



(51) International Patent Classification:

C07J 43/00 (2006.01) A61P 5/32 (2006.01)
A61K 31/58 (2006.01)

(21) International Application Number:

PCT/EP2014/050267

(22) International Filing Date:

9 January 2014 (09.01.2014)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/751,290 11 January 2013 (11.01.2013) US
1311910.2 3 July 2013 (03.07.2013) GB

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

(72) Inventors: **CAMPOS, Sebastien Andre**; GlaxoSmithKline, Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY (GB). **HARLING, John David**; GlaxoSmithKline, Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY (GB). **MIAH, Afjal Hussain**; GlaxoSmithKline, Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY (GB). **SMITH, Ian Edward David**; GlaxoSmithKline, Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY (GB).

(74) Agent: **LEAROYD, Stephanie Anne**; GlaxoSmithKline, Global Patents CN925.1, 980 Great West Road, Brentford Middlesex TW8 9GS (GB).

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

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

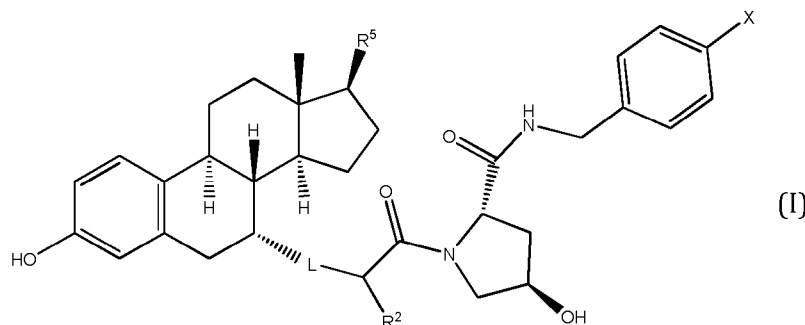
Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

Published:

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

(54) Title: PROTEOLYSIS TARGETING CHIMERAS (PROTACS) DIRECTED TO THE MODULATION OF THE ESTROGEN RECEPTOR



(57) Abstract: A compound of formula (I): or a pharmaceutically acceptable salt thereof, compositions, combinations and medicaments containing said compounds and processes for their preparation. The invention also relates to the use of said compounds, combinations, compositions and medicaments, for example as inhibitors of the activity of the estrogen receptor, including degrading the estrogen receptor, the treatment of diseases and conditions mediated by the estrogen receptor.

PROTEOLYSIS TARGETING CHIMERAS (PROTACS) DIRECTED TO THE MODULATION OF THE ESTROGEN RECEPTOR

FIELD OF THE INVENTION

The present invention relates to compounds, compositions, combinations and medicaments containing said compounds and processes for their preparation. The invention also relates to the use of said compounds, combinations, compositions and medicaments, for example as inhibitors of the activity of the estrogen receptor, including degrading the estrogen receptor, the treatment of diseases and conditions mediated by the estrogen receptor, in particular for the treatment of breast cancer.

BACKGROUND OF THE INVENTION

The estrogen receptor (ER) is a member of the nuclear hormone receptor family and functions as a ligand-activated transcription factor involved with the up and down regulation of gene expression. The natural hormone for the estrogen receptor is 17 β -estradiol (E2) and closely related metabolites. Binding of estradiol to the estrogen receptor causes a dimerization of the receptor and the dimer in turn binds to estrogen response elements (ERE's) on DNA. The ER-DNA complex recruits other transcription factors responsible for the transcription of DNA downstream from the ERE into mRNA which is eventually translated into protein. Alternatively the interaction of ER with DNA may be indirect through the intermediacy of other transcription factors, most notably fos and jun. Since the expression of a large number of genes is regulated by the estrogen receptor and since the estrogen receptor is expressed in many cell types, modulation of the estrogen receptor through binding of either natural hormones or synthetic ER ligands can have profound effects on the physiology and pathophysiology of the organism.

A variety of diseases have their aetiology and/or pathology mediated by the ER. Collectively these diseases are called estrogen-dependent diseases. Estrogens are critical for sexual development in females. In addition, estrogens play an important role in maintaining bone density, regulation of blood lipid levels, and appear to have neuroprotective effects. Consequently decreased estrogen production in post-menopausal women is associated with a number of diseases such as osteoporosis, atherosclerosis, depression and cognitive disorders. Conversely certain types of proliferative diseases such as breast and uterine cancer and endometriosis are stimulated by estrogens and therefore antiestrogens (*i.e.* estrogen antagonists) have utility in the prevention and treatment of these types of disorders.

There are two different forms of the estrogen receptor, usually referred to as α and β , each encoded by a separate gene (*ESR1* and *ESR2*, respectively).

Both ERs are widely expressed in different tissue types, however there are some notable differences in their expression patterns. The *ER α* is found in endometrium, breast cancer cells, ovarian stroma cells, and the hypothalamus. In males, *ER α* protein is found in the epithelium of the efferent ducts. The expression of the *ER β* protein has been documented in kidney, brain, bone, heart, lungs, intestinal mucosa, prostate, and endothelial cells. Development therefore of selective ligands may therefore preserve the beneficial aspects of estrogen.

Breast Cancer is the most common malignancy to affect women and worldwide, the incidence of the disease is increasing. Estrogens, in particular, act as endocrine growth factors for at least one-third of breast cancers, and depriving the tumour of this stimulus is a recognised therapy for advanced disease. In premenopausal women, this is achieved by the ablation of ovarian function through surgical, radiotherapeutic, or medical means and, in postmenopausal women, by the use of aromatase inhibitors.

An alternative approach to estrogen withdrawal is to antagonise estrogen with antiestrogens. These are drugs that bind to and compete for estrogen receptors (ER) present in estrogen-responsive tissue. Conventional nonsteroidal antiestrogens, such as tamoxifen, compete efficiently for ER binding but their effectiveness is often limited by the partial agonism they display, which results in an incomplete blockade of estrogen-mediated activity. A specific or "pure" antiestrogen with high affinity for ER and without any agonist effects, may have advantages over conventional nonsteroidal anti estrogens in the treatment of estrogen-dependent disease. Fulvestrant is the first of a new class of potent pure anti estrogens and is completely free of the partial agonist, estrogen-like activity, associated with currently available antiestrogens like tamoxifen.

It would be desirable to investigate other approaches to antagonise the ER receptor.

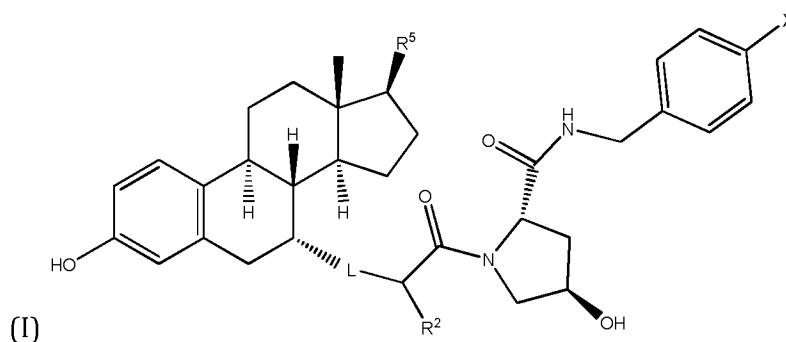
One approach would be to develop selective ER down regulators or degraders that reduce ER expression at either the transcript or protein level.

Several methods are available for the manipulation of protein levels, including proteolysis targeting chimeric molecules (PROTACs) which contain a ligand that recognizes the target protein linked to a ligand that binds to a specific E3 ubiquitin ligase. It would be desirable to have a small molecule which can simultaneously bind ER and an E3 ubiquitin ligase and which promotes ubiquitination of ER and leads to degradation of ER by the Proteosome. One suitable E3 ubiquitin ligase is the von Hippel-Lindau tumour suppressor (VHL).

The present inventors have identified compounds which are capable of inhibiting estrogen receptor function including compounds which degrade the estrogen receptor.

SUMMARY OF THE INVENTION

In one aspect there is provided a compound of formula (I):



Wherein

L is a linking group comprising a length of 6-16 atoms in shortest length having the formula $-(CH_2)_n - (R^1CH_2CH_2)_m (OCH_2)_q CONH -$;

n is 0-6;

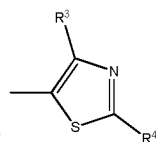
m is 2-10;

q is 0 or 1

each R¹ is independently -O-, -NH-, -N(C₁₋₃ alkyl)-, or a 4-6 membered heterocyclyl group containing 2 N atoms linked to the carbons in the chain via the ring N atoms (optionally substituted by oxo).;

R² is C₁₋₆ straight or branched alkyl, C₃₋₆ cycloalkyl

X is, oxazol-5-yl or



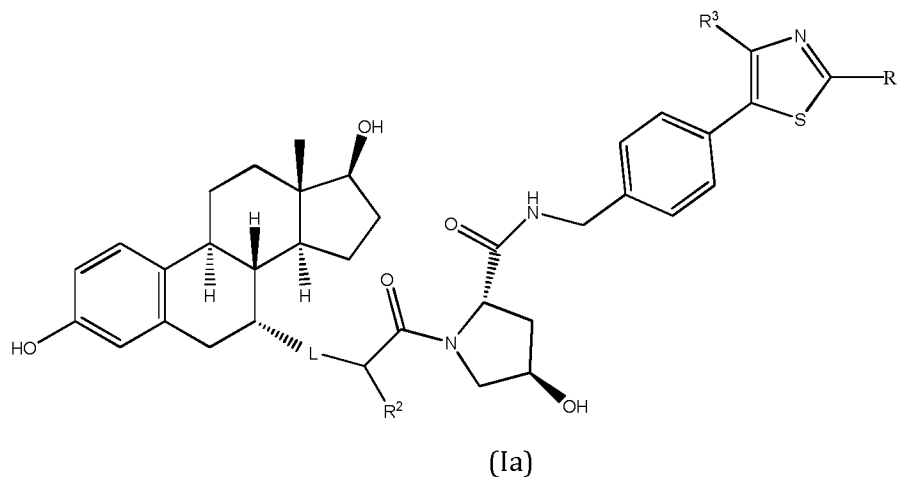
R³ is H or CH₃;

5 R⁴ is H or CH₃;

R⁵ is OH or OC₁₋₃alkyl

or a pharmaceutically acceptable salt thereof.

In one aspect there is provided a compound of formula (I) which is of formula (1a):



10

wherein L is a linking group having the following structure:

$-(CH_2)_n - (R^1CH_2CH_2)_m (OCH_2)_qCONH -$;

n is 0-6;

15 m is 2-10;

q is 0 or 1

each R¹ is independently -O-, -NH-, -N(C₁₋₃ alkyl)-, or a 4-6 membered heterocyclyl group containing 2 N atoms linked to the carbons in the chain via the ring N atoms;

R² is C₁₋₆ straight or branched alkyl ;

20 R³ is H or CH₃;

R⁴ is H or CH₃;

or a pharmaceutically acceptable salt thereof.

In a further aspect of the present invention, there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof for use in therapy, in particular in the treatment of diseases and conditions mediated by the estrogen receptor.

5

In a further aspect of the present invention, there is provided a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and one or more of pharmaceutically acceptable carriers, diluents and excipients.

10 In a further aspect of the present invention, there is provided a method of treating diseases and conditions mediated by the estrogen receptor in a subject comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

15 In a further aspect of the present invention, there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in treating diseases and conditions mediated by the estrogen receptor.

20 In a further aspect there is provided a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent.

In a further aspect there is provided a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent for use in therapy, particularly for treating diseases and conditions mediated by the estrogen receptor.

25

In a further aspect of the invention there is provided a combination comprising compound of formula (I) or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent for use in treating diseases and conditions mediated by the estrogen receptor.

30 In a further aspect there is provided a method of treating diseases and conditions mediated by the estrogen receptor comprising administering to a human in need thereof a therapeutically

effective amount of a combination comprising compound of formula (I) or a pharmaceutically acceptable salt thereof, and at least one further therapeutic agent.

5 In a further aspect there is provided the use of a combination comprising compound of formula (I) or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent in the manufacture of a medicament for treating diseases and conditions mediated by the estrogen receptor.

10 In a further aspect there is provided a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and at least one anti-neoplastic agent.

15 In a further aspect there is provided a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and at least one anti-neoplastic agent, for use in therapy, in particular for diseases and conditions mediated by the estrogen receptor.

In a further aspect there is provided a combination comprising a compound of formula (I) or pharmaceutically acceptable salt thereof and at least one anti-neoplastic agent, for use in treating diseases and conditions mediated by the estrogen receptor.

20 In a further aspect there is provided the use of a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and at least one anti-neoplastic agent, in the manufacture of a medicament for treating diseases and conditions mediated by the estrogen receptor.

25 In a further aspect there is provided a method of treating diseases and conditions mediated by the estrogen receptor, comprising administering to a human in need thereof a therapeutically effective amount of a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and at least one anti-neoplastic agent.

30 In a further aspect there is provided a pharmaceutical composition comprising a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof

and at least one further therapeutic agent, particularly at least one anti-neoplastic agent and one or more of pharmaceutically acceptable carriers, diluents and excipients.

In a further aspect there is provided a method of degrading the estrogen receptor comprising administration comprising administering to a human in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof .

DETAILED DESCRIPTION OF THE INVENTION

As used herein, "a compound of the invention" includes all solvates, complexes, polymorphs, radiolabelled derivatives, stereoisomers and optical isomers of the compounds of formula (I) and salts thereof.

As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

As used herein, the term "pharmaceutically acceptable" refers to those compounds, materials, compositions, and dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, the term "alkyl" and "alkylene" refers to a saturated hydrocarbon chain having the specified number of member atoms.

As used herein, the term "heterocyclic" or the term "heterocyclyl" refers to a three to twelve-membered non-aromatic heterocyclic ring, being saturated and containing the specified nitrogenatom substitutions.

The compounds of the invention may exist in solid or liquid form. In solid form, compound of the invention may exist in a continuum of solid states ranging from fully amorphous to fully crystalline. The term 'amorphous' refers to a state in which the material lacks long range order at the molecular level and, depending upon the temperature, may exhibit the physical properties of a solid or a liquid. Typically such materials do not give distinctive X-ray diffraction patterns and, while exhibiting the properties of a solid, are more formally described as a liquid. Upon heating, a change from solid to liquid properties occurs which is characterized by a change of state, typically second order ('glass transition'). The term 'crystalline' refers to a solid phase in which the material has a regular ordered internal structure at the molecular level and gives a distinctive X-ray diffraction pattern with defined peaks. Such materials when heated sufficiently will also exhibit the properties of a liquid, but the change from solid to liquid is characterized by a phase change, typically first order ('melting point').

The compound of formula (I) may exist in solvated and unsolvated forms. As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I) or a salt) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. The skilled artisan will appreciate that pharmaceutically acceptable solvates may be formed for crystalline compounds wherein solvent molecules are incorporated into the crystalline lattice during crystallization. The incorporated solvent molecules may be water molecules or non-aqueous such as ethanol, isopropanol, DMSO, acetic acid, ethanolamine, and ethyl acetate molecules. Crystalline lattice incorporated with water molecules are typically referred to as "hydrates". Hydrates include stoichiometric hydrates as well as compositions containing variable amounts of water. The present invention includes all such solvates.

The compounds of the invention may have the ability to crystallize in more than one form, a characteristic, which is known as polymorphism, and it is understood that such polymorphic forms ("polymorphs") are within the scope of the invention. Polymorphism generally can occur as a response to changes in temperature or pressure or both and can also result from variations in the crystallization process. Polymorphs can be distinguished by various physical characteristics known in the art such as x-ray diffraction patterns, solubility and melting point.

It is also noted that the compounds of formula (I) may form tautomers. It is understood that all tautomers and mixtures of tautomers of the compounds of the present invention are included within the scope of the compounds of the present invention.

5 As used herein, the term “estrogen receptor inhibitor”, or “inhibitor” refers to any compound or treatment capable of inhibiting or reducing the expression or activity of the estrogen receptor. The inhibitor is preferably selective.

In one embodiment, R^2 is $-C(CH_3)_3$ or $-CH(CH_3)_2$.

10 In one embodiment, each R^1 is O.

In one embodiment n is 4 or 5.

In one embodiment m is 3-10.

In one embodiment R^3 and R^4 are CH_3 .

In one embodiment R^3 is CH_3 and R^4 is H.

15 In one embodiment the linker is

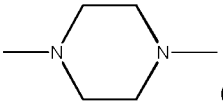
$(CH_2)_4 (OCH_2CH_2)_3 OCH_2 CONH$;

$(CH_2)_4 (OCH_2CH_2)_2 OCH_2 CONH$;

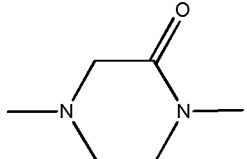
$(CH_2)_4 (OCH_2CH_2)_4 OCH_2 CONH$;

$(CH_2)_5 N(CH_3) CH_2 CH_2 (OCH_2CH_2)_3 CONH$;

20 $(CH_2)_5 N(CH_3) CH_2 CH_2 (OCH_2CH_2)_2 CONH$;

$(CH_2)_5$  $CH_2 CH_2 (OCH_2CH_2)_2 OCH_2 CONH$;

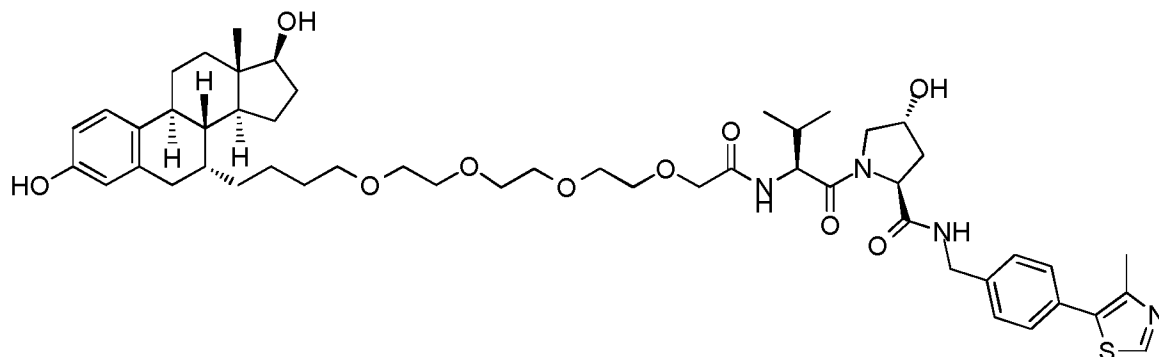
$(CH_2)_6 (OCH_2CH_2)_2 OCH_2 CONH$;

Or $(CH_2)_4$  $CH_2 CH_2 OCH_2 CH_2 OCH_2 CONH$.

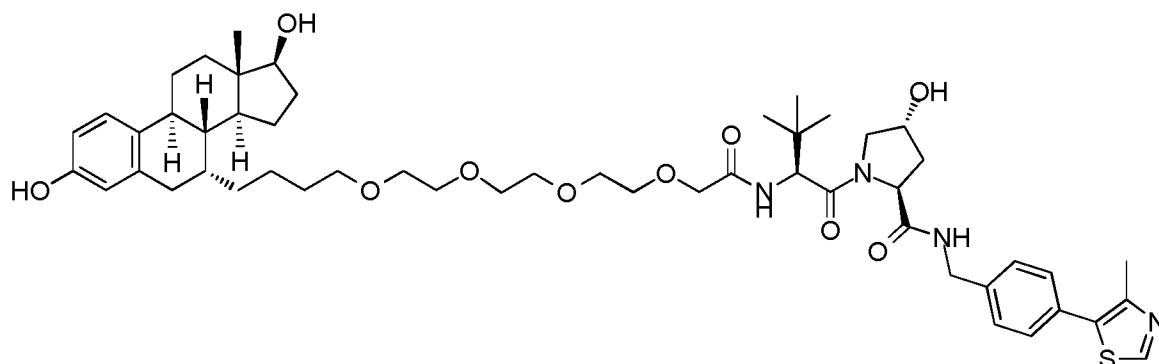
25 While aspects for each variable have generally been listed above separately for each variable this invention includes those compounds in which several or each aspect in formula (I) is selected from each of the aspects listed above. Therefore, this invention is intended to include all combinations of aspects for each variable.

Examples of compounds of the prevent invention include the following:

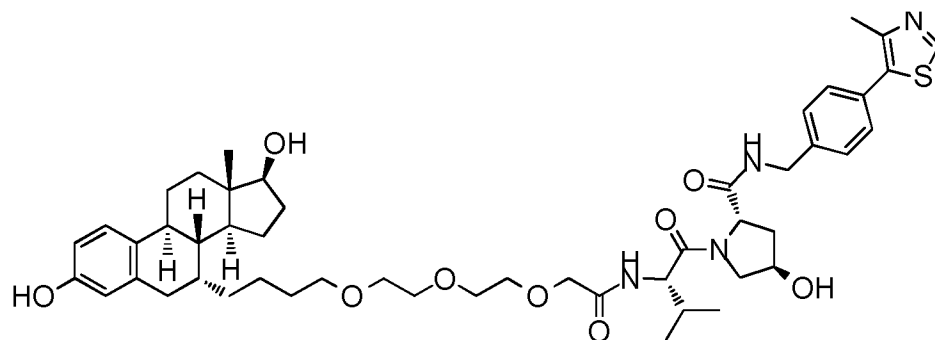
(2*S*,4*R*)-1-((*S*)-19-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-Dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-2-isopropyl-4-oxo-6,9,12,15-tetraoxa-3-
 5 azanonadecan-1-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



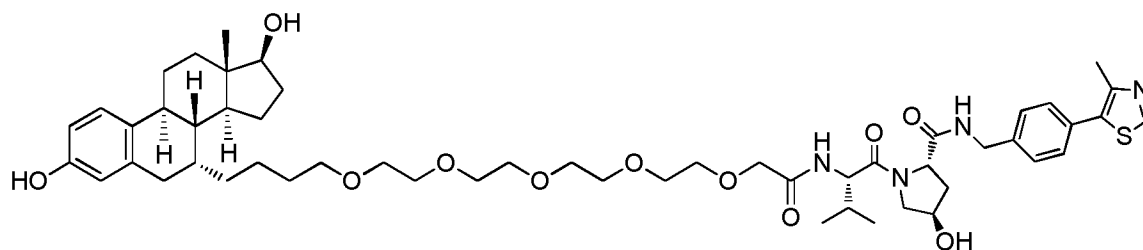
(2*S*,4*R*)-1-((*S*)-2-(*Tert*-butyl)-19-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-4-oxo-6,9,12,15-tetraoxa-3-azonadecan-1-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-
 10 carboxamide



(2*S*,4*R*)-1-((*S*)-16-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-Dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-2-isopropyl-4-oxo-6,9,12-trioxa-3-azahexadecan-1-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide

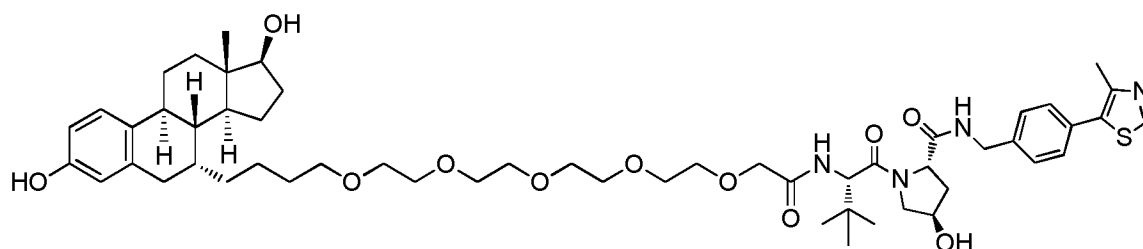


(2*S*,4*R*)-1-((*S*)-22-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-2-isopropyl-4-oxo-6,9,12,15,18-pentaoxa-3-azadocosan-1-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



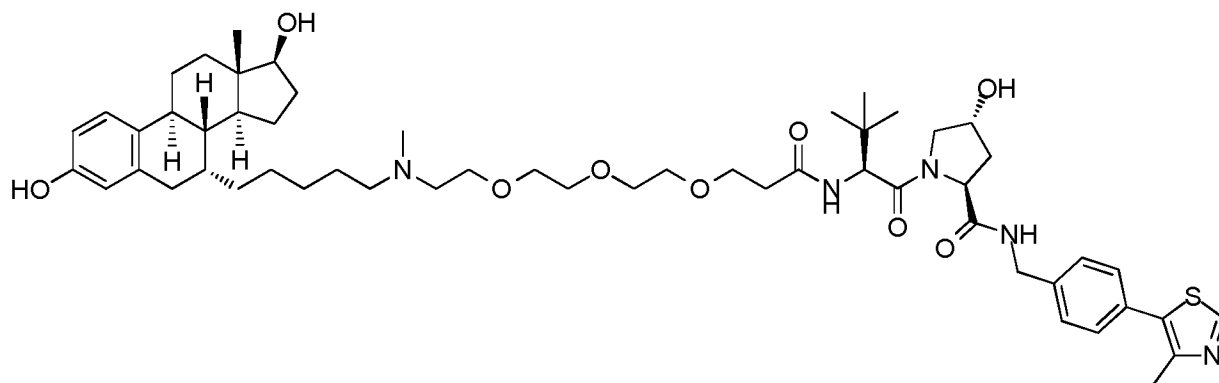
5

(2*S*,4*R*)-1-((*S*)-2-(*Tert*-butyl)-22-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-4-oxo-6,9,12,15,18-pentaoxa-3-azadocosan-1-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide

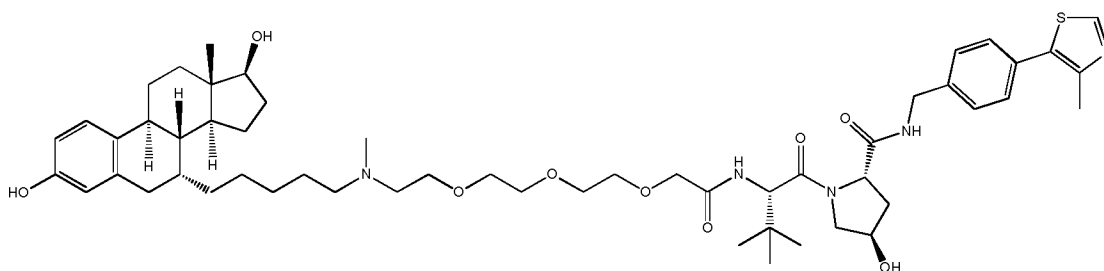


10

(2*S*,4*R*)-1-((*S*)-2-(*Tert*-butyl)-21-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-16-methyl-4-oxo-7,10,13-trioxa-3,16-diazahenicosan-1-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide

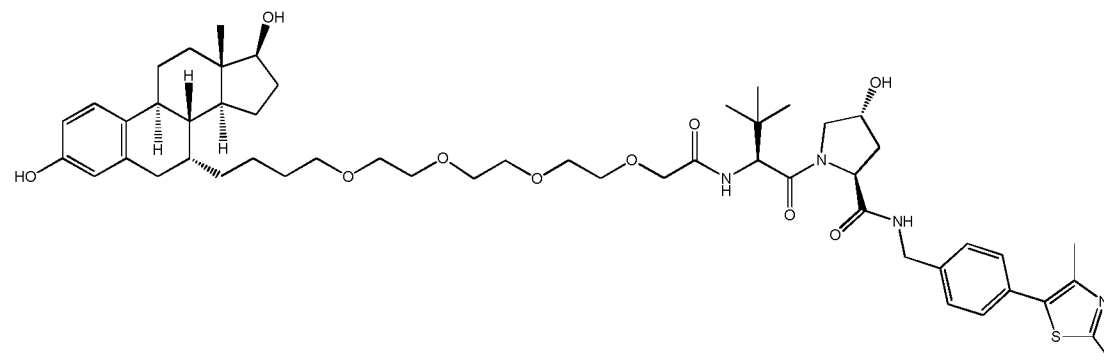


(2S,4R)-1-((S)-2-(tert-butyl)-20-((7R,8R,9S,13S,14S,17S)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)-15-methyl-4-oxo-6,9,12-trioxa-3,15-diazaicosan-1-oyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



5

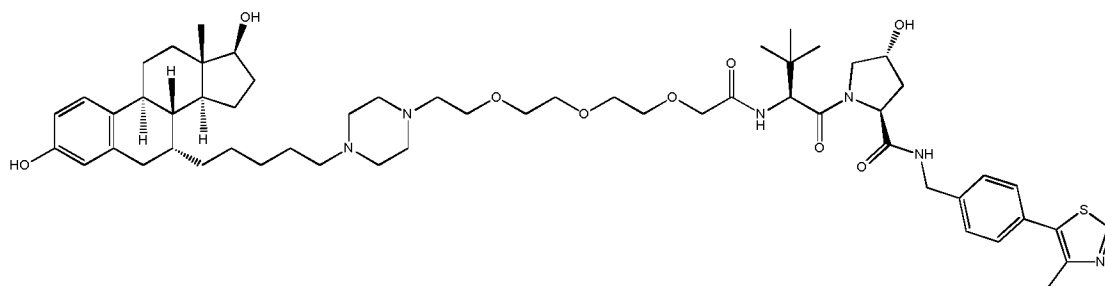
(2S,4R)-1-((S)-2-(tert-butyl)-19-((7R,8R,9S,13S,14S,17S)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)-4-oxo-6,9,12,15-tetraoxa-3-azanonadecan-1-oyl)-N-(4-(2,4-dimethylthiazol-5-yl)benzyl)-4-hydroxypyrrolidine-2-carboxamide



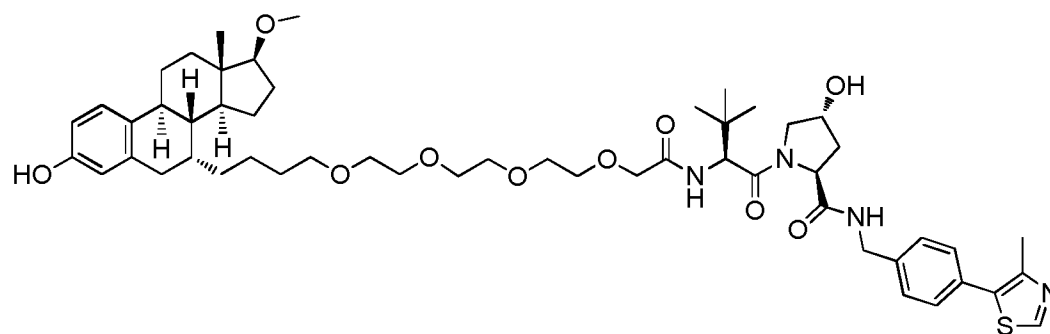
10

(2S,4R)-1-((S)-2-(tert-butyl)-14-(4-(5-((7R,8R,9S,13S,14S,17S)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)pentyl)piperazin-1-yl)-4-oxo-6,9,12-trioxa-3-azatetradecan-1-oyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide

15

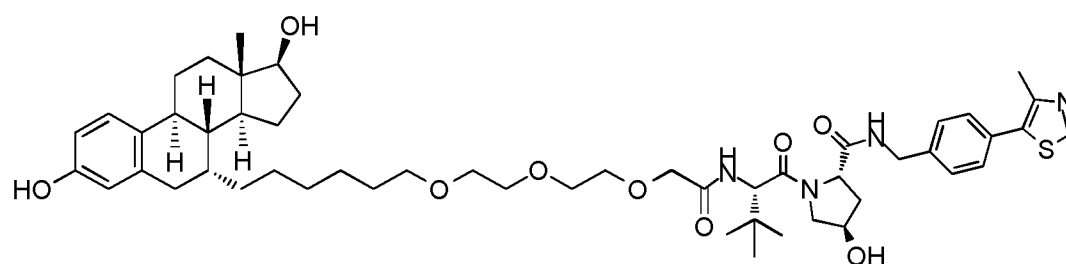


(2S,4R)-1-((S)-2-(Tert-butyl)-19-((7R,8R,9S,13S,14S,17S)-3-hydroxy-17-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)-4-oxo-6,9,12,15-tetraoxa-3-azanonadecan-1-oyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



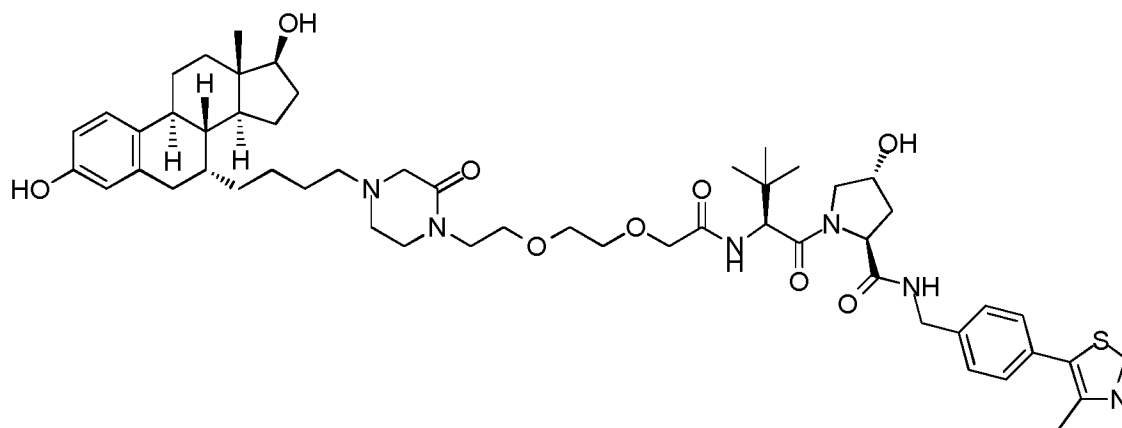
ied by chromatography on silica using a gradient elution from 0% to 85% methyl *tert*-butyl ether in cyclohexane to afford *the title compound* (3.91 g, 10.3 mmol, 51% yield). LCMS RT= 1.30 min, ES+ve *m/z* 359.3./361.3 [M+H]⁺.

(2S,4R)-1-((S)-2-(Tert-butyl)-18-((7R,8R,9S,13S,14S,17S)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)-4-oxo-6,9,12-trioxa-3-azaoctadecan-1-oyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide

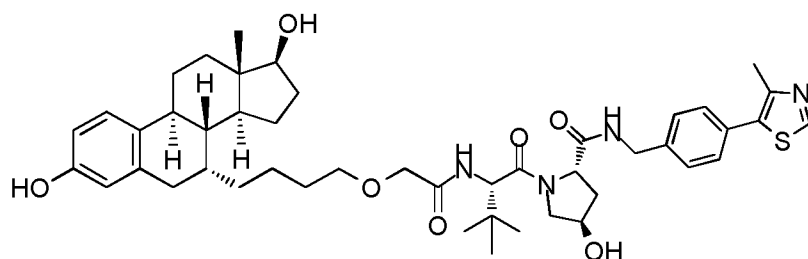


(2S,4R)-1-((S)-2-(2-(2-(2-(4-(4-((7R,8R,9S,13S,14S,17S)-3,17-Dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)butyl)-2-

oxopiperazin-1-yl)ethoxy)ethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



(2S,4R)-1-((S)-2-(2-(4-((7R,8R,9S,13S,14S,17S)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)butoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



The compounds of Formula (I) may be in the form of a salt. Typically, the salts of the present invention are pharmaceutically acceptable salts. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention. For a review on suitable salts see Berge et al, J. Pharm. Sci. 1977, 66, 1-19.

Suitable pharmaceutically acceptable salts can include acid addition salts. A pharmaceutically acceptable acid addition salt can be formed by reaction of a compound of formula (I) with a suitable inorganic or organic acid (such as hydrobromic, hydrochloric, sulfuric, nitric, phosphoric, p-toluenesulfonic, benzenesulfonic, methanesulfonic, ethanesulfonic, naphthalenesulfonic such as 2-naphthalenesulfonic), optionally in a suitable solvent such as an organic solvent, to give the salt which is usually isolated for example by crystallisation and filtration. A pharmaceutically acceptable acid addition salt of a compound of formula (I) can

comprise or be for example a hydrobromide, hydrochloride, sulfate, nitrate, phosphate, p-toluenesulfonate, benzenesulfonate, methanesulfonate, ethanesulfonate, naphthalenesulfonate (e.g. 2-naphthalenesulfonate) salt.

5 Other non-pharmaceutically acceptable salts, e.g. trifluoroacetates, may be used, for example in the isolation of compounds of the invention, and are included within the scope of this invention.

The invention includes within its scope all possible stoichiometric and non-stoichiometric forms of the compounds of formula (I).

10

While it is possible that, for use in therapy, the compound of the invention may be administered as the raw chemical, it is possible to present the active ingredient as a pharmaceutical composition. Accordingly, the invention further provides pharmaceutical compositions comprising a compound of the invention and one or more pharmaceutically acceptable carriers, diluents, or
15 excipients. The carrier(s), diluents(s) or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipient thereof. In accordance with another aspect of the invention there is also provided a process for the preparation of a pharmaceutical composition including the agent, or pharmaceutically acceptable salts thereof, with one or more pharmaceutically acceptable carriers, diluents or excipients. The
20 pharmaceutical composition can be for use in the treatment and/or prophylaxis of any of the conditions described herein.

Pharmaceutical compositions may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Preferred unit dosage compositions are those containing a daily dose or sub-dose, or an appropriate fraction thereof, of an active
25 ingredient. Such unit doses may therefore be administered once or more than once a day. Such pharmaceutical compositions may be prepared by any of the methods well known in the pharmacy art.

Pharmaceutical compositions may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, inhaled, intranasal, topical
30 (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such compositions may be prepared by any

method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

Pharmaceutical compositions adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Powders are prepared by reducing the compound to a suitable fine size and mixing with a similarly prepared pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavouring, preservative, dispersing and colouring agent can also be present.

Capsules are made by preparing a powder mixture, as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, glidants, lubricants, sweetening agents, flavours, disintegrating agents and colouring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginat, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting with a

binder such as syrup, starch paste, acacia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavoured aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners or saccharin or other artificial sweeteners, and the like can also be added.

Where appropriate, dosage unit compositions for oral administration can be microencapsulated. The composition can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax or the like.

The compounds of the invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Pharmaceutical compositions adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time.

Pharmaceutical compositions adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

For treatments of the eye or other external tissues, for example mouth and skin, the compositions are preferably applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-
5 water cream base or a water-in-oil base.

Pharmaceutical compositions adapted for topical administrations to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

Pharmaceutical compositions adapted for topical administration in the mouth include
10 lozenges, pastilles and mouth washes.

Pharmaceutical compositions adapted for rectal administration may be presented as suppositories or as enemas.

Dosage forms for nasal or inhaled administration may conveniently be formulated as aerosols, solutions, suspensions drops, gels or dry powders.

15 Pharmaceutical compositions adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

Pharmaceutical compositions adapted for parental administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the composition isotonic with the blood of the intended recipient; and
20 aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The compositions may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders,
25 granules and tablets.

It should be understood that in addition to the ingredients particularly mentioned above, the compositions may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

A therapeutically effective amount of the agent will depend upon a number of factors including, for example, the age and weight of the subject, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration, and will ultimately be at the discretion of the attendant physician or veterinarian. In particular, the subject to be
5 treated is a mammal, particularly a human.

The agent may be administered in a daily dose. This amount may be given in a single dose per day or in a number (such as two, three, four, five or six) of sub-doses per day such that the total daily dose is the same.

Suitably, the amount of the compound of the invention administered according to the
10 present invention will be an amount selected from 0.01mg to 1g per day (calculated as the free or unsalted compound).

We have found that the compounds defined in the present invention, or a pharmaceutically acceptable salt thereof, or pharmaceutical compositions containing them, are capable of degrading the estrogen-receptor.
15

Accordingly, the compounds of the present invention are expected to be potentially
useful agents in the treatment of diseases or medical conditions mediated alone or in part
by the estrogen receptor.
20

Provided herein are methods of treatment or prevention of diseases, disorders and conditions mediated by the estrogen receptor. A method may comprise administering to a subject, e.g. a subject in need thereof, a therapeutically effective amount of a compound of the invention.

Thus in one aspect there is provided a compound of the invention for use in therapy

25 Thus in one aspect there is provided a compound of the invention for use in treating diseases, disorders or conditions mediated by the estrogen receptor

Thus in one aspect there is provided the use of a compound of the invention in the manufacture of a medicament for treating diseases, disorders or conditions mediated by the estrogen receptor.

In a further aspect there is provided a method of treatment of diseases, disorders or conditions mediated by the estrogen receptor in a mammal comprising administering a therapeutically effective amount of a compound of the invention.

The compound of the invention are useful in the treatment of estrogen receptor associated conditions. An "estrogen receptor-associated condition," as used herein, denotes a condition or disorder which can be treated by modulating the function or activity of an estrogen receptor in a subject, wherein treatment comprises prevention, partial alleviation or cure of the condition or disorder. Modulation may occur locally, for example, within certain tissues of the subject, or more extensively throughout a subject being treated for such a condition or disorder.

In one aspect the estrogen mediated disease or condition is breast cancer.

As indicated, therapeutically effective amounts of the compound of the invention are discussed above. The therapeutically effective amount of the further therapeutic agents of the present invention will depend upon a number of factors including, for example, the age and weight of the mammal, the precise condition requiring treatment, the severity of the condition, the nature of the formulation, and the route of administration. Ultimately, the therapeutically effective amount will be at the discretion of the attendant physician or veterinarian. The relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

The compounds of the present invention may be used in combination with or include one or more other therapeutic agents and may be administered either sequentially or simultaneously by any convenient route in separate or combined pharmaceutical compositions.

The compounds of the present invention and further therapeutic agent(s) may be employed in combination by administration simultaneously in a unitary pharmaceutical composition including both compounds. Alternatively, the combination may be administered separately in separate pharmaceutical compositions, each including one of the compounds in a sequential manner wherein, for example, the compound of the invention is administered first and the other second and *vice versa*. Such sequential administration may be close in time (e.g. simultaneously) or remote in time. Furthermore, it does not matter if the compounds are administered in the same dosage form, e.g. one compound may be administered topically and the other compound may be administered orally. Suitably, both compounds are administered orally.

The combinations may be presented as a combination kit. By the term "combination kit" "or kit of parts" as used herein is meant the pharmaceutical composition or compositions that are used to administer the combination according to the invention. When both compounds are administered simultaneously, the combination kit can contain both compounds in a single pharmaceutical composition, such as a tablet, or in separate pharmaceutical compositions. When the compounds are not administered simultaneously, the combination kit will contain each compound in separate pharmaceutical compositions either in a single package or in separate pharmaceutical compositions in separate packages.

The combination kit can also be provided by instruction, such as dosage and administration instructions. Such dosage and administration instructions can be of the kind that are provided to a doctor, for example by a drug product label, or they can be of the kind that are provided by a doctor, such as instructions to a patient.

When the combination is administered separately in a sequential manner wherein one is administered first and the other second or vice versa, such sequential administration may be close in time or remote in time. For example, administration of the other agent several minutes to several dozen minutes after the administration of the first agent, and administration of the other agent several hours to several days after the administration of the first agent are included, wherein the lapse of time is not limited. For example, one agent may be administered once a day, and the other agent may be administered 2 or 3 times a day, or one agent may be administered once a week, and the other agent may be administered once a day and the like.

It will be clear to a person skilled in the art that, where appropriate, the other therapeutic ingredients(s) may be used in the form of salts, for example as alkali metal or amine salts or as acid addition salts, or prodrugs, or as esters, for example lower alkyl esters, or as solvates, for example hydrates, to optimise the activity and/or stability and/or physical characteristics, such as solubility, of the therapeutic ingredient. It will be clear also that, where appropriate, the therapeutic ingredients may be used in optically pure form.

When combined in the same composition it will be appreciated that the two compounds must be stable and compatible with each other and the other components of the composition and may be

formulated for administration. When formulated separately they may be provided in any convenient composition, conveniently, in such a manner as known for such compounds in the art.

When the compound of formula (I) is used in combination with a second therapeutic agent
5 active against the same disease, condition or disorder, the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

In the embodiment, the compound of compound of formula (I) or a pharmaceutically acceptable salt thereof may be employed with other therapeutic methods of cancer treatment. In
10 particular, in anti-neoplastic therapy, combination therapy with other chemotherapeutic, hormonal, antibody agents as well as surgical and/or radiation treatments other than those mentioned above are envisaged.

As indicated, therapeutically effective amounts of the compound of compound of formula (I) or a pharmaceutically acceptable salt thereof are discussed above. The therapeutically effective
15 amount of the further therapeutic agents of the present invention will depend upon a number of factors including, for example, the age and weight of the mammal, the precise condition requiring treatment, the severity of the condition, the nature of the formulation, and the route of administration. Ultimately, the therapeutically effective amount will be at the discretion of the attendant physician or veterinarian. The relative timings of administration will be selected in order
20 to achieve the desired combined therapeutic effect.

In one embodiment, the further anti-cancer therapy is surgical and/or radiotherapy.

In one embodiment, the further anti-cancer therapy is at least one additional anti-neoplastic agent.

Any anti-neoplastic agent that has activity versus a susceptible tumor being treated may be
25 utilized in the combination. Typical anti-neoplastic agents useful include, but are not limited to, anti-microtubule agents such as diterpenoids and vinca alkaloids; platinum coordination complexes; alkylating agents such as nitrogen mustards, oxazaphosphorines, alkylsulfonates, nitrosoureas, and triazenes; antibiotic agents such as anthracyclins, actinomycins and bleomycins; topoisomerase II inhibitors such as epipodophyllotoxins; antimetabolites such as purine and
30 pyrimidine analogues and anti-folate compounds; topoisomerase I inhibitors such as camptothecins; hormones and hormonal analogues; signal transduction pathway inhibitors; non-

receptor tyrosine angiogenesis inhibitors; immunotherapeutic agents; proapoptotic agents; and cell cycle signaling inhibitors.

Anti-microtubule or anti-mitotic agents:

Anti-microtubule or anti-mitotic agents are phase specific agents active against the microtubules of tumor cells during M or the mitosis phase of the cell cycle. Examples of anti-microtubule agents include, but are not limited to, diterpenoids and vinca alkaloids.

Diterpenoids, which are derived from natural sources, are phase specific anti -cancer agents that operate at the G₂/M phases of the cell cycle. It is believed that the diterpenoids stabilize the β -tubulin subunit of the microtubules, by binding with this protein. Disassembly of the protein appears then to be inhibited with mitosis being arrested and cell death following. Examples of diterpenoids include, but are not limited to, paclitaxel and its analog docetaxel.

Paclitaxel, 5 β ,20-epoxy-1,2 α ,4,7 β ,10 β ,13 α -hexa-hydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine; is a natural diterpene product isolated from the Pacific yew tree *Taxus brevifolia* and is commercially available as an injectable solution TAXOL®. It is a member of the taxane family of terpenes. Paclitaxel has been approved for clinical use in the treatment of refractory ovarian cancer in the United States (Markman et al., Yale Journal of Biology and Medicine, 64:583, 1991; McGuire et al., Ann. Intern. Med., 111:273,1989) and for the treatment of breast cancer (Holmes et al., J. Nat. Cancer Inst., 83:1797,1991.) It is a potential candidate for treatment of neoplasms in the skin (Einzig et. al., Proc. Am. Soc. Clin. Oncol., 20:46) and head and neck carcinomas (Forastire et. al., Sem. Oncol., 20:56, 1990). The compound also shows potential for the treatment of polycystic kidney disease (Woo et. al., Nature, 368:750. 1994), lung cancer and malaria. Treatment of patients with paclitaxel results in bone marrow suppression (multiple cell lineages, Ignoff, R.J. et. al, Cancer Chemotherapy Pocket Guide, 1998) related to the duration of dosing above a threshold concentration (50nM) (Kearns, C.M. et. al., Seminars in Oncology, 3(6) p.16-23, 1995).

Docetaxel, (2R,3S)- N-carboxy-3-phenylisoserine,N-*tert*-butyl ester, 13-ester with 5 β -20-epoxy-1,2 α ,4,7 β ,10 β ,13 α -hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate; is commercially available as an injectable solution as TAXOTERE®. Docetaxel is indicated for the treatment of breast cancer. Docetaxel is a semisynthetic derivative of paclitaxel *q.v.*, prepared using
5 a natural precursor, 10-deacetyl-baccatin III, extracted from the needle of the European Yew tree.

Vinca alkaloids are phase specific anti-neoplastic agents derived from the periwinkle plant. Vinca alkaloids act at the M phase (mitosis) of the cell cycle by binding specifically to tubulin. Consequently, the bound tubulin molecule is unable to polymerize into microtubules. Mitosis is
10 believed to be arrested in metaphase with cell death following. Examples of vinca alkaloids include, but are not limited to, vinblastine, vincristine, and vinorelbine.

Vinblastine, vincalureoblastine sulfate, is commercially available as VELBAN® as an injectable solution. Although, it has possible indication as a second line therapy of various solid
15 tumors, it is primarily indicated in the treatment of testicular cancer and various lymphomas including Hodgkin's Disease; and lymphocytic and histiocytic lymphomas. Myelosuppression is the dose limiting side effect of vinblastine.

Vincristine, vincalureoblastine, 22-oxo-, sulfate, is commercially available as ONCOVIN® as
20 an injectable solution. Vincristine is indicated for the treatment of acute leukemias and has also found use in treatment regimens for Hodgkin's and non-Hodgkin's malignant lymphomas. Alopecia and neurologic effects are the most common side effect of vincristine and to a lesser extent myelosuppression and gastrointestinal mucositis effects occur.

Vinorelbine, 3',4'-didehydro -4'-deoxy-C'-norvincalureoblastine [R-(R*,R*)-2,3-
25 dihydroxybutanedioate (1:2)(salt)], commercially available as an injectable solution of vinorelbine tartrate (NAVELBINE®), is a semisynthetic vinca alkaloid. Vinorelbine is indicated as a single agent or in combination with other chemotherapeutic agents, such as cisplatin, in the treatment of various solid tumors, particularly non-small cell lung, advanced breast, and hormone refractory
30 prostate cancers. Myelosuppression is the most common dose limiting side effect of vinorelbine.

Platinum coordination complexes:

Platinum coordination complexes are non-phase specific anti-cancer agents, which are interactive with DNA. The platinum complexes enter tumor cells, undergo, aquation and form intra- and interstrand crosslinks with DNA causing adverse biological effects to the tumor. Examples of platinum coordination complexes include, but are not limited to, oxaliplatin, cisplatin and carboplatin.

Cisplatin, cis-diamminedichloroplatinum, is commercially available as PLATINOL® as an injectable solution. Cisplatin is primarily indicated in the treatment of metastatic testicular and ovarian cancer and advanced bladder cancer.

Carboplatin, platinum, diammine [1,1-cyclobutane-dicarboxylate(2-)-O,O'], is commercially available as PARAPLATIN® as an injectable solution. Carboplatin is primarily indicated in the first and second line treatment of advanced ovarian carcinoma.

Alkylating agents:

Alkylating agents are non-phase anti-cancer specific agents and strong electrophiles. Typically, alkylating agents form covalent linkages, by alkylation, to DNA through nucleophilic moieties of the DNA molecule such as phosphate, amino, sulfhydryl, hydroxyl, carboxyl, and imidazole groups. Such alkylation disrupts nucleic acid function leading to cell death. Examples of alkylating agents include, but are not limited to, nitrogen mustards such as cyclophosphamide, melphalan, and chlorambucil; alkyl sulfonates such as busulfan; nitrosoureas such as carmustine; and triazenes such as dacarbazine.

Cyclophosphamide, 2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate, is commercially available as an injectable solution or tablets as CYTOXAN®. Cyclophosphamide is indicated as a single agent or in combination with other chemotherapeutic agents, in the treatment of malignant lymphomas, multiple myeloma, and leukemias.

Melphalan, 4-[bis(2-chloroethyl)amino]-L-phenylalanine, is commercially available as an injectable solution or tablets as ALKERAN®. Melphalan is indicated for the palliative treatment of multiple myeloma and non-resectable epithelial carcinoma of the ovary. Bone marrow suppression is the most common dose limiting side effect of melphalan.

Chlorambucil, 4-[bis(2-chloroethyl)amino]benzenebutanoic acid, is commercially available as LEUKERAN® tablets. Chlorambucil is indicated for the palliative treatment of chronic lymphatic leukemia, and malignant lymphomas such as lymphosarcoma, giant follicular lymphoma, and Hodgkin's disease.

Busulfan, 1,4-butanediol dimethanesulfonate, is commercially available as MYLERAN® TABLETS. Busulfan is indicated for the palliative treatment of chronic myelogenous leukemia.

Carmustine, 1,3-[bis(2-chloroethyl)-1-nitrosourea, is commercially available as single vials of lyophilized material as BiCNU®. Carmustine is indicated for the palliative treatment as a single agent or in combination with other agents for brain tumors, multiple myeloma, Hodgkin's disease, and non-Hodgkin's lymphomas.

Dacarbazine, 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide, is commercially available as single vials of material as DTIC-Dome®. Dacarbazine is indicated for the treatment of metastatic malignant melanoma and in combination with other agents for the second line treatment of Hodgkin's Disease.

Antibiotic anti-neoplastics :

Antibiotic anti-neoplastics are non-phase specific agents, which bind or intercalate with DNA. Typically, such action results in stable DNA complexes or strand breakage, which disrupts ordinary function of the nucleic acids leading to cell death. Examples of antibiotic anti-neoplastic agents include, but are not limited to, actinomycins such as dactinomycin, anthrocyclins such as daunorubicin and doxorubicin; and bleomycins.

Dactinomycin, also known as Actinomycin D, is commercially available in injectable form as COSMEGEN®. Dactinomycin is indicated for the treatment of Wilm's tumor and rhabdomyosarcoma.

Daunorubicin, (8S-cis-)-8-acetyl-10-[(3-amino-2,3,6-trideoxy- α -L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12 naphthacenedione hydrochloride, is commercially available as a liposomal injectable form as DAUNOXOME® or as an injectable as CERUBIDINE®. Daunorubicin is indicated for remission induction in the treatment of acute nonlymphocytic leukemia and advanced HIV associated Kaposi's sarcoma.

Doxorubicin, (8S, 10S)-10-[(3-amino-2,3,6-trideoxy- α -L-lyxo-hexopyranosyl)oxy]-8-glycoloyl, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12 naphthacenedione hydrochloride, is commercially available as an injectable form as RUBEX® or ADRIAMYCIN RDF®. Doxorubicin is primarily indicated for the treatment of acute lymphoblastic leukemia and acute myeloblastic leukemia, but is also a useful component in the treatment of some solid tumors and lymphomas.

Bleomycin, a mixture of cytotoxic glycopeptide antibiotics isolated from a strain of *Streptomyces verticillus*, is commercially available as BLENOXANE®. Bleomycin is indicated as a palliative treatment, as a single agent or in combination with other agents, of squamous cell carcinoma, lymphomas, and testicular carcinomas.

Topoisomerase II inhibitors:

Topoisomerase II inhibitors include, but are not limited to, epipodophyllotoxins.

Epipodophyllotoxins are phase specific anti-neoplastic agents derived from the mandrake plant. Epipodophyllotoxins typically affect cells in the S and G₂ phases of the cell cycle by forming a ternary complex with topoisomerase II and DNA causing DNA strand breaks. The strand breaks accumulate and cell death follows. Examples of epipodophyllotoxins include, but are not limited to, etoposide and teniposide.

Etoposide, 4'-demethyl-epipodophyllotoxin 9[4,6-O-(R)-ethylidene- β -D-glucopyranoside], is commercially available as an injectable solution or capsules as VePESID® and is commonly

known as VP-16. Etoposide is indicated as a single agent or in combination with other chemotherapy agents in the treatment of testicular and non-small cell lung cancers.

Teniposide, 4'-demethyl-epipodophyllotoxin 9[4,6-0-(R)-thenylidene- β -D-glucopyranoside], is commercially available as an injectable solution as VUMON® and is commonly known as VM-26. Teniposide is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia in children.

Antimetabolite neoplastic agents:

Antimetabolite neoplastic agents are phase specific anti-neoplastic agents that act at S phase (DNA synthesis) of the cell cycle by inhibiting DNA synthesis or by inhibiting purine or pyrimidine base synthesis and thereby limiting DNA synthesis. Consequently, S phase does not proceed and cell death follows. Examples of antimetabolite anti-neoplastic agents include, but are not limited to, fluorouracil, methotrexate, cytarabine, mecaptopurine, thioguanine, and gemcitabine.

5-fluorouracil, 5-fluoro-2,4- (1H,3H) pyrimidinedione, is commercially available as fluorouracil. Administration of 5-fluorouracil leads to inhibition of thymidylate synthesis and is also incorporated into both RNA and DNA. The result typically is cell death. 5-fluorouracil is indicated as a single agent or in combination with other chemotherapy agents in the treatment of carcinomas of the breast, colon, rectum, stomach and pancreas. Other fluoropyrimidine analogs include 5-fluoro deoxyuridine (floxuridine) and 5-fluorodeoxyuridine monophosphate.

Cytarabine, 4-amino-1- β -D-arabinofuranosyl-2 (1H)-pyrimidinone, is commercially available as CYTOSAR-U® and is commonly known as Ara-C. It is believed that cytarabine exhibits cell phase specificity at S-phase by inhibiting DNA chain elongation by terminal incorporation of cytarabine into the growing DNA chain. Cytarabine is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia. Other cytidine analogs include 5-azacytidine and 2',2'-difluorodeoxycytidine (gemcitabine).

5 Mercaptopurine, 1,7-dihydro-6H-purine-6-thione monohydrate, is commercially available as PURINETHOL®. Mercaptopurine exhibits cell phase specificity at S-phase by inhibiting DNA synthesis by an as of yet unspecified mechanism. Mercaptopurine is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia. A useful mercaptopurine analog is azathioprine.

10 Thioguanine, 2-amino-1,7-dihydro-6H-purine-6-thione, is commercially available as TABLOID®. Thioguanine exhibits cell phase specificity at S-phase by inhibiting DNA synthesis by an as of yet unspecified mechanism. Thioguanine is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia. Other purine analogs include pentostatin, erythrohydroxynonyladenine, fludarabine phosphate, and cladribine.

15 Gemcitabine, 2'-deoxy-2', 2'-difluorocytidine monohydrochloride (β -isomer), is commercially available as GEMZAR®. Gemcitabine exhibits cell phase specificity at S-phase and by blocking progression of cells through the G1/S boundary. Gemcitabine is indicated in combination with cisplatin in the treatment of locally advanced non-small cell lung cancer and alone in the treatment of locally advanced pancreatic cancer.

20 Methotrexate, N-[4[[[2,4-diamino-6-pteridiny] methyl]methylamino] benzoyl]-L-glutamic acid, is commercially available as methotrexate sodium. Methotrexate exhibits cell phase effects specifically at S-phase by inhibiting DNA synthesis, repair and/or replication through the inhibition of dihydrofolic acid reductase which is required for synthesis of purine nucleotides and thymidylate. Methotrexate is indicated as a single agent or in combination with other chemotherapy agents in the treatment of choriocarcinoma, meningeal leukemia, non-Hodgkin's lymphoma, and carcinomas of the breast, head, neck, ovary and bladder.

Topoisomerase I inhibitors:

30 Camptothecins, including, camptothecin and camptothecin derivatives are available or under development as Topoisomerase I inhibitors. Camptothecins cytotoxic activity is believed to be related to its Topoisomerase I inhibitory activity. Examples of camptothecins include, but are

not limited to irinotecan, topotecan, and the various optical forms of 7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20-camptothecin described below.

Irinotecan HCl, (4S)-4,11-diethyl-4-hydroxy-9-[(4-piperidinopiperidino) carbonyloxy]-1H-pyrano[3',4',6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione hydrochloride, is commercially available as the injectable solution CAMPTOSAR®. Irinotecan is a derivative of camptothecin which binds, along with its active metabolite SN-38, to the topoisomerase I – DNA complex. It is believed that cytotoxicity occurs as a result of irreparable double strand breaks caused by interaction of the topoisomerase I : DNA : irinotecan or SN-38 ternary complex with replication enzymes. Irinotecan is indicated for treatment of metastatic cancer of the colon or rectum.

Topotecan HCl, (S)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1H-pyrano[3',4',6,7]indolizino[1,2-b]quinoline-3,14-(4H,12H)-dione monohydrochloride, is commercially available as the injectable solution HYCAMTIN®. Topotecan is a derivative of camptothecin which binds to the topoisomerase I – DNA complex and prevents religation of single strand breaks caused by Topoisomerase I in response to torsional strain of the DNA molecule. Topotecan is indicated for second line treatment of metastatic carcinoma of the ovary and small cell lung cancer.

20 Hormones and hormonal analogues:

Hormones and hormonal analogues are useful compounds for treating cancers in which there is a relationship between the hormone(s) and growth and/or lack of growth of the cancer. Examples of hormones and hormonal analogues useful in cancer treatment include, but are not limited to, adrenocorticosteroids such as prednisone and prednisolone which are useful in the treatment of malignant lymphoma and acute leukemia in children ; aminoglutethimide and other aromatase inhibitors such as anastrozole, letrozole, vorazole, and exemestane useful in the treatment of adrenocortical carcinoma and hormone dependent breast carcinoma containing estrogen receptors; progestins such as megestrol acetate useful in the treatment of hormone dependent breast cancer and endometrial carcinoma; estrogens, estrogens, and anti-estrogens such as fulvestrant, flutamide, nilutamide, bicalutamide, cyproterone acetate and 5 α -reductases such as finasteride and dutasteride, useful in the treatment of prostatic carcinoma and benign prostatic

hypertrophy; anti-estrogens such as tamoxifen, toremifene, raloxifene, droloxifene, idoxifene, as well as selective estrogen receptor modulators (SERMS) such those described in U.S. Patent Nos. 5,681,835, 5,877,219, and 6,207,716, useful in the treatment of hormone dependent breast carcinoma and other susceptible cancers; and gonadotropin-releasing hormone (GnRH) and analogues thereof which stimulate the release of leutinizing hormone (LH) and/or follicle stimulating hormone (FSH) for the treatment prostatic carcinoma, for instance, LHRH agonists and antagonists such as goserelin acetate and luprolide.

Signal transduction pathway inhibitors:

Signal transduction pathway inhibitors are those inhibitors, which block or inhibit a chemical process which evokes an intracellular change. As used herein this change is cell proliferation or differentiation. Signal transduction inhibitors useful in the present invention include inhibitors of receptor tyrosine kinases, non-receptor tyrosine kinases, SH2/SH3 domain blockers, serine/threonine kinases, phosphatidylinositol-3 kinases, myo-inositol signaling, and Ras oncogenes.

Several protein tyrosine kinases catalyse the phosphorylation of specific tyrosyl residues in various proteins involved in the regulation of cell growth. Such protein tyrosine kinases can be broadly classified as receptor or non-receptor kinases.

Receptor tyrosine kinases are transmembrane proteins having an extracellular ligand binding domain, a transmembrane domain, and a tyrosine kinase domain. Receptor tyrosine kinases are involved in the regulation of cell growth and are generally termed growth factor receptors. Inappropriate or uncontrolled activation of many of these kinases, i.e. aberrant kinase growth factor receptor activity, for example by over-expression or mutation, has been shown to result in uncontrolled cell growth. Accordingly, the aberrant activity of such kinases has been linked to malignant tissue growth. Consequently, inhibitors of such kinases could provide cancer treatment methods. Growth factor receptors include, for example, epidermal growth factor receptor (EGFr), platelet derived growth factor receptor (PDGFr), erbB2, erbB4, ret, vascular endothelial growth factor receptor (VEGFr), tyrosine kinase with immunoglobulin-like and epidermal growth factor homology domains (TIE-2), insulin growth factor -I (IGFI) receptor,

macrophage colony stimulating factor (cfms), BTK, ckit, cmet, fibroblast growth factor (FGF) receptors, Trk receptors (TrkA, TrkB, and TrkC), ephrin (eph) receptors, and the RET protooncogene. Several inhibitors of growth receptors are under development and include ligand antagonists, antibodies, tyrosine kinase inhibitors and anti-sense oligonucleotides. Growth factor
5 receptors and agents that inhibit growth factor receptor function are described, for instance, in Kath, John C., *Exp. Opin. Ther. Patents* (2000) 10(6):803-818; Shawver et al *DDT* Vol 2, No. 2 February 1997; and Lofts, F. J. et al, "Growth factor receptors as targets", *New Molecular Targets for Cancer Chemotherapy*, ed. Workman, Paul and Kerr, David, CRC press 1994, London.

10 Tyrosine kinases, which are not growth factor receptor kinases are termed non-receptor tyrosine kinases. Non-receptor tyrosine kinases useful in the present invention, which are targets or potential targets of anti-cancer drugs, include cSrc, Lck, Fyn, Yes, Jak, cAbl, FAK (Focal adhesion kinase), Brutons tyrosine kinase, and Bcr-Abl. Such non-receptor kinases and agents which inhibit non-receptor tyrosine kinase function are described in Sinh, S. and Corey, S.J., (1999) *Journal of Hematotherapy and Stem Cell Research* 8 (5): 465 – 80; and Bolen, J.B., Brugge, J.S., (1997) *Annual review of Immunology*. 15: 371-404.
15

SH2/SH3 domain blockers are agents that disrupt SH2 or SH3 domain binding in a variety of enzymes or adaptor proteins including, PI3-K p85 subunit, Src family kinases, adaptor molecules
20 (Shc, Crk, Nck, Grb2) and Ras-GAP. SH2/SH3 domains as targets for anti-cancer drugs are discussed in Smithgall, T.E. (1995), *Journal of Pharmacological and Toxicological Methods*. 34(3) 125-32.

Inhibitors of Serine/Threonine Kinases including MAP kinase cascade blockers which
25 include blockers of Raf kinases (rafk), Mitogen or Extracellular Regulated Kinase (MEKs), and Extracellular Regulated Kinases (ERKs); and Protein kinase C family member blockers including blockers of PKCs (alpha, beta, gamma, epsilon, mu, lambda, iota, zeta). Ikb kinase family (IKKa, IKKb), PKB family kinases, akt kinase family members, and TGF beta receptor kinases. Such Serine/Threonine kinases and inhibitors thereof are described in Yamamoto, T., Taya, S., Kaibuchi, K., (1999), *Journal of Biochemistry*. 126 (5) 799-803; Brodt, P, Samani, A., and Navab, R. (2000), *Biochemical Pharmacology*, 60. 1101-1107; Massague, J., Weis-Garcia, F. (1996) *Cancer Surveys*.
30

27:41-64; Philip, P.A., and Harris, A.L. (1995), *Cancer Treatment and Research*. 78: 3-27, Lackey, K. et al *Bioorganic and Medicinal Chemistry Letters*, (10), 2000, 223-226; U.S. Patent No. 6,268,391; and Martinez-Iacaci, L., et al, *Int. J. Cancer* (2000), 88(1), 44-52.

5 Inhibitors of Phosphatidylinositol-3 Kinase family members including blockers of PI3-kinase, ATM, DNA-PK, and Ku are also useful in the present invention. Such kinases are discussed in Abraham, R.T. (1996), *Current Opinion in Immunology*. 8 (3) 412-8; Canman, C.E., Lim, D.S. (1998), *Oncogene* 17 (25) 3301-3308; Jackson, S.P. (1997), *International Journal of Biochemistry and Cell Biology*. 29 (7):935-8; and Zhong, H. et al, *Cancer res*, (2000) 60(6), 1541-1545.

10 Also useful in the present invention are Myo-inositol signaling inhibitors such as phospholipase C blockers and Myo-inositol analogues. Such signal inhibitors are described in Powis, G., and Kozikowski A., (1994) *New Molecular Targets for Cancer Chemotherapy* ed., Paul Workman and David Kerr, CRC press 1994, London.

15 Another group of signal transduction pathway inhibitors are inhibitors of Ras Oncogene. Such inhibitors include inhibitors of farnesyltransferase, geranyl-geranyl transferase, and CAAX proteases as well as anti-sense oligonucleotides, ribozymes and immunotherapy. Such inhibitors have been shown to block ras activation in cells containing wild type mutant ras, thereby acting as antiproliferation agents. Ras oncogene inhibition is discussed in Scharovsky, O.G., Rozados, V.R., Gervasoni, S.I. Matar, P. (2000), *Journal of Biomedical Science*. 7(4) 292-8; Ashby, M.N. (1998), *Current Opinion in Lipidology*. 9 (2) 99 – 102; and *Biochim. Biophys. Acta*, (1989) 1423(3):19-30.

25 As mentioned above, antibody antagonists to receptor kinase ligand binding may also serve as signal transduction inhibitors. This group of signal transduction pathway inhibitors includes the use of humanized antibodies to the extracellular ligand binding domain of receptor tyrosine kinases. For example Imclone C225 EGFR specific antibody (see Green, M.C. et al, *Monoclonal Antibody Therapy for Solid Tumors*, *Cancer Treat. Rev.*, (2000), 26(4), 269-286); Herceptin ® erbb2 antibody (see *Tyrosine Kinase Signalling in Breast cancer:erbB Family Receptor Tyrosine Kinases*, *Breast cancer Res.*, 2000, 2(3), 176-183); and 2CB VEGFR2 specific antibody (see Brekken,

R.A. et al, Selective Inhibition of VEGFR2 Activity by a monoclonal Anti-VEGF antibody blocks tumor growth in mice, Cancer Res. (2000) 60, 5117-5124).

Anti-angiogenic agents:

- 5 (i) Anti-angiogenic agents including non-receptor MEK angiogenesis inhibitors may also be useful. Anti-angiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, (for example the anti-vascular endothelial cell growth factor antibody bevacizumab [Avastin™], and compounds that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v \beta 3$ function, endostatin and angiostatin);

10

Immunotherapeutic agents:

- Agents used in immunotherapeutic regimens may also be useful in combination with the compounds of formula (I). Immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies

15

Proapoptotic agents:

Agents used in proapoptotic regimens (e.g., bcl-2 antisense oligonucleotides) may also be used in the combination of the present invention.

20

Cell cycle signalling inhibitors

- 25 Cell cycle signalling inhibitors inhibit molecules involved in the control of the cell cycle. A family of protein kinases called cyclin dependent kinases (CDKs) and their interaction with a family of proteins termed cyclins controls progression through the eukaryotic cell cycle. The coordinate activation and inactivation of different cyclin/CDK complexes is necessary for normal progression

through the cell cycle. Several inhibitors of cell cycle signalling are under development. For instance, examples of cyclin dependent kinases, including CDK2, CDK4, and CDK6 and inhibitors for the same are described in, for instance, Rosania et al, Exp. Opin. Ther. Patents (2000) 10(2):215-230.

5

In one embodiment, the combination of the present invention comprises a compound of formula I or a salt or solvate thereof and at least one anti-neoplastic agent selected from anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase II inhibitors, antimetabolites, topoisomerase I inhibitors, hormones and hormonal analogues, signal transduction pathway inhibitors, non-receptor tyrosine MEK angiogenesis inhibitors, immunotherapeutic agents, proapoptotic agents, and cell cycle signaling inhibitors.

10

In one embodiment, the combination of the present invention comprises a compound of formula I or a salt or solvate thereof and at least one anti-neoplastic agent which is an anti-microtubule agent selected from diterpenoids and vinca alkaloids.

15

In a further embodiment, at least one anti-neoplastic agent is a diterpenoid.

In a further embodiment, at least one anti-neoplastic agent is a vinca alkaloid.

In one embodiment, the combination of the present invention comprises a compound of formula I or a salt or solvate thereof and at least one anti-neoplastic agent, which is a platinum coordination complex.

20

In a further embodiment, at least one anti-neoplastic agent is paclitaxel, carboplatin, or vinorelbine.

In a further embodiment, at least one anti-neoplastic agent is carboplatin.

In a further embodiment, at least one anti-neoplastic agent is vinorelbine.

In a further embodiment, at least one anti-neoplastic agent is paclitaxel.

25

In one embodiment, the combination of the present invention comprises a compound of formula I and salts or solvates thereof and at least one anti-neoplastic agent which is a signal transduction pathway inhibitor.

In a further embodiment the signal transduction pathway inhibitor is an inhibitor of a growth factor receptor kinase VEGFR2, TIE2, PDGFR, BTK, erbB2, EGFr, IGFR-1, TrkA, TrkB, TrkC, or c-fms.

In a further embodiment the signal transduction pathway inhibitor is an inhibitor of a serine/threonine kinase rafk, akt, or PKC-zeta.

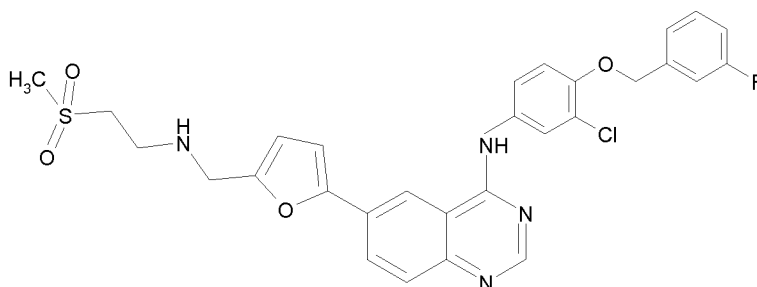
In a further embodiment the signal transduction pathway inhibitor is an inhibitor of a non-receptor tyrosine kinase selected from the src family of kinases.

In a further embodiment the signal transduction pathway inhibitor is an inhibitor of c-src.

In a further embodiment the signal transduction pathway inhibitor is an inhibitor of Ras oncogene selected from inhibitors of farnesyl transferase and geranylgeranyl transferase.

In a further embodiment the signal transduction pathway inhibitor is an inhibitor of a serine/threonine kinase selected from the group consisting of PI3K.

In a further embodiment the signal transduction pathway inhibitor is a dual EGFr/erbB2 inhibitor, for example N-{3-Chloro-4-[(3-fluorobenzyl) oxy]phenyl}-6-[5-([2-(methanesulphonyl) ethyl]amino)methyl]-2-furyl]-4-quinazolinamine (structure below):



In one embodiment, the combination of the present invention comprises a compound of formula I or a salt or solvate thereof and at least one anti-neoplastic agent which is a cell cycle signaling inhibitor.

In further embodiment, cell cycle signaling inhibitor is an inhibitor of CDK2, CDK4 or CDK6.

Particular components of combination therapy include combinations with other anti-estrogens including tamoxifen and /or fulvestrant.

In one embodiment the mammal in the methods and uses of the present invention is a human.

General Synthetic Methods

Compounds of general formula (I) may be prepared by methods known in the art of organic synthesis as set forth in the specific Examples described below. In all of the methods, it is well understood that protecting groups for sensitive or reactive groups may be employed where necessary in accordance with general principles of chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Green and P. G. M. Wuts (1999) Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection of processes as well as the reaction conditions and order of their execution shall be consistent with the preparation of compounds of Formula (I).

Experimental

Abbreviations:

DCM: dichloromethane.

DIPEA: *N,N*-diisopropylethylamine.

DMF: *N,N*-dimethylformamide.

h: hour.

HATU: 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate.

HPLC: high-performance liquid chromatography.

LCMS: liquid chromatography-mass spectrometry

Min: minutes.

NMR: Nuclear magnetic resonance.

RT: retention time.

*t*Bu: *tert*-butoxide.

TFA: trifluoroacetic acid.

THF: tetrahydrofuran.

LCMS Method :

The analysis was conducted on an Acquity UPLC BEH C18 column (50mm x 2.1mm internal diameter 1.7µm packing diameter) at 40°C.

The solvents employed were:

5

A = 0.1% v/v solution of formic acid in water.

B = 0.1% v/v solution of formic acid in acetonitrile.

The gradient employed was as follows:

10

Time (minutes)	Flow Rate (mL/min)	% A	% B
0	1	97	3
1.5	1	0	100
1.9	1	0	100
2.0	1	97	3

The UV detection was an averaged signal from wavelength of 210nm to 350nm and mass spectra were recorded on a mass spectrometer using alternate-scan positive and negative mode electrospray ionization.

15

The following illustrates the mobile phases and gradients used when compounds underwent purification by mass-directed autopreparative HPLC.

Mass-Directed Autopreparative HPLC (Formic Acid Modifier)

20

The HPLC analysis was conducted on a Sunfire C18 column (150mm x 30mm internal diameter, 5µm packing diameter) at ambient temperature.

The solvents employed were:

25

A = 0.1% v/v solution of formic acid in water.

B = 0.1% v/v solution of formic acid in acetonitrile.

Mass-Directed Autopreparative HPLC (Trifluoroacetic Acid Modifier)

- 5 The HPLC analysis was conducted on a Sunfire C18 column (150mm x 30mm internal diameter, 5µm packing diameter) at ambient temperature.

The solvents employed were:

- 10 A = 0.1% v/v solution of trifluoroacetic acid in water.
B = 0.1% v/v solution of trifluoroacetic acid in acetonitrile.

Mass-Directed Autopreparative HPLC (Ammonium Bicarbonate Modifier)

- 15 The HPLC analysis was conducted on an XBridge C18 column (150mm x 30mm internal diameter, 5µm packing diameter) at ambient temperature.

The solvents employed were:

- 20 A = 10 mM ammonium bicarbonate in water adjusted to pH 10 with ammonia solution.
B = acetonitrile.

- For each of the mass-directed autopreparative purifications, irrespective of the modifier used, the
25 gradient employed was dependent upon the retention time of the particular compound undergoing purification as recorded in the analytical LCMS, and was as follows:

For compounds with an analytical LCMS retention time below 0.6 minutes the following gradient was used:

30

Time (minutes)	Flow Rate (mL/min)	% A	% B
0	40	99	1

1	40	99	1
10	40	70	30
11	40	1	99
15	40	1	99

For compounds with an analytical LCMS retention time between 0.6 and 0.9 minutes the following gradient was used:

Time (minutes)	Flow Rate (mL/min)	% A	% B
0	40	85	15
1	40	85	15
10	40	45	55
11	40	1	99
15	40	1	99

5

For compounds with an analytical LCMS retention time between 0.9 and 1.2 minutes the following gradient was used:

Time (minutes)	Flow Rate (mL/min)	% A	% B
0	40	70	30
1	40	70	30
10	40	15	85
11	40	1	99
15	40	1	99

10 For compounds with an analytical LCMS retention time between 1.2 and 1.4 minutes the following gradient was used:

Time (minutes)	Flow Rate (mL/min)	% A	% B
---------------------------	-------------------------------	------------	------------

0	40	50	50
1	40	50	50
10	40	1	99
11	40	1	99
15	40	1	99

For compounds with an analytical LCMS retention time greater than 1.4 minutes (LCMS method A) or greater than 3.6 minutes (LCMS method B) the following gradient was used:

Time (minutes)	Flow Rate (mL/min)	% A	% B
0	40	20	80
1	40	20	80
10	40	1	99
11	40	1	99
15	40	1	99

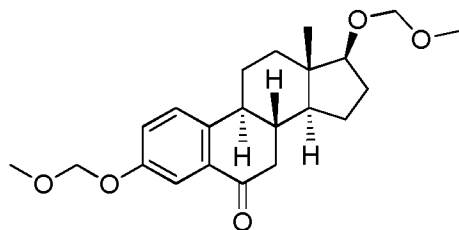
5

The UV detection was an averaged signal from wavelength of 210nm to 350nm and mass spectra were recorded on a mass spectrometer using alternate-scan positive and negative mode electrospray ionization.

10

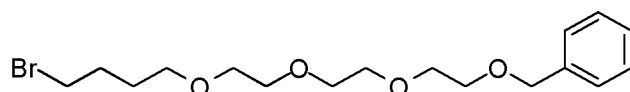
The chemical names were generated using ACD Name Pro version 6.02 from Advanced Chemistry Development, Inc.

15



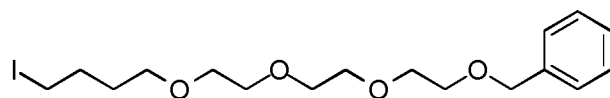
(8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-6-one can be prepared according to the process described by Xiang-Rong Jiang, J. Walter Sowell, Bao Ting Zhu, *Steroids*, **2006**, 71, 334-342. (doi:10.1016/j.steroids.2005.11.008).

5 **15-Bromo-1-phenyl-2,5,8,11-tetraoxapentadecane**



To a suspension of sodium hydride, 60 % w/w in mineral oil (0.250 g, 6.24 mmol) in DMF (2 mL) was added a solution of 2-(2-(2-(benzyloxy)ethoxy)ethoxy)ethanol (1 g, 4.16 mmol) (commercially available from for example Fluorochem) in DMF (2 mL) at 0 °C. After stirring for 25 minutes, 1,4-dibromobutane (commercially available from for example Aldrich) (4.04 g, 18.73 mmol) dissolved in DMF (2 mL) was added dropwise to the mixture. The reaction was stirred under an atmosphere of nitrogen for 2.5 hours. A further aliquot of sodium hydride, 60 % w/w in mineral oil (0.250 g, 6.24 mmol) was added and the reaction was stirred at 0 °C for 30 minutes. The reaction was warmed to room temperature and stirred for 30 minutes. A final aliquot of sodium hydride, 60 % w/w in mineral oil (0.250 g, 6.24 mmol) was added and the reaction stirred at room temperature for 2 hours then left standing over the weekend. The reaction mixture was filtered through celite and the solid washed with DCM. The filtrate was partitioned between DCM (30 mL) and water (30 mL). The organic extract was washed with brine (2 x 30 mL), dried using a hydrophobic frit and concentrated under reduced pressure. The product was purified by chromatography on silica using a gradient elution from 0% to 100% methyl *tert*-butyl ether in cyclohexane to afford *the title compound* (711 mg, 1.89 mmol, 46% yield). LCMS RT= 1.16 min, ES+ve *m/z* 375.2/377.1 [M+H]⁺.

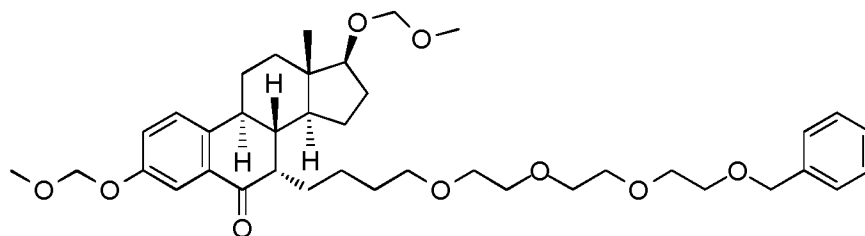
15-Iodo-1-phenyl-2,5,8,11-tetraoxapentadecane



A mixture of 15-bromo-1-phenyl-2,5,8,11-tetraoxapentadecane (711 mg, 1.894 mmol) and sodium iodide (568 mg, 3.79 mmol) in acetone (10 mL) was heated under reflux conditions for 4 hours. The reaction was cooled to room temperature. The mixture was filtered through celite and the solid washed with acetone. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (30 mL) and washed with water (30 mL) and brine (2 x 30 mL). The organic extract

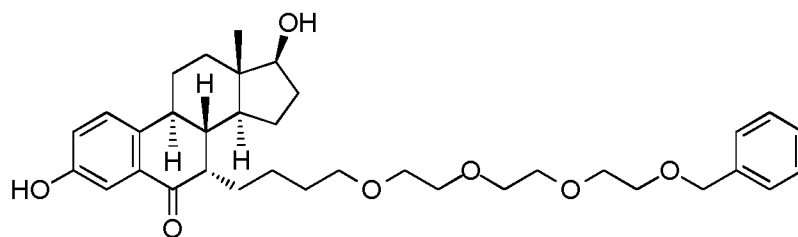
was dried using a hydrophobic frit and concentrated under reduced pressure to afford *the title compound* (759 mg, 1.797 mmol, 95% yield). LCMS RT= 1.23 min, ES+ve m/z 440.0 $[M+NH_4]^+$.

(7*S*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-Bis(methoxymethoxy)-13-methyl-7-(1-phenyl-2,5,8,11-tetraoxapentadecan-15-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-6-one



A solution of KOtBu in THF (1M, 1.282 mL, 1.282 mmol) was added to a cooled solution (0 °C) of (8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-6-one (240 mg, 0.641 mmol) in anhydrous THF (2 mL). The reaction mixture was stirred at 0 °C for 45 minutes and then cooled to -78 °C. A solution of 15-iodo-1-phenyl-2,5,8,11-tetraoxapentadecane (789 mg, 1.868 mmol) in THF (1 mL) was added dropwise. The solution was stirred at -78 °C for 2 minutes, allowed to warm to 0 °C and stirred for 1.5 hours at that temperature. The reaction was partitioned between water (30 mL) and ethyl acetate (30 mL). The organic extract was dried using a hydrophobic frit and concentrated under reduced pressure. The product was purified by chromatography on silica using a gradient elution from 0% to 100% ethyl acetate in cyclohexane to afford *the title compound* (234 mg, 0.350 mmol, 55% yield). LCMS RT= 1.48 min, ES+ve m/z 669.3 $[M+H]^+$, 686.4 $[M+NH_4]^+$.

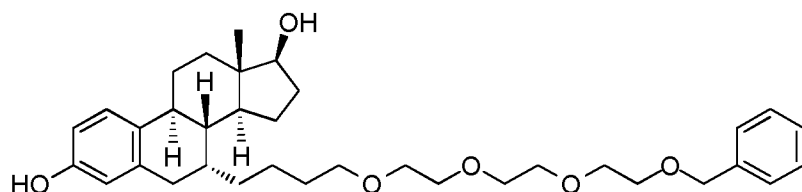
(7*S*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-Dihydroxy-13-methyl-7-(1-phenyl-2,5,8,11-tetraoxapentadecan-15-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-6-one



A solution of aqueous HCl (6M, 2.3 mL, 13.80 mmol) was added to a solution of (7*S*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(methoxymethoxy)-13-methyl-7-(1-phenyl-2,5,8,11-

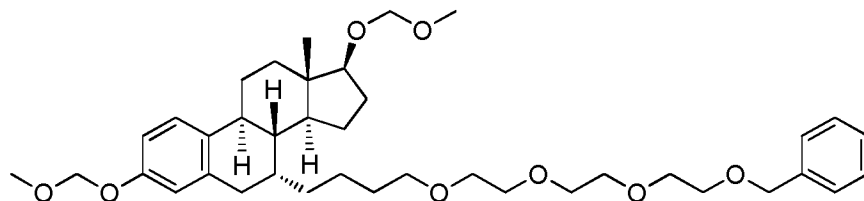
tetraoxapentadecan-15-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-6-one (234 mg, 0.350 mmol) in THF (2.3 mL). The reaction mixture was stirred at room temperature for 16 hours. Water (30 mL) was added and the product was extracted with ethyl acetate (50 mL). The organic extract was washed with brine (2 x 30 mL), dried using a hydrophobic frit and concentrated under reduced pressure to afford *the title compound* (200 mg, 0.344 mmol, 98% yield). LCMS RT= 1.07 min, ES+ve m/z 581.3 $[M+H]^+$, 598.3 $[M+NH_4]^+$.

(7R,8R,9S,13S,14S,17S)-13-Methyl-7-(1-phenyl-2,5,8,11-tetraoxapentadecan-15-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3,17-diol



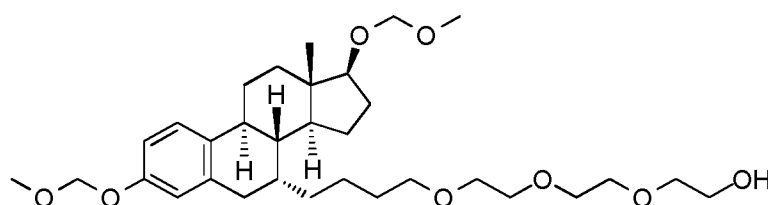
Triethylsilane (commercially available from for example Aldrich) (0.550 mL, 3.44 mmol) was added to a solution of (7S,8R,9S,13S,14S,17S)-3,17-dihydroxy-13-methyl-7-(1-phenyl-2,5,8,11-tetraoxapentadecan-15-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-6-one (200 mg, 0.344 mmol) in TFA (2 mL, 26.0 mmol). The reaction was stirred at room temperature under an atmosphere of nitrogen for 16 hours. The mixture was partitioned between ethyl acetate (30 mL) and brine (30 mL). The organic extract was washed with brine (2 x 30 mL), dried using a hydrophobic frit and concentrated under reduced pressure. The residue was dissolved in MeOH (5 mL) and treated with aqueous NaOH (2M, 5 mL, 10.00 mmol). The reaction mixture was stirred at room temperature for 3 hours. The solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate (30 mL) and a 10 % citric acid solution (30 mL). The organic extract was washed with brine (30 mL), dried using a hydrophobic frit and concentrated under reduced pressure. The product was purified by reverse phase chromatography using a gradient elution from 5% to 95% acetonitrile (+ 0.1% formic acid) in water (+ 0.1% formic acid) to afford *the title compound* (150 mg, 0.265 mmol, 77% yield). LCMS RT= 1.18 min, ES+ve m/z 567.3 $[M+H]^+$, 584.3 $[M+NH_4]^+$.

15-((7R,8R,9S,13S,14S,17S)-3,17-Bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)-1-phenyl-

2,5,8,11-tetraoxapentadecane

A vial was charged with (7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-13-methyl-7-(1-phenyl-2,5,8,11-tetraoxapentadecan-15-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol (150 mg, 0.265 mmol) and DIPEA (0.555 mL, 3.18 mmol) in THF (10 mL). The vial was sealed, the solution was cooled to 0 °C and chloro(methoxy)methane (commercially available from for example Aldrich) (0.2 mL, 2.63 mmol) was added. The reaction mixture was warmed to room temperature, stirred for 1 hour and heated at 70 °C for 40 hours. The reaction was cooled to room temperature. The reaction was partitioned between ethyl acetate (100 mL) and water (100 mL). The organic extract was washed with brine (2 x 50 mL), dried using a hydrophobic frit and concentrated under reduced pressure. The product was purified by chromatography on silica using a gradient elution from 0% to 100% methyl *tert*-butyl ether in cyclohexane to afford *the title compound* (122 mg, 0.186 mmol, 70% yield). LCMS RT= 1.60 min, ES+ve *m/z* 672.5 [*M*+NH₄]⁺.

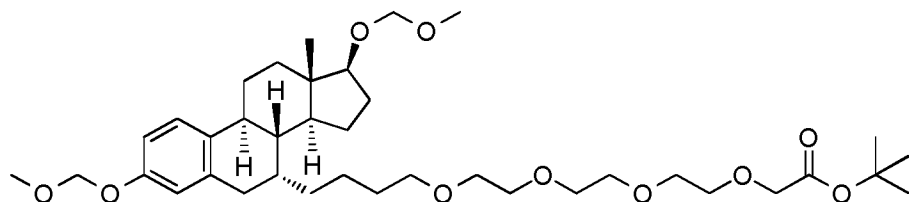
2-(2-(2-(4-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-Bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)butoxy)ethoxy)ethoxy)ethanol



A mixture of 15-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-1-phenyl-2,5,8,11-tetraoxapentadecane (115 mg, 0.176 mmol) and 10 % w/w palladium on carbon (100 mg, 0.094 mmol) in ethanol (4 mL) was stirred at room temperature under an atmosphere of hydrogen for 1.5 hours. The palladium on carbon was filtered through celite and the filtrate evaporated under reduced pressure. The residue was partitioned between ethyl acetate (15 mL) and brine (15 mL). The organic extract was dried using a hydrophobic frit and concentrated under reduced pressure to

afford *the title compound* (81 mg, 0.143 mmol, 82% yield). LCMS RT= 1.36 min, ES+ve m/z 582.4 $[M+NH_4]^+$.

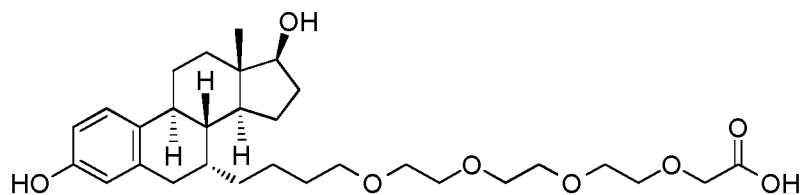
***Tert*-butyl 16-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-3,6,9,12-tetraoxahexadecan-1-oate**



Sodium hydride, 60 % w/w in mineral oil (10 mg, 0.250 mmol) was added to a cooled solution (0 °C) of 2-(2-(2-(4-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-

yl)butoxy)ethoxy)ethoxy)ethanol (81 mg, 0.143 mmol) in DMF (2 mL). The reaction was stirred at that temperature for 10 minutes and *tert*-butyl 2-bromoacetate (commercially available from for example Aldrich) (32 μ L, 0.217 mmol) was added. The reaction was stirred at 0 °C for 1 hour and at room temperature for further 2 hours. The reaction mixture was partitioned between ethyl acetate (30 mL) and water (30 mL). The organic layer was washed with brine (30 mL), dried (hydrophobic frit) and concentrated under reduced pressure. The product was purified by chromatography on silica using a gradient elution from 0% to 100% methyl *tert*-butyl ether in cyclohexane to afford *the title compound* (60 mg, 0.088 mmol, 62% yield). LCMS RT= 1.57 min, ES+ve m/z 696.5 $[M+NH_4]^+$.

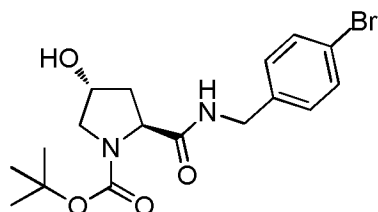
16-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-Dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-3,6,9,12-tetraoxahexadecan-1-oic acid



***Tert*-butyl 16-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-3,6,9,12-tetraoxahexadecan-1-oate** (133 mg, 0.196 mmol) was dissolved in THF (1.5 mL) and treated with aqueous HCl (6M, 1.5 mL, 9.00 mmol). The reaction mixture was stirred at room temperature for 8 hours. The reaction mixture was subjected directly to purification by mass-directed automated

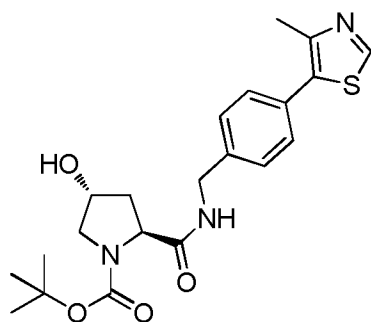
preparative HPLC (formic acid modifier) to afford *the title compound* (60 mg, 0.112 mmol, 57% yield). LCMS RT= 0.89 min, ES+ve m/z 535.3 $[M+H]^+$, 552.3 $[M+NH_4]^+$.

(2*S*,4*R*)-*Tert*-butyl 2-((4-bromobenzyl)carbamoyl)-4-hydroxypyrrolidine-1-carboxylate



- 5 An ice-cooled mixture of (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid (commercially available from for example Aldrich) (7.95 g, 34.4 mmol) and (4-bromophenyl)methanamine (commercially available from for example FluroChem) (6.4 g, 34.4 mmol) in DMF (200 mL) was treated with DIPEA (18.02 mL, 103 mmol) and then with HATU (14.39 g, 37.8 mmol) and the mixture was stirred at ambient temperature for 30 minutes. The reaction
10 was quenched with water (200 mL) and extracted with ethyl acetate (2 x 200 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (2 x 300 mL), water (100 mL), brine (200 mL), dried over magnesium sulphate and evaporated to dryness. The product was purified by chromatography on silica using a gradient elution from 0% to 10% methanol in DCM to afford *the title compound* (12.9 g, 32.3 mmol, 94% yield). LCMS RT= 0.87 min, ES+ve m/z
15 399.2/401.2 $[M+H]^+$.

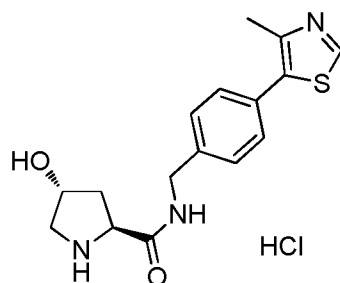
(2*S*,4*R*)-*Tert*-butyl 4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carboxylate



- A mixture of (2*S*,4*R*)-*tert*-butyl 2-((4-bromobenzyl)carbamoyl)-4-hydroxypyrrolidine-1-carboxylate (12.9 g, 32.3 mmol), 4-methylthiazole (commercially available from for example Aldrich) (5.88 mL, 64.6 mmol), palladium(II) acetate (commercially available from for example Aldrich) (0.145 g, 0.646 mmol) and potassium acetate (6.34 g, 64.6 mmol) in *N*-methyl-2-
20

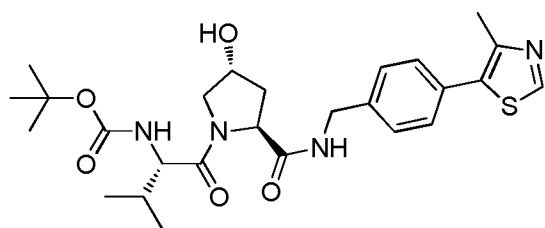
pyrrolidone (80 mL) was stirred at 120 °C under nitrogen for 18 hours. Water (100 ml) was added and the product was extracted with ethyl acetate (4 x 300 mL). The combined organic phase was washed with brine (5 x 200 mL), dried over magnesium sulphate and evaporated to dryness. The product was purified by chromatography on silica using a gradient elution from 0% to 10% methanol in DCM to afford *the title compound* (8 g, 19.2 mmol, 59% yield). LCMS RT= 0.75 min, ES+ve m/z 418.4 [M+H]⁺.

(2*S*,4*R*)-4-Hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide, hydrochloride



(2*S*,4*R*)-*Tert*-butyl 4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carboxylate (8 g, 19.16 mmol) was dissolved in methanol (30 mL) and DCM (20 mL) and treated with HCl in dioxane (4M, 8.08 mL, 32.3 mmol). The reaction mixture was stirred at ambient temperature for 2 hours. The solvent was removed under reduced pressure and the residue was triturated with DCM, filtered and dried under reduced pressure to afford *the title compound* (6.7 g, 18.9 mmol, 99% yield). LCMS RT= 0.49 min, ES+ve m/z 318.3 [M+H]⁺.

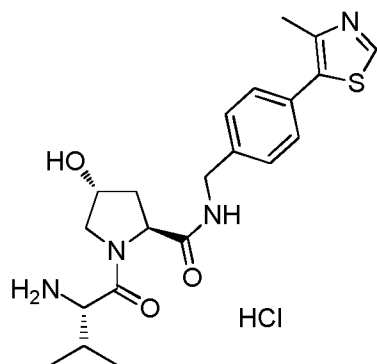
***Tert*-butyl ((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)carbamate**



A stirred mixture of (2*S*,4*R*)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide, hydrochloride (125 mg, 0.35 mmol) and (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanoic acid (commercially available from for example Aldrich) (77 mg, 0.35 mmol) in DMF (0.9 mL) was treated with DIPEA (0.22 mL, 1.3 mmol) and then with HATU (134 mg, 0.35 mmol)

and the mixture was stirred at ambient temperature for 1 hour. The reaction mixture was subjected directly to purification by mass-directed automated preparative HPLC (formic acid modifier) to afford *the title compound* (120 mg, 0.232 mmol, 72% yield). LCMS RT= 0.87 min, ES+ve m/z 517.3 $[M+H]^+$.

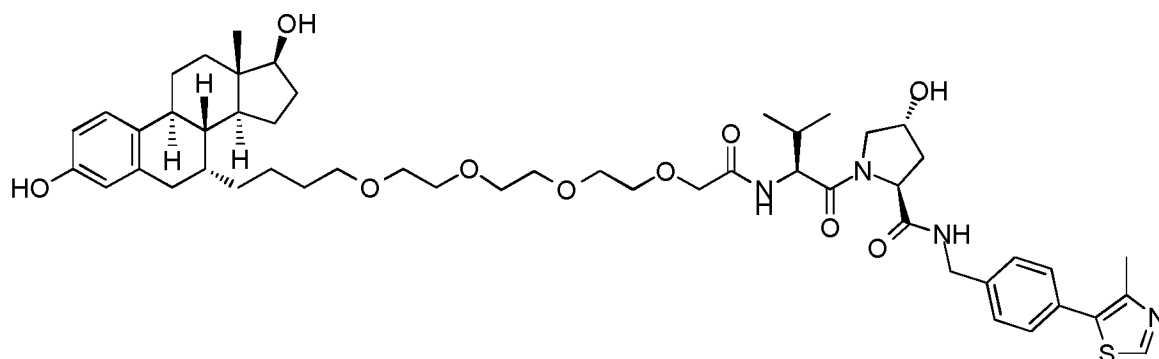
5 **(2*S*,4*R*)-1-((*S*)-2-amino-3-methylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide, hydrochloride**



A solution of *tert*-butyl ((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)carbamate (287 mg, 0.56 mmol) in THF (5 mL) was treated with HCl in 1,4-dioxan (4M, 10 mL, 40 mmol) and stirred at ambient temperature for 2 hours. The mixture was evaporated to dryness to afford *the title compound* (224 mg, 0.49 mmol, quantitative). LCMS RT= 0.55 min, ES+ve m/z 417.3 $[M+H]^+$.

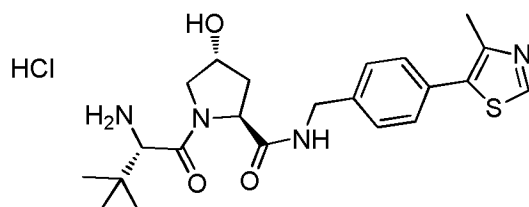
Example 1:

15 **(2*S*,4*R*)-1-((*S*)-19-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-Dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-2-isopropyl-4-oxo-6,9,12,15-tetraoxa-3-azanonadecan-1-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**



HATU (16 mg, 0.042 mmol) was added to a mixture of (2*S*,4*R*)-1-((*S*)-2-amino-3-methylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide, hydrochloride (25 mg, 0.055 mmol), 16-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-3,6,9,12-tetraoxahexadecan-1-oic acid (15 mg, 0.028 mmol) and DIPEA (0.05 mL, 0.286 mmol) in DMF (1 mL). The reaction was stirred at room temperature for 30 minutes. The reaction mixture was subjected directly to purification by mass-directed automated preparative HPLC (formic acid modifier) to afford *the title compound* (20 mg, 0.021 mmol, 76% yield). LCMS RT= 0.99 min, ES+ve *m/z* 933.3 [M+H]⁺.

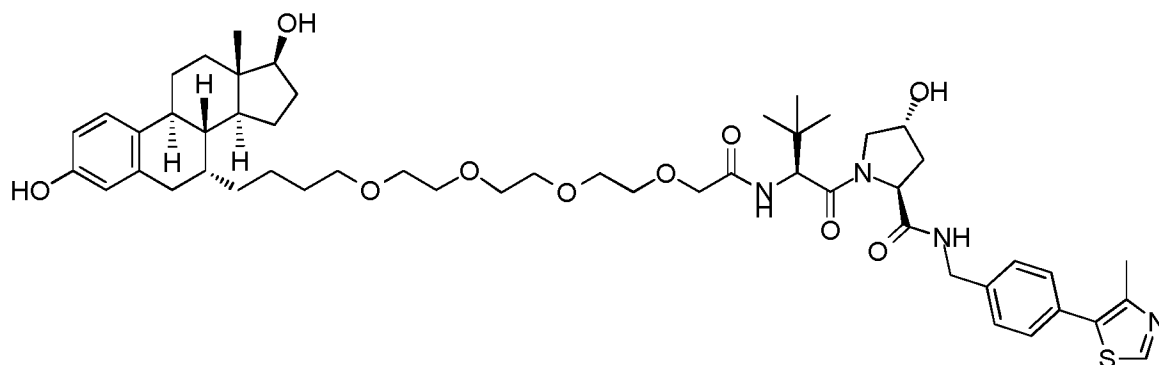
(2*S*,4*R*)-1-((*S*)-2-Amino-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide, hydrochloride



A stirred mixture of (2*S*,4*R*)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide, hydrochloride (70 mg, 0.20 mmol) and (*S*)-2-((*tert*-butoxycarbonyl)amino)-3,3-dimethylbutanoic acid (commercially available from for example Fluka) (50 mg, 0.22 mmol) in DMF (1 mL) was treated with DIPEA (0.14 mL, 0.79 mmol) and then with HATU (90 mg, 0.24 mmol), and stirred at ambient temperature for 30 minutes. The reaction mixture was subjected directly to purification by mass-directed automated preparative HPLC (formic acid modifier) to give the intermediate boc-protected product. The intermediate was then dissolved in a mixture of dichloromethane (0.5 mL) and methanol (0.1 mL) and treated with HCl in 1,4-dioxane (4M, 0.25 mL, 1.0 mmol). After stirring at ambient temperature for 1 hour, the reaction mixture was evaporated to dryness and the residue triturated to a solid with dichloromethane and dried under vacuum to afford *the title compound* (76 mg, 0.163 mmol, 82% yield). LCMS RT= 0.58 min, ES+ve *m/z* 431.2 [M+H]⁺.

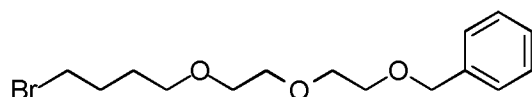
Example 2:

(2*S*,4*R*)-1-((*S*)-2-(*Tert*-butyl)-19-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-4-oxo-6,9,12,15-tetraoxa-3-azanonadecan-1-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



HATU (22 mg, 0.058 mmol) was added to a mixture of (2*S*,4*R*)-1-((*S*)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide, hydrochloride (25 mg, 0.054 mmol), 16-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-3,6,9,12-tetraoxahexadecan-1-oic acid (23 mg, 0.043 mmol) and DIPEA (0.040 mL, 0.229 mmol) in DMF (1 mL). The reaction was stirred at room temperature for 10 minutes. The reaction mixture was subjected directly to purification by mass-directed automated preparative HPLC (formic acid modifier) to afford *the title compound* (26 mg, 0.027 mmol, 64% yield). LCMS RT= 1.02 min, ES+ve *m/z* 947.8 [M+H]⁺.

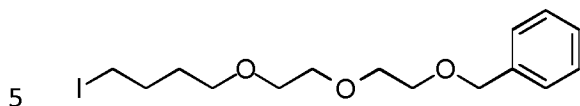
((2-(2-(4-Bromobutoxy)ethoxy)ethoxy)methyl)benzene



To a suspension of sodium hydride, 60 % w/w in mineral oil (0.92 g, 22.9 mmol) in DMF (5 mL) was added a solution of 2-(2-(benzyloxy)ethoxy)ethanol (commercially available from for example Aldrich) (2.74 mL, 15.29 mmol) in DMF (5 mL) at 0 °C. After stirring for 25 min, 1,4-dibromobutane (commercially available from for example Aldrich) (14.9 g, 68.8 mmol) dissolved in DMF (5 mL) was added dropwise to the mixture. The reaction was warmed to ambient temperature and stirred under an atmosphere of nitrogen for 2.5 hours. A further aliquot of sodium hydride, 60 % w/w in mineral oil (0.92 g, 22.9 mmol) was added and the reaction was stirred at 0 °C for 30 minutes and at ambient temperature for 30 minutes. A final aliquot of sodium hydride, 60 % w/w in mineral oil (0.92 g, 22.9 mmol) was added and the reaction stirred at ambient temperature for 2 hours then left standing overnight. The reaction mixture was filtered through celite and the solid washed with DCM. The filtrate was partitioned between DCM (30 mL) and water (30 mL). The organic extract was washed with brine (2 x 30 mL), dried using a hydrophobic frit, and concentrated under

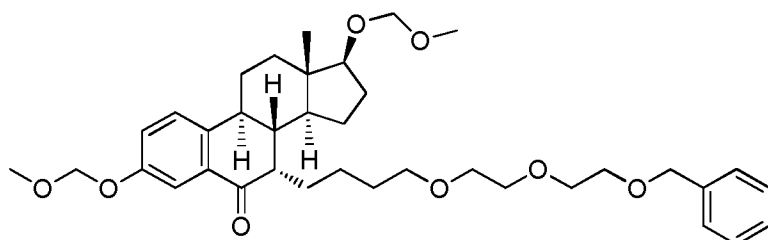
reduced pressure. The product was purified by chromatography on silica using a using a gradient elution from 0% to 80% methyl *tert*-butyl ether in cyclohexane to afford *the title compound* (3 g, 9.06 mmol, 59% yield). LCMS RT= 1.19 min, ES+ve *m/z* 331.2/333.2 [M+H]⁺.

((2-(2-(4-Iodobutoxy)ethoxy)ethoxy)methyl)benzene



A mixture of ((2-(2-(4-bromobutoxy)ethoxy)ethoxy)methyl)benzene (3 g, 9.06 mmol) and sodium iodide (2.72 g, 18.11 mmol) in acetone (10 mL) was heated under reflux conditions for 3 hours. The reaction was cooled to room temperature. The mixture was filtered through celite and the solid washed with acetone. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (30 mL) and washed with water (30 mL) and brine (2 x 30 mL). The organic extract was dried using a hydrophobic frit and concentrated under reduced pressure. The product was purified by chromatography on silica using a using a gradient elution from 0% to 50% methyl *tert*-butyl ether in cyclohexane to afford *the title compound* (3.1 g, 8.2 mmol, 90% yield). LCMS RT= 1.25 min, ES+ve *m/z* 379.2 [M+H]⁺.

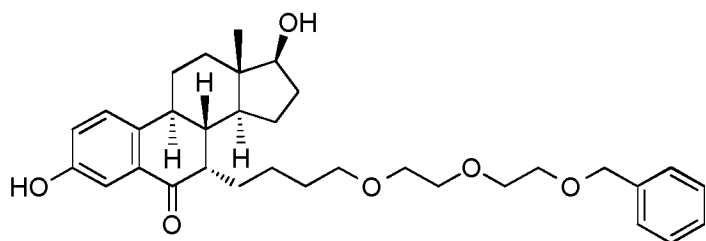
15 **(7S,8R,9S,13S,14S,17S)-7-(4-(2-(2-(Benzyloxy)ethoxy)ethoxy)butyl)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-6-one**



A solution of KOtBu, in THF (1M, 3.2 mL, 3.2 mmol) was added to a cooled solution (0 °C) of (8R,9S,13S,14S,17S)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-6-one (600 mg, 1.6 mmol) in anhydrous THF (6 mL). The reaction mixture was stirred at 0 °C for 45 minutes and then cooled to -78 °C. A solution of ((2-(2-(4-Iodobutoxy)ethoxy)ethoxy)methyl)benzene (910 mg, 2.4 mmol) in THF (3 mL) was added dropwise. The solution was stirred at -78 °C for 2 minutes then allowed to warm to 0 °C and stirred for 1.5 hours at that temperature. The reaction was partitioned between water (30 mL) and ethyl

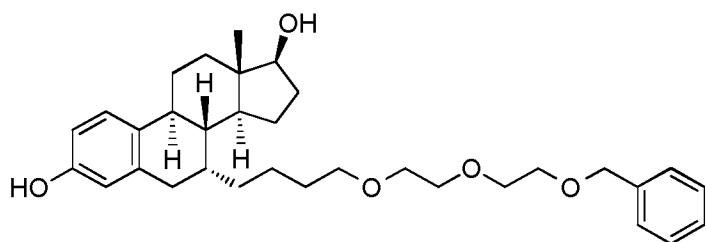
acetate (30 mL). The organic extract was separated, dried using a hydrophobic frit and concentrated under reduced pressure. The product was purified by chromatography on silica using a gradient elution from 0% to 50% ethyl acetate in cyclohexane to afford *the title compound* (450 mg, 0.72 mmol, 45% yield). LCMS RT= 1.49 min, ES+ve m/z 625.5 $[M+H]^+$.

5 **(7*S*,8*R*,9*S*,13*S*,14*S*,17*S*)-7-(4-(2-(2-(Benzyloxy)ethoxy)ethoxy)butyl)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-6-one**



A solution of aqueous HCl (6M, 4.6 mL, 27.6 mmol) was added to a solution of (7*S*,8*R*,9*S*,13*S*,14*S*,17*S*)-7-(4-(2-(2-(benzyloxy)ethoxy)ethoxy)butyl)-3,17-bis(methoxymethoxy)-
 10 13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-6-one (470 mg, 0.752 mmol) in THF (4.6 mL). The reaction mixture was stirred at room temperature for 18 hours. Water (30 mL) was added and the product was extracted with ethyl acetate (50 mL). The organic extract was washed with brine (2 x 30 mL), dried using a hydrophobic frit and concentrated under reduced pressure to afford *the title compound* (390 mg, 0.727 mmol, 97% yield). LCMS RT= 1.08
 15 min, ES+ve m/z 537.2 $[M+H]^+$, 554.2 $[M+NH_4]^+$.

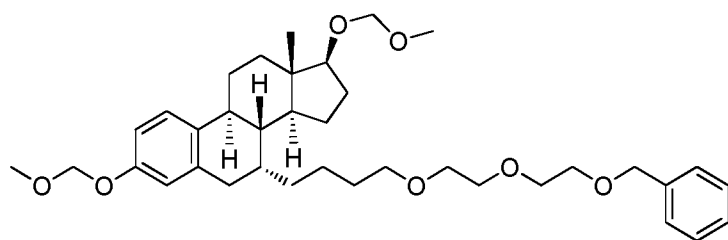
(7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-7-(4-(2-(2-(Benzyloxy)ethoxy)ethoxy)butyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol



Triethylsilane (commercially available from for example Aldrich) 1.161 mL, 7.27 mmol) was added
 20 to a solution of (7*S*,8*R*,9*S*,13*S*,14*S*,17*S*)-7-(4-(2-(2-(benzyloxy)ethoxy)ethoxy)butyl)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-6-one (390 mg, 0.727 mmol) in TFA (4.2 mL, 54.5 mmol). The reaction was stirred at room temperature

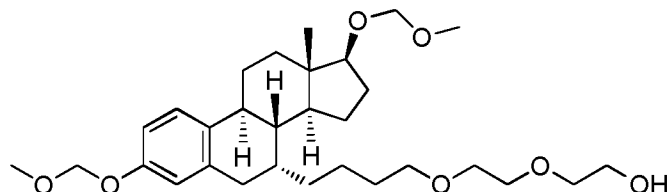
under an atmosphere of nitrogen for 18 hours. The mixture was partitioned between ethyl acetate (50 mL) and brine (50 mL). The organic extract was washed with brine (2 x 30 mL), saturated sodium bicarbonate (30 mL), dried using a hydrophobic frit and concentrated under reduced pressure. The residue was dissolved in MeOH (10 mL) and treated with aqueous NaOH (2M, 5 mL, 10.0 mmol). The reaction mixture was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate (30 mL) and aqueous HCl solution (1M, 20 mL). The organic extract was washed with brine (20 mL), dried using a hydrophobic frit and concentrated under reduced pressure. The product was purified by reverse phase chromatography using a gradient elution from 5% to 95% acetonitrile (+ 0.1% formic acid) in water (+ 0.1% formic acid) to afford *the title compound* (270 mg, 0.517 mmol, 71% yield). LCMS RT= 1.18 min, ES+ve m/z 523.5 $[M+H]^+$, 540.5 $[M+NH_4]^+$.

(7R,8R,9S,13S,14S,17S)-7-(4-(2-(2-(Benzyloxy)ethoxy)ethoxy)butyl)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene



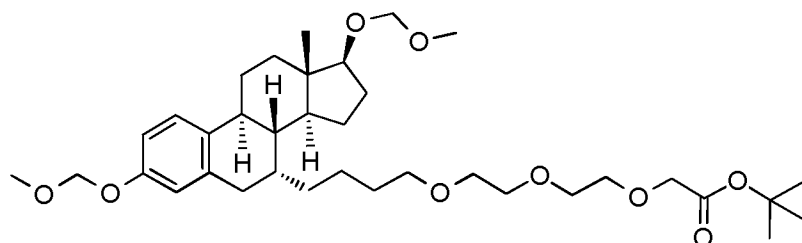
Chloro(methoxy)methane (commercially available from for example Aldrich) (0.390 mL, 5.14 mmol) was added to a cooled (0 °C) solution of (7R,8R,9S,13S,14S,17S)-7-(4-(2-(2-(benzyloxy)ethoxy)ethoxy)butyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3,17-diol (270 mg, 0.517 mmol) and DIPEA (1.083 mL, 6.20 mmol) in THF (16 mL). The reaction mixture was warmed to room temperature, stirred for 1 hour and then heated at 70 °C for 40 hours. The reaction mixture was cooled to 0 °C, additional DIPEA (0.271 mL, 1.550 mmol) and chloro(methoxy)methane (0.098 mL, 1.291 mmol) was added. The reaction was heated to 70 °C and stirred for a further 24 hours. The reaction was cooled to room temperature, and was partitioned between ethyl acetate (100 mL) and water (100 mL). The organic extract was washed with brine (2 x 50 mL), dried using a hydrophobic frit and concentrated under reduced pressure. The product was purified by chromatography on silica using a gradient elution from 0% to 100% methyl *tert*-butyl ether in cyclohexane to afford *the title compound* (220 mg, 0.36 mmol, 70% yield). LCMS RT= 1.62 min, ES+ve m/z 628.6 $[M+NH_4]^+$.

2-(2-(4-((7R,8R,9S,13S,14S,17S)-3,17-Bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)butoxy)ethoxy)ethanol



5 A mixture of (7R,8R,9S,13S,14S,17S)-7-(4-(2-(2-(benzyloxy)ethoxy)ethoxy)butyl)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene (220 mg, 0.36 mmol) and 10 % w/w palladium on carbon (100 mg, 0.094 mmol) in ethanol (4 mL) was stirred at room temperature under an atmosphere of hydrogen for 1 hour. The palladium on carbon was filtered through celite, washed with ethanol (50 ml) and
10 the filtrate was evaporated under reduced pressure to afford *the title compound* (186 mg, 0.357 mmol, 99% yield) LCMS RT= 1.36 min, ES+ve *m/z* 521.5 [M+H]⁺, 538.5 [M+NH₄]⁺.

***Tert*-butyl 2-(2-(2-(4-((7R,8R,9S,13S,14S,17S)-3,17-is(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)butoxy)ethoxy)ethoxy)acetate**

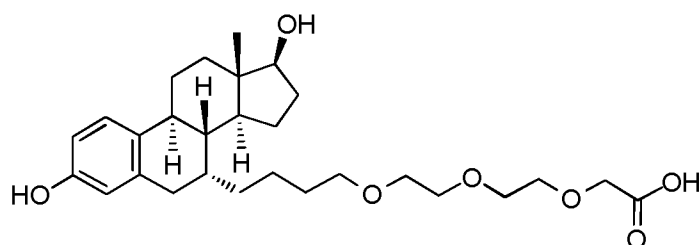


15 Sodium hydride, 60 % w/w mineral oil (25.0 mg, 0.625 mmol) was added to a cooled solution (0 °C) of 2-(2-(4-((7R,8R,9S,13S,14S,17S)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)butoxy)ethoxy)ethanol (186 mg, 0.357 mmol) in DMF (4.5 mL). The reaction was stirred at 0 °C for 10 minutes and *tert*-
20 butyl 2-bromoacetate (commercially available from for example Aldrich) (79 µL, 0.536 mmol) was added. The reaction was stirred at 0 °C for 1 hour and at room temperature for a further 6 hours. The reaction was cooled to 0 °C and additional sodium hydride, 60 % w/w in mineral oil (15.72 mg, 0.393 mmol), followed by *tert*-butyl 2-bromoacetate (0.053 mL, 0.357 mmol) was added. The reaction was stirred at room temperature for a further 18 hours. The reaction mixture was

partitioned between ethyl acetate (30 mL) and water (30 mL). The organic layer separated, washed with brine (30 mL), dried using a hydrophobic frit and concentrated under reduced pressure. The product was purified by chromatography on silica using a gradient elution from 0% to 100% methyl *tert*-butyl ether in cyclohexane to afford *the title compound* (90 mg, 0.142 mmol, 40% yield).

5 LCMS RT= 1.56 min, ES+ve m/z 652.6 $[M+NH_4]^+$, 657.5 $[M+Na]^+$.

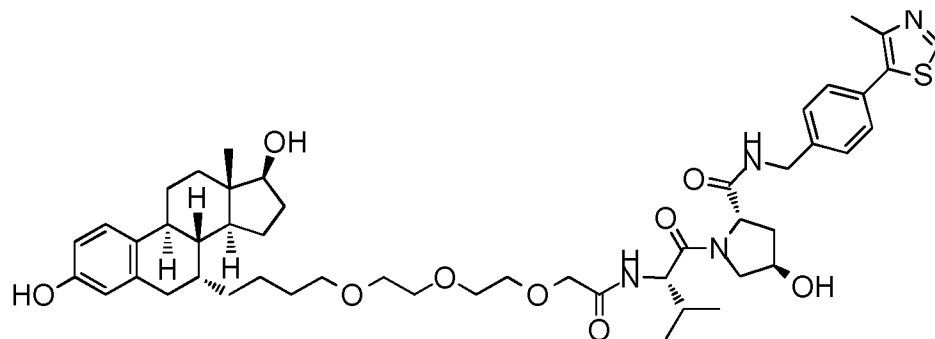
2-(2-(2-(4-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-Dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)butoxy)ethoxy)ethoxy)acetic acid



Tert-butyl 2-(2-(2-(4-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)butoxy)ethoxy)ethoxy)acetate (80 mg, 0.126 mmol) was dissolved in THF (1 mL) and treated with aqueous HCl (6*M*, 1 mL, 6.0 mmol). The reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was subjected directly to purification by mass-directed automated preparative HPLC (formic acid modifier) to afford *the title compound* (23 mg, 0.047 mmol, 37% yield). LCMS RT= 0.89 min, ES+ve m/z 491.4 $[M+H]^+$.

Example 3:

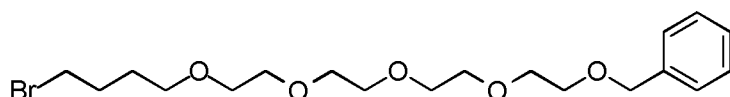
(2*S*,4*R*)-1-((*S*)-16-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-Dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-2-isopropyl-4-oxo-6,9,12-trioxa-3-azahexadecan-1-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



HATU (12 mg, 0.03 mmol) was added to a mixture of (2*S*,4*R*)-1-((*S*)-2-amino-3-methylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide, hydrochloride (23 mg, 0.05 mmol), 2-(2-(2-(4-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-

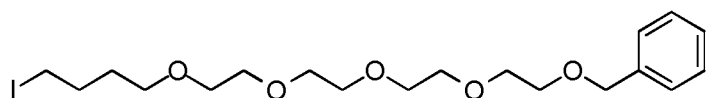
5 yl)butoxy)ethoxy)ethoxy)acetic acid (10 mg, 0.02 mmol) and DIPEA (0.04 mL, 0.20 mmol) in DMF (0.8 mL). The reaction was stirred at room temperature for 30 min. The reaction mixture was subjected directly to purification by mass-directed automated preparative HPLC (formic acid modifier) to afford *the title compound* (15 mg, 0.017 mmol, 84% yield). LCMS RT= 0.98 min, ES+ve *m/z* 889.7 [M+H]⁺.

10 18-Bromo-1-phenyl-2,5,8,11,14-pentaoxaoctadecane



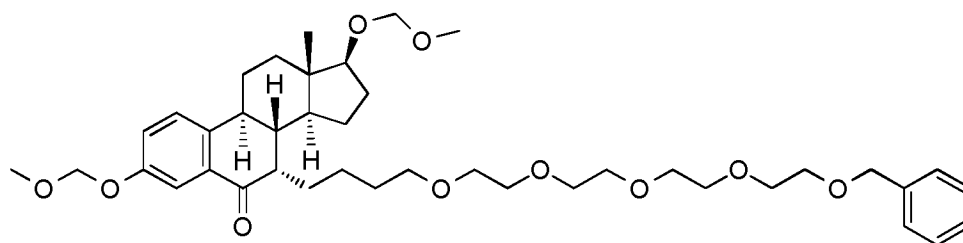
To a suspension of sodium hydride, 60 % w/w in mineral oil (0.85 g, 21.3 mmol) in DMF (8 mL) was added a solution of 1-phenyl-2,5,8,11-tetraoxatridecan-13-ol (commercially available from for example TCI Europe Fine Chemicals) (4.0 g, 14.2 mmol) in DMF (8 mL) at 0 °C. After stirring for 25 minutes, 1,4-dibromobutane (commercially available from for example Aldrich) (7.62 mL, 63.8 mmol) dissolved in DMF (8 mL) was added dropwise to the mixture. The reaction was warmed to room temperature and stirred under an atmosphere of nitrogen for 30 minutes. A further aliquot of sodium hydride, 60 % w/w in mineral oil (0.85 g, 21.3 mmol) was added and the reaction was stirred at room temperature overnight. Another aliquot of sodium hydride, 60 % w/w in mineral oil (0.85 g, 21.3 mmol) was added and the reaction stirred at room temperature for 2 hours. A final aliquot of sodium hydride, 60 % w/w in mineral oil (0.43 g, 10.6 mmol) was added and the reaction stirred at room temperature for 1 hour. The reaction mixture was filtered through celite and the solid washed with DCM. The filtrate was partitioned between DCM (50 mL) and water (50 mL). The organic extract was washed with brine (2 x 50 mL), dried using a hydrophobic frit and concentrated under reduced pressure. The product was purified by chromatography on silica using a gradient elution from 0% to 85% methyl *tert*-butyl ether in cyclohexane to afford *the title compound* (3.93 g, 9.37 mmol, 63% yield). LCMS RT= 1.16 min, ES+ve *m/z* 419.3/421.2 [M+H]⁺.

18-Iodo-1-phenyl-2,5,8,11,14-pentaoxaoctadecane



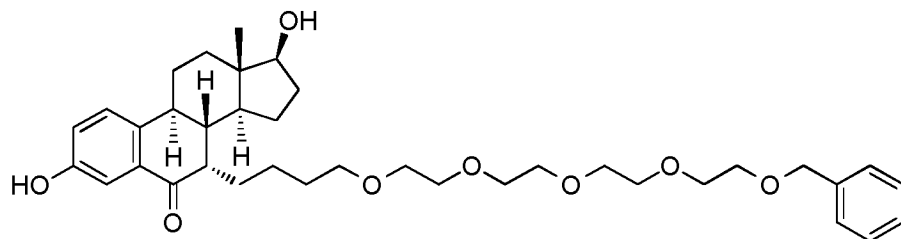
A mixture of 18-bromo-1-phenyl-2,5,8,11,14-pentaoxaoctadecane (2.08 g, 4.91 mmol) and sodium iodide (1.47 g, 9.82 mmol) in acetone (10 mL) was heated under reflux conditions for 3 hours. The reaction was cooled to room temperature, filtered through celite and the solid was washed with acetone. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (30 mL), and washed with water (30 mL) and brine (2 x 30 mL). The organic extract was dried using a hydrophobic frit and concentrated under reduced pressure to afford *the title compound* (759 mg, 1.80 mmol, 95% yield). LCMS RT= 1.21 min, ES+ve m/z 467.0 $[M+H]^+$, 484.0 $[M+NH_4]^+$.

(7S,8R,9S,13S,14S,17S)-3,17-Bis(methoxymethoxy)-13-methyl-7-(1-phenyl-2,5,8,11,14-pentaoxaoctadecan-18-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-6-one



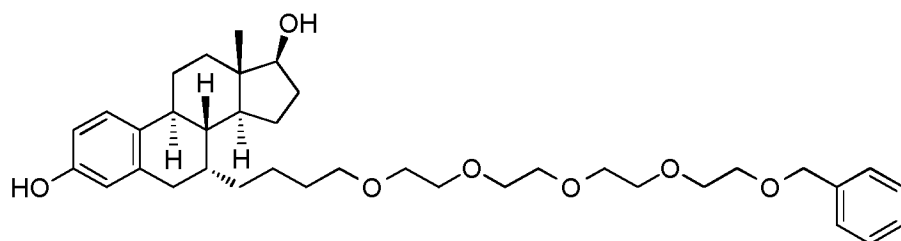
A solution of KO^tBu in THF (1M, 5.34 mL, 5.34 mmol) was added to a cooled solution (0 °C) of (8R,9S,13S,14S,17S)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-6-one (1 g, 2.67 mmol) in anhydrous THF (10 mL). The reaction mixture was stirred at 0 °C for 45 minutes and then cooled to -78 °C. 18-Iodo-1-phenyl-2,5,8,11,14-pentaoxaoctadecane (1.87 g, 4.01 mmol) in THF (5 mL) was added dropwise. The solution was stirred at -78 °C for 2 minutes, allowed to warm to 0 °C and stirred for 1.5 hours at that temperature. The reaction was partitioned between water (50 mL) and ethyl acetate (2 x 50 mL). The organic extracts were dried using a hydrophobic frit and concentrated under reduced pressure. The product was purified by chromatography on silica using a gradient elution from 0% to 100% ethyl acetate in cyclohexane to afford *the title compound* (883 mg, 1.24 mmol, 46% yield). LCMS RT= 1.47 min, ES+ve m/z 713.5 $[M+H]^+$.

(7S,8R,9S,13S,14S,17S)-3,17-Dihydroxy-13-methyl-7-(1-phenyl-2,5,8,11,14-pentaoxaoctadecan-18-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-6-one



A solution of aqueous HCl (6M, 9.2 mL, 55.2 mmol) was added to a solution of (7S,8R,9S,13S,14S,17S)-3,17-bis(methoxymethoxy)-13-methyl-7-(1-phenyl-2,5,8,11,14-pentaoxaoctadecan-18-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-6-one (883 mg, 1.24 mmol) in THF (9.2 mL). The reaction mixture was stirred at room temperature for 18 hours. Water (30 mL) was added and the product was extracted with ethyl acetate (50 mL). The organic extract was washed with brine (2 x 30mL), dried using a hydrophobic frit and concentrated under reduced pressure to afford *the title compound* (772 mg, 1.23 mmol, 99% yield). LCMS RT= 1.06 min, ES+ve m/z 625.3 [M+H]⁺, 642.3 [M+NH₄]⁺.

10 **(7R,8R,9S,13S,14S,17S)-13-Methyl-7-(1-phenyl-2,5,8,11,14-pentaoxaoctadecan-18-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3,17-diol**

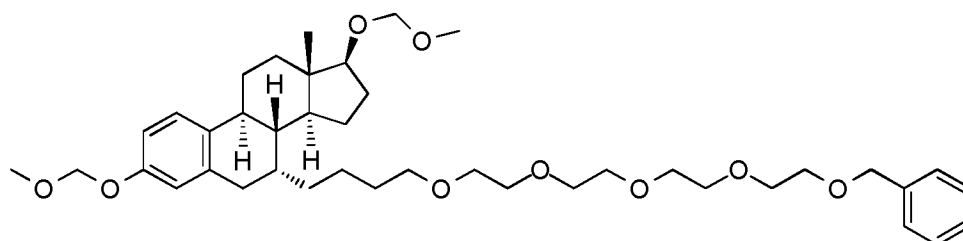


Triethylsilane (commercially available from for example Aldrich) (2.0 mL, 12.9 mmol) was added to a solution of (7S,8R,9S,13S,14S,17S)-3,17-dihydroxy-13-methyl-7-(1-phenyl-2,5,8,11,14-pentaoxaoctadecan-18-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-6-one (830 mg, 1.29 mmol) in TFA (8.5 mL, 110 mmol). The reaction was stirred at room temperature under an atmosphere of nitrogen for 16 hours. The mixture was partitioned between ethyl acetate (50 mL) and brine (50 mL). The organic extract was washed with brine (2 x 50 mL), saturated sodium bicarbonate (50 mL), dried using a hydrophobic frit and concentrated under reduced pressure. The residue was dissolved in MeOH (10 mL) and treated with aqueous NaOH (2M, 10 mL, 20.0 mmol). The reaction mixture was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate (40 mL) and 1M HCl solution (20 mL). The organic extract was washed with brine (20 mL), dried using a hydrophobic frit and concentrated under reduced pressure. The product was purified by reverse

phase chromatography using a gradient elution from 5% to 90% acetonitrile (+ 0.1% formic acid) in water (+ 0.1% formic acid) to afford *the title compound* (375 mg, 0.614 mmol, 47% yield). LCMS RT= 1.17 min, ES+ve m/z 611.5 $[M+H]^+$, 628.6 $[M+NH_4]^+$.

18-((7R,8R,9S,13S,14S,17S)-3,17-Bis(methoxymethoxy)-13-methyl-

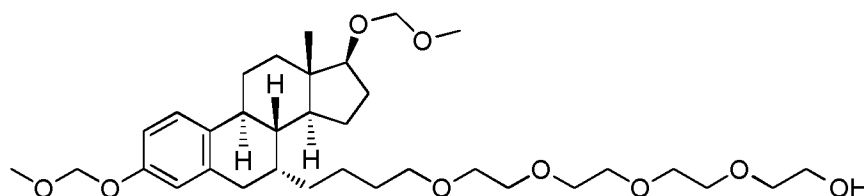
5 **7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)-1-phenyl-2,5,8,11,14-pentaoxaoctadecane**



Chloro(methoxy)methane (commercially available from for example Aldrich) (0.5 mL, 6.58 mmol) was added to a cooled (0 °C) solution of (7R,8R,9S,13S,14S,17S)-13-methyl-7-(1-phenyl-2,5,8,11,14-pentaoxaoctadecan-18-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3,17-diol (375 mg, 0.614 mmol) and DIPEA (1.5 mL, 8.59 mmol) in THF (20 mL). The reaction mixture was warmed to room temperature, stirred for 1 hour and heated at 70 °C for 72 hours. The reaction was cooled to room temperature. The reaction was partitioned between ethyl acetate (100 mL) and water (100 mL). The organic extract was washed with brine (2 x 50 mL), dried using a hydrophobic frit and concentrated under reduced pressure. The product was purified by chromatography on silica using a gradient elution from 0% to 100% methyl *tert*-butyl ether in cyclohexane to afford *the title compound* (357 mg, 0.51 mmol, 72% yield). LCMS RT= 1.60 min, ES+ve m/z 716.7 $[M+NH_4]^+$, 721.7 $[M+Na]^+$.

16-((7R,8R,9S,13S,14S,17S)-3,17-Bis(methoxymethoxy)-13-methyl-

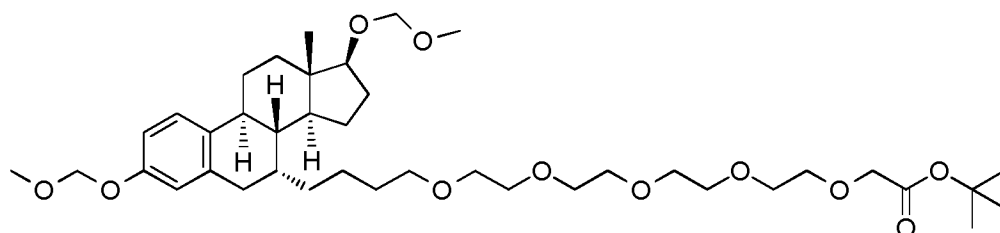
20 **7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)-3,6,9,12-tetraoxahexadecan-1-ol**



A mixture of 18-((7R,8R,9S,13S,14S,17S)-3,17-bis(methoxymethoxy)-13-methyl-

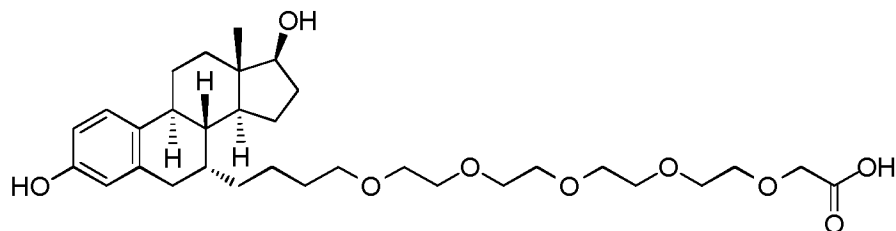
7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)-1-phenyl-2,5,8,11,14-pentaoxaoctadecane (357 mg, 0.444 mmol) and 10 % w/w palladium on carbon (157 mg, 0.148 mmol) in ethanol (5 mL) was stirred at room temperature under an atmosphere of hydrogen for 1.5 hours. The palladium on carbon was filtered through celite and the filtrate evaporated under reduced pressure to afford *the title compound* (300 mg, 0.41 mmol, 93% yield) LCMS RT= 1.37 min, ES+ve m/z 609.6 [M+H]⁺, 631.6 [M+Na]⁺.

***Tert*-butyl 19-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-7-yl)-3,6,9,12,15-pentaoxanonadecan-1-oate**



Sodium hydride, 60 % w/w in mineral oil (30 mg, 0.75 mmol) was added to a cooled solution (0 °C) of 16-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-7-yl)-3,6,9,12-tetraoxahexadecan-1-ol (300 mg, 0.43 mmol) in DMF (5 mL). The reaction was stirred at that temperature for 10 minutes and *tert*-butyl 2-bromoacetate (0.095 mL, 0.643 mmol) was added. The reaction was stirred at 0 °C for 1 hour and then at room temperature for a further 18 hours. The reaction mixture was partitioned between ethyl acetate (30 mL) and water (30 mL). The water layer was extracted with additional ethyl acetate (2 x 30 mL), and the combined organic layers were washed with brine (2 x 30 mL), dried (hydrophobic frit) and concentrated under reduced pressure. The product was purified by chromatography on silica using a gradient elution from 0% to 100% methyl *tert*-butyl ether in cyclohexane to afford *the title compound* (177 mg, 0.245 mmol, 57% yield). LCMS RT= 1.58 min, ES+ve m/z 740.6 [M+NH₄]⁺, 745.6 [M+Na]⁺.

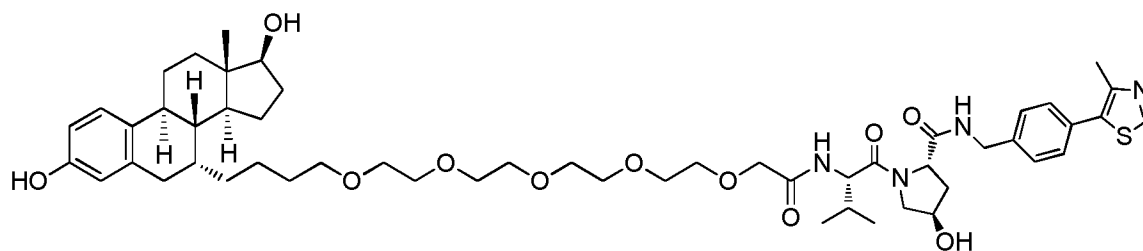
19-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-Dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-7-yl)-3,6,9,12,15-pentaoxanonadecan-1-oic acid



Tert-butyl 19-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-3,6,9,12,15-pentaoxonadecan-1-oate (177 mg, 0.189 mmol) was dissolved in THF (2 mL) and treated with aqueous HCl (6*M*, 2 mL, 12.0 mmol). The reaction mixture was stirred at room temperature for 7 hours. The reaction mixture was subjected directly to purification by mass-directed automated preparative HPLC (formic acid modifier) to afford *the title compound* (64 mg, 0.111 mmol, 59% yield). LCMS RT= 0.92 min, ES+ve *m/z* 579.4 [*M*+*H*]⁺, 596.5 [*M*+NH₄]⁺.

Example 4:

(2*S*,4*R*)-1-((*S*)-22-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-Dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-2-isopropyl-4-oxo-6,9,12,15,18-pentaoxa-3-azadocosan-1-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide

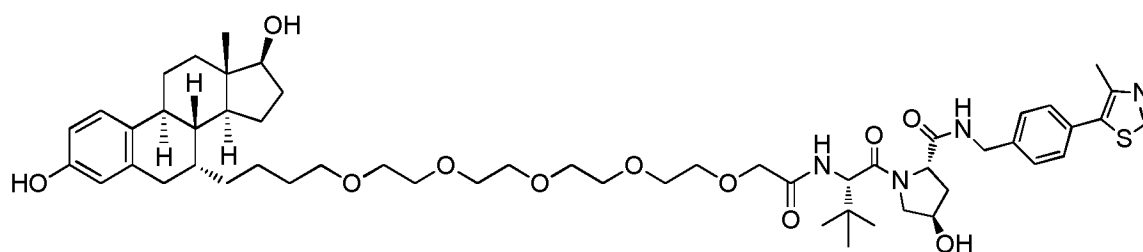


HATU (16 mg, 0.04 mmol) was added to a mixture of (2*S*,4*R*)-1-((*S*)-2-amino-3-methylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide, hydrochloride (25 mg, 0.06 mmol), 19-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-3,6,9,12,15-pentaoxonadecan-1-oic acid (16 mg, 0.03 mmol) and DIPEA (0.048 mL, 0.28 mmol) in DMF (0.8 mL). The reaction was stirred at room temperature for 30 minutes. The reaction mixture was subjected directly to purification by mass-

directed automated preparative HPLC (formic acid modifier) to afford *the title compound* (17.7 mg, 0.018 mmol, 65% yield). LCMS RT= 0.99 min, ES+ve m/z 977.4 [M+H]⁺.

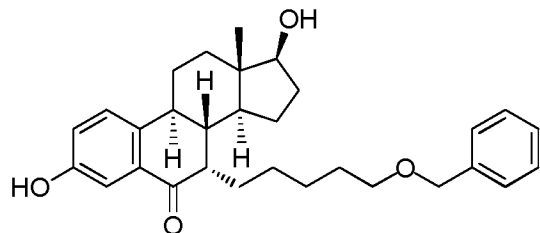
Example 5:

(2*S*,4*R*)-1-((*S*)-2-(*Tert*-butyl)-22-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-4-oxo-6,9,12,15,18-pentaoxa-3-azadocosan-1-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



HATU (16 mg, 0.04 mmol) was added to a mixture of (2*S*,4*R*)-1-((*S*)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide, hydrochloride (25 mg, 0.05 mmol), 19-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-3,6,9,12,15-pentaoxanonadecan-1-oic acid (16 mg, 0.03 mmol) and DIPEA (0.048 mL, 0.28 mmol) in DMF (0.8 mL). The reaction was stirred at room temperature for 30 minutes. The reaction mixture was subjected directly to purification by mass-directed automated preparative HPLC (formic acid modifier) to afford *the title compound* (17.5 mg, 0.017 mmol, 63% yield). LCMS RT= 1.03 min, ES+ve m/z 991.4 [M+H]⁺.

(7*S*,8*R*,9*S*,13*S*,14*S*,17*S*)-7-(5-(Benzyloxy)pentyl)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-6-one

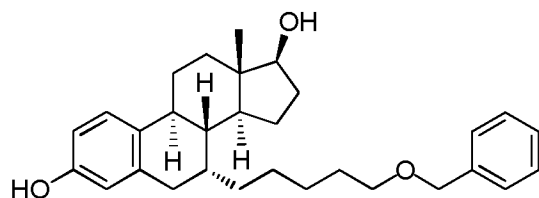


A solution of KOtBu in THF (1M, 4.81 mL, 4.81 mmol) was added to a cooled solution (0 °C) of (8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-

6*H*-cyclopenta[*a*]phenanthren-6-one (900 mg, 2.403 mmol) in anhydrous THF (10 mL). The reaction mixture was stirred at 0 °C for 45 minutes and then cooled to -78 °C. (((5-Iodopentyl)oxy)methyl)benzene (can be prepared following the procedure described in *J. Chem. Soc., Perkin Trans. 1* **1990**, 129-132) (2.193 g, 7.21 mmol) in THF (0.5 mL) was added dropwise.

5 The solution was stirred at -78 °C for 2 minutes and allowed to warm to room temperature and stirred for 1 hour at that temperature. The reaction was partitioned between water (70 mL) and ethyl acetate (70 mL). The organic extract was dried using a hydrophobic frit and concentrated under reduced pressure. The intermediate was purified by chromatography on silica using a gradient elution from 0% to 50% ethyl acetate in cyclohexane. The residue was dissolved in THF
10 (16 mL) and aqueous HCl (6M, 16 mL, 96 mmol) was added. The reaction was stirred at room temperature for 16 hours. The reaction mixture was partitioned between ethyl acetate (20 mL) and water (20 mL). The organic extract was dried (hydrophobic frit) and concentrated under reduced pressure. The product was purified by reverse phase chromatography using a gradient elution from 5% to 85% acetonitrile (+ 0.1% formic acid) in water (+ 0.1% formic acid) to afford *the title*
15 *compound* (487 mg, 1.053 mmol, 44% yield). LCMS RT= 1.16 min, ES+ve *m/z* 463.4 [M+H]⁺.

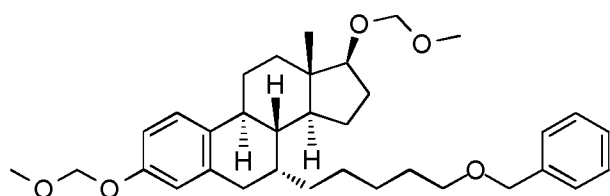
(7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-7-(5-(Benzyloxy)pentyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol



Triethylsilane (1.681 mL, 10.53 mmol) was added to a solution of (7*S*,8*R*,9*S*,13*S*,14*S*,17*S*)-7-(5-(benzyloxy)pentyl)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-
20 cyclopenta[*a*]phenanthren-6-one (487 mg, 1.053 mmol) in TFA (6 mL, 78 mmol). The reaction was stirred at room temperature under an atmosphere of nitrogen for 16 hours. The mixture was partitioned between ethyl acetate (30 mL) and brine (30 mL). The organic extract was washed with brine (2 x 30 mL), dried using a hydrophobic frit and concentrated under reduced pressure. The
25 residue was dissolved in MeOH (4 mL) and treated with aqueous NaOH (2M, 4 mL, 8.00 mmol). The reaction mixture was stirred at room temperature for 3 hours. The solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate (30 mL) and water (30 mL). The organic extract was washed with brine (30 mL), dried (hydrophobic frit) and concentrated under reduced pressure. The product was purified by reverse phase chromatography using a

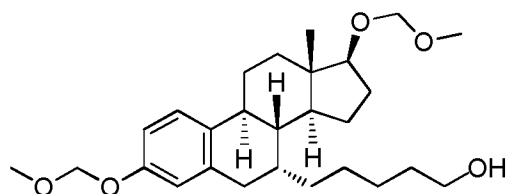
gradient elution from 10% to 95% acetonitrile (+ 0.1% formic acid) in water (+ 0.1% formic acid) to afford *the title compound* (410 mg, 0.914 mmol, 87% yield). LCMS RT= 1.30 min, ES+ve m/z 449.1 $[M+H]^+$.

(7R,8R,9S,13S,14S,17S)-7-(5-(Benzyloxy)pentyl)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene



Chloro(methoxy)methane (0.7 mL, 9.22 mmol) was added to solution of (7R,8R,9S,13S,14S,17S)-7-(5-(benzyloxy)pentyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3,17-diol (410 mg, 0.914 mmol) and DIPEA (2 mL, 11.45 mmol) in THF (8 mL). The reaction vessel was sealed, placed under an atmosphere of nitrogen and heated at 70 °C for 2 days. The reaction was cooled to room temperature. The reaction was partitioned between ethyl acetate (50 mL) and brine (50 mL). The organic extract was washed with brine (2 x 50 mL), dried using a hydrophobic frit and concentrated under reduced pressure. The product was purified by chromatography on silica using a gradient elution from 0% to 100% methyl *tert*-butyl ether in cyclohexane to afford *the title compound* (474 mg, 0.883 mmol, 97% yield). LCMS RT= 1.72 min, ES+ve m/z 554.5 $[M+NH_4]^+$.

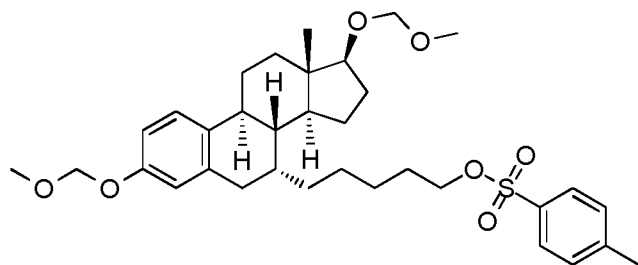
5-((7R,8R,9S,13S,14S,17S)-3,17-Bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)pentan-1-ol



A mixture of (7R,8R,9S,13S,14S,17S)-7-(5-(benzyloxy)pentyl)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene (474 mg, 0.883 mmol) and 10% w/w palladium on carbon (100 mg, 0.094 mmol) in ethanol (5 mL) and methyl *tert*-butyl ether (2 mL) was stirred at room temperature under an atmosphere of hydrogen for 1.5 hours. The palladium was filtered through celite and the filtrate concentrated under reduced

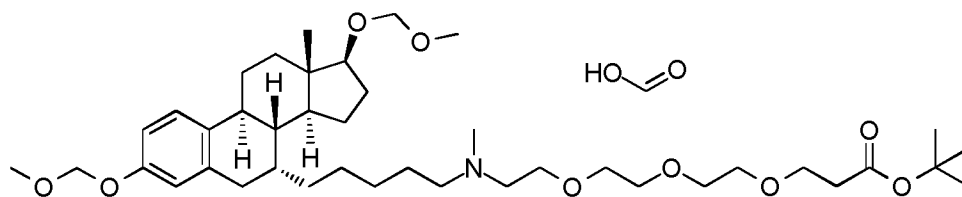
pressure to afford *the title compound* (371 mg, 0.831 mmol, 94% yield). LCMS RT= 1.39 min, ES+ve m/z 447.5 $[M+H]^+$ (weak ionisation).

5-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)pentyl 4-methylbenzenesulfonate



4-Methylbenzene-1-sulfonyl chloride (400 mg, 2.098 mmol) was added to 5-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)pentan-1-ol (371 mg, 0.831 mmol) in pyridine (5 mL). The reaction mixture was stirred at room temperature for 20 hours. The reaction mixture was partitioned between ethyl acetate (30 mL) and aqueous HCl (2M, 30 mL). The organic extract was washed with sat Na_2CO_3 (30 mL), brine (30 mL), dried (hydrophobic frit) and concentrated under reduced pressure. The product was purified by chromatography on silica using a gradient elution from 0% to 100% methyl *tert*-butyl ether in cyclohexane to afford *the title compound* (401 mg, 0.667 mmol, 80% yield). LCMS RT= 1.60 min, ES+ve m/z 623.4 $[M+Na]^+$.

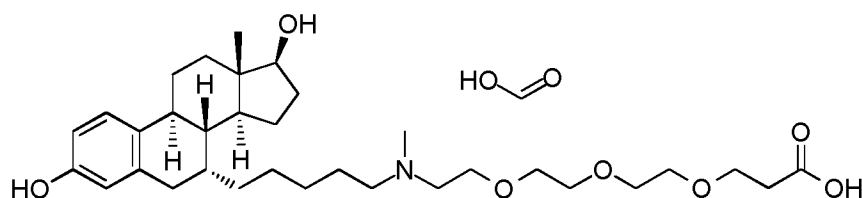
***Tert*-butyl 18-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-13-methyl-4,7,10-trioxa-13-azaoctadecan-1-oate, formic acid salt**



A microwave vial was charged with 5-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)pentyl 4-methylbenzenesulfonate (100 mg, 0.166 mmol), *tert*-butyl 5,8,11-trioxa-2-azatetradecan-14-oate (can be prepared following the procedure described in WO2012054110A2) (145 mg, 0.499 mmol)

and DIPEA (0.291 mL, 1.664 mmol) in THF (2 mL). The vial was sealed and placed under an atmosphere of nitrogen using a vacuum purge. The reaction was heated at 75 °C for 48 hours. The reaction was cooled to room temperature. The reaction mixture was subjected directly to purification by mass-directed automated preparative HPLC (formic acid modifier) to afford *the title compound* (102 mg, 0.133 mmol, 80% yield). LCMS RT= 1.22 min, ES+ve m/z 720.6 [M+H]⁺.

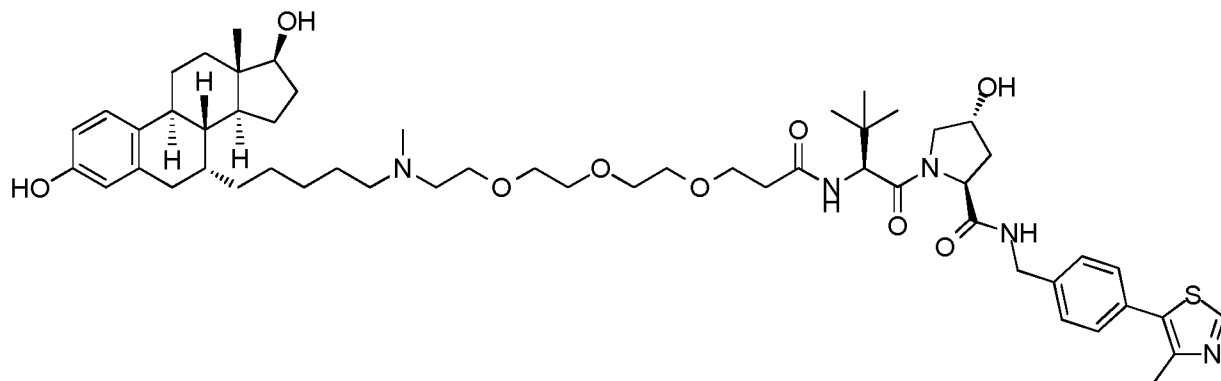
18-((7R,8R,9S,13S,14S,17S)-3,17-Dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)-13-methyl-4,7,10-trioxa-13-azaoctadecan-1-oic acid, formic acid salt



Tert-butyl 18-((7R,8R,9S,13S,14S,17S)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)-13-methyl-4,7,10-trioxa-13-azaoctadecan-1-oate, formic acid salt (100 mg, 0.131 mmol) was dissolved in THF (1 mL) and treated with aqueous HCl (6M, 1 mL, 6.00 mmol). The reaction was stirred at room temperature for 6 hours. The reaction mixture was subjected directly to purification by mass-directed automated preparative HPLC (formic acid modifier) to afford *the title compound* (24 mg, 0.039 mmol, 30% yield). LCMS RT= 0.74 min, ES+ve m/z 576.5 [M+H]⁺.

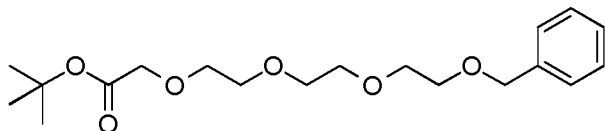
Example 6:

(2S,4R)-1-((S)-2-(*Tert*-butyl)-21-((7R,8R,9S,13S,14S,17S)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)-16-methyl-4-oxo-7,10,13-trioxa-3,16-diazahenicosan-1-oyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



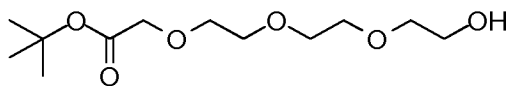
HATU (13 mg, 0.034 mmol) was added to a mixture of (2*S*,4*R*)-1-((*S*)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide, hydrochloride (13 mg, 0.028 mmol), 18-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-13-methyl-4,7,10-trioxa-13-azaoctadecan-1-oic acid, formic acid salt (12 mg, 0.019 mmol) and DIPEA (0.03 mL, 0.172 mmol) in DMF (0.8 mL). The reaction was stirred at room temperature for 10 minutes. The reaction mixture was subjected directly to two purifications by mass-directed automated preparative HPLC (formic acid modifier followed by ammonium carbonate modifier) to afford *the title compound* (13 mg, 0.013 mmol, 68 % yield). LCMS RT= 0.84 min, ES+ve *m/z* 988.8 [M+H]⁺.

***tert*-Butyl 1-phenyl-2,5,8,11-tetraoxatriodecan-13-oate**



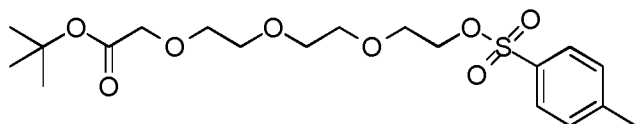
Potassium *tert*-butoxide (commercially available from for example Aldrich) (7.71 g, 68.7 mmol) was added to a stirred solution of 2-(2-(2-(benzyloxy)ethoxy)ethoxy)ethanol (commercially available from for example Fluorochem) (15 g, 62.4 mmol) in *tert*-butanol (200 mL) and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was cooled to 0 °C, *tert*-butyl 2-bromoacetate (commercially available from for example Aldrich) (16.59 mL, 112 mmol) was added, and the mixture was stirred at room temperature overnight. DCM (300 mL) was added and the organic phase was washed with water (300 mL) and then brine (2 x 200 mL). The organic extract was dried using a hydrophobic frit and concentrated under reduced pressure to give the crude product as a yellow oil. The product was purified by chromatography on silica using a gradient elution from 0% to 100% methyl *tert*-butyl ether in cyclohexane to afford *the title compound* (13.3 g, 37.5 mmol, 60% yield). LCMS RT= 1.10 min, ES+ve *m/z* 372.4 [M+NH₄]⁺.

***tert*-Butyl 2-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)acetate**



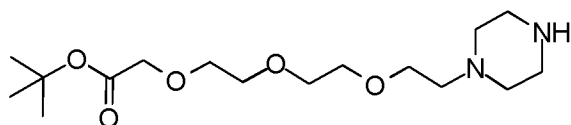
A mixture of *tert*-butyl 1-phenyl-2,5,8,11-tetraoxatridecan-13-oate (13.3 g, 37.5 mmol) and palladium on carbon (10% w/w, 11.38 g, 10.69 mmol) in ethanol (200 mL) was stirred at room temperature under an atmosphere of hydrogen for 1.5 h. The palladium on carbon was filtered
 5 through celite and the filtrate was evaporated under reduced pressure to afford *the title compound* (9.74 g, 36.8 mmol, 98% yield) as a yellow oil. ¹H NMR (400MHz, DMSO-d₆) δ = 4.54 (s, 1H), 3.99 (s, 2H), 3.60 - 3.40 (m, 12H), 1.43 (s, 9H).

***tert*-Butyl 2-(2-(2-(2-(tosyloxy)ethoxy)ethoxy)ethoxy)acetate**



Tosylchloride (commercially available from for example Aldrich) (11.94 g, 62.6 mmol) was added to a cooled solution (0 °C) of *tert*-butyl 2-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)acetate (9.74 g, 36.8 mmol) in pyridine (150 mL). The reaction was stirred at room temperature for 16 h. The reaction mixture was partitioned between ethyl acetate (300 mL) and aqueous HCl (2M, 300 mL). The organic extract was washed with further aqueous HCl (2M, 300 mL), saturated K₂CO₃ (100 mL)
 15 and brine (100 mL). The organic extract was dried using MgSO₄ and concentrated under reduced pressure to afford *the title compound* (10.3 g, 24.6 mmol, 67% yield) as a yellow oil. LCMS RT= 1.14 min, ES+ve 436.2 [M+NH₄]⁺.

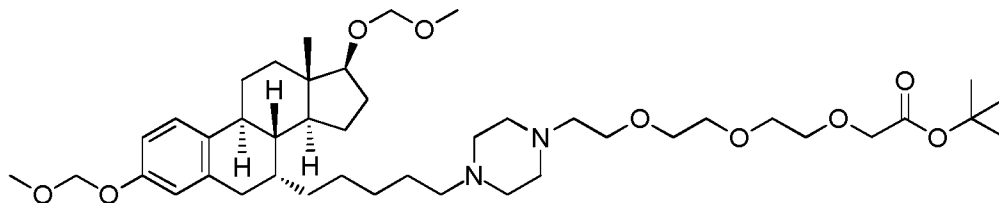
***tert*-Butyl 2-(2-(2-(2-(piperazin-1-yl)ethoxy)ethoxy)ethoxy)acetate**



A microwave vial was charged with *tert*-butyl 2-(2-(2-(2-(tosyloxy)ethoxy)ethoxy)ethoxy)acetate (500 mg, 1.195 mmol), piperazine (commercially available from for example Aldrich) (1 g, 11.61 mmol) and THF (3 mL). The vial was sealed and heated at 50 °C for 3 h. The reaction was cooled to room temperature, filtered and the filtrate was concentrated under reduced pressure. The product was purified by chromatography on aminopropyl (NH₂) using a gradient elution from 0% to 5%
 25 methanol in DCM to afford *the title compound* (274 mg, 0.824 mmol, 69 % yield) as a colourless oil.

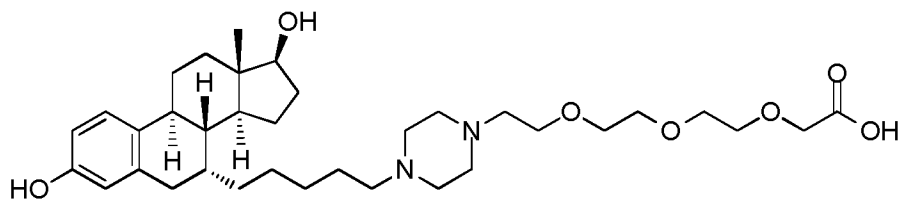
¹H NMR (400MHz, CHLOROFORM-d) δ = 4.03 (s, 2H), 3.75 - 3.61 (m, 10H), 2.91 (t, J =4.9 Hz, 4H), 2.58 (t, J =6.1 Hz, 2H), 2.55 - 2.41 (m, 4H), 1.49 (s, 9H).

***tert*-Butyl 2-(2-(2-(2-(4-(5-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[*a*]phenanthren-7-yl)pentyl)piperazin-1-yl)ethoxy)ethoxy)ethoxy)acetate, formic acid salt**



A vial was charged with 5-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[*a*]phenanthren-7-yl)pentyl 4-methylbenzenesulfonate (100 mg, 0.166 mmol), *tert*-butyl 2-(2-(2-(2-(piperazin-1-yl)ethoxy)ethoxy)ethoxy)acetate (274 mg, 0.824 mmol), DIPEA (0.3 mL, 1.718 mmol) and THF (2 mL). The vial was sealed and placed under an atmosphere of nitrogen using a vacuum purge. The reaction was heated at 70 °C for 72 h. The reaction was cooled to room temperature and the product was directly subjected to purification by mass-directed automated preparative HPLC (formic acid modifier) to afford the *title compound* (69 mg, 0.085 mmol, 51 % yield) as a colourless glass. LCMS RT= 1.15 min, ES+ve 761.4 [M+H]⁺.

2-(2-(2-(2-(4-(5-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[*a*]phenanthren-7-yl)pentyl)piperazin-1-yl)ethoxy)ethoxy)ethoxy)acetic acid, formic acid salt

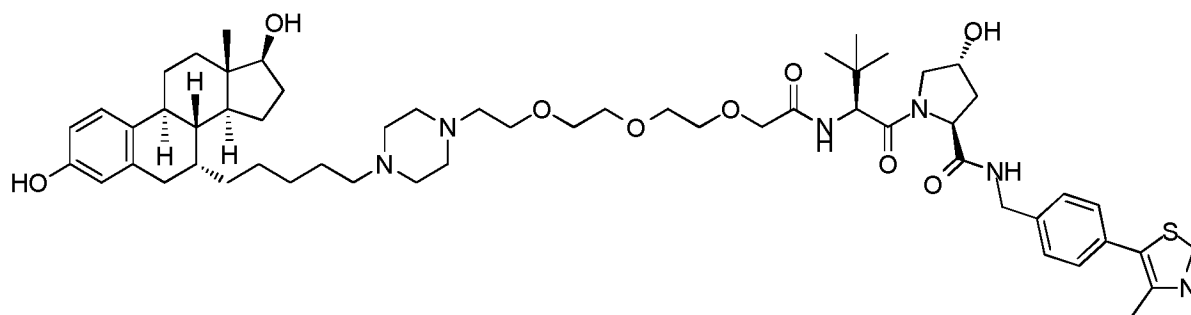


A mixture of *tert*-butyl 2-(2-(2-(2-(4-(5-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[*a*]phenanthren-7-yl)pentyl)piperazin-1-yl)ethoxy)ethoxy)ethoxy)acetate, formic acid salt (69 mg, 0.085 mmol) and aqueous HCl (6M, 0.8 mL, 4.80 mmol) in THF (0.8 mL) was stirred at room temperature for 7 h. The reaction mixture was directly subjected to purification by mass-directed automated preparative HPLC (formic acid modifier) to afford the *title compound* (36 mg, 0.054 mmol, 64 % yield) as a

colourless glass. LCMS RT= 0.64 min, ES+ve 617.3 [M+H]⁺.

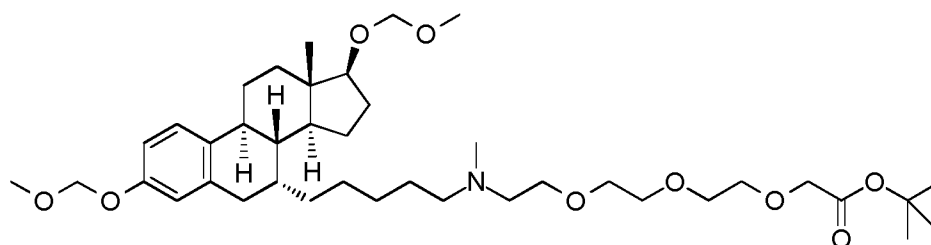
Example 7:

(2*S*,4*R*)-1-((*S*)-2-(*tert*-butyl)-14-(4-(5-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)pentyl)piperazin-1-yl)-4-oxo-6,9,12-trioxa-3-azatetradecan-1-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



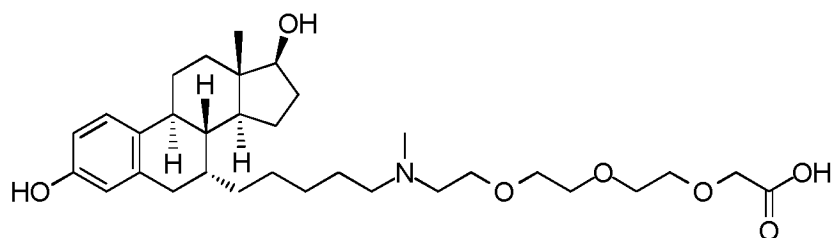
HATU (15 mg, 0.039 mmol) was added to a mixture of 2-(2-(2-(2-(4-(5-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)pentyl)piperazin-1-yl)ethoxy)ethoxy)ethoxy)acetic acid, formic acid salt (18 mg, 0.027 mmol), (2*S*,4*R*)-1-((*S*)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide, hydrochloride, DIPEA (50 μL, 0.286 mmol) and DMF (0.8 mL). The reaction was stirred at ambient temperature for 30 minutes before being directly subjected to purification by mass-directed automated preparative HPLC (ammonium carbonate modifier) to afford the title compound (15 mg, 0.015 mmol, 54 % yield). LCMS RT= 0.81 min, ES+ve 1029.5 [M+H]⁺.

***tert*-Butyl 17-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-12-methyl-3,6,9-trioxa-12-azaheptadecan-1-oate, formic acid salt**



A vial was charged with *tert*-butyl 2-(2-(2-(2-(tosyloxy)ethoxy)ethoxy)ethoxy)acetate (500 mg, 1.195 mmol) and methanamine, 33% w/w in ethanol (commercially available from for example Aldrich) (2 mL). The vial was sealed and heated at 50 °C for 3 h. The solvent was removed under reduced pressure. The intermediate was purified by chromatography on aminopropyl sulphonic acid (SCX): the column was first washed with MeOH (3 column volumes) and the product released by elution with ammonia in methanol (2M, 3 column volumes). The ammonia fraction was concentrated under reduced pressure to give 285 mg of a colourless oil. A vial was charged with the obtained colourless oil (285 mg), 5-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[*a*]phenanthren-7-yl)pentyl 4-methylbenzenesulfonate (140 mg, 0.233 mmol), DIPEA (0.4 mL, 2.290 mmol) and THF (2 mL). The vial was sealed and placed under an atmosphere of nitrogen using a vacuum purge. The reaction was heated at 75 °C for 48 h. The reaction was cooled to room temperature and the product was directly subjected to purification by mass-directed automated preparative HPLC (formic acid modifier) to afford the *title compound* (50 mg, 0.066 mmol, 29 % yield). LCMS RT= 1.23 min, ES+ve 706.4 [M+H]⁺.

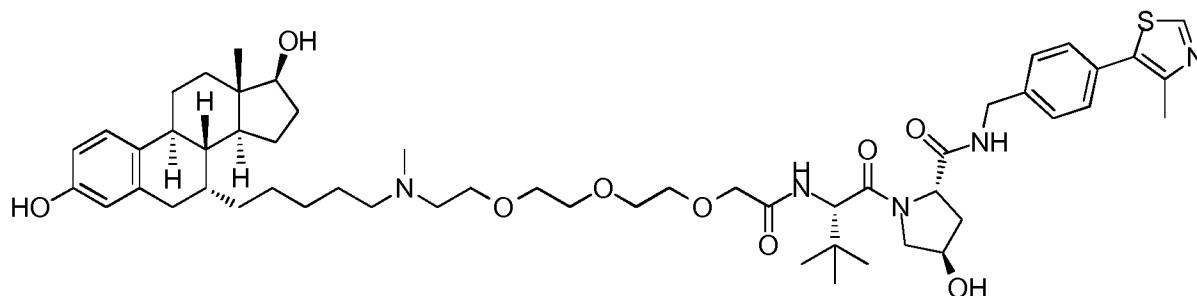
17-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-Dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[*a*]phenanthren-7-yl)-12-methyl-3,6,9-trioxa-12-azaheptadecan-1-oic acid, formic acid salt



Aqueous HCl (6M, 0.45 mL, 2.70 mmol) was added to a solution of *tert*-butyl 17-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[*a*]phenanthren-7-yl)-12-methyl-3,6,9-trioxa-12-azaheptadecan-1-oate, formic acid salt (50 mg, 0.066 mmol) in THF (0.45 mL). The reaction was stirred at ambient temperature for 6 h. The reaction mixture was directly subjected to purification by mass-directed automated preparative HPLC (formic acid modifier) to afford the *title compound* (14 mg, 0.023 mmol, 35 % yield). LCMS RT= 0.71 min, ES+ve 562.3 [M+H]⁺.

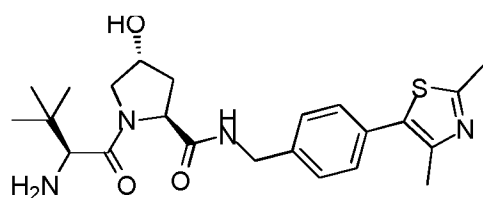
Example 8:

(2*S*,4*R*)-1-((*S*)-2-(*tert*-Butyl)-20-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-15-methyl-4-oxo-6,9,12-trioxa-3,15-diazaicosan-1-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



5 HATU (14 mg, 0.037 mmol) was added to a mixture of 17-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-12-methyl-3,6,9-trioxa-12-azaheptadecan-1-oic acid, formic acid salt (14 mg, 0.023 mmol), (2*S*,4*R*)-1-((*S*)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide, hydrochloride (16 mg, 0.034 mmol), DIPEA (0.05 mL, 0.286 mmol) and DMF (0.8 mL). The reaction was stirred at ambient temperature for 30 minutes before being directly subjected to purification by mass-directed automated preparative HPLC (ammonium carbonate modifier) to afford the *title compound* (17 mg, 0.017 mmol, 76 % yield). LCMS RT= 0.85 min, ES+ve 974.5 [M+H]⁺.

15 **(2*S*,4*R*)-1-((*S*)-2-Amino-3,3-dimethylbutanoyl)-*N*-(4-(2,4-dimethylthiazol-5-yl)benzyl)-4-hydroxypyrrolidine-2-carboxamide, hydrochloride**



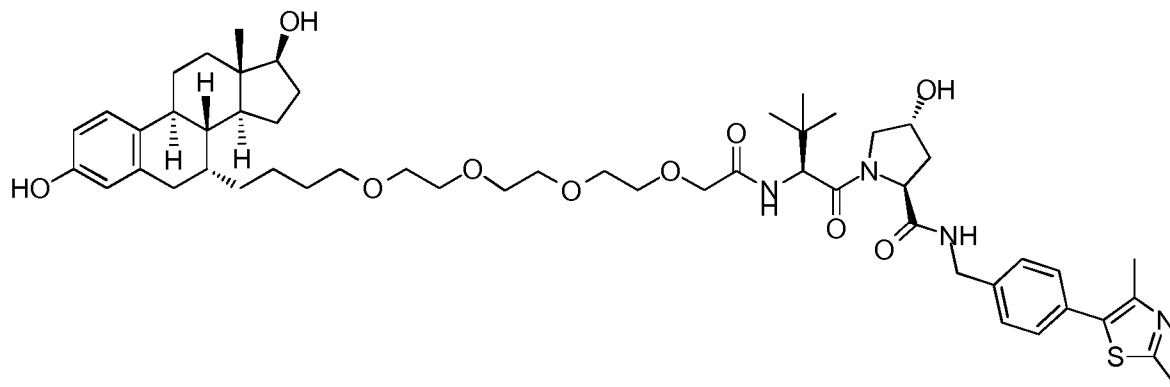
HCl

HATU (30 mg, 0.079 mmol) was added to a solution of (2*S*,4*R*)-*N*-(4-(2,4-dimethylthiazol-5-yl)benzyl)-4-hydroxypyrrolidine-2-carboxamide hydrochloride (24 mg, 0.065 mmol), DIPEA (0.1 mL, 0.573 mmol) and (*S*)-2-((*tert*-butoxycarbonyl)amino)-3,3-dimethylbutanoic acid (20 mg, 0.086 mmol) in DMF (0.8 mL). The reaction mixture was stirred at room temperature for 25 minutes and was then subjected directly to purification by mass-directed automated preparative HPLC (formic acid modifier) to afford the Boc intermediate compound. This residue was dissolved in MeOH:DCM

(1:1, 1 mL) and treated with HCl in dioxane (4M, 0.2 mL, 0.800 mmol). The reaction was stirred at ambient temperature for 3 h. The solvent was removed under reduced pressure. The solid was dried in the oven to afford the *title compound* (26 mg, 0.054 mmol, 83 % yield) as an off white solid. LCMS RT= 0.60 min, ES+ve 445.1 [M+H]⁺.

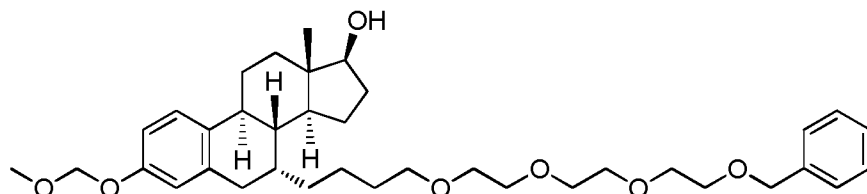
5 **Example 9:**

(2*S*,4*R*)-1-((*S*)-2-(*tert*-Butyl)-19-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-4-oxo-6,9,12,15-tetraoxa-3-azanonadecan-1-oyl)-*N*-(4-(2,4-dimethylthiazol-5-yl)benzyl)-4-hydroxypyrrolidine-2-carboxamide



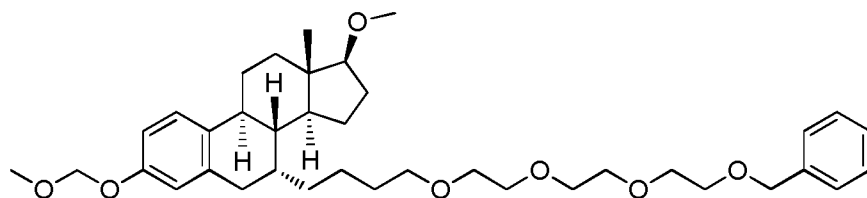
10 HATU (15 mg, 0.039 mmol) was added to a mixture of (2*S*,4*R*)-1-((*S*)-2-amino-3,3-dimethylbutanoyl)-*N*-(4-(2,4-dimethylthiazol-5-yl)benzyl)-4-hydroxypyrrolidine-2-carboxamide, hydrochloride (26 mg, 0.054 mmol), 16-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-3,6,9,12-tetraoxahexadecan-1-oic acid (15 mg, 0.028 mmol) and DIPEA (0.05 mL, 0.286 mmol) in DMF (0.8 mL). The reaction was stirred at room temperature for 30 minutes. The reaction mixture was subjected directly to purification by mass-directed automated preparative HPLC (formic acid modifier) to afford the *title compound* (14 mg, 0.015 mmol, 52 % yield). LCMS RT= 1.04 min, ES+ve 961.4 [M+H]⁺.

20 **(7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3-(Methoxymethoxy)-13-methyl-7-(1-phenyl-2,5,8,11-tetraoxapentadecan-15-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-ol**



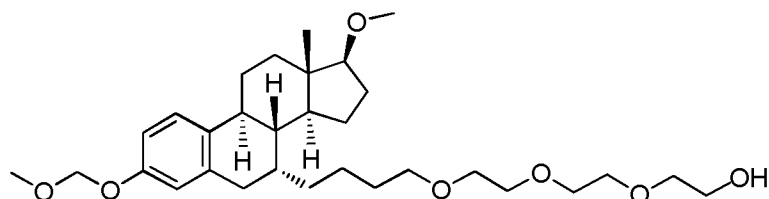
Sodium hydride, 60 % w/w in mineral oil (15 mg, 0.381 mmol) was added to a cooled solution (0 °C) of (7R,8R,9S,13S,14S,17S)-13-methyl-7-(1-phenyl-2,5,8,11-tetraoxapentadecan-15-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3,17-diol (180 mg, 0.318 mmol) in DMF (2 mL). The reaction was stirred for 25 minutes and then chloro(methoxy)methane (commercially available from for example Aldrich) (0.036 mL, 0.476 mmol) was added. The reaction was slowly warmed to room temperature and stirred under a nitrogen atmosphere for 2 hours. Ethyl acetate (30 mL) was added and the mixture was washed with saturated aqueous ammonium chloride solution (20 mL), followed by brine (25 mL). The organic layer was dried using a hydrophobic frit and concentrated under reduced pressure. Toluene (20 mL) was added and the mixture was evaporated to dryness to afford *the title compound* (190 mg, 0.311 mmol, 98% yield). LCMS RT= 1.38 min, ES+ve m/z 628.6 $[M+NH_4]^+$.

15-((7R,8R,9S,13S,14S,17S)-17-Methoxy-3-(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)-1-phenyl-2,5,8,11-tetraoxapentadecane



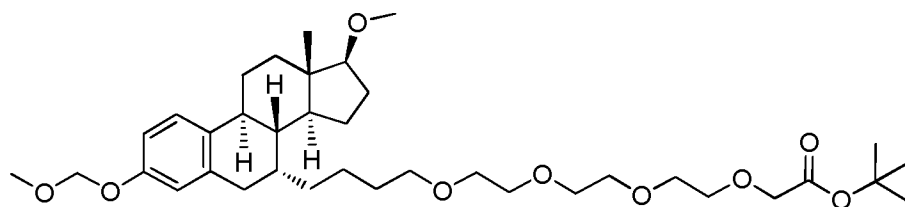
Sodium hydride, 60 % w/w in mineral oil (31 mg, 0.786 mmol) was added to a cooled (0 °C) solution of (7R,8R,9S,13S,14S,17S)-3-(methoxymethoxy)-13-methyl-7-(1-phenyl-2,5,8,11-tetraoxapentadecan-15-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-ol (0.185 mL, 0.393 mmol) in DMF (2 mL) and the mixture was stirred under a nitrogen atmosphere for 30 minutes. Iodomethane (0.029 mL, 0.471 mmol) was added and the reaction was warmed to room temperature and stirred for 18 hours. The reaction was partitioned between ethyl acetate (30 mL) and water (20 mL). The organic extract was washed with brine (2 x 20 mL), dried using a hydrophobic frit and concentrated under reduced pressure to afford *the title compound* (240 mg, 0.384 mmol, 98% yield). LCMS RT= 1.59 min, ES+ve m/z 642.5 $[M+NH_4]^+$, 647.5 $[M+Na]^+$.

2-(2-(2-(4-((7R,8R,9S,13S,14S,17S)-17-Methoxy-3-(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)butoxy)ethoxy)ethoxy)ethanol



5 A mixture of 15-((7R,8R,9S,13S,14S,17S)-17-methoxy-3-(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)-1-phenyl-2,5,8,11-tetraoxapentadecane (240 mg, 0.384 mmol) and 10 % w/w palladium on carbon (133 mg, 0.125 mmol) in ethanol (8 mL) was stirred at room temperature under an atmosphere of hydrogen for 1.5 hours. The palladium on carbon was filtered through celite and the filtrate evaporated under
 10 reduced pressure to afford to afford *the title compound* (190 mg, 0.355 mmol, 93% yield). LCMS RT= 1.34 min, ES+ve m/z 557.5 $[M+Na]^+$.

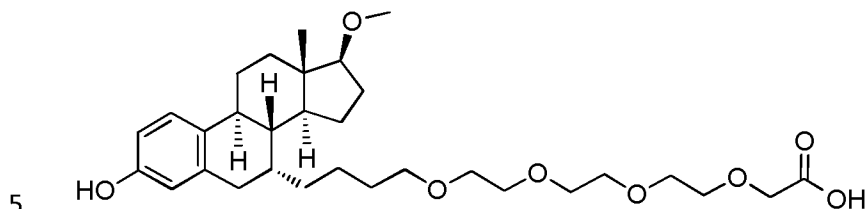
***tert*-Butyl 16-((7R,8R,9S,13S,14S,17S)-17-methoxy-3-(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)-3,6,9,12-tetraoxahexadecan-1-oate**



15 Sodium hydride, 60 % w/w in mineral oil (28 mg, 0.692 mmol) was added to a cooled solution (0 °C) of 2-(2-(2-(4-((7R,8R,9S,13S,14S,17S)-17-methoxy-3-(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)butoxy)ethoxy)ethoxy)ethanol (185 mg, 0.346 mmol) in DMF (1.3 mL). The reaction was stirred
 20 at 0 °C for 30 minutes and *tert*-butyl 2-bromoacetate (commercially available from for example Aldrich) (0.10 mL, 0.69 mmol) was added. The reaction was stirred at 0 °C for 1 hour and was then stirred at room temperature for 4 hours. The reaction mixture was partitioned between ethyl acetate (30 mL) and water (30 mL). The organic layer separated, washed with brine (30 mL), dried using a hydrophobic frit and concentrated under reduced pressure. The product was purified by
 25 chromatography on silica using a gradient elution from 0% to 100% methyl *tert*-butyl ether in

cyclohexane to afford *the title compound* (124 mg, 0.191 mmol, 55% yield). LCMS RT= 1.56 min, ES+ve m/z 671.5 $[M+Na]^+$.

16-((7R,8R,9S,13S,14S,17S)-3-Hydroxy-17-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)-3,6,9,12-tetraoxahexadecan-1-oic acid

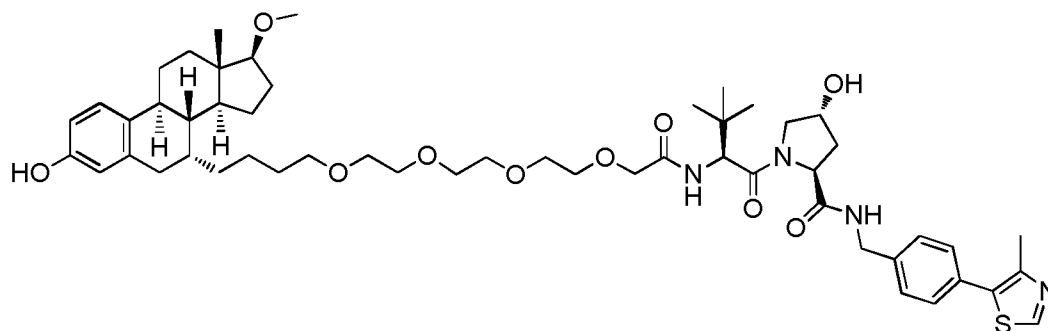


Tert-butyl 16-((7R,8R,9S,13S,14S,17S)-17-methoxy-3-(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)-3,6,9,12-tetraoxahexadecan-1-oate (80 mg, 0.123 mmol) was dissolved in THF (0.9 mL) and treated with aqueous HCl (6M, 0.9 mL, 5.40 mmol). The reaction was stirred at room temperature overnight. The reaction mixture was then subjected directly to purification by mass-directed automated preparative HPLC (formic acid modifier) to afford *the title compound* (36 mg, 0.066 mmol, 53% yield). LCMS RT= 1.17 min, ES+ve m/z 549.2 $[M+H]^+$, 566.2 $[M+NH_4]^+$.

10

Example 10:

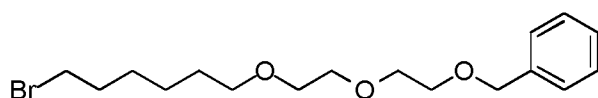
15 **(2S,4R)-1-((S)-2-(*Tert*-butyl)-19-((7R,8R,9S,13S,14S,17S)-3-hydroxy-17-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)-4-oxo-6,9,12,15-tetraoxa-3-azanonadecan-1-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**



20 HATU (37 mg, 0.10 mmol) was added to a mixture of (2S,4R)-1-((S)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide,

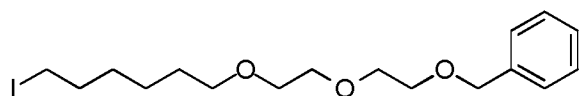
hydrochloride (77 mg, 0.164 mmol), 16-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3-hydroxy-17-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-3,6,9,12-tetraoxahexadecan-1-oic acid (36 mg, 0.066 mmol) and DIPEA (0.115 mL, 0.656 mmol) in DMF (1.6 mL). The reaction was stirred at room temperature for 30 minutes, and was subjected directly to purification by mass-directed automated preparative HPLC (formic acid modifier) to afford *the title compound* (48 mg, 0.05 mmol, 76% yield). LCMS RT= 1.25 min, ES+ve *m/z* 961.7 [M+H]⁺.

((2-(2-((6-Bromohexyl)oxy)ethoxy)ethoxy)methyl)benzene



To a cooled suspension (0 °C) of sodium hydride, 60 % w/w in mineral oil (1.22 g, 30.6 mmol) in DMF (8 mL) was added a solution of 2-(2-(benzyloxy)ethoxy)ethanol (commercially available from for example Aldrich) (4 g, 20.4 mmol) in DMF (8 mL). After stirring for 25 minutes, 1,6-dibromohexane (commercially available from for example Aldrich) (14.1 mL, 92 mmol) dissolved in (DMF) (8 mL) was added dropwise to the mixture. The reaction was stirred under an atmosphere of nitrogen for 30 minutes. A further aliquot of sodium hydride, 60 % w/w in mineral oil (1.22 g, 30.6 mmol) was added and the reaction was stirred at room temperature for an additional 1 hour. The reaction mixture was filtered through celite and the solid was washed with DCM. The filtrate was partitioned between DCM (50 mL) and water (50 mL). The organic extract was separated, washed with brine (2 x 50 mL), dried using a hydrophobic frit and concentrated under reduced pressure. The product was purified by chromatography on silica using a gradient elution from 0% to 85% methyl *tert*-butyl ether in cyclohexane to afford *the title compound* (3.91 g, 10.3 mmol, 51% yield). LCMS RT= 1.30 min, ES+ve *m/z* 359.3./361.3 [M+H]⁺.

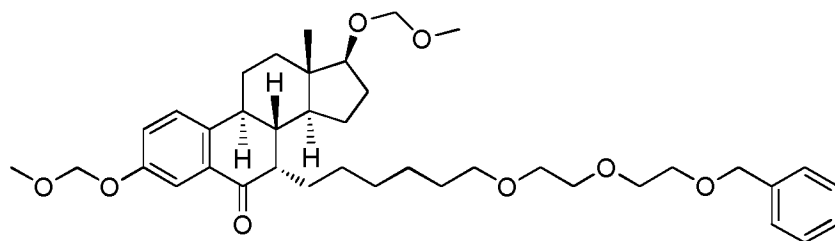
((2-(2-((6-Iodohexyl)oxy)ethoxy)ethoxy)methyl)benzene



A mixture of ((2-(2-((6-bromohexyl)oxy)ethoxy)ethoxy)methyl)benzene (3.91 g, 10.3 mmol) and sodium iodide (3.1 g, 20.7 mmol) in acetone (40 mL) was heated under reflux conditions overnight. The reaction was cooled to room temperature. The mixture was filtered through celite and the solid was washed with acetone. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (30 mL) and washed with water (30 mL) and brine (2 x 30 mL). The

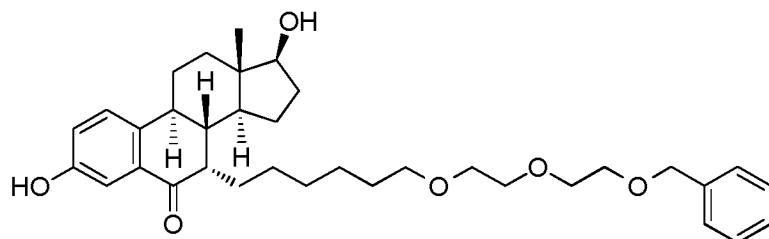
organic extract was dried using a hydrophobic frit and concentrated under reduced pressure to afford *the title compound* (4.31 g, 10.3 mmol, quantitative yield). LCMS RT= 1.37 min, ES+ve m/z 407.3 $[M+H]^+$.

(7*S*,8*R*,9*S*,13*S*,14*S*,17*S*)-7-(6-(2-(2-(Benzyloxy)ethoxy)ethoxy)hexyl)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-6-one



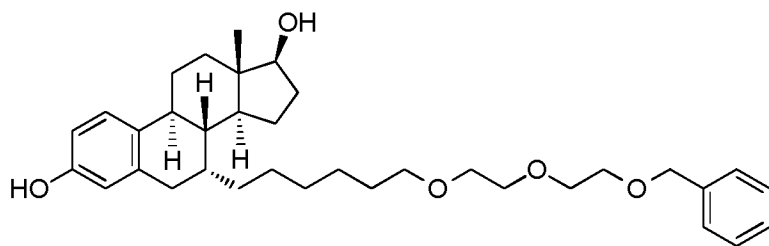
A solution of KO^tBu in THF (1M, 4.3 mL, 4.3 mmol) was added to a cooled solution (0 °C) of (8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-6-one (800 mg, 2.14 mmol) in anhydrous THF (8 mL). The reaction mixture was stirred at 0 °C for 45 minutes and then cooled to -78 °C. A solution of ((2-(2-((6-iodohexyl)oxy)ethoxy)ethoxy)methyl)benzene (1.34 g, 3.2 mmol) in THF (4 mL) was added dropwise. The solution was stirred at -78 °C for 2 minutes, then allowed to warm to room temperature and stirred overnight. The reaction was partitioned between water (30 mL) and ethyl acetate (30 mL). The organic extract was washed with brine (30 mL) dried using a hydrophobic frit and concentrated under reduced pressure. The product was purified by chromatography on silica using a gradient elution from 0% to 100% ethyl acetate in cyclohexane to afford *the title compound* (712 mg, 1.08 mmol, 51% yield). LCMS RT= 1.57 min, ES+ve m/z 653.2 $[M+H]^+$.

(7*S*,8*R*,9*S*,13*S*,14*S*,17*S*)-7-(6-(2-(2-(Benzyloxy)ethoxy)ethoxy)hexyl)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-6-one



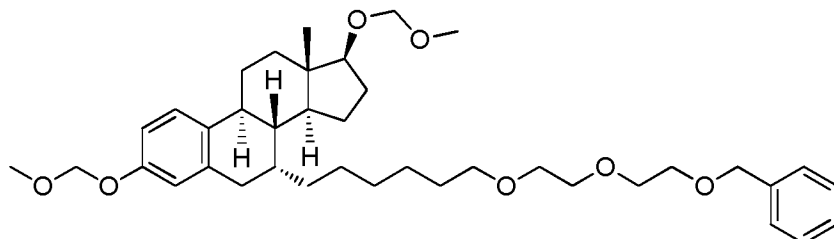
A solution of aqueous HCl (6M, 7.2 mL, 43.2 mmol) was added to a solution of (7S,8R,9S,13S,14S,17S)-7-(6-(2-(2-(benzyloxy)ethoxy)ethoxy)hexyl)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-6-one (710 mg, 1.1 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature overnight. Water (30 mL) was added and the product was extracted with ethyl acetate (50 mL). The organic extract was washed with brine (2 x 30mL), dried using a hydrophobic frit and concentrated under reduced pressure to afford *the title compound* (640 mg, 1.1 mmol, quantitative yield). LCMS RT= 1.17 min, ES+ve m/z 565.1 [M+H]⁺.

(7R,8R,9S,13S,14S,17S)-7-(6-(2-(2-(Benzyloxy)ethoxy)ethoxy)hexyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3,17-diol



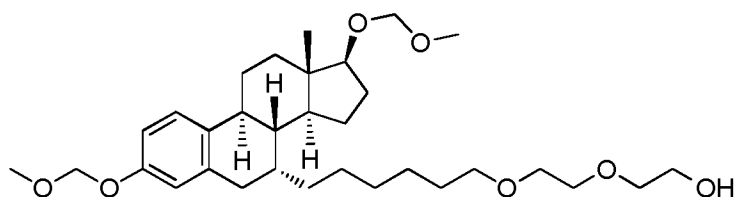
Triethylsilane (commercially available from for example Aldrich) (1.78 ml, 11.1 mmol) was added to a solution of (7S,8R,9S,13S,14S,17S)-7-(6-(2-(2-(benzyloxy)ethoxy)ethoxy)hexyl)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-6-one (640 mg, 1.11 mmol) in TFA (6.4 ml, 83 mmol). The reaction was stirred at room temperature under an atmosphere of nitrogen for 18 hours. The mixture was partitioned between ethyl acetate (50 mL) and brine (50 mL). The organic extract was washed with brine (2 x 50 mL), dried using a hydrophobic frit and concentrated under reduced pressure. The residue was dissolved in MeOH (10 mL) and treated with aqueous NaOH (2M, 6.67 ml, 13.35 mmol). The reaction mixture was stirred at room temperature for 1 hour and the solvent was then removed under reduced pressure. The residue was partitioned between ethyl acetate (40 mL) and aqueous HCl (1M, 20 mL). The organic extract was separated, washed with brine (20 mL), dried using a hydrophobic frit and concentrated under reduced pressure. The product was purified by reverse phase chromatography using a gradient elution from 5% to 95% acetonitrile (+ 0.1% formic acid) in water (+ 0.1% formic acid) to afford *the title compound* (300 mg, 0.521 mmol, 47% yield). LCMS RT= 1.28 min, ES+ve m/z 551.5 [M+H]⁺.

(7R,8R,9S,13S,14S,17S)-7-(6-(2-(2-(Benzyloxy)ethoxy)ethoxy)hexyl)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene



- 5 Chloro(methoxy)methane (commercially available from for example Aldrich) (0.4 mL, 5.27 mmol) was added to a cold (0 °C) solution of (7R,8R,9S,13S,14S,17S)-7-(6-(2-(2-(benzyloxy)ethoxy)ethoxy)hexyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3,17-diol (300 mg, 0.521 mmol) and DIPEA (1.2 mL, 6.87 mmol) in THF (10 mL). The reaction mixture was warmed to room temperature, stirred for 1 hour and then
- 10 heated at 70 °C for 3 days. The reaction was cooled to room temperature and the reaction was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic extract was separated, washed with brine (2 x 50 mL), dried using a hydrophobic frit and concentrated under reduced pressure. The product was purified by chromatography on silica using a gradient elution from 0% to 100% methyl *tert*-butyl ether in cyclohexane to afford *the title compound* (307 mg, 0.413 mmol,
- 15 79% yield). LCMS RT= 1.68 min, ES+ve *m/z* 656.6 [M+NH₄]⁺, 661.6 [M+Na]⁺.

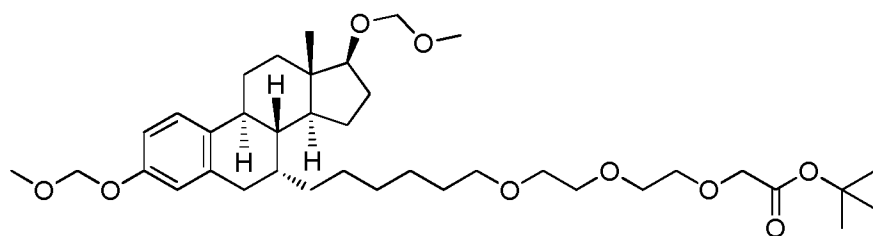
2-(2-((6-((7R,8R,9S,13S,14S,17S)-3,17-Bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)hexyl)oxy)ethoxy)ethanol



- 20 A mixture of (7R,8R,9S,13S,14S,17S)-7-(6-(2-(2-(benzyloxy)ethoxy)ethoxy)hexyl)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene (307 mg, 0.413 mmol) and 10 % w/w palladium on carbon (88 mg, 0.083 mmol) in ethanol (10 mL) was stirred at room temperature under an atmosphere of hydrogen for 1.5 hours. The palladium on carbon was filtered through celite and the filtrate

evaporated under reduced pressure to afford *the title compound* (211 mg, 0.358 mmol, 87% yield).
LCMS RT= 1.46 min, ES+ve m/z 549.6 $[M+H]^+$, 566.3 $[M+NH_4]^+$.

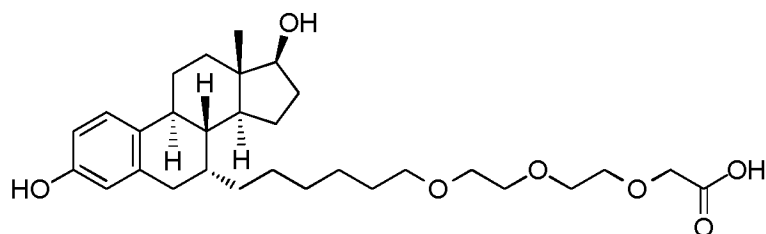
***tert*-Butyl 2-(2-(2-((6-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)hexyl)oxy)ethoxy)ethoxy)acetate**



Sodium hydride, 60 % w/w in mineral oil (29 mg, 0.715 mmol) was added to a cooled solution (0 °C) of 2-(2-((6-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-

yl)hexyl)oxy)ethoxy)ethanol (211 mg, 0.358 mmol) in DMF (2.5 mL). The reaction was stirred at 0 °C for 10 minutes, *tert*-butyl 2-bromoacetate (commercially available from for example Aldrich) (0.11 mL, 0.715 mmol) was added and the reaction was stirred for an additional 1 hour. The reaction mixture was partitioned between ethyl acetate (30 mL) and water (30 mL). The aqueous layer was separated, extracted with additional ethyl acetate (2 x 30 mL). The combined organic layers were washed with brine (2 x 30 mL), dried using a hydrophobic frit and concentrated under reduced pressure. The product was purified by chromatography on silica using a gradient elution from 0% to 100% methyl *tert*-butyl ether in cyclohexane to afford *the title compound* (214 mg, 0.245 mmol, 69% yield). LCMS RT= 1.65 min, ES+ve m/z 680.6 $[M+NH_4]^+$, 685.6 $[M+Na]^+$.

2-(2-(2-((6-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-Dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)hexyl)oxy)ethoxy)ethoxy)acetic acid

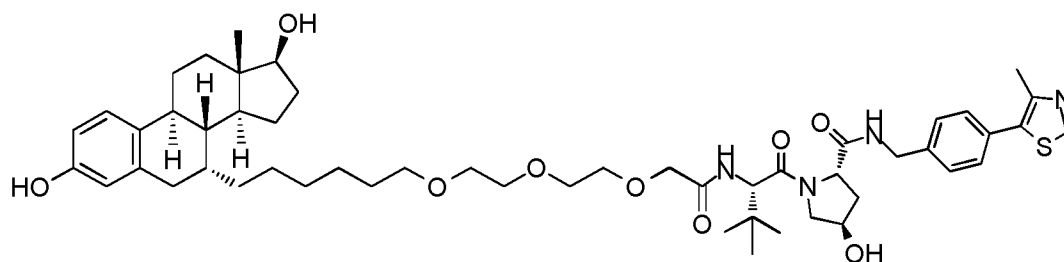


***Tert*-butyl 2-(2-(2-((6-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-**

yl)hexyl)oxy)ethoxy)ethoxy)acetate (214 mg, 0.245 mmol) was dissolved in THF (0.8 mL) and treated with aqueous HCl (6M, 0.85 mL, 5.10 mmol). The reaction was stirred at room temperature overnight. The reaction mixture was then subjected directly to purification by mass-directed automated preparative HPLC (formic acid modifier) to afford *the title compound* (27 mg, 0.05 mmol, 21% yield). LCMS RT= 0.99 min, ES+ve m/z 519.5 $[M+H]^+$.

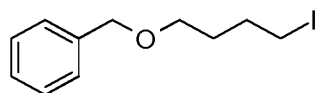
Example 11:

(2*S*,4*R*)-1-((*S*)-2-(*Tert*-butyl)-18-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-4-oxo-6,9,12-trioxa-3-azaoctadecan-1-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



HATU (23 mg, 0.06 mmol) was added to a mixture of (2*S*,4*R*)-1-((*S*)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide hydrochloride (27 mg, 0.06 mmol), 2-(2-(2-((6-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)hexyl)oxy)ethoxy)ethoxy)acetic acid (27 mg, 0.05 mmol) and DIPEA (0.035 mL, 0.20 mmol) in DMF (0.8 mL). The reaction was stirred at room temperature for 30 minutes, and was then subjected directly to purification by mass-directed automated preparative HPLC (formic acid modifier) to afford *the title compound* (12 mg, 0.013 mmol, 26% yield). LCMS RT= 1.10 min, ES+ve m/z 937.7 $[M+H]^+$.

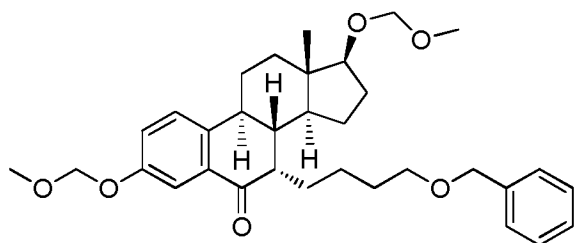
((4-Iodobutoxy)methyl)benzene



A mixture of ((4-bromobutoxy)methyl)benzene (commercially available from for example TCL Europe) (4 g, 16.5 mmol) and sodium iodide (4.93 g, 32.9 mmol) in acetone (40 mL) was heated under reflux conditions overnight. The reaction mixture was cooled to room temperature, filtered

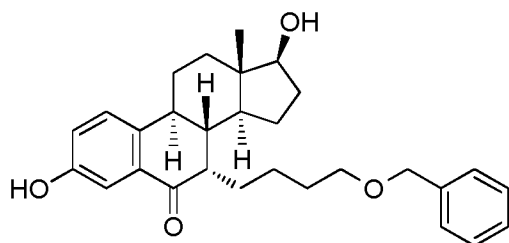
through celite and the solid was washed with acetone. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (30 mL), washed with water (30 mL) and brine (2 x 30 mL). The organic extract was dried using a hydrophobic frit and concentrated under reduced pressure. The product was purified by chromatography on silica using a gradient elution from 0% to 10% ethyl acetate in cyclohexane to afford *the title compound* (3.95 g, 13.1 mmol, 79% yield). LCMS RT= 1.30 min, ES+ve m/z 291.1 [M+H]⁺.

(7S,8R,9S,13S,14S,17S)-7-(4-(Benzyloxy)butyl)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-6-one



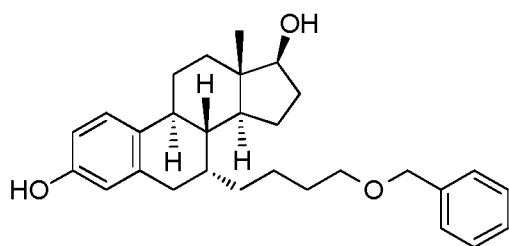
A solution of KOtBu in THF (1M, 10.7 mL, 10.7 mmol) was added to a cooled solution (0 °C) of (8R,9S,13S,14S,17S)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-6-one (2 g, 5.34 mmol) in THF (20 mL). The reaction mixture was stirred at 0 °C for 45 minutes and then cooled to -78 °C. ((4-iodobutoxy)methyl)benzene (2.32 g, 8.01 mmol) in THF (10 mL) was added dropwise. The solution was stirred at -78 °C for 2 minutes, then allowed to warm to room temperature and stirred overnight. The reaction mixture was partitioned between water (30 mL) and ethyl acetate (30 mL). The organic extract was separated, washed with brine (30 mL), dried using a hydrophobic frit and concentrated under reduced pressure. The product was purified by chromatography on silica using a gradient elution from 0% to 40% ethyl acetate in cyclohexane to afford *the title compound* (1.78 g, 2.89 mmol, 54% yield). LCMS RT= 1.54 min, ES+ve m/z 537.5 [M+H]⁺, 87% purity.

(7S,8R,9S,13S,14S,17S)-7-(4-(Benzyloxy)butyl)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-6-one



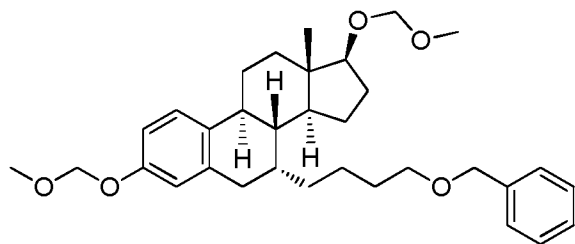
A solution of aqueous HCl (6M, 19.3 mL, 116 mmol) was added to a solution of (7S,8R,9S,13S,14S,17S)-7-(4-(benzyloxy)butyl)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-6-one (1.78 g, 2.89 mmol, 87% purity) in THF (20 mL). The reaction mixture was stirred at room temperature overnight. Water (30 mL) was added and the product was extracted with ethyl acetate (50 mL). The organic extract was washed with brine (2 x 30 mL), dried using a hydrophobic frit and concentrated under reduced pressure to afford *the title compound* (1.47 g, 2.88 mmol, quantitative yield). LCMS RT= 1.10 min, ES+ve *m/z* 449.0 [M+H]⁺, 88% purity.

(7R,8R,9S,13S,14S,17S)-7-(4-(Benzyloxy)butyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3,17-diol



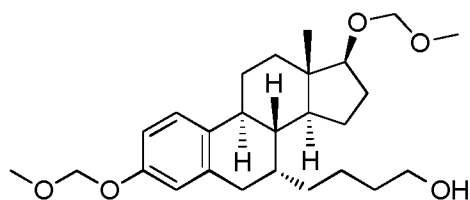
Triethylsilane (commercially available from for example Aldrich) (4.6 mL, 28.8 mmol) was added to a solution of (7S,8R,9S,13S,14S,17S)-7-(4-(benzyloxy)butyl)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-6-one (1.47 g, 2.88 mmol, 88% purity) in TFA (16.7 mL, 216 mmol). The reaction was stirred at room temperature under an atmosphere of nitrogen for 18 hours. The mixture was partitioned between ethyl acetate (50 mL) and brine (50 mL). The organic extract was washed with brine (2 x 50 mL), saturated sodium bicarbonate (50 mL), dried using a hydrophobic frit and concentrated under reduced pressure. The residue was dissolved in MeOH (10 mL) and treated with aqueous NaOH (2M, 13.5 mL, 27.0 mmol). The reaction mixture was stirred at room temperature for 1 hour and the solvent was then removed under reduced pressure. The residue was partitioned between ethyl acetate (40 mL) and aqueous HCl (1M, 20 mL). The organic extract was separated, washed with brine (20 mL), dried using a hydrophobic frit and concentrated under reduced pressure. The product was purified by reverse phase chromatography using a gradient elution from 5% to 95% acetonitrile (+ 0.1% formic acid) in water (+ 0.1% formic acid) to afford *the title compound* (583 mg, 1.33 mmol, 46% yield). LCMS RT= 1.23 min, ES+ve *m/z* 435.2 [M+H]⁺.

(7R,8R,9S,13S,14S,17S)-7-(4-(Benzyloxy)butyl)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene



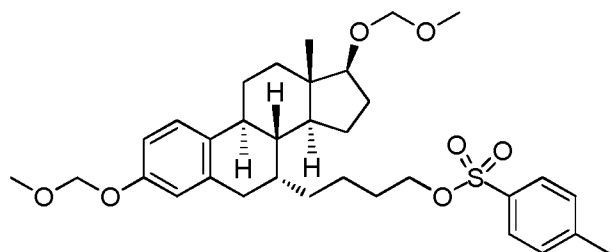
Chloro(methoxy)methane (commercially available from for example Aldrich) (0.5 mL, 6.58 mmol) was added to a cold (0 °C) solution of (7R,8R,9S,13S,14S,17S)-7-(4-(benzyloxy)butyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3,17-diol (583 mg, 1.33 mmol) and DIPEA (1.5 mL, 8.59 mmol) in THF (15 mL). The reaction mixture was warmed to room temperature, stirred for 1 hour and heated at 70 °C for 3 days. The reaction was cooled to room temperature and the reaction was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic extract was washed with brine (2 x 50 mL), dried using a hydrophobic frit and concentrated under reduced pressure. The product was purified by chromatography on silica using a gradient elution from 0% to 100% methyl *tert*-butyl ether in cyclohexane to afford *the title compound* (620 mg, 1.15 mmol, 52% yield). LCMS RT= 1.65 min, ES+ve *m/z* 523.5 [M+H]⁺, 540.5 [M+NH₄]⁺.

4-((7R,8R,9S,13S,14S,17S)-3,17-Bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)butan-1-ol



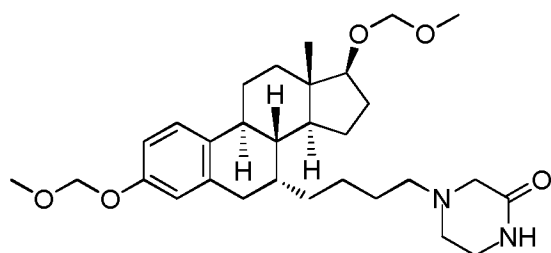
A mixture of (7R,8R,9S,13S,14S,17S)-7-(4-(benzyloxy)butyl)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene (620 mg, 1.15 mmol) and 10 % w/w palladium on carbon (244 mg, 0.229 mmol) in ethanol (10 mL) was stirred at room temperature under an atmosphere of hydrogen for 1.5 hours. The palladium on carbon was filtered through celite and the filtrate evaporated under reduced pressure to afford *the title compound* (462 mg, 1.07 mmol, 58% yield). LCMS RT= 1.31 min, ES+ve *m/z* 433.4 [M+H]⁺.

4-((7R,8R,9S,13S,14S,17S)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)butyl methylbenzenesulfonate **4-**



5 Tosyl chloride (commercially available from for example Aldrich) (279 mg, 1.462 mmol) was added to a solution of 4-((7R,8R,9S,13S,14S,17S)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)butan-1-ol (250 mg, 0.578 mmol) in pyridine (5 mL), and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was partitioned between ethyl acetate (30 mL) and aqueous HCl (2M, 10 30 mL). The organic extract was separated, washed with saturated sodium bicarbonate solution (30 mL), brine (30 mL), dried using a hydrophobic frit and concentrated under reduced pressure. The product was purified by chromatography on silica using a gradient elution from 0% to 100% methyl *tert*-butyl ether in cyclohexane to afford *the title compound* (140 mg, 0.239 mmol, 42% yield). LCMS RT= 1.58 min, ES+ve *m/z* 604.3 [M+NH₄]⁺.

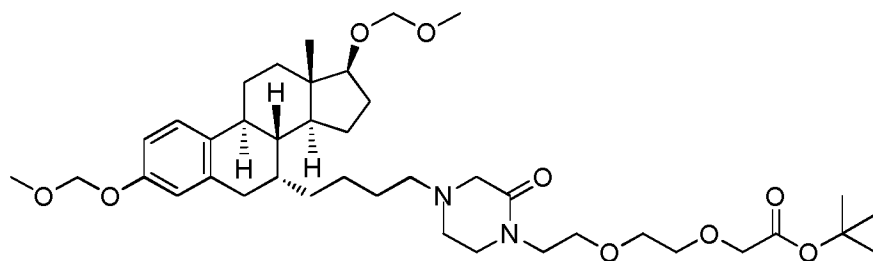
15 **4-(4-((7R,8R,9S,13S,14S,17S)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)butyl)piperazin-2-one**



A vial was charged with 4-((7R,8R,9S,13S,14S,17S)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)butyl 4- 20 methylbenzenesulfonate (140 mg, 0.239 mmol), piperazin-2-one (commercially available from for example Aldrich) (72 mg, 0.716 mmol) and DIPEA (0.21 mL, 1.2 mmol) in THF (2 mL). The vial was sealed and the reaction was heated at 80° C for 72 hours. The reaction mixture was cooled and then

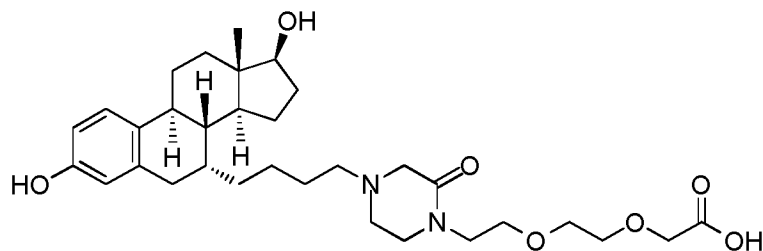
subjected directly to purification by mass-directed automated preparative HPLC (ammonium carbonate modifier) to afford *the title compound* (80 mg, 0.155 mmol, 65% yield). LCMS RT= 0.97 min, ES+ve m/z 515.5 [M+H]⁺.

***tert*-Butyl 2-(2-(2-(4-(4-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(methoxymethoxy)-13-methyl-
5 7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)butyl)-2-oxopiperazin-1-yl)ethoxy)ethoxy)acetate**



Sodium hydride, 60 % w/w in mineral oil (12 mg, 0.311 mmol) was added to a cooled solution (0 °C) of 4-(4-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(methoxymethoxy)-13-methyl-
10 7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)butyl)piperazin-2-one (80 mg, 0.155 mmol) in DMF (1 mL). The reaction was stirred at 0 °C for 30 minutes and *tert*-butyl 2-(2-(2-(tosyloxy)ethoxy)ethoxy)acetate (116 mg, 0.311 mmol) was added. The reaction was warmed to room temperature and stirred for 4 hours. The reaction mixture was then heated to 80 °C and left to stir overnight. The reaction was cooled to 0 °C, additional sodium hydride, 60 % w/w
15 in mineral oil (12 mg, 0.311 mmol) and *tert*-butyl 2-(2-(2-(tosyloxy)ethoxy)ethoxy)acetate (116 mg, 0.311 mmol) was added. The reaction was heated to 80 °C and stirred for an additional 72 hours. The reaction mixture was partitioned between ethyl acetate (30 mL) and saturated sodium bicarbonate solution (20 mL). The organic layer was separated, washed with brine (30 mL), dried using a hydrophobic frit and concentrated under reduced pressure. The crude product was purified
20 by chromatography on silica using a gradient elution from 0% to 25% MeOH in DCM to afford *the title compound* (30 mg, 0.042 mmol, 27% yield). LCMS RT= 1.15 min, ES+ve m/z 717.6 [M+H]⁺.

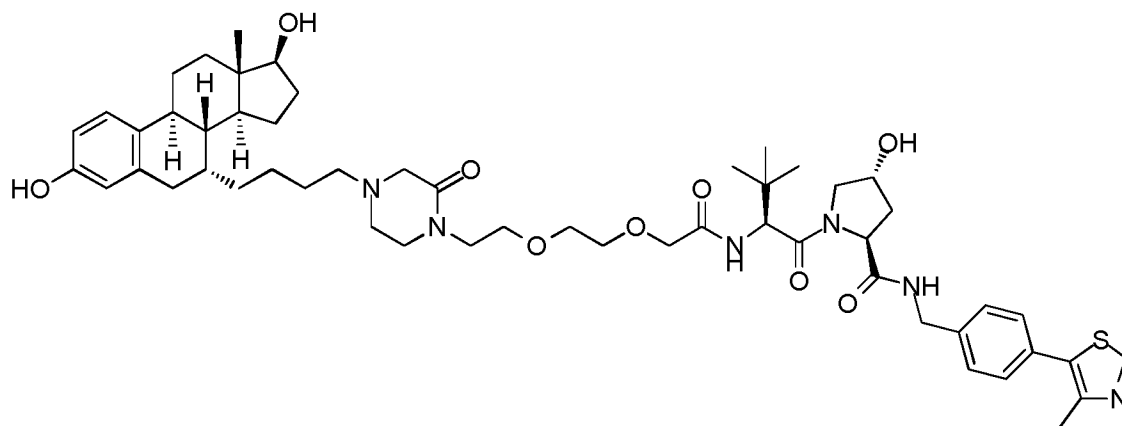
**2-(2-(2-(4-(4-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-Dihydroxy-13-methyl-
7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)butyl)-2-
25 oxopiperazin-1-yl)ethoxy)ethoxy)acetic acid**



Tert-butyl 2-(2-(2-(4-(4-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)butyl)-2-oxopiperazin-1-yl)ethoxy)ethoxy)acetate (26 mg, 0.036 mmol) was dissolved in THF (0.4 mL) and treated with aqueous HCl (6M, 0.4 mL, 2.4 mmol). The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was then subjected directly to purification by mass-directed automated preparative HPLC (formic acid modifier) to afford *the title compound* (6 mg, 10.5 μ mol, 29% yield). LCMS RT= 0.62 min, ES+ve *m/z* 573.5 [M+H]⁺.

Example 12:

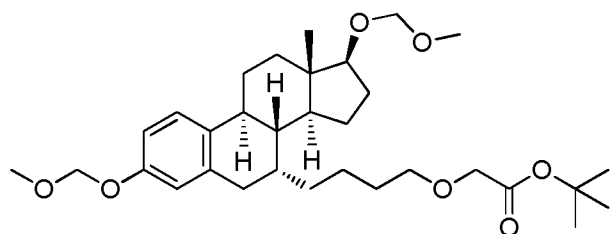
- 10 **(2*S*,4*R*)-1-((*S*)-2-(2-(2-(2-(4-(4-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-Dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)butyl)-2-oxopiperazin-1-yl)ethoxy)ethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**



- 15 HATU (5 mg, 0.014 mmol) was added to a mixture of (2*S*,4*R*)-1-((*S*)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide, hydrochloride (10 mg, 0.021 mmol), 2-(2-(2-(4-(4-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)butyl)-2-oxopiperazin-1-yl)ethoxy)ethoxy)acetic acid (6 mg, 11 μ mol) and DIPEA (11 μ L, 0.063 mmol) in

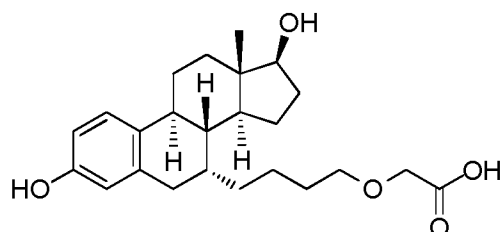
DMF (0.6 mL). The reaction was stirred at room temperature for 30 minutes, and was subjected directly to purification by mass-directed automated preparative HPLC (formic acid modifier) to afford *the title compound* (5 mg, 5.1 μ mol, 48% yield). LCMS RT= 0.78 min, ES+ve m/z 985.7 $[M+H]^+$.

- 5 ***tert*-Butyl 2-(4-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)butoxy)acetate**



- 10 Sodium hydride, 60 % w/w in mineral oil (33 mg, 0.83 mmol) was added to a cooled solution (0 °C) of 4-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)butan-1-ol (180 mg, 0.416 mmol) in DMF (4 mL). The reaction was stirred at 0 °C for 30 minutes, *tert*-butyl 2-bromoacetate (commercially available from for example Aldrich) (0.12 mL, 0.832 mmol) was
- 15 added, and the reaction was stirred for an additional 1 hour. The reaction mixture was partitioned between ethyl acetate (30 mL) and water (30 mL). The aqueous layer was separated, extracted with additional ethyl acetate (2 x 30 mL). The combined organic layers were washed with saturated ammonium chloride solution (30 mL), brine (2 x 30 mL), dried using a hydrophobic frit and concentrated under reduced pressure. The product was purified by
- 20 chromatography on silica using a gradient elution from 0% to 100% methyl *tert*-butyl ether in cyclohexane to afford *the title compound* (85 mg, 0.048 mmol, 12% yield). LCMS RT= 1.60 min, ES+ve m/z 564.5 $[M+NH_4]^+$, 569.5 $[M+Na]^+$.

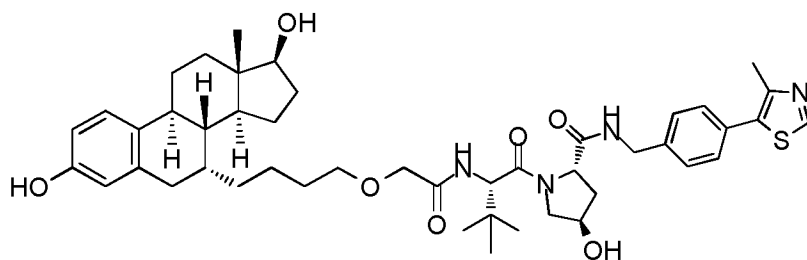
- 25 **2-(4-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)butoxy)acetic acid**



tert-Butyl 2-(4-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)butoxy)acetate (85 mg, 0.048 mmol) was dissolved in THF (0.8 mL) and treated with aqueous HCl (6M, 0.85 mL, 5.1 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was then diluted with DMSO (0.2 mL) and subjected directly to purification by mass-directed automated preparative HPLC (formic acid modifier) to afford *the title compound* (7.5 mg, 0.018 mmol, 37% yield). LCMS RT= 0.87 min, ES+ve *m/z* 403.5 [M+H]⁺.

Example 13:

(2*S*,4*R*)-1-((*S*)-2-(2-(4-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)butoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



HATU (8 mg, 0.021 mmol) was added to a mixture of (2*S*,4*R*)-1-((*S*)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide, hydrochloride (10 mg, 0.021 mmol), 2-(4-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)butoxy)acetic acid (7.5 mg, 0.018 mmol) and DIPEA (0.012 mL, 0.072 mmol) in DMF (0.8 mL). The reaction was stirred at room temperature for 30 minutes, and was then subjected directly to purification by mass-directed automated preparative HPLC (formic acid modifier) to afford *the title compound* (4.4 mg, 5.4 μmol, 30% yield). LCMS RT= 0.99 min, ES+ve *m/z* 815.6 [M+H]⁺.

Estrogen receptor alpha (ERα) degradation and cell count imaging assay

Compounds were assessed for ERα degradation and cell count effects in an MCF-7 cell line using high content imaging. 50ul of MCF-7 cell suspension in media was dispensed to each well of black walled, clear bottomed, PDL-coated plates, containing a defined concentration of test compound dissolved in DMSO covering concentration range from 0.03uM to 30uM. Cells were incubated in the presence of

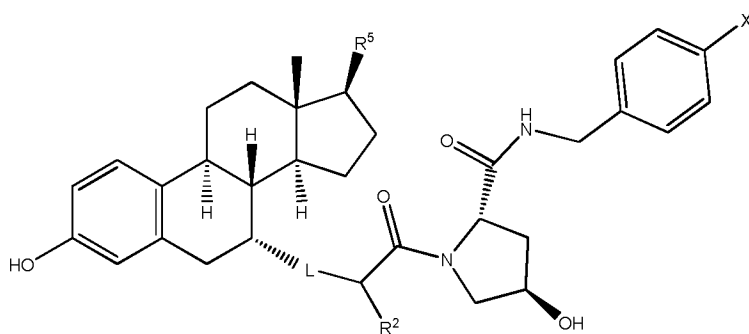
compound for 24 hours at 37°C, 5% CO₂ before cells were fixed. After incubation with the fixative solution (4% formaldehyde) the wells were aspirated and a solution containing detergent was added to permeabilise the cells followed by addition of blocking solution containing 1%BSA (bovine serum albumin) to block the non-specific binding sites. After a further incubation for 1 hour this solution was aspirated from the wells and the ERa specific antibody diluted in blocking solution at concentration 1µg/ml (anti ERa, cat no sc-543, Santa Cruz) was added. Following incubation with the antibody for 2 hours the cells were washed with a PBS-based solution before addition of a secondary anti rabbit fluorescently-labelled Alexa Fluor 488 goat antibody at 2µg/ml concentration (cat no11008, Invitrogen) and a nuclear staining dye Hoechst33342 at 1µg/ml concentration (cat no H3570, invitrogen). Following a further incubation for 1 hour the cells were again washed with the PBS-based solution. The plates were then imaged and the intensity of ERa staining in the nucleus and cell count measured. ERa degradation activity was expressed relative to DMSO, giving 0% degradation, and an in-house degrader molecule classified as giving 100% activity. Cell count reduction was expressed relative to DMSO, classified as 0% reduction.

All Examples showed evidence of ERa degradation in this assay relative to the DMSO control at 1µM concentration.

CLAIMS

1. A compound of formula (I):

In one aspect there is provided a compound of formula (I):



(I)

Wherein

L is a linking group comprising a length of 6-16 atoms in shortest length having the formula $-(CH_2)_n - (R^1CH_2CH_2)_m (OCH_2)_qCONH -$;

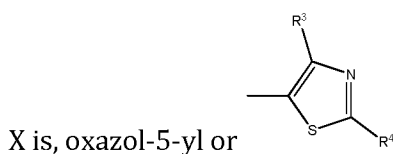
n is 0-6;

m is 2-10;

q is 0 or 1

each R^1 is independently $-O-$, $-NH-$, $-N(C_{1-3} \text{ alkyl})-$, or a 4-6 membered heterocyclyl group containing 2 N atoms linked to the carbons in the chain via the ring N atoms (optionally substituted by oxo).;

R^2 is C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl



R^3 is H or CH_3 ;

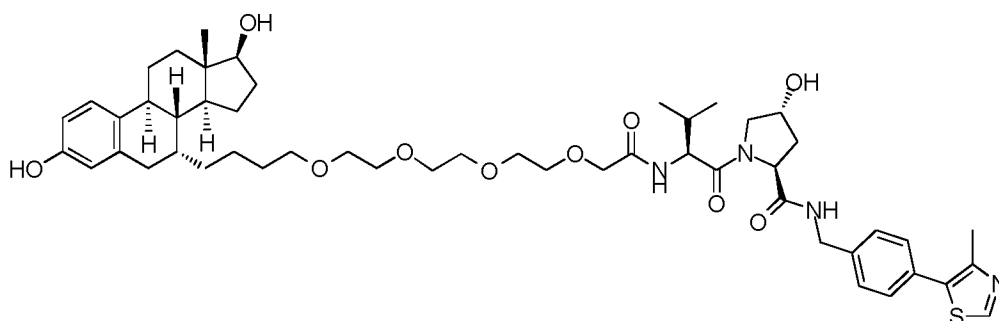
R^4 is H or CH_3 ;

R^5 is OH or OC_{1-3} alkyl

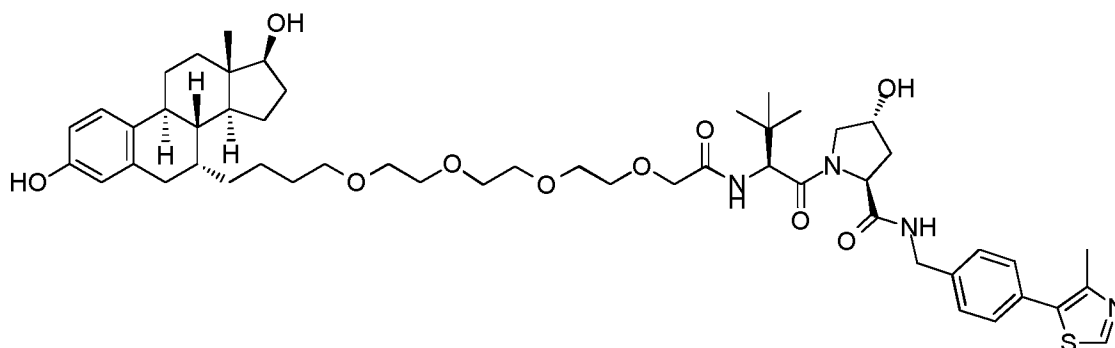
or a pharmaceutically acceptable salt thereof.

2. A compound of formula (I) according to claim 1 which is

5 (2*S*,4*R*)-1-((*S*)-19-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-Dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-2-isopropyl-4-oxo-6,9,12,15-tetraoxa-3-azanonadecan-1-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide

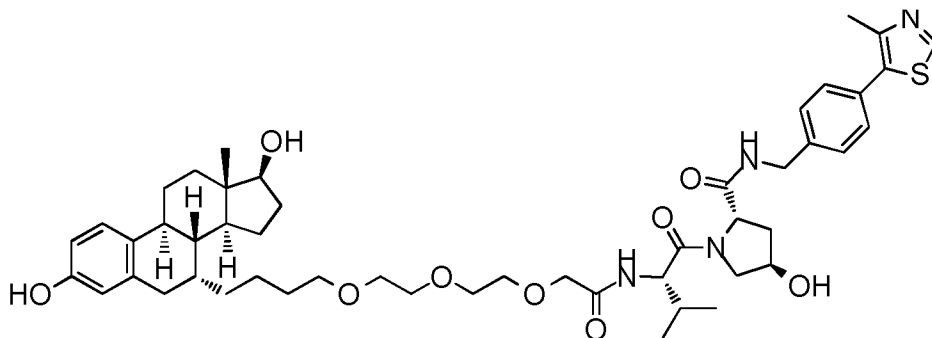


10 (2*S*,4*R*)-1-((*S*)-2-(*Tert*-butyl)-19-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-4-oxo-6,9,12,15-tetraoxa-3-azanonadecan-1-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide

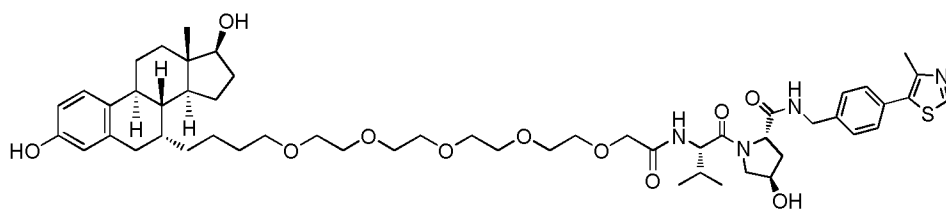


15 (2*S*,4*R*)-1-((*S*)-16-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-Dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-2-isopropyl-4-oxo-6,9,12-trioxa-3-azahexadecan-1-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide

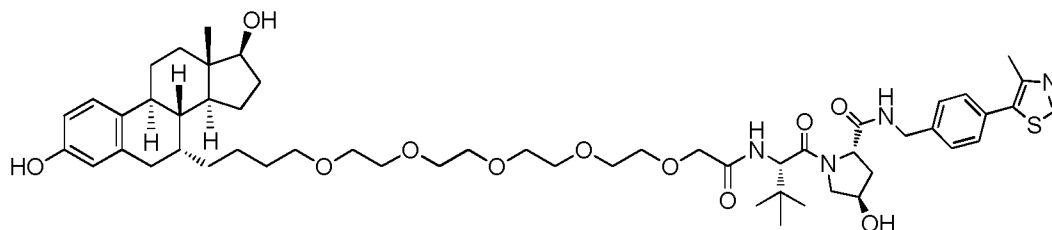
20



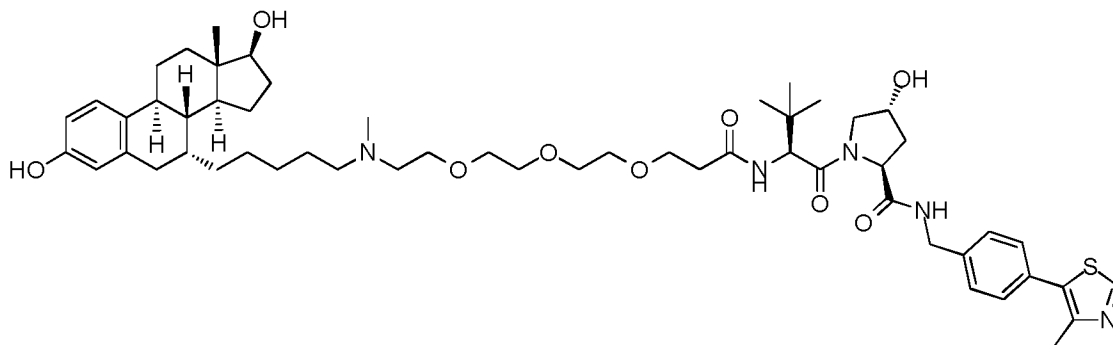
(2*S*,4*R*)-1-((*S*)-22-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-Dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-2-isopropyl-4-oxo-6,9,12,15,18-pentaoxa-3-azadocosan-1-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



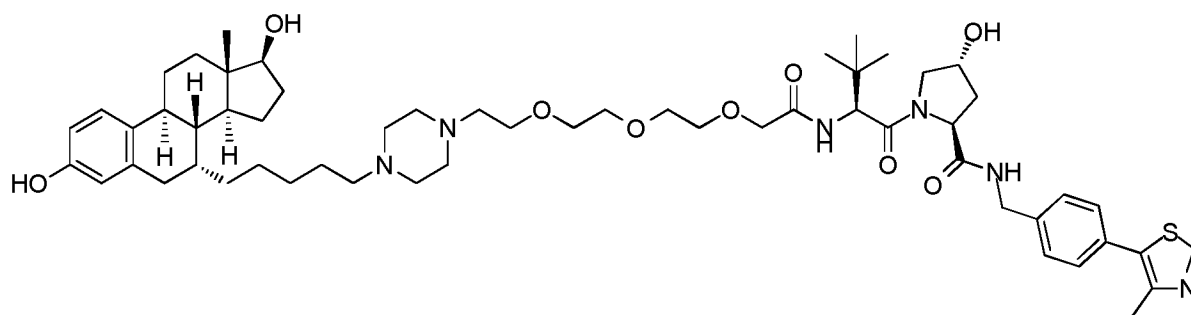
(2*S*,4*R*)-1-((*S*)-2-(*Tert*-butyl)-22-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-4-oxo-6,9,12,15,18-pentaoxa-3-azadocosan-1-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



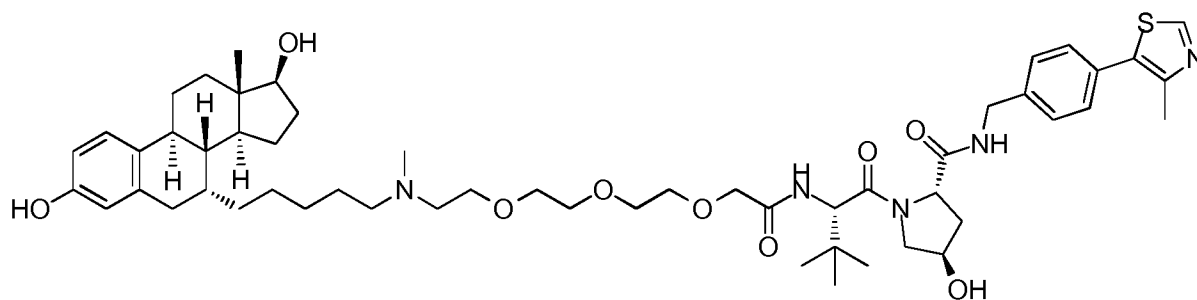
(2*S*,4*R*)-1-((*S*)-2-(*Tert*-butyl)-21-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)-16-methyl-4-oxo-7,10,13-trioxa-3,16-diazahenicosan-1-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



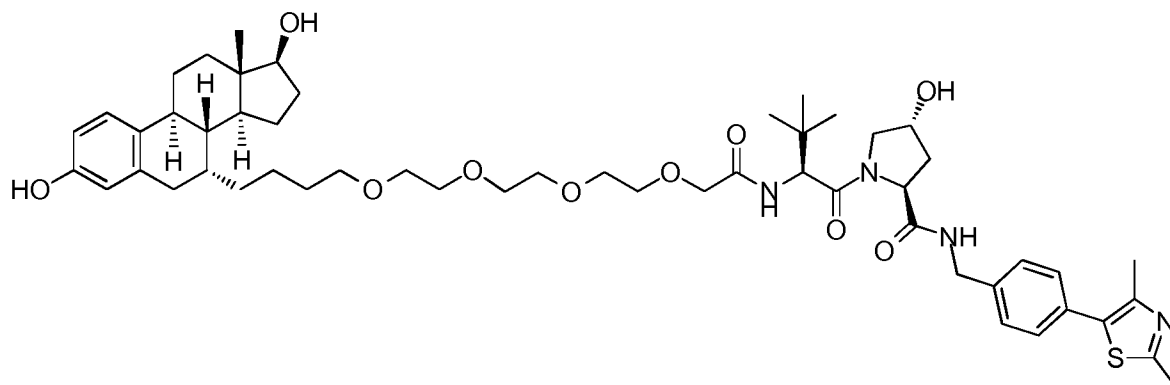
(2S,4R)-1-((S)-2-(*tert*-butyl)-14-(4-(5-((7R,8R,9S,13S,14S,17S)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)pentyl)piperazin-1-yl)-4-oxo-6,9,12-trioxa-3-azatetradecan-1-oyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



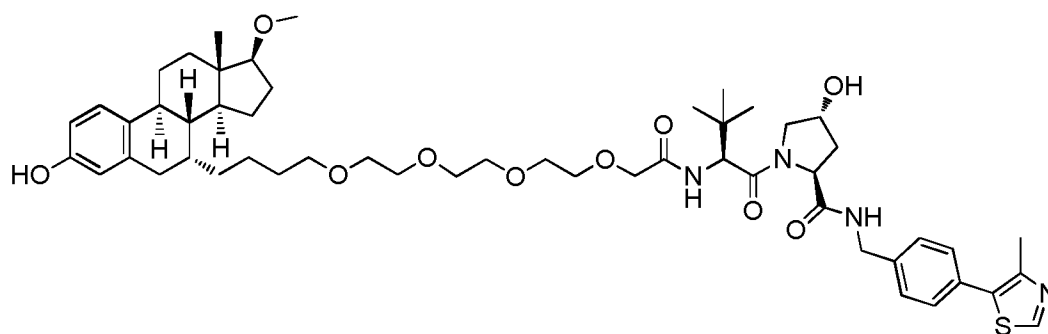
(2S,4R)-1-((S)-2-(*tert*-Butyl)-20-((7R,8R,9S,13S,14S,17S)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)-15-methyl-4-oxo-6,9,12-trioxa-3,15-diazaicosan-1-oyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



(2S,4R)-1-((S)-2-(*tert*-Butyl)-19-((7R,8R,9S,13S,14S,17S)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)-4-oxo-6,9,12,15-tetraoxa-3-azanonadecan-1-oyl)-N-(4-(2,4-dimethylthiazol-5-yl)benzyl)-4-hydroxypyrrolidine-2-carboxamide

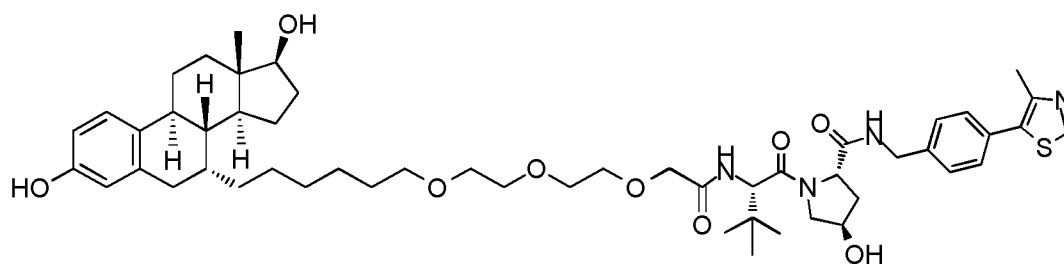


(2S,4R)-1-((S)-2-(Tert-butyl)-19-((7R,8R,9S,13S,14S,17S)-3-hydroxy-17-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)-4-oxo-6,9,12,15-tetraoxa-3-azanonadecan-1-oyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide

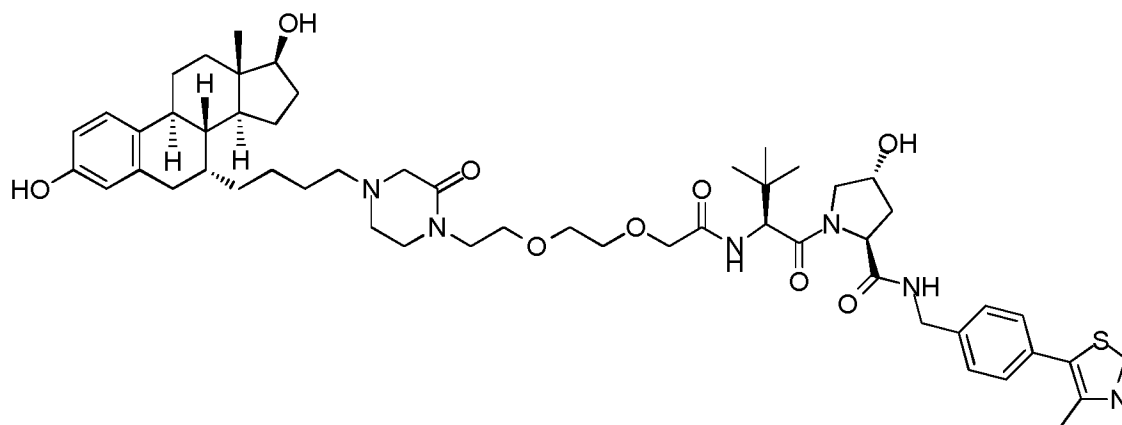


ied by chromatography on silica using a gradient elution from 0% to 85% methyl *tert*-butyl ether in cyclohexane to afford *the title compound* (3.91 g, 10.3 mmol, 51% yield). LCMS RT= 1.30 min, ES+ve *m/z* 359.3./361.3 [M+H]⁺.

(2S,4R)-1-((S)-2-(Tert-butyl)-18-((7R,8R,9S,13S,14S,17S)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl)-4-oxo-6,9,12-trioxa-3-azaoctadecan-1-oyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide

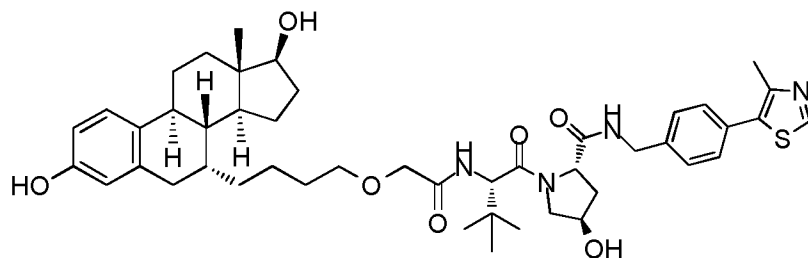


(2*S*,4*R*)-1-((*S*)-2-(2-(2-(2-(4-(4-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-Dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)butyl)-2-oxopiperazin-1-yl)ethoxy)ethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



5

(2*S*,4*R*)-1-((*S*)-2-(2-(4-((7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)butoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



10

and pharmaceutically acceptable salts thereof.

3. A compound of formula (I) or a pharmaceutically acceptable salt thereof according to claims 1-2 for use in therapy, in particular in the treatment of diseases and conditions mediated by the estrogen receptor.

15

4. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claims 1-2 and one or more of pharmaceutically acceptable carriers, diluents and excipients.

20

5. A method of treating diseases and conditions mediated by the estrogen receptor in a subject comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claims 1-2.

5 6. The use of a compound of formula (I), or a pharmaceutically acceptable salt thereof according to claims 1-2 in the manufacture of a medicament for use in treating diseases and conditions mediated by the estrogen receptor.

7. A combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claims 1-2 and at least one further therapeutic agent.

8. A combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claims 1-2 and at least one further therapeutic agent for use in therapy, particularly for treating diseases and conditions mediated by the estrogen receptor.

9 A combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claims 1-2 and at least one further therapeutic agent for use in treating diseases and conditions mediated by the estrogen receptor.

10. A method of treating diseases and conditions mediated by the estrogen receptor comprising administering to a human in need thereof a therapeutically effective amount of a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claims 1-2 and at least one further therapeutic agent .

11. The use of a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claims 1-2 and at least one further therapeutic agent in the manufacture of a medicament for treating diseases and conditions mediated by the estrogen receptor.

12. A combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claims 1-2 and at least one anti-neoplastic agent.

13. A combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claims 1-2 and at least one anti-neoplastic agent, for use in therapy.

5 14. In a further aspect there is provided a combination comprising a compound of formula (I) or pharmaceutically acceptable salt thereof according to claims 1-2 and at least one anti-neoplastic agent, for use in treating diseases and conditions mediated by the estrogen receptor.

10 15. the use of a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claims 1-2 and at least one anti-neoplastic agent, in the manufacture of a medicament for treating diseases and conditions mediated by the estrogen receptor.

15 16. a method of treating diseases and conditions mediated by the estrogen receptor, comprising administering to a human in need thereof a therapeutically effective amount of a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claims 1-2 and at least one anti-neoplastic agent.

20 17. I a pharmaceutical composition comprising a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claims 1-2 and at least one further therapeutic agent, particularly at least one anti-neoplastic agent and one or more of pharmaceutically acceptable carriers, diluents and excipients.

25 18. A method of treating breast cancer comprising administering to human in need thereof, a therapeutically effect amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claims 1-2

30 19. A method of degrading the estrogen receptor comprising administration comprising administering to a human in need thereof a therapeutically effective amount of a compound of Formula (I) according to claims 1-2 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/050267

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07J43/00 A61K31/58 A61P5/32
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)

C07J 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, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CYRUS, KEDRA ET AL: "Impact of linker length on the activity of PROTACs", MOLECULAR BIOSYSTEMS , 7(2), 359-364 CODEN: MBOIBW; ISSN: 1742-206X, 2011, XP002721196, DOI: 10.1039/C0MB00074D page 360; figure 2 page 361; figure 3; compounds 11-17 ----- -/--	1-19



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

10 March 2014

Date of mailing of the international search report

19/03/2014

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Watchorn, Peter

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2014/050267

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CYRUS KEDRA ET AL: "Jostling for position: optimizing linker location in the design of estrogen receptor-targeting PROTACs.", CHEMMEDCHEM 5 JUL 2010, vol. 5, no. 7, 5 July 2010 (2010-07-05), pages 979-985, XP002721197, ISSN: 1860-7187 page 980; figure 1 page 981; compound 4 page 982; compound 24 page 982, column 1, paragraph 2 - page 983, column 1, paragraph 1 -----	1-19
Y	CYRUS KEDRA ET AL: "Two-headed PROTAC: an effective new tool for targeted protein degradation.", CHEMBIOCHEM : A EUROPEAN JOURNAL OF CHEMICAL BIOLOGY 26 JUL 2010, vol. 11, no. 11, 26 July 2010 (2010-07-26), pages 1531-1534, XP002721198, ISSN: 1439-7633 page 1532, column 1, paragraph 2 - column 2, paragraph 1; figure 1; compounds 3,4 -----	1-19
Y	BUCKLEY DENNIS L ET AL: "Small-molecule inhibitors of the interaction between the E3 ligase VHL and HIF1[alpha].", ANGEWANDTE CHEMIE (INTERNATIONAL ED. IN ENGLISH) 12 NOV 2012, vol. 51, no. 46, 12 November 2012 (2012-11-12), pages 11463-11467, XP002721199, ISSN: 1521-3773 page 11463, column 1, paragraph 2-3 page 11464; table 1; compounds 1, 3, 4, 6 -----	1-19
X,P	WO 2013/106643 A2 (UNIV YALE [US]; GLAXOSMITHKLINE IP DEV LTD [GB]; CAMBRIDGE ENTPR LTD U) 18 July 2013 (2013-07-18) page 52, paragraph 3 page 282, paragraph 1 page 291 page 292 page 298 page 303 page 304 page 308 -----	1-19

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2014/050267

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
W0 2013106643	A2	18-07-2013	NONE
