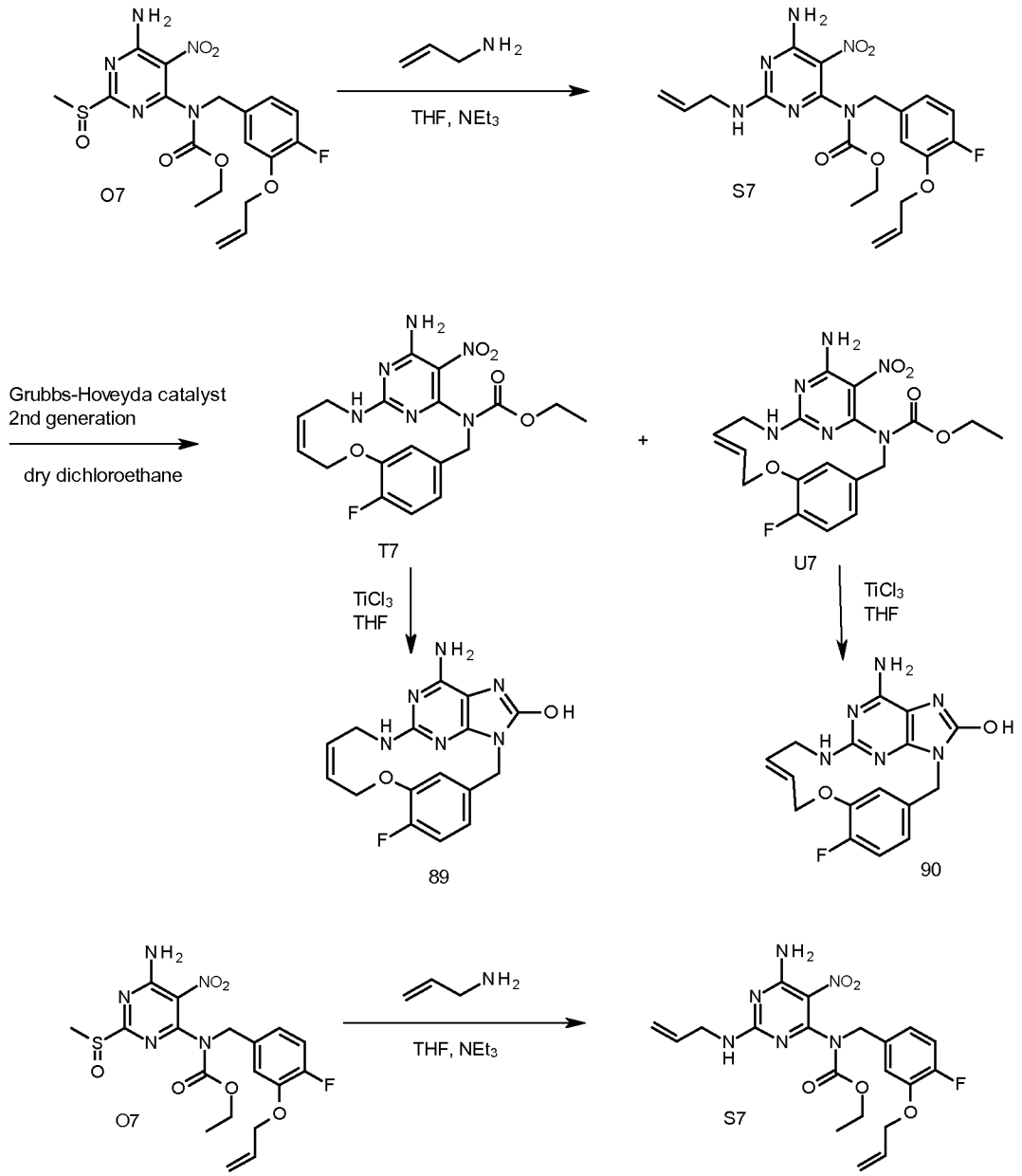
At 0°C, $TiCl_3$ (10.2 mL; 11.923 mmol) was added drop wise to a mixture of R7 (250 mg; 0.596 mmol) in THF (30 mL). The mixture was stirred at 0°C for 4h then at RT overnight. Water was added and the mixture was basified with K_2CO_3. The mixture was filtered through a pad of celite®. The celite® was washed with EtOAc/CH_3OH 70/30. The layers were decanted and the organic layer was evaporated until dryness. The crude compound was dissolved into DMF then 2 g of SiO_2 was added and the resulting mixture was evaporated until dryness. Purification was carried out by flash chromatography over silica gel (solid deposit) (15-40 µm, 25 g, CH_2Cl_2/CH_3OH/NH_4OH: 95/5/0.5). The pure fractions were collected and evaporated to dryness to give 20 mg of final compound 87 after crystallization from CH_3CN (17% yield).



Synthesis of final compound 88:

Final compound 88 was obtained from intermediate Q7 (250 mg, 0.596 mmol) with the procedure described for final compound 87, yielding 9 mg (4% yield).

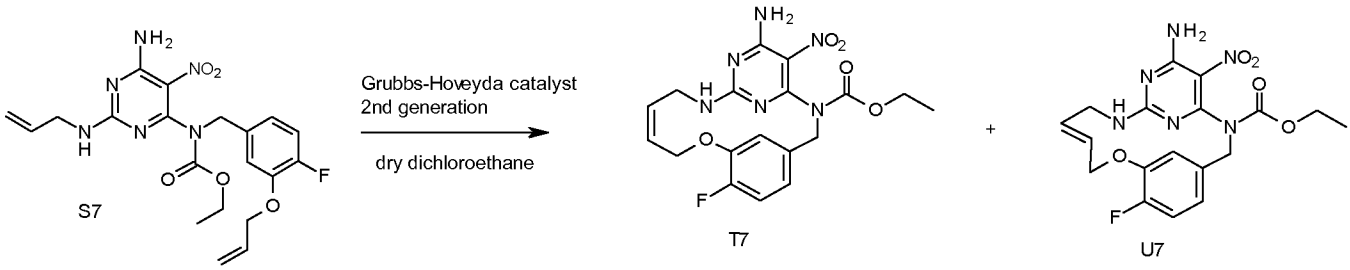
Overall Scheme in the preparation of final products: method 31



Synthesis of intermediate S7:

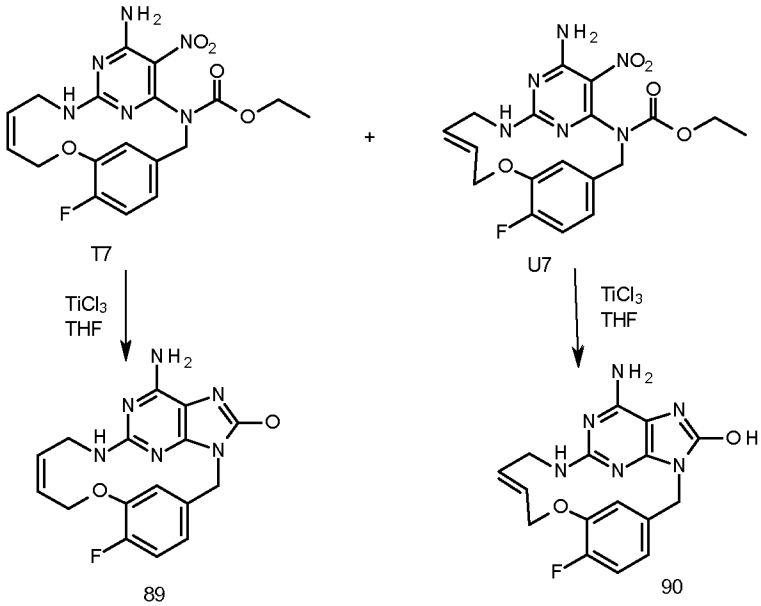
At 0°C, allylamine (1.46 mL, 19.407 mmol) was added drop wise to a mixture of Q7 (8.0 g, 17.642 mmol) and NEt_3 (4.905 mL, 35.285 mmol) in THF (100 mL). The mixture was stirred at RT for 3h. Water and EtOAc were added. The layers were decanted. The mixture was extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated. The crude was purified by flash chromatography over silica gel (15-40 µm, 120 g, $CH_2Cl_2/CH_3OH/NH_4OH$: 99.5/0.5).

The pure fractions were collected and evaporated to dryness to give 5.8 g of intermediate S7 (74% yield).



Synthesis of intermediates T7 and U7:

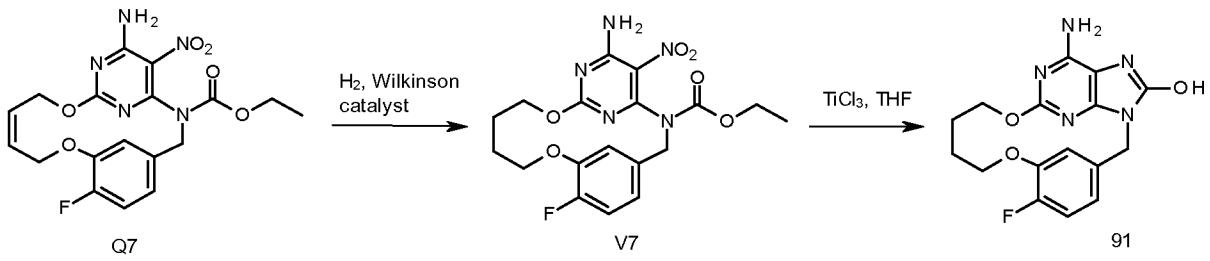
The intermediates T7 and U7 were synthesized with the method described for intermediates Q7 and R7.



Synthesis of final compounds 89 and 90:

Final compounds 89 and 90 were synthesized with the method described for final compounds 87 and 88.

Overall Scheme in the preparation of final products: method 32



Synthesis of intermediate V7:

A mixture of Q7 (200 mg, 0.477 mmol) and Wilkinson's catalyst (88.2 mg, 0.0954 mmol) in THF/MeOH (50/50) (30mL) was stirred at RT under a 8 bar pressure of H_2 for 20h. The mixture was evaporated until dryness to give 0.30 g of intermediate V7 directly used in the next step.

Synthesis of final compound 91:

Final compound 91 was synthesized with the method described for final compounds 87 and 88.

LCMS methods:

General procedure *VDR2 (for methods V300xV30xx.olp)*

The LC measurement was performed using a UPLC (Ultra Performance Liquid Chromatography) Acquity (Waters) system comprising a binary pump with degasser, an autosampler, a diode-array detector (DAD) and a column as specified in the respective methods below, the column is hold at a temperature of 40°C. Flow from the column was brought to a MS detector. The MS detector was configured with an electrospray ionization source. The capillary needle voltage was 3 kV and the source temperature was maintained at 130 °C on the Quattro (triple quadrupole mass spectrometer from Waters). Nitrogen was used as the nebulizer gas. Data acquisition was performed with a Waters-Micromass MassLynx-Openlynx data system.

Method V3014V3001

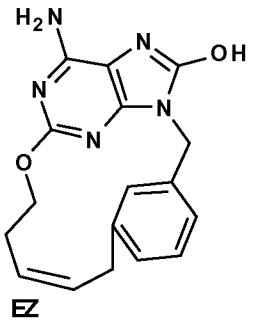
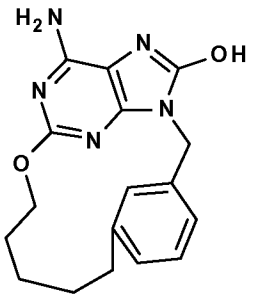
In addition to the general procedure VDR2: Reversed phase UPLC was carried out on a Waters HSS (High Strength Silica) T3 column (1.8 µm, 2.1 x 100 mm) with a flow rate of 0.35 ml/min. Two mobile phases (mobile phase A: 95 % 7 mM ammonium acetate / 5 % acetonitrile; mobile phase B: 100 % acetonitrile) were employed to run a gradient condition from 99 % A (hold for 0.5 minutes) to 15 % A and 85 % B in 4.5 minutes, hold for 2 min and back to the initial conditions in 0.5 min, hold for 1.5 minutes. An

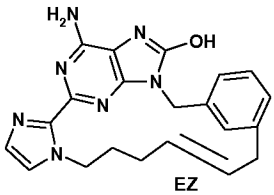
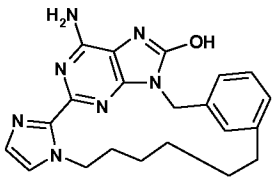
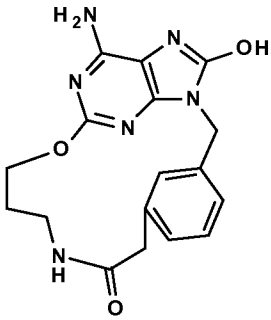
injection volume of 2 µL was used. Cone voltage was 20 V for positive and negative ionization mode. Mass spectra were acquired by scanning from 100 to 1000 in 0.2 seconds using an interscan delay of 0.1 seconds.

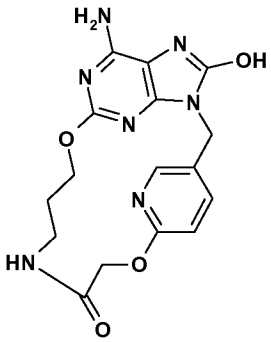
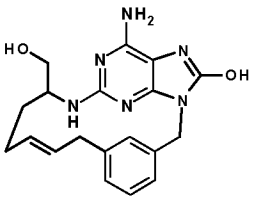
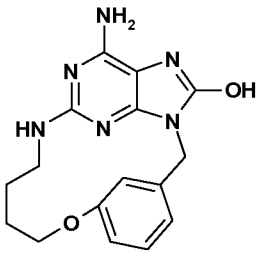
Method V3018V3001

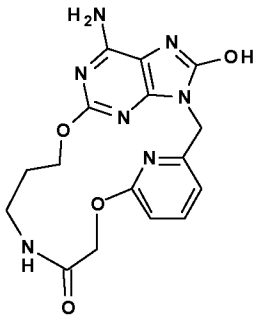
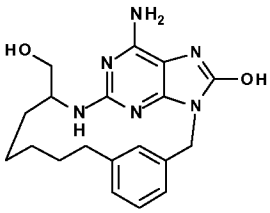
In addition to the general procedure VDR2: Reversed phase UPLC was carried out on a Waters Acquity BEH (bridged ethylsiloxane/silica hybrid) C18 column (1.7 µm, 2.1 x 100 mm) with a flow rate of 0.343 ml/min. Two mobile phases (mobile phase A: 95 % 7 mM ammonium acetate / 5 % acetonitrile; mobile phase B: 100 % acetonitrile) were employed to run a gradient condition from 84.2 % A and 15.8 % B (hold for 0.49 minutes) to 10.5 % A and 89.5 % B in 2.18 minutes, hold for 1.94 min and back to the initial conditions in 0.73 min, hold for 0.73 minutes. An injection volume of 2 µl was used. Cone voltage was 20V for positive and negative ionization mode. Mass spectra were acquired by scanning from 100 to 1000 in 0.2 seconds using an interscan delay of 0.1 seconds.

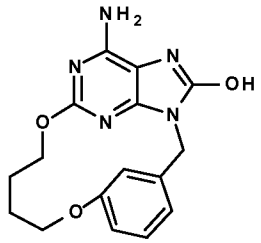
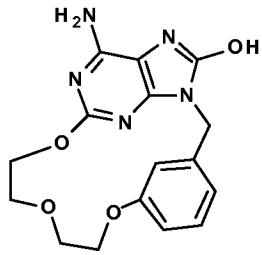
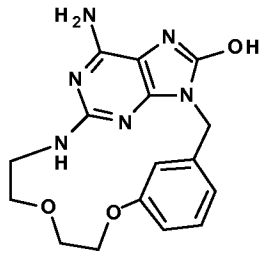
Table 1. Compounds of formula (I).

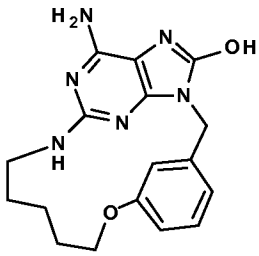
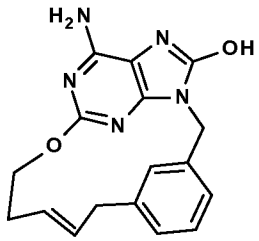
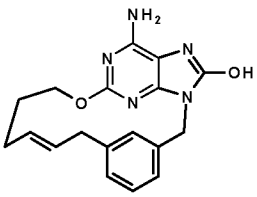
#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
1		323.1	324	2.52, V3018V3001	Method 1	^{1}H NMR (500MHz, DMSO-d_6) δ (ppm) 9.91 (br. s., 1H), 8.00 - 8.11 (m, 1H), 7.04 - 7.24 (m, 3H), 6.43 (s, 2H), 5.36 - 5.77 (m, 2H), 4.82 (d, J = 4.7 Hz, 2H), 4.63 - 4.69 (m, 1H), 4.45 - 4.57 (m, 1H), 3.17 - 3.32 (m, 2H), 2.34 - 2.43 (m, 2H)
2		325.2	326	2.62, V3018V3001	Method 2	^{1}H NMR (500MHz, DMSO-d_6) δ□(ppm) 9.93 (s, 1H), 7.57 (s, 1H), 7.14 - 7.20 (m, 1H), 7.04 (d, J = 7.3 Hz, 1H), 6.93 (d, J = 7.3 Hz, 1H), 6.36 (br. s., 2H), 4.83 (s, 2H),

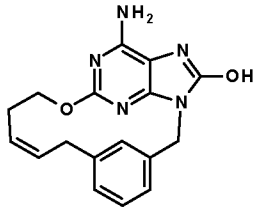
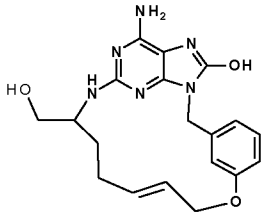
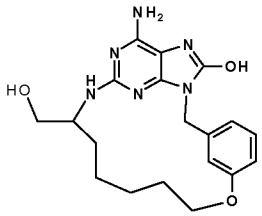
#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
						4.15 (t, J = 6.8 Hz, 2H), 2.60 - 2.69 (m, 2H), 1.68 (br. s., 2H), 1.18 - 1.34 (m, 4H)
3		387.2	388	2.47, V3018V3001	Method 3	^{1}H NMR (500MHz, DMSO-d_6) δ (ppm) 9.91 - 10.50 (m, 1H), 6.91 - 7.37 (m, 6H), 6.57 - 6.70 (m, 2H), 5.21 - 5.54 (m, 2H), 4.82 - 4.92 (m, 2H), 4.11 - 4.30 (m, 2H), 3.18 - 3.32 (m, 2H), 2.03 - 2.23 (m, 2H), 1.60 - 1.90 (m, 2H)
4		389.2	390	2.57, V3018V3001	Method 4	^{1}H NMR (500MHz, DMSO-d_6) δ□(ppm) 11.25 (s, 1H), 7.87 (d, J = 1.3 Hz, 1H), 7.72 (s, 1H), 7.04 - 7.31 (m, 6H), 4.98 (s, 2H), 4.41 - 4.49 (m, 2H), 2.58 - 2.65 (m, 2H), 1.62 - 1.72 (m, 2H), 1.52 - 1.61 (m, 2H), 1.13 - 1.25 (m, 2H), 0.99 - 1.11 (m, 2H)
5		354.1	355	2.52, V3014V3001	Method 5	^{1}H NMR (500MHz, DMSO-d_6) δ□(ppm) 10.40 - 10.67 (m, 1H), 8.25 (t, J = 5.5 Hz, 1H), 7.74 (s, 1H), 6.83 - 7.27 (m, 5H), 4.79 (s, 2H), 4.53 (t, J = 7.6 Hz, 2H), 3.36 (s, 2H), 3.03 - 3.13 (m, 2H), 1.66 (s, 2H)

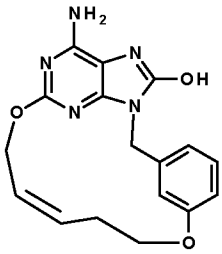
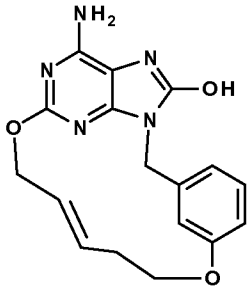
#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
6		371.1	372	2.40, V3014V3001	Method 6	^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm) 10.42 (br. s., 1H), 8.31 (s, 1H), 7.59 (t, *J* = 4.80 Hz, 1H), 7.50 (dd, *J* = 2.02, 8.59 Hz, 1H), 6.83 - 7.32 (m, 2H), 6.80 (d, *J* = 8.59 Hz, 1H), 4.86 (br. s., 2H), 4.67 (br. s., 2H), 3.70 (br. s., 2H), 3.09 (br. s., 2H), 1.72 - 1.82 (m, 2H)
7		366.2	367	2.25, V3018V3001	Method 7	^{1}H NMR (500 MHz, DMSO-d$_6$) δ (ppm) 9.53 (s, 1H), 7.92 (s, 1H), 7.13 - 7.22 (m, 2H), 7.07 (d, *J* = 7.25 Hz, 1H), 5.87 (s, 2H), 5.68 (d, *J* = 10.09 Hz, 1H), 5.38 - 5.47 (m, 1H), 5.20 - 5.30 (m, 1H), 4.77 (d, 1H), 4.66 (d, 1H), 4.57 (t, 1H), 4.25 - 4.36 (m, 1H), 3.39 - 3.47 (m, 1H), 3.34 - 3.39 (m, 1H), 3.18 - 3.30 (m, 2H), 2.05 - 2.18 (m, 2H), 1.70 - 1.80 (m, 1H), 1.40 - 1.51 (m, 1H)
8		326.1	327	2.26, V3018V3001	Method 8	^{1}H NMR (500 MHz, DMSO-d$_6$) δ (ppm) 9.64 (br. s., 1H), 9.36 (s, 1H), 7.08 (t, *J* = 7.70 Hz, 1H), 6.76 (d, *J* = 7.70 Hz, 1H), 6.71 (s, 1H), 6.62 (dd, *J* = 1.73, 7.70 Hz, 1H), 6.06 (s, 2H), 4.71 (s, 2H), 3.39 (t, *J* = 6.46 Hz, 4H), 1.76 - 1.92 (m,

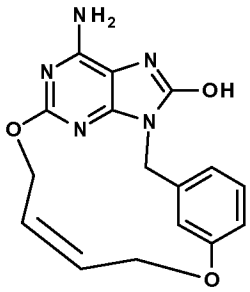
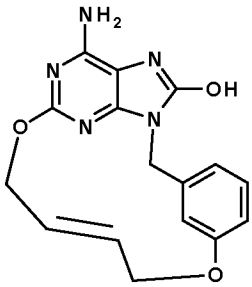
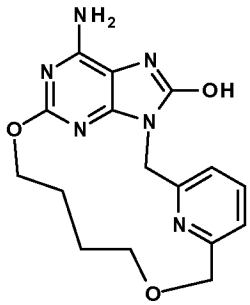
#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
						4H)
9		371.1	372	2.49, V3014V3001	Method 9	^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 10.00 (br. s., 1H), 7.97 (t, *J* = 5.83 Hz, 1H), 7.68 (t, *J* = 7.72 Hz, 1H), 7.00 (d, *J* = 7.72 Hz, 1H), 6.80 (d, *J* = 7.72 Hz, 1H), 6.39 (s, 2H), 4.65 - 4.94 (m, 4H), 4.20 (t, *J* = 7.72 Hz, 2H), 2.96 - 3.12 (m, 2H), 1.50 - 1.73 (m, 2H)
10		368.2	369	2.33, V3018V3001	Method 10	^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 9.61 (s, 1H), 7.43 (s, 1H), 7.15 - 7.26 (m, 1H), 7.07 - 7.14 (m, 1H), 7.02 (d, *J* = 7.25 Hz, 1H), 5.92 (s, 2H), 5.56 (d, *J* = 10.09 Hz, 1H), 4.95 (d, *J* = 14.50 Hz, 1H), 4.47 - 4.63 (m, 2H), 4.06 - 4.23 (m, 1H), 3.34 - 3.39 (m, 1H), 3.22 - 3.30 (m, 1H), 2.55 - 2.68 (m, 2H), 1.67 - 1.84 (m, 1H), 1.46 - 1.61 (m, 1H), 1.22 - 1.45 (m, 5H), 0.97 - 1.14 (m, 1H)

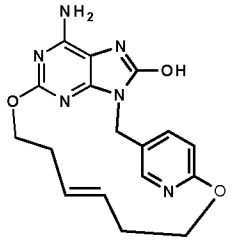
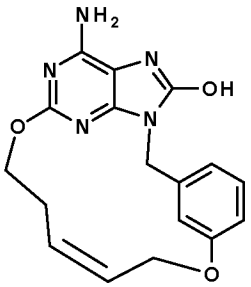
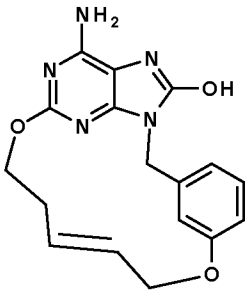
#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
11		327.1	328	2.23, V3018V3001	Method 11	^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 9.93 (br. s., 1H), 7.92 (s, 1H), 7.15 (t, *J* = 7.72 Hz, 1H), 6.81 (d, *J* = 7.72 Hz, 1H), 6.66 - 6.77 (m, 1H), 6.39 (br. s., 2H), 4.82 (s, 2H), 4.57 (t, *J* = 5.99 Hz, 2H), 4.27 (t, *J* = 6.62 Hz, 2H), 1.44 - 1.73 (m, 4H)
12		343.1	344	2.12, V3018V3001	Method 12	^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 9.93 (br. s., 1H), 7.72 (s, 1H), 7.16 (t, *J* = 7.88 Hz, 1H), 6.95 (d, *J* = 7.88 Hz, 1H), 6.78 (dd, *J* = 1.89, 7.88 Hz, 1H), 6.43 (br. s., 2H), 4.82 (s, 2H), 4.66 (t, *J* = 4.57 Hz, 2H), 3.99 - 4.07 (m, 2H), 3.59 (td, *J* = 4.57, 12.14 Hz, 4H)
13		342.1	343	1.97, V3018V3001	Method 8	^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 9.75 (br. s., 1H), 9.36 (br. s., 1H), 7.09 (t, *J* = 7.88 Hz, 1H), 6.73 (d, *J* = 7.88 Hz, 1H), 6.68 (s, 1H), 6.62 (d, *J* = 7.88 Hz, 1H), 6.16 (s, 2H), 4.73 (s, 2H), 3.45 - 3.69 (m, 8H)

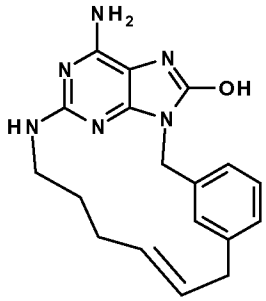
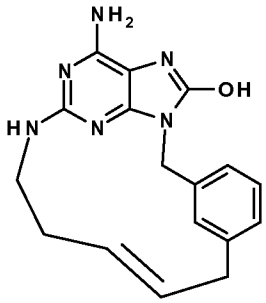
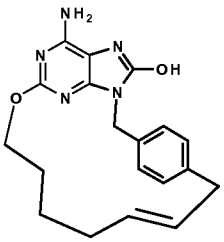
#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
14		340.2	341	2.37, V3018V3001	Method 12	^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 9.65 (s, 1H), 7.48 (s, 1H), 7.19 (t, *J* = 7.72 Hz, 1H), 6.90 (d, *J* = 7.72 Hz, 1H), 6.77 (dd, *J* = 1.89, 7.72 Hz, 1H), 6.10 (t, *J* = 6.31 Hz, 1H), 5.99 (s, 2H), 4.75 (s, 2H), 3.87 - 3.99 (m, 2H), 3.42 (q, *J* = 6.31 Hz, 2H), 1.60 - 1.78 (m, 2H), 1.39 - 1.50 (m, 2H), 1.29 - 1.39 (m, 2H)
15		323.1	324	2.49, V3018V3001	Method 14	^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 9.76 - 10.25 (m, 1H), 8.07 (s, 1H), 6.95 - 7.29 (m, 3H), 6.44 (s, 2H), 5.57 - 5.81 (m, 1H), 5.29 - 5.54 (m, 1H), 4.82 (s, 2H), 4.66 (br. s., 2H), 3.20 (d, *J* = 6.31 Hz, 2H), 2.39 (br. s., 2H)
16		337.2	338	2.65, V3018V3001	Method 13	^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 9.95 (s, 1H), 7.81 (s, 1H), 6.94 - 7.39 (m, 3H), 6.39 (s, 2H), 5.14 - 5.62 (m, 2H), 4.78 (s, 2H), 4.54 (s, 2H), 1.59 - 2.31 (m, 5H), 1.23 (br. s., 1H)

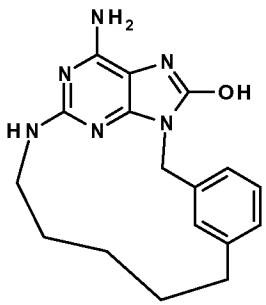
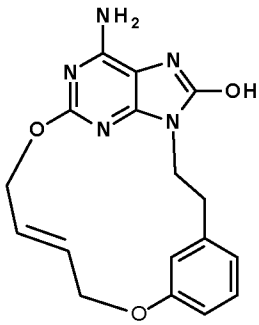
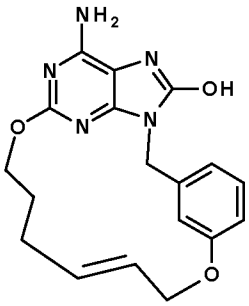
#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
17		323.1	324	2.51, V3018V3001	Method 14	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.92 (br. s., 1H), 8.03 (br. s., 1H), 7.17 - 7.25 (m, 1H), 7.08 - 7.16 (m, 2H), 6.43 (br. s., 2H), 5.68 - 5.77 (m, 1H), 5.47 - 5.57 (m, 1H), 4.81 (s, 2H), 4.43 - 4.53 (m, 2H), 3.28 - 3.32 (br. s., 2H), 2.34 - 2.42 (m, 2H)
18		382.2	383	2.13, V3018V3001	Method 15	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.62 (s, 1H), 7.17 (t, *J* = 8.20 Hz, 1H), 7.11 (s, 1H), 6.99 (d, *J* = 8.20 Hz, 1H), 6.78 (dd, *J* = 1.89, 8.20 Hz, 1H), 5.91 (s, 2H), 5.71 (dt, *J* = 6.50, 15.76 Hz, 1H), 5.58 (d, *J* = 9.77 Hz, 1H), 5.50 (dt, *J* = 4.89, 15.76 Hz, 1H), 4.83 (d, *J* = 9.77 Hz, 1H), 4.48 - 4.73 (m, 4H), 4.09 - 4.23 (m, 1H), 3.38 - 3.48 (m, 2H), 1.97 - 2.08 (m, 2H), 1.62 - 1.75 (m, 1H), 1.29 - 1.40 (m, 1H)
19		384.2	385	2.19, V3018V3001	Method 10	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.64 (s, 1H), 7.16 - 7.23 (m, 1H), 7.12 (br. s., 1H), 7.01 (d, *J* = 7.25 Hz, 1H), 6.80 (dd, *J* = 1.73, 8.04 Hz, 1H), 5.95 (s, 2H), 5.64 (d, *J* = 9.14 Hz, 1H),

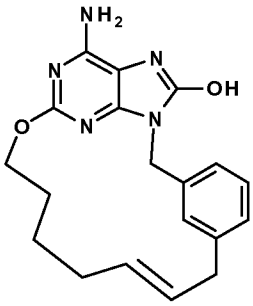
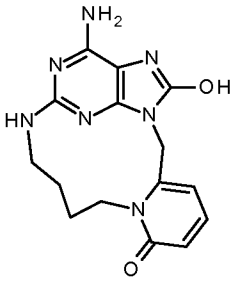
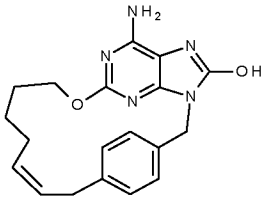
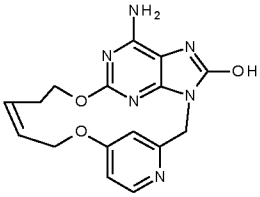
#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
						4.85 (d, *J* = 14.19 Hz, 1H), 4.52 - 4.67 (m, 2H), 4.03 - 4.16 (m, 2H), 3.91 - 4.03 (m, 1H), 3.37 - 3.50 (m, 2H), 1.24 - 1.68 (m, 8H)
20		339.1	340	2.37, V3018V3001	Method 16	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.99 (br. s., 1H), 7.57 (br. s., 1H), 7.21 (t, *J* = 7.70 Hz, 1H), 6.94 (d, *J* = 7.70 Hz, 1H), 6.78 (dd, *J* = 1.58, 7.70 Hz, 1H), 6.49 (br. s., 2H), 5.74 - 5.85 (m, 1H), 5.59 - 5.69 (m, 1H), 5.13 (d, *J* = 7.57 Hz, 2H), 4.85 (s, 2H), 3.90 - 4.02 (m, 2H), 2.45 - 2.50 (m, 2H)
21		339.1	340	2.32, V3018V3001	Method 16	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.94 (br. s., 1H), 7.15 - 7.25 (m, 2H), 6.92 (d, *J* = 7.57 Hz, 1H), 6.83 (dd, *J* = 1.73, 7.57 Hz, 1H), 6.44 (br. s., 2H), 5.76 (dt, *J* = 7.00, 15.61 Hz, 1H), 5.46 (dt, *J* = 5.12, 15.61 Hz, 1H), 4.76 - 4.84 (m, 4H), 4.05 - 4.13 (m, 2H), 2.27 - 2.38 (m, 2H)

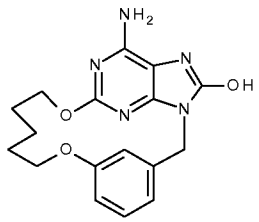
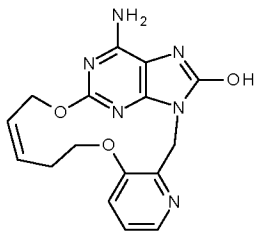
#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
22		325.1	326	2.19, V3018V3001	Method 16	^{1}H NMR (500 MHz, DMSO-d_6) δ 10.25 (br. s., 1H), 7.91 (br. s., 1H), 7.18 (t, *J* = 7.25 Hz, 1H), 6.87 (d, *J* = 7.25 Hz, 1H), 6.79 (d, *J* = 7.25 Hz, 1H), 6.54 (br. s., 2H), 5.30 - 5.48 (m, 2H), 5.12 (br. s., 2H), 4.81 (br. s., 2H), 4.76 (br. s., 2H)
23		325.1	326	2.15, V3018V3001	Method 16	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.96 (br. s., 1H), 7.55 (s, 1H), 7.16 (t, *J* = 7.25 Hz, 1H), 6.88 (d, *J* = 7.25 Hz, 1H), 6.80 (dd, *J* = 1.73, 7.25 Hz, 1H), 6.44 (br. s., 2H), 5.61 - 5.77 (m, 2H), 4.78 (s, 4H), 4.56 (d, *J* = 4.73 Hz, 2H)
24		342.1	343	1.75, V3018V3001	Method 17	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.98 (br. s., 1H), 7.73 (t, *J* = 7.57 Hz, 1H), 7.25 (dd, *J* = 7.57, 13.24 Hz, 2H), 6.37 (br. s., 2H), 4.99 (s, 2H), 4.41 (s, 2H), 4.21 (t, *J* = 7.25 Hz, 2H), 3.61 (t, *J* = 5.83 Hz, 2H), 1.38 - 1.56 (m, 4H)

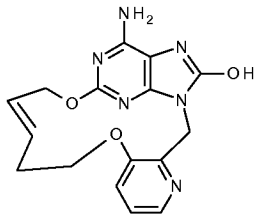
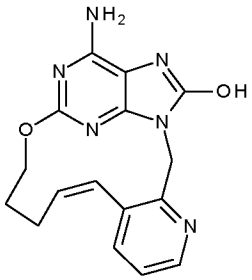
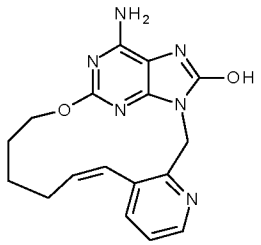
#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
25		354.1	355	2.2, V3018V3001	Method 16	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.86 (br. s., 1H), 8.19 (d, *J* = 2.53 Hz, 1H), 7.50 (dd, *J* = 2.02, 8.59 Hz, 1H), 6.64 (d, *J* = 8.59 Hz, 1H), 6.14 (s, 2H), 5.17 - 5.25 (m, 2H), 4.80 (s, 2H), 4.67 (br. s., 2H), 3.80 - 3.89 (m, 2H), 2.25 - 2.37 (m, 2H), 1.83 - 1.91 (m, 2H)
26		339.1	340	2.37, V3018V3001	Method 16	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.84 (br. s., 1H), 7.28 (d, *J* = 1.26 Hz, 1H), 7.16 - 7.24 (m, 1H), 6.96 (d, *J* = 7.25 Hz, 1H), 6.76 - 6.82 (m, 1H), 6.46 (br. s., 2H), 5.38 - 5.50 (m, 2H), 4.74 (s, 2H), 4.68 (d, *J* = 3.78 Hz, 2H), 4.57 (t, *J* = 7.57 Hz, 2H), 2.43 - 2.53 (m, 2H)
27		339.1	340	2.35, V3018V3001	Method 16	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.97 (br. s., 1H), 7.18 (t, *J* = 7.25 Hz, 1H), 7.03 (s, 1H), 6.93 (d, *J* = 7.25 Hz, 1H), 6.75 (d, *J* = 7.25 Hz, 1H), 6.52 (br. s., 2H), 5.43 - 5.56 (m, 2H), 4.79 (s, 2H), 4.56 - 4.62 (m, 2H), 4.42 - 4.47 (m, 2H), 2.32 - 2.39 (m, 2H)

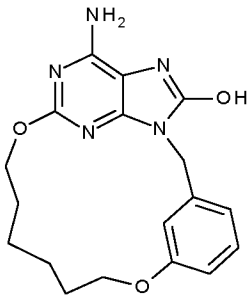
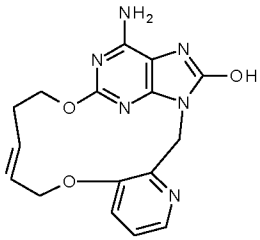
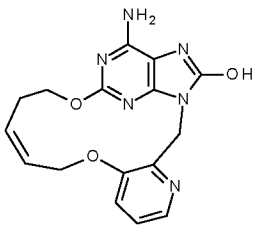
#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
28		336.2	337	2.59, V3018V3001	Method 7	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.57 (s, 1H), 7.85 (s, 1H), 7.12 - 7.24 (m, 2H), 7.08 (d, *J* = 7.25 Hz, 1H), 5.80 - 5.99 (m, 3H), 5.44 - 5.52 (m, 1H), 5.31 - 5.39 (m, 1H), 4.71 (s, 2H), 3.46 - 3.54 (m, 2H), 3.27 - 3.40 (m, 2H), 1.97 - 2.16 (m, 2H), 1.57 (br. s., 2H)
29		322.2	323	2.45, V3018V3001	Method 7	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.54 (br. s., 1H), 8.19 (br. s., 1H), 6.97 - 7.24 (m, 3H), 6.27 (br. s., 1H), 5.92 (br. s., 2H), 5.56 - 5.68 (m, 1H), 5.44 - 5.56 (m, 1H), 4.75 (s, 2H), 3.25 - 3.78 (m, 2H), 3.14 - 3.24 (m, 2H), 2.12 - 2.24 (m, 2H)
30		351.2	352	2.75, V3018V3001	Method 14	^{1}H NMR (500 MHz, DMSO-d_6) δ 10.09 (br. s., 1H), 7.05 (s, 4H), 6.37 (br. s., 2H), 5.60 - 5.73 (m, 1H), 4.83 - 4.96 (m, 3H), 3.67 - 3.72 (m, 2H), 3.12 - 3.17 (m, 2H), 1.91 (br. s., 2H), 1.03 - 1.19 (m, 4H)

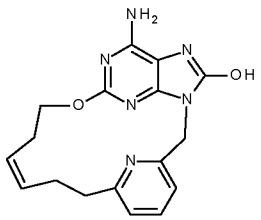
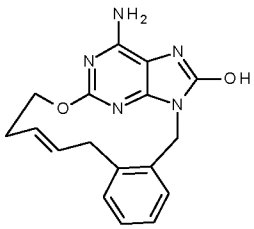
#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
31		324.2	325	2.52, V3018V3001	Method 10	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.63 (br. s., 1H), 7.63 (s, 1H), 7.10 - 7.20 (m, 1H), 7.01 (d, *J* = 7.58 Hz, 1H), 6.95 (d, *J* = 7.58 Hz, 1H), 6.09 (t, *J* = 6.06 Hz, 1H), 5.88 (s, 2H), 4.77 (s, 2H), 3.08 - 3.18 (m, 2H), 2.59 - 2.70 (m, 2H), 1.69 (br. s., 2H), 1.13 - 1.31 (m, 4H)
32		339.1	340	2.15, V3018V3001	Method 18	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.73 (br. s., 1H), 6.85 - 6.93 (m, 2H), 6.58 (dd, *J* = 1.58, 8.20 Hz, 1H), 6.37 (d, *J* = 8.20 Hz, 1H), 6.26 (br. s., 2H), 5.66 - 5.74 (m, 1H), 5.55 (br. d., *J* = 16.39 Hz, 1H), 4.63 - 4.69 (m, 4H), 4.03 (t, *J* = 5.20 Hz, 2H), 2.97 (t, *J* = 5.20 Hz, 2H)
33		353.1	354	2.46, V3018V3001	Method 16	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.97 (br. s., 1H), 7.08 - 7.21 (m, 2H), 6.85 (d, *J* = 7.57 Hz, 1H), 6.78 (dd, *J* = 1.89, 7.57 Hz, 1H), 6.39 (br. s., 2H), 5.75 - 5.84 (m, 1H), 5.51 (dt, *J* = 5.24, 15.68 Hz, 1H), 4.74 - 4.79 (m, 2H), 4.67 (d, *J* = 4.73 Hz, 2H), 4.21 - 4.27 (m, 2H), 2.02 - 2.08 (m, 2H), 1.55 - 1.66 (m, 2H)

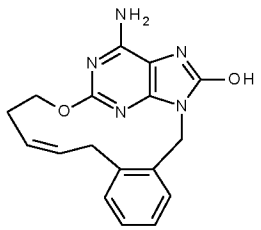
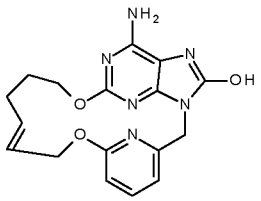
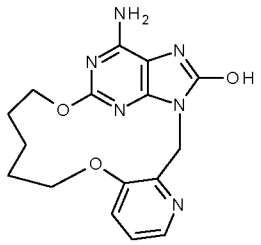
#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
34		351.2	352	2.82, V3018V3001	Method 14	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.94 (br. s., 1H), 7.29 (d, *J* = 6.94 Hz, 1H), 7.17 - 7.25 (m, 2H), 7.10 (d, *J* = 6.94 Hz, 1H), 6.41 (br. s., 2H), 5.42 (br. s., 2H), 4.79 (br. s., 2H), 4.16 - 4.24 (m, 2H), 3.23 (br. s., 2H), 2.03 (br. s., 2H), 1.77 (br. s., 2H), 1.41 (br. s., 2H)
35		327,1	328	1.81, V3018V3001	Method 8	^{1}H NMR (500 MHz, DMSO-d_6) δ 11.30 (br. s., 1H), 9.64 (s, 1H), 7.33 (dd, *J* = 6.9, 8.8 Hz, 1H), 6.24 (d, *J* = 8.8 Hz, 1H), 5.96 (br. s., 3H), 4.71 (s, 2H), 3.30 - 3.48 (m, 4H), 1.70 - 1.94 (m, 4H)
36		351,2	352	2.77, V3018V3001	Method 14 Method 26 (metathesis reaction)	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.99 (br. s., 1H), 7.13 (d, *J* = 7.6 Hz, 2H), 7.02 (d, *J* = 7.6 Hz, 2H), 6.34 (br. s., 2H), 5.92 (dt, *J* = 7.6, 10.1 Hz, 1H), 5.45 (dt, *J* = 8.0, 10.1 Hz, 1H), 4.87 (s, 2H), 3.82 (t, *J* = 7.6 Hz, 2H), 3.21 - 3.29 (m, 2H), 1.59 - 1.77 (m, 2H), 0.60 - 0.92 (m, 4H)
37		340,1	341	2.03, V3018V3001	Method 21	^{1}H NMR (500 MHz, DMSO-d_6) δ 10.21 (br. s., 1H), 8.23 (d, *J* = 5.6 Hz, 1H), 7.33 (d, *J* = 1.9 Hz, 1H),

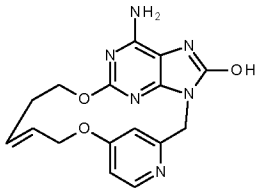
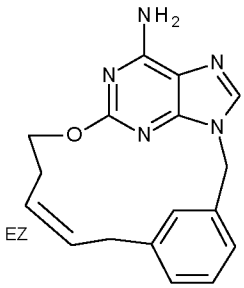
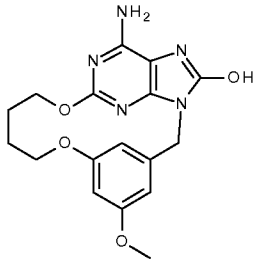
#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
						6.81 (dd, *J* = 1.9, 5.6 Hz, 1H), 6.57 (br. s., 2H), 5.51 (dt, *J* = 7.6, 10.7 Hz, 1H), 5.42 (dt, *J* = 5.6, 10.7 Hz, 1H), 4.88 (s, 2H), 4.78 (d, *J* = 5.6 Hz, 2H), 4.51 (t, *J* = 7.6 Hz, 2H)
38		341.1	342	2.4, V3018V3001	Method 19	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.94 (s, 1H), 7.39 (s, 1H), 7.20 (t, *J* = 7.7 Hz, 1H), 6.91 (d, *J* = 7.7Hz, 1H), 6.81 (d, *J* = 7.7 Hz, 1H), 6.45 (br. s., 2H), 4.82 (s, 2H), 4.49 (t, *J* = 6.5 Hz, 2H), 3.98 (t, *J* = 7.3 Hz, 2H), 1.62 - 1.76 (m, 2H), 1.50 - 1.61 (m, 2H), 1.32 - 1.45 (m, 2H)
39		340.1	341	1.88, V3018V3001	Method 20	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (br. s., 1H), 7.96 (d, *J* = 4.6 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.21 (dd, *J* = 4.6, 8.1 Hz, 1H), 6.33 (s, 2H), 5.45 (dt, *J* = 7.6, 10.6 Hz, 1H), 5.30 (dt, *J* = 5.6, 10.6 Hz, 1H), 4.88 (s, 2H), 4.32 - 4.55 (m, 4H), 2.42 - 2.48 (m, 2H)

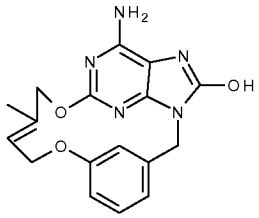
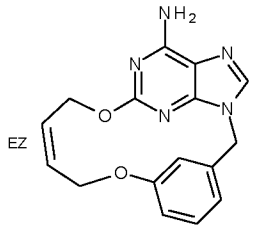
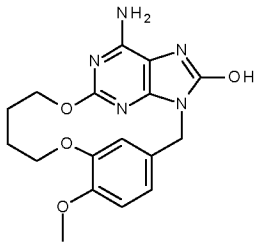
#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
40		340.1	341	1.94, V3018V3001	Method 20	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.77 (br. s., 1H), 7.91 (d, *J* = 4.0 Hz, 1H), 7.47 (d, *J* = 8.6 Hz, 1H), 7.18 (dd, *J* = 4.0, 8.6 Hz, 1H), 6.34 (s, 2H), 5.70 (dt, *J* = 6.5, 15.4 Hz, 1H), 5.24 (dt, *J* = 5.5, 15.4 Hz, 1H), 4.93 (s, 2H), 4.56 (d, *J* = 5.5 Hz, 2H), 4.45 (t, *J* = 6.5 Hz, 2H), 2.35 - 2.42 (m, 2H)
41		324.1	325	2.06, V3018V3001	Method 21	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.76 (s, 1H), 8.33 (d, *J* = 3.5 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.20 (dd, *J* = 3.5, 7.6 Hz, 1H), 6.83 (d, *J* = 11.6 Hz, 1H), 6.29 (br. s., 2H), 5.79 - 6.00 (m, 1H), 4.93 (d, *J* = 13.6 Hz, 1H), 4.81 (d, *J* = 13.6 Hz, 1H), 4.45 - 4.67 (m, 1H), 3.78 - 3.98 (m, 1H), 2.18 - 2.36 (m, 1H), 2.01 - 2.14 (m, 1H), 1.54 - 1.83 (m, 2H)
42		338.1	339	2.21, V3018V3001	Method 21	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (br. s., 1H), 8.32 (dd, *J* = 1.5, 4.6 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.25 (dd, *J* = 4.6, 7.6 Hz, 1H), 6.86 (d, *J* = 12.1 Hz, 1H), 6.32 (s, 2H), 5.70 - 5.85 (m, 1H),

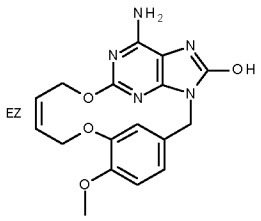
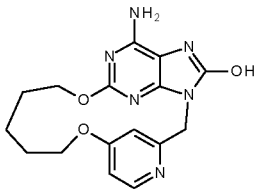
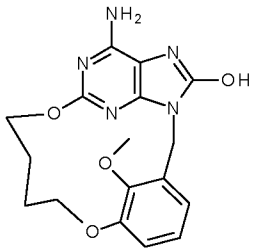
#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
						5.00 (d, *J* = 14.7 Hz, 1H), 4.80 (d, *J* = 14.7 Hz, 1H), 3.75 (dt, *J* = 4.6, 11.4 Hz, 1H), 3.54 (dt, *J* = 4.6, 11.4 Hz, 1H), 1.93 - 2.47 (m, 3H), 1.24 - 1.65 (m, 3H)
43		355.2	356	2.53, V3018V3001	Method 19	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.94 (br. s., 1H), 7.13 - 7.30 (m, 2H), 6.98 (d, *J* = 7.3 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.41 (br. s., 2H), 4.80 (s, 2H), 4.34 (t, *J* = 6.8 Hz, 2H), 4.13 (t, *J* = 6.3 Hz, 2H), 1.56 (m, 4H), 1.42 (m, 4H)
44		340.1	341	1.85, V3018V3001	Method 21	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.78 (br. s., 1H), 8.04 (d, *J* = 4.0 Hz, 1H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.24 (dd, *J* = 4.0, 7.6 Hz, 1H), 6.30 (s, 2H), 6.12 (dt, *J* = 7.0, 15.7 Hz, 1H), 5.54 (dt, *J* = 5.0, 15.7 Hz, 1H), 5.01 (s, 2H), 4.49 (d, *J* = 5.0 Hz, 2H), 4.18 - 4.28 (m, 2H), 2.23 - 2.36 (m, 2H)
45		340.1	341	1.99, V3018V3001	Method 21	^{1}H NMR (500 MHz, DMF) δ 10.14 (br. s., 1H), 8.29 (d, *J* = 4.1 Hz, 1H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.43 (dd, *J* = 4.1, 7.9 Hz,

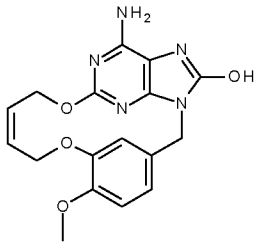
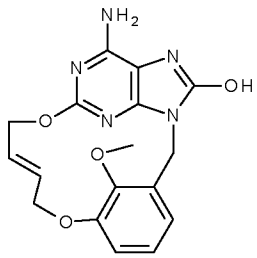
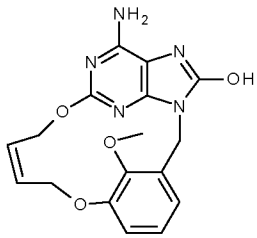
#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
						1H), 6.66 (br. s., 2H), 6.10 (dt, *J* = 5.7, 10.4 Hz, 1H), 5.90 (dt, *J* = 8.4, 10.4 Hz, 1H), 5.29 (s, 2H), 5.13 (d, *J* = 5.7 Hz, 2H), 3.96 - 4.18 (m, 2H), 2.58 - 2.76 (m, 2H)
46		338.1	339	2.09, V3018V3001	Method 21	^{1}H NMR (500 MHz, DMSO-d_6) δ 10.00 (br. s., 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.39 (br. s., 2H), 5.39 (dt, *J* = 7.2, 10.4 Hz, 1H), 5.16 (dt, *J* = 7.4, 10.4 Hz, 1H), 4.95 (s, 2H), 3.71 (t, *J* = 7.4 Hz, 2H), 2.63 - 2.71 (m, 2H), 2.25 - 2.34 (m, 2H), 1.96 - 2.06 (m, 2H)
47		323.1	324	2.44, V3018V3001	Method 21	^{1}H NMR (500 MHz, DMSO-d_6) δ 10.22 (br. s., 1H), 7.30 (dd, *J* = 1.9, 7.3 Hz, 1H), 7.12 - 7.21 (m, 2H), 7.10 (dd, *J* = 2.2, 7.3 Hz, 1H), 6.47 (br. s., 2H), 5.55 (dt, *J* = 4.0, 15.7 Hz, 1H), 5.18 (dt, *J* = 7.2, 15.7 Hz, 1H), 4.89 (s, 2H), 4.07 - 4.24 (m, 2H), 3.37 - 3.66 (m, 2H), 2.11 - 2.33 (m, 2H)

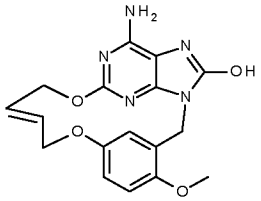
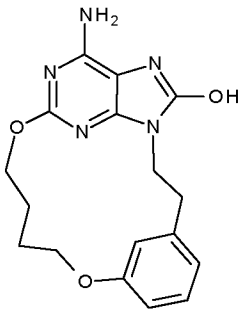
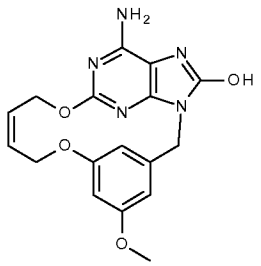
#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
48		323.1	324	2.52, V3018V3001	Method 21	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.02 (br. s., 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.03 - 7.23 (m, 3H), 6.43 (br. s., 2H), 6.16 (dt, *J* = 8.0, 9.6 Hz, 1H), 5.78 (dt, *J* = 8.0, 9.6 Hz, 1H), 5.03 - 5.29 (m, 1H), 4.73 - 5.01 (m, 2H), 4.07 - 4.38 (m, 1H), 3.65 - 4.02 (m, 1H), 2.13 - 2.31 (m, 2H)
49		354.1	355	2.43, V3018V3001	Method 21	^{1}H NMR (500 MHz, DMSO-d_6) δ 10.00 (br. s., 1H), 7.60 (t, *J* = 7.7 Hz, 1H), 6.80 (d, *J* = 7.3 Hz, 1H), 6.65 (d, *J* = 8.2 Hz, 1H), 6.41 (br. s., 2H), 5.81 (dt, *J* = 7.7, 15.5 Hz, 1H), 5.58 (dt, *J* = 5.4, 15.5 Hz, 1H), 4.87 (s, 2H), 4.84 (d, *J* = 5.4 Hz, 2H), 4.10 (t, *J* = 7.7 Hz, 2H), 1.90 - 2.07 (m, 2H), 1.48 - 1.66 (m, 2H)
50		342.1	343	2.03, V3018V3001	Method 19	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.80 (br. s., 1H), 8.03 (d, *J* = 4.6 Hz, 1H), 7.40 (d, *J* = 8.1 Hz, 1H), 7.24 (dd, *J* = 4.6, 8.1 Hz, 1H), 6.32 (br. s., 2H), 4.98 (s, 2H), 3.99 - 4.35 (m, 4H), 1.50 - 1.86 (m, 6H)

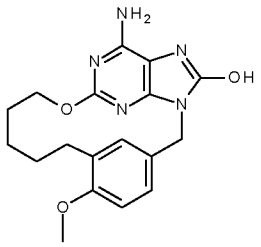
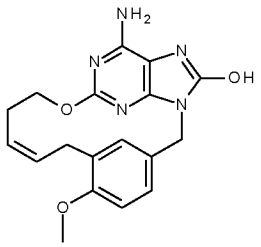
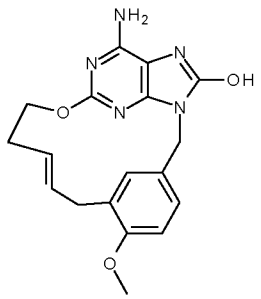
#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
51		340.1	341	1.97, V3018V3001	Method 21	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (br. s., 1H), 8.23 (d, *J* = 6.1 Hz, 1H), 6.85 (d, *J* = 2.0 Hz, 1H), 6.76 (dd, *J* = 2.0, 6.1 Hz, 1H), 6.51 (s, 2H), 5.50 (dt, *J* = 7.0, 15.7 Hz, 1H), 5.40 (dt, *J* = 5.6, 15.7 Hz, 1H), 4.90 (s, 2H), 4.59 (d, *J* = 5.6 Hz, 2H), 4.45 - 4.56 (m, 2H), 2.19 - 2.41 (m, 2H)
52		307.1	308	2.56, V3018V3001	Method 22	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.17 (br. s., 1H), 8.07 (s, 0.3H), 8.02 (s, 0.7H), 7.29 (d, *J* = 7.6 Hz, 0.3H), 7.10 - 7.25 (m, 4H), 7.07 (d, *J* = 7.3 Hz, 0.7H), 5.63 - 5.75 (m, 1H), 5.55 (td, *J* = 6.6, 10.7 Hz, 0.3H), 5.43 (td, *J* = 7.5, 15.3 Hz, 0.7H), 5.22 (s, 1.4H), 5.21 (s, 0.6H), 4.64 - 4.77 (m, 1.4H), 4.49 - 4.60 (m, 0.6H), 3.30 (d, *J* = 7.9 Hz, 0.6H), 3.18 (d, *J* = 7.9 Hz, 1.4H), 2.37 - 2.45 (m, 2H)
53		357.1	358	2.23, V3018V3001	Method 23	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (br. s., 1H), 7.51 (s, 1H), 6.38 (s, 3H), 6.30 (s, 1H), 4.77 (s, 2H), 4.55 (t, *J* = 6.3 Hz, 2H), 4.24 (t, *J* =

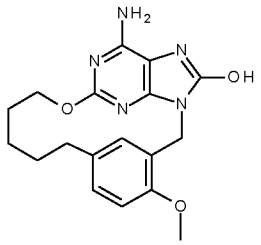
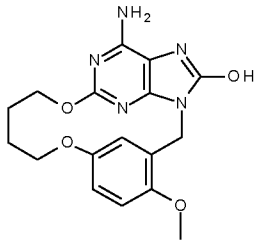
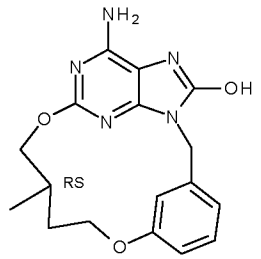
#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
						6.3 Hz, 2H), 3.66 (s, 3H), 1.40 - 1.73 (m, 4H)
54		339.1	340	2.25, V3018V3001	Method 16	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.98 (br. s., 1H), 7.39 (s, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 6.79 (dd, *J* = 1.7, 7.6 Hz, 1H), 6.43 (br. s., 2H), 5.37 (t, *J* = 5.5 Hz, 1H), 4.77 (s, 2H), 4.65 (d, *J* = 5.5 Hz, 2H), 4.59 (s, 2H), 1.57 (s, 3H)
55		309.1	310	2.17, V3018V3001	Method 22	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (s, 0.5H), 8.08 (s, 0.5H), 8.06 (br. s., 0.5H), 7.64 (s, 0.5H), 7.08 - 7.24 (m, 3H), 7.05 (d, *J* = 7.1 Hz, 0.5H), 6.99 (d, *J* = 7.6 Hz, 0.5H), 6.73 - 6.86 (m, 1H), 5.70 - 5.82 (m, 0.5H), 5.63 (dt, *J* = 3.6, 16.2 Hz, 0.5H), 5.28 - 5.50 (m, 1H), 5.16 (s, 3H), 4.69 - 4.92 (m, 2H), 4.54 (d, *J* = 5.6 Hz, 1H)
56		357.1	358	1.99, V3018V3001	Method 23	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (br. s, 1H), 7.88 (s, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 6.35 (br. s., 2H), 4.77 (s, 2H),

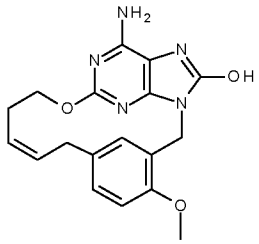
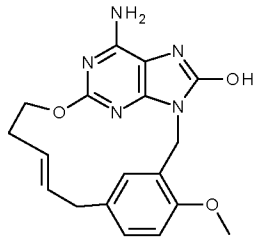
#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
						4.45 - 4.63 (m, 2H), 4.08 - 4.34 (m, 2H), 3.68 (s, 3H), 1.44 - 1.72 (m, 4H)
57		355.1	356	1.94, V3018V3001	Method 23	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (br. s., 1H), 7.84 (br. s., 1H), 6.65 - 6.98 (m, 2H), 6.42 (br. s., 2H), 5.26 - 5.48 (m, 2H), 4.95 - 5.21 (m, 2H), 4.77 - 4.90 (m, 2H), 4.71 (br. s., 2H), 3.71 (br. s., 3H)
58		342.1	343	2.01, V3018V3001	Method 24	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (br. s, 1H), 8.24 (d, *J* = 5.6 Hz, 1H), 7.28 (d, *J* = 1.5 Hz, 1H), 6.79 (dd, *J* = 1.5, 5.6 Hz, 1H), 6.46 (br. s., 2H), 4.92 (s, 2H), 4.44 (t, *J* = 6.3 Hz, 2H), 4.05 - 4.16 (m, 2H), 1.62 - 1.78 (m, 2H), 1.49 - 1.63 (m, 2H), 1.19 - 1.37 (m, 2H)
59		357.1	358	2.2, V3018V3001	Method 23 Method 25 (metathesis reaction)	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.93 (br. s., 1H), 6.98 (d, *J* = 7.2 Hz, 1H), 6.91 (t, *J* = 7.2 Hz, 1H), 6.70 (d, *J* = 7.2 Hz, 1H), 6.31 (br. s., 2H), 4.92 (d, *J* = 13.5 Hz, 1H), 4.82 (d, *J* = 13.5 Hz, 1H), 4.47 - 4.61 (m, 1H), 4.31 - 4.46 (m, 1H), 3.87 - 3.98 (m, 1H), 3.83 (s,

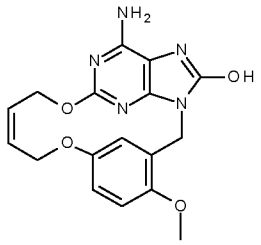
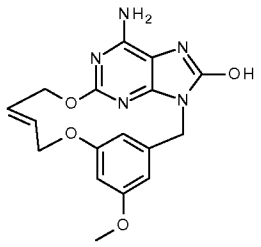
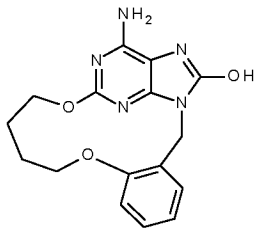
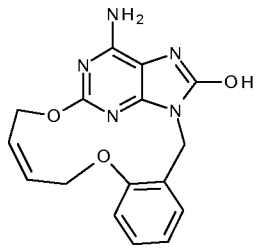
#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
						3H), 3.46 - 3.61 (m, 1H), 1.47 - 1.77 (m, 2H), 1.04 - 1.36 (m, 2H)
60		355.1	356	1.93, V3018V3001	Method 23	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 7.84 (s, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.41 (br. s., 2H), 5.26 - 5.47 (m, 2H), 4.99 - 5.23 (m, 2H), 4.75 - 4.91 (m, 2H), 4.71 (s, 2H), 3.71 (s, 3H)
61		355.1	356	2.15, V3018V3001	Method 25	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (br. s., 1H), 6.80 - 7.03 (m, 2H), 6.63 (d, *J* = 6.6 Hz, 1H), 6.33 (br. s., 2H), 5.76 - 5.90 (m, 1H), 5.04 (dd, *J* = 5.8, 16.0 Hz, 1H), 4.92 (q, *J* = 14.1 Hz, 2H), 4.69 - 4.84 (m, 2H), 4.44 (d, *J* = 13.6 Hz, 1H), 3.86 - 3.98 (m, 1H), 3.78 (s, 3H)
62		355.1	356	2.15, V3018V3001	Method 25	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 6.79 - 6.88 (m, 2H), 6.69 - 6.77 (m, 1H), 6.31 (s, 2H), 5.60 - 5.81 (m, 1H), 5.32 - 5.46 (m, 2H), 5.19 - 5.31 (m, 1H), 4.92 (d, *J* = 13.6 Hz, 1H), 4.80 (d, *J* = 13.6 Hz, 1H), 4.27 - 4.40 (m, 1H), 4.10 - 4.26

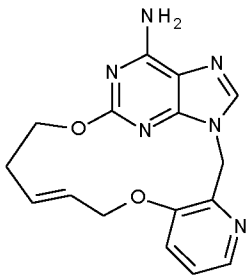
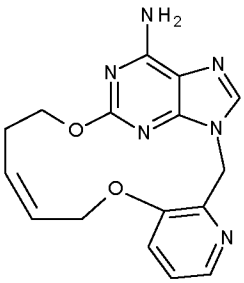
#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
						(m, 1H), 3.83 (s, 3H)
63		355.1	356	2.05, V3018V3001	Method 25	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (br. s., 1H), 6.99 (d, *J* = 2.5 Hz, 1H), 6.87 (dd, *J* = 2.5, 9.0 Hz, 1H), 6.82 (d, *J* = 9.0 Hz, 1H), 6.41 (br. s., 2H), 5.62 (dt, *J* = 6.6, 16.0 Hz, 1H), 5.34 (dt, *J* = 3.5, 16.0 Hz, 1H), 4.79 (s, 2H), 4.72 (d, *J* = 3.5 Hz, 2H), 4.33 (d, *J* = 6.6 Hz, 2H), 3.68 (s, 3H)
64		341.1	342	2.13, V3018V3001	Method 18 Method 24	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.79 (br. s, 1H), 7.16 (s, 1H), 6.88 (t, *J* = 7.7 Hz, 1H), 6.62 (dd, *J* = 1.9, 7.7 Hz, 1H), 6.36 (d, *J* = 7.7 Hz, 1H), 6.25 (br. s., 2H), 4.26 - 4.34 (m, 2H), 4.16 - 4.25 (m, 2H), 3.97 - 4.11 (m, 2H), 2.90 - 3.00 (m, 2H), 1.49 - 1.70 (m, 4H)
65		355.1	356	2.19, V3018V3001	Method 25	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.00 (br. s., 1H), 7.52 (s, 1H), 6.43 (s, 3H), 6.35 (s, 1H), 5.25 - 5.50 (m, 2H), 4.96 - 5.22 (m, 2H), 4.74 - 4.85 (m, 2H), 4.72 (s, 2H), 3.68 (s, 3H)

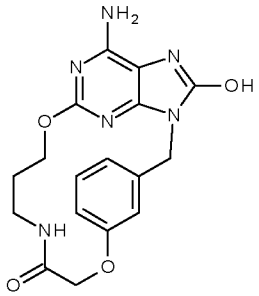
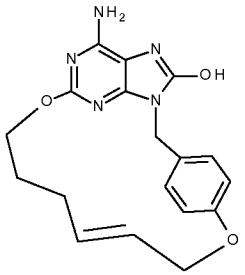
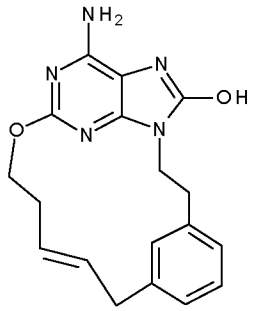
#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
66		355.2	356	2.58, V3018V3001	Method 23	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (br. s., 1H), 7.55 (br. s., 1H), 6.96 (d, *J* = 8.1 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 6.32 (br. s., 2H), 4.78 (s, 2H), 3.97 - 4.34 (m, 2H), 3.71 (s, 3H), 2.56 - 2.67 (m, 2H), 1.53 - 1.82 (m, 2H), 1.14 - 1.45 (m, 4H)
67		353.1	354	2.53, V3018V3001	Method 23	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (br. s., 1H), 7.79 (br. s., 1H), 7.12 (d, *J* = 8.1 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 6.40 (br. s., 2H), 5.66 (dt, *J* = 8.0, 10.7 Hz, 1H), 5.57 (dt, *J* = 7.1, 10.7 Hz, 1H), 4.75 (s, 2H), 4.46 (t, *J* = 8.0 Hz, 2H), 3.74 (s, 3H), 3.21 (d, *J* = 7.1 Hz, 2H), 2.16 - 2.40 (m, 2H)
68		353.1	354	2.5, V3018V3001	Method 23	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.83 (br. s., 1H), 8.10 (s, 1H), 7.12 (d, *J* = 8.1 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 6.38 (br. s., 2H), 5.69 (dt, *J* = 8.0, 15.7 Hz, 1H), 5.43 (dt, *J* = 7.1, 15.7 Hz, 1H), 4.76 (s, 2H), 4.62 - 4.73 (m, 2H), 3.73 (s, 3H), 3.08 (d, *J* = 7.1 Hz, 2H), 2.36 - 2.46 (m,

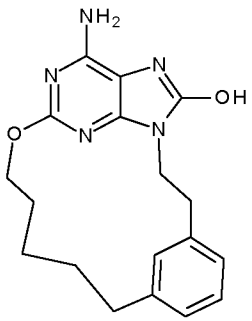
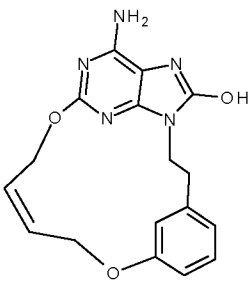
#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
						2H)
69		355.2	356	2.53, V3018V3001	Method 23	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.82 (br. s., 1H), 7.39 (br. s., 1H), 7.03 (d, *J* = 8.1 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 6.30 (br. s., 2H), 4.83 (s, 2H), 3.87 - 4.24 (m, 2H), 3.64 (s, 3H), 2.54 - 2.70 (m, 2H), 1.52 - 1.78 (m, 2H), 1.10 - 1.36 (m, 4H)
70		357.1	358	2.14, V3018V3001	Method 25 Method 24	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.78 (br. s., 1H), 7.77 (br. s., 1H), 6.84 (d, *J* = 8.5 Hz, 1H), 6.77 (dd, *J* = 2.5, 8.5 Hz, 1H), 6.31 (br. s., 2H), 4.85 (s, 2H), 4.38 (t, *J* = 7.1 Hz, 2H), 4.07 - 4.27 (m, 2H), 3.66 (s, 3H), 1.57 - 1.69 (m, 2H), 1.40 - 1.56 (m, 2H)
71		341.1	342	2.34, V3018V3001	Method 16 (metathesis reaction) Method 23 (D6 & 56)	^{1}H NMR (500 MHz, DMSO-d_6) δ 10.00 (br. s., 1H), 7.91 (s, 1H), 7.14 (t, *J* = 7.7Hz, 1H), 6.79 (d, *J* = 7.7 Hz, 1H), 6.74 (dd, *J* = 1.9, 7.7 Hz, 1H), 6.44 (br. s., 2H), 4.96 (d, *J* = 13.9 Hz, 1H), 4.87 – 4.93 (m, 1H), 4.67 (d, *J* = 13.9 Hz, 1H), 4.48 - 4.61

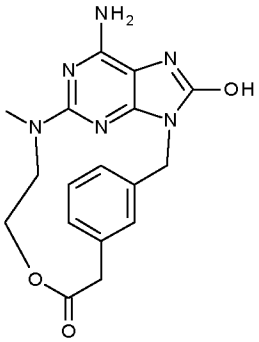
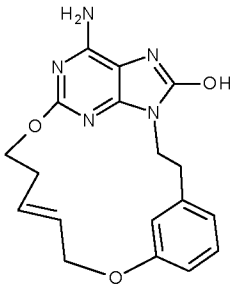
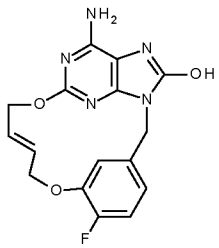
#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
						(m, 1H), 4.01 - 4.15 (m, 1H), 3.78 – 3.88 (m, 1H), 1.66 - 1.79 (m, 1H), 1.48 – 1.61 (m, 2H), 0.85 (d, *J* = 6.9 Hz, 3H)
72		353.1	354	2.47, V3018V3001	Method 23	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (br. s., 1H), 7.92 (d, *J* = 2.0 Hz, 1H), 7.07 (dd, *J* = 2.0, 8.1 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 6.38 (s, 2H), 5.71 (dt, *J* = 8.0, 10.7 Hz, 1H), 5.39 (dt, *J* = 7.6, 10.7 Hz, 1H), 4.88 (s, 2H), 4.25 - 4.39 (m, 2H), 3.73 (s, 3H), 3.24 (d, *J* = 7.6 Hz, 2H), 2.25 - 2.40 (m, 2H)
73		353.1	354	2.48, V3018V3001	Method 23	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (br. s., 1H), 7.61 (d, *J* = 2.0 Hz, 1H), 7.01 (dd, *J* = 2.0, 8.1 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 6.43 (br. s., 2H), 5.56 (dt, *J* = 7.0, 15.7 Hz, 1H), 5.28 (dt, *J* = 6.6, 15.7 Hz, 1H), 4.89 (s, 2H), 4.41 - 4.59 (m, 2H), 3.78 (s, 3H), 3.07 (d, *J* = 6.6 Hz, 2H), 2.22 - 2.37 (m, 2H)

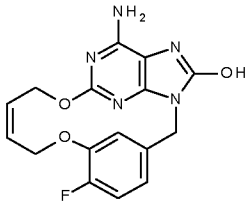
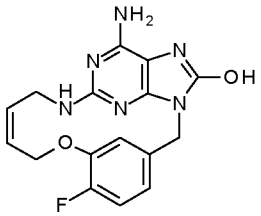
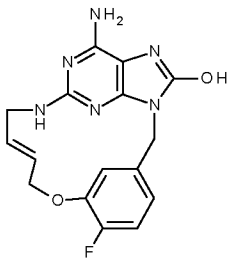
#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
74		355.1	356	2.11, V3018V3001	Method 25	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (br. s., 1H), 7.81 (br. s., 1H), 6.83 (d, *J* = 8.6 Hz, 1H), 6.78 (d, *J* = 8.6 Hz, 1H), 6.38 (br. s., 2H), 5.29 – 5.49 (m, 2H), 4.95 – 5.15 (m, 2H), 4.82 (br. s., 2H), 4.65 – 4.78 (m, 2H), 3.68 (s, 3H)
75		355.1	356	2.16, V3018V3001	Method 25	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (br. s., 1H), 7.17 (s, 1H), 6.49 (br. s., 2H), 6.42 (s, 1H), 6.37 (s, 1H), 5.63 - 5.71 (m, 2H), 4.75 - 4.80 (m, 2H), 4.73 (s, 2H), 4.56 (d, *J* = 4.6 Hz, 2H), 3.65 (s, 3H)
76		327.1	328	2.33, V3018V3001	Method 23 (D6 & 56)	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.86 (br. s., 1H), 7.49 (dd, *J* = 1.5, 7.6 Hz, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 6.88 (t, *J* = 7.6 Hz, 1H), 6.34 (s, 2H), 4.88 (br. s., 2H), 4.14 - 4.30 (m, 2H), 4.02 - 4.13 (m, 2H), 1.77 - 2.16 (m, 4H)
77		325.1	326	2.19, V3018V3001	Method 25	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (br. s., 1H), 7.35 (dd, *J* = 1.5, 7.6 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 6.89 (t, *J* =

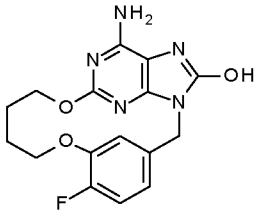
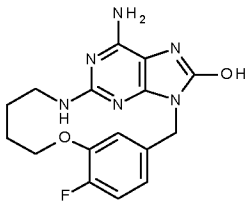
#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
						7.6 Hz, 1H), 6.34 (s, 2H), 6.04 (dt, *J* = 8.0, 10.7 Hz, 1H), 5.66 (dt, *J* = 7.0, 10.7 Hz, 1H), 4.83 (br. s., 6H)
78		324.1	325	2.03, V3018V3001	Method 26	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (d, *J* = 4.0 Hz, 1H), 7.81 (s, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.34 (dd, *J* = 4.0, 8.0 Hz, 1H), 7.02 (s, 2H), 6.3 (dt, *J* = 7.0, 15.7 Hz, 1H), 5.65 (dt, *J* = 5.1, 15.7 Hz, 1H), 5.40 (s, 2H), 4.42 - 4.57 (m, 2H), 4.37 (d, *J* = 5.1 Hz, 2H), 2.35 - 2.45 (m, 2H)
79		324.1	325	2.11, V3018V3001	Method 26	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.15 (d, *J* = 4.1 Hz, 1H), 8.11 (s, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.30 (dd, *J* = 4.1, 8.2 Hz, 1H), 7.14 (br. s., 2H), 5.95 (dt, *J* = 7.0, 10.7 Hz, 1H), 5.80 (dt, *J* = 7.6, 10.7 Hz, 1H), 5.40 (br. s., 2H), 4.59 (d, *J* = 7.0 Hz, 2H), 4.24 (t, *J* = 7.6 Hz, 2H), 2.55 - 2.62 (m, 2H)

#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
80		370.1	371	2.03, V3018V3001	Method 27	^{1}H NMR (500 MHz, DMSO-d_6) δ 10.48 (br. s., 1H), 7.34 - 7.72 (m, 2H), 7.26 (t, *J* = 7.3 Hz, 1H), 7.07 (d, *J* = 7.3 Hz, 1H), 6.98 (s, 1H), 6.90 (dd, *J* = 2.5, 7.3 Hz, 1H), 4.87 (s, 2H), 4.75 (s, 2H), 4.21 - 4.14 (m, 2H), 3.41 - 3.50 (m, 2H), 1.75 - 1.90 (m, 2H)
81		353.1	354	2.31, V3018V3001	Method 16 (O4) Method 23 (metathesis reaction & final cyclisation)	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.95 (br. s., 1H), 7.12 (d, *J* = 8.2 Hz, 2H), 6.83 (d, *J* = 8.2 Hz, 2H), 6.29 (br. s., 2H), 5.53 (dt, *J* = 6.6, 15.7 Hz, 1H), 5.27 (dt, *J* = 5.4, 15.7 Hz, 1H), 4.87 (s, 2H), 4.67 (d, *J* = 5.4 Hz, 2H), 3.59 (t, *J* = 6.6 Hz, 2H), 1.90 - 2.10 (m, 2H), 1.53 - 1.71 (m, 2H)
82		337.2	338	2.45, V3018V3001	Method 18 (D5) Method 14 (15)	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.81 (br. s., 1H), 7.12 (s, 1H), 6.99 (t, *J*=7.2 Hz, 1H), 6.84 (d, *J*=7.2 Hz, 1H), 6.76 (d, *J*=7.2 Hz, 1H), 6.29 (br. s., 2H), 5.52 (dt, *J*=5.7 , 15.5 Hz, 1H), 5.15 (dt, *J*=4.9 , 15.5 Hz, 1H), 4.45 (t, *J*=4.9 Hz, 2H), 4.04 (t, *J*=5.7 Hz, 2H), 3.07 - 3.2 (m, 4H),

#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
						2.15 - 2.41 (m, 2H)
83		339.2	340	2.57, V3018V3001	Method 24	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.85 (br. s., 1H), 7.23 (s, 1H), 6.79 - 6.91 (m, 2H), 6.42 - 6.53 (m, 1H), 6.24 (br. s., 2H), 4.08 (t, *J*=6.5 Hz, 2H), 3.91 - 4.01 (m, 2H), 2.85 - 2.97 (m, 2H), 2.53 - 2.60 (m, 2H), 1.66 (quin, *J*=6.8 Hz, 2H), 1.28 (quin, *J*=6.8 Hz, 2H), 1.12 (quin, *J*=6.8 Hz, 2H)
84		339.1	340	2.28, V3018V3001	Method 18	^{1}H NMR (500 MHz, DMSO-d_6) δ 10.09 (br. s, 1H), 7.42 (s, 1H), 7.07 (t, *J*=7.6 Hz, 1H), 6.63 -6.77 (m, 2H), 6.55 (br. s., 2H), 5.64 (dt, *J*=4.7, 11.5 Hz, 1H), 5.54 (dt, *J*=5.7, 11.5 Hz, 1H), 4.89 -5.12 (m, 2H), 4.75 (d, *J*=5.7 Hz, 2H), 3.94 (t, *J*=6.8 Hz, 2H), 2.85 (t, *J*=6.8 Hz, 2H)

#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
85		354.1	355	2.2, V3018V3001	Method 28	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.63 (s, 1H), 8.04 (s, 1H), 7.22 (t, *J*=7.2 Hz, 1H), 7.16 (d, *J*=7.2 Hz, 1H), 7.10 (d, *J*=7.2 Hz, 1H), 6.07 (br. s., 2H), 4.79 (s, 2H), 4.25 - 4.31 (m, 2H), 3.76 -4.19 (m, 2H), 3.63 (s, 2H), 3.00 (s, 3H)
86		353.1	354	2.2, V3018V3001	Method 29	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.71 (s, 1H), 6.86 (t, *J*=7.7 Hz, 1H), 6.77 (s, 1H), 6.62 (dd, *J*=1.9, 7.7 Hz, 1H), 6.33 (d, *J*=7.7 Hz, 1H), 6.21 (s, 2H), 5.63 (dt, *J*=6.3, 15.4 Hz, 1H), 5.55 (dt, *J*=4.4, 15.4 Hz, 1H), 4.57 (d, *J*=4.4 Hz, 2H), 4.32 (t, *J*=5.20Hz, 2H), 3.97 (t, *J*=6.0 Hz, 2H), 2.96 (t, *J*=6.0 Hz, 2H), 2.22 - 2.40 (m, 2H)
87		343.1	344	2.18, V3018V3001	Method 30	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.99 (br. s., 1H), 7.63 (dd, *J*=1.9, 8.2 Hz, 1H), 7.11 (dd, *J*=8.2, 11.0 Hz, 1H), 6.70 - 6.96 (m, 1H), 6.46 (br. s., 2H), 5.76 (dt, *J*=6.3 , 16.1 Hz, 1H), 5.65 (dt, *J*=3.8 , 16.1 Hz, 1H),), 4.78 - 4.85 (m, 2H), 4.77 (s, 2H), 4.57 (d, *J*=6.3

#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
						Hz, 2H)
88		343.1	344	2.18, V3018V3001	Method 30	^{1}H NMR (500 MHz, DMSO-d_6) δ 10.02 (br. s., 1H), 8.05 (d, *J*=8.2 Hz, 1H), 7.11 (dd, *J*=8.2, 11.2 Hz, 1H), 6.72 - 6.93 (m, 1H), 6.48 (br. s., 2H), 5.32 - 5.50 (m, 2H), 4.98 - 5.28 (m, 2H), 4.81 - 4.97 (m, 2H), 4.79 (s, 2H)
89		342.1	343	2.14, V3018V3001	Method 31	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.66 (br. s., 1H), 8.10 (d, *J*=8.2 Hz, 1H), 7.09 (dd, *J*=8.2, 11.2 Hz, 1H), 6.62 - 6.90 (m, 1H), 6.29 (t, *J*=6.8 Hz, 1H), 6.02 (br. s., 2H), 5.12 - 5.45 (m, 2H), 4.77 - 5.06 (m, 2H), 4.70 (s, 2H), 3.52 - 4.32 (m, 2H)
90		342.1	343	2.13, V3018V3001	Method 31	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.64 (br. s., 1H), 7.75 (dd, *J*=1.7, 8.4 Hz, 1H), 7.07 (dd, *J*=8.4, 11.2 Hz, 1H), 6.72 - 6.93 (m, 1H), 6.48 (t, *J*=5.5 Hz, 1H), 5.98 (s, 2H), 5.68 (dt, *J*=6.0 , 15.8 Hz, 1H), 5.59 (dt, *J*=3.8 , 15.8 Hz, 1H), 4.70 (s, 2H), 4.59 (d, *J*=6.0 Hz, 2H), 3.63 - 3.86

#	STRUCTURE	Exact Mass	Mass Found [M+H]	LCMS Ret Time, Method	Synthesis method	NMR
						(m, 2H)
91		345.1	346	2.21, V3018V3001	Method 32	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.92 (br. s., 1H), 8.08 (d, *J*=8.2 Hz, 1H), 7.09 (dd, *J*=8.2, 11.7 Hz, 1H), 6.62 - 6.91 (m, 1H), 6.41 (br. s., 2H), 4.81 (s, 2H), 4.57 (t, *J*=6.5 Hz, 2H), 4.35 (t, *J*=6.8 Hz, 2H), 1.62 - 1.74 (m, 2H), 1.50 - 1.60 (m, 2H)
92		344.1	345	2.2, V3018V3001	Method 32	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.58 (s, 1H), 8.16 (d, *J*=8.5 Hz, 1H), 7.08 (dd, *J*=8.5, 11.7 Hz, 1H), 6.59 - 6.88 (m, 1H), 6.23 (t, *J*=6.5 Hz, 1H), 5.94 (s, 2H), 4.74 (s, 2H), 4.29 (t, *J*=7.3 Hz, 2H), 3.38 - 3.57 (m, 2H), 1.53 - 1.72 (m, 2H), 1.26 - 1.47 (m, 2H)

Biological Activity of compounds of formula (I)

Description of Biological Assays

5 **Assessment of TLR7 and TLR8 activity**

The ability of compounds to activate human TLR7 and TLR8 was assessed in a cellular reporter assay using HEK293 cells transiently transfected with a TLR7 or TLR8 expression vector and NFκB-luc reporter construct. Briefly, HEK293 cells were grown in culture medium (DMEM supplemented with 10% FCS and 2 mM Glutamine). For
10 transfection of cells in 10 cm dishes, cells were detached with Trypsin-EDTA, transfected with a mix of CMV-TLR7 or TLR8 plasmid (750 ng), NFκB-luc plasmid (375 ng) and a transfection reagent and incubated 48 hours at 37°C in a humidified 5% CO_2 atmosphere. Transfected cells were then detached with Trypsin-EDTA, washed in PBS and resuspended in medium to a density of 1.67 x 10^5 cells/mL. Thirty microliters
15 of cells were then dispensed into each well in 384-well plates, where 10 μL of compound in 4% DMSO was already present. Following 6 hours incubation at 37°C, 5% CO_2, the luciferase activity was determined by adding 15 μl of Steady Lite Plus substrate (Perkin Elmer) to each well and readout performed on a ViewLux ultraHTS microplate imager (Perkin Elmer). Dose response curves were generated from
20 measurements performed in quadruplicates. Lowest effective concentrations (LEC) values, defined as the concentration that induces an effect which is at least two fold above the standard deviation of the assay, were determined for each compound.

In parallel, a similar dilution series of compound was used (10 μL of compound in 4% DMSO) with 30 μL per well of cells transfected with NFκB-luc reporter construct
25 alone (1.67 x 10^5 cells/mL). Six hours after incubation at 37°C, 5% CO_2, the luciferase activity was determined by adding 15 μl of Steady Lite Plus substrate (Perkin Elmer) to each well and readout performed on a ViewLux ultraHTS microplate imager (Perkin Elmer). Counterscreen data is reported as LEC.

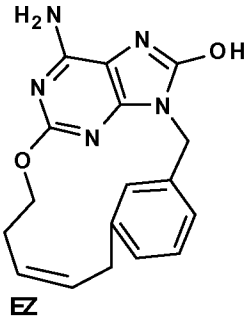
30 **Measurement of interferon production in human PBMC**

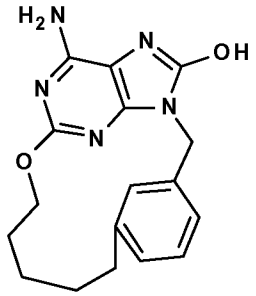
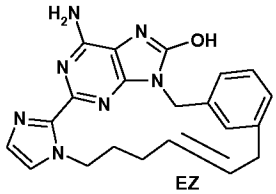
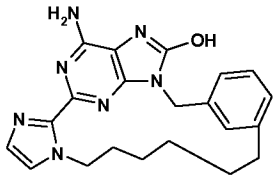
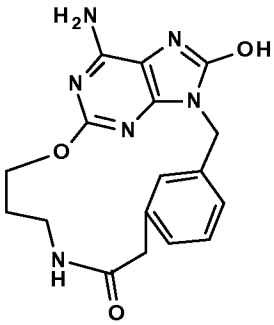
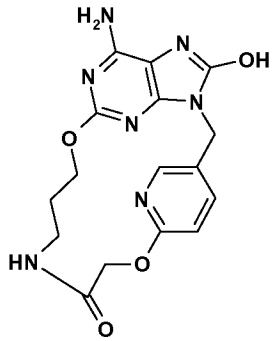
Activation of human TLR7 results in robust production of interferon by plasmacytoid dendritic cells present in human blood. The potential of compounds to induce interferon was evaluated by determination of interferon in the conditioned media from peripheral blood mononuclear cells (PBMC). The presence of interferon in the samples was
35 determined, using an interferon reporter cell line stably expressing an interferon-stimulated responsive elements (ISRE)-luc reporter construct. The ISRE element with sequence GAAACTGAAACT is highly responsive to the STAT1-STAT2-IRF9 transcription factor, which becomes activated upon binding of IFN-I to the IFN

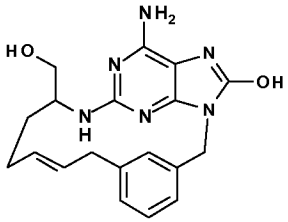
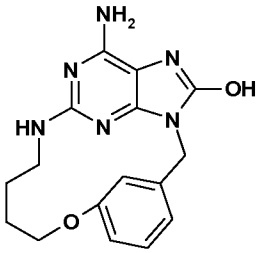
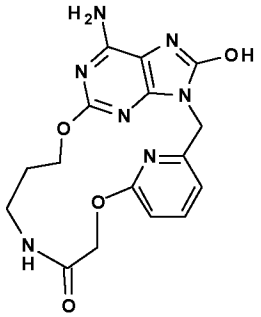
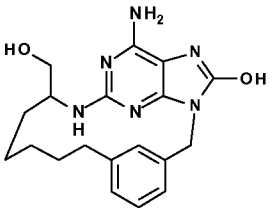
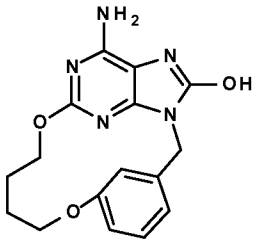
receptor. Briefly, PBMCs were prepared from buffy coats of at least two donors using a standard Ficoll centrifugation protocol. Isolated PBMCs were resuspended in RPMI medium supplemented with 10% human AB serum and 2 x 10^5 cells/well were dispensed into 384-well plates containing compounds (70 µL total volume). After overnight incubation of the PBMCs with the compounds, 10 µL of supernatant was transferred to 384-well plates containing 5 x 10^3 HEK-ISRE-luc cells/well in 30 µL (plated the day before). Following 24 hours of incubation, activation of the ISRE elements was measured by assaying luciferase activity using 40 µL/well Steady Lite Plus substrate (Perkin Elmer) and measured with ViewLux ultraHTS microplate imager (Perkin Elmer). The stimulating activity of each compound on the HEK-ISRE-luc cells was reported as LEC. The LEC in turn indicates the degree of ISRE activation on transfer of a defined amount of PBMC culture medium. Recombinant interferon alfa-2a (Roferon-A) was used as a standard control compound.

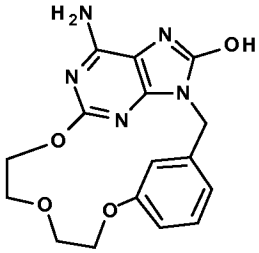
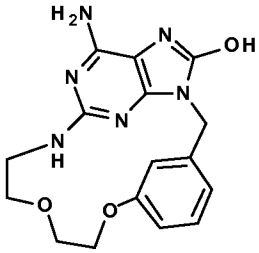
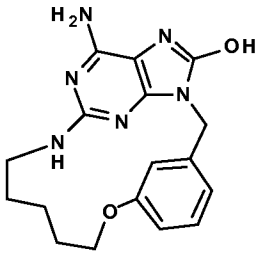
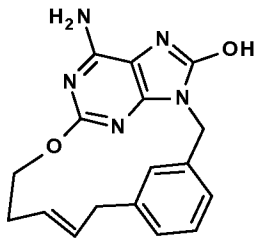
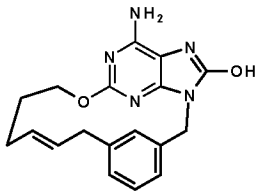
The LEC values for the compounds in table 2 on HEK293 TLR8-NFκB-luc were >10 µM for compound 6, 20.46 µM for compound 39, >19.49 µM for compound 40, 11.16 µM for compound 41, >10 µM for compound 44, 5.48 µM for compound 47, >10 µM for compound 63, 0.27 µM for compound 75 and >25 µM for all other compounds.
The LEC values for the compounds in table 2 on HEK293 NFκB-luc were greater than the highest tested concentration (> 10 µM for compounds 6, 44 and 63, and > 25 µM for all other compounds).

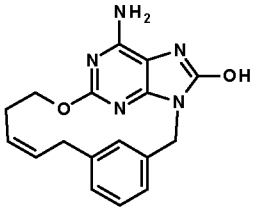
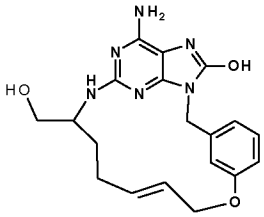
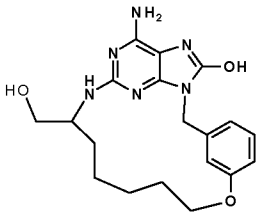
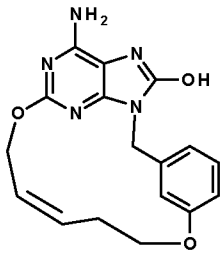
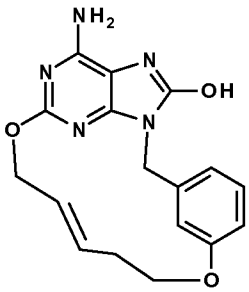
Table 2. Compounds of formula (I)
n represents the number of experiments performed.

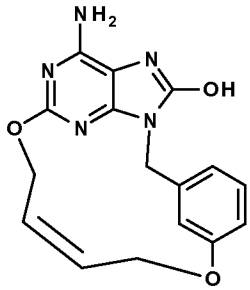
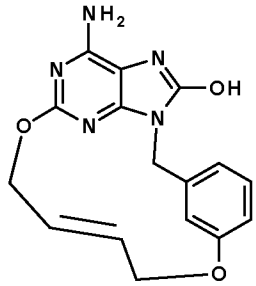
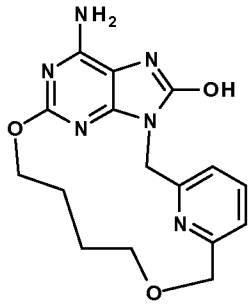
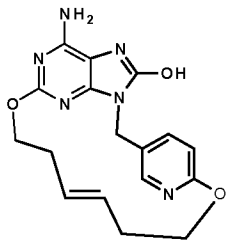
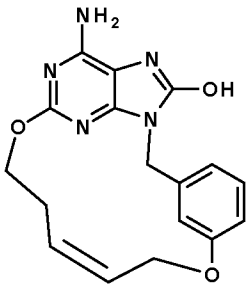
#	STRUCTURE	HEK293 TLR7-NFκB-*luc* (LEC; µM)	n	PBMC HEK-ISRE-*luc* (LEC; µM)	n
1		0.154	5	0.081	5

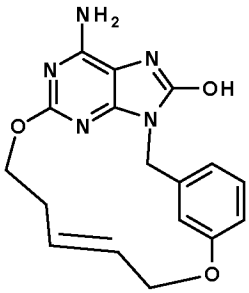
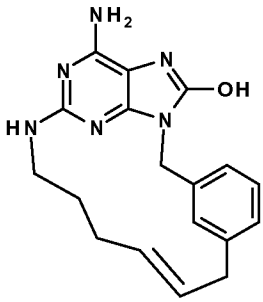
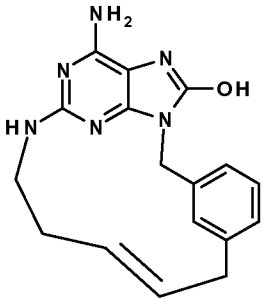
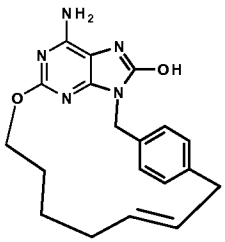
#	STRUCTURE	HEK293 TLR7-NFκB-*luc* (LEC; μM)	n	PBMC HEK-ISRE-*luc* (LEC; μM)	n
2		0.51	1	0.22	2
3		1.05	1	0.14	1
4		3.27	1	0.64	2
5		0.24	1	0.044	2
6		> 10	1	1.73	2

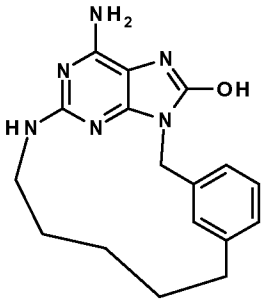
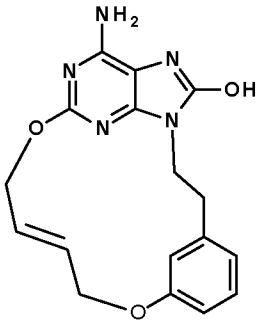
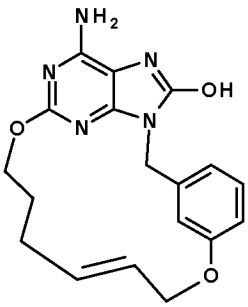
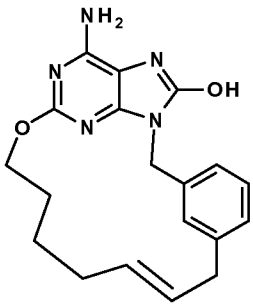
#	STRUCTURE	HEK293 TLR7-NFκB-*luc* (LEC; μM)	n	PBMC HEK-ISRE-*luc* (LEC; μM)	n
7		0.87	1	0.31	2
8		2.42	1	0.68	4
9		0.30	1	0.098	2
10		5.26	1	0.53	2
11		0.050	2	0.022	4

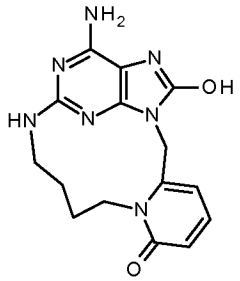
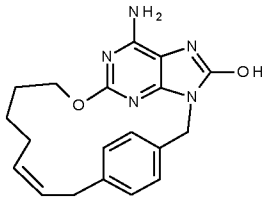
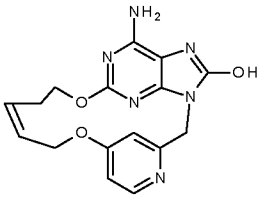
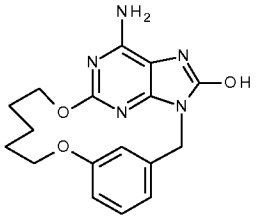
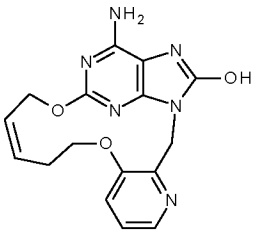
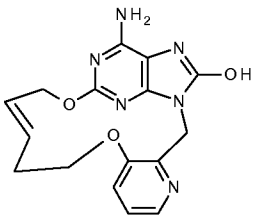
#	STRUCTURE	HEK293 TLR7-NFκB-*luc* (LEC; μM)	n	PBMC HEK-ISRE-*luc* (LEC; μM)	n
12		0.39	1	0.043	4
13		14.69	1	4.7	2
14		1.68	1	0.51	3
15		0.12	6	0.016	11
16		0.375	12	0.11	7

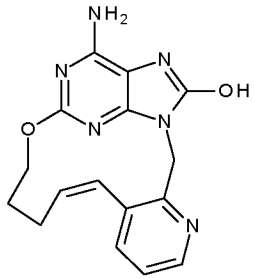
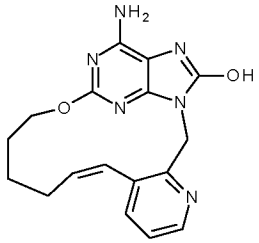
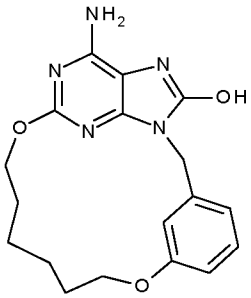
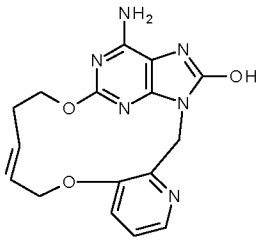
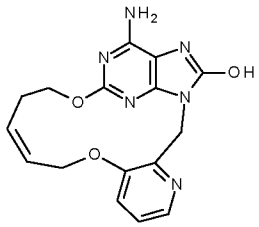
#	STRUCTURE	HEK293 TLR7-NFκB-*luc* (LEC; μM)	n	PBMC HEK-ISRE-*luc* (LEC; μM)	n
17		0.067	4	0.013	6
18		0.82	1	0.056	2
19		2.24	1	0.14	2
20		0.74	1	0.15	2
21		0.3	1	0.05	2

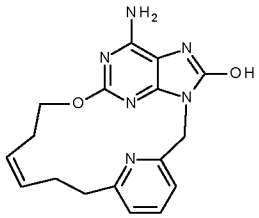
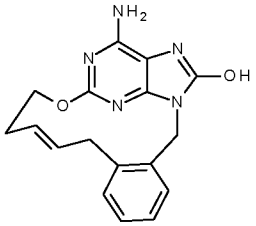
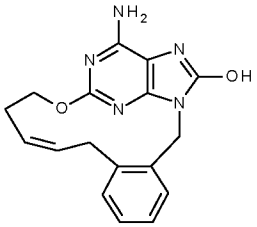
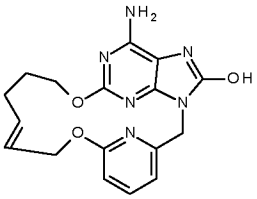
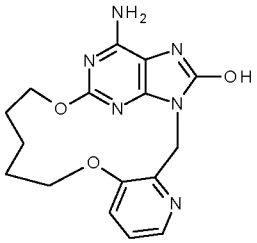
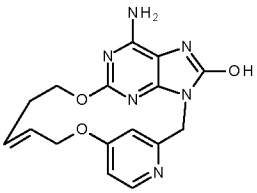
#	STRUCTURE	HEK293 TLR7-NFκB-*luc* (LEC; μM)	n	PBMC HEK-ISRE-*luc* (LEC; μM)	n
22		0.12	1	0.054	4
23		0.043	1	0.012	2
24		1.05	1	0.15	2
25		20.22	1	3.61	4
26		0.027	1	0.093	4

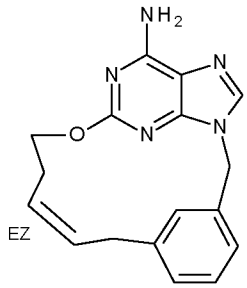
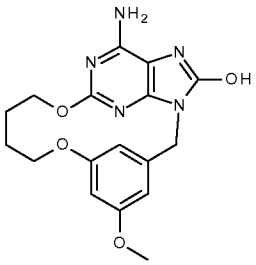
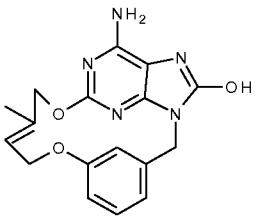
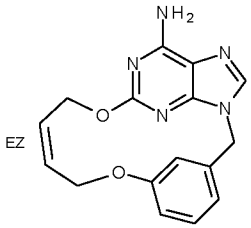
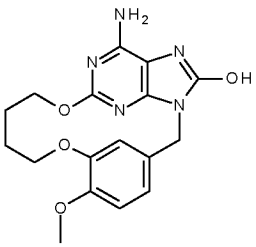
#	STRUCTURE	HEK293 TLR7-NFκB-*luc* (LEC; μM)	n	PBMC HEK-ISRE-*luc* (LEC; μM)	n
27		1.31	6	0.11	6
28		0.77	1	0.26	4
29		0.81	1	0.15	2
30		0.87	1	0.56	2

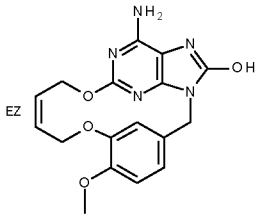
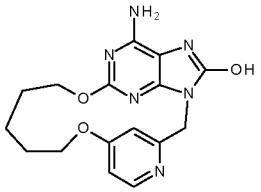
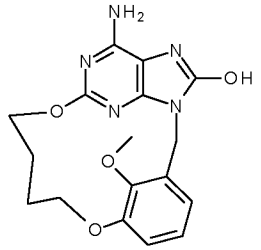
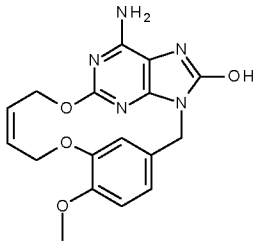
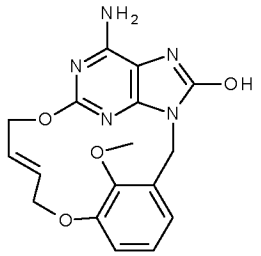
#	STRUCTURE	HEK293 TLR7-NFκB-*luc* (LEC; μM)	n	PBMC HEK-ISRE-*luc* (LEC; μM)	n
31		1.36	2	0.263	6
32		0.92	2	0.12	4
33		0.17	2	0.11	4
34		9.81	1	0.032	2

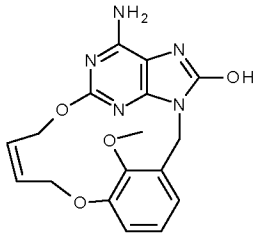
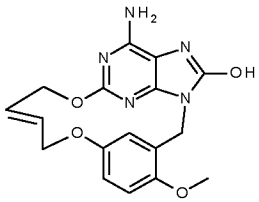
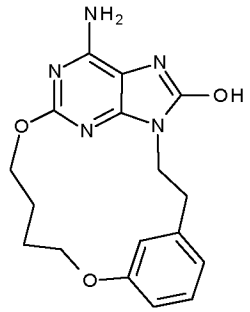
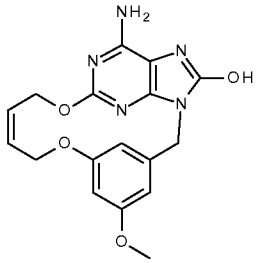
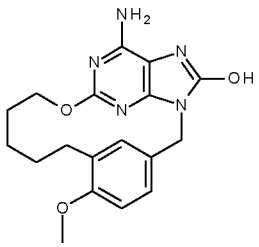
#	STRUCTURE	HEK293 TLR7-NFκB-*luc* (LEC; μM)	n	PBMC HEK-ISRE-*luc* (LEC; μM)	n
35		1.68	1	0.41	2
36		12.45	1	0.68	2
37		0.8	1	0.12	2
38		0.53	3	0.027	2
39		1.16	2	0.22	4
40		1.3	3	0.15	4

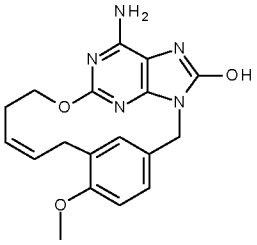
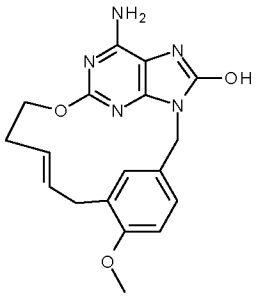
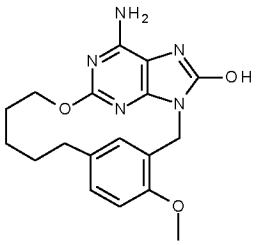
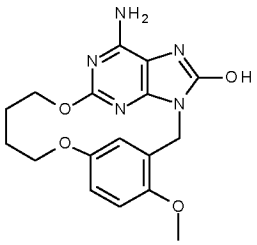
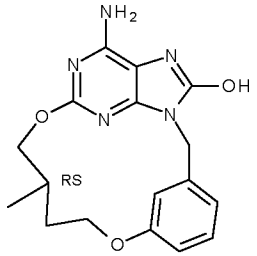
#	STRUCTURE	HEK293 TLR7-NFκB-*luc* (LEC; μM)	n	PBMC HEK-ISRE-*luc* (LEC; μM)	n
41		1.93	2	0.48	4
42		2.28	2	0.5	4
43		0.11	2	0.034	4
44		5.77	2	0.62	2
45		0.108	2	0.01	6

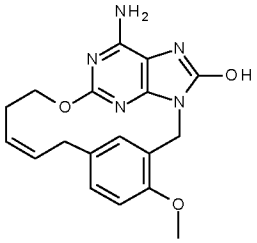
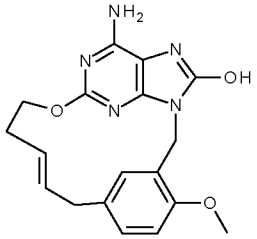
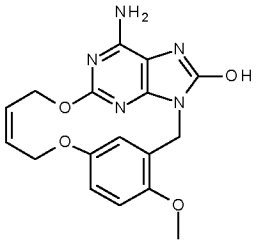
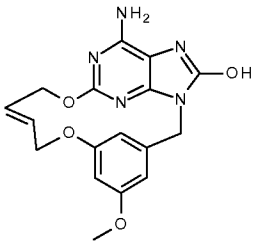
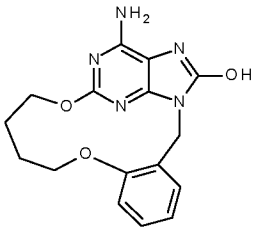
#	STRUCTURE	HEK293 TLR7-NFκB-*luc* (LEC; μM)	n	PBMC HEK-ISRE-*luc* (LEC; μM)	n
46		6.49	1	1.13	2
47		3.43	3	2.34	4
48		0.64	1	2.04	2
49		0.21	1	0.16	2
50		1.19	1	0.24	2
51		0.74	1	0.069	2

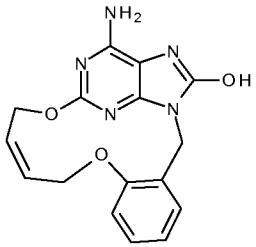
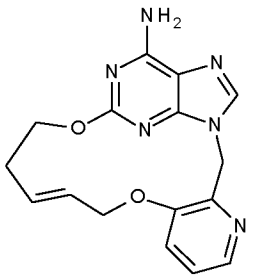
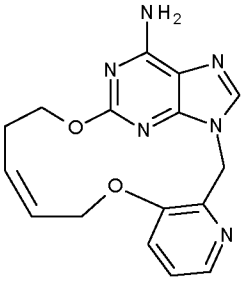
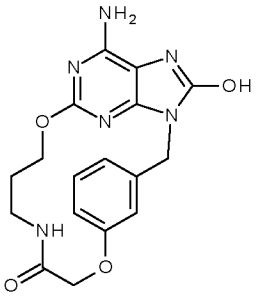
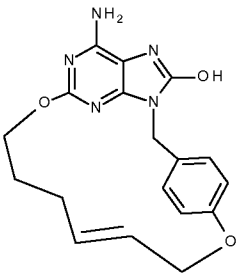
#	STRUCTURE	HEK293 TLR7-NFκB-*luc* (LEC; μM)	n	PBMC HEK-ISRE-*luc* (LEC; μM)	n
52		7.96	1	4.8	2
53		0.029	1	0.01	2
54		0.041	2	0.026	4
55		> 25	1	15.31	2
56		0.056	2	0.01	4

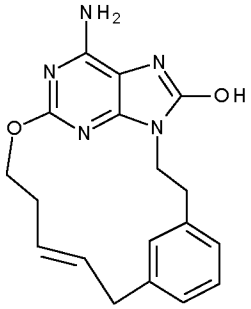
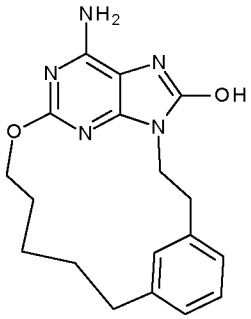
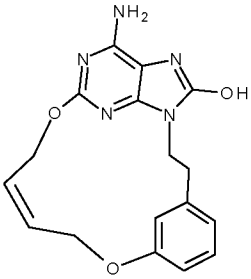
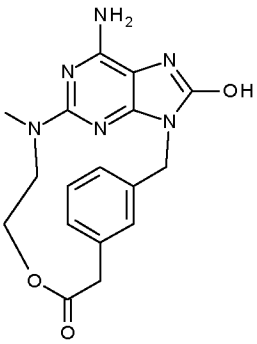
#	STRUCTURE	HEK293 TLR7-NFκB-*luc* (LEC; μM)	n	PBMC HEK-ISRE-*luc* (LEC; μM)	n
57		0.08	1	0.021	2
58		0.63	3	0.086	4
59		4.41	1	1.92	2
60		0.088	1	0.033	2
61		4.7	1	4.98	2

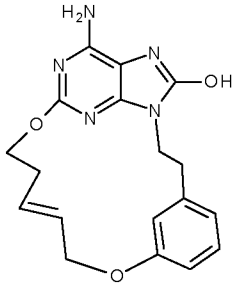
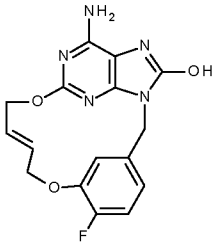
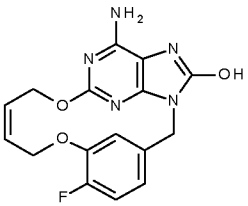
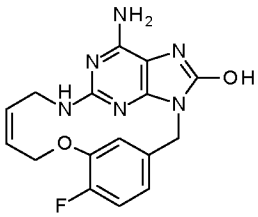
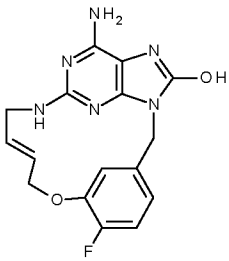
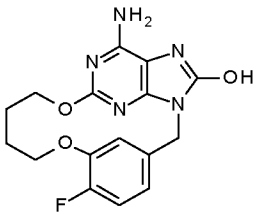
#	STRUCTURE	HEK293 TLR7-NFκB-*luc* (LEC; μM)	n	PBMC HEK-ISRE-*luc* (LEC; μM)	n
62		7.26	1	2.03	2
63		0.12	1	0.031	2
64		1.49	1	0.5	2
65		0.038	2	0.03	2
66		0.032	1	0.018	2

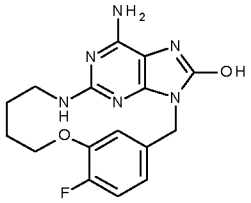
#	STRUCTURE	HEK293 TLR7-NFκB-*luc* (LEC; μM)	n	PBMC HEK-ISRE-*luc* (LEC; μM)	n
67		0.0024	1	0.0028	2
68		0.006	1	0.0057	2
69		0.2	1	0.039	2
70		0.15	1	0.04	2
71		0.12	1	0.04	2

#	STRUCTURE	HEK293 TLR7-NFκB-*luc* (LEC; μM)	n	PBMC HEK-ISRE-*luc* (LEC; μM)	n
72		0.018	1	0.0029	2
73		0.045	1	0.01	2
74		0.1	1	0.044	2
75		0.0068	1	0.0026	2
76		0.12	1	0.064	2

#	STRUCTURE	HEK293 TLR7-NFκB-*luc* (LEC; μM)	n	PBMC HEK-ISRE-*luc* (LEC; μM)	n
77		0.53	1	0.1	2
78		9.68	1	2 > 25	2
79		2.34	1	1.78	2
80		0.041	3	0.087	4
81		4.59	1	0.63	2

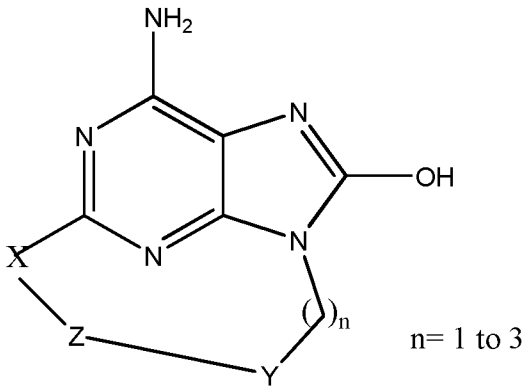
#	STRUCTURE	HEK293 TLR7-NFκB-*luc* (LEC; μM)	n	PBMC HEK-ISRE-*luc* (LEC; μM)	n
82		3.95	1		
83		> 25	1	2.66	4
84		3.4	1	0.51	2
85		0.33	2	12.48	4

#	STRUCTURE	HEK293 TLR7-NFκB-*luc* (LEC; μM)	n	PBMC HEK-ISRE-*luc* (LEC; μM)	n
86		7.91	1	2.43	2
87		0.034	1		
88		0.11	1		
89		0.4	1		
90		0.063	1		
91		0.14	1		

#	STRUCTURE	HEK293 TLR7-NFκB-*luc* (LEC; μM)	n	PBMC HEK-ISRE-*luc* (LEC; μM)	n
92		0.47	1		

Claims

1. Compound having formula (I)

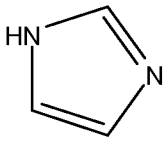


(I)

n= 1 to 3

and pharmaceutically accepted salts thereof, wherein

X is oxygen, nitrogen, sulfur or

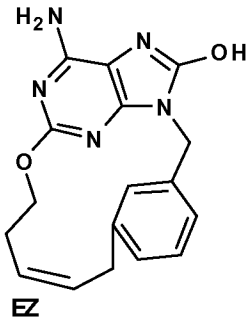


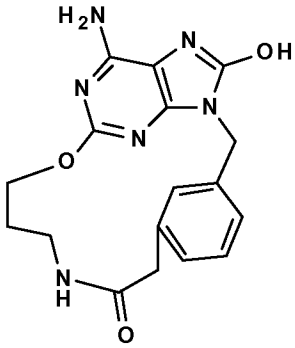
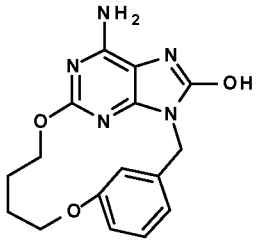
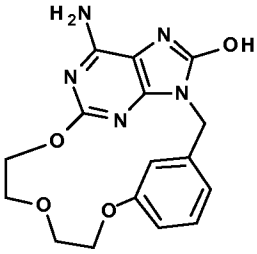
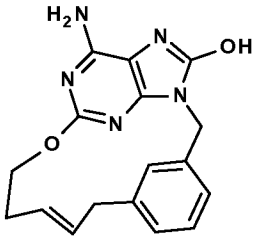
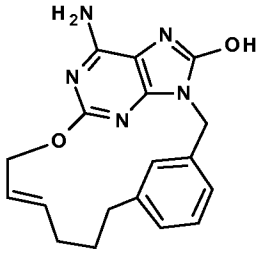
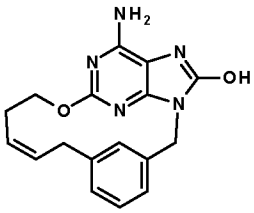
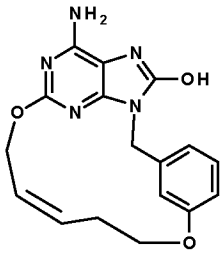
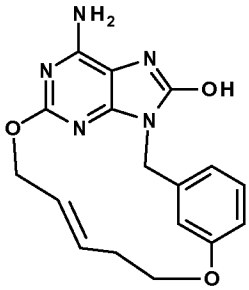
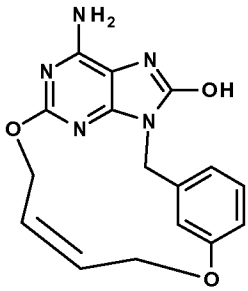
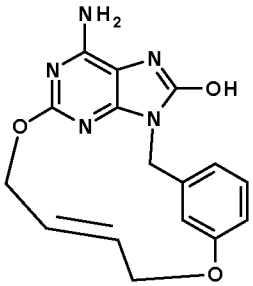
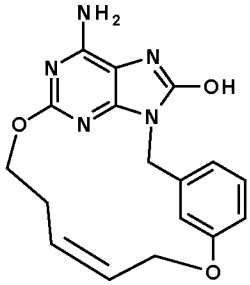
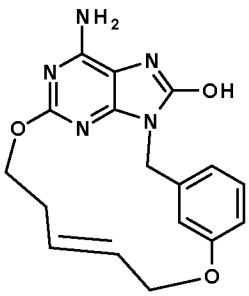
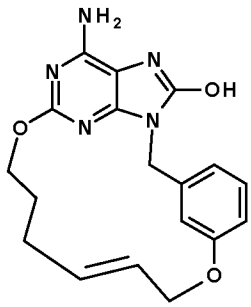
,

Y represents an aromatic ring or heterocyclic ring comprising at least a nitrogen, optionally substituted by one or more substituents independently selected from C_{1-6}alkyl, C_{1-4}alkoxy, trifluoromethyl or halogen,

Z represents C_{1-10} saturated or unsaturated alkyl optionally substituted by an alkyl or alkylhydroxyl;
or Z represents C_{1-6}alkyl -NH-C(O)- C_{1-6}alkyl- or C_{1-6}alkyl -NH-C(O)- C_{1-6}alkyl -O-;
or Z represents C_{1-10}alkyl -O- wherein said alkyl is unsaturated or saturated and can optionally be substituted by an alkyl or alkylhydroxyl ,
or Z represents C_{1-6}alkyl-O-C_{1-6}alkyl- wherein said alkyl is unsaturated or saturated and can optionally be substituted by an alkyl or alkylhydroxyl
or Z represents C_{1-6}alkyl-O-C_{1-6}alkyl-O- wherein said alkyl is unsaturated or saturated and can optionally be substituted by an alkyl or alkylhydroxyl.

2. Compound according to claim 1 having one of the following formula's selected from the group of:



,

,

,

,

,

,

,

,

,

,

,

,

or

.

3. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof according to claim 1

or 2 together with one or more pharmaceutically acceptable excipients, diluents or carriers.

4. A compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof according to claim 1 or 2, or a pharmaceutical composition according to claim 3 for use as a medicament.

5. A compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof according to claim 1 or 2, or a pharmaceutical composition according to claim 3, for use in the treatment of a disorder in which the modulation of TLR7 is involved.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/064763

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D487/16 C07D498/16 A61K31/52 A61P31/00
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 A61K A61P

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, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHRISTELLE MOREAU ET AL: "Synthesis of cyclic adenosine 5'-diphosphate ribose analogues: a C2'endo/syn"southern" ribose conformation underlies activity at the sea urchin cADPR receptor", ORGANIC & BIOMOLECULAR CHEMISTRY, vol. 9, no. 1, 1 January 2011 (2011-01-01) , page 278, XP055036410, ISSN: 1477-0520, DOI: 10.1039/c0ob00396d abstract page 278; figure 1 Scheme 1, page 279 table 1 and 3	1-5

-/--

[X] Further documents are listed in the continuation of Box C.

[X] 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	Date of mailing of the international search report
1 August 2013	07/08/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Marzi, Elena

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/064763

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2009/005687 A1 (GILEAD SCIENCES INC [US]; GRAUPE MICHAEL [US]; HALCOMB RANDALL L [US]) 8 January 2009 (2009-01-08) page 1, lines 9-11 claims 1-45 -----	1-5
A	WO 2009/134624 A1 (MERCK & CO INC [US]; LIVERTON NIGEL J [US]; MCCAULEY JOHN A [US]; BUTC) 5 November 2009 (2009-11-05) page 1, lines 5-8 claims 1-24 -----	1-5

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2013/064763

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009005687 A1	08-01-2009	AR 067182 A1	30-09-2009
		AU 2008271127 A1	08-01-2009
		CA 2691444 A1	08-01-2009
		CN 101784548 A	21-07-2010
		CO 6251258 A2	21-02-2011
		EA 200971081 A1	29-10-2010
		EC SP109905 A	30-04-2010
		EP 2170888 A1	07-04-2010
		JP 2010532353 A	07-10-2010
		KR 20100039368 A	15-04-2010
		NZ 582090 A	25-05-2012
		TW 200914454 A	01-04-2009
		US 2009047249 A1	19-02-2009
		US 2011236348 A1	29-09-2011
		US 2012244121 A1	27-09-2012
		WO 2009005687 A1	08-01-2009
WO 2009134624 A1	05-11-2009	AU 2009241445 A1	05-11-2009
		CA 2720850 A1	05-11-2009
		CN 102014911 A	13-04-2011
		EP 2271345 A1	12-01-2011
		JP 2011518882 A	30-06-2011
		US 2011046161 A1	24-02-2011
		WO 2009134624 A1	05-11-2009