

Description

Title of Invention: PIPERAZINE-SUBSTITUTED BENZOTH-IOPHENES FOR TREATMENT OF MENTAL DISORDERS

Technical Field

- [0001] The present application relates to novel compounds which are prodrugs of brexpiprazole. The novel compounds of the invention, upon administration to a subject, undergo chemical conversion by one or more metabolic processes to release an active pharmacological agent in vivo. Brexpiprazole, sold under the Rexulti (registered trademark), is an atypical antipsychotic indicated for use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) in adults and the treatment of schizophrenia in adults and pediatric patients ages 13 years and older.

Background Art

- [0002] Brexpiprazole, 7-[4-(4-benzo[b]thiophen-4-yl-piperazin-1-yl)butoxy]-1H-quinolin-2-one, or a salt thereof has dopamine D₂ receptor partial agonistic activity, serotonin 5-HT_{2A} receptor antagonistic activity, and adrenaline α_1 receptor antagonistic activity. In addition to the activity, brexpiprazole or a salt thereof is known to have serotonin uptake or reuptake inhibitory activity as well and have a wide range of therapeutic possibilities against various nervous system disorders (PTL 1 and 2).
- [0003] Drug designing in the medicinal field includes chemical conversion or modification of one or more functional groups of a known drug molecule to improve its pharmaceutical or pharmacokinetic properties, such as enhancing drug efficacy and delaying in-vivo metabolism. Such a chemical conversion or modification includes formation of a conjugate of multiple API molecules with a carrier moiety (PTL 3). There has been a need for novel compounds that can be converted into brexpiprazole in vivo with improved pharmaceutical or pharmacokinetic properties, less side effects, and enhanced tolerability and safety.

Citation List

Patent Literature

- [0004] [PTL 1] WO2006/112464
[PTL 2] WO2013/035892
[PTL3] WO2012/088441

Summary of Invention

Technical Problem

- [0005] An object of the present invention is to provide novel compounds with antipsychotic

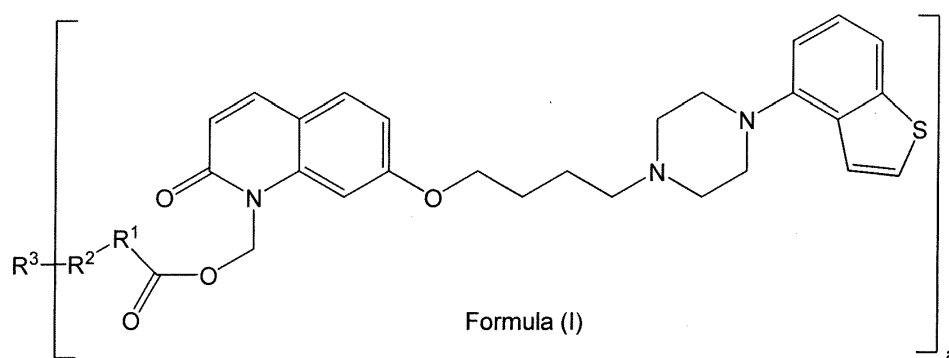
activity, with acceptable pharmaceutical or pharmacokinetic properties, side effects, tolerability, and safety as compared with well-known typical and atypical antipsychotic drugs including brexpiprazole.

Solution to Problem

[0006] This invention describes compounds, or pharmaceutically acceptable salts thereof, which have antipsychotic activity. The compounds, or pharmaceutically acceptable salts thereof, in accordance with the present invention are thus of use in medicine, for example in the treatment and/or prophylaxis of humans with diseases and conditions that are antipsychotic related.

[0007] In one embodiment the present invention provides a compound represented by Formula (I), its individual geometrical isomers, its individual enantiomers, its individual diastereoisomers, its individual tautomers, its individual zwitterions or pharmaceutically acceptable salts thereof:

[Chem.1]



wherein:

a is 2 or 3;

R¹ is optionally substituted linear or branched C₁₋₂₀ alkylene; optionally substituted C₂₋₁₀ alkenylene; optionally substituted divalent C₃₋₈ cycloalkyl; optionally substituted divalent heterocycle; optionally substituted divalent C₆₋₁₀ aryl; -NH(optionally substituted linear or branched C₁₋₂₀ alkylene); or optionally substituted divalent C₃₋₈ cycloalkenyl;

R² is -C(O)-, -O-C(O)-, -C(O)-NR^a-CH₂-, -O-, -CH₂-, -NR^a-C(O)-, or a direct bond;

R³ is optionally substituted non-aromatic divalent or trivalent heterocycle, optionally substituted aromatic divalent or trivalent heterocycle, or optionally substituted linear or branched C₁₋₂₀ alkylene;

R^a is hydrogen or optionally substituted linear or branched C₁₋₂₀ alkyl;

when a is 2, R³ is divalent;

when a is 3, R³ is trivalent; and

R² and R³ are connected with covalent bond(s);
provided that when R¹ is linear alkylene and R² is -CH₂- or a direct bond, R³ is not linear alkylene.

Advantageous Effects of Invention

[0008] A compound of Formula (I), or a pharmaceutically acceptable salt thereof, includes a structure wherein brexpiprazole is chemically modified, e.g., multiple brexpiprazole molecules are covalently linked with each other via a chemical linker. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, may undergo chemical conversion to an active pharmacological agent, brexpiprazole, upon administration to a subject under physiological conditions including one or more metabolic processes to release brexpiprazole in vivo.

[0009] A compound of Formula (I), or a pharmaceutically acceptable salt thereof, may have at least one pharmacological activity selected from the following:

- stability in subcutaneous tissue, e.g., low conversion to the parent drug, brexpiprazole, in subcutaneous tissue;
- rapid conversion to brexpiprazole in systemic circulation;
- suitable PK profile as a long acting injection (LAI), e.g., a longer duration of action per dose than the parent drug;
- low irritability at the injection site.

Brief Description of Drawings

[0010] [Fig.1]Fig. 1 provides the XRPD pattern of Form A of a compound of Example 10.
[Fig.2]Fig. 2 provides a DSC thermogram of Form A of a compound of Example 10.
[Fig.3]Fig. 3 provides the XRPD pattern of Form B of a compound of Example 10.
[Fig.4]Fig. 4 provides a DSC thermogram of Form B of a compound of Example 10.
[Fig.5]Fig. 5 provides the XRPD pattern of Form 1 of a compound of Example 19.
[Fig.6]Fig. 6 provides a TGA profile of Form 1 of a compound of Example 19.
[Fig.7]Fig. 7 provides a DSC thermogram of Form 1 of a compound of Example 19.
[Fig.8]Fig. 8 shows a PK profile (plasma brexpiprazole concentration - time) when a compound of Example 10 was administered via SC to rats according to Test 4 (Mean ± S.D.; N=3). The upper line shows a PK profile of Example 10 aqueous suspension (1.9 μm). The lower line show a PK profile of Example 10 aqueous suspension (3.4 μm).
[Fig.9]Fig. 9 shows a PK profile (plasma brexpiprazole concentration - time) when a compound of Example 19 was administered via SC to rats according to Test 4 (Mean ± S.D.; N=3). The upper line shows a PK profile of Example 19 aqueous suspension (0.8 μm). The lower line show a PK profile of Example 19 aqueous suspension (1.5 μm).

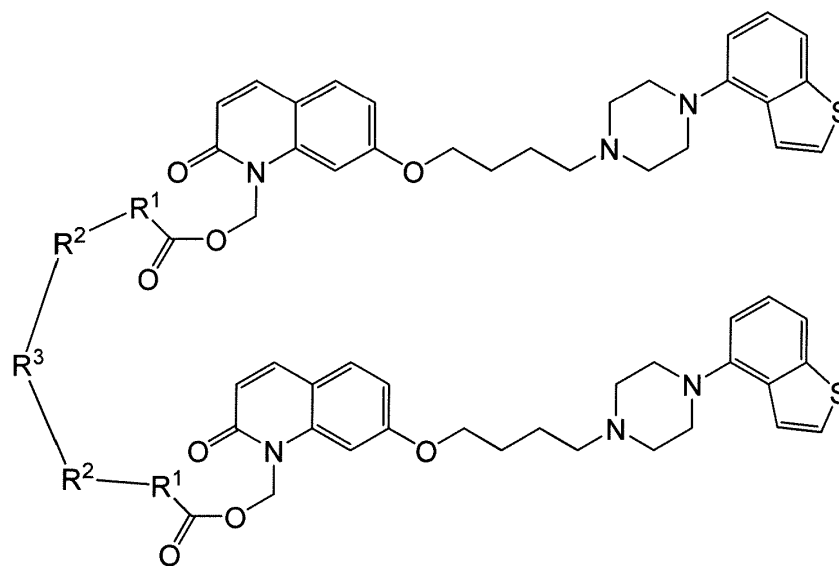
Description of Embodiments

[0011] Depending on the value of “a”, Formula (I) can be represented by Formula (IA) or by

Formula (IB). For clarity purposes, Formula (IA) and Formula (IB) are represented below.

When $a = 2$, Formula (I) is represented by Formula (IA), as described below:

[Chem.2]



Formula (IA)

When $a = 3$, Formula (I) is represented by Formula (IB), as described below:

[illegible]
$$\left[\text{R}^6 - \text{R}^5 - \text{R}^4 - \text{C}(=\text{O}) - \text{O} - \text{C}_6\text{H}_4 - \text{NH} - \text{C}_6\text{H}_4 - \text{O} - (\text{CH}_2)_4 - \text{N} - (\text{CH}_2)_4 - \text{N} - \text{C}_6\text{H}_4 - \text{S} - \text{C}_6\text{H}_4 \right]_n$$

b is 2 or 3;

R^4 is optionally substituted linear or branched C_{1-20} alkylene; optionally substituted C_{2-10} alkenylene; optionally substituted divalent C_{3-8} cycloalkyl; optionally substituted divalent heterocycle; optionally substituted divalent C_{6-10} aryl; -NH(optionally substituted linear or branched C_{1-20} alkylene); or optionally substituted divalent C_{3-8} cycloalkenyl;

R^5 is -C(O)-, -O-C(O)-, -C(O)-NR^b-CH₂-, -O-, -CH₂-, -NR^b-C(O)-, or a direct bond;

R^6 is optionally substituted non-aromatic divalent or trivalent heterocycle, or an optionally substituted aromatic divalent or trivalent heterocycle, or optionally substituted linear or branched C_{1-20} alkylene;

R^b is hydrogen or optionally substituted linear or branched C_{1-20} alkyl;

when b is 2, R^6 is divalent;

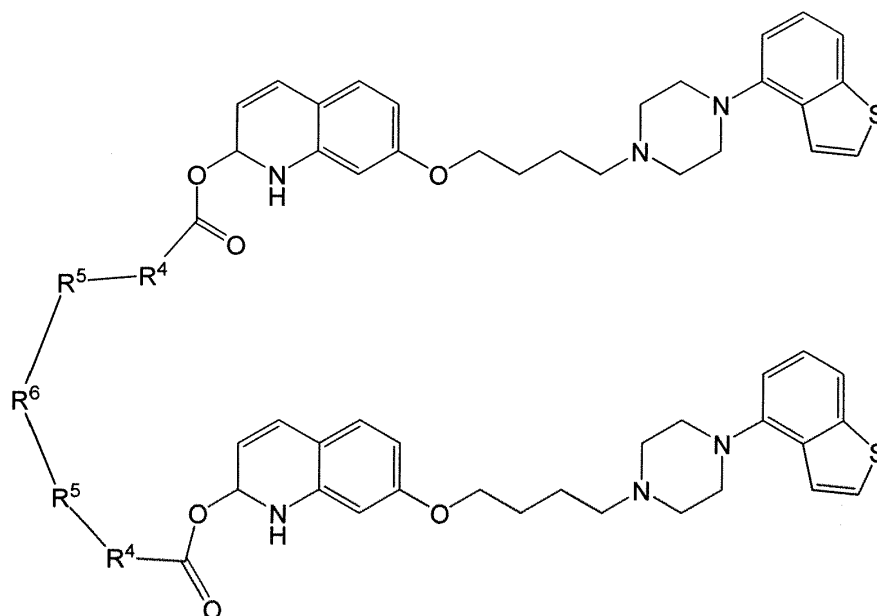
when b is 3, R^6 is trivalent; and

R^5 and R^6 are connected with covalent bond(s).

[0013] Depending on the value of “ b ”, Formula (II) can be represented by Formula (IIA) or by Formula (IIB). For clarity purposes, Formula (IIA) and Formula (IIB) are represented below.

When $b = 2$, Formula (II) is represented by Formula (IIA), as described below:

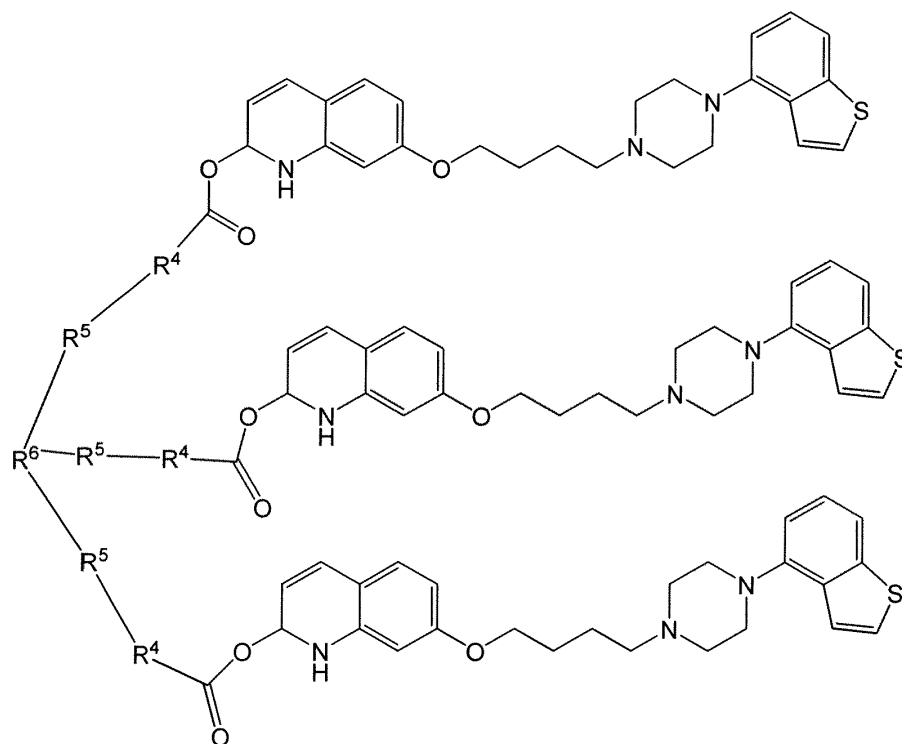
[Chem.5]



Formula (IIA)

When $b = 3$, Formula (II) is represented by Formula (IIB), as described below:

[Chem.6]



Formula (IIB)

[0014] In one embodiment the present invention provides a compound represented by the Formula (I), wherein:

a is 2 or 3;

R¹ is optionally substituted linear or branched C₂₋₁₆ alkylene, wherein one or more methylene groups can be replaced with a functional group selected from -O- or -NH-, or one or more methylene groups can be replaced with a spiro cyclopentane, or a divalent piperidine, or one or more methylene groups can be replaced with a divalent 1,3,5-triazole cycle; ethylene; optionally substituted divalent cyclohexyl; optionally substituted divalent azetidine; or optionally substituted divalent piperidine;

R² is -C(O)-, -O-C(O)-, -C(O)-N(CH₃)-CH₂-, -C(O)-NH-CH₂-, -O-, -NH-C(O)-, -CH₂-, or a direct bond;

R³ is optionally substituted divalent or trivalent piperazine, optionally substituted divalent or trivalent 2,5-diazabicyclo[2.2.2]octane, optionally substituted divalent or trivalent 2,5-diazabicyclo[2.2.1]heptane, optionally substituted divalent or trivalent octahydropyrrolo[3,4-c]pyrrole, optionally substituted divalent or trivalent pyrazine, optionally substituted divalent or trivalent 3,9-diazaspiro[5,5]undecane, optionally substituted divalent or trivalent 1,4,7-triazonane, optionally substituted divalent or

trivalent 2,6-diazaspiro[3.3]heptane, optionally substituted divalent or trivalent 1,3,5-triazine, optionally substituted divalent or trivalent 1,3-thiazol, or optionally substituted linear or branched C₂₋₆ alkylene;
 when a is 2, R³ is divalent;
 when a is 3, R³ is trivalent; and
 R² and R³ are connected with covalent bond(s).

[0015] In one embodiment the present invention provides a compound represented by the Formula (I), wherein:

a is 2;

R¹ is optionally substituted linear or branched C₂₋₁₆ alkylene, wherein one or more methylene groups can be replaced with an oxygen or amino group, or one or more methylene groups can be replaced with a spiro cyclopentane, or a divalent piperidine, or one or more methylene groups can be replaced with a divalent 1,3,5-triazole cycle; ethylene; optionally substituted divalent cyclohexyl; optionally substituted divalent azetidine; or optionally substituted divalent piperidine;

R² is -C(O)-, -O-C(O)-, -C(O)-N(CH₃)-CH₂-, -C(O)-NH-CH₂-, -CH₂-, -NH-C(O)-, or a direct bond; and

R³ is optionally substituted divalent piperazine, optionally substituted divalent 2,5-diazabicyclo[2.2.2]octane, optionally substituted divalent 2,5-diazabicyclo[2.2.1]heptane, optionally substituted divalent octahydropyrrolo[3,4-c]pyrrole, optionally substituted divalent pyrazine, optionally substituted divalent 3,9-diazaspiro[5,5]undecane, optionally substituted divalent 2,6-diazaspiro[3.3]heptane, optionally substituted divalent 1,3-thiazol, or optionally substituted linear or branched C₂₋₆ alkylene.

[0016] In one embodiment the present invention provides a compound represented by the Formula (I), wherein:

a is 3;

R¹ is optionally substituted linear or branched C₂₋₆ alkylene, wherein one or more methylene groups can be replaced with a divalent piperidine;

R² is -C(O)-, -O-, or a direct bond; and

R³ is optionally substituted trivalent 1,4,7-triazonane, or optionally substituted trivalent 1,3,5-triazine.

[0017] In one embodiment the present invention provides a compound represented by the Formula (I), wherein:

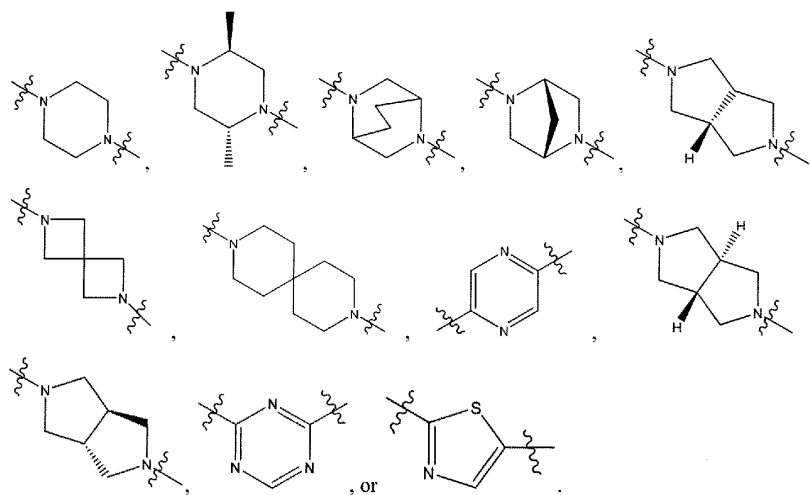
a is 2;

R¹ is -CH=CH-, -(CH₂)₂-, -(CH₂)₄-, -(CH₂)₅-, -(CH₂)₆-, -(CH₂)₇-, -NH-(CH₂)₇-, -(CH₂)₈-, -(CH₂)₉-, -(CH₂)₁₂-, -(CH₂)₁₆-,

Chemical structures illustrating various substituted rings and linkages, including cyclohexane, cyclopentane, and various substituted alkanes, with wavy lines indicating attachment points.

R³ is -(CH₂)₄-,

[Chem.8]

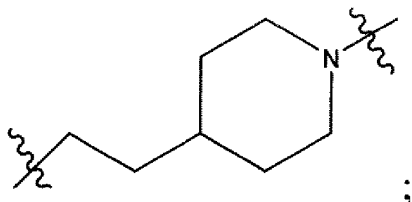


[0018] In one embodiment the present invention provides a compound represented by the Formula (I), wherein:

a is 3;

R¹ is -(CH₂)₂-, -(CH₂)₅-, or

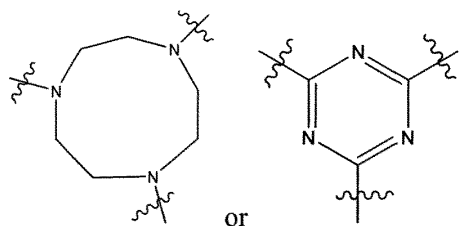
[Chem.9]



R² is -C(O)-, -O-, or a direct bond; and

R³ is

[Chem.10]



[0019] In one embodiment the present invention provides a compound represented by the Formula (I), wherein a is 2;

R^1 is optionally substituted linear or branched C_{1-20} alkylene;

R^2 is $-C(O)-$, and

R^3 is optionally substituted divalent piperazine.

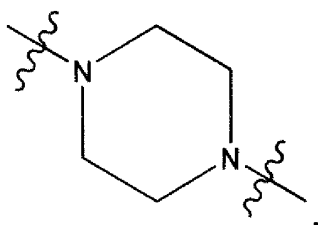
[0020] In another embodiment the present invention provides a compound represented by the Formula (I), wherein a is 2;

R^1 is optionally substituted linear or branched C_{1-20} alkylene;

R^2 is $-C(O)-$, and

R^3 is

[Chem.11]



[0021] The term “alkyl”, as used herein, refers to saturated hydrocarbon moieties having linear or branched moieties or combinations thereof and containing 1 to 20 carbon atoms. One or more methylene ($-CH_2-$) groups of the alkyl group can be replaced by oxygen, sulfur, sulfoxide, amino group, carbonyl, carboxyl, sulfonyl, sulfate, sulfonate, amide, sulfonamide, by a divalent C_{3-8} cycloalkyl, by a divalent heterocycle, or by a divalent aryl group. Alkyl groups can have one or more chiral centers. Alkyl groups can be independently substituted by halogen atoms, hydroxyl groups, cycloalkyl groups, amino groups, heterocyclic groups, aryl groups, carboxylic acid groups,

phosphonic acid groups, sulphonic acid groups, phosphoric acid groups, nitro groups, amide groups, or sulfonamide groups. Monovalent alkyl groups can be independently represented by their formulae $-C_nH_{2n+1}$ or by their abbreviated conventional names.

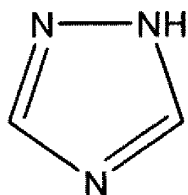
- [0022] The term “alkylene”, as used herein, refers to saturated divalent (bivalent) hydrocarbon moieties having linear or branched moieties or combinations thereof and containing 1 to 20 carbon atoms. One or more methylene ($-CH_2-$) groups of the alkylene group can be replaced by oxygen, sulfur, sulfoxide, amino group, carbonyl, carboxyl, sulfonyl, sulfate, sulfonate, amide, sulfonamide, by a divalent C_{3-8} cycloalkyl, by a divalent heterocycle, or by a divalent aryl group. Alkylene groups can have one or more chiral centers. Alkylene groups can be independently substituted by halogen atoms, hydroxyl groups, cycloalkyl groups, amino groups, heterocyclic groups, aryl groups, carboxylic acid groups, phosphonic acid groups, sulphonic acid groups, phosphoric acid groups, nitro groups, amide groups, or sulfonamide groups. Alkylene groups can be independently represented by their formulae $-C_nH_{2n}-$.
- [0023] The term “halogen”, as used herein, refers to an atom of chlorine, bromine, fluorine, iodine.
- [0024] The term “alkenyl”, as used herein, refers to a hydrocarbon radical having 2 to 10 carbon atoms, derived from a saturated alkyl, having at least one double bond. One or more methylene ($-CH_2-$) groups of the alkenyl can be replaced by oxygen, sulfur, sulfoxide, amino group, carbonyl, carboxyl, sulfonyl, sulfate, sulfonate, amide, sulfonamide, by a divalent C_{3-8} cycloalkyl, by a divalent heterocycle, or by a divalent aryl group. C_{2-10} alkenyl can be in the E or Z configuration. Alkenyl groups can be substituted by alkyl groups, as defined above, or by halogen atoms.
- [0025] The term “alkenylene”, as used herein, refers to a divalent (bivalent) hydrocarbon radical having 2 to 10 carbon atoms, derived from a saturated alkylene, having at least one double bond. One or more methylene ($-CH_2-$) groups of the alkenylene can be replaced by oxygen, sulfur, sulfoxide, amino group, carbonyl, carboxyl, sulfonyl, sulfate, sulfonate, amide, sulfonamide, by a divalent C_{3-8} cycloalkyl, by a divalent heterocycle, or by a divalent aryl group. C_{2-10} alkenylene can be in the E or Z configuration. Alkenylene groups can be substituted by alkyl groups, as defined above, or by halogen atoms.
- [0026] The term “heterocycle” as used herein, refers to a 3 to 12 membered ring, which can be aromatic or non-aromatic, saturated or unsaturated, containing at least one heteroatom selected from oxygen, amino group, sulfur, or combinations of at least two thereof, interrupting the carbocyclic ring structure. The heterocyclic ring can be interrupted by a $C=O$; the S and N heteroatoms can be oxidized. Heterocycles can be monocyclic or polycyclic, trivalent, divalent or monovalent or spiro. Heterocyclic ring moieties can be substituted by halogen atoms, sulfonyl groups, sulfoxide groups, nitro

groups, cyano groups, $-OC_{1-6}$ alkyl groups, $-SC_{1-6}$ alkyl groups, $-C_{1-8}$ alkyl groups, $-C_{2-6}$ alkenyl groups, $-C_{2-6}$ alkynyl groups, ketone groups, alkylamino groups, amino groups, aryl groups, C_{3-8} cycloalkyl groups or hydroxyl groups. Examples of heterocycles are: 1,3,5-triazole, azetidine, piperidine, piperazine, 2,5-diazabicyclo[2.2.2]octane, 2,5-diazabicyclo[2.2.1]heptane, octahydropyrrolo[3,4-c]pyrrole, pyrazine, 3,9-diazaspiro[5,5]undecane, 1,4,7-triazonane, 2,6-diazaspiro[3.3]heptane, 1,3,5-triazine, and 1,3-thiazol. Heterocycle groups can be independently substituted by halogen atoms, or hydroxyl groups.

- [0027] The term “aryl” as used herein, refers to an organic moiety derived from an aromatic hydrocarbon consisting of a ring containing 6 to 10 carbon atoms, by removal of one hydrogen atom. Aryl can be substituted by halogen atoms, sulfonyl C_{1-6} alkyl groups, sulfoxide C_{1-6} alkyl groups, sulfonamide groups, carboxycyclic acid groups, C_{1-6} alkyl carboxylates (ester) groups, amide groups, nitro groups, cyano groups, $-OC_{1-6}$ alkyl groups, $-SC_{1-6}$ alkyl groups, $-C_{1-6}$ alkyl groups, $-C_{2-6}$ alkenyl groups, $-C_{2-6}$ alkynyl groups, ketone groups, aldehydes, alkylamino groups, amino groups, aryl groups, C_{3-8} cycloalkyl groups or hydroxyl groups. Aryls can be monocyclic or polycyclic. Aryl moieties can be divalent or monovalent.
- [0028] The term “cycloalkyl”, as used herein, refers to a monovalent or divalent (bivalent) saturated carbocycle group of 3 to 8 carbon atoms. Cycloalkyl groups can be spiro, monocyclic or polycyclic. Cycloalkyl groups can be independently substituted by halogen atoms, sulfonyl groups, sulfoxide groups, sulfonyl C_{1-8} alkyl groups, sulfoxide C_{1-8} alkyl groups, sulfonamide groups, nitro groups, cyano groups, $-OC_{1-8}$ alkyl groups, $-SC_{1-8}$ alkyl groups, $-C_{1-8}$ alkyl groups, $-C_{2-6}$ alkenyl groups, $-C_{2-6}$ alkynyl groups, ketone groups, alkylamino groups, amino groups, aryl groups, C_{3-8} cycloalkyl groups or hydroxyl groups.
- [0029] The term “cycloalkenyl”, as used herein, refers to a monovalent or divalent group of 3 to 8 carbon atoms derived from a saturated cycloalkyl having at least one double bond. Cycloalkenyl groups can be monocyclic or polycyclic. Cycloalkenyl groups can be independently substituted by halogen atoms, sulfonyl groups, sulfoxide groups, sulfonyl C_{1-8} alkyl groups, sulfoxide C_{1-8} alkyl groups, sulfonamide groups, nitro groups, cyano groups, $-OC_{1-8}$ alkyl groups, $-SC_{1-8}$ alkyl groups, $-C_{1-8}$ alkyl groups, $-C_{2-6}$ alkenyl groups, $-C_{2-6}$ alkynyl groups, ketone groups, alkylamino groups, amino groups, aryl groups, C_{3-8} cycloalkyl groups or hydroxyl groups.
- [0030] The term “hydroxyl” as used herein, represents a group of formula “-OH”.
- [0031] The term “carbonyl” as used herein, represents a group of formula “-C(O)-”.
- [0032] The term “ketone” as used herein, represents an organic compound having a carbonyl group linked to a carbon atom such as $-(CO)R^x$, wherein R^x can be alkyl, aryl, cycloalkyl, cycloalkenyl, or heterocycle as defined above.

- [0033] The term “amine” or “amino” as used herein, represents a group of formula “-NR^xR^y”, wherein R^x and R^y can be the same or independently H, alkyl, aryl, cycloalkyl, cycloalkenyl, or heterocycle as defined above.
- [0034] The term “carboxyl” as used herein, represents a group of formula “-C(O)O-”.
- [0035] The term “sulfonyl” as used herein, represents a group of formula “-SO₂-”.
- [0036] The term “sulfate” as used herein, represents a group of formula “-O-S(O)₂-O-”.
- [0037] The term “sulfonate” as used herein, represents a group of the formula “-S(O)₂-O-”.
- [0038] The term “carboxylic acid” as used herein, represents a group of formula “-C(O)OH”.
- [0039] The term “nitro” as used herein, represents a group of formula “-NO₂”.
- [0040] The term “cyano” as used herein, represents a group of formula “-CN”.
- [0041] The term “amide” as used herein, represents a group of formula “-C(O)NR^xR^y” wherein R^x and R^y can be the same or independently H, alkyl, aryl, cycloalkyl, cycloalkenyl, or heterocycle as defined above.
- [0042] The term “sulfonamide” as used herein, represents a group of formula “-S(O)₂NR^xR^y” wherein R^x and R^y can be the same or independently H, alkyl, aryl, cycloalkyl, cycloalkenyl, or heterocycle as defined above.
- [0043] The term “azide” as used herein, represents a group of formula “-N=N⁺=N-” or “-N₃”.
- [0044] The term “sulfoxide” as used herein, represents a group of formula “-S(O)-”.
- [0045] The term “phosphonic acid” as used herein, represents a group of formula “-P(O)(OH)₂”.
- [0046] The term “phosphoric acid” as used herein, represents a group of formula “-OP(O)(OH)₂”.
- [0047] The term “sulphonic acid” as used herein, represents a group of formula “-S(O)₂OH”.
- [0048] The formula “H”, as used herein, represents a hydrogen atom.
- [0049] The formula “O”, as used herein, represents an oxygen atom.
- [0050] The formula “N”, as used herein, represents a nitrogen atom.
- [0051] The formula “S”, as used herein, represents a sulfur atom.
- [0052] The term “1,3,5-triazole” as used herein, represents structure.

[Chem.12]



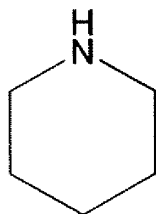
[0053] The term “azetidine” as used herein, represents structure.

[Chem.13]



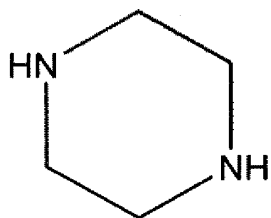
[0054] The term “piperidine” as used herein, represents structure.

[Chem.14]

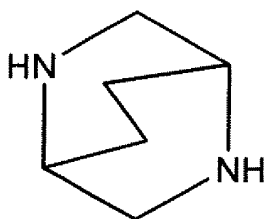


[0055] The term “piperazine” as used herein, represents structure.

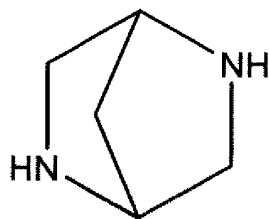
[Chem.15]



[0056] The term “2,5-diazabicyclo[2.2.2]octane” as used herein, represents structure.
[Chem.16]

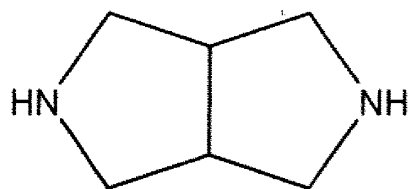


[0057] The term “2,5-diazabicyclo[2.2.1]heptane” as used herein, represents structure.
[Chem.17]



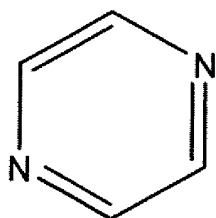
[0058] The term “octahydropyrrolo[3,4-c]pyrrole” as used herein, represents structure.

[Chem.18]



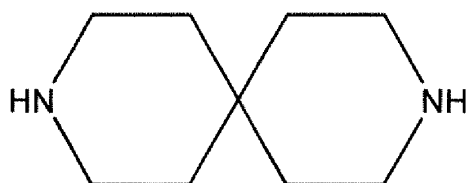
[0059] The term “pyrazine” as used herein, represents structure.

[Chem.19]



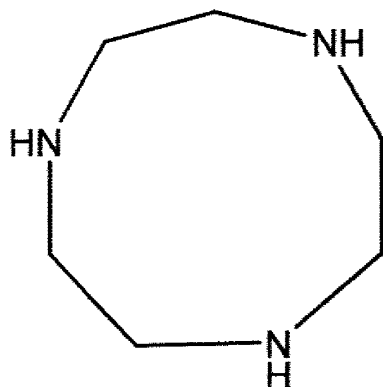
[0060] The term “3,9-diazaspiro[5,5]undecane” as used herein, represents structure.

[Chem.20]

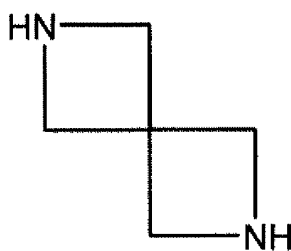


[0061] The term “1,4,7-triazonane” as used herein, represents structure.

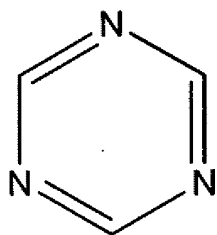
[Chem.21]



[0062] The term “2,6-diazaspiro[3.3]heptane” as used herein, represents a group of formula.
[Chem.22]

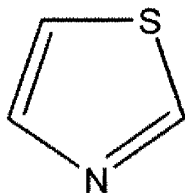


[0063] The term “1,3,5-triazine” as used herein, represents a group of formula.
[Chem.23]

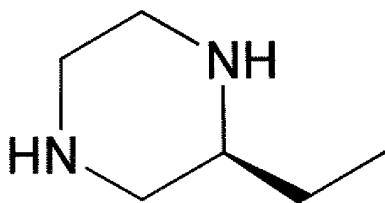


[0064] The term “1,3-thiazol” as used herein, represents a group of formula.

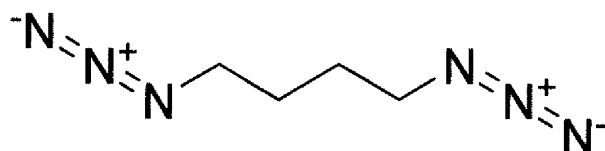
[Chem.24]



[0065] The term “(2S)-2-ethylpiperazine” as used herein, represents a group of formula.
[Chem.25]

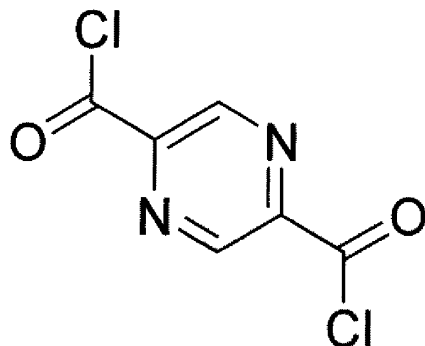


[0066] The term “1,4-diazidobutane” as used herein, represents a group of formula.
[Chem.26]



[0067] The term “pyrazine-2,5-dicarbonyl dichloride” as used herein, represents a group of formula.

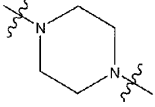
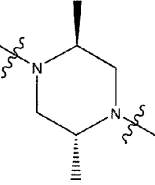
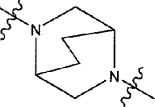
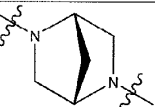
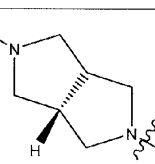
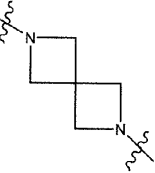
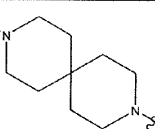
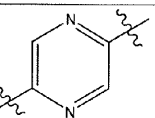
[Chem.27]

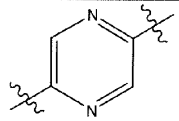
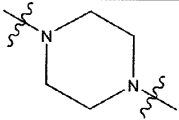
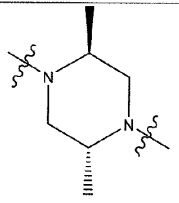
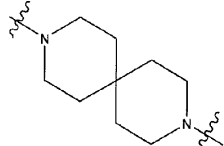
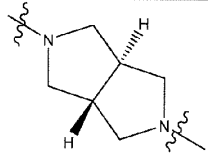
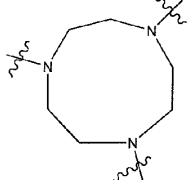
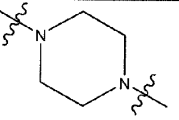
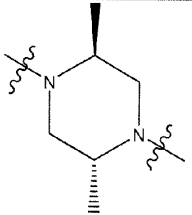


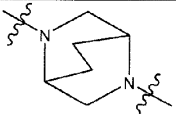
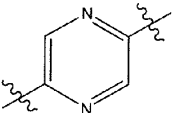
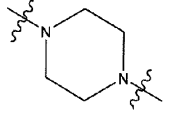
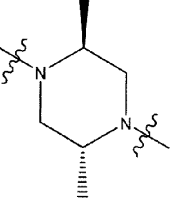
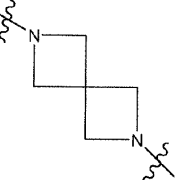
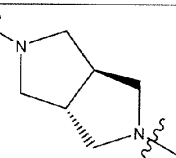
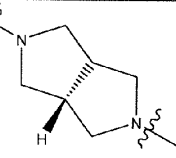
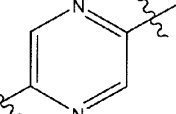
[0068] Above names, formulae and structures can be used interchangeably in the specification referring to the same item. In the Formulas (I, IA, IB, II, IIA and IIB), described throughout the specification, it should be apparent to one of skill in the art that the “R” groups and their values are in accordance with permitted valence so the substitution results in a stable compound represented by these formulas.

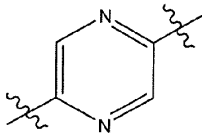
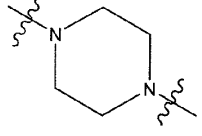
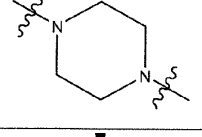
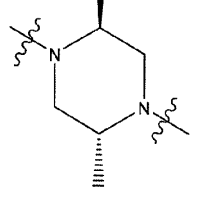
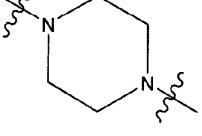
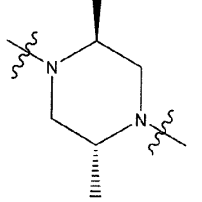
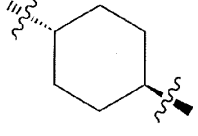
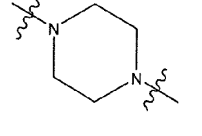
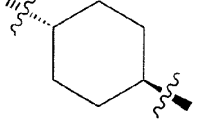
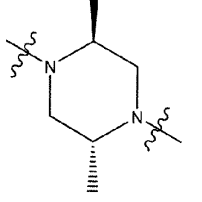
[0069] In another aspect, the invention provides compounds having Formula (I), wherein the values of -R¹-, -R²-, R³ and “a” are represented in Table 1:

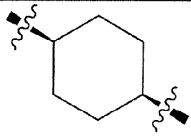
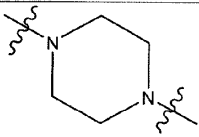
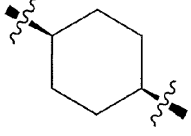
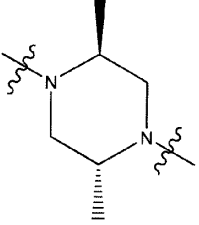
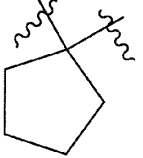
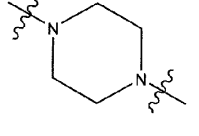
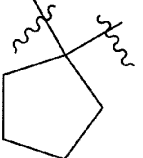
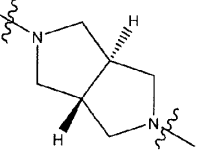
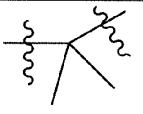
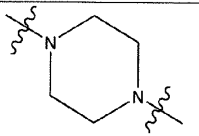
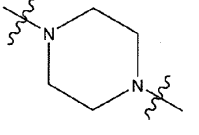
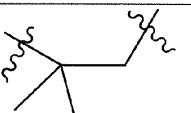
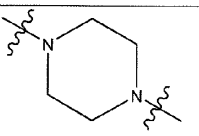
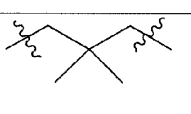
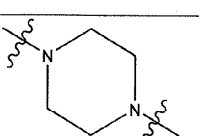
[Table 1]

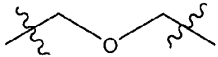
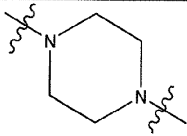
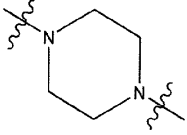
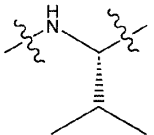
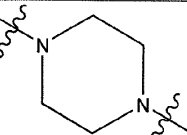
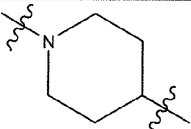
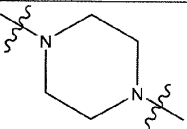
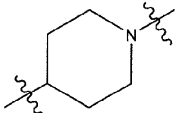
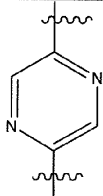
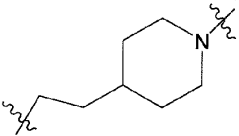
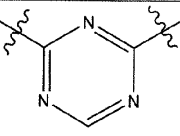
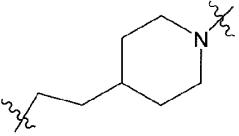
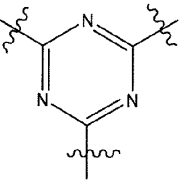
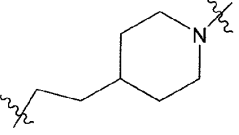
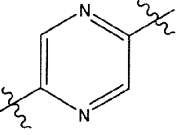
Compound	-R ¹ -	-R ² -	R ³ -	a
Example 1	-(CH ₂) ₄ -	-C(O)-		2
Example 2	-(CH ₂) ₆ -	-C(O)-		2
Example 3	-(CH ₂) ₆ -	-C(O)-		2
Example 4	-(CH ₂) ₆ -	-C(O)-		2
Example 5	-(CH ₂) ₆ -	-C(O)-		2
Example 6	-(CH ₂) ₆ -	-C(O)-		2
Example 7	-(CH ₂) ₆ -	-C(O)-		2
Example 8	-(CH ₂) ₆ -	-C(O)-NH- CH ₂ -		2

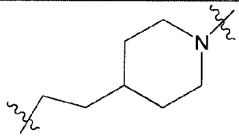
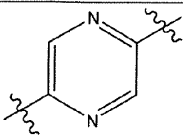
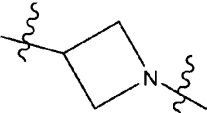
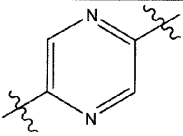
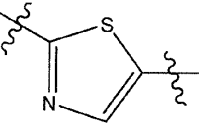
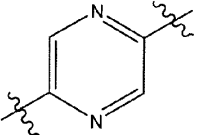
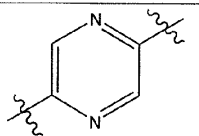
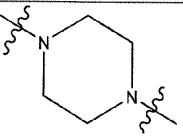
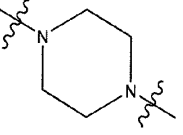
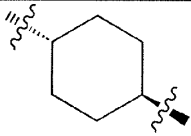
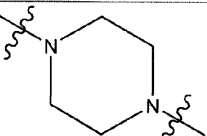
Example 9	$-(\text{CH}_2)_6-$	$-\text{C}(\text{O})-\text{NMe}-\text{CH}_2-$		2
Example 10	$-(\text{CH}_2)_2-$	$-\text{C}(\text{O})-$		2
Example 11	$-(\text{CH}_2)_2-$	$-\text{C}(\text{O})-$		2
Example 12	$-(\text{CH}_2)_2-$	$-\text{C}(\text{O})-$		2
Example 13	$-(\text{CH}_2)_2-$	$-\text{C}(\text{O})-$		2
Example 14	$-(\text{CH}_2)_2-$	$-\text{C}(\text{O})-$		3
Example 15	$-(\text{CH}_2)_8-$	$-\text{C}(\text{O})-$		2
Example 16	$-(\text{CH}_2)_8-$	$-\text{C}(\text{O})-$		2

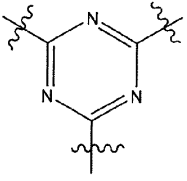
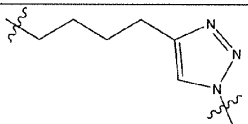
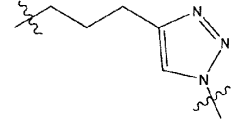
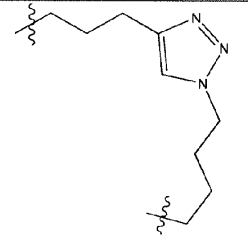
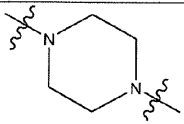
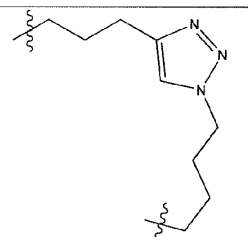
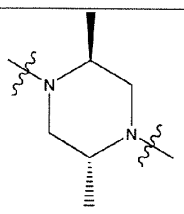
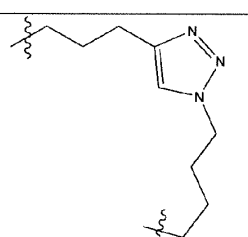
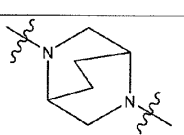
Example 17	$-(\text{CH}_2)_8-$	$-\text{C}(\text{O})-$		2
Example 18	$-(\text{CH}_2)_8-$	$-\text{C}(\text{O})-\text{NMe}-\text{CH}_2-$		2
Example 19	$-(\text{CH}_2)_6-$	$-\text{C}(\text{O})-$		2
Example 20	$-(\text{CH}_2)_4-$	$-\text{C}(\text{O})-$		2
Example 21	$-(\text{CH}_2)_4-$	$-\text{C}(\text{O})-$		2
Example 22	$-(\text{CH}_2)_4-$	$-\text{C}(\text{O})-$		2
Example 23	$-(\text{CH}_2)_4-$	$-\text{C}(\text{O})-$		2
Example 24	$-(\text{CH}_2)_4-$	$-\text{C}(\text{O})-\text{NMe}-\text{CH}_2-$		2

Example 25	$-(\text{CH}_2)_4-$	$-\text{C}(\text{O})-\text{NH}-\text{CH}_2-$		2
Example 26	$-\text{CH}=\text{CH}-$	$-\text{C}(\text{O})-$		2
Example 27	$-(\text{CH}_2)_{12}-$	$-\text{C}(\text{O})-$		2
Example 28	$-(\text{CH}_2)_{12}-$	$-\text{C}(\text{O})-$		2
Example 29	$-(\text{CH}_2)_{16}-$	$-\text{C}(\text{O})-$		2
Example 30	$-(\text{CH}_2)_{16}-$	$-\text{C}(\text{O})-$		2
Example 31		$-\text{C}(\text{O})-$		2
Example 32		$-\text{C}(\text{O})-$		2

Example 33		-C(O)-		2
Example 34		-C(O)-		2
Example 35		-C(O)-		2
Example 36		-C(O)-		2
Example 37		-C(O)-		2
Example 38		-C(O)-		2
Example 39		-C(O)-		2
Example 40		-C(O)-		2

Example 41		-C(O)-		2
Example 42	-NH-(CH ₂) ₇ -	-C(O)-		2
Example 43		-C(O)-		2
Example 44		-C(O)-		2
Example 45		-C(O)-		2
Example 46		Direct bond		2
Example 47		Direct bond		3
Example 48		-CH ₂ -		2

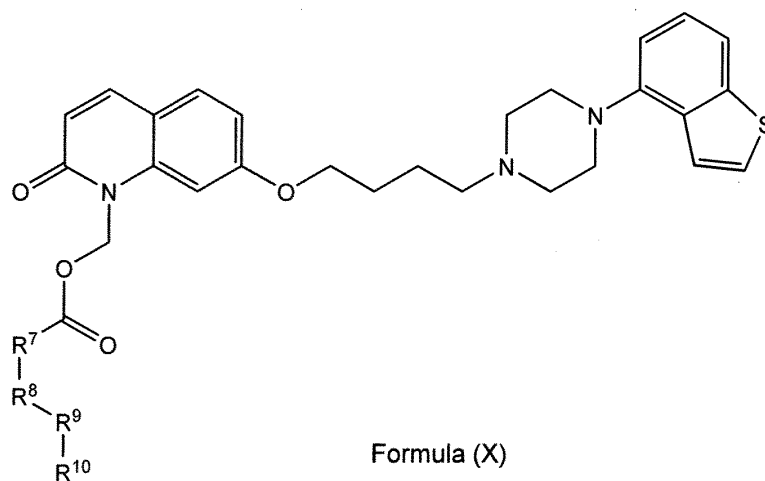
Example 49		-C(O)-		2
Example 50		-C(O)-		2
Example 51	-(CH ₂) ₄ -	-NH-C(O)-		2
Example 52	-(CH ₂) ₄ -	-NH-C(O)-		2
Example 53	-(CH ₂) ₉ -	-NH-C(O)-		2
Example 54	-(CH ₂) ₅ -	Direct bond		2
Example 55	-(CH ₂) ₅ -	-O-C(O)-		2
Example 56		-CH ₂ -		2

Example 57	$-(\text{CH}_2)_5-$	$-\text{O}-$		3
Example 58		Direct bond	$-(\text{CH}_2)_4-$	2
Example 59		Direct bond	$-(\text{CH}_2)_4-$	2
Example 60		$-\text{C}(\text{O})-$		2
Example 61		$-\text{C}(\text{O})-$		2
Example 62		$-\text{C}(\text{O})-$		2

Example 63		-C(O)-		2
Example 64		-C(O)-		2

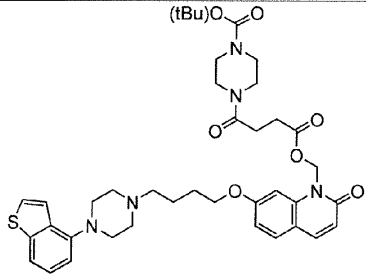
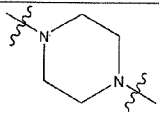
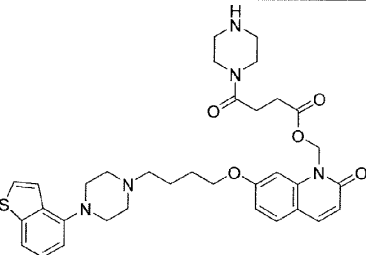
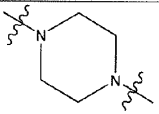
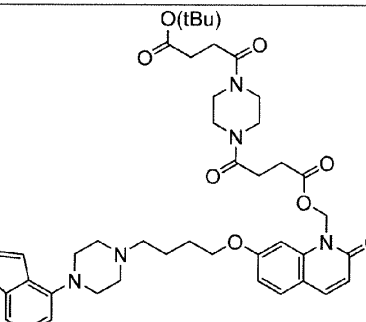
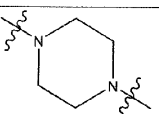
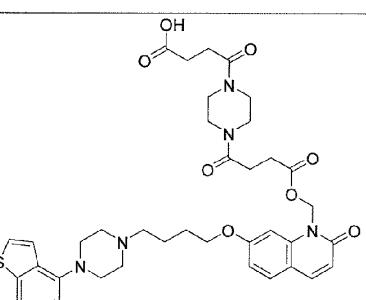
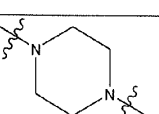
[0070] In still another aspect, the invention also provides compounds having Formula (X):

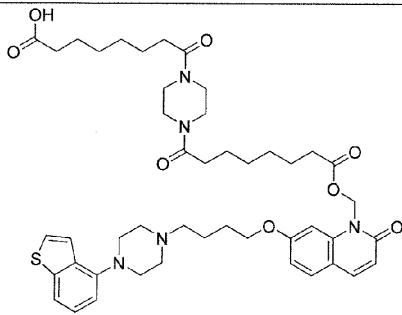
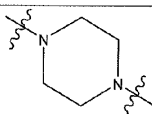
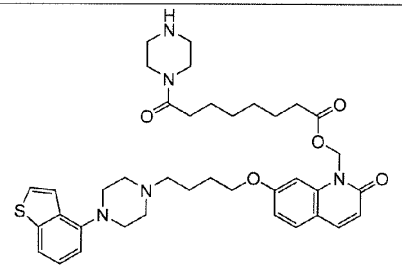
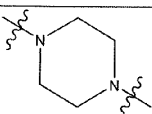
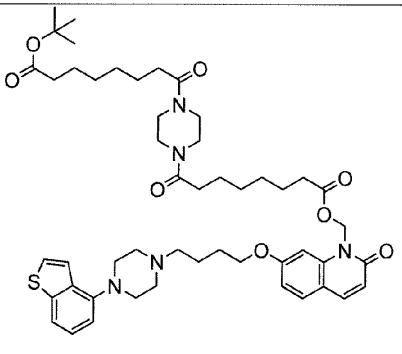
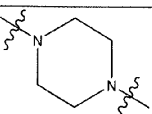
[Chem.28]



wherein representative and illustrative values of R^7 , R^8 , R^9 , and R^{10} are shown in Table 2:

[Table 2]

Formula (X)	R ⁷	R ⁸	R ⁹	R ¹⁰
 Int84	-(CH ₂) ₂ -	-C(O)-		- C(O)(tBu).
 Int85	-(CH ₂) ₂ -	-C(O)-		H
 Int86	-(CH ₂) ₂ -	-C(O)-		-C(O)- (CH ₂) ₂ - C(O)(tBu).
	-(CH ₂) ₂ -	-C(O)-		COOH

Int87 	-(CH ₂) ₆ -	-C(O)-		COOH
Int90 	-(CH ₂) ₆ -	-C(O)-		H
Int91 	-(CH ₂) ₆ -	-C(O)-		-C(O)- (CH ₂) ₆ - C(O)(tBu)

- [0071] Some compounds of Formula (I) and of Formula (II) and some of their intermediates have at least one asymmetric center in their structure. This asymmetric center may be present in an R or S configuration, and said R and S notations are used in correspondence with the rules described in Pure Appl. Chem. (1976), 45, 11-13.
- [0072] The term “pharmaceutically acceptable salts” refers to salts or complexes that retain the desired biological activity of the above identified compounds. The “pharmaceutically acceptable salts” according to the invention include therapeutically active base or acid salt forms, which the compounds of Formula (I) and of Formula (II) are able to form.
- [0073] The acid addition salt form of a compound of Formula (I) and of Formula (II) that

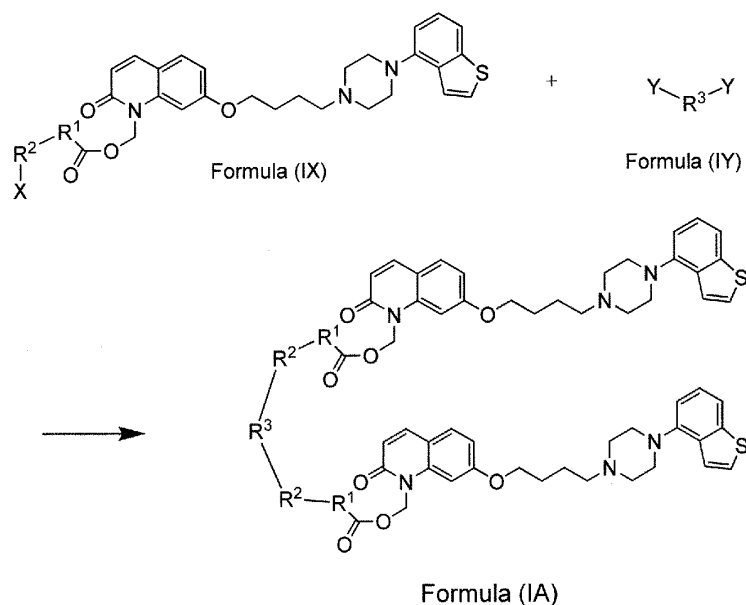
occurs in its free form as a base can be obtained by treating the free base with an appropriate acid such as an inorganic acid, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; or an organic acid such as for example, acetic acid, hydroxyacetic acid, propanoic acid, lactic acid, pyruvic acid, malonic acid, fumaric acid, maleic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pantoic acid, citric acid, methylsulfonic acid, ethanesulfonic acid, benzenesulfonic acid, formic acid and the like (Handbook of Pharmaceutical Salts, P. Heinrich Stahl & Camille G. Wermuth (Eds), Verlag Helvetica Chimica Acta- Zurich, 2002, 329-345).

- [0074] The base addition salt form of a compound of Formula (I) and of Formula (II) that occurs in its acid form can be obtained by treating the acid with an appropriate base such as an inorganic base, for example, sodium hydroxide, magnesium hydroxide, potassium hydroxide, calcium hydroxide, ammonia and the like; or an organic base such as for example, L-arginine, ethanolamine, betaine, benzathine, morpholine and the like. (Handbook of Pharmaceutical Salts, P. Heinrich Stahl & Camille G. Wermuth (Eds), Verlag Helvetica Chimica Acta- Zurich, 2002, 329-345).
- [0075] Compounds of Formula (I) and of Formula (II) and their salts can be in the form of a solvate, which is included within the scope of the present invention. Such solvates include for example hydrates, alcoholates and the like.
- [0076] Compounds of Formulae (I) and (II) may be the compound itself or any forms of its crystal polymorphs.
- [0077] The compounds provided herein can be synthesized according to procedures described herein. The synthetic methods described herein are merely exemplary, and the compounds disclosed herein may also be synthesized by alternate routes utilizing alternative synthetic strategies, appreciated by those of ordinary skill in the art. At this stage, those skilled in the art will appreciate that many additional compounds that fall under the scope of the invention may be prepared by performing various common chemical reactions. Details of certain specific chemical transformations are provided in the examples. Those skilled in the art will be able to routinely modify and/or adapt the following schemes to synthesize any compounds of the invention covered by Formula (I), respectively Formula (IA) or Formula (IB). Generally, the compounds of Formula (I), Formula (IA) or Formula (IB) respectively, can be synthesized according to the following schemes. Any variable ("R" groups) used in the following schemes are the variables as defined for Formula (I), unless otherwise noted. All starting materials are either commercially available or known in the art and may be synthesized by employing known procedures using ordinary skill. Starting materials may also be synthesized via the procedures disclosed herein. Suitable reaction conditions, such as solvents, reaction temperatures, and reagents, for the Schemes discussed in this

section, may be also found in the Experimental section.

[0078] Scheme 1: Reaction for compounds of Formula (IA)

[Chem.29]



wherein R¹, R² and R³ are as defined herein. Compounds of general Formula (IA) can be prepared from intermediates of Formula (IX) and Formula (IY) through a coupling reaction as shown in Scheme 1.

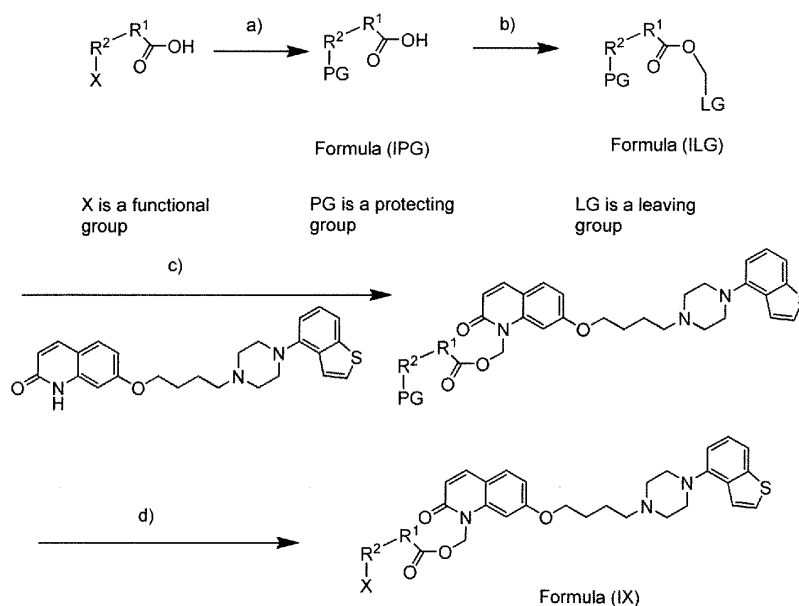
[0079] Examples of the reactive group "X" in Formula (IX) participating in a coupling reaction, can be an alkyl carboxylate, a carboxylic acid, an alkyne, an alkyl ether, an amine, an alkyl sulfonate, a nitro group, or an alcohol.

[0080] Examples of the reactive group "Y" in Formula (IY) participating in a coupling reaction, can be an azide, an amine, an acyl chloride, a halogenated alkyl, or a halogenated cyclic moiety. Intermediates wherein "Y" is an azide are Int78 and the intermediates described in Table 7. Other intermediates covered by Formula (IY) are Int04, Int05, Int08, Int09, piperazine, (2R,5S)-2,5-dimethylpiperazine, 2,5-diazabicyclo[2.2.2]octane, octahydropyrrolo[3,4-c]pyrrole, 2,6-diazaspiro[3.3]heptane, 3,9-diazaspiro[5,5]undecane, 1-[5-(aminomethyl)pyrazin-2-yl]methanamine, methyl({5-[(methylamino)methyl]pyrazin-2-yl}methyl)amine, (2S)-2-ethylpiperazine, pyrazine-2,5-dicarbonyl dichloride, 2,4-dichloro-1,3,5-triazine, 2,5-bis(bromomethyl)pyrazine, 1,3-thiazole-2,5-dicarbonyl dichloride, 1,4-diazidobutane, and (2S)-2-ethylpiperazine. Some of the intermediates covered by

Formula (IY) are commercially available.

- [0081] The reaction in Scheme 1 can be an amide coupling reaction, using an appropriate amide coupling reagent (e.g., TBTU) and an organic base (e.g., TEA), or an aromatic or non-aromatic nucleophilic substitution or a copper catalysed Huisgen cycloaddition reaction according to methods described in the literature or known to those skilled in the art. The amount of the amide coupling reagent to be used can be generally at least an equimolar amount, preferably equimolar to 1.5-fold molar amount, relative to the compound of Formula (IX).
- [0082] The reaction in Scheme 1 can be performed neat or in a suitable solvent. Examples of suitable solvents include water, ethers such as dioxane, tetrahydrofuran, diethyl ether, diethylene glycol dimethylether, ethylene glycol dimethylether and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; lower alcohols such as methanol, ethanol, isopropanol and the like; ketones such as acetone, methylethyl ketone and the like; polar solvents such as N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), hexamethylphosphoric acid triamide, acetonitrile and the like.
- [0083] The proportion of the compound of Formula (IX) and the compound of Formula (IY) to be used in the Scheme 1, is generally at least 1.5-fold mol, preferably about 1.5- to 3-fold mol, of the latter relative to the former. The above-mentioned reaction is performed generally at room temperature to 200°C, preferably room temperature to 150°C, and completes in about 1 to 72 hr.
- [0084] In the cases wherein group “X” is a terminal alkyne, as described in Intermediate Int77, the compounds of general Formula (IA) can be prepared via a copper catalyzed Huisgen cycloaddition reaction. Group “Y” is an azide in the intermediates of Formula (IY) participating in this reaction. Example 58 and the examples described in Table 11 have been synthesized via this reaction.
- [0085] Some intermediates of Formula (IX) can be prepared according to the reaction described in Scheme 2. Such intermediates are Int02, Int03, Int39, Int42, Int47, Int48, Int49, Int50, Int52, Int57, Int59, Int60, Int68, Int69, Int70, Int73, Int74 and the intermediates described in Table 4, Table 5, and Table 6. Int26 is described by Formula (IPG). Some intermediates of Formula (ILG) are Int01 and the intermediates described in Table 3.
- [0086] Scheme 2: Reaction for intermediates of Formula (IX)

[Chem.30]

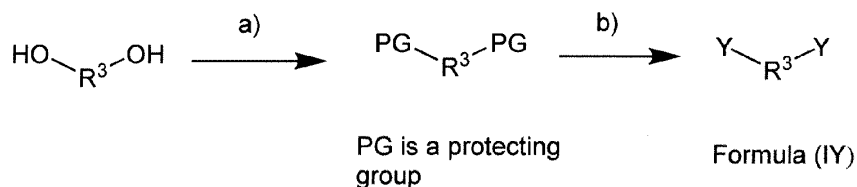


- a) Protection of functional group “X” wherein suitable protecting groups can be tert-butyl (t-Bu), tert-butyloxycarbonyl (Boc), tert-butyldimethylsilyl (TBDMS),
- b) Alkylation in the presence of alkylating agents such as chloromethyl chlorosulfate, in the presence of a quaternary ammonium salt (TBA- HSO_4)
- c) Alkylation in the presence of a base such as NaH and in the presence of heat
- d) Deprotection of functional group “X” wherein suitable deprotecting reagents can be TFA, HCl or TBAF.

[0087] Some intermediates of Formula (IY) can be prepared according to the reaction described in Scheme 3. Int05 is such intermediate.

Scheme 3: Reaction for intermediates of Formula (IY)

[Chem.31]



- a) Protection of the alcohol function; suitable protecting groups are Boc, phthalimide
- b) Deprotection in the presence of known reagents (hydrazine)

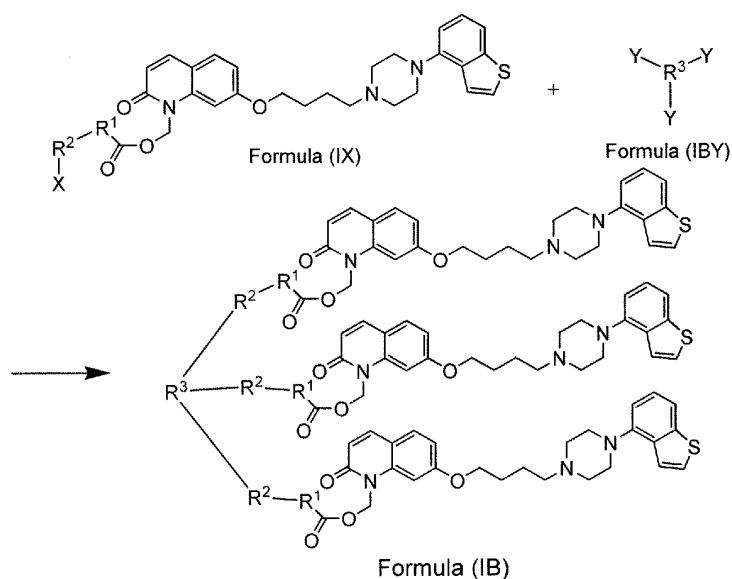
[0088] Some intermediates of Formula (IY), wherein Y is an azide, can be prepared via an

amide coupling reaction, wherein the starting material is an alkyl carboxylic acid. Amide coupling reagents such as HATU or TBTU and organic bases such as TEA or DIPEA, can be used, according to methods described in the literature or known to those skilled in the art.

[0089] The compounds of Formula (IB) can be prepared according to the general reaction described in Scheme 4.

Scheme 4: Reaction for compounds of Formula (IB)

[Chem.32]



The reactants of Formula (IBY) were generally commercially available, otherwise they can be prepared by reactions known in the literature with which one of skill in the art will be familiar with.

[0090] It should be appreciated that the general synthetic procedures and specific examples provided herein are illustrative only and should not be construed as limiting the scope of the present disclosure in any manner.

[0091] DETAILED DESCRIPTION OF THE INVENTION

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention claimed. As used herein, the use of the singular includes the plural unless specifically stated otherwise.

[0092] It will be readily apparent to those skilled in the art that some of the compounds of the invention may contain one or more asymmetric centers, such that the compounds may exist in enantiomeric as well as in diastereomeric forms. Unless it is specifically

noted otherwise, the scope of the present invention includes all enantiomers, diastereomers and racemic mixtures. Some of the compounds of the invention may form salts with pharmaceutically acceptable acids or bases, and such pharmaceutically acceptable salts of the compounds described herein are also within the scope of the invention.

[0093] The present invention includes all pharmaceutically acceptable isotopically enriched compounds. Any compounds of the invention and intermediates may contain one or more isotopic atoms enriched or different than the natural ratio such as deuterium ^2H (or D) in place of hydrogen ^1H (or H) or use of ^{13}C enriched material in place of ^{12}C and the like. Similar substitutions can be employed for N, O and S, etc. Examples of isotope atoms include deuterium (^2H or D), tritium (^3H), ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{32}P , ^{35}S , ^{36}Cl , ^{37}Cl , ^{18}F , ^{123}I , ^{125}I , and the like. The use of isotopes may assist in analytical as well as therapeutic aspects of the invention. For example, use of deuterium may increase the in vivo half-life by altering the metabolism (rate) of the compounds of the invention. These compounds can be prepared in accord with the preparations described by use of isotopically enriched reagents.

[0094] In certain embodiments, compounds of Formulae (I) and (II), or pharmaceutically acceptable salts thereof, may have the mean particle size measured by laser diffractometry, e.g., using a laser diffraction particle size distribution measuring device, ranging from 0.05 to 10 μm , for example, 0.1 to 10 μm , for example, 0.1 to 5 μm , for example, 0.1 to 3.4 μm , for example, 0.2 to 1.9 μm , for example, 0.2 to 0.4 μm . Suitable mean particle sizes may be beneficial to provide a desired absorption rate and/or acceptable irritability at the injection site. The term "mean particle size" as used herein refers to the volume mean diameter as measured by laser-light scattering (LLS). A particle size distribution is measured by LLS, and a corresponding mean particle size is calculated from the particle size distribution.

[0095] Medical uses

Compounds of Formulae (I) and (II), or pharmaceutically acceptable salts thereof, may be converted into brexpiprazole in systemic circulation upon administration to a subject. Multivalent brexpiprazole molecules may undergo bioconversion into intermediates including N-hydroxymethyl brexpiprazole in vivo, such as in the plasma, which will be hydrolyzed to brexpiprazole via enzyme-mediated hydrolysis. Brexpiprazole is useful for treating and/or preventing central nervous system disorders, which are antipsychotic related, such as schizophrenia; refractory, intractable or chronic schizophrenia; emotional disturbance; psychotic disorder; mood disorder; bipolar I type disorder; bipolar II type disorder; depression; endogenous depression; major depressive disorder (MDD); melancholy and refractory depression; dysthymic disorder; cyclothymic disorder; panic attack; panic disorder; agoraphobia; social

phobia; obsessive-compulsive disorder; post-traumatic stress disorder; generalized anxiety disorder; acute stress disorder; hysteria; somatization disorder; conversion disorder; pain disorder; hypochondriasis; factitious disorder; dissociative disorder; sexual dysfunction; sexual desire disorder; sexual arousal disorder; erectile dysfunction; anorexia nervosa; bulimia nervosa; sleep disorder; adjustment disorder; alcohol abuse; alcohol intoxication; drug addiction; stimulant intoxication; narcotism; anhedonia; iatrogenic anhedonia; anhedonia of a psychic or mental cause; anhedonia associated with depression; anhedonia associated with schizophrenia; delirium; cognitive impairment; cognitive impairment associated with Alzheimer's disease, Parkinson's disease and other neurodegenerative diseases; cognitive impairment caused by Alzheimer's disease; Parkinson's disease and associated neurodegenerative diseases; cognitive impairment of schizophrenia; cognitive impairment caused by refractory, intractable or chronic schizophrenia; vomiting; motion sickness; obesity; migraine; pain (ache); mental retardation; autism disorder (autism); Tourette's disorder; tic disorder; attention-deficit/hyperactivity disorder; conduct disorder; Down's syndrome; impulsive symptoms associated with dementia (e.g., agitation associated with Alzheimer's disease); and borderline personality disorder. Accordingly, Compounds of Formulae (I) and (II) may also be useful for treating and/or preventing central nervous system disorders.

[0096] The term "prophylaxis", "prevention", or "preventing" is used herein to mean the provision in advance, and as such may involve preventing symptoms of a disease or disorder in a subject or preventing recurrence of symptoms of a disease or disorder in an afflicted subject and is not limited to complete prevention of an affliction. The term "treatment" or "treating" as used herein includes the control, mitigation, reduction, or modulation of the disease state or its symptoms. A subject will typically be a subject in need of treatment or prophylaxis according to the invention. A subject is typically a mammal. Suitably, the subject is a human.

[0097] Pharmaceutical compositions

In one embodiment of the invention, a medical preparation (herein also referred to as a "pharmaceutical composition") comprising a compound of Formula (I) or (II), or a pharmaceutically acceptable salt thereof, as an active ingredient is provided.

[0098] A medical preparation herein may be selected from various forms depending on therapeutic objectives. Any administration routes of a medical preparation may be chosen depending on dosage forms, the age and sex of a patient to be administered, disease status, and other conditions. A medical preparation may be administered orally, intravenously, intramuscularly, intradermally, subcutaneously, intraperitoneally, or rectally as necessary. Examples of the medical preparation include tablets, pills, powders, liquids, suspensions, emulsions, granules, capsules, suppositories, and in-

jections (liquids, suspensions, etc.). Tablets include coated tablets such as sugar-coated tablets, gelatin-coated tablets, enteric-coated tablets, film-coated tablets, double tablets, and multilayered tablets.

- [0099] A compound of Formula (I) or (II), or a pharmaceutically acceptable salt thereof, may be combined with a pharmaceutically acceptable carrier to be formulated into any forms of a medical preparation. Examples of the carrier include commonly used substances for a component of a medical preparation, including excipients such as lactose; binders such as polyvinylpyrrolidone; disintegrants such as starch; absorption aids such as sodium lauryl sulfate; humectants such as glycerin and starch; adsorbents such as colloidal silicic acid; and lubricants such as magnesium stearate and polyethylene glycol; diluents; fillers; bulking agents; and surfactants.
- [0100] Pharmaceutically acceptable carriers to be used in formulating into a tablet specifically include excipients such as lactose; binders such as polyvinylpyrrolidone; disintegrants such as starch; absorption aids such as sodium lauryl sulfate; humectants such as glycerin and starch; adsorbents such as colloidal silicic acid; and lubricants such as magnesium stearate and polyethylene glycol.
- [0101] Pharmaceutically acceptable carriers to be used in formulating into a pill specifically include excipients such as glucose; binders such as gum arabic powder; and disintegrants such as laminaran.
- [0102] Pharmaceutically acceptable diluents to be used in formulating into a liquid, emulsion, or suspension specifically include water. Any ordinary solubilizing agents and/or buffers as well as colorants, preservatives, aromatics, flavorings, and sweeteners may also be comprised in the preparation, and other drugs may also be comprised as necessary.
- [0103] Pharmaceutically acceptable carriers to be used in formulating into a suppository specifically include cocoa butter.
- [0104] In some embodiments, a compound of Formula (I) or (II), or a pharmaceutically acceptable salt thereof, may be formulated into the form of a liquid, emulsion, or suspension to prepare an injection. In one embodiment, the injection is preferably sterilized, and is also preferably isotonic with blood. The injection may be formulated with diluents which are conventionally used and include water, ethanol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol, and polyoxyethylene sorbitan fatty acid esters. The injection may also comprise stabilizers such as polymeric stabilizers including Poloxamer 188, 338; PEG200, 1000, 4000; PPG 4000, and surfactants such as PS20, 80; sodium deoxycholate, sodium cholate, sodium dodecyl sulfate. The isotonic injection may comprise a sufficient amount of sodium chloride and soothing agents, such as glucose, amino acids, and glycerin, and may also optionally comprise other agents, such as coloring agents, preserving agents, perfumes,

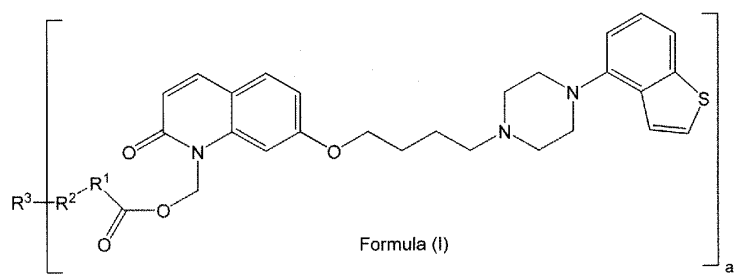
and sweetening agents. Preferably, the injection is an intramuscular injection or subcutaneous injection.

- [0105] The amount (herein also referred to as "effective amount") of a compound of Formula (I) or (II), or a pharmaceutically acceptable salt thereof, comprised in a medical preparation may be, but is not limited thereto, any amounts conventionally used in the art, and preferably includes any amounts of 1% to 70% of the medical preparation. The dose of a compound of Formula (I) or (II), or a pharmaceutically acceptable salt thereof, to be administered may be any doses selected depending on administration routes, the age and sex of a patient to be administered, the severity of diseases, and other conditions, and includes 0.01 to 100 mg, preferably 0.1 to 50 mg, per 1 kg of body weight per day. The dose may be administered once or separately in several times, such as two to four times.
- [0106] A compound of Formula (I) or (II), or a pharmaceutically acceptable salt thereof, may be used or administered in combination with at least one therapeutic or preventive drug or standard-of-care agent, which may be referred to as a combined drug herein, useful for one of the above-mentioned diseases. When a compound of Formula (I) or (II), or a pharmaceutically acceptable salt thereof, is used in combination with a combined drug, a compound of Formula (I) or (II), or a pharmaceutically acceptable salt thereof, and the drug may be administered simultaneously or at the same time, separately or sequentially at about the same time, or separately or sequentially at different times with a suitable interval in between. A compound of Formula (I) or (II), or a pharmaceutically acceptable salt thereof, and the combined drug may be formulated into separate preparations or mixed and formulated into a single preparation.

[0107] Embodiments

Clause 1: A compound having Formula (I), or a pharmaceutically acceptable salt thereof:

[Chem.33]



wherein:

a is 2 or 3;

R¹ is optionally substituted linear or branched C₁₋₂₀ alkylene; optionally substituted C₂₋₁₀ alkenylene; optionally substituted divalent C₃₋₈ cycloalkyl; optionally substituted divalent heterocycle; optionally substituted divalent C₆₋₁₀ aryl; -NH(optionally substituted linear or branched C₁₋₂₀ alkylene); or optionally substituted divalent C₃₋₈ cycloalkenyl;

R² is -C(O)-, -O-C(O)-, -C(O)-NR^a-CH₂-, -O-, -CH₂-, -NR^a-C(O)-, or a direct bond;

R³ is optionally substituted non-aromatic divalent or trivalent heterocycle, optionally substituted aromatic divalent or trivalent heterocycle, or optionally substituted linear or branched C₁₋₂₀ alkylene;

R^a is hydrogen or optionally substituted linear or branched C₁₋₂₀ alkyl;

when a is 2, R³ is divalent;

when a is 3, R³ is trivalent; and

R² and R³ are connected with covalent bond(s);

provided that when R¹ is linear alkylene and R² is -CH₂- or a direct bond, R³ is not linear alkylene.

[0108] Clause 2: A compound according to clause 1, or a pharmaceutically acceptable salt thereof, wherein:

a is 2 or 3;

R¹ is optionally substituted linear or branched C₂₋₁₆ alkylene, wherein one or more methylene groups can be replaced with a functional group selected from -O- or -NH-, or one or more methylene groups can be replaced with a spiro cyclopentane, or a divalent piperidine, or one or more methylene groups can be replaced with a divalent 1,3,5-triazole cycle; ethylene; optionally substituted divalent cyclohexyl; optionally substituted divalent azetidine; or optionally substituted divalent piperidine;

R² is -C(O)-, -O-C(O)-, -C(O)-N(CH₃)-CH₂-, -C(O)-NH-CH₂-, -O-, -NH-C(O)-, -CH₂-, or a direct bond;

R³ is optionally substituted divalent or trivalent piperazine, optionally substituted divalent or trivalent 2,5-diazabicyclo[2.2.2]octane, optionally substituted divalent or trivalent 2,5-diazabicyclo[2.2.1]heptane, optionally substituted divalent or trivalent octahydropyrrolo[3,4-c]pyrrole, optionally substituted divalent or trivalent pyrazine, optionally substituted divalent or trivalent 3,9-diazaspiro[5,5]undecane, optionally substituted divalent or trivalent 1,4,7-triazonane, optionally substituted divalent or trivalent 2,6-diazaspiro[3.3]heptane, optionally substituted divalent or trivalent 1,3,5-triazine, optionally substituted divalent or trivalent 1,3-thiazol, or optionally substituted linear or branched C₂₋₆ alkylene;

when a is 2, R³ is divalent; and

when a is 3, R³ is trivalent.

[0109] Clause 3: A compound according to clause 1 or 2, or a pharmaceutically acceptable salt thereof, wherein:

a is 2;

R¹ is optionally substituted linear or branched C₂₋₁₆ alkylene, wherein one or more methylene groups can be replaced with an oxygen or amino group, or one or more methylene groups can be replaced with a spiro cyclopentane, or a divalent piperidine, or one or more methylene groups can be replaced with a divalent 1,3,5-triazole cycle; ethylene; optionally substituted divalent cyclohexyl; optionally substituted divalent azetidine; or optionally substituted divalent piperidine;

R² is -C(O)-, -O-C(O)-, -C(O)-N(CH₃)-CH₂-, -C(O)-NH-CH₂-, -CH₂-, -NH-C(O)-, or a direct bond; and

R³ is optionally substituted divalent piperazine, optionally substituted divalent 2,5-diazabicyclo[2.2.2]octane, optionally substituted divalent 2,5-diazabicyclo[2.2.1]heptane, optionally substituted divalent octahydropyrrolo[3,4-c]pyrrole, optionally substituted divalent pyrazine, optionally substituted divalent 3,9-diazaspiro[5,5]undecane, optionally substituted divalent 2,6-diazaspiro[3.3]heptane, optionally substituted divalent 1,3-thiazol, or optionally substituted linear or branched C₂₋₆ alkylene.

[0110] Clause 4: A compound according to clause 1 or 2, or a pharmaceutically acceptable salt thereof, wherein:

a is 3;

R¹ is optionally substituted linear or branched C₂₋₆ alkylene, wherein one or more methylene groups can be replaced with a divalent piperidine;

R² is -C(O)-, -O-, or a direct bond; and

R³ is optionally substituted trivalent 1,4,7-triazonane, or optionally substituted trivalent 1,3,5-triazine.

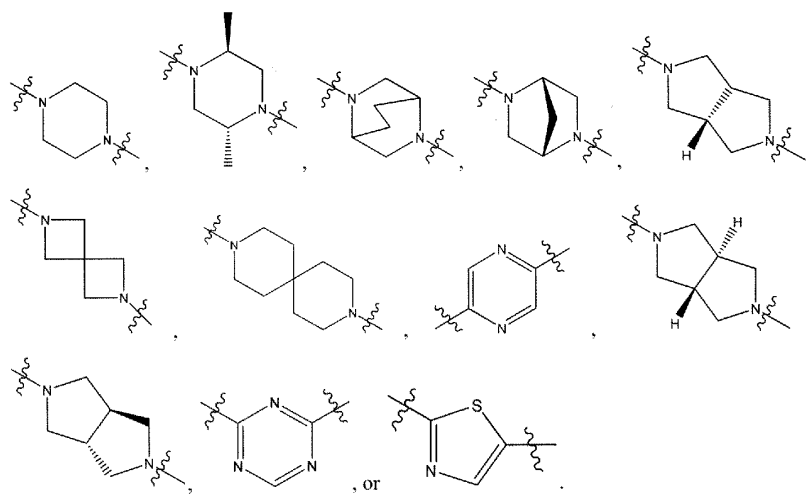
[0111] Clause 5: A compound according to any one of clauses 1 to 3, or a pharmaceutically acceptable salt thereof, wherein:

a is 2;

R¹ is -CH=CH-, -(CH₂)₂-, -(CH₂)₄-, -(CH₂)₅-, -(CH₂)₆-, -(CH₂)₇-, -(CH₂)₈-, -(CH₂)₉-, -(CH₂)₁₂-, -(CH₂)₁₆-, -NH-(CH₂)₇-,

R² is -C(O)-, -O-C(O)-, -C(O)-N(CH₃)-CH₂-, -C(O)-NH-CH₂-, -CH₂-, -NH-C(O)-, or a direct bond; and
R³ is -(CH₂)₄-,

[Chem.35]

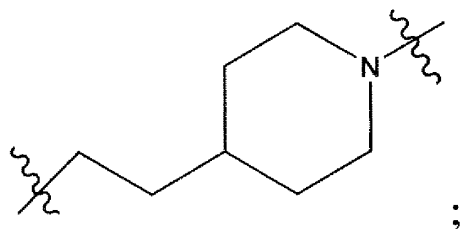


[0112] Clause 6: A compound according to clause 1 or 2, or a pharmaceutically acceptable salt thereof, wherein:

a is 3;

R^1 is $-(CH_2)_2-$, $-(CH_2)_5-$, or

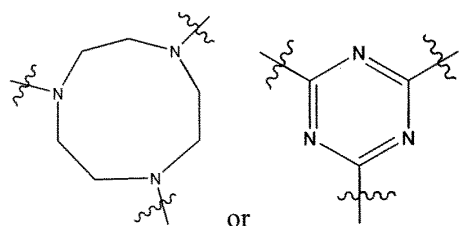
[Chem.36]



R^2 is $-C(O)-$, $-O-$, or a direct bond; and

R^3 is

[Chem.37]



- [0113] Clause 7: A compound according to clause 1, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:
- (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-6-(4-{6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexanoyl}piperazin-1-yl)-6-oxohexanoate;
- (7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-8-[(2R,5S)-4-{8-[(7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanoyl}-2,5-dimethylpiperazin-1-yl]-8-oxooctanoate;
- (7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-8-(5-{8-[(7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanoyl}-2,5-diazabicyclo[2.2.2]octan-2-yl)-8-oxooctanoate;
- (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-8-[(1S,4S)-5-{8-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanoyl}-2,5-diazabicyclo[2.2.1]heptan-2-yl]-8-oxooctanoate; tris(trifluoroacetic acid);
- (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-8-(5-{8-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanoyl}-octahydropyrrolo[3,4-c]pyrrol-2-yl)-8-oxooctanoate;
- (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-8-(6-{8-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanoyl}-2,6-diazaspiro[3.3]heptan-2-yl)-8-oxooctanoate;
- (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-8-(9-{8-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanoyl}-3,9-diazaspiro[5.5]undecan-3-yl)-8-oxooctanoate;

ooctanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-7-([5-({8-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-ooctanamido)methyl}pyrazin-2-yl)methyl}carbamoyle)heptanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-7-([5-({8-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-N-methyl-8-ooctanamido)methyl}pyrazin-2-yl)methyl}(methyl)carbamoyle)heptanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutanoyl}piperazin-1-yl)-4-oxobutanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-[(2S,5R)-4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutanoyl}-2,5-dimethylpiperazin-1-yl)-4-oxobutanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-(9-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutanoyl}-3,9-diazaspiro[5.5]undecan-3-yl)-4-oxobutanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl

4-[(3ar,6ar)-5-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutanoyl}-octahydropyrrolo[3,4-c]pyrrol-2-yl]-4-oxobutanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-[4,7-bis({4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutanoyl})-1,4,7-triazonan-1-yl]-4-oxobutanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-10-(4-{10-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-10-oxodecanoyl}piperazin-1-yl)-10-oxodecanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-10-[(2R,5S)-4-{10-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-10-oxodecanoyl}-2,5-dimethylpiperazin-1-yl]-10-oxodecanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-10-(5-{10-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-

-dihydroquinolin-1-yl)methoxy]-10-oxodecanoyl)-2,5-diazabicyclo[2.2.2]octan-2-yl)-10-oxodecanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-9-([5-([10-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-N-methyl-10-oxodecanamido)methyl]pyrazin-2-yl)methyl}(methyl)carbamoyl)nonanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-8-(4-{8-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanoyl}piperazin-1-yl)-8-oxooctanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-6-[(2S,5R)-4-{6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexanoyl]-2,5-dimethylpiperazin-1-yl]-6-oxohexanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-6-(6-{6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexanoyl]-2,6-diazaspiro[3.3]heptan-2-yl)-6-oxohexanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-6-[(3ar,6ar)-5-{6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexanoyl]-octahydropyrrolo[3,4-c]pyrrol-2-yl]-6-oxohexanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-6-(5-{6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexanoyl]-octahydropyrrolo[3,4-c]pyrrol-2-yl)-6-oxohexanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-5-([5-([6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-N-methyl-6-oxohexanamido)methyl]pyrazin-2-yl)methyl}(methyl)carbamoyl)pentanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-5-([5-([6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexanamido)methyl]pyrazin-2-yl)methyl}carbamoyl)pentanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-(2E)-4-{4-[(2E)-4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobut-2-enoyl]piperazin-1-yl}-4-oxobut-2-enoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl

1)methyl-14-(4-{14-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-14-oxotetradecanoyl}piperazin-1-yl)-14-oxotetradecanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-14-[(2S,5R)-4-{14-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-14-oxotetradecanoyl}-2,5-dimethylpiperazin-1-yl]-14-oxotetradecanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-18-(4-{18-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-18-oxooctadecanoyl}piperazin-1-yl)-18-oxooctadecanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-18-[(2S,5R)-4-{18-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-18-oxooctadecanoyl}-2,5-dimethylpiperazin-1-yl]-18-oxooctadecanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-(1r,4r)-4-{4-[(1r,4r)-4-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}cyclohexanecarbonyl]piperazine-1-carbonyl}cyclohexane-1-carboxylate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-(1r,4r)-4-[(2S,5R)-2,5-dimethyl-4-[(1r,4r)-4-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}cyclohexanecarbonyl]piperazine-1-carbonyl]cyclohexane-1-carboxylate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-(1s,4s)-4-{4-[(1s,4s)-4-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}cyclohexanecarbonyl]piperazine-1-carbonyl}cyclohexane-1-carboxylate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-(1s,4s)-4-[(2S,5R)-2,5-dimethyl-4-[(1s,4s)-4-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}cyclohexanecarbonyl]piperazine-1-carbonyl]cyclohexane-1-carboxylate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-1-[4-(1-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}cyclopentanecarbonyl]piperazine-1-carbonyl]cyclopentane-1-carboxylate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-1-[(3ar,6ar)-5-(1-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-

oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl)cyclopentanecarbonyl)-octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)cyclopentane-1-carboxylate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-3-(4-{3-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-2,2-dimethyl-3-oxopropanoyl}piperazin-1-yl)-2,2-dimethyl-3-oxopropanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 4-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-2,2-dimethyl-4-oxobutanoyl}piperazin-1-yl)-3,3-dimethyl-4-oxobutanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-3,3-dimethyl-4-oxobutanoyl}piperazin-1-yl)-2,2-dimethyl-4-oxobutanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-5-(4-{5-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-3,3-dimethyl-5-oxopentanoyl}piperazin-1-yl)-3,3-dimethyl-5-oxopentanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-2-{2-[4-(2-{2-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-2-oxoethoxy}acetyl)piperazin-1-yl]-2-oxoethoxy}acetate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-N-(8-{4-[8-({[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}amino)octanoyl]piperazin-1-yl}-8-oxooctyl)carbamate;
 (7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-N-[(2S)-1-{4-[(2S)-2-({[(7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}amino)-3-methylbutanoyl]piperazin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-[4-(1-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}piperidine-4-carbonyl)piperazine-1-carbonyl]piperidine-1-carboxylate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-1-[5-(4-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}piperidine-1-carbonyl)pyrazine-2-carbonyl]piperidine-4-carboxylate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-3-{1-[4-(4-{3-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-3-oxopropyl}piperidin-1-yl)-1,3,5-triazin-2-yl]piperidin-4-yl}propanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-3-{1-[4,6-bis(4-{3-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-3-oxopropyl}piperidin-1-yl)-1,3,5-triazin-2-yl]piperidin-4-yl}propanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-3-{1-[(5-{4-{3-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-3-oxopropyl}piperidin-1-yl)methyl]pyrazin-2-yl)methyl}piperidin-4-yl}propanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-3-{1-[5-(4-{3-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-3-oxopropyl}piperidine-1-carbonyl)pyrazine-2-carbonyl]piperidin-4-yl}propanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-1-[5-(3-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}azetidine-1-carbonyl)pyrazine-2-carbonyl]azetidine-3-carboxylate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-5-{[5-({5-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-5-oxopentyl}carbamoyl)-1,3-thiazol-2-yl]formamido}pentanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-5-{[5-({5-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-5-oxopentyl}carbamoyl)pyrazin-2-yl]formamido}pentanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-10-{[5-({10-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-10-oxodecyl}carbamoyl)pyrazin-2-yl]formamido}decanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-6-(4-{6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexyl}piperazin-1-yl)hexanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-6-{4-[(6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexyl}oxy)carbonyl]piperazine-1-carbonyloxy}h

exanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-(1r,4r)-4-[(4-{[(1r,4r)-4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}cyclohexyl)methyl]piperazin-1-yl)methyl]cyclohexane-1-carboxylate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-6-{[4,6-bis({6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexyl}oxy)-1,3,5-triazin-2-yl]oxy}hexanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-5-{1-[4-(4-{5-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-5-oxopentyl]-1H-1,2,3-triazol-1-yl)butyl]-1H-1,2,3-triazol-4-yl}pentanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-{1-[4-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutyl]-1H-1,2,3-triazol-1-yl)butyl]-1H-1,2,3-triazol-4-yl}butanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-[1-(5-{4-[5-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutyl]-1H-1,2,3-triazol-1-yl)pentanoyl]piperazin-1-yl]-5-oxopentyl)-1H-1,2,3-triazol-4-yl]butanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-(1-{5-[(2S,5R)-4-[5-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutyl]-1H-1,2,3-triazol-1-yl)pentanoyl]-2,5-dimethylpiperazin-1-yl]-5-oxopentyl)-1H-1,2,3-triazol-4-yl)butanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-[1-(5-{5-[5-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutyl]-1H-1,2,3-triazol-1-yl)pentanoyl]-2,5-diazabicyclo[2.2.2]octan-2-yl]-5-oxopentyl)-1H-1,2,3-triazol-4-yl]butanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-[1-(6-{4-[6-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutyl]-1H-1,2,3-triazol-1-yl)hexanoyl]piperazin-1-yl]-6-oxohexyl)-1H-1,2,3-triazol-4-yl]butanoate; and

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-(1-{6-[(2S,5R)-4-[6-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutyl]-1H-1,2,3-triazol-1-yl)hexanoyl]-2,5-dimethylpiperazin-1-yl]-6-oxohexyl)-1H-1,2,3-triazol-4-yl)butanoate.

[0114] Clause 8: A compound according to clause 6, or a pharmaceutically acceptable salt

thereof, wherein the compound is selected from the group consisting of:

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-[4,7-bis({4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutanoyl})-1,4,7-triazonan-1-yl]-4-oxobutan

oate;
(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-3-{1-[4,6-bis(4-{3-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-3-oxopropyl}piperidin-1-yl)-1,3,5-triazin-2-yl]piperidin-4-yl}propanoate; and

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-6-{[4,6-bis({6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexyl}oxy)-1,3,5-triazin-2-yl]oxy}hexanoate.

[0115] Clause 9: A compound according to clause 1, or a pharmaceutically acceptable salt thereof, wherein:

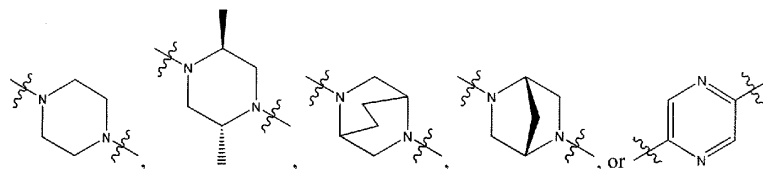
a is 2;

R¹ is -(CH₂)₂-, -(CH₂)₄-, -(CH₂)₅-, -(CH₂)₆-, -(CH₂)₇-, -(CH₂)₈-, -(CH₂)₉-, -(CH₂)₁₂-, or -(CH₂)₁₆-;

R² is -C(O)-, -CH₂-, or a direct bond; and

R³ is

[Chem.38]



[0116] Clause 10: A compound according to clause 9, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-6-(4-{6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexanoyl}piperazin-1-yl)-6-oxohexanoate;

(7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-8-[(2R,5S)-4-{8-[(7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanoyl}-2,5-dimethylpiperazin-1-yl]-8-oxooctanoate;

(7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-8-(5-{8-[(7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-

-dihydroquinolin-1-yl)methoxy]-8-oxooctanoyl}-2,5-diazabicyclo[2.2.2]octan-2-yl)-8-oxooctanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-8-[(1S,4S)-5-{8-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanoyl}-2,5-diazabicyclo[2.2.1]heptan-2-yl]-8-oxooctanoate; tris(trifluoroacetic acid);

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutanoyl}piperazin-1-yl)-4-oxobutanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-[(2S,5R)-4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutanoyl}-2,5-dimethylpiperazin-1-yl]-4-oxobutanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-10-(4-{10-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-10-oxodecanoyl}piperazin-1-yl)-10-oxodecanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-10-[(2R,5S)-4-{10-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-10-oxodecanoyl}-2,5-dimethylpiperazin-1-yl]-10-oxodecanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-10-(5-{10-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-10-oxodecanoyl}-2,5-diazabicyclo[2.2.2]octan-2-yl)-10-oxodecanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-8-(4-{8-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanoyl}piperazin-1-yl)-8-oxooctanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-6-[(2S,5R)-4-{6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexanoyl}-2,5-dimethylpiperazin-1-yl]-6-oxohexanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-14-(4-{14-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-14-oxotetradecanoyl}piperazin-1-yl)-14-oxotetradecanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-14-[(2S,5R)-4-{14-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-14-oxotetradecanoyl}-2,5-dimethylpiperazin-

1-yl]-14-oxotetradecanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-18-(4-{18-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-18-oxooctadecanoyl}piperazin-1-yl)-18-oxooctadecanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-18-[(2S,5R)-4-{18-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-18-ooctadecanoyl}-2,5-dimethylpiperazin-1-yl]-18-oxooctadecanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-N-(8-{4-[8-({[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}amino)octanoyl]piperazin-1-yl}-8-oxooctyl)carbamate; and
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-6-(4-{6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexyl}piperazin-1-yl)hexanoate.

[0117] Clause 11: A compound according to clause 1, or a pharmaceutically acceptable salt thereof, wherein:

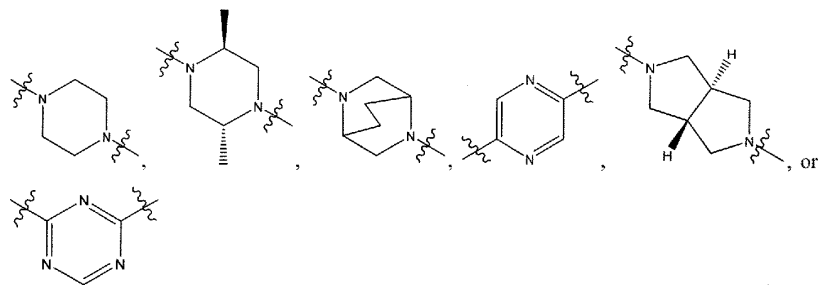
a is 2;

R¹ is

Chemical structures 1-10 are defined as follows:

- 1: 1,4-disubstituted cyclohexane.
- 2: 1,2-disubstituted cyclopentane.
- 3: 1,1-disubstituted ethane.
- 4: 1,1-disubstituted propane.
- 5: 1,1-disubstituted butane.
- 6: 1,3-disubstituted butane.
- 7: 1,3-disubstituted pentane.
- 8: 1,3-disubstituted hexane.
- 9: 1,3-disubstituted heptane.
- 10: 1,3-disubstituted octane.

[Chem.40]



[0118] Clause 12: A compound according to clause 11, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-(1r,4r)-4-{4-[(1r,4r)-4-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}cyclohexanecarbonyl]piperazine-1-carbonyl}cyclohexane-1-carboxylate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-(1r,4r)-4-[(2S,5R)-2,5-dimethyl-4-[(1r,4r)-4-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}cyclohexanecarbonyl]piperazine-1-carbonyl]cyclohexane-1-carboxylate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-(1s,4s)-4-{4-[(1s,4s)-4-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}cyclohexanecarbonyl]piperazine-1-carbonyl}cyclohexane-1-carboxylate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-(1s,4s)-4-[(2S,5R)-2,5-dimethyl-4-[(1s,4s)-4-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}cyclohexanecarbonyl]piperazine-1-carbonyl]cyclohexane-1-carboxylate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-1-[4-(1-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}cyclopentanecarbonyl)piperazine-1-carbonyl]cyclopentane-1-carboxylate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-1-[(3ar,6ar)-5-(1-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}cyclopentanecarbonyl)-octahydropyrrolo[3,4-c]pyrrole-2-carbonyl]cyclopentane-1-carboxylate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-3-(4-{3-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-2,2-dimethyl-3-oxopropanoyl}piperazin-1-yl)-2,2-dimethyl-3-oxopropanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-2,2-dimethyl-4-oxobutanoyl}piperazin-1-yl)-3,3-dimethyl-4-oxobutanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-3,3-dimethyl-4-oxobutanoyl}piperazin-1-yl)-2,2-dime

thyl-4-oxobutanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-5-(4-{5-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-3,3-dimethyl-5-oxopentanoyl}piperazin-1-yl)-3,3-dimethyl-5-oxopentanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-2-{2-[4-(2-{2-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-2-oxoethoxy}acetyl)piperazin-1-yl]-2-oxoethoxy}acetate;

(7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-N-[(2S)-1-{4-[(2S)-2-({[(7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}amino)-3-methylbutanoyl]piperazin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-[4-(1-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}piperidine-4-carbonyl)piperazine-1-carbonyl]piperidine-1-carboxylate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-1-[5-(4-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}piperidine-1-carbonyl)pyrazine-2-carbonyl]piperidine-4-carboxylate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-3-{1-[4-(4-{3-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-3-oxopropyl}piperidin-1-yl)-1,3,5-triazin-2-yl]piperidin-4-yl}propanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-3-[1-({5-[(4-{3-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-3-oxopropyl}piperidin-1-yl)methyl]pyrazin-2-yl}methyl)piperidin-4-yl}propanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-3-{1-[5-(4-{3-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-3-oxopropyl}piperidine-1-carbonyl)pyrazine-2-carbonyl]piperidin-4-yl}propanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-1-[5-(3-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}azetidine-1-carbonyl)pyrazine-2-carbonyl]azetidine-3-carboxylate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl

1)methyl-(1r,4r)-4-[(4-{[(1r,4r)-4-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}cyclohexyl)methyl]piperazin-1-yl)methyl]cyclohexane-1-carboxylate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-5-{1-[4-(4-{5-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-5-oxopentyl}-1H-1,2,3-triazol-1-yl)butyl]-1H-1,2,3-triazol-4-yl}pentanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-{1-[4-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutyl}-1H-1,2,3-triazol-1-yl)butyl]-1H-1,2,3-triazol-4-yl}butanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-[1-(5-{4-[5-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutyl]-1H-1,2,3-triazol-1-yl)pentanoyl]piperazin-1-yl}-5-oxopentyl)-1H-1,2,3-triazol-4-yl]butanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-(1-{5-[(2S,5R)-4-[5-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutyl]-1H-1,2,3-triazol-1-yl)pentanoyl]-2,5-dimethylpiperazin-1-yl]-5-oxopentyl}-1H-1,2,3-triazol-4-yl)butanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-[1-(5-{5-[5-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutyl]-1H-1,2,3-triazol-1-yl)pentanoyl]-2,5-diazabicyclo[2.2.2]octan-2-yl]-5-oxopentyl)-1H-1,2,3-triazol-4-yl]butanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-[1-(6-{4-[6-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutyl]-1H-1,2,3-triazol-1-yl)hexanoyl]piperazin-1-yl]-6-oxohexyl)-1H-1,2,3-triazol-4-yl]butanoate; and

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-(1-{6-[(2S,5R)-4-[6-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutyl]-1H-1,2,3-triazol-1-yl)hexanoyl]-2,5-dimethylpiperazin-1-yl]-6-oxohexyl}-1H-1,2,3-triazol-4-yl)butanoate.

[0119] Clause 13: A compound according to clause 1, or a pharmaceutically acceptable salt thereof, wherein:

a is 2;

R¹ is -(CH₂)₂-, -(CH₂)₄-, -(CH₂)₆-, or -(CH₂)₉-;

R² is -C(O)-, -C(O)-N(CH₃)-CH₂-, -C(O)-NH-CH₂-, or -NH-C(O)-; and

R³ is












(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1

-yl)methyl-6-[(3ar,6ar)-5-{6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexanoyl}-octahydropyrrolo[3,4-c]pyrrol-2-yl]-6-oxohexanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-6-(5-{6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexanoyl}-octahydropyrrolo[3,4-c]pyrrol-2-yl)-6-oxohexanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-5-([5-([6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-N-methyl-6-oxohexanamido)methyl]pyrazin-2-yl)methyl)(methyl)carbamoyl)pentanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-5-([5-([6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexanamido)methyl]pyrazin-2-yl)methyl)carbamoyl)pentanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-5-([5-([5-([6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-5-oxopentyl)carbamoyl)-1,3-thiazol-2-yl]formamido)pentanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-5-([5-([5-([6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-5-oxopentyl)carbamoyl]pyrazin-2-yl]formamido)pentanoate; and

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-10-([5-([10-([6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-10-oxodecyl)carbamoyl]pyrazin-2-yl]formamido)decanoate.

- [0121] Clause 15: A compound according to any one of clauses 1 to 14, or a pharmaceutically acceptable salt thereof, including any of all the example compounds described herein, having the mean particle size measured by laser diffractometry ranging from 0.05 to 10 μm .
- [0122] Clause 16: A pharmaceutical composition comprising a compound according to any one of clauses 1 to 15, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
- [0123] Clause 17: A medicament for treating and/or preventing a central nervous system disorder, comprising a compound according to any one of clauses 1 to 15, or a pharmaceutically acceptable salt thereof.
- [0124] Clause 18: The medicament according to clause 17, wherein the central nervous

system disorder is selected from the group consisting of schizophrenia; refractory, intractable or chronic schizophrenia; emotional disturbance; psychotic disorder; mood disorder; bipolar I type disorder; bipolar II type disorder; depression; endogenous depression; major depressive disorder (MDD); melancholy and refractory depression; dysthymic disorder; cyclothymic disorder; panic attack; panic disorder; agoraphobia; social phobia; obsessive-compulsive disorder; post-traumatic stress disorder; generalized anxiety disorder; acute stress disorder; hysteria; somatization disorder; conversion disorder; pain disorder; hypochondriasis; factitious disorder; dissociative disorder; sexual dysfunction; sexual desire disorder; sexual arousal disorder; erectile dysfunction; anorexia nervosa; bulimia nervosa; sleep disorder; adjustment disorder; alcohol abuse; alcohol intoxication; drug addiction; stimulant intoxication; narcotism; anhedonia; iatrogenic anhedonia; anhedonia of a psychic or mental cause; anhedonia associated with depression; anhedonia associated with schizophrenia; delirium; cognitive impairment; cognitive impairment associated with Alzheimer's disease, Parkinson's disease and other neurodegenerative diseases; cognitive impairment caused by Alzheimer's disease; Parkinson's disease and associated neurodegenerative diseases; cognitive impairment of schizophrenia; cognitive impairment caused by refractory, intractable or chronic schizophrenia; vomiting; motion sickness; obesity; migraine; pain (ache); mental retardation; autism disorder (autism); Tourette's disorder; tic disorder; attention-deficit/hyperactivity disorder; conduct disorder; Down's syndrome; impulsive symptoms associated with dementia (e.g., agitation associated with Alzheimer's disease); and borderline personality disorder.

[0125] Clause 19: Use of a compound according to any one of clauses 1 to 15, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating and/or preventing a central nervous system disorder.

[0126] Clause 20: The use according to clause 19, wherein the central nervous system disorder is selected from the group consisting of schizophrenia; refractory, intractable or chronic schizophrenia; emotional disturbance; psychotic disorder; mood disorder; bipolar I type disorder; bipolar II type disorder; depression; endogenous depression; major depressive disorder (MDD); melancholy and refractory depression; dysthymic disorder; cyclothymic disorder; panic attack; panic disorder; agoraphobia; social phobia; obsessive-compulsive disorder; post-traumatic stress disorder; generalized anxiety disorder; acute stress disorder; hysteria; somatization disorder; conversion disorder; pain disorder; hypochondriasis; factitious disorder; dissociative disorder; sexual dysfunction; sexual desire disorder; sexual arousal disorder; erectile dysfunction; anorexia nervosa; bulimia nervosa; sleep disorder; adjustment disorder; alcohol abuse; alcohol intoxication; drug addiction; stimulant intoxication; narcotism; anhedonia; iatrogenic anhedonia; anhedonia of a psychic or mental cause; anhedonia

associated with depression; anhedonia associated with schizophrenia; delirium; cognitive impairment; cognitive impairment associated with Alzheimer's disease, Parkinson's disease and other neurodegenerative diseases; cognitive impairment caused by Alzheimer's disease; Parkinson's disease and associated neurodegenerative diseases; cognitive impairment of schizophrenia; cognitive impairment caused by refractory, intractable or chronic schizophrenia; vomiting; motion sickness; obesity; migraine; pain (ache); mental retardation; autism disorder (autism); Tourette's disorder; tic disorder; attention-deficit/hyperactivity disorder; conduct disorder; Down's syndrome; impulsive symptoms associated with dementia (e.g., agitation associated with Alzheimer's disease); and borderline personality disorder.

[0127] Clause 21: A method for treating and/or preventing a central nervous system disorder, comprising administering a compound according to any one of clauses 1 to 15, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

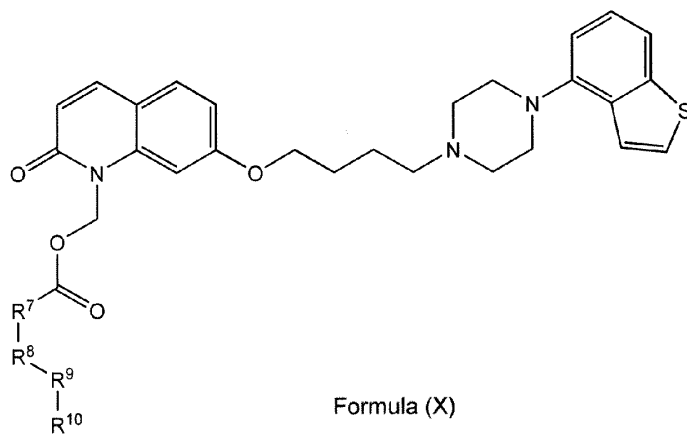
[0128] Clause 22: The method according to clause 21, wherein the central nervous system disorder is selected from the group consisting of schizophrenia; refractory, intractable or chronic schizophrenia; emotional disturbance; psychotic disorder; mood disorder; bipolar I type disorder; bipolar II type disorder; depression; endogenous depression; major depressive disorder (MDD); melancholy and refractory depression; dysthymic disorder; cyclothymic disorder; panic attack; panic disorder; agoraphobia; social phobia; obsessive-compulsive disorder; post-traumatic stress disorder; generalized anxiety disorder; acute stress disorder; hysteria; somatization disorder; conversion disorder; pain disorder; hypochondriasis; factitious disorder; dissociative disorder; sexual dysfunction; sexual desire disorder; sexual arousal disorder; erectile dysfunction; anorexia nervosa; bulimia nervosa; sleep disorder; adjustment disorder; alcohol abuse; alcohol intoxication; drug addiction; stimulant intoxication; narcotism; anhedonia; iatrogenic anhedonia; anhedonia of a psychic or mental cause; anhedonia associated with depression; anhedonia associated with schizophrenia; delirium; cognitive impairment; cognitive impairment associated with Alzheimer's disease, Parkinson's disease and other neurodegenerative diseases; cognitive impairment caused by Alzheimer's disease; Parkinson's disease and associated neurodegenerative diseases; cognitive impairment of schizophrenia; cognitive impairment caused by refractory, intractable or chronic schizophrenia; vomiting; motion sickness; obesity; migraine; pain (ache); mental retardation; autism disorder (autism); Tourette's disorder; tic disorder; attention-deficit/hyperactivity disorder; conduct disorder; Down's syndrome; impulsive symptoms associated with dementia (e.g., agitation associated with Alzheimer's disease); and borderline personality disorder.

[0129] Clause 23: A compound according to any one of clauses 1 to 15, or a pharmaceutically acceptable salt thereof, for use in treating and/or preventing a central

nervous system disorder.

- [0130] Clause 24: The compound for use according to clause 23, wherein the central nervous system disorder is selected from the group consisting of schizophrenia; refractory, intractable or chronic schizophrenia; emotional disturbance; psychotic disorder; mood disorder; bipolar I type disorder; bipolar II type disorder; depression; endogenous depression; major depressive disorder (MDD); melancholy and refractory depression; dysthymic disorder; cyclothymic disorder; panic attack; panic disorder; agoraphobia; social phobia; obsessive-compulsive disorder; post-traumatic stress disorder; generalized anxiety disorder; acute stress disorder; hysteria; somatization disorder; conversion disorder; pain disorder; hypochondriasis; factitious disorder; dissociative disorder; sexual dysfunction; sexual desire disorder; sexual arousal disorder; erectile dysfunction; anorexia nervosa; bulimia nervosa; sleep disorder; adjustment disorder; alcohol abuse; alcohol intoxication; drug addiction; stimulant intoxication; narcotism; anhedonia; iatrogenic anhedonia; anhedonia of a psychic or mental cause; anhedonia associated with depression; anhedonia associated with schizophrenia; delirium; cognitive impairment; cognitive impairment associated with Alzheimer's disease, Parkinson's disease and other neurodegenerative diseases; cognitive impairment caused by Alzheimer's disease; Parkinson's disease and associated neurodegenerative diseases; cognitive impairment of schizophrenia; cognitive impairment caused by refractory, intractable or chronic schizophrenia; vomiting; motion sickness; obesity; migraine; pain (ache); mental retardation; autism disorder (autism); Tourette's disorder; tic disorder; attention-deficit/hyperactivity disorder; conduct disorder; Down's syndrome; impulsive symptoms associated with dementia (e.g., agitation associated with Alzheimer's disease); and borderline personality disorder.
- [0131] Clause 25: A process of preparing a compound according to any one of clauses 1 to 15, or a pharmaceutically acceptable salt thereof, as described herein.
- [0132] Clause 26: An intermediate compound in the process of preparing a compound according to any one of clauses 1 to 15, or a pharmaceutically acceptable salt thereof, as described herein.
- [0133] Clause 27: A compound having Formula (X), or a salt thereof:

[Chem.42]

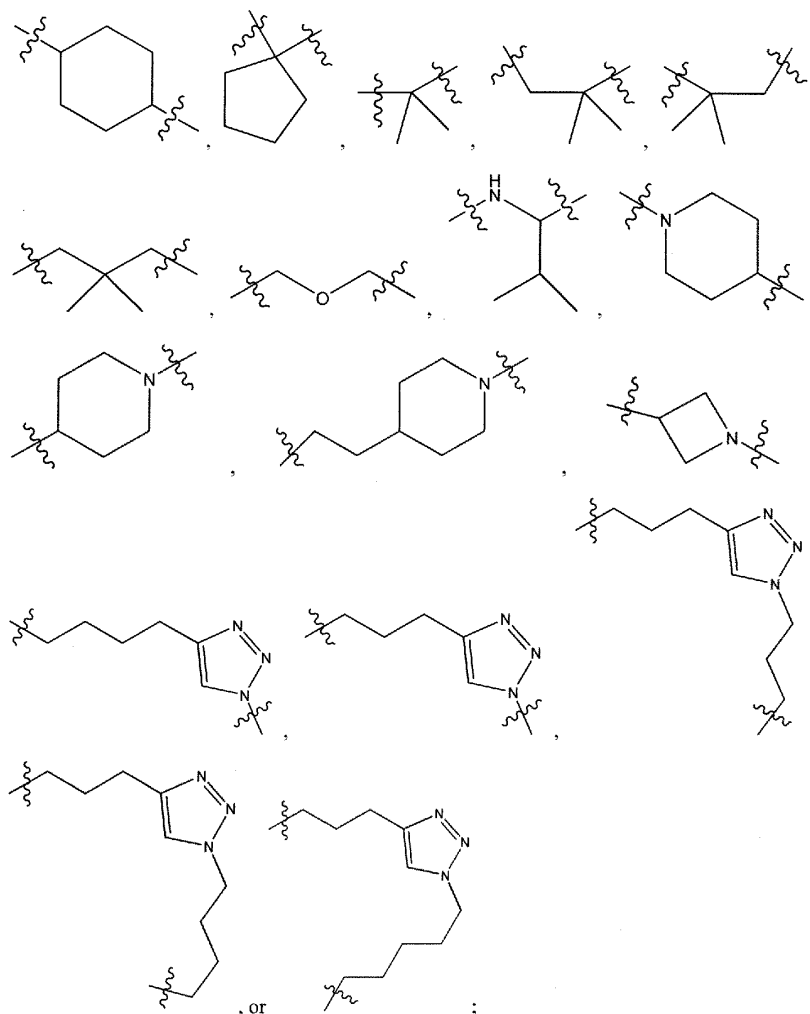


Formula (X)

wherein:

R⁷ is -CH=CH-, -(CH₂)₂-, -(CH₂)₄-, -(CH₂)₅-, -(CH₂)₆-, -(CH₂)₇-, -(CH₂)₈-, -(CH₂)₉-, -(CH₂)₁₂-, -(CH₂)₁₆-,

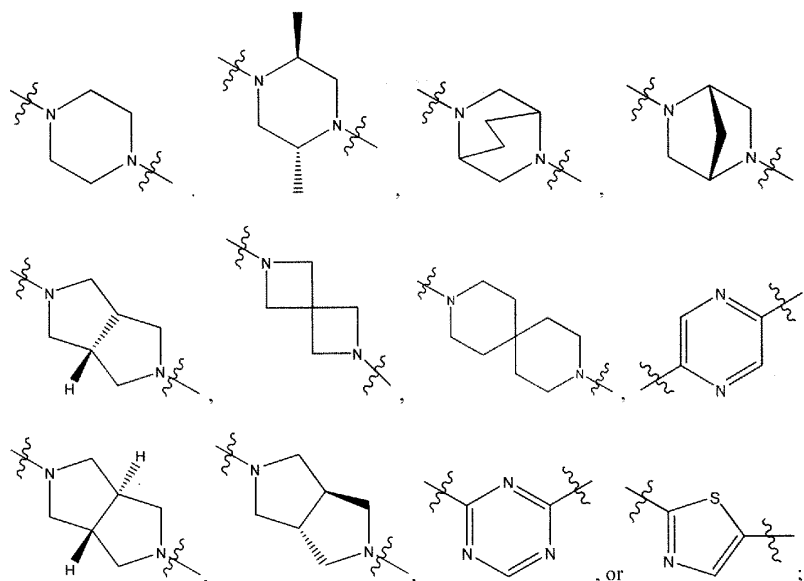
[Chem.43]



R^8 is -C(O)-, -C(O)-N(CH₃)-CH₂-, -C(O)-NH-CH₂-, -CH₂-, -NH-C(O)-, or a direct bond;

R^9 is -(CH₂)₄-;

[Chem.44]



and

R^{10} is $-(CH_2)_2-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-(CH_2)_7-$, $-(CH_2)_8-$, $-(CH_2)_9-$, H, $-COOH$, $-C(O)-(CH_2)_{2-10}-C(O)H$, $-C(O)-(CH_2)_{2-10}-C(O)(tBu)$, or $-C(O)(tBu)$.

[0134] The following examples are for illustrative purposes only and are not intended, nor should they be construed as limiting the invention in any manner. Those skilled in the art will appreciate that variations and modifications of the following examples can be made without exceeding the spirit or scope of the invention. As will be evident to those skilled in the art, individual isomeric forms can be obtained by separation of mixtures thereof in conventional manner. For example, in the case of diastereoisomeric isomers, chromatographic separation may be employed.

Examples

[0135] General Experimental Details and methods

Analytical method

Instruments, materials and methods employed for analyses

1H -NMR spectra were performed on 400 Agilent INOVA, 500 Agilent VNMRs, 600 Agilent INOVA spectrometers operating at 400, 500, 600 MHz (proton frequency), or on a Bruker Avance III 400 spectrometers. Chemical shifts are reported as δ values in ppm using residual solvent peak as internal reference. Coupling constants (J values) are given in hertz (Hz) and multiplicities are reported using the following abbreviation (s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, h = heptet, m = multiplet, br. s = broad singlet, nd = not determined, dd = double-doublet, ddd = double-

double-doublet, quin = quintuplet, td = triple doublet, tt = triple triplet, qd = quadruple doublet).

[0136] LC/UV/MS Analytical Methods

LC/MS retention times are estimated to be affected by an experimental error of + 0.5 min. LC/MS may be recorded under the following conditions: diode array DAD chromatographic traces, mass chromatograms and mass spectra may be taken on UPLC/PDA/MS Acquity™ system coupled with Micromass ZQ™ or Waters SQD single quadrupole mass spectrometer operated in positive and/or negative electron spray ES ionization mode and/or Fractionlynx system used in analytical mode coupled with ZQ™ single quadrupole operated in positive and/or negative ES ionisation mode. Quality Control methods used operated under low pH conditions or under high pH conditions:

Method 1, low pH conditions column: Acquity CSH C18 2.1 x 50 mm 1.7 µm, the column temperature was 40°C; mobile phase solvent A was milliQ water + 0.1% HCOOH, mobile phase solvent B MeCN + 0.1% HCOOH. The flow rate was 1 mL/min.

The gradient table was t = 0 min 97% A 3% B, t = 1.5 min 0.1% A 99.9% B, t = 1.9 min 0.1% A 99.9% B and t = 2 min 97% A 3% B. The UV detection range was 210-350 nm and ES+/ES- range was 100 to 1900 AMU.

Method 2, high pH conditions: column: Kinetex EVO C18 2.1 x 50 mm 1.7 µm, the column temperature was 40°C; mobile phase solvent A was 10 mM aqueous solution of NH₄HCO₃ adjusted to pH = 10 with ammonia, mobile phase solvent B MeCN. The flow rate was 1 mL/min. The gradient table was t = 0 min 97% A 3% B, t = 1.5 min 0.1% A 99.9% B, t = 1.9 min 0.1% A 99.9% B and t = 2 min 97% A 3% B. The UV detection range was 210-350 nm and ES+/ES- range was 100 to 1200 AMU.

Method 3, low pH conditions column: Acquity Peptide BEH C18 2.1 x 50 mm 1.7 µm, the column temperature was 40°C; mobile phase solvent A was milliQ water + 0.05% TFA, mobile phase solvent B MeCN + 0.05% TFA. The flow rate was 0.7 mL/min.

The gradient table was t = 0 min 97% A 3% B, t = 3.0 min 20% A 80% B, t = 3.5 min 5% A 95% B, t = 3.9 min 5% A 95% B and t = 4 min 97% A 3% B. The UV detection range was 210-350 nm and ES+/ES- range was 100 to 1900 AMU.

Method 4, low pH conditions column: Acquity Peptide BEH C18 2.1 x 50 mm 1.7 µm, the column temperature was 40°C; mobile phase solvent A was milliQ water + 0.05% TFA, mobile phase solvent B MeCN + 0.05% TFA. The flow rate was 0.7 mL/min.

The gradient table was t = 0 min 97% A 3% B, t = 0.5 min 97% A 3% B, t = 3.0 min 40% A 60% B, t = 3.5 min 5% A 95% B, t = 3.9 min 5% A 95% B and t = 4 min 97%

A 3% B. The UV detection range was 210-350 nm and ES+/ES- range was 100 to 1900 AMU.

[0137] HPLC Semi-preparative Methods

Semiprep. HPLC was performed using a MDAP Waters apparatus with mass spectrometry detection (MS:ZQ2000) and DAD detection 220, equipped with CSH C18 (30 x 100 mm, 5 μ m) column and 1 mL injection loop. A gradient of MeCN in H₂O + HCOOH from 50% to 70% in 10 min. (flow = 40.00 mL/min.) was used as mobile phase.

[0138] Chemical Names of the compounds were generated with Structure To Name ChemAxon MarvinSketch Software.

[0139] All reagents, for which the synthesis is not described in the experimental part, are either commercially available, or are known compounds or may be formed from known compounds by known methods by a person skilled in the art.

[0140] The following abbreviations are used in the examples:

2-MeTHF = 2-methyltetrahydrofuran

atm = atmosphere

Boc = tert-butyloxycarbonyl

Boc₂O = di-tert-butyl dicarbonate

cHex = cyclohexane

CuI = copper(I) iodide

DCM = dichloromethane

DIAD = diisopropyl azodicarboxylate

DIPEA = N,N-diisopropylethylamine

DMAP = 4-(dimethylamino)pyridine

DMF = dimethylformamide

DMSO = dimethylsulfoxide

EtOAc = ethyl acetate

HCOOH = formic acid

h = hour

HATU =

1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium-3-oxid hexafluorophosphate

HCl = hydrochloric acid

HBTU =

[(1H-1,2,3-benzotriazol-1-yl-oxy)(dimethylamino)methylidene]dimethylazanium; hexafluoro-lambda5-phosphanuide

HCl = hydrochloric acid

H₂O = water

IPA = propan-2-ol

K_2CO_3 = potassium carbonate

LC-MS = liquid chromatography/mass spectrometry

MeCN = acetonitrile

MeOH = methanol

MsCl = methanesulfonyl chloride

N_2 = nitrogen

NaH = sodium hydride

NaOH = sodium hydroxide

Na_2SO_4 = sodium sulfate

$NaHCO_3$ = sodium bicarbonate

Na_2CO_3 = sodium carbonate

NH_4Cl = ammonium chloride

nHex = n-hexane

Pd/C = palladium on carbon

$Pd(OAc)_2$ = palladium(II) acetate

PPh_3 = triphenylphosphine

Py = pyridine

quant. = quantitative

Rt = retention time

RT = room temperature

Sec. = seconds

s.s. = saturated solution

TBA- HSO_4 = tetrabutylammonium hydrogensulfate

TBTU = O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate

TEA = triethylamine

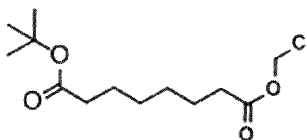
TFA = trifluoroacetic acid

THF = tetrahydrofuran

[0141] Preparation of intermediates

Int01: 1-tert-butyl 8-chloromethyl octanedioate

[Chem.45]



To a mixture of 8-[(2-methylpropan-2-yl)oxy]-8-oxooctanoic acid (3.7 g) in DCM

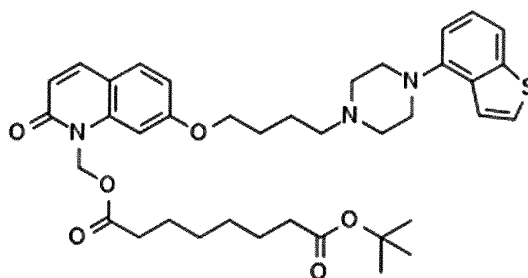
(35 mL) and H₂O (44 mL) was added NaHCO₃ (5.4 g,) and TBA-HSO₄ (5.5 g). The mixture was cooled at 0°C and a solution of chloromethyl chlorosulfate (1.6 mL) in 8 mL of DCM was added dropwise. Then the reaction was allowed to stir at RT for 3 h. The mixture was diluted with DCM and washed with H₂O. Organic layer was dried over Na₂SO₄, filtered, and concentrated under vacuum. The crude obtained was purified by chromatography on a silica gel cartridge (eluent = from 0% to 10% of EtOAc in cHex) to provide Int01 (2.76 g).

¹H NMR (400 MHz, CHLOROFORM-d) δ 5.70 (s, 2H), 2.38 (t, J = 7.45 Hz, 2H), 2.20 (t, J = 7.45 Hz, 2H), 1.72 - 1.55 (m, 4H), 1.44 (s, 9H), 1.40 - 1.26 (m, 4H).

[0142] Int02:

1-(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 8-tert-butyl octanedioate

[Chem.46]



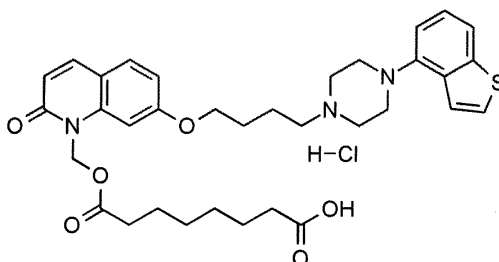
Under N₂ atmosphere NaH (60% in mineral oil, 0.14 g) was added to 1,4-Dioxane (30 mL), then 7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-1,2-dihydroquinolin-2-one (1.4 g) was added and the reaction was stirred at RT for 15 min. Then a solution Int01 (1.35 g) in 1,4-Dioxane (7 mL) was added dropwise. The reaction mixture was stirred at 60°C (ext. temp.) for 2.5 h. The reaction was cooled down to RT, diluted with EtOAc and quenched with NH₄Cl s.s.. The obtained mixture was extracted with EtOAc (2x). Combined organic layers were dried over a phase separator and the solvent was concentrated under vacuum. The crude obtained was purified by chromatography on silica gel cartridge (eluent = from 10% to 100% of EtOAc in cHex) to give Int02 (2.9 g)

LC-MS (ESI): m/z (M+1): 676.4, Rt= 0.98 min. (Method 1).

[0143] Int03:

8-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanoic acid hydrochloride

[Chem.47]

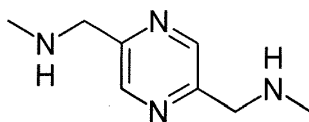


To a solution of Int02 (2.9 g) in DCM (91 mL) was added at RT dropwise TFA (5.25 mL). The mixture was stirred at RT for 48 h at RT. The solvent was evaporated and residue TFA was partially co-evaporated with Toluene. Then 1,4-Dioxane (10 mL) and HCl 4N in 1,4-dioxane (15 mL) were added and then the mixture was evaporated in high vacuum to give a yellow oil. This was taken up with DCM and washed twice with NaHCO₃ s.s., the organic phase was filtered over a phase separator and acidified (pH=3-4) using 1.8 mL of aqueous HCl (1M). The organic phase was washed with H₂O (2x) dried over Na₂SO₄, filtered and concentrated under vacuum, affording Int03 (2.0 g).

LC-MS (ESI): m/z (M+1): 620.0, Rt= 0.68 min. (Method 1).

[0144] Int04: methyl({ 5-[(methylamino)methyl]pyrazin-2-yl}methyl)amine

[Chem.48]

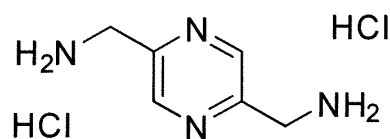


A 2M solution of methanamine (8 mL) in THF was diluted with additional THF (10 mL) and cooled down to 0°C. 2,5-bis(bromomethyl)pyrazine (0.28 g) in THF (3 mL) was added dropwise at 0°C. The reaction mixture was sealed in a vial and stirred at RT for 5 h. Then the solvent was removed in high vacuum and the residue was purified on a SCX column (eluent = MeOH then 2M ammonia in MeOH), to afford crude Int04 (174 mg).

¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.53 (s, 2H), 3.89 (d, J = 2.32 Hz, 4H), 2.49 (d, J = 1.63 Hz, 6H).

[0145] Int05: 1-[5-(aminomethyl)pyrazin-2-yl]methanamine dihydrochloride

[Chem.49]



Step A: To a solution of [5-(hydroxymethyl)pyrazin-2-yl]methanol (50 mg) in dry THF (3.5 mL), PPh_3 (206 mg) and Phthalimide (105 mg) were added at RT. The mixture was cooled down to 0°C and DIAD (0.16 mL) was added dropwise. The mixture was allowed to stir at RT for 3 hours. The reaction mixture was filtered over a phase separator and washed with MeCN. The solid residue was dried under vacuum affording

2-({5-[(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)methyl]pyrazin-2-yl)methyl)-2,3-dihydro-1H-isoindole-1,3-dione (127 mg).

LC-MS (ESI): m/z ($M+1$): 399.1, $R_t = 0.96$ min. (Method 1).

Step B: To a suspension of

2-({5-[(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)methyl]pyrazin-2-yl)methyl)-2,3-dihydro-1H-isoindole-1,3-dione (127 mg) in DCM (4 mL), hydrazine (0.04 mL) was added and the mixture was refluxed for 3 h. The mixture was cooled to RT and TEA (0.2 mL) and Boc_2O (0.21 g) were added, and the resulting mixture was stirred at 35°C for 24 h. The mixture was cooled to RT and the solid was filtered off. The organic layer was washed with H_2O , the organic phase was filtered over a phase separator and evaporated in high vacuum. The crude obtained was purified by chromatography on a silica gel cartridge (eluent = 0% to 40% of EtOAc in cHex), to give tert-butyl N-

{[5-({[(tert-butoxy)carbonyl]amino)methyl}pyrazin-2-yl)methyl}carbamate (48 mg).

LC-MS (ESI): m/z ($M+1$): 399.2, $R_t = 0.90$ min. (Method 1).

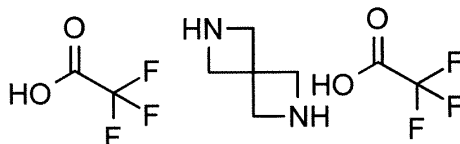
Step C: To a solution of tert-butyl N-

[[5-[(2-methylpropan-2-yl)oxycarbonylamino]methyl]pyrazin-2-yl)methyl]carbamate (48 mg) in 1,4-dioxane (2 mL), HCl 4M in 1,4-dioxane (0.57 mL) was added and the reaction mixture was stirred at RT overnight. Then more HCl 4M in 1,4-dioxane (0.2 mL) was added and the mixture was stirred at RT for further 6 h. The mixture was evaporated with high vacuum to yield crude Int05 (31 mg).

^1H NMR (400 MHz, DMSO-d_6) δ 8.81 (s, 2H), 8.47 (s, 6H), 4.31 (s, 4H).

[0146] Int08: 2,6-diazaspiro[3.3]heptane bis(trifluoroacetic acid) salt

[Chem.50]

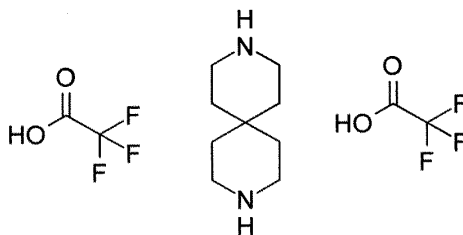


To a solution of tert-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate (100 mg) in DCM (4 mL), was added TFA (0.6 mL) dropwise at 0°C. After 3 h of stirring at RT the mixture was evaporated with high vacuum to Int08 (197 mg).

¹H NMR (400 MHz, CHLOROFORM-d) δ 4.07 (s, 8H), 2.25 (s, 2H).

[0147] Int09: 3,9-diazaspiro[5.5]undecane bis(trifluoroacetic acid) salt

[Chem.51]



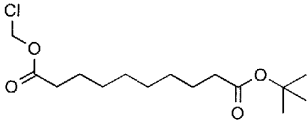
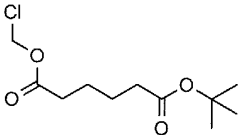
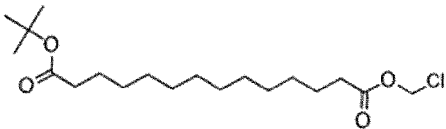
[0148] Int09 was prepared following the procedure described for Int08, starting from tert-butyl 3,9-diazaspiro[5.5]undecane-3-carboxylate (0.10 g), to afford Int09 (0.197 g).

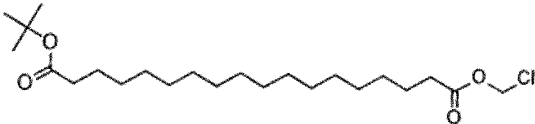
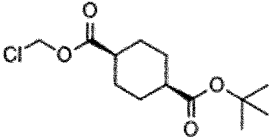
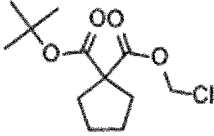
¹H NMR (400 MHz, DMSO-d₆) δ 8.47 (brs, 4H), 3.05 (dq, J = 8.63, 4.88 Hz, 8H), 1.63 (t, J = 5.92 Hz, 8H).

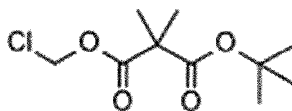
Intermediates Int10, Int13, Int18, Int21, Int27, Int30, Int33, Int36, Int39, Int41, Int44, Int55, Int58, Int61, Int63, Int66, Int71 and Int75 were synthesized according to the method used to synthesize Int01.

[0149] The starting materials used in the synthesis of each compound as well as their characterization are tabulated in Table 3.

[Table 3]

Table 3	
Int10: 1-tert-butyl 10-chloromethyl decanedioate	
	
starting material	10-(tert-butoxy)-10-oxodecanoic acid (4.74 g)
¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 5.72 (s, 2 H), 2.40 (t, J=7.48 Hz, 2 H), 2.22 (t, J=7.48 Hz, 2 H), 1.58 - 1.72 (m, 4 H), 1.46 (s, 9 H), 1.33 (br. s., 8 H)
Yield	1.27 g
Int13: 1-tert-butyl 6-chloromethyl hexanedioate	
	
starting material	6-[(2-methylpropan-2-yl)oxy]-6-oxohexanoic acid 2.4 g
¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 5.69 (s, 2H), 2.40 (t, J = 7.14 Hz, 2H), 2.23 (t, J = 7.06 Hz, 2H), 1.56 - 1.75 (m, 4H), 1.43 (s, 9H)
Yield	1.15 g
Int18: 1-tert-butyl 14-chloromethyl tetradecanedioate	
	
starting material	14-(tert-butoxy)-14-oxotetradecanoic acid (1.0 g)
¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 5.70 (s, 2 H), 2.38 (t, J = 7.5 Hz, 2 H), 2.20 (t, J = 7.5 Hz, 2 H), 1.58 - 1.72 (m, 4 H), 1.46 (s, 9 H), 1.33 (br. s., 8 H)

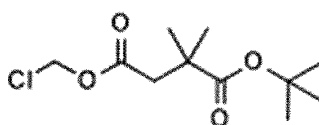
CHLOROFORM- <i>d</i>)	1.61 (dt, <i>J</i> = 32.1, 7.2 Hz, 4 H), 1.44 (s, 9 H), δ 1.27 (d, <i>J</i> = 12.1 Hz, 16 H)
Yield	810 mg
Int21: 1-tert-butyl 18-chloromethyl octadecanedioate	
	
starting material	18-(tert-butoxy)-18-oxooctadecanoic acid (1.0 g)
¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 5.70 (s, 2H), 2.38 (t, <i>J</i> = 7.49 Hz, 2H), 2.20 (t, <i>J</i> = 7.51 Hz, 2H), 1.58 – 1.70 (m, 4 H), 1.44 (s, 9 H), δ 1.27 (d, <i>J</i> = 11.86 Hz, 24 H)
Yield	532 mg
Int27: 1-tert-butyl 4-chloromethyl (1s,4s)-cyclohexane-1,4-dicarboxylate	
	
starting material	Int26 (2.1 g)
¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 5.73 (d, <i>J</i> = 5.8 Hz, 2H), 2.55 (tt, <i>J</i> = 7.7, 4.3 Hz, 1H), 2.39 (ddd, <i>J</i> = 11.9, 7.4, 4.6 Hz, 1H), 1.99 – 1.81 (m, 4H), 1.78 – 1.59 (m, 4H), 1.47 (s, 9H)
Yield	1.1 g
Int30: 1-tert-butyl 1-chloromethyl cyclopentane-1,1-dicarboxylate	
	
starting material	1-[(tert-butoxy)carbonyl]cyclopentane-1-carboxylic acid (1.9 g)
¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 5.76 (s, 2 H), 2.13 - 2.24 (m, 4 H), 1.67 - 1.79 (m, 4 H), 1.44 - 1.51 (m, 9 H)
Yield	1.4 g

Int33: 1-tert-butyl 3-chloromethyl 2,2-dimethylpropanedioate

starting material	3-(tert-butoxy)-2,2-dimethyl-3-oxopropanoic acid (2.3 g)
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¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 5.76 (s, 2 H), 1.47 (s, 9 H), 1.44 (s, 6 H)
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Yield	1.5 g
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Int36: 1-tert-butyl 4-chloromethyl 2,2-dimethylbutanedioate

starting material	4-(tert-butoxy)-2,2-dimethyl-4-oxobutanoic acid and 4-(tert-butoxy)-3,3-dimethyl-4-oxobutanoic acid (0.97 g)
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¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 5.70 (s, 2 H), 2.62 (s, 2 H), 1.45 (s, 9 H), 1.26 (s, 6 H)
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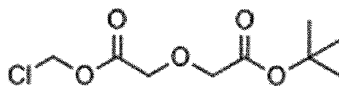
Yield	0.2 g
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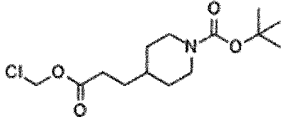
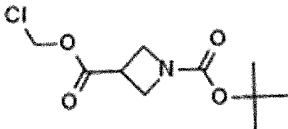
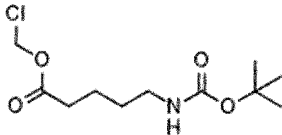
Int41: 1-tert-butyl 5-chloromethyl 3,3-dimethylpentanedioate

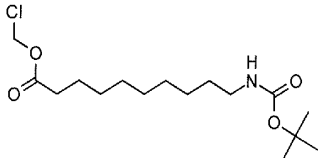
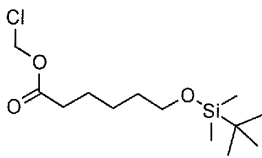
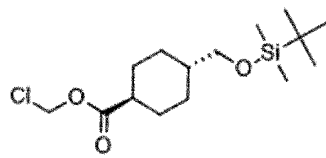
starting material	5-(tert-butoxy)-3,3-dimethyl-5-oxopentanoic acid (4.9 g)
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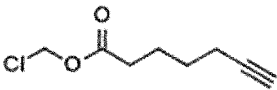
¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 5.72 (s, 2 H), 2.53 (s, 2 H), 2.34 (s, 2 H), 1.47 (s, 9 H), 1.15 (s, 6 H).
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Yield	1.0 g
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Int44: chloromethyl 2-[2-(tert-butoxy)-2-oxoethoxy]acetate

starting material	2-[2-(tert-butoxy)-2-oxoethoxy]acetic acid (2.6 g)
¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 5.76 (s, 2H), 4.31 (s, 2H), 4.11 (s, 2H), 1.48 (s, 9H)
Yield	1.6 g
Int55: tert-butyl 4-[3-(chloromethoxy)-3-oxopropyl]piperidine-1-carboxylate	
	
starting material	3-{1-[(tert-butoxy)carbonyl]piperidin-4-yl}propanoate (2.5 g)
LC-MS Method 1	LC-MS (ESI): m/z (M ⁺): 306.1, Rt= 1.17 min.
Yield	1.66 g
Int58: 1-tert-butyl 3-chloromethyl azetidine-1,3-dicarboxylate	
	
starting material	1-[(tert-butoxy)carbonyl]azetidine-3-carboxylic acid (2.5 g)
¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 5.75 (s, 2H), 4.12 (d, J = 7.4 Hz, 4H), 3.41 (p, J = 7.3 Hz, 1H), 1.44 (s, 9H)
Yield	1.41 g
Int61: chloromethyl 5-[(tert-butoxy)carbonyl]amino}pentanoate	
	
starting material	5-[(tert-butoxy)carbonyl]amino}pentanoic acid 5 g
¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 5.62 - 5.81 (m, 1 H), 4.55 (br s, 1 H), 3.15 (q, J=6.3 Hz, 1 H), 2.43 (t, J=7.3 Hz, 1 H), 1.64 - 1.78 (m, 2 H), 1.49 - 1.62 (m, 2 H), 1.45

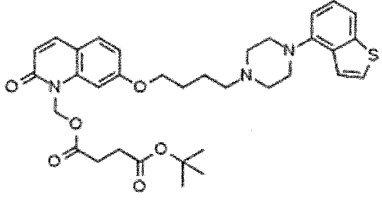
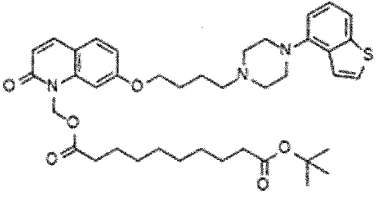
	(s, 9 H)
Yield	1.0 g
Int63: chloromethyl 10-[[[(tert-butoxy)carbonyl]amino]decanoate 	
starting material	10-[[[(tert-butoxy)carbonyl]amino]decanoic acid (2.5 g)
¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 5.73 (s, 2 H) 3.12 (q, J=6.38 Hz, 2 H) 2.40 (t, J=7.48 Hz, 2 H) 1.67 (quin, J=7.32 Hz, 2 H) 1.45 - 1.49 (m, 11 H) 1.28 - 1.37 (m, 10 H)
Yield	1.0 g
Int66: chloromethyl-chloromethyl-6-[[[(tert-butyldimethylsilyl)oxy]hexanoate 	
starting material	6-[[[(tert-butyldimethylsilyl)oxy]hexanoic acid (2.14 g)
¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 5.71 (s, 2 H) 3.58 - 3.66 (m, 2 H) 2.40 (t, J=7.48 Hz, 2 H) 1.69 (quin, J=7.59 Hz, 2 H) 1.49 - 1.60 (m, 2 H) 1.34 - 1.46 (m, 2 H) 0.88 - 0.94 (m, 9 H) 0.01 - 0.08 (m, 6 H)
Yield	1.37 g
Int71: chloromethyl (1r,4r)-4-[[[(tert-butyldimethylsilyl)oxy]methyl]cyclohexane-1-carboxylate 	
starting material	(1r,4r)-4-[[[(tert-butyldimethylsilyl)oxy]methyl]cyclohexane-1-

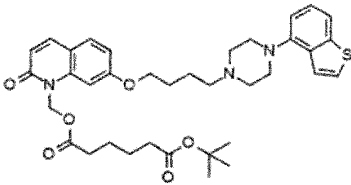
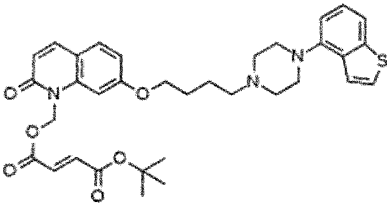
	carboxylic acid (1.7 g)
¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 5.69 - 5.74 (m, 2 H), 3.38 - 3.45 (m, 2 H), 2.30 (tt, J=12.21, 3.52 Hz, 1 H), 1.98 - 2.09 (m, 2 H), 1.79 - 1.94 (m, 2 H), 1.37 - 1.54 (m, 3 H), 0.83 - 1.08 (m, 11 H), 0.01 - 0.08 (m, 6 H)
Yield	927 mg
Int75: chloromethyl hept-6-ynoate 	
starting material	hept-6-ynoic acid (2.5 g)
¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 5.72 (s, 2H), 2.44 (t, J = 7.4 Hz, 2H), 2.24 (td, J = 7.0, 2.7 Hz, 2H), 1.98 (t, J = 2.7 Hz, 1H), 1.88 - 1.73 (m, 2H), 1.70 - 1.53 (m, 2H)
Yield	1.7 g

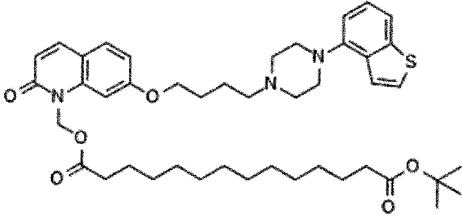
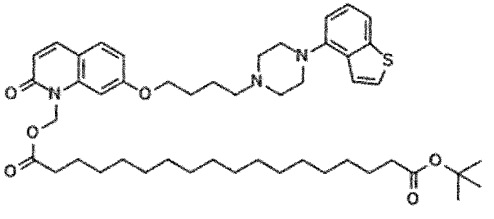
[0150] Intermediates Int06, Int11, Int14, Int16, Int19, Int22, Int24, Int28, Int31, Int32, Int34, Int37, Int45, Int53, Int72, Int76 and Int77 were synthesized according to the method used to synthesize Int02.

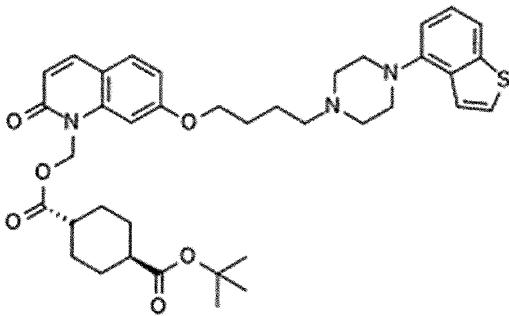
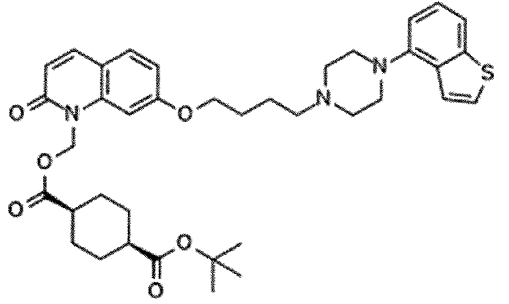
[0151] The starting materials used in the synthesis of each compound as well as their characterization are tabulated in Table 4.

[Table 4]

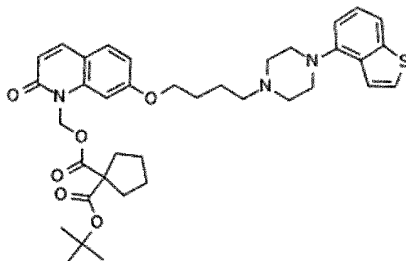
Table 4	
Int06: 1-(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 4-tert-butyl butanedioate	
	
starting material	7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-1,2-dihydroquinolin-2-one (1.83 g) 1-tert-butyl 4-chloromethyl butanedioate (1.41 g)
LC-MS Method 1	LC-MS (ESI): m/z (M^{-1}): 620.3, R_t = 0.89 min
Yield	1.55 g
Int11: 1-(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 10-tert-butyl decanedioate	
	
starting material	Int10 (1.17 g)
LC-MS Method 4	LC-MS (ESI): m/z (M^{-1}): 704.7, R_t = 3.22 min
Yield	1.20 g

Int14: 1-(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 6-tert-butyl hexanedioate	
	
starting material	7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-1,2-dihydroquinolin-2-one (1.24 g) Int13 (1.15 g)
LC-MS Method 4	LC-MS (ESI): m/z (M^{+1}): 648.6, R_t = 2.82 min
Yield	0.72 g
Int16: 1-(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 4-tert-butyl (2E)-but-2-enedioate	
	
starting material	7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-1,2-dihydroquinolin-2-one (360 mg) 1-tert-butyl 4-chloromethyl (2E)-but-2-enedioate (380 mg)
LC-MS Method 4	LC-MS (ESI): m/z (M^{+1}): 618.3, R_t = 0.92 min
Yield	170 mg
Int19: 1-(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 14-tert-butyl tetradecanedioate	

	
starting material	7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-1,2-dihydroquinolin-2-one (0.60 g) Int18 (0.8 g)
¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 7.64 (d, J = 9.5 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.50 – 7.37 (m, 3H), 7.29 (d, J = 7.8 Hz, 1H), 6.94 – 6.78 (m, 3H), 6.53 (d, J = 9.5 Hz, 1H), 6.35 (s, 2H), 4.11 (q, J = 6.0 Hz, 2H), 3.21 (s, 4H), 2.74 (s, 4H), 2.64 – 2.49 (m, 2H), 2.37 (t, J = 7.5 Hz, 2H), 2.20 (t, J = 7.5 Hz, 2H), 2.02 – 1.90 (m, 2H), 1.79 (q, J = 7.8 Hz, 2H), 1.64 (t, J = 7.2 Hz, 2H), 1.45 (s, 9H), 1.33 – 1.16 (m, 18H)
Yield	615 mg
Int22: 1-(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 18-tert-butyl octadecanedioate	
	
starting material	7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-1,2-dihydroquinolin-2-one (343 mg) Int21 (532 mg)
LC-MS Method 4	LC-MS (ESI): <i>m/z</i> (<i>M</i> ⁺): 816.6, <i>R</i> _t = 3.46 min
Yield	362 mg
Int24: 1-(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-	

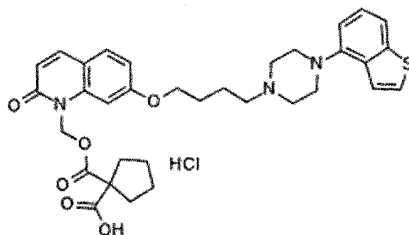
dihydroquinolin-1-yl)methyl 4-tert-butyl cyclohexane-1,4-dicarboxylate 	
starting material	7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-1,2-dihydroquinolin-2-one (0.94 g) 1-tert-butyl 4-chloromethyl (1r,4r)-cyclohexane-1,4-dicarboxylate (0.9 g)
LC-MS Method 1	LC-MS (ESI): m/z (M^{+1}): 674.4, R_t = 0.95 min
Yield	1.2 g
Int28: 1-(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 4-tert-butyl (1s,4s)-cyclohexane-1,4-dicarboxylate 	
starting material	7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-1,2-dihydroquinolin-2-one (1.1 g) Int27 (1.12 g)
LC-MS Method 1	LC-MS (ESI): m/z (M^{+1}): 674.3, R_t = 0.93 min
Yield	1.1 g

Int31: 1-(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 1-tert-butyl cyclopentane-1,1-dicarboxylate



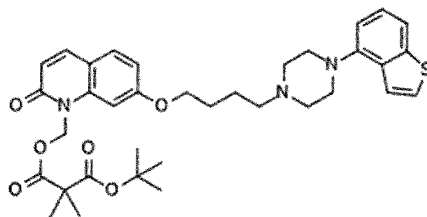
starting material	7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-1,2-dihydroquinolin-2-one (1.8 g) Int30 (1.38 g)
LC-MS Method 1	LC-MS (ESI): m/z (M^{+1}): 660.3, R_t = 0.93 min
Yield	2.0 g

Int32: 1-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonylcyclopentane-1-carboxylic acid hydrochloride

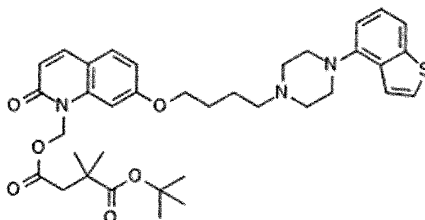


starting material	Int31 (2.0 g)
LC-MS Method 1	LC-MS (ESI): m/z (M^{+1}): 604.4, R_t = 0.8 min
1H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 5.76 (s, 2 H), 1.47 (s, 9 H), 1.44 (s, 6 H)
Yield	3.4 g

Int34: 1-(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-

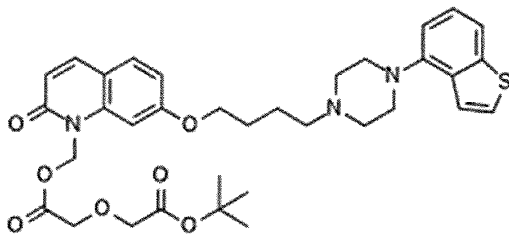
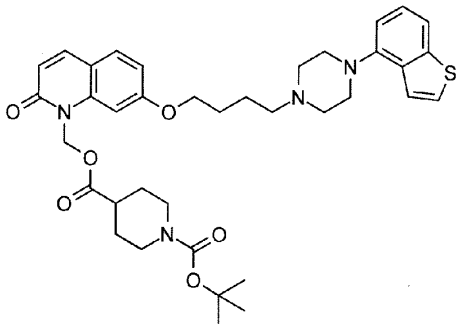
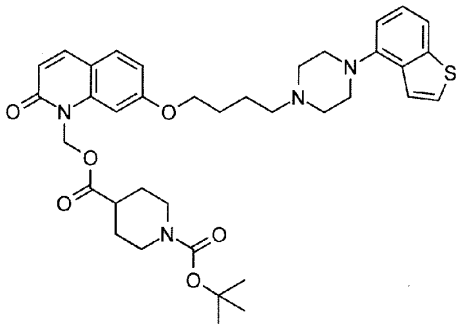
dihydroquinolin-1-yl)methyl 3-tert-butyl 2,2-dimethylpropanedioate

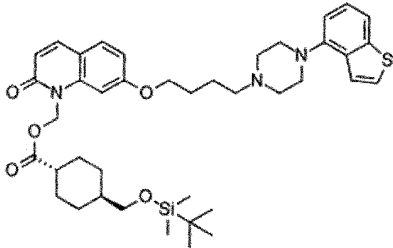
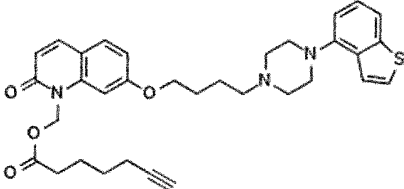
starting material	7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-1,2-dihydroquinolin-2-one (2.8 g) Int33 (1.5 g)
LC-MS Method 1	LC-MS (ESI): m/z (M^{+1}): 634.2, R_t = 0.88 min.
Yield	260 mg

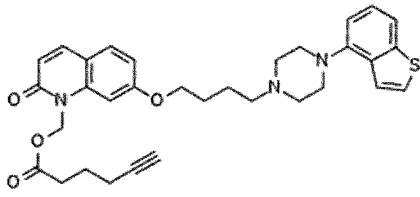
Int37: 4-(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 1-tert-butyl 2,2-dimethylbutanedioate

starting material	7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-1,2-dihydroquinolin-2-one (0.2 g) Int36 (0.2 g)
LC-MS Method 1	LC-MS (ESI): m/z (M^{+1}): 648.4, R_t = 0.90 min.
Yield	0.19 g

Int45: (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 2-[2-(tert-butoxy)-2-oxoethoxy]acetate

	
starting material	7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-1,2-dihydroquinolin-2-one (2.0 g) Int44 (1.6 g)
LC-MS Method 1	LC-MS (ESI): m/z (M^{+1}): 636.5, R_t = 0.82 min
Yield	1.4 g
Int53: 4-(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 1-tert-butyl piperidine-1,4-dicarboxylate 	
starting material	7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-1,2-dihydroquinolin-2-one (0.86 g) 1-tert-butyl 4-chloromethyl piperidine-1,4-dicarboxylate (0.81 g)
LC-MS Method 1	LC-MS (ESI): m/z (M^{+1}): 675.0, R_t = 0.88 min
Yield	0.98 g
Int72: (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-(1 <i>r</i> ,4 <i>r</i>)-4-[[<i>tert</i> -butyldimethylsilyl]oxy]methyl]cyclohexane-1-carboxylate 	

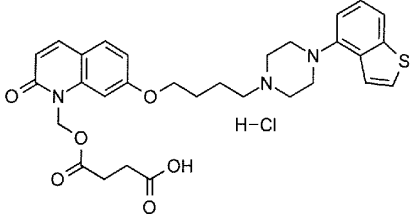
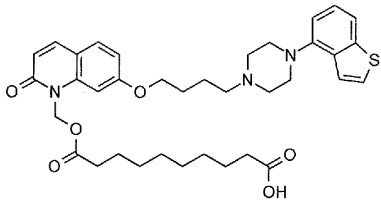
	
starting material	7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-1,2-dihydroquinolin-2-one (830 mg) Int71 (927 mg)
LC-MS Method 1	LC-MS (ESI): m/z (M^{+1}): 718.2, R_t = 1.17 min
Yield	970 mg
Int76: (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl hept-6-ynoate	
	
starting material	7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-1,2-dihydroquinolin-2-one (800 mg) Int75 (656 mg)
LC-MS Method 1	LC-MS (ESI): m/z (M^{+1}): 572.1, R_t = 0.85 min
Yield	670 mg
Int77: (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl hex-5-ynoate	

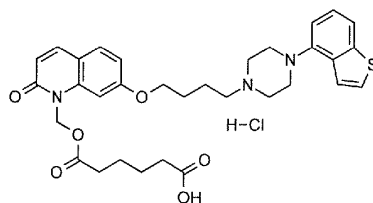
	
starting material	7-({5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-1,2-dihydroquinolin-2-one (950 mg) chloromethyl hex-5-ynoate (703 mg)
LC-MS Method 1	LC-MS (ESI): m/z (M^{+1}): 558.4, R_t = 0.77 min
Yield	640 mg

[0152] Intermediates Int07, Int12, Int15, Int17, Int20, Int23, Int25, Int29, Int35, Int38, Int40, Int43, Int46, Int54 and Int65, were synthesized according to the method used to synthesize Int03.

[0153] The starting materials used in the synthesis of each compound as well as their characterization are tabulated in Table 5.

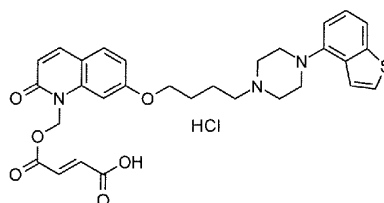
[Table 5]

Table 5	
Int07: 4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutanoic acid hydrochloride	
	
starting material	Int06 (1.55 g)
LC-MS Method 1	LC-MS (ESI): m/z (M^{+1}): 564.5, R_t = 0.68 min.
Yield	1.8 g
Int12: 10-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-10-oxodecanoic acid	
	
starting material	Int11 (1.2 g)
LC-MS Method 1	LC-MS (ESI): m/z (M^{+1}): 648.3, R_t = 0.88 min
Yield	1.06 g
Int15: 6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-	

dihydroquinolin-1-yl)methoxy]-6-oxohexanoic acid hydrochloridestarting material **Int14** (1.35 g)LC-MS LC-MS (ESI): m/z (M^{+1}): 592.3, R_t = 0.73 min

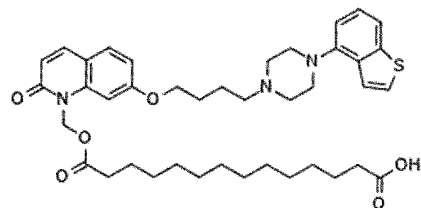
Method 1

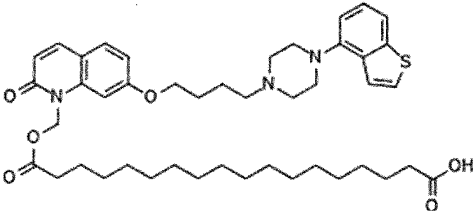
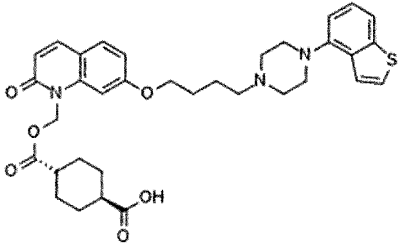
Yield 0.85 g

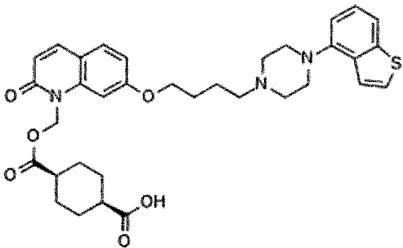
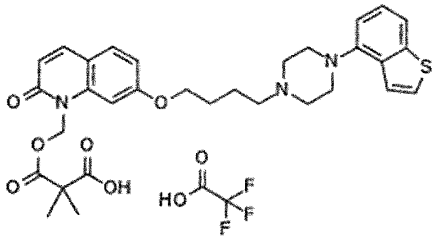
Int17: (2E)-4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobut-2-enoic acid hydrochloridestarting material **Int15** (170 mg)LC-MS LC-MS (ESI): m/z (M^{+1}): 562.3, R_t = 0.74 min

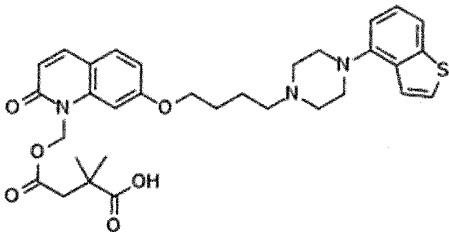
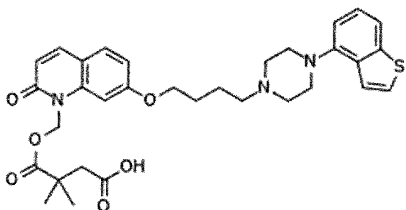
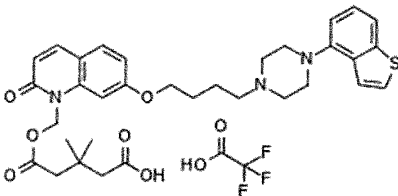
Method 1

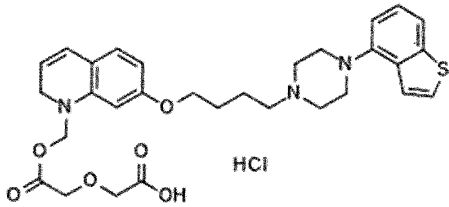
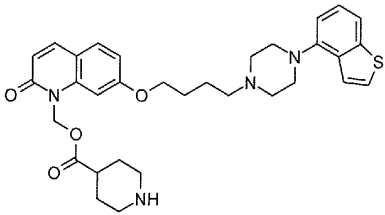
Yield 136 mg

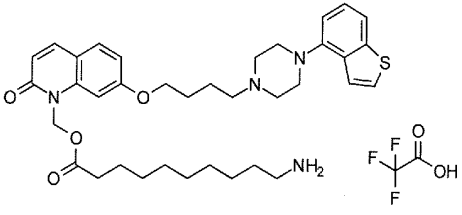
Int20: 14-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-14-oxotetradecanoic acid

starting material	Int19 (615 mg)
LC-MS Method 1	LC-MS (ESI): m/z (M^{+1}): 704.6, R_t = 0.96 min
Yield	830 mg
Int23: 18-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-18-oxooctadecanoic acid 	
starting material	Int22 (362 mg)
LC-MS Method 1	LC-MS (ESI): m/z (M^{+1}): 760.4, R_t = 1.16 min
Yield	398 mg
Int25: 4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonylcyclohexane-1-carboxylic acid 	
starting material	Int24 (1.2 g)
LC-MS Method 1	LC-MS (ESI): m/z (M^{+1}): 618.3, R_t = 0.76 min
Yield	900 mg
Int29: (1s,4s)-4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonylcyclohexane-1-carboxylic acid	

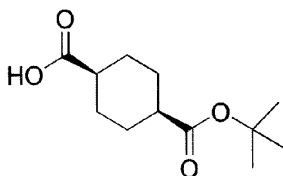
	
starting material	Int28 (1.1 g)
LC-MS	LC-MS (ESI): m/z (M^+): 618.8, R_t = 0.75 min
Method 1	
Yield	1.4 g
Int35: 3-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-2,2-dimethyl-3-oxopropanoic acid trifluoroacetic acid salt	
	
starting material	Int34 (260 mg)
LC-MS	LC-MS (ESI): m/z (M^+): 578.2, R_t = 0.76 min
Method 1	
Yield	144 mg
Int38: 4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-2,2-dimethyl-4-oxobutanoic acid	

	
starting material	Int37 (194 mg)
LC-MS Method 1	LC-MS (ESI): m/z (M^{+1}): 592.3, R_t = 0.86 min
Yield	180 mg
Int40: 4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-3,3-dimethyl-4-oxobutanoic acid	
	
starting material	Int39 (120 mg)
LC-MS Method 1	LC-MS (ESI): m/z (M^{+1}): 592.4, R_t = 0.74 min
Yield	130 mg
Int43: 5-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-3,3-dimethyl-5-oxopentanoic acid trifluoroacetic acid	
	

starting material	Int42 (610 mg)
LC-MS Method 4	LC-MS (ESI): m/z (M^{+1}): 606.5, R_t = 2.51 min
Yield	850 mg
Int46: 2-{2-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-1,2-dihydroquinolin-1-yl)methoxy]-2-oxoethoxy}acetic acid hydrochloride	
	
starting material	Int45 (1.4 g)
LC-MS Method 1	LC-MS (ESI): m/z (M^{+1}): 580.3, R_t = 0.70 min
Yield	1.12 g
Int54: (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl piperidine-4-carboxylate	
	
starting material	Int53 (0.98 g)
LC-MS Method 1	LC-MS (ESI): m/z (M^{+1}): 575.3, R_t = 0.66 min
Yield	813 mg
Int65: (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 10-aminodecanoate trifluoroacetic acid salt	

	
starting material	Int64 (0.71 g)
LC-MS	LC-MS (ESI): m/z (M^+): 633.3, Rt= 0.62 min
Method 1	
Yield	1 g

[0154] Int26: (1s,4s)-4-[(tert-butoxy)carbonyl]cyclohexane-1-carboxylic acid
[Chem.52]

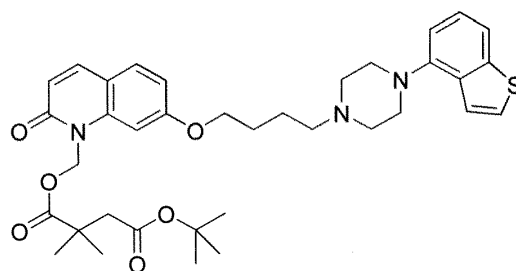


A suspension of (1s,4s)-cyclohexane-1,4-dicarboxylic acid (4.0 g) in Toluene (30 mL) was refluxed for 10 minutes to give a clear solution; then it was allowed to reach 100°C and N,N-Dimethylformamide di-tert-butyl acetal (11.1 mL) was added dropwise over 5 minutes. The mixture was refluxed for 5 h, then it was cooled down to RT and the solvent was evaporated under vacuum. The crude obtained was purified by chromatography on a silica gel cartridge (eluent = from 20% to 50% of EtOAc in cHex) to give Int26 (2.1 g).

^1H NMR (400 MHz, CHLOROFORM-d) δ ppm 2.51 (tt, J = 7.5, 4.3 Hz, 1H), 2.36 (tt, J = 7.5, 4.2 Hz, 1H), 2.01 - 1.80 (m, 4H), 1.67 (dddd, J = 16.9, 12.5, 7.8, 4.3 Hz, 5H), 1.44 (d, J = 2.7 Hz, 9H).

[0155] Int39:
1-(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 4-tert-butyl 2,2-dimethylbutanedioate

[Chem.53]



Step A: Int39 was prepared following the procedure described for Int01, starting from a mixture of 4-(tert-butoxy)-2,2-dimethyl-4-oxobutanoic acid and 4-(tert-butoxy)-3,3-dimethyl-4-oxobutanoic acid (0.97 g), to afford a mixture of 4-tert-butyl 1-chloromethyl 2,2-dimethylbutanedioate and 1-tert-butyl 4-chloromethyl 2,2-dimethylbutanedioate (0.45 g).

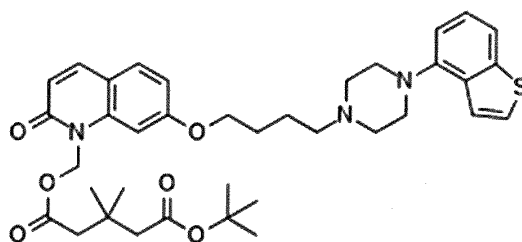
Step B: The mixture obtained was reacted with 7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-1,2-dihydroquinolin-2-one (0.45 g), following the procedure described for Int02. The obtained mixture was further purified by chiral semi-preparative HPLC on Column Chiralcel OJ-H (eluent = nHex/EtOH : 80/20), to afford Int39 (120 mg).

¹H NMR (500 MHz, CHLOROFORM-d) δ ppm 7.62 (d, J=9.6 Hz, 1 H), 7.56 (d, J=7.9 Hz, 1 H), 7.37 - 7.46 (m, 3 H), 7.26 - 7.31 (m, 1 H), 6.94 (d, J=2.0 Hz, 1 H), 6.90 (d, J=7.7 Hz, 1 H), 6.84 (dd, J=8.6, 2.0 Hz, 1 H), 6.52 (d, J=9.6 Hz, 1 H), 6.35 (br s, 2 H), 4.14 (t, J=6.2 Hz, 2 H), 3.20 (br s, 4 H), 2.73 (br s, 4 H), 2.52 - 2.57 (m, 2 H), 2.51 (s, 2 H), 1.85 - 1.98 (m, 2 H), 1.70 - 1.83 (m, 2 H), 1.38 (s, 9 H), 1.26 (s, 6 H).

[0156] Int42:

1-(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 5-tert-butyl 3,3-dimethylpentanedioate

[Chem.54]



Under N₂ atmosphere, NaH (60% in mineral oil, 0.154 g) was added to a suspension of 7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-1,2-dihydroquinolin-2-one

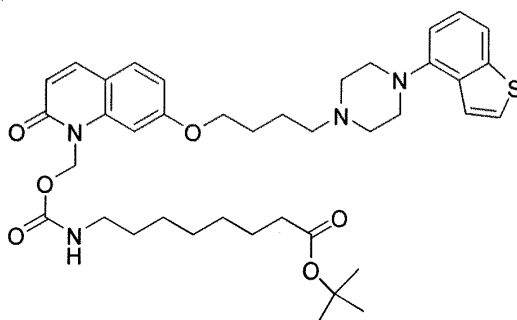
(1.67 g) in 2-MeTHF (20 mL) at RT. The reaction was stirred at 70°C (ext. temp.) for 30 min, then it was cooled down to RT and a solution of Int41 (1.0 g) in 2-MeTHF (10 mL) was added dropwise. The reaction mixture was stirred at 70°C (ext. temp.) for 3 h. The reaction was cooled down to RT, diluted with EtOAc and quenched with NH₄Cl s.s.. The obtained mixture was extracted with EtOAc (2x). Combined organic layers were dried over a phase separator and the solvent was evaporated under vacuum. The crude obtained was purified by chromatography on a silica gel cartridge (eluent = from 10% to 100% of EtOAc in cHex) to give Int42 (610 mg).

LC-MS (ESI): m/z (M+1): 662.6, Rt= 2.91 min. (Method 4).

[0157] Int47: tert-butyl

8-({[(7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}amino)octanoate

[Chem.55]



Under N₂ atmosphere NaH (60% in mineral oil, 24 mg) was added to DMF (2 mL) and 2-MeTHF (2 mL) at RT, then

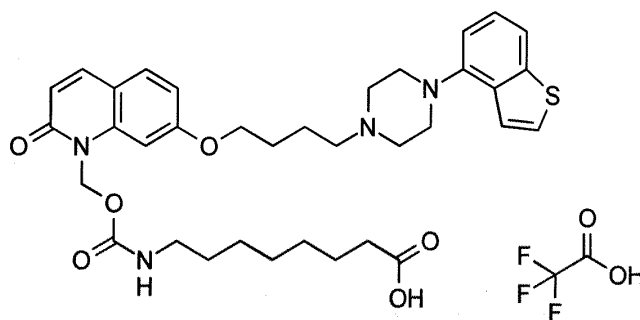
7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-1,2-dihydroquinolin-2-one (220 mg) was added and the reaction was stirred at 60°C for 5 min then cooled to -18°C. A solution of chloromethyl 4-nitrophenyl carbonate (153 mg) in DMF (2 mL) was added dropwise. The reaction mixture was stirred at -18°C for 18 h. Cold NH₄Cl s.s. was added, and the mixture was extracted with DCM (2x). Combined organic layers were dried over a phase separator and the solvent was evaporated under vacuum to afford a solution of

[7-[4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy]-2-oxoquinolin-1-yl]methyl (4-nitrophenyl) carbonate in DMF. To this, a solution of tert-butyl 8-aminooctanoate (109 mg) in DCM (5 mL) and TEA (0.35 mL) were added at RT and the reaction mixture was stirred at RT for 16 h. Volatiles were removed under vacuum and the crude obtained was purified by chromatography on a C-18 cartridge (eluent = from 0% to 100% MeCN in 0.1% of TFA in H₂O), to afford Int47 (98 mg).

LC-MS (ESI): m/z (M+1): 705.7, Rt = 3.0 min (Method 3).

[0158] Int48:

8-([(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl)amino)octanoic acid trifluoroacetic acid salt
[Chem.56]

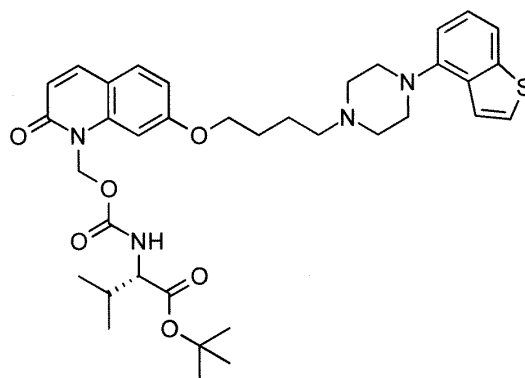


To a solution of tert-butyl Int47 (98 mg) in DCM (4 mL), TFA (0.24 mL) was added dropwise at RT. The reaction was stirred at RT for 16 h. Toluene (10 mL) was added and volatiles were evaporated under vacuum, affording Int48 (100 mg).

LC-MS (ESI): m/z (M+1): 649.6, Rt= 2.52 min. (Method 3).

[0159] Int49: tert-butyl

(2S)-2-([(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl)amino)-3-methylbutanoate
[Chem.57]

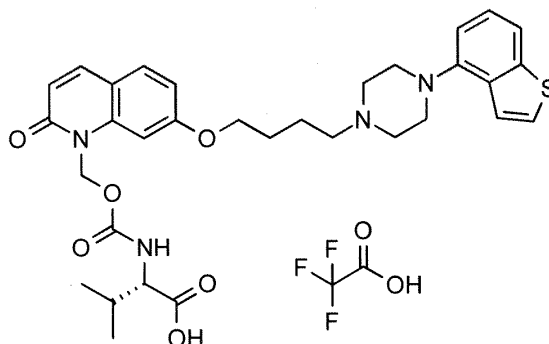


Int49 was prepared following the procedure described for Int47, starting from 7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-1,2-dihydroquinolin-2-one (500 mg), tert-butyl (2S)-2-amino-3-methylbutanoate hydrochloride (360 mg) and chloromethyl 4-nitrophenyl carbonate (350 mg), to afford Int49 (570 mg).

LC-MS (ESI): m/z (M+1): 663.3, Rt= 0.88 min. (Method 1).

[0160] Int50:

(2S)-2-(((7-({4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}amino)-3-methylbutanoic acid trifluoroacetic acid salt
[Chem.58]

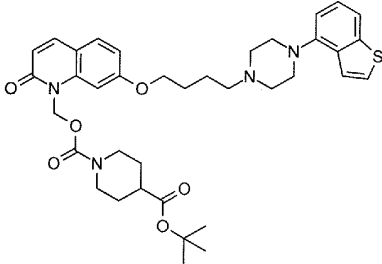


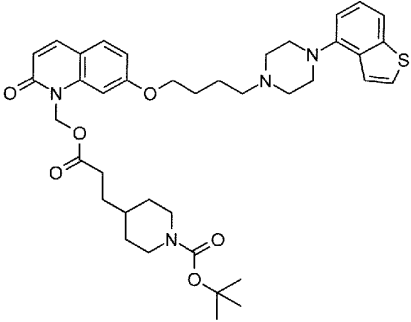
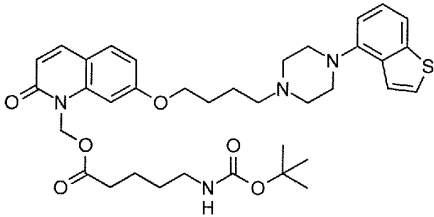
Int50 was prepared following the procedure described for Int48, starting from Int49 (570 mg), to afford Int50 (370 mg).

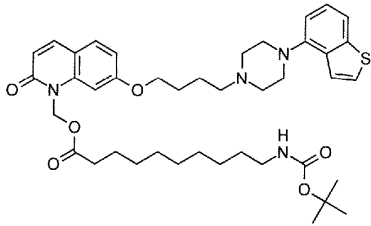
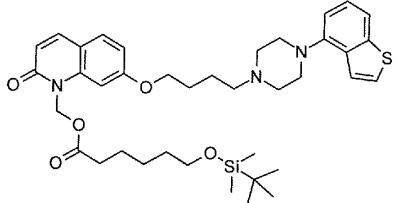
LC-MS (ESI): m/z (M+1): 607.2, Rt= 0.75 min. (Method 1).

[0161] Intermediates Int51, Int56, Int62, Int64, and Int67 were synthesized according to the method used to synthesize Int49. The starting materials used in the synthesis of each compound as well as their characterization are tabulated in Table 6.

[Table 6]

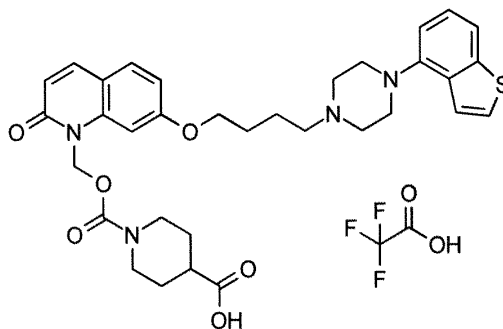
Table 6	
Int51: 1-(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 4-tert-butyl piperidine-1,4-dicarboxylate	
	
starting material	7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-1,2-dihydroquinolin-2-one (700 mg) tert-butyl piperidine-4-carboxylate hydrochloride (537 mg) chloromethyl (4-nitrophenyl) carbonate (486 mg)
LC-MS Method 1	LC-MS (ESI): m/z (M^{-1}): 675.6, R_t = 0.9 min
Yield	800 mg
Int56: tert-butyl 4-{3-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-3-oxopropyl}piperidine-1-carboxylate	

	
starting material	7-[4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy]-1H-quinolin-2-one (1.22 g) Int55 (1.66 g)
LC-MS Method 1	LC-MS (ESI): m/z (M^{+1}): 703.5, R_t = 0.93 min
Yield	1.28 g
Int62: (7-[4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy]-2-oxo-1,2-dihydroquinolin-1-yl)methyl 5-[(tert-butoxy)carbonyl]amino}pentanoate	
	
starting material	7-[4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy]-1,2-dihydroquinolin-2-one (1.19 g) Int61 (1.0 g)
LC-MS Method 1	LC-MS (ESI): m/z (M^{+1}): 663.2, R_t = 0.91 min.
Yield	0.98 g
Int64: (7-[4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy]-2-oxo-1,2-dihydroquinolin-1-yl)methyl 10-[(tert-butoxy)carbonyl]amino}decanoate	

	
starting material	7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-1,2-dihydroquinolin-2-one (1.0 g) Int63 (0.8 g)
LC-MS Method 4	LC-MS (ESI): m/z (M ⁺): 733.6, Rt= 3.11 min
Yield	0.71 g
Int67: (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 6-[(tert-butyldimethylsilyl)oxy]hexanoate	
	
starting material	7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-1,2-dihydroquinolin-2-one (1.34 g) Int66 (1.37 g)
LC-MS Method 1	LC-MS (ESI): m/z (M ⁺): 692.24, Rt= 1.2 min
Yield	1.1 g

[0162] Int52:

1-[[7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl]piperidine-4-carboxylic acid trifluoroacetic acid salt
[Chem.59]



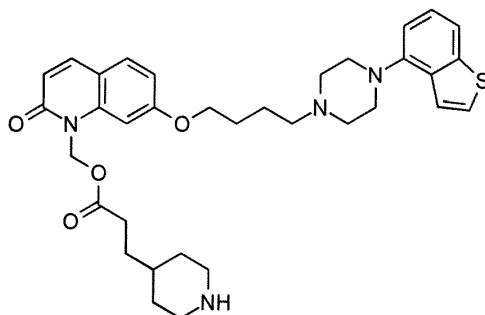
Int52 was prepared following the procedure described for Int48, starting from Int51 (800 mg), to afford Int52 (545 mg, 63% yield).

LC-MS (ESI): m/z (M+1): 619.5, R_t = 2.35 min. (Method 3).

[0163] Int57:

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 3-(piperidin-4-yl)propanoate

[Chem.60]



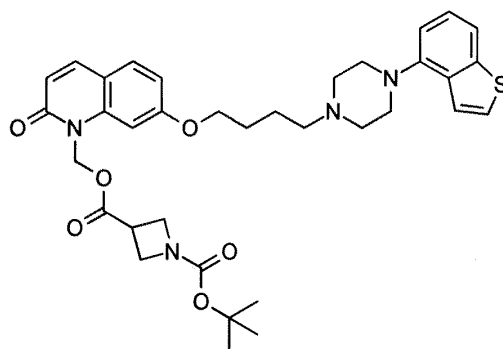
Int57 was prepared following the procedure described for Int54, starting from Int56 (1.28 g), to afford Int57 (1.24 g).

LC-MS (ESI): m/z (M+1): 603.3, R_t = 0.55 min. (Method 1).

[0164] Int59:

3-(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 1-tert-butyl azetidine-1,3-dicarboxylate

[Chem.61]

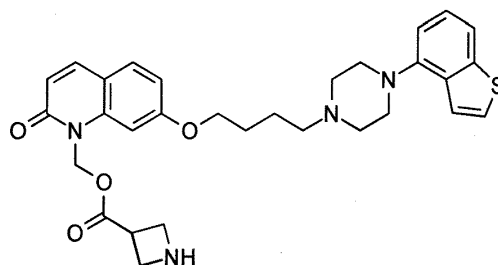


Int59 was prepared following the procedure described for Int49, starting from 7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-1,2-dihydroquinolin-2-one (1.6 g), and Int58 (1.4 g), to afford Int59 (1.9 g).

LC-MS (ESI): m/z (M+1): 647.5, R_t = 0.83 min. (Method 1).

[0165] Int60:

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl azetidine-3-carboxylate
[Chem.62]

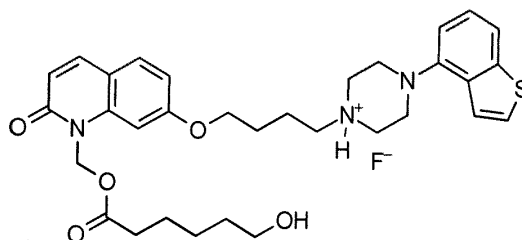


Int60 was prepared following the procedure described for Int54, starting from Int59 (1.9 g) to afford Int60 (1.6 g).

LC-MS (ESI): m/z (M+1): 547.3, Rt= 0.53 min. (Method 1).

[0166] Int68:

4-(1-benzothiophen-4-yl)-1-{4-[(1-{[(6-hydroxyhexanoyl)oxy]methyl}-2-oxo-1,2-dihydroquinolin-7-yl)oxy]butyl}piperazin-1-ium fluoride
[Chem.63]



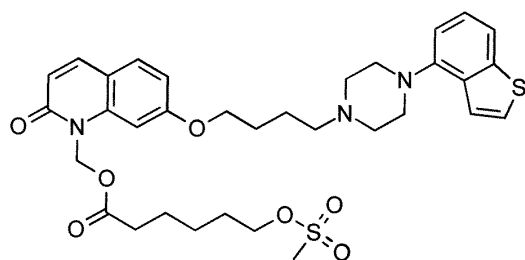
N-ethyl-diisopropylamine tris(hydrofluoride) (1.5 mL) was added to a solution of Int67 (1 g) in THF (8 mL) at 0°C. The reaction was stirred at RT for 7 h. NaHCO₃ s.s. was added and the mixture was extracted with EtOAc (2 x). Combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and evaporated under vacuum. The crude obtained was triturated with Ether:EtOAc 90:10, to afford Int68 (775 mg).

LC-MS (ESI): m/z (M+1): 578.2, Rt= 0.73 min. (Method 1)

[0167] Int69:

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 6-(methanesulfonyloxy)hexanoate

[Chem.64]



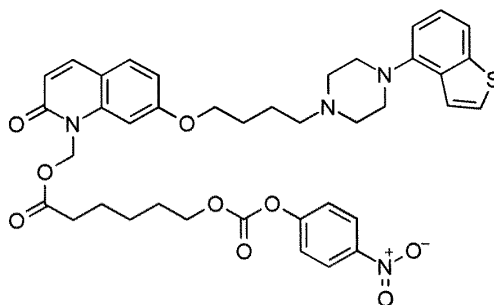
MsCl (0.06 mL) was added to a mixture of Int68 (250 mg), TEA (0.16 mL) and DMAP (4.8 mg) in DCM (4.3 mL) at 0°C. The reaction was stirred at RT for 3 h. The reaction mixture was diluted with DCM and washed with H₂O (x2) and brine. The organic phase was dried over Na₂SO₄, filtered and the solvent was evaporated under vacuum. The crude obtained was purified by chromatography on a silica gel cartridge (eluent = from 0% to 10% of MeOH in DCM) to give Int69 (223 mg).

LC-MS (ESI): m/z (M+1): 656.4, Rt= 0.8 min. (Method 1).

[0168] Int70:

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 6-[[4-(4-nitrophenoxycarbonyl)oxy]hexanoate

[Chem.65]

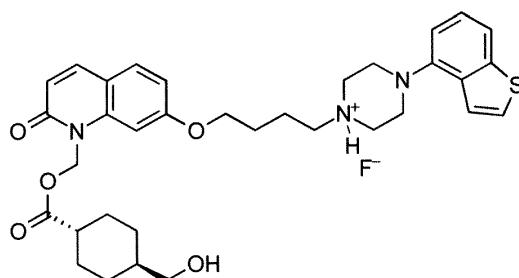


Py (0.01 mL) was added to a solution of Int68 (32.0 mg) in DCM (1 mL) at 0°C, followed by 4-nitrophenyl chloroformate (11 mg). The reaction was stirred at RT overnight. The reaction mixture was diluted with DCM and washed with NaHCO₃ s.s. (5x). The organic phase was dried over a phase separator and evaporated under vacuum. The crude obtained was purified by chromatography on a silica gel cartridge (eluent = from 0% to 100% of MeOH in MeCN), to give Int70 (20 mg).

LC-MS (ESI): m/z (M+1): 743.4, Rt= 0.96 min. (Method 1).

[0169] Int73: 4-(1-benzothiophen-4-yl)-1-{4-[(2-oxo-1-{[(1r,4r)-4-(hydroxymethyl)cyclohexanecarbonyloxy]methyl}-1,2-dihydroquinolin-7-yl)oxy]butyl}piperazin-1-ium fluoride

[Chem.66]



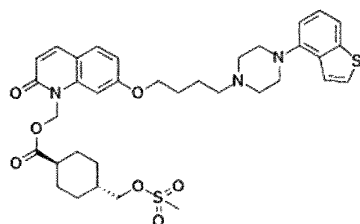
Int73 was prepared following the procedure described for Int68, starting from Int72 (970 mg), to afford Int73 (744 mg).

LC-MS (ESI): m/z ($M+1$): 604.2, R_t = 0.75 min. (Method 1).

[0170] Int74:

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl (1r,4r)-4-[(methanesulfonyloxy)methyl]cyclohexane-1-carboxylate

[Chem.67]

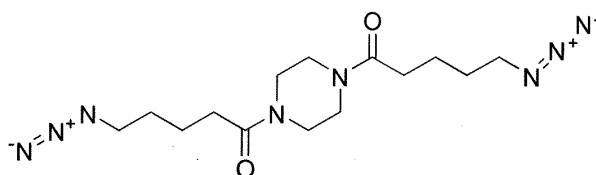


Int74 was prepared following the procedure described for Int69, starting from Int73 (250 mg), to afford Int74 (237 mg, 87% yield).

LC-MS (ESI): m/z ($M+1$): 682.1, R_t = 0.82 min. (Method 1).

[0171] Int78: 5-azido-1-[4-(5-azidopentanoyl)piperazin-1-yl]pentan-1-one

[Chem.68]



DIPEA (0.36 mL) and HBTU (660 mg) were added to a solution of 5-azidopentanoic acid (0.350 mL) and piperazine (60 mg) in THF (5 mL) and the reaction was stirred at RT overnight. The reaction mixture was diluted with EtOAc and washed with NaHCO_3 .

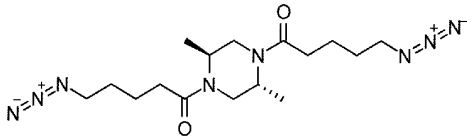
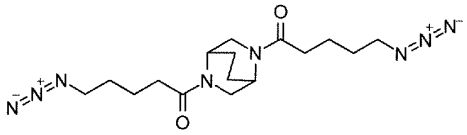
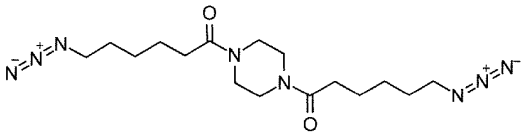
s.s. (x2). The organic phase was dried over a phase separator and the solvent was evaporated at 37°C under vacuum. The crude obtained was purified by chromatography on a C18-cartridge (eluent = 5% to 50 % of MeCN in H₂O) to give Int78 (170 mg).

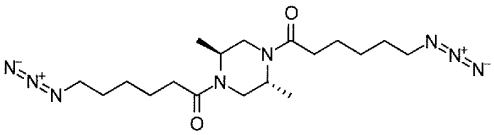
LC-MS (ESI): m/z ($M+1$): 337.2, R_t = 0.82 min. (Method 1).

[0172] Intermediates Int79, Int80, Int81 and Int82 were synthesized according to the method used to synthesize Int78.

[0173] The starting materials used in the synthesis of each compound as well as their characterization are tabulated in Table 7.

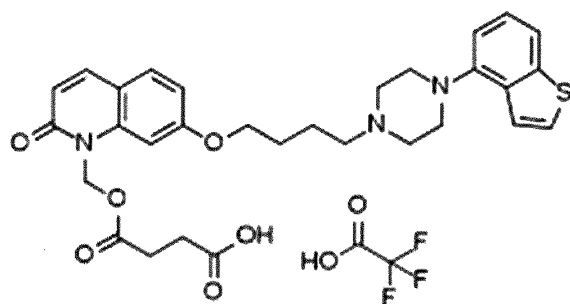
[Table 7]

Table 7	
Int79: 5-azido-1-[(2S,5R)-4-(5-azidopentanoyl)-2,5-dimethylpiperazin-1-yl]pentan-1-one	
	
starting material	(2R,5S)-2,5-dimethylpiperazine (80 mg)
LC-MS Method 1	LC-MS (ESI): m/z (M^{+1}): 365.3, R_t = 0.91 min
Yield	200 mg
Int80: 5-azido-1-[5-(5-azidopentanoyl)-2,5-diazabicyclo[2.2.2]octan-2-yl]pentan-1-one	
	
starting material	2,5-diazabicyclo[2.2.2]octane dihydrochloride (61 mg)
LC-MS Method 1	LC-MS (ESI): m/z (M^{+1}): 363.2, R_t = 0.85 min
Yield	75 mg
Int81: 6-azido-1-[4-(6-azidohexanoyl)piperazin-1-yl]hexan-1-one	
	
starting material	6-azidohexanoic acid (460 mg) and piperazine (100 mg)
LC-MS	LC-MS (ESI): m/z (M^{+1}): 365.2, R_t = 0.94 min

Method 1	
Yield	300 mg
Int82: 6-azido-1-[(2S,5R)-4-(6-azidohexanoyl)-2,5-dimethylpiperazin-1-yl]hexan-1-one	
	
starting material	(2R,5S)-2,5-dimethylpiperazine (80 mg)
LC-MS	LC-MS (ESI): m/z (M^+): 393.3, R_t = 1.03 min
Method 1	
Yield	60 mg

[0174] **Int83:**

4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutanoic acid trifluoroacetic acid
[Chem.69]



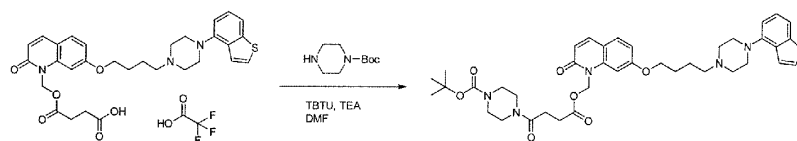
TFA (6.1 mL, 80 mmol) was added dropwise at RT to a solution of Int06 (6.2 g, 10 mmol) in DCM (85 mL). The mixture was stirred at RT for 20 hours. Then additional TFA (6.1 mL, 80 mmol) was added, and the mixture was stirred for further 8 hours at RT. The solvent was evaporated and residual TFA was partially co-evaporated with Toluene. The residue was concentrated under vacuum to afford 4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutanoic acid trifluoroacetic acid (6.9 g, 10.2 mmol, quantitative yield).

LC-MS (ESI): m/z ($M+1$): 564.5, R_t = 2.28 min. (Method 4).

[0175] **Int84: tert-butyl**

4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutanoyl}piperazine-1-carboxylate

[Chem.70]



To a solution of Int83 (710 mg, 1.05 mmol) in dry DMF (5 mL) was added TBTU (405 mg, 1.26 mmol). After 5 minutes TEA (0.58 mL, 4.2 mmol) and tert-butyl piperazine-1-carboxylate (215 mg, 1.16 mmol) in DMF (10 mL) were added and the reaction was stirred at RT for 3 hours. H₂O and DCM were added to the reaction mixture, the mixture phases were separated and the aqueous phase was extracted with DCM (3 times). Combined organic layers were washed with brine, dried over Na₂SO₄, filtered, concentrated under vacuum. The crude obtained was purified by chromatography on a silica gel cartridge (eluent = from neat DCM to 6% of MeOH in DCM) to give tert-butyl

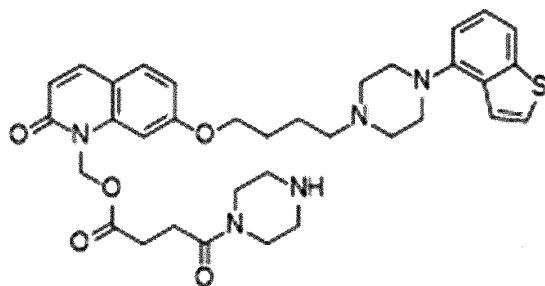
4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutanoyl}piperazine-1 carboxylate (0.50 g, 0.68 mmol, 64% yield).

LC-MS (ESI): m/z (M+1): 732.6, Rt = 2.05 min. (Method 4).

[0176] Int85:

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 4-oxo-4-(piperazin-1-yl)butanoate

[Chem.71]



Int85 was prepared following the procedure described for Int03, starting from Int84 (150 mg, 0.156 mmol) to afford

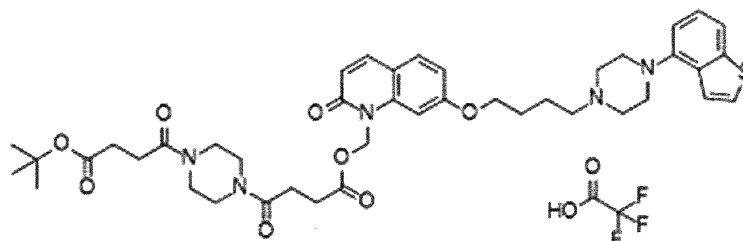
(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 4-oxo-4-(piperazin-1-yl)butanoate (93 mg, 0.147 mmol, 95% yield).

LC-MS (ESI): m/z (M+1): 632.4, Rt = 1.40-1.50 min. (Method 4).

[0177] Int86:

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 4-{4-[4-(tert-butoxy)-4-oxobutanoyl]piperazin-1-yl}-4-oxobutanoate trifluoroacetic acid

[Chem.72]



Int86 was prepared following the procedure described for Int6, starting from Int85 (90 mg, 0.142 mmol) and 4-tert-butoxy-4-oxo-butanoic acid (30 mg, 0.17 mmol) to afford

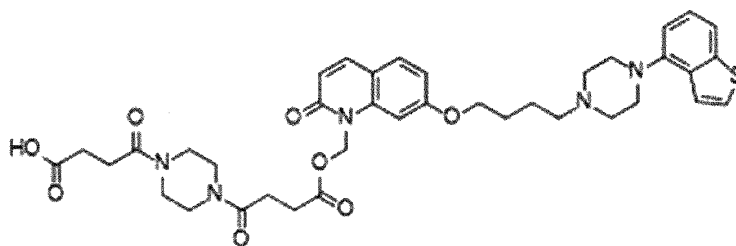
(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 4-{4-[4-(tert-butoxy)-4-oxobutanoyl]piperazin-1-yl}-4-oxobutanoate trifluoroacetic acid (70 mg, 55% yield).

LC-MS (ESI): m/z (M+1): m/z (M+1): 788.6, Rt = 2.02 min. (Method 4).

[0178] Int87:

4-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutanoyl]piperazin-1-yl)-4-oxobutanoic acid

[Chem.73]



Int87 was prepared following the procedure described for Int03, starting from Int86 (70 mg, 0.089 mmol) to afford

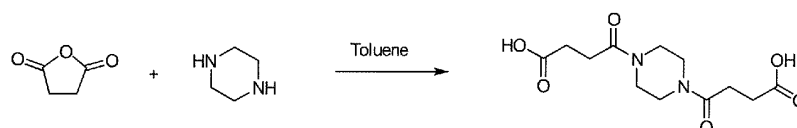
4-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutanoyl]piperazin-1-yl)-4-oxobutanoic acid (12 mg, 0.016 mmol, 17% yield).

LC-MS (ESI): m/z (M+1): 732.5, Rt = 1.66 min. (Method 4).

¹H NMR (500 MHz, DMSO-d₆) δ ppm 10.44 - 13.97 (m, 2 H), 8.13 (s, 1 H), 7.89 (d,

J=9.5 Hz, 1 H), 7.69 (d, J=5.5 Hz, 1 H), 7.66 (d, J=9.1 Hz, 1 H), 7.61 (d, J=8.1 Hz, 1 H), 7.40 (d, J=5.4 Hz, 1 H), 7.27 (t, J=7.8 Hz, 1 H), 6.92 - 6.97 (m, 2 H), 6.89 (br d, J=7.5 Hz, 1 H), 6.43 (d, J=9.5 Hz, 1 H), 6.16 - 6.29 (m, 2 H), 4.16 (t, J=6.4 Hz, 2 H), 3.23 - 3.53 (m, 8 H), 3.07 (br s, 4 H), 2.59 - 2.74 (m, 4 H), 2.47 - 2.53 (m, 2 H), 2.31 - 2.81 (m, 8 H), 1.76 - 1.87 (m, 2H), 1.62 - 1.72 (m, 2 H).

[0179] Int88: 4-[4-(3-carboxypropanoyl)piperazin-1-yl]-4-oxobutanoic acid
[Chem.74]

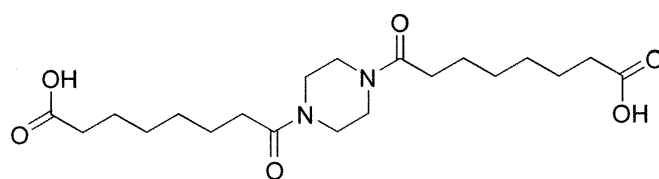


A suspension of piperazine (1.0 g, 11.6 mmol) and oxolane-2,5-dione (2.3 g, 23.2 mmol) in Toluene (15 mL) was stirred at 110°C for 1 hour. Then DMF (5 mL) was added and the suspension was further stirred at 110°C for further 4 hours. The solvent was evaporated under reduced pressure. The solid residue was taken up with EtOH, filtered, and washed with EtOH. The solid residue was dried under vacuo to provide 4-[4-(3-carboxypropanoyl)piperazin-1-yl]-4-oxobutanoic acid (2.51 g, 8.8 mmol, 76% yield).

LC-MS (ESI): m/z (M+1): 287.2, Rt = 0.39 min. (Method 1).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 12.05 (s, 2H), 3.52 - 3.39 (m, 8H), 2.56 (t, J = 6.6 Hz, 4H), 2.44 (dd, J = 7.3, 5.6 Hz, 4H).

[0180] Int89: 8,8'-(piperazine-1,4-diyl)bis(8-oxooctanoic acid)
[Chem.75]



Int89 is prepared in a similar way to methods described herein.

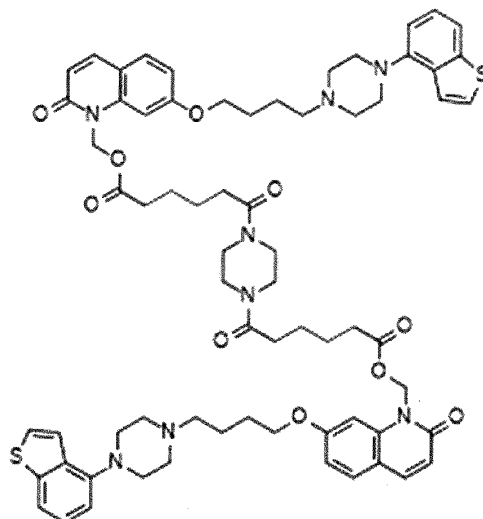
[0181] Preparation of final compounds

Example 01:

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl

6-(4-{6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroqui

nolin-1-yl)methoxy]-6-oxohexanoyl]piperazin-1-yl)-6-oxohexanoate
[Chem.76]



To a solution of Int15 (0.19 g) in dry DMF (13 mL) was added TBTU (543 mg). After 5 minutes was added TEA (0.54 mL) and piperazine (50 mg) and the reaction was stirred at RT overnight. More piperazine (17 mg) and TEA (0.15 mL) were added and the reaction was stirred at RT for further 1h. H₂O and DCM were added to the reaction mixture, the mixture phases were separated and the aqueous phase was extracted with DCM (3 times). Combined organic layers were washed with brine, dried over Na₂SO₄, filtered, concentrated under vacuum. The crude obtained was purified by chromatography on a silica gel cartridge (eluent = from neat DCM to 3% of MeOH in DCM) to give Example 01 (660 mg)

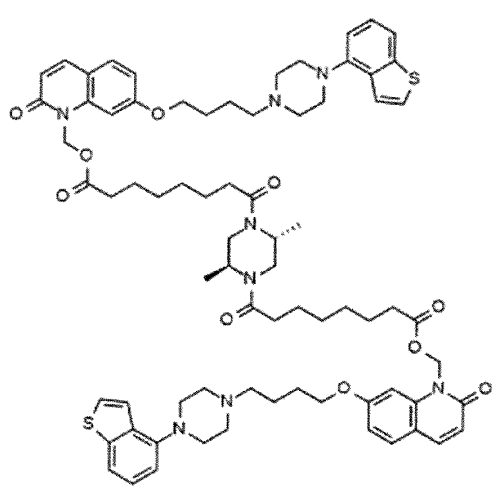
LC-MS (ESI): m/z (M+1): 1233.7, Rt= 2.72 min. (Method 4).

¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.49 (s, 2 H), 7.63 (d, J=9.6 Hz, 2 H), 7.55 (d, J=8.1 Hz, 2 H), 7.46 (d, J=8.6 Hz, 2 H), 7.37 - 7.43 (m, 4 H), 7.18 - 7.34 (m, 2 H), 6.82 - 6.94 (m, 6 H), 6.68 (br t, J=5.0 Hz, 2 H), 6.50 (d, J=9.4 Hz, 2 H), 6.32 (br s, 4 H), 4.56 (d, J=5.5 Hz, 4 H), 4.09 (t, J=6.1 Hz, 4 H), 3.21 (br s, 8 H), 2.75 (br s, 8 H), 2.56 (br t, J=7.3 Hz, 4 H), 2.36 (t, J=7.3 Hz, 4 H), 2.22 (t, J=7.6 Hz, 4 H), 1.87 - 1.98 (m, 4 H), 1.78 (quin, J=7.3 Hz, 4 H), 1.51 - 1.69 (m, 8 H), 1.28 - 1.43 (m, 8 H).

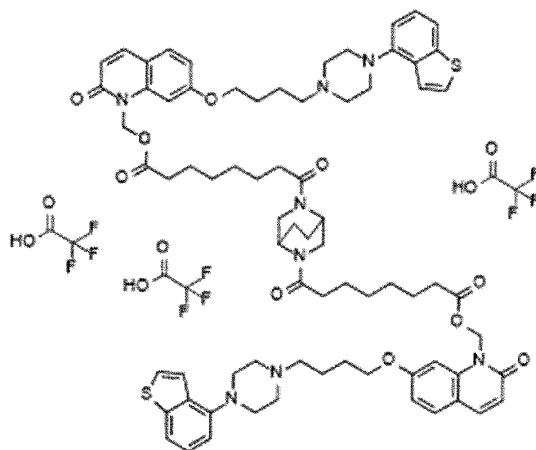
[0182] Examples 02, 03, 05, 06, 07, 09, 11, 13, 14, 15, 16, 17, 18, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, and 44 were synthesized according to the method used to synthesize Example 01.

[0183] The reactants used in the synthesis of each compound as well as their characterization are tabulated in Table 8.

[Table 8]

Table 8	
Example 02 (7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 8-[(2R,5S)-4-{8-[(7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanoyl}-2,5-dimethylpiperazin-1-yl]-8-oxooctanoate	
	
Reactants	
Int03 (106 mg)	(2R,5S)-2,5-dimethylpiperazine (6.6 mg)
LC-MS Method 4	LC-MS (ESI): m/z (M^{+1}): 1317.1, R_t = 2.24 min
^1H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 7.63 (d, J =9.4 Hz, 2 H), 7.56 (d, J =8.1 Hz, 2 H), 7.46 (d, J =8.6 Hz, 2 H), 7.37 - 7.44 (m, 4 H), 7.28 - 7.32 (m, 2 H), 6.81 - 6.93 (m, 6 H), 6.52 (d, J =9.4 Hz, 2 H), 6.33 (br s, 4 H), 4.09 (t, J =6.2 Hz, 4 H), 3.96 - 4.92 (m, 2 H), 3.15 - 3.26 (m, 8 H), 2.86 - 4.40 (m, 4 H), 2.67 - 2.82 (m, 8 H), 2.55 (t, J =7.3 Hz, 4 H), 2.33 - 2.44 (m, 4 H), 2.16 - 2.31 (m, 4 H), 1.86 - 1.97 (m, 4 H), 1.72 - 1.84 (m, 4 H), 1.58 - 1.72 (m, 8 H), 1.30 - 1.43 (m, 8 H), 1.03 - 1.24 (m, 6 H)
Yield	20 mg
Example 03 (7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-	

yl)methyl 8-(5-{8-[(7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanoyl}-2,5-diazabicyclo[2.2.2]octan-2-yl)-8-oxooctanoate tris(trifluoroacetic acid) salt



Reactants

Int03

(58 mg)

2,5-diazabicyclo[2.2.2]octane dihydrochloride

(8 mg)

¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.65 (br d, J=8.3 Hz, 4 H), 7.43 - 7.51 (m, 4 H), 7.28 - 7.36 (m, 4 H), 6.96 (d, J=7.7 Hz, 2 H), 6.91 (s, 2 H), 6.84 (br d, J=8.8 Hz, 2 H), 6.55 (dd, J=9.2, 2.4 Hz, 2 H), 6.34 (br s, 4 H), 4.01 - 4.15 (m, 4 H), 4.01 - 4.91 (m, 2 H), 3.84 (br d, J=11.4 Hz, 4 H), 3.51 - 3.75 (m, 8 H), 3.37 - 3.49 (m, 4 H), 3.25 - 3.32 (m, 4 H), 3.14 - 3.24 (m, 4 H), 2.37 (t, J=7.5 Hz, 4 H), 2.13 - 2.33 (m, 4 H), 2.02 - 2.11 (m, 4 H), 1.91 - 2.00 (m, 4 H), 1.70 - 2.01 (m, 4 H), 1.48 - 1.69 (m, 8 H), 1.27 - 1.39 (m, 8 H)

LC-MS Method 3

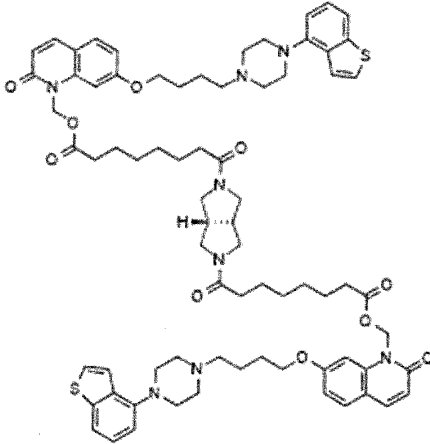
LC-MS (ESI): *m/z* (*M*⁺): 1315.7, *R*_t= 2.36 min

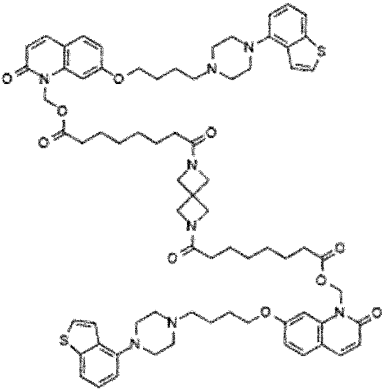
Yield

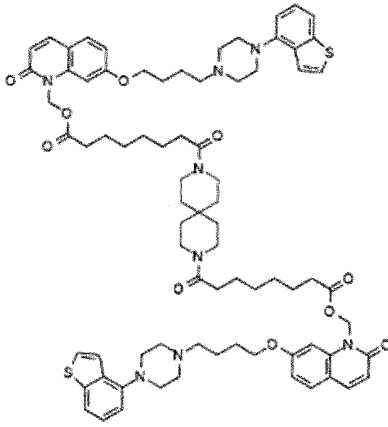
30 mg

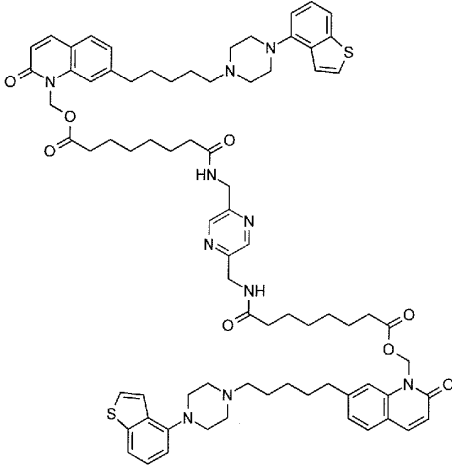
Example 05

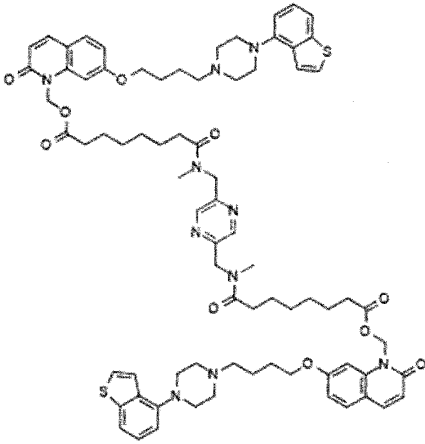
(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 8-(5-{8-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanoyl}-octahydropyrrolo[3,4-c]pyrrol-2-yl)-8-oxooctanoate

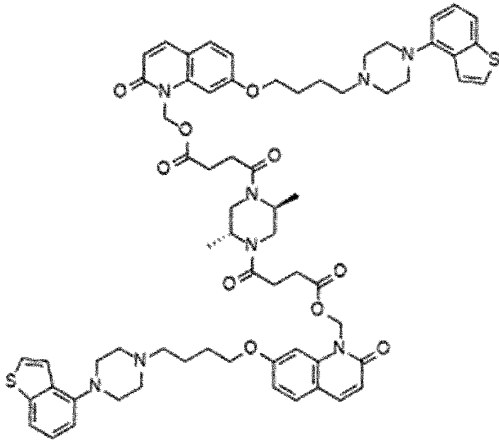
	
Reactants	
Int03 (200 mg)	1,2,3,3a,4,5,6,6a-octahydropyrrolo[3,4-c]pyrrole dihydrochloride (27 mg)
LC-MS Method 4	LC-MS (ESI): <i>m/z</i> (<i>M</i> / <i>2</i> +1): 658.6, <i>R</i> _t = 2.64 min
¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 7.63 (d, <i>J</i> =9.4 Hz, 2 H), 7.56 (d, <i>J</i> =8.1 Hz, 2 H), 7.46 (d, <i>J</i> =8.6 Hz, 2 H), 7.37 - 7.43 (m, 4 H), 7.22 - 7.32 (m, 2 H), 6.87 - 6.93 (m, 4 H), 6.82 - 6.87 (m, 2 H), 6.52 (d, <i>J</i> =9.6 Hz, 2 H), 6.33 (s, 4 H), 4.09 (t, <i>J</i> =6.1 Hz, 4 H), 3.56 - 3.86 (m, 4 H), 3.12 - 3.45 (m, 12 H), 2.73 - 3.05 (m, 10 H), 2.61 (br t, <i>J</i> =7.1 Hz, 4 H), 2.37 (t, <i>J</i> =7.5 Hz, 4 H), 2.19 (t, <i>J</i> =7.6 Hz, 4 H), 1.87 - 2.00 (m, 4 H), 1.80 (quin, <i>J</i> =7.3 Hz, 4 H), 1.52 - 1.72 (m, 8 H), 1.23 - 1.43 (m, 8 H)
Yield	116 mg
Example 06 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 8-(6-{8-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanoyl}-2,6-diazaspiro[3.3]heptan-2-yl)-8-oxooctanoate	

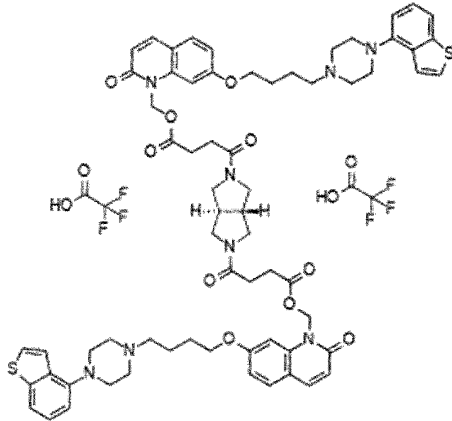
	
Reactants	
Int03 (100 mg)	Int08 (24 mg)
LC-MS Method 3	LC-MS (ESI): m/z (M^{-1}): 1302.7, R_t = 2.12 min
1H NMR (500 MHz, CHLOROFORM- d)	δ ppm 7.63 (d, J =9.5 Hz, 2 H), 7.56 (d, J =8.1 Hz, 2 H), 7.46 (d, J =8.6 Hz, 2 H), 7.36 - 7.43 (m, 4 H), 7.23 - 7.30 (m, 2 H), 6.90 (d, J =7.5 Hz, 2 H), 6.88 (d, J =1.9 Hz, 2 H), 6.85 (dd, J =8.6, 2.1 Hz, 2 H), 6.52 (d, J =9.5 Hz, 2 H), 6.33 (br s, 4 H), 4.07 - 4.09 (m, 4 H), 4.03 - 4.22 (m, 8 H), 3.20 (br s, 8 H), 2.73 (br s, 8 H), 2.50 - 2.59 (m, 4 H), 2.36 (t, J =7.5 Hz, 4 H), 2.02 (t, J =7.5 Hz, 4 H), 1.85 - 1.95 (m, 4 H), 1.78 (quin, J =7.5 Hz, 4 H), 1.61 - 1.69 (m, 4 H), 1.55 - 1.60 (m, 4 H), 1.25 - 1.37 (m, 8 H)
Yield	17 mg
Example 07 (7-([4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy]-2-oxo-1,2-dihydroquinolin-1-yl)methyl 8-(9-([8-([7-([4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy]-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanoyl]-3,9-diazaspiro[5.5]undecan-3-yl)-8-oxooctanoate	

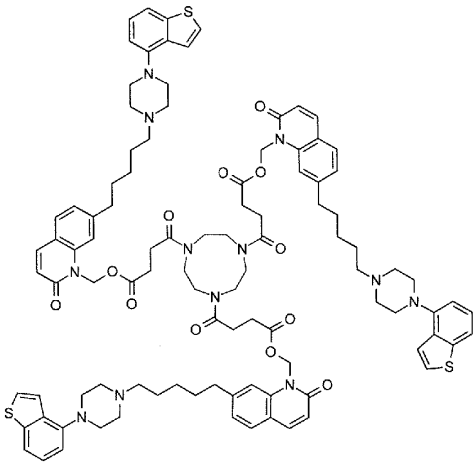
	
Reactants	
Int03 (180 mg)	Int09 (47 mg)
LC-MS Method 3	LC-MS (ESI): m/z (M^+): 1357.8, R_t = 2.29 min.
1H NMR (500 MHz, CHLOROFORM- d)	δ ppm 7.63 (d, J =9.5 Hz, 2 H), 7.56 (d, J =8.1 Hz, 2 H), 7.46 (d, J =8.5 Hz, 2 H), 7.38 - 7.43 (m, 4 H), 7.24 - 7.31 (m, 2 H), 6.87 - 6.92 (m, 4 H), 6.85 (dd, J =8.6, 2.1 Hz, 2 H), 6.52 (d, J =9.5 Hz, 2 H), 6.34 (br s, 4 H), 4.09 (t, J =6.2 Hz, 4 H), 3.29 - 3.65 (m, 8 H), 3.20 (br s, 8 H), 2.74 (br s, 8 H), 2.52 - 2.59 (m, 4 H), 2.37 (t, J =7.5 Hz, 4 H), 2.24 - 2.31 (m, 4 H), 1.88 - 1.95 (m, 4 H), 1.78 (dt, J =15.0, 7.5 Hz, 4 H), 1.55 - 1.69 (m, 8 H), 1.40 - 1.51 (m, 8 H), 1.26 - 1.39 (m, 8 H)
Yield	77 mg
Example 08 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 7-({[5-({[8-({[7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanamido)methyl]pyrazin-2-yl)methyl}carbamoyl]heptanoate	

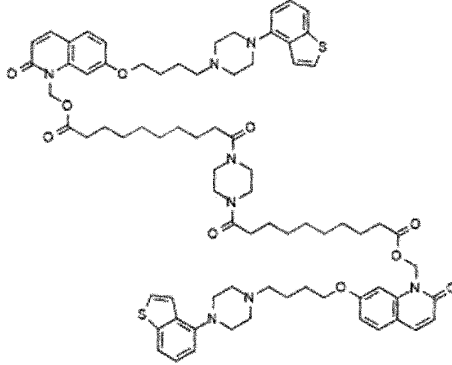
	
Reactants	
Int03 (110 mg)	Int05 (16 mg)
LC-MS Method 3	LC-MS (ESI): m/z (M^{+1}): 1342.9, R_t = 2.09 min.
^1H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 8.49 (s, 2 H), 7.63 (d, J =9.6 Hz, 2 H), 7.55 (d, J =8.1 Hz, 2 H), 7.46 (d, J =8.6 Hz, 2 H), 7.37 - 7.43 (m, 4 H), 7.18 - 7.34 (m, 2 H), 6.82 - 6.94 (m, 6 H), 6.68 (br t, J =5.0 Hz, 2 H), 6.50 (d, J =9.4 Hz, 2 H), 6.32 (br s, 4 H), 4.56 (d, J =5.5 Hz, 4 H), 4.09 (t, J =6.1 Hz, 4 H), 3.21 (br s, 8 H), 2.75 (br s, 8 H), 2.56 (br t, J =7.3 Hz, 4 H), 2.36 (t, J =7.3 Hz, 4 H), 2.22 (t, J =7.6 Hz, 4 H), 1.87 - 1.98 (m, 4 H), 1.78 (quin, J =7.3 Hz, 4 H), 1.51 - 1.69 (m, 8 H), 1.28 - 1.43 (m, 8 H)
Yield	30 mg
Example 09 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 7-({[5-({8-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-N-methyl-8-oxooctanamido)methyl}pyrazin-2-yl)methyl](methyl)carbamoyl}heptanoate	

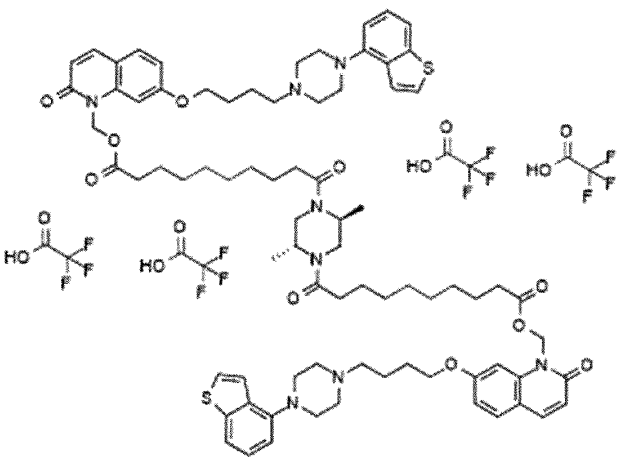
	
Reactants	
Int03 (191 mg)	Int04 (25 mg)
LC-MS Method 3	LC-MS (ESI): <i>m/z</i> (<i>M</i> / <i>2</i> +1): 685.9, <i>R</i> _t = 1.99 min
¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 8.45 (s, 2 H), 7.63 (d, <i>J</i> =9.6 Hz, 2 H), 7.55 (d, <i>J</i> =8.1 Hz, 2 H), 7.45 (d, <i>J</i> =8.6 Hz, 2 H), 7.40 (q, <i>J</i> =5.6 Hz, 4 H), 7.19 - 7.32 (m, 2 H), 6.87 - 6.92 (m, 4 H), 6.84 (dd, <i>J</i> =8.6, 2.0 Hz, 2 H), 6.48 - 6.58 (m, 2 H), 6.34 (br s, 4 H), 4.48 - 4.82 (m, 4 H), 4.09 (t, <i>J</i> =6.2 Hz, 4 H), 3.20 (br s, 8 H), 2.93 - 3.12 (m, 6 H), 2.73 (br s, 8 H), 2.50 - 2.61 (m, 4 H), 2.26 - 2.43 (m, 8 H), 1.85 - 1.97 (m, 4 H), 1.50 - 1.83 (m, 12 H), 1.27 - 1.44 (m, 8 H)
Yield	36 mg
Example 11 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 4-[(2 <i>S</i> ,5 <i>R</i>)-4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutanoyl}-2,5-dimethylpiperazin-1-yl]-4-oxobutanoate	

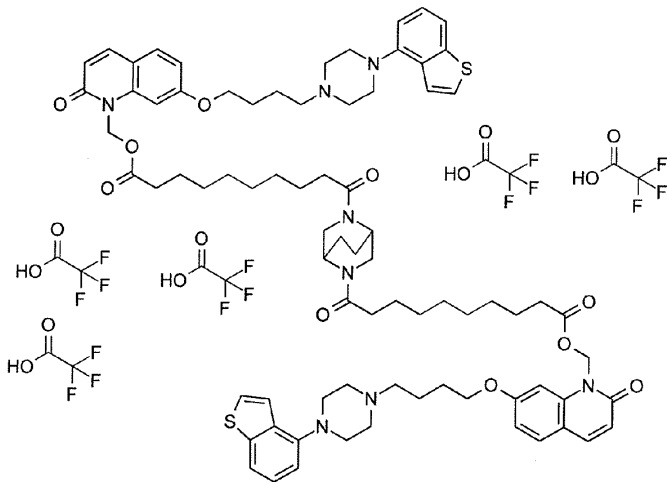
	
Reactants	
Int07 (333 mg)	(2R,5S)-2,5-dimethylpiperazine (23 mg)
LC-MS Method 4	LC-MS (ESI): m/z (M^+): 1205.6, R_t = 2.71 min
1H NMR (500 MHz, CHLOROFORM- <i>d</i>)	δ ppm 7.63 (d, J =9.5 Hz, 2 H), 7.57 (d, J =8.1 Hz, 2 H), 7.44 (d, J =8.6 Hz, 2 H), 7.37 - 7.42 (m, 4 H), 7.23 - 7.29 (m, 2 H), 6.90 (dd, J =7.6, 0.8 Hz, 2 H), 6.87 (d, J =1.9 Hz, 2 H), 6.84 (dd, J =8.6, 1.9 Hz, 2 H), 6.51 (d, J =9.5 Hz, 2 H), 6.15 - 6.44 (m, 4 H), 4.11 - 4.17 (m, 4 H), 3.92 - 4.81 (m, 2 H), 3.22 - 3.33 (m, 8 H), 2.87 - 3.08 (m, 8 H), 2.77 - 2.85 (m, 4 H), 2.75 - 4.24 (m, 4 H), 2.37 - 2.75 (m, 8 H), 1.85 - 2.00 (m, 8 H), 0.93 - 1.14 (m, 6 H)
Yield	50 mg
Example 13 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 4-[(3ar,6ar)-5-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutanoyl}-octahydropyrrolo[3,4-c]pyrrol-2-yl]-4-oxobutanoate bis(trifluoroacetic acid) salt	

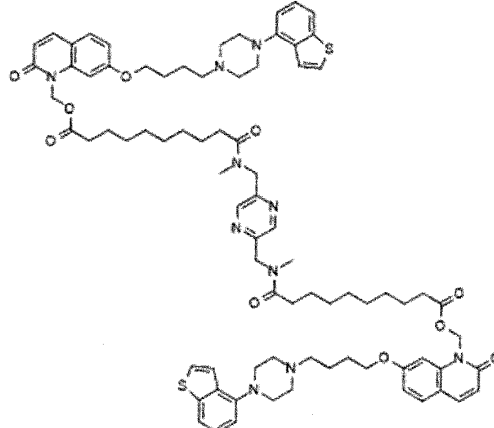
	
Reactants	
Int07 (194 mg)	1,2,3,3a,4,5,6,6a-octahydropyrrolo[3,4-c]pyrrole dihydrochloride (30 mg)
LC-MS Method 3	LC-MS (ESI): m/z (M^+): 1203.9, R_t = 1.93 min
^1H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 7.60 - 7.72 (m, 4 H), 7.41 - 7.52 (m, 4 H), 7.24 - 7.37 (m, 4 H), 6.95 (d, J =7.6 Hz, 2 H), 6.80 - 6.91 (m, 4 H), 6.54 (d, J =9.9 Hz, 2 H), 6.34 (br s, 4 H), 4.09 - 4.25 (m, 4 H), 3.77 - 3.88 (m, 4 H), 3.49 - 3.58 (m, 4 H), 3.36 - 3.47 (m, 4 H), 3.24 - 3.34 (m, 4 H), 3.11 - 3.24 (m, 4 H), 2.42 - 3.95 (m, 16 H), 2.06 - 2.18 (m, 4 H), 1.90 - 2.00 (m, 4 H), 1.43 - 2.26 (m, 2 H)
Yield	45 mg
Example 14 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 4-[4,7-bis({4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutanoyl})-1,4,7-triazonan-1-yl]-4-oxobutanoate	

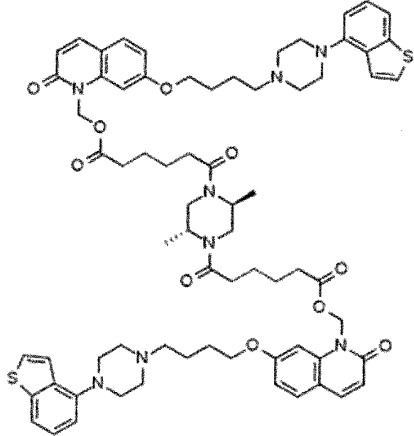
	
Reactants	
Int07 (200 mg)	1,4,7-triazonane (14 mg)
LC-MS Method 3	LC-MS (ESI): m/z (M^+): 1767.3, R_t = 2.74 min
1H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 7.50 - 7.62 (m, 6 H), 7.34 - 7.46 (m, 9 H), 7.20 - 7.31 (m, 3 H), 6.74 - 6.96 (m, 9 H), 6.47 (d, J =9.5 Hz, 3 H), 6.28 (br s, 6 H), 4.12 (br t, J =6.0 Hz, 6 H), 3.01 - 3.84 (m, 24 H), 2.40 - 2.91 (m, 30 H), 1.72 - 1.94 (m, 12 H)
Yield	15 mg
Example 15 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 4-[4,7-bis({4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutanoyl})-1,4,7-triazonan-1-yl]-4-oxobutanoate	

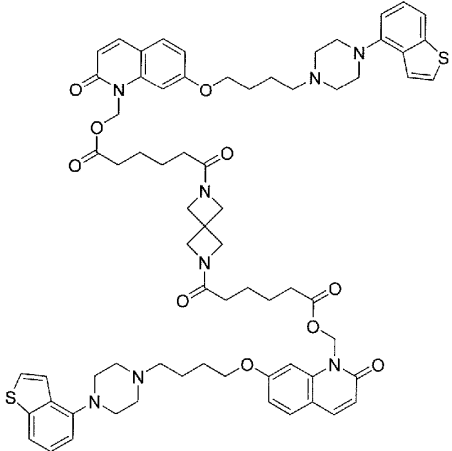
	
Reactants	
Int12 (250 mg)	piperazine (14 mg)
LC-MS Method 3	LC-MS (ESI): m/z (M^+): 1346.7, R_t = 2.34 min
1H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 7.63 (d, J =9.4 Hz, 2 H), 7.55 (d, J =7.9 Hz, 2 H), 7.45 (d, J =8.6 Hz, 2 H), 7.36 - 7.43 (m, 4 H), 7.22 - 7.31 (m, 2 H), 6.87 - 6.92 (m, 4 H), 6.85 (dd, J =8.7, 2.1 Hz, 2 H), 6.52 (d, J =9.4 Hz, 2 H), 6.34 (s, 4 H), 4.09 (t, J =6.2 Hz, 4 H), 3.32 - 3.68 (m, 8 H), 3.20 (br s, 8 H), 2.73 (br s, 8 H), 2.51 - 2.59 (m, 4 H), 2.36 (t, J =7.6 Hz, 4 H), 2.29 (t, J =7.6 Hz, 4 H), 1.84 - 1.96 (m, 4 H), 1.72 - 1.83 (m, 4 H), 1.51 - 1.72 (m, 12 H), 1.19 - 1.37 (m, 12 H)
Yield	72 mg
Example 16 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 10-[(2R,5S)-4-{10-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-10-oxodecanoyl}-2,5-dimethylpiperazin-1-yl]-10-oxodecanoate tetrakis(trifluoroacetic acid) salt	

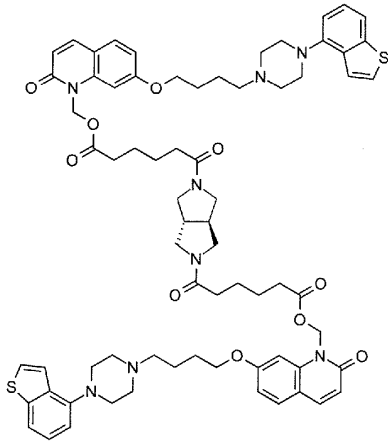
	
Reactants	
Int12 (240 mg)	(2R,5S)-2,5-dimethylpiperazine (18 mg)
LC-MS Method 3	LC-MS (ESI): m/z (M^+): 1374.0, R_t = 2.41 min
1H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 10.75 - 12.91 (m, 2 H), 7.67 (t, J =9.5 Hz, 4 H), 7.50 (d, J =8.7 Hz, 2 H), 7.47 (d, J =5.5 Hz, 2 H), 7.29 - 7.37 (m, 4 H), 6.97 (d, J =7.7 Hz, 2 H), 6.94 (s, 2 H), 6.86 (dd, J =8.6, 2.0 Hz, 2 H), 6.54 - 6.67 (m, 2 H), 6.35 (s, 4 H), 4.10 (t, J =5.7 Hz, 4 H), 4.02 - 5.04 (m, 2 H), 3.87 (br d, J =11.5 Hz, 4 H), 3.54 - 3.65 (m, 4 H), 3.26 - 3.34 (m, 4 H), 3.26 - 3.52 (m, 4 H), 3.12 - 3.26 (m, 4 H), 2.81 - 4.44 (m, 4 H), 2.33 - 2.42 (m, 4 H), 2.22 - 2.53 (m, 4 H), 2.04 - 2.18 (m, 4 H), 1.87 - 2.00 (m, 4 H), 1.61 (br d, J =6.8 Hz, 8 H), 1.22 - 1.35 (m, 16 H), 0.94 - 1.21 (m, 6 H)
Yield	29 mg
Example 17 7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 10-(5-{10-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-10-oxodecanoyl}-2,5-diazabicyclo[2.2.2]octan-2-yl)-10-oxodecanoate pentakis(trifluoroacetic acid) salt	

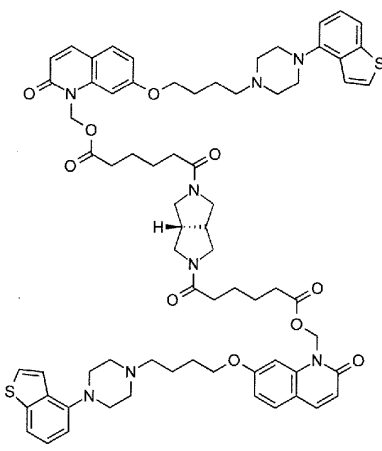
	
Reactants	
Int12 (98 mg)	2,5-diazabicyclo[2.2.2]octane dihydrochloride (12 mg)
LC-MS Method 4	LC-MS (ESI): m/z (M^{+1}): 1372.8, R_t = 2.61 min
1H NMR (400 MHz, CHLOROFORM- d)	δ ppm 10.68 - 12.42 (m, 2 H), 7.62 - 7.73 (m, 4 H), 7.42 - 7.53 (m, 4 H), 7.28 - 7.36 (m, 4 H), 6.90 - 7.00 (m, 4 H), 6.85 (br d, J =8.6 Hz, 2 H), 6.59 (dt, J =9.4, 1.5 Hz, 2 H), 6.35 (br s, 4 H), 4.02 - 4.89 (m, 2 H), 4.01 - 4.16 (m, 4 H), 3.86 (br d, J =11.2 Hz, 4 H), 3.48 - 3.78 (m, 8 H), 3.35 - 3.46 (m, 4 H), 3.27 - 3.34 (m, 4 H), 3.12 - 3.27 (m, 4 H), 2.33 - 2.40 (m, 4 H), 2.16 - 2.44 (m, 4 H), 2.04 - 2.14 (m, 4 H), 1.91 - 2.00 (m, 4 H), 1.70 - 2.15 (m, 4 H), 1.51 - 1.68 (m, 8 H), 1.25 (br s, 16 H)
Yield	39 mg
Example 18 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 9-({5-[(10-{(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-N-methyl-10-oxodecanamido)methyl}pyrazin-2-yl)methyl;(methyl)carbamoyl}nonanoate	

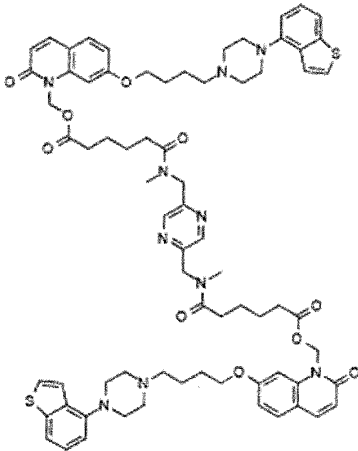
	
Reactants	
Int12 (106 mg)	Int05 (15 mg)
LC-MS Method 4	LC-MS (ESI): m/z (M ⁺): 1425.8, Rt= 3.04 min
¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 8.30 - 8.59 (m, 2 H), 7.63 (d, J=9.4 Hz, 2 H), 7.55 (d, J=8.1 Hz, 2 H), 7.46 (d, J=8.6 Hz, 2 H), 7.40 (q, J=5.5 Hz, 4 H), 7.17 - 7.33 (m, 2 H), 6.79 - 6.94 (m, 6 H), 6.52 (d, J=9.4 Hz, 2 H), 6.34 (br s, 4 H), 4.52 - 4.76 (m, 4 H), 4.09 (t, J=6.2 Hz, 4 H), 3.20 (br s, 8 H), 2.93 - 3.11 (m, 6 H), 2.74 (br s, 8 H), 2.55 (br t, J=7.3 Hz, 4 H), 2.25 - 2.42 (m, 8 H), 1.85 - 2.01 (m, 4 H), 1.72 - 1.83 (m, 4 H), 1.56 - 1.70 (m, 8 H), 1.21 - 1.36 (m, 16 H)
Yield	5 mg
Example 20 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 6-[(2S,5R)-4-{6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexanoyl}-2,5-dimethylpiperazin-1-yl]-6-oxohexanoate	

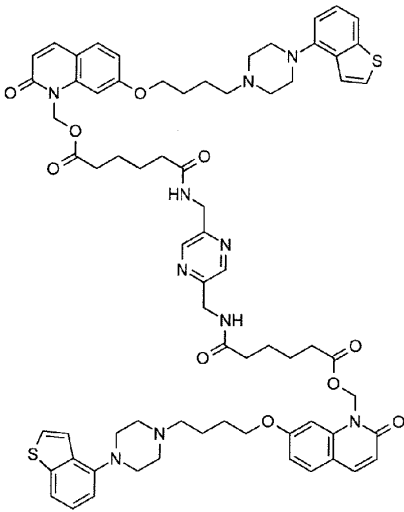
	
Reactants	
Int15 (0.20 g)	(2R,5S)-2,5-dimethylpiperazine (16 mg)
LC-MS Method 4	LC-MS (ESI): m/z (M ⁺): 1261.8, Rt= 2.94 min
¹ H NMR (500 MHz, CHLOROFORM- <i>d</i>)	δ ppm 7.63 (d, J=9.5 Hz, 2 H), 7.55 (d, J=8.0 Hz, 2 H), 7.46 (d, J=8.6 Hz, 2 H), 7.41 - 7.43 (m, 2 H), 7.38 - 7.40 (m, 2 H), 7.24 - 7.30 (m, 2 H), 6.87 - 6.92 (m, 4 H), 6.85 (dt, J=8.6, 1.8 Hz, 2 H), 6.48 - 6.55 (m, 2 H), 6.33 (br s, 4 H), 4.10 (t, J=6.2 Hz, 4 H), 3.95 - 4.90 (m, 2 H), 3.20 (br s, 8 H), 2.85 - 4.38 (m, 4 H), 2.74 (br s, 8 H), 2.55 (br t, J=7.4 Hz, 4 H), 2.19 - 2.49 (m, 8 H), 1.86 - 1.98 (m, 4 H), 1.78 (quin, J=7.5 Hz, 4 H), 1.63 - 1.74 (m, 8 H), 0.95 - 1.24 (m, 6 H)
Yield	39 mg
Example 21 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 6-(6-{6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexanoyl}-2,6-diazaspiro[3.3]heptan-2-yl)-6-oxohexanoate	

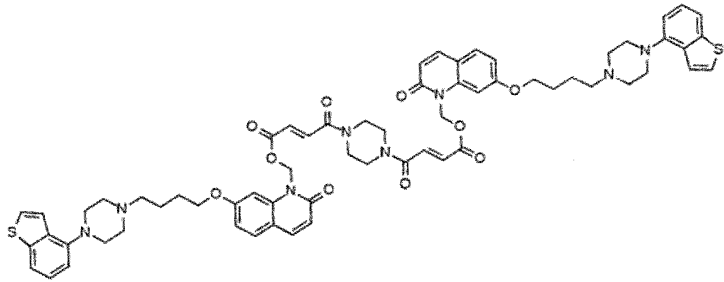
	
Reactants	
Int15 (0.20 g)	Int08 (44 mg)
LC-MS Method 3	LC-MS (ESI): m/z (M^{-1}): 1245.7, R_t = 1.99 min
1H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 7.62 (d, J =9.5 Hz, 2 H), 7.55 (d, J =8.0 Hz, 2 H), 7.44 (d, J =8.7 Hz, 2 H), 7.36 - 7.43 (m, 4 H), 7.24 - 7.30 (m, 2 H), 6.93 (s, 2 H), 6.89 (d, J =7.7 Hz, 2 H), 6.84 (dd, J =8.7, 2.0 Hz, 2 H), 6.50 (d, J =9.5 Hz, 2 H), 6.31 (br s, 4 H), 4.14 (t, J =6.0 Hz, 4 H), 3.52 (s, 8 H), 3.19 (br s, 8 H), 2.73 (br s, 8 H), 2.61 (s, 4 H), 2.48 - 2.58 (m, 4 H), 1.86 - 1.97 (m, 4 H), 1.72 - 1.85 (m, 4 H), 1.41 (s, 12 H)
Yield	110 mg
Example 22 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 6-[(3ar,6ar)-5-{6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexanoyl]-octahydropyrrolo[3,4-c]pyrrol-2-yl]-6-oxohexanoate	

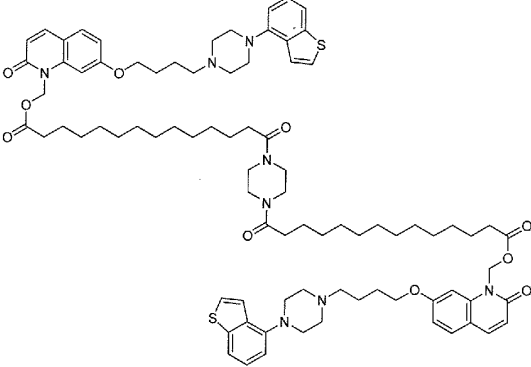
	
Reactants	
Int15 (0.20 g)	1,2,3,3a,4,5,6,6a-octahydropyrrolo[3,4-c]pyrrole dihydrochloride (28 mg)
LC-MS Method 3	LC-MS (ESI): m/z (M ⁺): 1260.0, Rt= 1.99 min
¹ H NMR (500 MHz, CHLOROFORM- <i>d</i>)	δ ppm 7.63 (d, J=9.5 Hz, 2 H), 7.55 (d, J=8.1 Hz, 2 H), 7.46 (d, J=8.6 Hz, 2 H), 7.37 - 7.43 (m, 4 H), 7.22 - 7.32 (m, 2 H), 6.87 - 6.92 (m, 4 H), 6.85 (dt, J=8.6, 1.9 Hz, 2 H), 6.52 (dd, J=9.5, 1.8 Hz, 2 H), 6.33 (br s, 4 H), 4.10 (t, J=6.3 Hz, 4 H), 3.45 - 3.91 (m, 4 H), 3.20 (br s, 8 H), 2.91 - 3.14 (m, 4 H), 2.74 (br s, 8 H), 2.50 - 2.61 (m, 4 H), 2.42 (br t, J=6.7 Hz, 4 H), 2.18 - 2.30 (m, 4 H), 1.97 - 2.30 (m, 2 H), 1.86 - 1.95 (m, 4 H), 1.78 (quin, J=7.5 Hz, 4 H), 1.65 - 1.74 (m, 8 H).
Yield	129 mg
Example 23 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 6-(5-{6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexanoyl}-octahydropyrrolo[3,4-c]pyrrol-2-yl)-6-oxohexanoate	

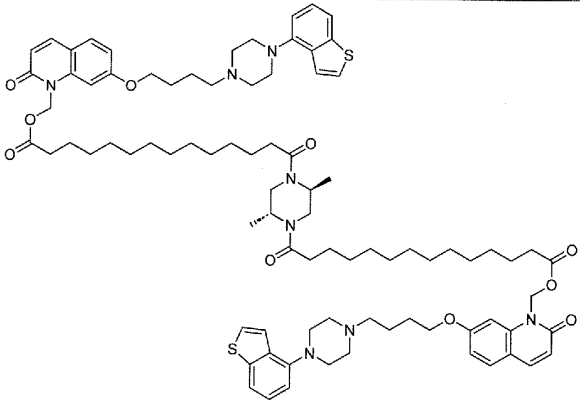
	
Reactants	
Int15 (0.20 g)	1,2,3,3a,4,5,6,6a-octahydropyrrolo[3,4-c]pyrrole dihydrochloride (25 mg)
LC-MS Method 3	LC-MS (ESI): m/z (M ⁺): 1260.0, Rt= 1.99 min
¹ H NMR (500 MHz, CHLOROFORM- <i>d</i>)	δ ppm 7.63 (d, J=9.5 Hz, 2 H), 7.55 (d, J=8.0 Hz, 2 H), 7.45 (d, J=8.6 Hz, 2 H), 7.37 - 7.43 (m, 4 H), 7.11 - 7.32 (m, 2 H), 6.80 - 6.94 (m, 6 H), 6.51 (dd, J=9.5, 1.9 Hz, 2 H), 6.32 (br s, 4 H), 4.09 (br t, J=6.0 Hz, 4 H), 3.58 - 3.78 (m, 4 H), 3.22 - 3.40 (m, 4 H), 3.12 - 3.44 (m, 8 H), 2.78 - 3.01 (m, 2 H), 2.63 - 3.02 (m, 8 H), 2.55 (br t, J=7.4 Hz, 4 H), 2.41 (br t, J=6.2 Hz, 4 H), 2.17 - 2.28 (m, 4 H), 1.85 - 1.98 (m, 4 H), 1.74 - 1.83 (m, 4 H), 1.64 - 1.73 (m, 8 H)
Yield	110 mg
Example 24 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 5-({[5-({6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-N-methyl-6-oxohexanamido)methyl}pyrazin-2-yl)methyl](methyl)carbamoyl}pentanoate	

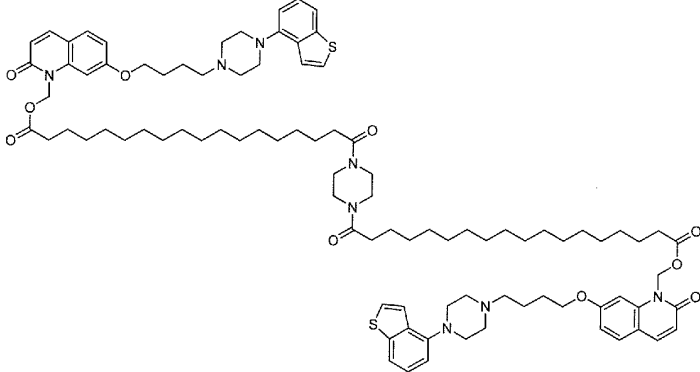
	
Reactants	
Int15 (0.32 g)	Int04 (38 mg)
LC-MS Method 3	LC-MS (ESI): m/z (M^{+1}): 1313.9, Rt= 2.03 min
^1H NMR (500 MHz, CHLOROFORM- <i>d</i>)	δ ppm 8.29 - 8.54 (m, 2 H), 7.60 - 7.67 (m, 2 H), 7.52 - 7.58 (m, 2 H), 7.43 - 7.47 (m, 2 H), 7.38 - 7.43 (m, 4 H), 7.25 - 7.30 (m, 2 H), 6.87 - 6.94 (m, 4 H), 6.85 (dd, J=8.5, 2.2 Hz, 2 H), 6.47 - 6.56 (m, 2 H), 6.33 (br s, 4 H), 4.54 - 4.71 (m, 4 H), 4.09 (t, J=6.2 Hz, 4 H), 3.20 (br s, 8 H), 2.90 - 3.09 (m, 6 H), 2.73 (br s, 8 H), 2.50 - 2.58 (m, 4 H), 2.28 - 2.48 (m, 8 H), 1.85 - 1.97 (m, 4 H), 1.78 (dt, J=14.8, 7.5 Hz, 4 H), 1.63 - 1.74 (m, 8 H)
Yield	143 mg
Example 25 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 5-({[5-({6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexanamido)methyl}pyrazin-2-yl)methyl]carbamoyl}pentanoate	

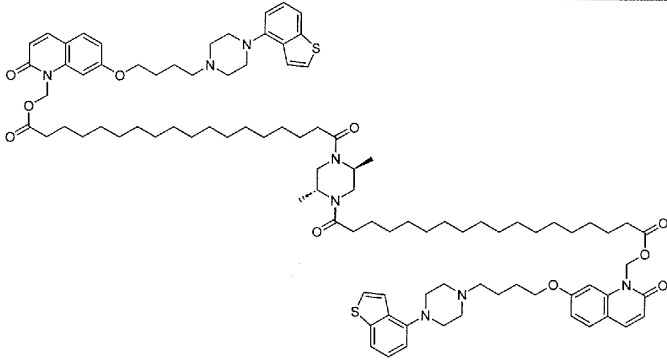
	
Reactants	
Int15 (0.10 g)	Int05 (15 mg)
LC-MS Method 4	LC-MS (ESI): m/z (M^{+1}): 1285.8, Rt= 2.67 min
^1H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 8.48 (s, 2 H), 7.63 (d, J=9.4 Hz, 2 H), 7.55 (d, J=7.9 Hz, 2 H), 7.46 (d, J=8.6 Hz, 2 H), 7.36 - 7.43 (m, 4 H), 7.23 - 7.31 (m, 2 H), 6.82 - 6.93 (m, 6 H), 6.71 (br t, J=5.2 Hz, 2 H), 6.49 (d, J=9.4 Hz, 2 H), 6.31 (br s, 4 H), 4.56 (d, J=5.3 Hz, 4 H), 4.10 (t, J=6.2 Hz, 4 H), 3.20 (br s, 8 H), 2.60 - 2.87 (m, 8 H), 2.55 (br t, J=7.5 Hz, 4 H), 2.33 - 2.44 (m, 4 H), 2.19 - 2.32 (m, 4 H), 1.86 - 1.97 (m, 4 H), 1.74 - 1.85 (m, 4 H), 1.65 - 1.73 (m, 8 H)
Yield	41 mg
Example 26 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl (2E)-4-{4-[(2E)-4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobut-2-enoyl]piperazin-1-yl}-4-oxobut-2-enoate	

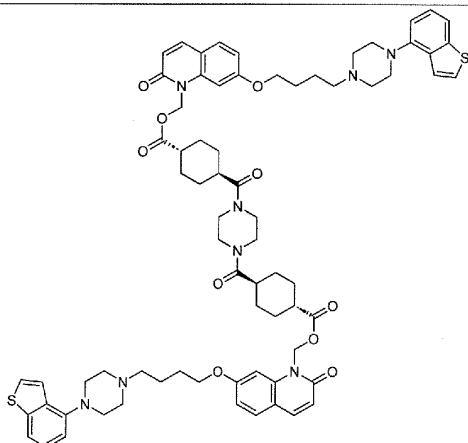
	
Reactant	
Int17 (136 mg)	piperazine
LC-MS Method 3	LC-MS (ESI): m/z (M^{+1}): 1173.8, Rt= 1.97 min
^1H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 7.65 (d, J=9.6 Hz, 2 H), 7.55 (d, J=8.0 Hz, 2 H), 7.48 (d, J=9.2 Hz, 2 H), 7.35 - 7.44 (m, 6 H), 7.24 - 7.30 (m, 2 H), 6.89 (d, J=7.7 Hz, 2 H), 6.85 - 6.88 (m, 4 H), 6.80 (d, J=15.4 Hz, 2 H), 6.53 (d, J=9.6 Hz, 2 H), 6.45 (br s, 4 H), 4.09 (br t, J=6.2 Hz, 4 H), 3.42 - 3.76 (m, 8 H), 3.19 (br s, 8 H), 2.73 (br s, 8 H), 2.54 (br t, J=7.3 Hz, 4 H), 1.86 - 1.98 (m, 4 H), 1.70 - 1.84 (m, 4 H)
Yield	8.8 mg
Example 27 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 14-(4-{14-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-14-oxotetradecanoyl}piperazin-1-yl)-14-oxotetradecanoate	

	
Reactant	
Int20 (300 mg)	Piperazine
LC-MS Method 4	LC-MS (ESI): <i>m/z</i> (M/2+H): 729.6, Rt= 2.69 min
¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 7.63 (d, <i>J</i> =9.4 Hz, 2 H), 7.56 (d, <i>J</i> =8.0 Hz, 2 H), 7.46 (d, <i>J</i> =8.6 Hz, 2 H), 7.41 - 7.44 (m, 2 H), 7.38 - 7.41 (m, 2 H), 7.25 - 7.32 (m, 2 H), 6.89 - 6.92 (m, 2 H), 6.89 (d, <i>J</i> =2.1 Hz, 2 H), 6.85 (dd, <i>J</i> =8.6, 2.1 Hz, 2 H), 6.53 (d, <i>J</i> =9.4 Hz, 2 H), 6.34 (s, 4 H), 4.09 (t, <i>J</i> =6.2 Hz, 4 H), 3.40 - 3.68 (m, 8 H), 3.21 (br s, 8 H), 2.74 (br s, 8 H), 2.55 (br t, <i>J</i> =7.2 Hz, 4 H), 2.37 (t, <i>J</i> =7.6 Hz, 4 H), 2.32 (br t, <i>J</i> =7.6 Hz, 4 H), 1.87 - 1.97 (m, 4 H), 1.72 - 1.85 (m, 4 H), 1.59 - 1.69 (m, 8 H), 1.17 - 1.37 (m, 32 H)
Yield	74 mg
Example 28 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 14-[(2S,5R)-4-{14-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-14-oxotetradecanoyl}-2,5-dimethylpiperazin-1-yl]-14-oxotetradecanoate	

	
Reactants	
Int20 (150 mg)	(2R,5S)-2,5-dimethylpiperazine (11 mg)
LC-MS Method 3	LC-MS (ESI): <i>m/z</i> (M+H): 1486.9, <i>Rt</i> = 2.86 min
¹ H NMR (500 MHz, CHLOROFORM- <i>d</i>)	δ ppm 7.63 (d, <i>J</i> =9.5 Hz, 2 H), 7.58 (d, <i>J</i> =8.1 Hz, 2 H), 7.46 (d, <i>J</i> =8.6 Hz, 2 H), 7.36 - 7.43 (m, 4 H), 7.18 - 7.32 (m, 2 H), 6.92 (d, <i>J</i> =7.1 Hz, 2 H), 6.89 (d, <i>J</i> =2.1 Hz, 2 H), 6.84 (dd, <i>J</i> =8.5, 2.2 Hz, 2 H), 6.53 (d, <i>J</i> =9.5 Hz, 2 H), 6.34 (br s, 4 H), 4.07 - 4.12 (m, 4 H), 4.01 - 4.94 (m, 2 H), 3.30 (br s, 8 H), 2.86 - 3.14 (m, 8 H), 2.85 - 4.43 (m, 4 H), 2.62 - 2.84 (m, 4 H), 2.37 (t, <i>J</i> =7.5 Hz, 4 H), 2.20 - 2.51 (m, 4 H), 1.53 - 1.99 (m, 16 H), 1.00 - 1.36 (m, 38 H)
Yield	14 mg
Example 29 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 18-(4-{18-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-18-oxooctadecanoyl}piperazin-1-yl)-18-oxooctadecanoate	

	
Reactant	
Int23 (282 mg)	Piperazine
LC-MS Method 4	LC-MS (ESI): <i>m/z</i> (M+H): 1570.8, <i>R</i> _t = 3.72 min
¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 7.63 (d, <i>J</i> =9.6 Hz, 2 H), 7.56 (d, <i>J</i> =7.9 Hz, 2 H), 7.45 (d, <i>J</i> =8.6 Hz, 2 H), 7.36 - 7.43 (m, 4 H), 7.28 - 7.33 (m, 2 H), 6.82 - 6.93 (m, 6 H), 6.53 (d, <i>J</i> =9.4 Hz, 2 H), 6.34 (s, 4 H), 4.09 (t, <i>J</i> =6.2 Hz, 4 H), 3.36 - 3.74 (m, 8 H), 3.21 (br s, 8 H), 2.74 (br s, 8 H), 2.55 (br t, <i>J</i> =7.5 Hz, 4 H), 2.28 - 2.43 (m, 8 H), 1.86 - 1.97 (m, 4 H), 1.72 - 1.84 (m, 4 H), 1.60 - 1.70 (m, 8 H), 1.16 - 1.41 (m, 48 H)
Yield	150 mg
Example 30 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 18-[(2S,5R)-4-{18-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-18-octadecanoyl}-2,5-dimethylpiperazin-1-yl]-18-oxooctadecanoate	

	
Reactants	
Int23 (116 mg)	(2R,5S)-2,5-dimethylpiperazine (6.2 mg)
LC-MS Method 4	LC-MS (ESI): <i>m/z</i> (M/2+H): 799.7, <i>Rt</i> = 3.57 min
¹ H NMR (500 MHz, CHLOROFORM- <i>d</i>)	δ ppm 7.63 (d, <i>J</i> =9.6 Hz, 2 H), 7.56 (d, <i>J</i> =8.1 Hz, 2 H), 7.46 (d, <i>J</i> =8.5 Hz, 2 H), 7.38 - 7.43 (m, 4 H), 7.25 - 7.30 (m, 2 H), 6.82 - 6.92 (m, 6 H), 6.53 (d, <i>J</i> =9.5 Hz, 2 H), 6.34 (br s, 4 H), 4.09 (t, <i>J</i> =6.2 Hz, 4 H), 3.91 - 4.94 (m, 2 H), 3.36 - 4.43 (m, 2 H), 3.21 (br s, 8 H), 2.90 - 3.51 (m, 2 H), 2.74 (br s, 8 H), 2.51 - 2.59 (m, 4 H), 2.16 - 2.49 (m, 8 H), 1.86 - 1.97 (m, 4 H), 1.78 (quin, <i>J</i> =7.5 Hz, 4 H), 1.56 - 1.71 (m, 8 H), 1.18 - 1.39 (m, 48 H), 1.04 - 1.30 (m, 6 H)
Yield	39 mg
Example 31 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl (1r,4r)-4-{4-[(1r,4r)-4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl]cyclohexanecarbonyl]piperazine-1-carbonyl}cyclohexane-1-carboxylate	



Reactant

Int25 (400 mg)

Piperazine

LC-MS Method 3

LC-MS (ESI): m/z (M+H): 1285.9, R_t = 2.75 min ^1H NMR (400 MHz, CHLOROFORM- d)

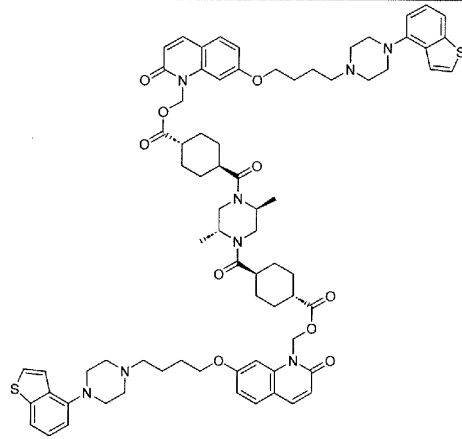
δ ppm 7.64 (d, J =9.4 Hz, 2 H), 7.55 (d, J =8.1 Hz, 2 H), 7.46 (d, J =8.6 Hz, 2 H), 7.37 - 7.43 (m, 4 H), 7.20 - 7.32 (m, 2 H), 6.81 - 6.94 (m, 6 H), 6.52 (d, J =9.4 Hz, 2 H), 6.33 (br s, 4 H), 4.08 (t, J =6.1 Hz, 4 H), 3.28 - 3.67 (m, 8 H), 3.20 (br s, 8 H), 2.73 (br s, 8 H), 2.55 (br t, J =7.3 Hz, 4 H), 2.30 - 2.49 (m, 4 H), 2.08 (br d, J =12.1 Hz, 4 H), 1.86 - 1.98 (m, 4 H), 1.70 - 1.83 (m, 8 H), 1.42 - 1.59 (m, 8 H)

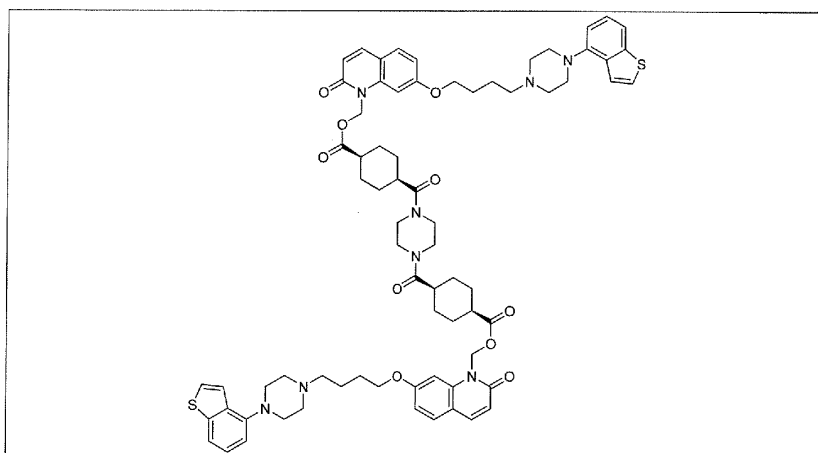
Yield

86 mg

Example 32

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl (1*r*,4*r*)-4-[(2*S*,5*R*)-2,5-dimethyl-4-[(1*r*,4*r*)-4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl]cyclohexanecarbonyl]piperazine-1-carbonyl]cyclohexane-1-carboxylate

	
Reactants	
Int25 (150 mg)	(2R,5S)-2,5-dimethylpiperazine (12.5 mg)
LC-MS Method 4	LC-MS (ESI): <i>m/z</i> (<i>M</i> / <i>2</i> + <i>H</i>): 658.3, <i>R</i> _t = 1.92 min
¹ H NMR (500 MHz, CHLOROFORM- <i>d</i>)	δ ppm 7.64 (d, <i>J</i> =9.5 Hz, 2 H), 7.55 (d, <i>J</i> =8.0 Hz, 2 H), 7.44 - 7.50 (m, 2 H), 7.41 - 7.43 (m, 2 H), 7.37 - 7.40 (m, 2 H), 7.25 - 7.31 (m, 2 H), 6.90 (d, <i>J</i> =7.7 Hz, 2 H), 6.81 - 6.88 (m, 4 H), 6.49 - 6.55 (m, 2 H), 6.33 (br s, 4 H), 4.06 - 4.11 (m, 4 H), 4.83 (br d, <i>J</i> =2.2 Hz, 2 H), 3.20 (br s, 8 H), 2.85 - 4.44 (m, 4 H), 2.73 (br s, 8 H), 2.55 (br t, <i>J</i> =7.1 Hz, 4 H), 2.26 - 2.50 (m, 4 H), 1.85 - 1.98 (m, 4 H), 1.73 - 1.85 (m, 4 H), 1.41 - 2.15 (m, 16 H), 0.95 - 1.24 (m, 6 H).
Yield	34 mg
Example 33 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl (1 <i>S</i> ,4 <i>S</i>)-4-{4-[(1 <i>S</i> ,4 <i>S</i>)-4-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}cyclohexanecarbonyl]piperazine-1-carbonyl}cyclohexane-1-carboxylate	



Reactant

Int29 (533 mg)

Piperazine

LC-MS Method 3

LC-MS (ESI): m/z (M+H): 1285.8, Rt= 2.12 min¹H NMR (500 MHz,
CHLOROFORM-*d*)

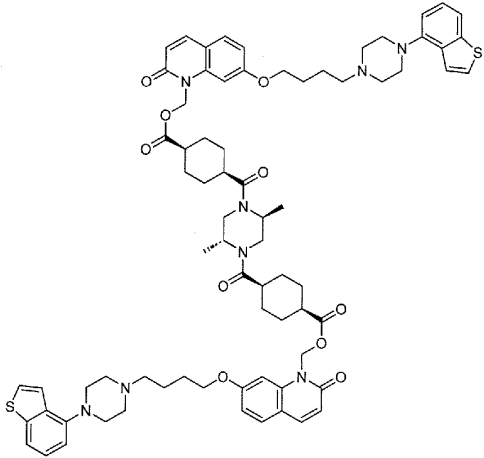
δ ppm 7.63 (d, J=9.5 Hz, 2 H), 7.56 (d, J=8.0 Hz, 2 H), 7.45 (d, J=8.6 Hz, 2 H), 7.38 - 7.42 (m, 4 H), 7.24 - 7.30 (m, 2 H), 6.87 - 6.92 (m, 4 H), 6.84 (dd, J=8.5, 2.1 Hz, 2 H), 6.52 (d, J=9.5 Hz, 2 H), 6.36 (br s, 4 H), 4.10 (br t, J=6.2 Hz, 4 H), 3.31 - 3.64 (m, 8 H), 3.22 (br s, 8 H), 2.81 (br s, 8 H), 2.55 - 2.69 (m, 6 H), 2.45 - 2.54 (m, 2 H), 2.17 (br d, J=3.6 Hz, 4 H), 1.87 - 1.96 (m, 4 H), 1.72 - 1.86 (m, 8 H), 1.54 - 1.62 (m, 8 H)

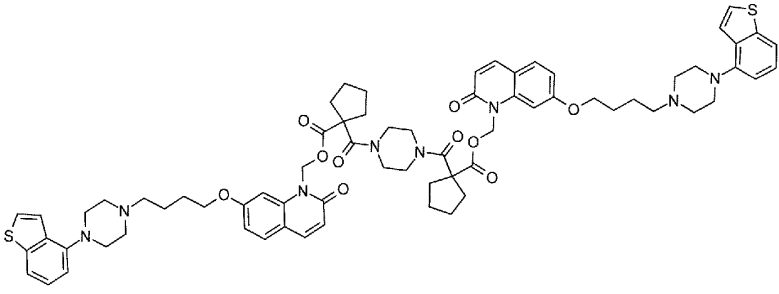
Yield

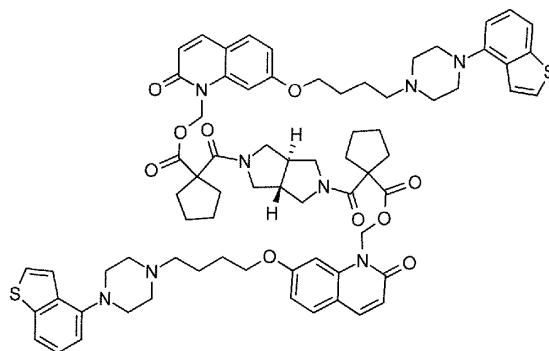
52 mg

Example 34

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl (1*S*,4*S*)-4-[(2*S*,5*R*)-2,5-dimethyl-4-[(1*S*,4*S*)-4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl]cyclohexanecarbonyl]piperazine-1-carbonyl]cyclohexane-1-carboxylate

	
Reactants	
Int29 (200 mg)	(2R,5S)-2,5-dimethylpiperazine (14 mg)
LC-MS Method 3	
¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 7.63 (d, <i>J</i> =9.5 Hz, 2 H), 7.52 - 7.58 (m, 2 H), 7.36 - 7.47 (m, 6 H), 7.25 - 7.32 (m, 2 H), 6.87 - 6.94 (m, 4 H), 6.84 (br d, <i>J</i> =8.8 Hz, 2 H), 6.52 (d, <i>J</i> =9.5 Hz, 2 H), 6.26 - 6.46 (m, 4 H), 4.10 (t, <i>J</i> =6.1 Hz, 4 H), 3.95 - 4.91 (m, 2 H), 3.10 - 3.28 (m, 8 H), 2.84 - 4.40 (m, 4 H), 2.68 - 2.82 (m, 8 H), 2.54 (br t, <i>J</i> =7.2 Hz, 4 H), 2.64 (br dd, <i>J</i> =7.1, 3.5 Hz, 4 H), 1.74 - 1.99 (m, 8 H), 1.53 - 2.32 (m, 16 H), 0.95 - 1.26 (m, 6 H)
Yield	17 mg
Example 35 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 1-[4-(1-{(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}cyclopentanecarbonyl)piperazine-1-carbonyl]cyclopentane-1-carboxylate	

	
Reactant	
Int32 (500 mg)	Piperazine
LC-MS Method 3	LC-MS (ESI): <i>m/z</i> (M+H): 1258.1, Rt= 2.19 min
¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 7.59 (d, J=9.4 Hz, 2 H), 7.55 (d, J=7.9 Hz, 2 H), 7.36 - 7.45 (m, 6 H), 7.28 (br t, J=7.8 Hz, 2 H), 6.90 (d, J=7.7 Hz, 2 H), 6.80 - 6.86 (m, 2 H), 6.76 (s, 2 H), 6.45 (d, J=9.6 Hz, 2 H), 6.33 (br s, 4 H), 4.06 (br t, J=6.2 Hz, 4 H), 3.20 (br s, 8 H), 2.98 - 3.48 (m, 8 H), 2.73 (br s, 8 H), 2.54 (br t, J=7.2 Hz, 4 H), 2.07 - 2.36 (m, 8 H), 1.82 - 1.95 (m, 4 H), 1.54 - 1.81 (m, 12 H)
Yield	100 mg
Example 36 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 1-[(3ar,6ar)-5-(1-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl]cyclopentanecarbonyl)-octahydropyrrolo[3,4-c]pyrrole-2-carbonyl]cyclopentane-1-carboxylate	



Reactants

Int32

(197 mg)

(3aR,6aR)-octahydropyrrolo[3,4-c]pyrrole
dihydrochloride
(30 mg)

LC-MS Method 3

LC-MS (ESI): *m/z* (M+H): 1284.9, *Rt*= 2.26 min

¹H NMR (400 MHz,
CHLOROFORM-*d*)

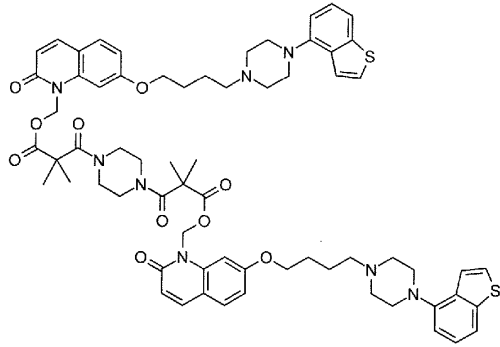
δ ppm 7.58 - 7.64 (m, 2 H), 7.56 (d, *J*=8.1 Hz, 2 H), 7.36 - 7.47 (m, 6 H), 7.27 - 7.31 (m, 2 H), 6.91 (d, *J*=7.7 Hz, 2 H), 6.77 - 6.88 (m, 4 H), 6.47 (dd, *J*=9.4, 3.9 Hz, 2 H), 5.84 - 6.75 (m, 4 H), 3.90 - 4.21 (m, 4 H), 3.12 - 3.29 (m, 8 H), 3.00 - 3.70 (m, 4 H), 2.66 - 2.88 (m, 8 H), 2.50 - 2.62 (m, 4 H), 2.49 - 2.99 (m, 4 H), 1.99 - 2.45 (m, 8 H), 1.86 - 1.98 (m, 4 H), 1.66 - 1.84 (m, 12 H), 1.18 - 1.49 (m, 2 H)

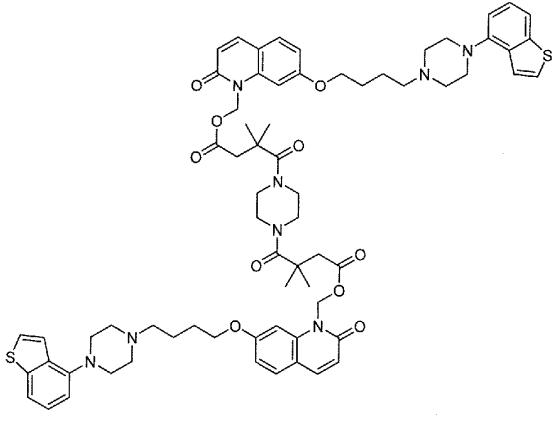
Yield

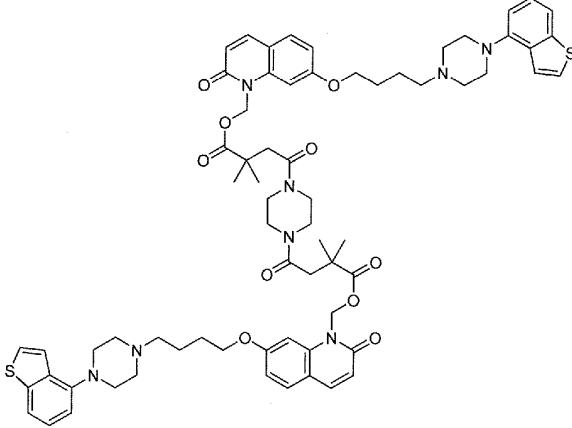
5.6 mg

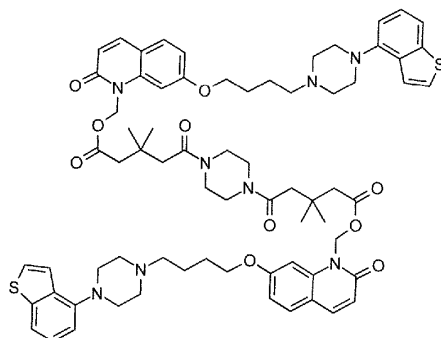
Example 37

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 3-(4-{3-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-2,2-dimethyl-3-oxopropanoyl}piperazin-1-yl)-2,2-dimethyl-3-oxopropanoate

	
Reactant	
Int35 (144 mg)	Piperazine
LC-MS Method 3	LC-MS (ESI): <i>m/z</i> (M+H): 1205.8, <i>R</i> _t = 2.08 min
¹ H NMR (500 MHz, DMSO- <i>d</i> ₆)	δ ppm 7.85 (d, <i>J</i> =9.6 Hz, 2 H), 7.68 (d, <i>J</i> =5.5 Hz, 2 H), 7.64 (d, <i>J</i> =9.3 Hz, 2 H), 7.60 (d, <i>J</i> =8.1 Hz, 2 H), 7.38 (d, <i>J</i> =5.6 Hz, 2 H), 7.26 (t, <i>J</i> =7.9 Hz, 2 H), 6.90 - 6.98 (m, 4 H), 6.85 (d, <i>J</i> =7.7 Hz, 2 H), 6.27 - 6.51 (m, 6 H), 4.00 - 4.14 (m, 4 H), 2.83 - 3.24 (m, 16 H), 2.55 - 2.67 (m, 8 H), 2.24 - 2.44 (m, 4 H), 1.68 - 1.86 (m, 4 H), 1.51 - 1.67 (m, 4 H), 1.31 (s, 12 H)
Yield	40 mg
Example 38 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 4-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-2,2-dimethyl-4-oxobutanoyl}piperazin-1-yl)-3,3-dimethyl-4-oxobutanoate	

	
Reactant	
Int38 (180 mg)	Piperazine
LC-MS Method 3	LC-MS (ESI): <i>m/z</i> (M+H): 1233.8, <i>Rt</i> = 2.09 min
¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 7.62 (d, <i>J</i> =9.5 Hz, 2 H), 7.55 (d, <i>J</i> =8.0 Hz, 2 H), 7.44 (d, <i>J</i> =8.7 Hz, 2 H), 7.36 - 7.43 (m, 4 H), 7.24 - 7.30 (m, 2 H), 6.93 (s, 2 H), 6.89 (d, <i>J</i> =7.7 Hz, 2 H), 6.84 (dd, <i>J</i> =8.7, 2.0 Hz, 2 H), 6.50 (d, <i>J</i> =9.5 Hz, 2 H), 6.31 (br s, 4 H), 4.14 (t, <i>J</i> =6.0 Hz, 4 H), 3.52 (s, 8 H), 3.19 (br s, 8 H), 2.73 (br s, 8 H), 2.61 (s, 4 H), 2.48 - 2.58 (m, 4 H), 1.86 - 1.97 (m, 4 H), 1.72 - 1.85 (m, 4 H), 1.41 (s, 12 H).
Yield	31 mg
Example 39 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 4-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-3,3-dimethyl-4-oxobutanoyl}piperazin-1-yl)-2,2-dimethyl-4-oxobutanoate	

	
Reactant	
Int40 (126 mg)	Piperazine
LC-MS Method 3	LC-MS (ESI): m/z (M+Na): 1256.1 R_t = 2.11 min
¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 7.62 (d, J =9.4 Hz, 2 H), 7.55 (br d, J =8.0 Hz, 2 H), 7.36 - 7.45 (m, 6 H), 7.24 - 7.30 (m, 2 H), 6.95 - 7.03 (m, 2 H), 6.89 (d, J =7.7 Hz, 2 H), 6.83 (br d, J =8.6 Hz, 2 H), 6.50 (br d, J =9.4 Hz, 2 H), 6.31 (br s, 4 H), 4.05 - 4.27 (m, 4 H), 3.20 (br s, 8 H), 3.11 - 3.49 (m, 8 H), 2.73 (br s, 8 H), 2.48 - 2.60 (m, 8 H), 1.70 - 1.94 (m, 8 H), 1.29 (s, 12 H).
Yield	38 mg
Example 40 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 5-(4-{5-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-3,3-dimethyl-5-oxopentanoyl}piperazin-1-yl)-3,3-dimethyl-5-oxopentanoate	



Reactant

Int43 (220 mg)

Piperazine

LC-MS Method 3

LC-MS (ESI): *m/z* (M+H): 1261.8, *R*_t= 2.12 min¹H NMR (500 MHz,
CHLOROFORM-*d*)

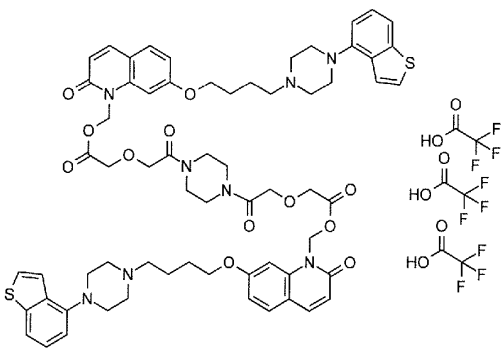
δ ppm 7.63 (br d, *J*=9.3 Hz, 2 H), 7.55 (d, *J*=8.1 Hz, 2 H), 7.46 (d, *J*=8.5 Hz, 2 H), 7.37 - 7.43 (m, 4 H), 7.22 - 7.30 (m, 2 H), 6.88 - 6.92 (m, 2 H), 6.82 - 6.88 (m, 4 H), 6.50 (d, *J*=9.5 Hz, 2 H), 6.29 (br s, 4 H), 4.10 (t, *J*=6.2 Hz, 4 H), 3.30 - 3.57 (m, 8 H), 3.20 (br s, 8 H), 2.73 (br s, 8 H), 2.61 (s, 4 H), 2.52 - 2.58 (m, 4 H), 2.33 - 2.49 (m, 4 H), 1.86 - 1.97 (m, 4 H), 1.73 - 1.83 (m, 4 H), 1.15 (br s, 12 H)

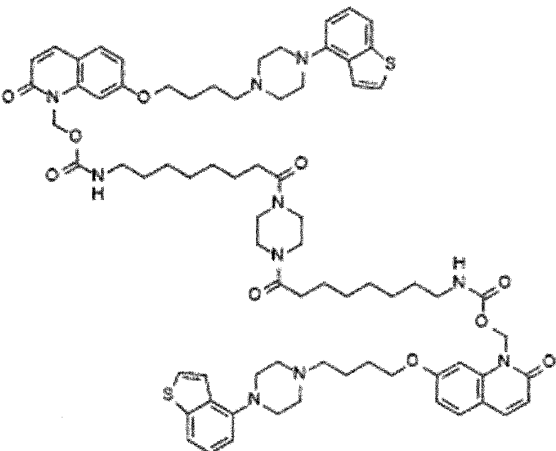
Yield

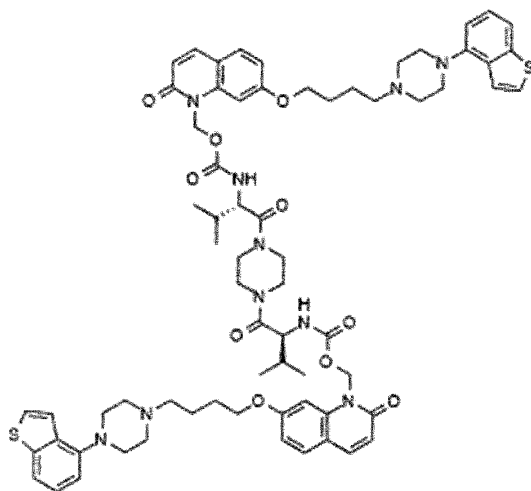
43 mg

Example 41

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 2-[2-[4-(2-{2-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-2-oxoethoxy}acetyl)piperazin-1-yl]-2-oxoethoxy}acetate tris(trifluoroacetic acid) salt

	
Reactant	
Int46 (250 mg)	Piperazine
LC-MS Method 3	LC-MS (ESI): <i>m/z</i> (M+H): 1209.9, <i>R</i> _t = 1.92 min
¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 7.64 (dd, <i>J</i> =8.7, 5.2 Hz, 4 H), 7.44 - 7.52 (m, 4 H), 7.28 - 7.34 (m, 4 H), 6.95 (d, <i>J</i> =7.7 Hz, 2 H), 6.90 (s, 2 H), 6.82 - 6.87 (m, 2 H), 6.53 (d, <i>J</i> =9.5 Hz, 2 H), 6.40 (br s, 4 H), 4.26 (s, 8 H), 4.08 - 4.15 (m, 4 H), 3.82 (br d, <i>J</i> =11.3 Hz, 4 H), 3.34 - 3.60 (m, 16 H), 3.24 - 3.32 (m, 4 H), 3.15 - 3.23 (m, 4 H), 1.89 - 2.17 (m, 8 H).
Yield	84 mg
Example 42 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl N-(8-{4-[8-({[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}amino)octanoyl]piperazin-1-yl}-8-oxooctyl)carbamate	

	
Reactants	
Int48 (111 mg)	piperazine (5.7 mg)
LC-MS Method 3	LC-MS (ESI): m/z (M^+): 1347.9, R_t = 2.14 min
1H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 7.62 (d, J =9.6 Hz, 2 H), 7.55 (d, J =8.1 Hz, 2 H), 7.36 - 7.48 (m, 6 H), 7.24 - 7.31 (m, 2 H), 7.16 (br s, 2 H), 6.90 (d, J =7.7 Hz, 2 H), 6.84 (dd, J =8.6, 2.0 Hz, 2 H), 6.51 (d, J =9.4 Hz, 2 H), 6.32 (s, 4 H), 4.92 (br s, 2 H), 4.12 (t, J =6.2 Hz, 4 H), 3.33 - 3.68 (m, 8 H), 3.01 - 3.28 (m, 12 H), 2.73 (br s, 8 H), 2.49 - 2.59 (m, 4 H), 2.30 (br t, J =7.5 Hz, 4 H), 1.84 - 1.98 (m, 4 H), 1.72 - 1.83 (m, 4 H), 1.56 - 1.68 (m, 4 H), 1.42 - 1.55 (m, 4 H), 1.32 (br s, 12 H)
Yield	7.4 mg
Example 43 (7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-N-[(2S)-1-{4-[(2S)-2-({(7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}amino)-3-methylbutanoyl]piperazin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate	



Reactants

Int50

(370 mg)

piperazine

(20 mg)

LC-MS Method 3

LC-MS (ESI): m/z (M⁺): 1264.8, Rt= 2.06 min¹H NMR (400 MHz,
CHLOROFORM-*d*)

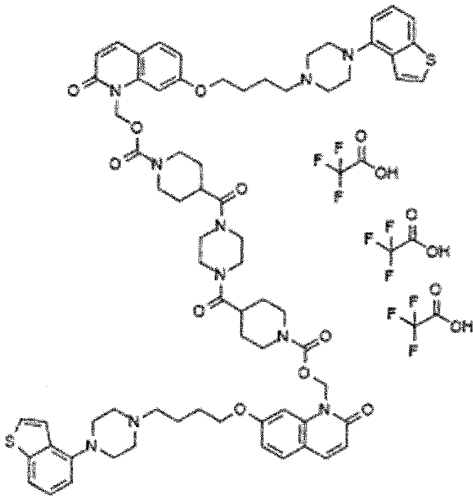
δ ppm 7.50 - 7.68 (m, 4 H), 7.34 - 7.49 (m, 6 H), 7.19 - 7.31 (m, 2 H),
6.95 - 7.12 (m, 2 H), 6.79 - 6.94 (m, 4 H), 6.46 - 6.57 (m, 2 H), 6.16 -
6.44 (m, 4 H), 5.29 - 6.08 (m, 2 H), 4.19 - 4.62 (m, 2 H), 3.97 - 4.18 (m,
4 H), 3.31 - 3.95 (m, 8 H), 3.02 - 3.26 (m, 8 H), 2.63 - 2.88 (m, 8 H),
2.42 - 2.62 (m, 4 H), 1.67 - 2.05 (m, 10 H), 0.78 - 1.07 (m, 12 H).

Yield

77 mg

Example 44

7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 4-[4-(1-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl]piperidine-4-carbonyl)piperazine-1-carbonyl]piperidine-1-carboxylate tris(trifluoroacetic acid) salt

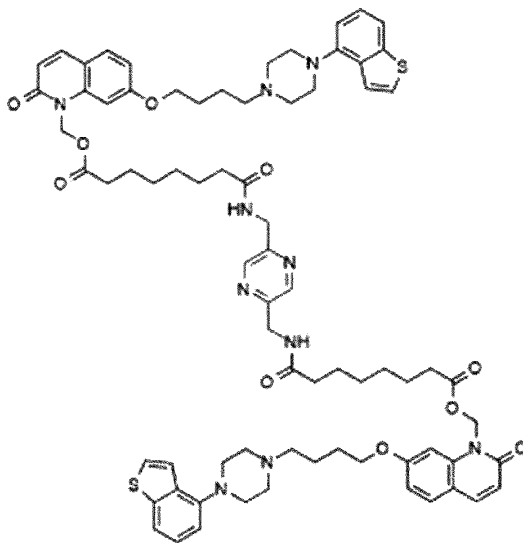
	
Reactants	
Int52 (272 mg)	piperazine (14 mg)
LC-MS Method 3	LC-MS (ESI): m/z (M^+): 1288.1, R_t = 1.99 min
^1H NMR (500 MHz, CHLOROFORM- <i>d</i>)	δ ppm 12.47 (br s, 2 H), 7.61 - 7.71 (m, 4 H), 7.42 - 7.52 (m, 4 H), 7.29 - 7.33 (m, 4 H), 7.10 (br s, 2 H), 6.96 (d, J =7.5 Hz, 2 H), 6.84 (dd, J =8.6, 2.1 Hz, 2 H), 6.57 (d, J =9.5 Hz, 2 H), 6.22 - 6.52 (m, 4 H), 4.11 (br t, J =5.4 Hz, 4 H), 4.01 - 4.33 (m, 4 H), 3.12 - 3.90 (m, 28 H), 2.79 - 2.92 (m, 4 H), 2.54 - 2.66 (m, 2 H), 2.04 - 2.15 (m, 4 H), 1.90 - 2.00 (m, 4 H), 1.50 - 1.79 (m, 8 H)
Yield	5.4 mg

[0184] Example 04: (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 8-[(1S,4S)-5-{8-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanoyl}-2,5-diazabicyclo[2.2.1]heptan-2-yl]-8-oxooctanoate; tris(trifluoroacetic acid)

[illegible]

7-({[5-({8-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanamido}methyl)pyrazin-2-yl]methyl}carbamoyl)heptanoate

[Chem.78]



To a solution of Int03 (110 mg) and Int05 (16 mg), in dry DMF (13 mL) was added TBTU (543 mg). After 5 minutes was added TEA (0.54 mL) and piperazine (50 mg) and the reaction was stirred at RT overnight. More piperazine (17 mg) and TEA (0.15 mL) were added and the reaction was stirred at RT for further 1h. H₂O and DCM were added to the reaction mixture, the mixture phases were separated and the aqueous phase was extracted with DCM (3 times). Combined organic layers were washed with brine, dried over Na₂SO₄, filtered, concentrated under vacuum. The crude obtained was purified by chromatography on a silica gel cartridge (eluent = from neat DCM to 3% of MeOH in DCM) to give Example 08 (30 mg).

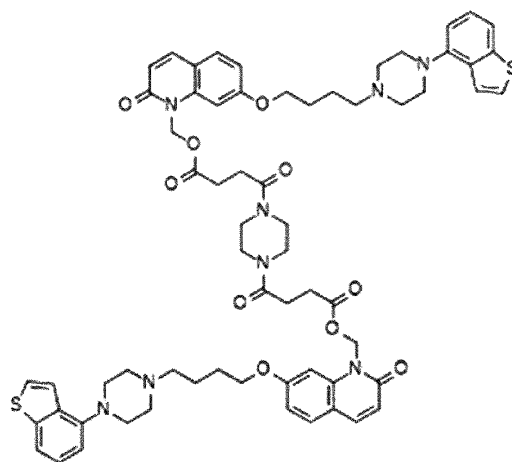
LC-MS (ESI): m/z (M+1): 1342.9, Rt= 2.09 min. (Method 3).

¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.49 (s, 2 H), 7.63 (d, J=9.6 Hz, 2 H), 7.55 (d, J=8.1 Hz, 2 H), 7.46 (d, J=8.6 Hz, 2 H), 7.37 - 7.43 (m, 4 H), 7.18 - 7.34 (m, 2 H), 6.82 - 6.94 (m, 6 H), 6.68 (br t, J=5.0 Hz, 2 H), 6.50 (d, J=9.4 Hz, 2 H), 6.32 (br s, 4 H), 4.56 (d, J=5.5 Hz, 4 H), 4.09 (t, J=6.1 Hz, 4 H), 3.21 (br s, 8 H), 2.75 (br s, 8 H), 2.56 (br t, J=7.3 Hz, 4 H), 2.36 (t, J=7.3 Hz, 4 H), 2.22 (t, J=7.6 Hz, 4 H), 1.87 - 1.98 (m, 4 H), 1.78 (quin, J=7.3 Hz, 4 H), 1.51 - 1.69 (m, 8 H), 1.28 - 1.43 (m, 8 H).

[0186] Example 10:

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutanoyl}piperazin-1-yl)-4-oxobutanoate

[Chem.79]



To a solution of Int07 (568 mg) in dry DMF (7.73 mL) was added TBTU (395 mg). After 5 minutes was added piperazine (37 mg) and TEA (0.26 mL). The mixture was stirred at RT for 16 hours. Water and DCM were added to the reaction mixture, extracted with DCM (3 times). Collected organic layers were dried over Na₂SO₄, filtered, concentrated with high vacuum. The crude obtained was purified by chromatography on a silica gel cartridge (eluent= from 0 to 6% of MeOH in DCM) to yield Example 10 (250 mg).

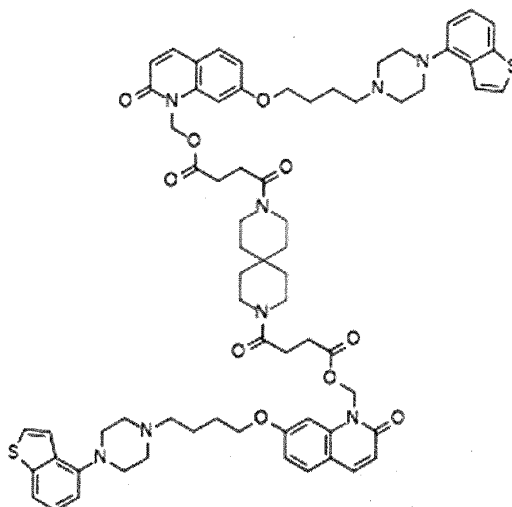
LC-MS (ESI): m/z (M+1): 1177.9, Rt= 1.99 min. (Method 3). ¹H NMR (600 MHz, CHLOROFORM-d) δ ppm 7.63 (d, J=9.6 Hz, 2 H), 7.55 (d, J=7.9 Hz, 2 H), 7.45 (d, J=8.6 Hz, 2 H), 7.40 (q, J=5.6 Hz, 4 H), 7.21 - 7.31 (m, 2 H), 6.87 - 6.92 (m, 4 H), 6.85 (dd, J=8.6, 2.3 Hz, 2 H), 6.51 (d, J=9.6 Hz, 2 H), 6.34 (br s, 4 H), 4.14 (t, J=6.1 Hz, 4 H), 3.28 - 3.62 (m, 8 H), 3.22 (br s, 8 H), 2.67 - 2.89 (m, 12 H), 2.51 - 2.66 (m, 8 H), 1.88 - 1.96 (m, 4 H), 1.80 (br d, J=6.6 Hz, 4 H).

[0187] Example 12:

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl

4-(9-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutanoyl}-3,9-diazaspiro[5.5]undecan-3-yl)-4-oxobutanoate

[Chem.80]



To a solution of Int07 (200 mg) and Int09 (57 mg), in dry DMF (13 mL) was added TBTU (543 mg). After 5 minutes was added TEA (0.54 mL) and piperazine (50 mg) and the reaction was stirred at RT overnight. More piperazine (17 mg) and TEA (0.15 mL) were added and the reaction was further stirred at RT for 1 h. H₂O and DCM were added to the reaction mixture, the mixture phases were separated and the aqueous phase was extracted with DCM (3 times). Combined organic layers were washed with brine, dried over Na₂SO₄, filtered, concentrated under vacuum. The crude obtained was purified by chromatography on a silica gel cartridge (eluent = from neat DCM to 3% of MeOH in DCM) to give Example 12 (41 mg).

LC-MS (ESI): m/z (M+1): 1245.7, Rt= 2.03 min. (Method 3).

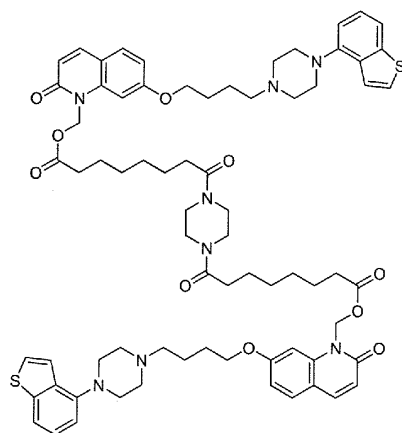
¹H NMR (500 MHz, CHLOROFORM-d) δ ppm 7.63 (d, J=9.5 Hz, 2 H), 7.56 (d, J=8.1 Hz, 2 H), 7.44 (d, J=8.6 Hz, 2 H), 7.36 - 7.42 (m, 4 H), 7.23 - 7.31 (m, 2 H), 6.87 - 6.94 (m, 4 H), 6.85 (dd, J=8.6, 2.2 Hz, 2 H), 6.52 (d, J=9.5 Hz, 2 H), 6.34 (br s, 4 H), 4.16 (t, J=5.9 Hz, 4 H), 3.31 - 3.63 (m, 8 H), 3.16 - 3.31 (m, 8 H), 2.78 - 3.10 (m, 8 H), 2.59 - 2.77 (m, 12 H), 1.82 - 1.96 (m, 8 H), 1.29 - 1.51 (m, 8 H).

[0188] Example 19:

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl

8-(4-{8-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanoyl}piperazin-1-yl)-8 oxooctanoate

[Chem.81]



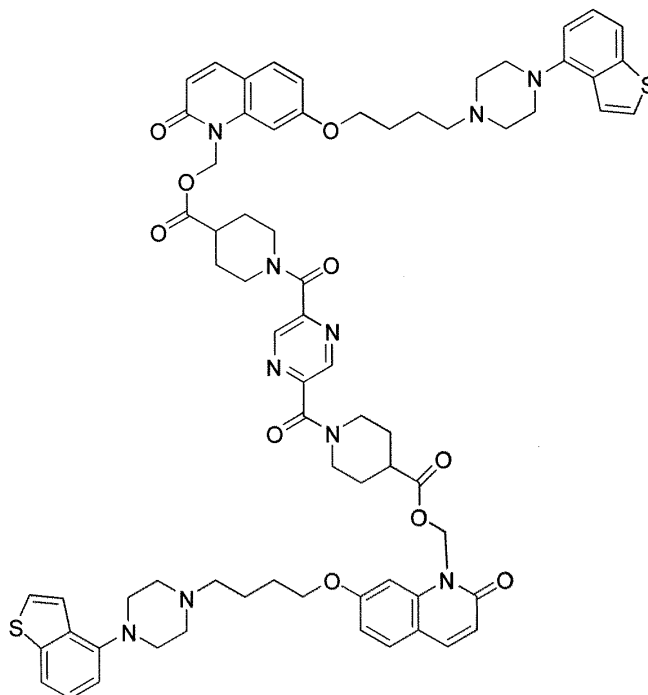
To a solution of Int03 (890 mg) in dry DMF (13 mL) was added TBTU (543 mg). After 5 minutes was added TEA (0.54 mL) and piperazine (50 mg) and the reaction was stirred at RT overnight. More piperazine (17 mg) and TEA (0.15 mL) were added and the reaction was further stirred at RT for 1 h. H₂O and DCM were added to the reaction mixture, the mixture phases were separated and the aqueous phase was extracted with DCM (3 times). Combined organic layers were washed with brine, dried over Na₂SO₄, filtered, concentrated under vacuum. The crude obtained was purified by chromatography on a silica gel cartridge (eluent = from neat DCM to 3% of MeOH in DCM) to give Example 19 (660 mg).

LC-MS (ESI): m/z (M+1): 1290.0, Rt= 2.17 min. (Method 3). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.88 (d, J=9.6 Hz, 2 H), 7.63 - 7.72 (m, 4 H), 7.59 (d, J=8.1 Hz, 2 H), 7.38 (d, J=5.7 Hz, 2 H), 7.25 (t, J=7.8 Hz, 2 H), 6.91 - 7.00 (m, 4 H), 6.86 (d, J=7.7 Hz, 2 H), 6.42 (d, J=9.4 Hz, 2 H), 6.27 (br s, 4 H), 4.13 (t, J=6.2 Hz, 4 H), 3.23 - 3.48 (m, 8 H), 3.04 (br s, 8 H), 2.60 (br s, 8 H), 2.43 (br t, J=7.0 Hz, 4 H), 2.28 - 2.37 (m, 4 H), 2.21 (t, J=7.3 Hz, 4 H), 1.75 - 1.86 (m, 4 H), 1.58 - 1.71 (m, 4 H), 1.50 (quin, J=7.2 Hz, 4 H), 1.34 - 1.44 (m, 4 H), 1.16 - 1.29 (m, 8 H).

[0189] Example 45:

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-1-[5-(4-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}piperidine-1-carbonyl)pyrazine-2-carbonyl]piperidine-4-carboxylate

[Chem.82]



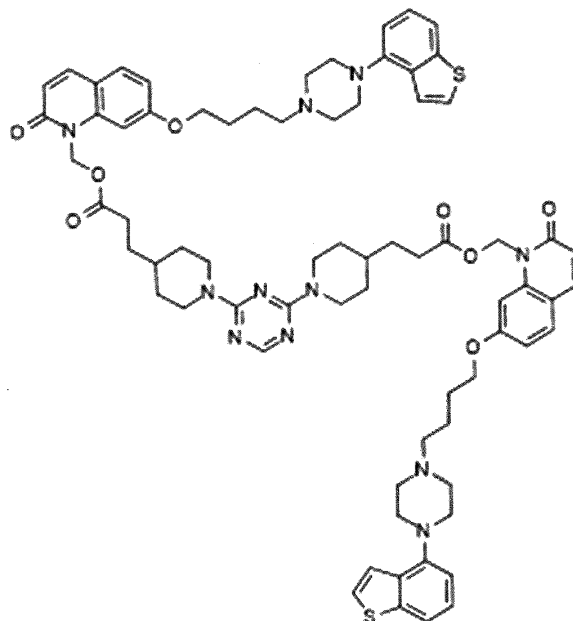
Pyrazine-2,5-dicarbonyl dichloride (36 mg) was added to a solution of Int54 (200 mg) and TEA (0.24 mL) in DCM (6 mL) at 0°C. The reaction was allowed to stir at RT for 1 h. The mixture was diluted with DCM and washed with H₂O and brine. Organic phase was dried over Na₂SO₄, filtered, and concentrated under vacuum. The crude obtained was purified by chromatography on a silica gel cartridge (eluent = from 0% to 10% of MeOH in DCM) to provide Example 45 (6 mg).

LC-MS (ESI): m/z (M+1): 1282.0, Rt= 2.72 min. (Method 3). ¹H NMR (600 MHz, DMSO-d₆) δ ppm 9.59 (br s, 2 H), 8.78 (s, 2 H), 7.91 (d, J=9.6 Hz, 2 H), 7.75 (d, J=5.6 Hz, 2 H), 7.64 - 7.73 (m, 4 H), 7.49 (d, J=5.6 Hz, 2 H), 7.31 (t, J=7.9 Hz, 2 H), 6.90 - 7.06 (m, 6 H), 6.45 (d, J=9.6 Hz, 2 H), 6.09 - 6.42 (m, 4 H), 4.16 (br t, J=5.4 Hz, 4 H), 3.64 - 4.40 (m, 4 H), 3.33 - 3.71 (m, 8 H), 3.30 (br d, J=3.0 Hz, 4 H), 3.04 - 3.60 (m, 8 H), 2.94 - 3.18 (m, 4 H), 2.77 (td, J=10.5, 4.1 Hz, 2 H), 1.70 - 2.02 (m, 12 H), 1.46 - 1.67 (m, 4 H).

[0190] Example 46:

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-3-{1-[4-(4-{3-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-3-oxopropyl}piperidin-1-yl)-1,3,5-triazin-2-yl]piperidin-4-yl}propanoate

[Chem.83]



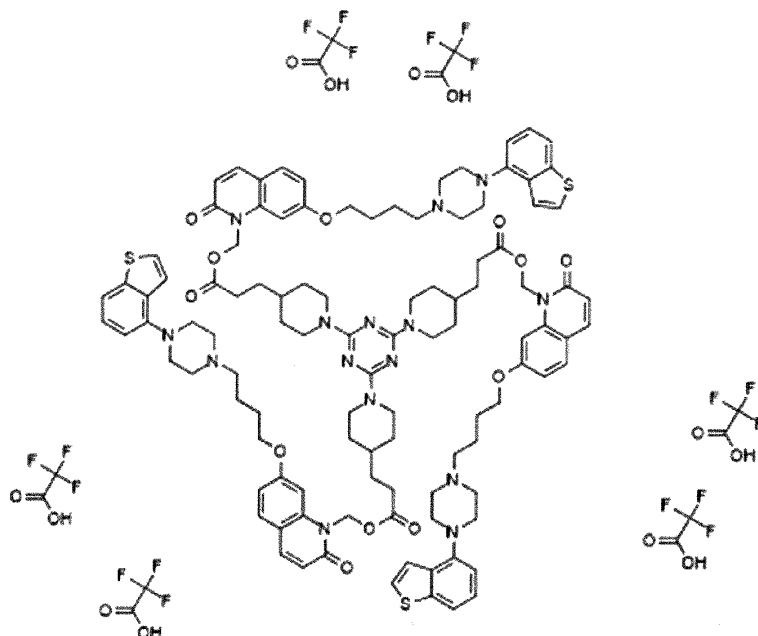
DIPEA (32 mg) was added to a solution of 2,4-dichloro-1,3,5-triazine (6.2 mg) and Int57 (49 mg) in DMF (1.2 mL). The reaction was stirred at RT 16 h. The mixture was diluted with EtOAc and washed with H₂O (2x) and brine (2x). The organic phase was dried over Na₂SO₄, filtered, and evaporated under vacuum. The crude obtained was purified by chromatography on a silica gel cartridge (eluent = from 0% to 10% of MeOH in DCM) followed by chromatography on a C-18 cartridge (eluent = from 5% to 50% of MeCN in 0.1% of HCOOH in H₂O). The product obtained was diluted with DCM and desalted with an excess of K₂CO₃. After 10 minutes of stirring the solid was filtered off and the solution was concentrated in vacuum, to afford Example 46 (17 mg).

LC-MS (ESI): m/z (M+1): 1293.0, Rt= 1.98 min. (Method 3). ¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.13 (s, 1 H), 7.63 (d, J=9.5 Hz, 2 H), 7.55 (d, J=8.0 Hz, 2 H), 7.46 (d, J=8.7 Hz, 2 H), 7.36 - 7.43 (m, 4 H), 7.23 - 7.32 (m, 2 H), 6.82 - 6.92 (m, 6 H), 6.53 (d, J=9.4 Hz, 2 H), 6.35 (br s, 4 H), 4.67 (br d, J=13.4 Hz, 4 H), 4.09 (t, J=6.1 Hz, 4 H), 3.20 (br s, 8 H), 2.72 (br s, 8 H), 2.61 - 2.70 (m, 4 H), 2.54 (t, J=7.4 Hz, 4 H), 2.41 (t, J=7.6 Hz, 4 H), 1.86 - 1.96 (m, 4 H), 1.72 - 1.82 (m, 4 H), 1.63 - 1.71 (m, 4 H), 1.42 - 1.64 (m, 6 H), 1.00 - 1.15 (m, 4 H).

[0191] Example 47:

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-3-{1-[4,6-bis(4-{3-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-3-oxopropyl}piperidin-1-yl)-1,3,5-triazin-2-y

1]piperidin-4-yl}propanoate hexakis(trifluoroacetic acid) salt
[Chem.84]



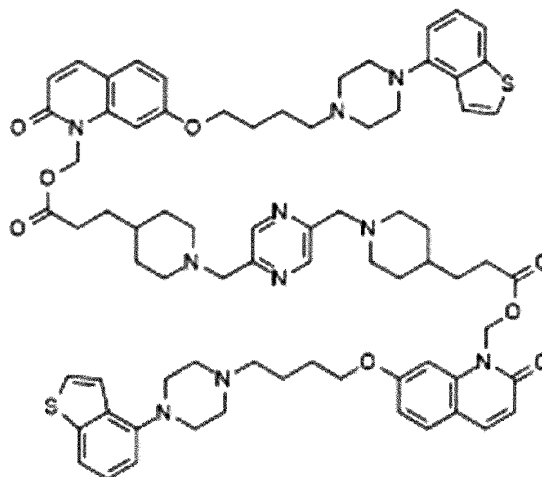
DIPEA (0.12 mL) was added to a solution of Int57 (199 mg) and 2,4,6-trichloro-1,3,5-triazine (20 mg) in DMF (4 mL) and the reaction was stirred at 60°C for 16 h. The mixture was cooled to RT, diluted with EtOAc and washed with H₂O (2x) and BRINE (2x). The organic phase was dried over Na₂SO₄, filtered, and concentrated under vacuum. The crude obtained was purified by chromatography on a silica gel cartridge (eluent = from 0% to 10% MeOH in DCM). The product was further purified by chromatography on a C-18 cartridge (eluent = from 5% to 50% of MeCN in 0.1% of HCOOH in H₂O), to Example 47 (51 mg).

LC-MS (ESI): m/z (M+1): 1885, Rt= 2.22 min. (Method 3). ¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 10.92 - 13.62 (m, 3 H), 7.64 (dd, J=8.9, 5.4 Hz, 6 H), 7.42 - 7.51 (m, 6 H), 7.28 - 7.34 (m, 6 H), 6.94 (d, J=7.5 Hz, 3 H), 6.90 (s, 3 H), 6.84 (br d, J=8.6 Hz, 3 H), 6.54 (d, J=9.6 Hz, 3 H), 6.35 (br s, 6 H), 4.46 (br d, J=12.7 Hz, 6 H), 4.08 (br t, J=5.6 Hz, 6 H), 3.79 (br d, J=11.0 Hz, 6 H), 3.47 - 3.61 (m, 6 H), 3.34 - 3.45 (m, 6 H), 3.07 - 3.30 (m, 12 H), 2.75 (br t, J=12.5 Hz, 6 H), 2.38 (br t, J=7.3 Hz, 6 H), 2.01 - 2.18 (m, 6 H), 1.64 - 1.99 (m, 12 H), 1.35 - 1.63 (m, 9 H), 1.09 (q, J=11.0 Hz, 6 H).

[0192] Example 48:

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-3-[1-({5-[4-{3-[7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-ox

o-1,2-dihydroquinolin-1-yl)methoxy]-3-oxopropyl}piperidin-1-yl)methyl]pyrazin-2-yl
 }methyl)piperidin-4-yl]propanoate
 [Chem.85]



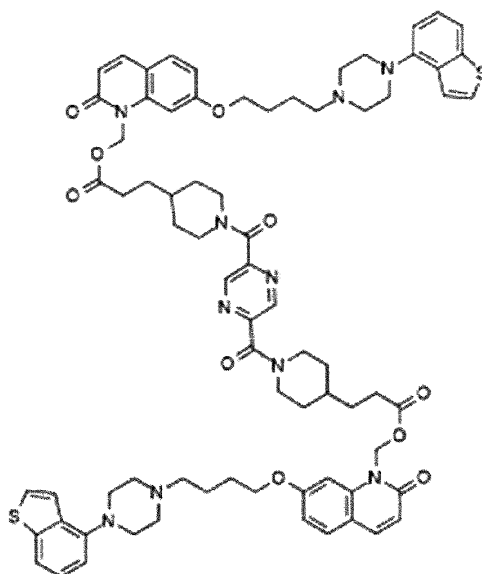
Example 48 was prepared following the procedure described for Example 46, starting from Int57 (150 mg) and 2,5-bis(bromomethyl)pyrazine (33 mg). The crude obtained was purified by chromatography on a silica gel cartridge (eluent = from 0% to 4% MeOH in DCM), to afford Example 48 (15 mg).

LC-MS (ESI): m/z (M+1): 1309, Rt= 1.77 min. (Method 3). ¹H NMR (500 MHz, CHLOROFORM-d) δ ppm 8.54 (s, 2 H), 7.63 (d, J=9.5 Hz, 2 H), 7.55 (d, J=8.2 Hz, 2 H), 7.46 (d, J=8.6 Hz, 2 H), 7.37 - 7.43 (m, 4 H), 7.23 - 7.31 (m, 2 H), 6.87 - 6.92 (m, 4 H), 6.85 (dd, J=8.5, 2.1 Hz, 2 H), 6.52 (d, J=9.5 Hz, 2 H), 6.34 (br s, 4 H), 4.09 (t, J=6.2 Hz, 4 H), 3.59 (s, 4 H), 3.01 - 3.36 (m, 8 H), 2.79 - 2.87 (m, 4 H), 2.62 - 2.79 (m, 8 H), 2.54 (br t, J=7.2 Hz, 4 H), 2.38 (t, J=7.8 Hz, 4 H), 1.87 - 2.01 (m, 8 H), 1.73 - 1.83 (m, 4 H), 1.46 - 1.64 (m, 8 H), 1.17 - 1.29 (m, 6 H).

[0193] Example 49:

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-3-{1-[5-(4-{3-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-3-oxopropyl}piperidine-1-carbonyl)pyrazine-2-carbonyl]piperidin-4-yl}propanoate

[Chem.86]



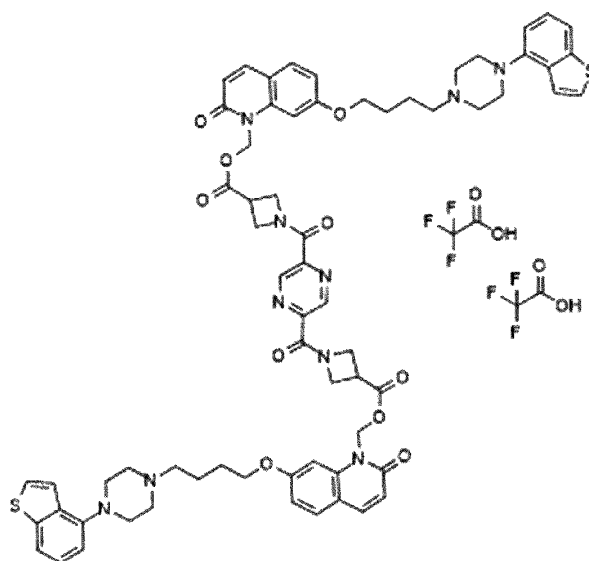
Pyrazine-2,5-dicarbonyl dichloride (43 mg) was added to a solution of Int57 (250 mg) and TEA (0.58 mL) in DMF (8 mL) at 0°C. The reaction was stirred at RT for 16 h. The reaction mixture was diluted with EtOAc and washed with H₂O and brine (2 x). The organic phase was dried over Na₂SO₄, filtered, and concentrated under vacuum. The crude obtained was purified by chromatography on a silica gel cartridge (eluent = from 0% to 10% MeOH in DCM), to afford Example 49 (35 mg)

LC-MS (ESI): m/z (M+1): 1338, Rt= 2.11 min. (Method 3). ¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.79 (s, 2 H), 7.64 (d, J=9.4 Hz, 2 H), 7.55 (d, J=7.9 Hz, 2 H), 7.47 (d, J=8.6 Hz, 2 H), 7.37 - 7.44 (m, 4 H), 7.20 - 7.31 (m, 2 H), 6.82 - 6.93 (m, 6 H), 6.53 (d, J=9.4 Hz, 2 H), 6.35 (br s, 4 H), 4.10 (t, J=6.2 Hz, 4 H), 3.73 - 4.80 (m, 4 H), 3.20 (br s, 8 H), 2.74 (br s, 8 H), 2.64 - 3.05 (m, 4 H), 2.55 (t, J=7.5 Hz, 4 H), 2.42 (t, J=7.5 Hz, 4 H), 1.86 - 1.98 (m, 4 H), 1.11 - 1.85 (m, 18 H).

[0194] Example 50:

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-1-[5-(3-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}azetidine-1-carbonyl)pyrazine-2-carbonyl]azetidine-3-carboxylate bis(trifluoroacetic acid) salt

[Chem.87]



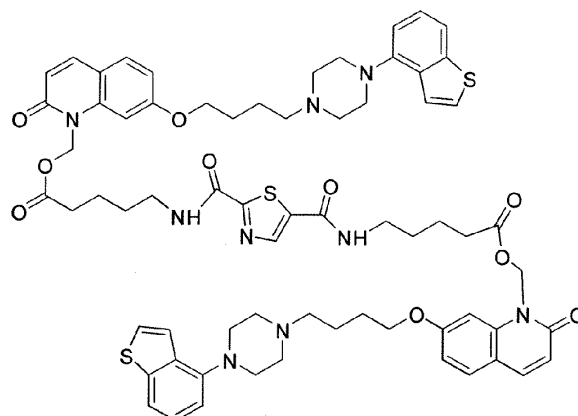
Example 50 was prepared following the procedure described for Example 49, starting from Int60 (350 mg) and pyrazine-2,5-dicarbonyl dichloride (66 mg), to afford Example 50 (8.2 mg).

LC-MS (ESI): m/z ($M+1$): 1225.9, R_t = 2.64 min. (Method 3). ^1H NMR (400 MHz, CHLOROFORM-d) δ ppm 11.32 - 13.18 (m, 3 H), 9.13 - 9.17 (m, 2 H), 7.59 - 7.73 (m, 4 H), 7.41 - 7.52 (m, 4 H), 7.27 - 7.36 (m, 4 H), 6.95 (dd, $J=7.6, 3.0$ Hz, 2 H), 6.89 (br d, $J=4.6$ Hz, 2 H), 6.85 (br d, $J=8.6$ Hz, 2 H), 6.56 (d, $J=9.4$ Hz, 2 H), 6.34 - 6.51 (m, 4 H), 4.85 (br d, $J=7.0$ Hz, 4 H), 4.33 - 4.46 (m, 4 H), 4.09 (br t, $J=5.5$ Hz, 4 H), 3.83 (br d, $J=10.7$ Hz, 4 H), 3.48 - 3.68 (m, 6 H), 3.40 (br t, $J=12.3$ Hz, 4 H), 3.09 - 3.32 (m, 8 H), 1.80 - 2.11 (m, 8 H).

[0195] Example 51:

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-5-({5-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-5-oxopentyl}carbonyl)-1,3-thiazol-2-yl]formamido} pentanoate

[Chem.88]



Step A: TFA (1.12 mL) was added dropwise to a solution of Int62 (0.68 g) in DCM (10 mL) at RT. The reaction was stirred at RT for 4 h. Toluene (20 mL) was added, and volatiles were evaporated under vacuum. The residue was dissolved in THF (10 mL), Toluene (20 mL) at RT and HCl 4M in 1,4-dioxane (1.2 mL) was added dropwise. After 10 minutes of stirring, the mixture was concentrated under vacuum, to afford Example 51-Step A:

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 5-aminopentanoate dihydrochloride salt (658 mg, quant. yield).

Step B: 1,3-thiazole-2,5-dicarbonyl dichloride (33 mg) was added to a solution of crude

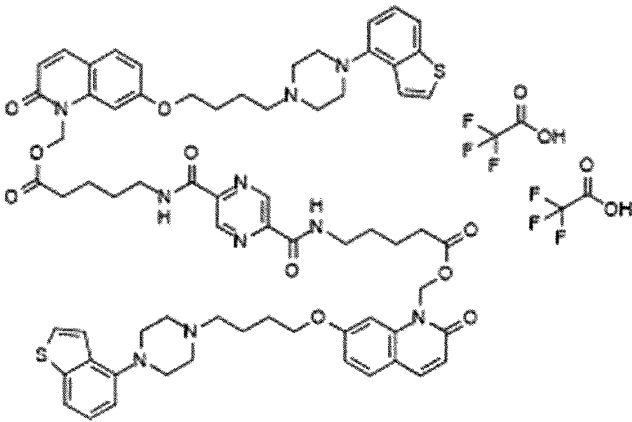
(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl 5-aminopentanoate dihydrochloride salt (0.20 g) in DMF (6 mL) at RT, followed by TEA (0.6 mL). The reaction was stirred at 100 °C for 3 h. The reaction was cooled down to RT, diluted with cold NH₄Cl s.s. and extracted with DCM (2 x). Combined organic layers were dried over a phase separator and concentrated under vacuum. The crude obtained was purified by chromatography on a C-18 cartridge (eluent = from 0% to 100% MeCN in 0.1% TFA in H₂O) followed by chromatography on a silica gel cartridge (eluent = from 0% to 10% MeOH in DCM), to afford Example 51 (3.3 mg)

LC-MS (ESI): m/z (M+1): 1257.7, Rt= 2.09 min. (Method 3).

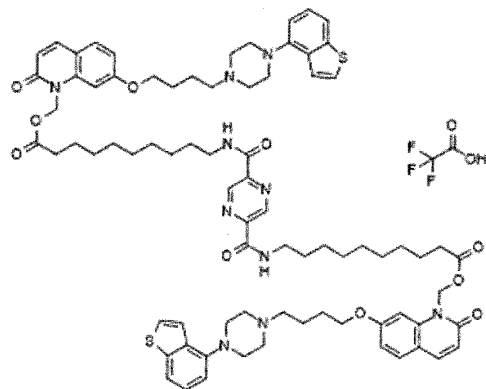
¹H NMR (500 MHz, CHLOROFORM-d) δ ppm 8.23 (s, 1 H), 7.61 - 7.69 (m, 2 H), 7.52 - 7.58 (m, 2 H), 7.44 - 7.50 (m, 2 H), 7.36 - 7.43 (m, 4 H), 7.32 (t, J=6.0 Hz, 1 H), 7.23 - 7.29 (m, 2 H), 6.83 - 6.93 (m, 6 H), 6.61 (br s, 1 H), 6.47 - 6.55 (m, 2 H), 6.23 - 6.39 (m, 4 H), 4.04 - 4.15 (m, 4 H), 3.37 - 3.49 (m, 4 H), 3.19 (br s, 8 H), 2.73 (br s, 8 H), 2.49 - 2.59 (m, 4 H), 2.40 - 2.48 (m, 4 H), 1.86 - 1.95 (m, 4 H), 1.71 - 1.81 (m, 8 H), 1.63 - 1.70 (m, 4 H)

[0196] Examples 52 and 53 were prepared following the procedure described for Example 51. The reactants used in the synthesis of each compound as well as their characterization are tabulated in Table 9.

[Table 9]

Table 9	
Example 52 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-5-[[5-({5-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-5-oxopentyl}carbamoyl)pyrazin-2-yl]formamido}pentanoate bis(trifluoroacetic acid) salt	
	
Reactants	
Example 51 -Step A (0.20 g)	pyrazine-2,5-dicarbonyl dichloride (32 mg)
LC-MS Method 3	LC-MS (ESI): m/z (M^{+1}): 1257.7, Rt= 2.09 min
^1H NMR (600 MHz, CHLOROFORM- <i>d</i>)	δ ppm 12.50 - 13.19 (m, 2 H), 9.24 (s, 2 H), 7.89 (t, $J=6.1$ Hz, 2 H), 7.62 - 7.67 (m, 4 H), 7.43 - 7.50 (m, 4 H), 7.28 - 7.33 (m, 4 H), 6.96 (d, $J=7.6$ Hz, 2 H), 6.89 (d, $J=2.0$ Hz, 2 H), 6.82 (dd, $J=8.7, 2.1$ Hz, 2 H), 6.55 (d, $J=9.6$ Hz, 2 H), 6.34 (br s, 4 H), 4.09 (t, $J=5.8$ Hz, 4 H), 3.84 (br d, $J=11.5$ Hz, 4 H), 3.55 (br d, $J=13.5$ Hz, 4 H), 3.48 (q, $J=6.6$ Hz, 4 H), 3.42 (br t, $J=12.0$ Hz, 4 H), 3.24 - 3.30 (m, 4 H), 3.19 (br t, $J=10.9$ Hz, 4 H), 2.45 (t, $J=7.2$ Hz, 4 H), 2.05 - 2.14 (m, 4 H), 1.90 - 2.00 (m, 4 H), 1.72 - 1.78 (m, 4 H), 1.64 - 1.71 (m, 4 H)
Yield	7 mg
Example 53	

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-10-[(5-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-10-oxodecyl)carbamoyl]pyrazin-2-yl]formamido}decanoate trifluoroacetic acid salt



Reactants

Int65

(0.10 g)

pyrazine-2,5-dicarbonyl dichloride

(11 mg)

LC-MS Method 3

LC-MS (ESI): m/z (M^{-1}): 1397.9, R_t = 2.53 min

1H NMR (400 MHz, CHLOROFORM- d)

δ ppm 9.29 - 9.32 (m, 2 H), 7.86 (br t, J =5.8 Hz, 2 H), 7.61 - 7.67 (m, 4 H), 7.42 - 7.49 (m, 4 H), 7.28 - 7.36 (m, 4 H), 6.96 (d, J =7.5 Hz, 2 H), 6.90 (s, 2 H), 6.83 (dd, J =8.6, 2.0 Hz, 2 H), 6.54 (d, J =9.4 Hz, 2 H), 6.34 (s, 4 H), 4.09 (t, J =5.6 Hz, 4 H), 3.01 - 4.00 (m, 22 H), 2.37 (t, J =7.6 Hz, 2 H), 1.88 - 2.19 (m, 8 H), 1.30 - 1.84 (m, 32 H)

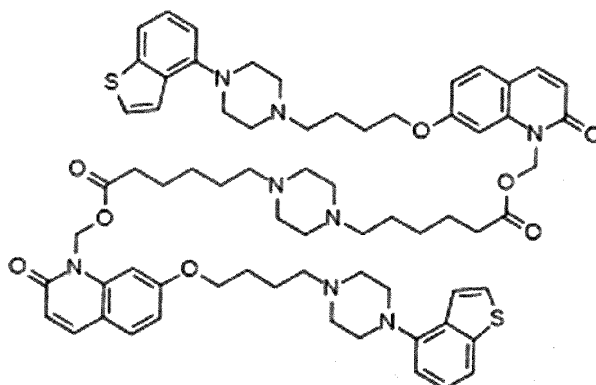
Yield

35 mg

[0197] Example 54:

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-6-(4-{6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexyl}piperazin-1-yl)hexanoate

[Chem.89]



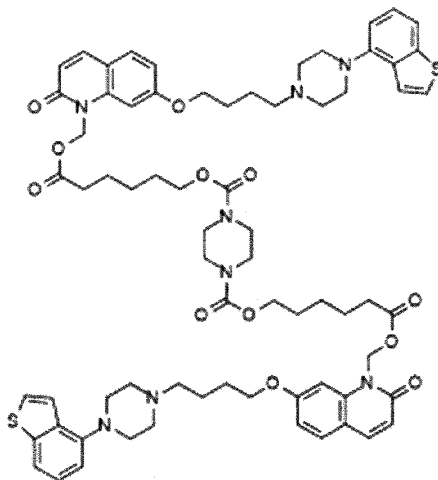
TEA (0.04 mL) and piperazine (9 mg) were added to a suspension of Int69 (140 mg) in DMF (1 mL). The mixture was stirred at 100°C for 5 h. The solution was cooled down to RT, diluted with EtOA and washed with H₂O (x2) and brine. The organic phase was dried over Na₂SO₄, filtered, and concentrated under vacuum. The crude obtained was purified by chromatography on a silica gel cartridge (eluent = from 0% to 10% MeOH in DCM), to afford Example 54 (40 mg)

LC-MS (ESI): m/z (M+1): 1207.0, Rt= 1.78 min. (Method 3). ¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.63 (d, J=9.5 Hz, 2 H), 7.55 (d, J=7.9 Hz, 2 H), 7.45 (d, J=8.4 Hz, 2 H), 7.37 - 7.43 (m, 4 H), 7.23 - 7.32 (m, 2 H), 6.80 - 6.93 (m, 6 H), 6.52 (d, J=9.5 Hz, 2 H), 6.34 (s, 4 H), 4.09 (t, J=6.2 Hz, 4 H), 3.20 (br s, 8 H), 2.65 - 2.91 (m, 8 H), 2.51 - 2.59 (m, 4 H), 2.34 - 2.40 (m, 4 H), 2.20 - 2.29 (m, 4 H), 2.16 - 2.64 (m, 8 H), 1.85 - 1.96 (m, 4 H), 1.73 - 1.82 (m, 4 H), 1.55 - 1.71 (m, 4 H), 1.40 - 1.50 (m, 4 H), 1.27 - 1.35 (m, 4 H).

[0198] Example 55:

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-6-{4-[(6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexyl}oxy)carbonyl]piperazine-1-carboxyloxy}hexanoate

[Chem.90]

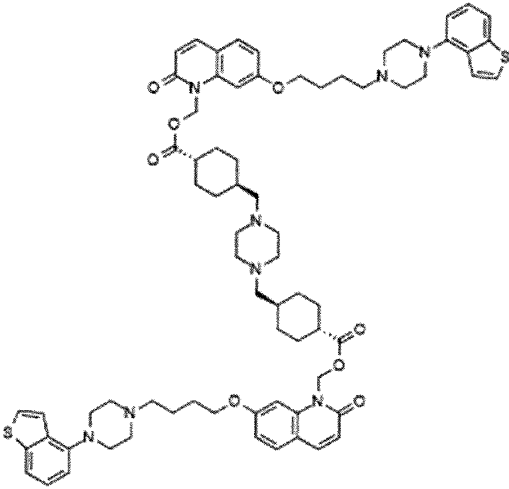


DIPEA (0.02 mL) was added to a solution of Int70 (20 mg) in DCM (1 mL) at 0°C, followed by piperazine (0.9 mg). The reaction was stirred at RT for 6 h. The reaction mixture was diluted with DCM and washed with Na₂CO₃ (2x). The organic phase was filtered over a phase separator and concentrated under vacuum. The crude obtained was purified by chromatography on a silica gel cartridge (eluent = from 0% to 10% MeOH in DCM), affording Example 55 (7 mg).

LC-MS (ESI): m/z (M+1): 1293.7, Rt= 2.23 min. (Method 3). ¹H NMR (600 MHz, CHLOROFORM-d) δ ppm 7.61 (d, J=9.6 Hz, 2 H), 7.54 (d, J=8.1 Hz, 2 H), 7.44 (d, J=8.6 Hz, 2 H), 7.39 - 7.41 (m, 2 H), 7.36 - 7.38 (m, 2 H), 7.25 - 7.28 (m, 2 H), 6.88 (d, J=7.6 Hz, 2 H), 6.86 (d, J=2.0 Hz, 2 H), 6.83 (dd, J=8.6, 2.1 Hz, 2 H), 6.50 (d, J=9.6 Hz, 2 H), 6.31 (br s, 4 H), 4.07 (t, J=6.3 Hz, 4 H), 4.03 (t, J=6.7 Hz, 4 H), 3.40 (br s, 8 H), 3.18 (br s, 8 H), 2.71 (br s, 8 H), 2.53 (br t, J=7.3 Hz, 4 H), 2.36 (t, J=7.5 Hz, 4 H), 1.85 - 1.94 (m, 4 H), 1.72 - 1.79 (m, 4 H), 1.66 (quin, J=7.7 Hz, 4 H), 1.58 - 1.64 (m, 4 H), 1.32 - 1.40 (m, 4 H).

[0199] Example 56 was prepared following the procedure described for Example 54. The reactants used in the synthesis of Example 56 as well as its characterization are tabulated in Table 10.

[Table 10]

Table 10	
Example 56 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-(1r,4r)-4-[(4-{[(1r,4r)-4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy[carbonyl]cyclohexyl)methyl]piperazin-1-yl)methyl]cyclohexane-1-carboxylate	
	
Reactants	
Int74 (136 mg)	piperazine (8.2 mg)
LC-MS Method 3	LC-MS (ESI): m/z (M ⁺): 1258.0, Rt= 1.9 min
¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>)	δ ppm 7.63 (d, J=9.4 Hz, 2 H), 7.55 (d, J=8.1 Hz, 2 H), 7.45 (d, J=9.2 Hz, 2 H), 7.37 - 7.43 (m, 4 H), 7.24 - 7.30 (m, 2 H), 6.90 (d, J=7.5 Hz, 2 H), 6.80 - 6.87 (m, 4 H), 6.53 (d, J=9.4 Hz, 2 H), 6.33 (br s, 4 H), 4.07 (t, J=6.2 Hz, 4 H), 3.20 (br s, 8 H), 2.73 (br s, 8 H), 2.54 (t, J=7.5 Hz, 4 H), 2.22 - 2.40 (m, 8 H), 2.04 (br d, J=7.0 Hz, 4 H), 1.94 - 2.01 (m, 4 H), 1.87 - 1.94 (m, 4 H), 1.72 - 1.87 (m, 8 H), 1.36 - 1.52 (m, 8 H), 0.77 - 0.92 (m, 4 H)
Yield	11 mg

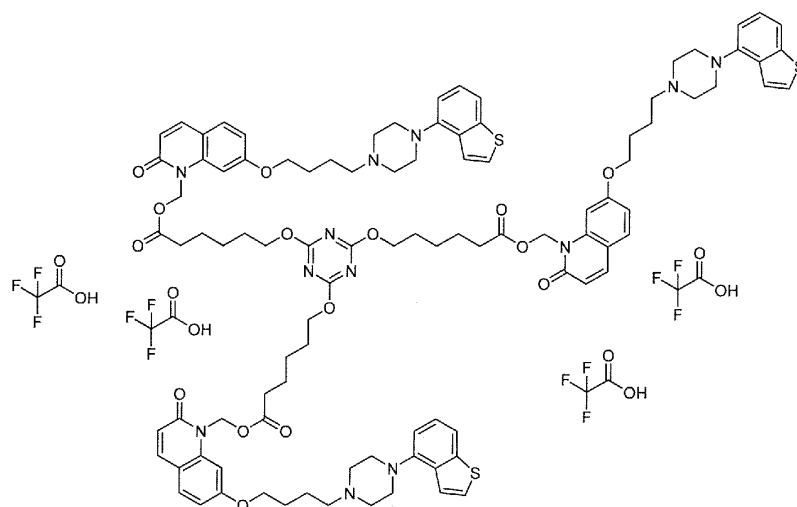
[0200] Example 57:

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-6-[[4,6-bis({6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexyl}oxy)-1,3,5-triazin-2-yl]oxy}hexanoat

e tetrakis(trifluoroacetic acid) salt

DIPEA (0.11 mL) was added dropwise solution of 2,4,6-trichloro-1,3,5-triazine (16 mg) and Int68 (150 mg) in MeCN (1 mL) at 0°C. The reaction was stirred at RT for 5 days. The reaction mixture was diluted with DCM (10 mL) and washed with H₂O (3 mL). The organic phase was dried over a phase separator and concentrate under vacuum. The crude obtained was purified on a silica gel cartridge (eluent = from 0% to 7% of MeOH in DCM) followed by chromatography on a C-18 cartridge (eluent = from 5% to 95% in 0.1% of TFA in H₂O), to afford Example 57 (7 mg).

[Chem.91]



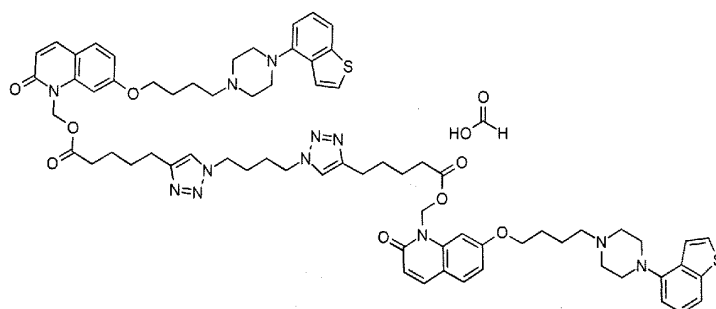
LC-MS (ESI): m/z (M+1): 1808.3, Rt= 2.32 min. (Method 3). ¹H NMR (500 MHz, CHLOROFORM-d) δ ppm 7.61 - 7.65 (m, 6 H), 7.41 - 7.49 (m, 6 H), 7.28 - 7.35 (m, 6 H), 6.94 (d, J=7.5 Hz, 3 H), 6.90 (d, J=1.8 Hz, 3 H), 6.83 (dd, J=8.6, 2.1 Hz, 3 H), 6.54 (d, J=9.5 Hz, 3 H), 6.32 (br s, 6 H), 4.30 (br t, J=6.6 Hz, 6 H), 4.06 - 4.13 (m, 6 H), 3.83 (br d, J=11.4 Hz, 6 H), 3.55 (br d, J=12.5 Hz, 6 H), 3.40 (br t, J=12.3 Hz, 6 H), 3.24 - 3.33 (m, 6 H), 3.19 (br t, J=10.4 Hz, 6 H), 2.37 (br t, J=7.5 Hz, 6 H), 2.06 - 2.13 (m, 6 H), 1.95 (br dd, J=13.0, 6.2 Hz, 6 H), 1.70 - 1.77 (m, 6 H), 1.67 (dt, J=15.3, 7.7 Hz, 6 H), 1.36 - 1.50 (m, 6 H).

[0201] Example 58:

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl

5-{1-[4-(4-{5-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-5-oxopentyl}-1H-1,2,3-triazol-1-yl)butyl]-1H-1,2,3-triazol-4-yl}pentanoate formic acid salt

[Chem.92]

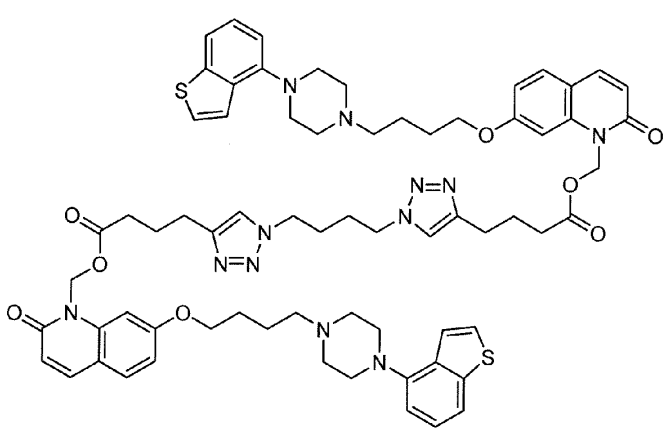


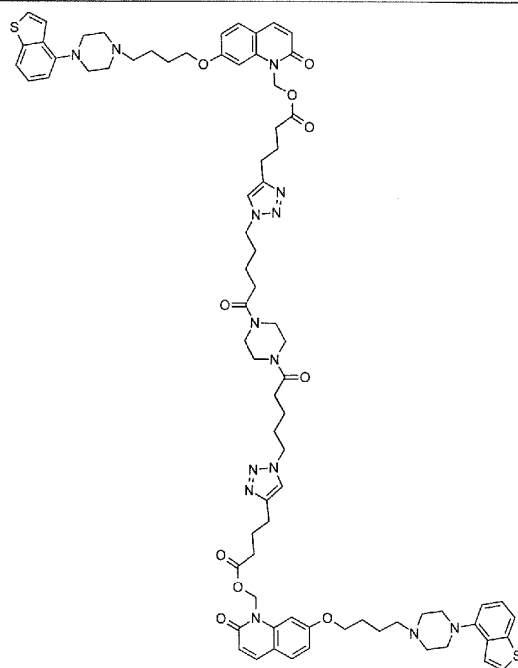
DIPEA (0.04 mL) and CuI (48 mg) were dissolved in degassed DMF (1.5 mL). Then, Int76 (357 mg) and 1,4-diazidobutane (35.0 mg) were added at RT and the reaction was stirred at 40°C overnight. The reaction mixture was cooled down to RT and directly purified by chromatography on a C18-cartridge (eluent = 3% to 40% of MeCN in 0.1% of HCOOH in H₂O), to give Example 58 (24 mg).

LC-MS (ESI): *m/z* (*M*/2+*H*): 642.6, *R*_t= 1.93 min. (Method 4). ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.88 (d, *J*=9.6 Hz, 2 H), 7.71 (s, 2 H), 7.67 (d, *J*=5.5 Hz, 2 H), 7.65 (d, *J*=8.6 Hz, 2 H), 7.59 (d, *J*=8.0 Hz, 2 H), 7.37 (d, *J*=5.4 Hz, 2 H), 7.25 (t, *J*=7.9 Hz, 2 H), 6.96 (d, *J*=1.8 Hz, 2 H), 6.94 (dd, *J*=8.6, 2.1 Hz, 2 H), 6.85 (d, *J*=7.5 Hz, 2 H), 6.42 (d, *J*=9.5 Hz, 2 H), 6.26 (br s, 4 H), 4.26 (br s, 4 H), 4.11 (t, *J*=6.4 Hz, 4 H), 3.03 (br s, 8 H), 2.59 (br s, 8 H), 2.55 (br t, *J*=6.9 Hz, 4 H), 2.42 (br t, *J*=7.1 Hz, 4 H), 2.33 - 2.37 (m, 4 H), 1.74 - 1.83 (m, 4 H), 1.69 (br s, 4 H), 1.62 (dt, *J*=14.5, 7.2 Hz, 4 H), 1.51 - 1.58 (m, 8 H).

[0202] Examples 59, 60, 61, 62, 63 and 64 were prepared following the procedure described for Example 58. The reactants used in the synthesis of each compound as well as their characterization are tabulated in Table 11.

[Table 11]

Table 11	
Example 59 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-{1-[4-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutyl}-1H-1,2,3-triazol-1-yl)butyl]-1H-1,2,3-triazol-4-yl}butanoate	
	
Reactants	
Int77 (0.30 g)	1,4-diazidobutane (30 mg)
LC-MS Method 3	LC-MS (ESI): <i>m/z</i> (M+H): 1256.8, Rt= 2.04 min
¹ H NMR (500 MHz, CHLOROFORM- <i>d</i>)	δ ppm 7.64 (d, J=9.5 Hz, 2 H), 7.57 (d, J=8.0 Hz, 2 H), 7.46 (d, J=8.6 Hz, 2 H), 7.36 - 7.43 (m, 4 H), 7.22 - 7.29 (m, 4 H), 6.88 - 6.93 (m, 4 H), 6.85 (dd, J=8.6, 2.1 Hz, 2 H), 6.52 (d, J=9.5 Hz, 2 H), 6.33 (br s, 4 H), 4.21 - 4.31 (m, 4 H), 4.03 - 4.13 (m, 4 H), 3.30 (br s, 8 H), 2.89 (br d, J=1.6 Hz, 8 H), 2.57 - 2.77 (m, 8 H), 2.43 (t, J=7.3 Hz, 4 H), 1.99 - 2.09 (m, 4 H), 1.79 - 1.97 (m, 12 H)
Yield	(52 mg).
Example 60 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-[1-(5-{4-[5-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutyl}-1H-1,2,3-triazol-1-yl)pentanoyl]piperazin-1-yl}-5-oxopentyl)-1H-1,2,3-triazol-4-yl]butanoate	



Reactants

Int78

(65 mg)

Int77

(320 mg)

LC-MS Method 4

LC-MS (ESI): m/z (M+H): 1452.0, Rt= 2.38 min¹H NMR (500 MHz, CHLOROFORM-*d*)

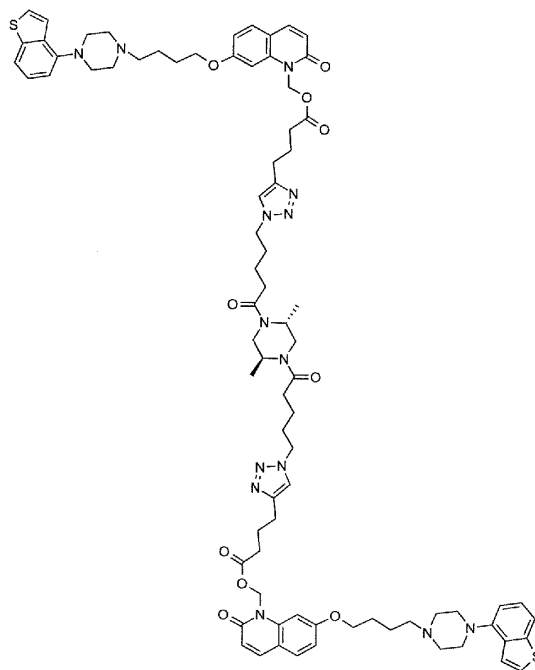
δ ppm 7.89 (d, J=9.6 Hz, 2 H), 7.78 (s, 2 H), 7.68 (d, J=5.5 Hz, 2 H), 7.65 (d, J=8.6 Hz, 2 H), 7.60 (d, J=8.1 Hz, 2 H), 7.38 (d, J=5.5 Hz, 2 H), 7.26 (t, J=7.8 Hz, 2 H), 6.99 (d, J=1.6 Hz, 2 H), 6.94 (dd, J=8.6, 2.1 Hz, 2 H), 6.86 (d, J=7.5 Hz, 2 H), 6.43 (d, J=9.5 Hz, 2 H), 6.27 (br s, 4 H), 4.26 (t, J=7.0 Hz, 4 H), 4.13 (t, J=6.4 Hz, 4 H), 3.31 - 3.53 (m, 8 H), 3.04 (br s, 8 H), 2.55 - 2.65 (m, 12 H), 2.36 - 2.45 (m, 8 H), 2.29 (t, J=7.4 Hz, 4 H), 1.80 - 1.88 (m, 4 H), 1.73 - 1.81 (m, 8 H), 1.62 (quin, J=7.2 Hz, 4 H), 1.41 (quin, J=7.1 Hz, 4 H)

Yield

50 mg

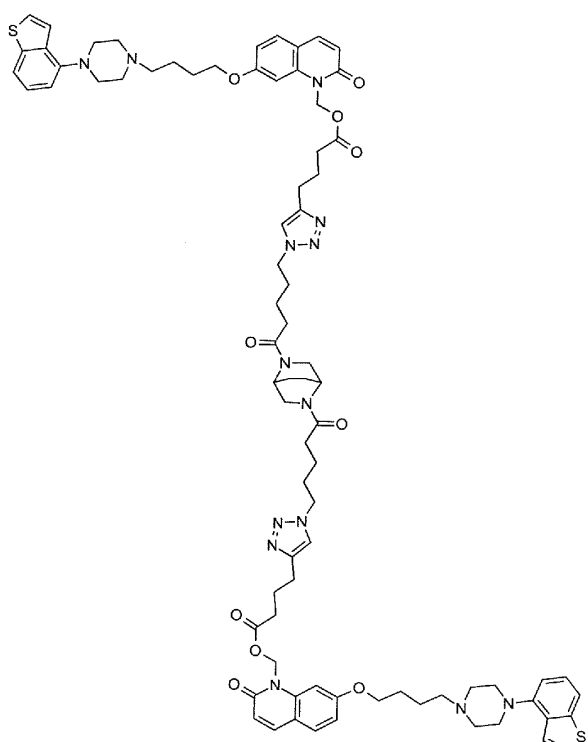
Example 61

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-(1-{5-[(2S,5R)-4-[5-(4-{4-(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutyl}-1H-1,2,3-triazol-1-yl)pentanoyl]-2,5-dimethylpiperazin-1-yl]-5-oxopentyl}-1H-1,2,3-triazol-4-yl)butanoate



Reactants

Int79 (65 mg)	Int77 (300 mg)
LC-MS Method 3	LC-MS (ESI): m/z (M+H): 1480.0, R_t = 2.06 min
^1H NMR (500 MHz, DMSO- d_6)	δ ppm 7.90 (d, J =9.6 Hz, 2 H), 7.81 (s, 2 H), 7.71 - 7.78 (m, 2 H), 7.68 (br d, J =8.5 Hz, 4 H), 7.47 (br d, J =1.0 Hz, 2 H), 7.30 (br t, J =7.7 Hz, 2 H), 6.88 - 7.04 (m, 6 H), 6.44 (d, J =9.5 Hz, 2 H), 6.27 (br s, 4 H), 4.28 (q, J =7.3 Hz, 4 H), 4.12 - 4.22 (m, 4 H), 3.96 - 4.67 (m, 2 H), 2.69 - 4.08 (m, 24 H), 2.59 - 2.67 (m, 4 H), 2.41 (t, J =7.3 Hz, 4 H),

	2.17 - 2.33 (m, 4 H), 1.72 - 1.96 (m, 16 H), 1.32 - 1.51 (m, 4 H), 0.79 - 1.11 (m, 6 H)
Yield	65 mg
Example 62 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-[1-(5-{5-[4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutyl}-1H-1,2,3-triazol-1-yl)pentanoyl]-2,5-diazabicyclo[2.2.2]octan-2-yl}-5-oxopentyl)-1H-1,2,3-triazol-4-yl]butanoate	
	
Reactants	
Int80 (30 mg)	Int77 (139 mg)
LC-MS Method 3	LC-MS (ESI): <i>m/z</i> (M/2+H): 1478.9, <i>Rt</i> = 1.84 min

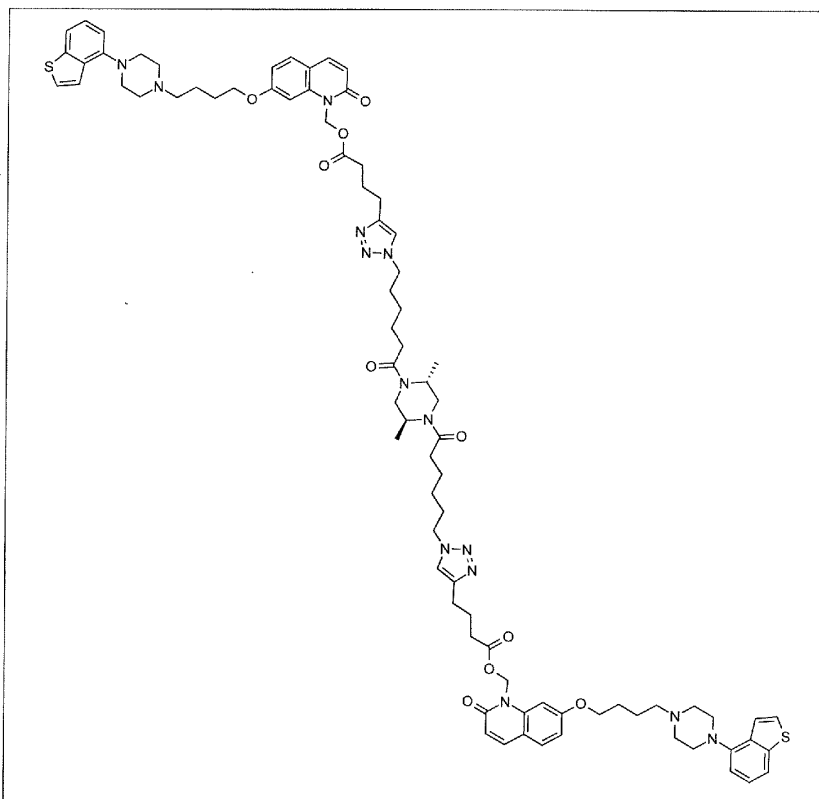
¹ H NMR (500 MHz, CHLOROFORM- <i>d</i>)	δ ppm 7.64 (d, J=9.6 Hz, 2 H), 7.58 (d, J=8.1 Hz, 2 H), 7.47 (d, J=8.5 Hz, 2 H), 7.35 - 7.44 (m, 4 H), 7.27 - 7.32 (m, 4 H), 6.92 (d, J=7.7 Hz, 2 H), 6.90 (d, J=2.1 Hz, 2 H), 6.85 (dd, J=8.6, 2.2 Hz, 2 H), 6.52 (d, J=9.5 Hz, 2 H), 6.33 (br s, 4 H), 4.27 - 4.35 (m, 4 H), 4.10 (br t, J=5.4 Hz, 4 H), 3.98 - 4.86 (m, 2 H), 3.42 - 3.69 (m, 4 H), 3.26 - 3.37 (m, 8 H), 2.94 - 3.13 (m, 8 H), 2.68 - 2.86 (m, 8 H), 2.14 - 2.63 (m, 8 H), 2.03 (quin, J=7.4 Hz, 4 H), 1.01 - 1.97 (m, 20 H)
Yield	50 mg

Example 63

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-[1-(6-{4-[6-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutyl]-1H-1,2,3-triazol-1-yl)hexanoyl]piperazin-1-yl}-6-oxohexyl)-1H-1,2,3-triazol-4-yl]butanoate

Reactants

Int81 (150 mg)	Int77 (690 mg)
LC-MS Method 3	LC-MS (ESI): <i>m/z</i> (M+H): 1480.9, Rt= 2.05 min
¹ H NMR (500 MHz, CHLOROFORM- <i>d</i>)	δ ppm 7.57 - 7.67 (m, 4 H), 7.47 (d, J=8.6 Hz, 2 H), 7.43 (d, J=5.4 Hz, 2 H), 7.32 - 7.39 (m, 2 H), 7.28 - 7.31 (m, 4 H), 6.97 (br d, J=7.0 Hz, 2 H), 6.90 (d, J=1.8 Hz, 2 H), 6.84 (dd, J=8.6, 2.1 Hz, 2 H), 6.53 (d, J=9.6 Hz, 2 H), 6.34 (br s, 4 H), 4.29 (t, J=7.1 Hz, 4 H), 4.12 (br t, J=5.6 Hz, 4 H), 3.35 - 3.63 (m, 8 H), 2.88 - 3.94 (m, 20 H), 2.75 (t, J=7.4 Hz, 4 H), 2.41 - 2.51 (m, 4 H), 2.30 (br t, J=7.3 Hz, 4 H), 2.04 (quin, J=7.4 Hz, 4 H), 1.96 (br s, 4 H), 1.89 (dt, J=15.0, 7.4 Hz, 4 H), 1.42 - 1.78 (m, 4 H), 1.16 - 1.40 (m, 8 H)
Yield	198 mg
Example 64 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-(1-{6-[(2S,5R)-4-[6-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutyl}-1H-1,2,3-triazol-1-yl)hexanoyl]-2,5-dimethylpiperazin-1-yl]-6-oxohexyl}-1H-1,2,3-triazol-4-yl)butanoate	



Reactants	
Int82 (35 mg)	Int77 (58 mg)
LC-MS Method 3	LC-MS (ESI): <i>m/z</i> (M+H): 1507.8, <i>Rt</i> = 2.15 min
¹ H NMR (500 MHz, CHLOROFORM- <i>d</i>)	δ ppm 7.61 - 7.69 (m, 4 H), 7.42 - 7.51 (m, 4 H), 7.28 - 7.35 (m, 6 H), 6.98 (dd, <i>J</i> =7.6, 4.2 Hz, 2 H), 6.90 (d, <i>J</i> =2.1 Hz, 2 H), 6.81 - 6.87 (m, 2 H), 6.53 (dd, <i>J</i> =9.5, 2.3 Hz, 2 H), 6.34 (br s, 4 H), 4.22 - 4.34 (m, 4 H), 4.13 (t, <i>J</i> =5.9 Hz, 4 H), 3.95 - 4.93 (m, 2 H), 3.12 - 3.32 (m, 4 H), 3.09 - 3.88 (m, 16 H), 2.83 - 4.39 (m, 4 H), 2.76 (br t, <i>J</i> =7.5 Hz, 4 H), 2.46 (t, <i>J</i> =7.3 Hz, 4 H), 2.13 - 2.38 (m, 8 H), 1.94 - 2.08 (m, 8 H), 1.84 - 1.93 (m, 4 H), 1.62 - 1.72 (m, 4 H), 1.28 - 1.39 (m, 4 H), 1.02 - 1.25 (m, 6 H)
	- 1.25 (m, 6 H)
Yield	36 mg

[0203] Preparation of Crystalline Forms

Instruments used herein are shown as follows:

XRPD: Empyrean, Malvern Panalytical

DSC: DSC Q2000 V24.11 Build 124, TA Instruments

TGA: TGA Q5000 V3.17 Build 265, TA Instruments

(1) The reference of Form A of a compound of Example 10 was prepared according to the following procedure:

A compound of Example 10 (48.0 mg, 0.040 mmol) was suspended in 2-propanol (2 mL). The suspension was warmed to 50°C and DCM was added at the same temperature. The suspension turns from pale pink wax to white solid. The solvent was concentrated in vacuo. A portion of white solid was recovered.

The solid was suspended in 2-propanol (2 mL). The suspension was warmed to 50°C and DCM (0.9 mL) was added at the same temperature. The suspension turns from pale pink wax to white solid and then to clear solution. At the end of DCM addition, opaque solution was observed and the heating was turned off; the suspension was left to reach room temperature over-weekend (in the heating mantle without stirring). A compound of Example 10 (48.0 mg, 0.040 mmol) was recovered by filtration and washed with cold IPA.

The characteristic XRPD peaks of Form A of a compound of Example 10 are shown as follows.

[Table 12]

Pos. [°2θ]	Height [cts]	FWHM Left [°2θ]	d-spacing [Å]	Rel. Int. [%]
5.3762	810.39	0.0669	16.43823	24.56
9.7057	2317.10	0.1338	9.11309	70.23
11.8073	270.30	0.0669	7.49530	8.19
12.1439	1079.27	0.0836	7.28831	32.71
12.5501	669.10	0.1171	7.05332	20.28
13.7226	528.33	0.0836	6.45319	16.01
14.3075	763.40	0.1004	6.19067	23.14
15.0465	391.36	0.0836	5.88823	11.86
16.2167	1733.96	0.1004	5.46588	52.56
16.7445	1519.95	0.1004	5.29475	46.07
20.5284	2537.92	0.0900	4.32297	76.93
21.2436	3299.15	0.1171	4.18247	100.00
21.7222	2251.56	0.1171	4.09141	68.25
23.7331	1661.70	0.1338	3.74910	50.37
27.5689	1376.47	0.1506	3.23556	41.72

The XRPD pattern of Form A is shown in Figure 1. Form A features at least one, two, three, four, five, or six XRPD peaks (°2θ) selected from about 5.4±0.2, 9.7±0.2, 11.8±0.2, 12.1±0.2, 12.6±0.2, 13.7±0.2, 14.3±0.2, 15.0±0.2, 16.2±0.2, 16.7±0.2, 20.5±0.2, 21.2±0.2, 21.7±0.2, 23.7±0.2, and 27.6±0.2.

DSC trace showed one endothermic event at 176°C attributable to the melt of Form A as shown in Figure 2. Form A has a DSC thermogram characterized by an endothermic peak at about 176±3°C.

[0204] (2) A compound of Example 10 (50 mg) was suspended in DMSO (20 vol). The system was heated to 75°C (temperature of the heating plate); dissolution was reached

around 70-71°C. The solution was cooled to 50°C, then seeded with a seed crystal of Form B (ca. 4-5 mg); the seed appeared persistent and the system was aged for ca. 10 minutes. Heating was turned off and the suspension was allowed to cool down to room temperature and left aging under stirring for the night. The following day the solid was isolated by filtration, deliquored in vacuum, then dried in vacuum oven at reduced pressure at 50°C for the night.

Output material: 44.1 mg (88%w/w uncorrected recovery)

The characteristic XRPD peaks of Form B are shown as follows.

[Table 13]

Pos. [°2θ]	Height [cts]	FWHM Left [°2θ]	d-spacing [Å]	Rel. Int. [%]
7.5407	316.11	0.1171	11.72396	6.11
8.8380	81.95	0.1004	10.00570	1.58
10.1029	176.66	0.1004	8.75562	3.41
11.0658	734.45	0.1338	7.99586	14.19
11.5450	1427.55	0.1171	7.66502	27.57
11.8612	474.30	0.1004	7.46137	9.16
12.5084	1485.38	0.1004	7.07671	28.69
15.4523	2327.94	0.0836	5.73451	44.96
15.6537	3740.39	0.1171	5.66118	72.24
16.4009	1626.02	0.1506	5.40490	31.41
17.3506	5177.53	0.1506	5.11113	100.00
18.4362	1623.43	0.1506	4.81254	31.36
19.8556	2076.67	0.1673	4.47160	40.11
21.0478	2018.21	0.1673	4.22094	38.98
21.9873	1825.51	0.1673	4.04266	35.26

The XRPD pattern of Form B is shown in Figure 3. Form B features at least one, two, three, four, five, or six XRPD peaks (°2θ) selected from about 7.5±0.2, 8.8±0.2, 10.1±0.2, 11.1±0.2, 11.5±0.2, 11.9±0.2, 12.5±0.2, 15.5±0.2, 15.7±0.2, 16.4±0.2, 17.4±0.2, 18.4±0.2, 19.9±0.2, 21.0±0.2, and 22.0±0.2.

DSC trace showed an initial small event of desolvation, followed by a main endothermic peak with onset at 159°C (enthalpy 83 J/g) as shown in Figure 4. Form B has a DSC thermogram characterized by an endothermic peak at about 159±3°C.

[0205] (3) The reference of Form 1 of a compound of Example 19 was prepared according to the following procedure:

A compound of Example 19 (55.4 g, 42.96 mmol) was suspended in ethanol (664.8 mL) and stirred at 47°C (external) for 2 days; then the suspension was left cooling at room temperature and stirred at this temperature for other 2 days. The product was collected by filtration and dried for 2 days at room temperature.

Output material: 45.3 g, 35.13 mmol, (81.7% yield) as white solid.

The characteristic XRPD peaks of Form 1 are shown as follows.

[Table 14]

Pos. [$^{\circ}2\theta$]	Height [cts]	FWHM Left [$^{\circ}2\theta$]	d-spacing [$\text{\AA}$]	Rel. Int. [%]
7.6404	1233.09	0.1506	11.57122	56.37
8.3409	2187.34	0.0836	10.60093	100.00
12.3596	256.10	0.1004	7.16161	11.71
12.7479	192.58	0.0836	6.94429	8.80
13.8609	405.20	0.1338	6.38911	18.52
15.4059	970.85	0.1171	5.75168	44.38
15.8375	1285.24	0.1338	5.59590	58.76
19.5749	1939.46	0.1673	4.53510	88.67
20.3058	1303.15	0.1506	4.37347	59.58
22.8990	1735.39	0.1506	3.88373	79.34

The XRPD pattern of Form 1 is shown in Figure 5. Form 1 features at least one, two, three, four, five, or six XRPD peaks ($^{\circ}2\theta$) selected from about 7.6 ± 0.2 , 8.3 ± 0.2 , 12.4 ± 0.2 , 12.7 ± 0.2 , 13.9 ± 0.2 , 15.4 ± 0.2 , 15.8 ± 0.2 , 19.6 ± 0.2 , 20.3 ± 0.2 , and 22.9 ± 0.2 . The TGA profile showed a weight loss of 2.7%w/w from ambient to 150°C ; the weight loss data is consistent with the theoretical amount required for a dihydrate (i.e. 2.7%w/w) as shown in Figure 6.

DSC trace showed one endothermic event at 81°C associated with the melt of the crystalline material as shown in Figure 7. Form 1 has a DSC thermogram characterized by an endothermic peak at about $81\pm3^{\circ}\text{C}$.

[0206] Test 1: Human Skin S9 Stability

Skin S9 from human donors (male and female) were stored at -80°C until use. On the day of the experiment, skin S9 were thawed rapidly in a waterbath at 37°C and diluted with 50 mM potassium phosphate buffer pH 7.4 to a protein concentration of 3.165 mg/mL. Test compounds were dissolved in DMSO to obtain 10 mM stock solutions. 5 μL of 10 mM stock solution in DMSO were diluted with 995 μL methanol to obtain 50 μM dosing solution. Positive control (clopidogrel) was dissolved in DMSO to 10 mM stock solution. 50 μM dosing solution was prepared by diluting 5 μL of 10mM stock solution in DMSO with 995 μL methanol. The general procedure consisted of incubation of test compound at 0.5 μM (final concentration) with 2.5 mg/ml of pooled Skin S9 (final concentration) plus NADPH regenerating system and UDPGA solution. Negative control was performed with pooled skin S9 without all cofactors. 5 μL of test compounds or positive control dosing solution were added to 395 μL of 3.165 mg/ml skin S9 solution in a 96 well plate (incubation plate) at 37°C for 5 minutes. The incubation reactions was initiated by adding 50 μL of pre-warmed NADPH regenerating system and 50 μL UDPGA or 100 μL buffer (for negative control) to the incubation mixtures. Test compounds were incubated in two replicates with and without cofactor while positive control was incubated in single with and without cofactor. The in-

cubation was performed in shaking water bath at 37°C for 1 hours. At each time point (after 0, 5, 15, 30, 45 and 60 min), 25 µL of spiked skin S9 suspension were collected, added to 25 µL of milliQ water and 150 µL of stop solution (acetonitrile containing 1% formic acid and Brexpiprazole-D8 0.2 µM) to precipitate proteins. Samples were mixed thoroughly and centrifuged at 3000 rpm at 4°C for 10min. Supernatant was collected (100 µL), diluted with 18% acetonitrile in Milli-Q water (200 µL) and then injected onto an LC MS/MS system to monitor the test compounds to internal standard peak area ratios as representative of the compound concentrations. Each time point was referenced to the zero time-point sample (as 100%) in order to determine the percentage of test compound remaining. The half-life was calculated from the relationship $T_{1/2} = -0.693/k$, where k is the slope of the concentration vs. time curve. Additionally, in each sample the active parent compound (brepiprazole) was quantified based on the MS response of brexpiprazole-D8 in the same sample. The stability results of exemplary compounds in human skin S9 are listed in Table 15. When multiple values were determined, mean half-life was calculated.

[0207]

[Table 15]

Table 15. Stability in human Skin S9			
Compound	Without Cofactor Half-life (min)	Compound	Without Cofactor Half-life (min)
Example 01	88.68	Example 28	>186.34
Example 02	113.97	Example 30	>186.34
Example 03	>186.34	Example 31	>186.34
Example 04	>186.34	Example 32	>186.34
Example 05	>186.34	Example 33	73.95
Example 06	>186.34	Example 34	75.77
Example 07	92.52	Example 35	106.63
Example 08	>186.34	Example 36	>186.34
Example 09	>186.34	Example 37	87.52
Example 10	>186.34	Example 38	95.20
Example 11	>186.34	Example 39	61.11
Example 13	>186.34	Example 45	121.75
Example 14	74.61	Example 51	>186.34
Example 15	120.88	Example 52	>186.34
Example 16	>186.34	Example 53	177.65
Example 17	>186.34	Example 58	146.95
Example 19	>186.34	Example 59	108.45
Example 20	146.37	Example 60	167.27
Example 22	>186.34	Example 61	128.92
Example 24	>186.34	Example 62	>186.34
Example 25	86.49	Example 63	>186.34
Example 27	>186.34	Example 64	114.94

[0208] Test 2: Human Hepatocytes Stability

Cryopreserved hepatocytes from human donors were stored in vapour phase of liquid nitrogen freezer until use. After thawing and prior to use, cell viability check was performed using Trypan Blue dye exclusion test. Incubations of test compounds and positive controls (testosterone and 7-OH coumarin) were carried out at the cell concentration of 0.5×10^6 cells/mL in William's medium E added with Glutamine 200 mM and HEPES 1M. 0.495 mL of cells suspension were dispensed to 48-well plate and pre

incubate at 37°C for at least 10 minutes.

Test compounds and positive controls were dissolved in DMSO to obtain a 10 mM, 50 mM and 5 mM stock solution for test compounds, testosterone and 7OH-coumarin respectively. Stock solutions were further diluted in methanol to achieve a final dosing solution of 50 μ M, 1 mM and 500 μ M solution for test compounds, testosterone and 7OH-coumarin respectively. All solutions were prepared immediately before the assay. 5 μ L of 50 μ M test compounds, 1000 μ M testosterone and 500 μ M 7-OH-coumarin were added to 0.495 mL of 0.5×10^6 cell suspensions to give final concentrations of 0.5 μ M for test compounds, 10 μ M for testosterone and 5 μ M for 7-OH-coumarin. The incubations were conducted at 37°C with gentle orbital shaking at 350 rpm in duplicate for test compounds and in single for positive controls. At each time point (0, 5, 10, 15, 20, 30, 45, 60, 90, 120 and 180 min) 30 μ L of incubation mixture from each well were added to 30 μ L of milliQ water and 180 μ L of stock solution (acetonitrile containing 1% formic acid and Brexpiprazole-D8 0.2 μ M) to precipitate protein. Samples were mixed thoroughly and centrifuged at 3000 rpm at 4°C for 10 min. Supernatant was collected (100 μ L), diluted with 18% acetonitrile in Milli-Q water (200 μ L) and then injected onto an LC MS/MS system to monitor the test compounds to internal standard peak area ratios as representative of the compound concentrations.

Metabolic stability was calculated from the ratio of peak area of the remaining test or positive control with internal standard versus time. First order elimination constant k (min^{-1}) was obtained from XLFit or Morphit Software log-linear plot by plotting the peak area ratio of the remaining test compound with internal standard versus time. Half life was obtained from the relationship $T_{1/2} = -0.693/k$. Values for CL_i was determined from the first order elimination constant k (min^{-1}) using the actual volume of the incubation (mL), the amount of hepatocytes in the incubation (million cells) and scaling factor per g liver for all species.

Additionally, in each sample the active parent compound (brexpiprazole) was quantified based on the MS response of brexpiprazole-D8 in the same sample.

The stability results of exemplary compounds in human plasma and human hepatocytes are listed in Table 16. When multiple values were determined, mean half-life was calculated.

[0209]

[Table 16]

Table 16. Stability Results for exemplary compounds in human hepatocytes		
Compound	Stability in Human Hepatocytes	
	Half-life	Formation of parent compound
Example 01	24.84	Yes
Example 02	45.00	Yes
Example 03	28.64	Yes
Example 04	20.03	Yes
Example 05	26.65	Yes
Example 08	19.52	Yes
Example 10	25.57	Yes
Example 11	23.41	Yes
Example 13	21.79	Yes
Example 19	55.89	Yes
Example 20	37.66	Yes
Example 21	29.87	Yes
Example 22	37.66	Yes
Example 23	21.19	Yes
Example 24	24.84	Yes
Example 25	21.46	Yes
Example 26	9.24	Yes
Example 27	26.05	Yes
Example 31	55.44	Yes
Example 34	44.42	Yes
Example 35	41.50	No
Example 37	28.88	Yes
Example 38	19.63	Yes
Example 39	28.40	Yes
Example 40	31.36	Yes
Example 41	13.25	Yes

Example 42	35.72	Yes
Example 43	28.88	Yes
Example 44	27.83	Yes
Example 45	28.29	Yes
Example 48	21.86	Yes
Example 50	27.61	Yes
Example 51	34.14	Yes
Example 52	22.87	Yes
Example 58	28.06	Yes
Example 59	21.39	Yes
Example 60	24.49	Yes
Example 61	21.06	Yes
Example 62	24.93	Yes
Example 63	21.52	Yes
Example 64	28.52	Yes

"Yes" means that parent compound was detected at least at one time point; difference in parent compound level was observed between test compounds incubation.

[0210] Test 3: Short Term Rat PK Study

The study protocol was designed to assess the pharmacokinetic (PK) profile after intravenous (IV) and subcutaneous (SC) administration of the test compounds in rats.

Male Sprague Dawley rats, obtained from Charles River, were acclimatized for a minimum of 5 days, in groups of 3 or 4 in cages in humidity- and temperature-controlled ventilation cupboards (relative humidity 45-65%, temperature 20-22°C and light approximately from 06:00 to 18:00 hours daily). The animals had free access to a standard rodent diet (Altromin 1324) and water ad libitum during the study.

The animals were randomly assigned to groups (n=3 per group) receiving IV or SC dose of a test compound. For IV administration, a test compound was dissolved in 5% N-methyl pyrrolidone and 10% Solutol HS15 in 50 mM acetate buffer (pH 5.5) and administered at a dose of 1 mg/kg. Blood samples were collected at 9 timepoints over a time period up to 24 hours post dose: 0.08, 0.25, 0.5, 1, 2, 4, 6, 8, and 24 hours post dose. For SC administration, a test compound was suspended in 1% hydroxymethyl propyl cellulose and 0.2% Tween 80 in water and administered at a dose of 30 mg/kg except for Example 24, which was administered at a dose of 45 mg/kg. Blood samples were collected at up to 20 timepoints over a time period up to 120 hours post dose: 3, 6, 10, 24, 27, 30, 34, 48, 51, 54, 58, 72, 75, 78, 82, 96, 99, 102, 106, and 120 hours

post dose. From both groups, blood samples aliquots were obtained from lateral tail vein and collected into K3EDTA tubes. After gentle mix following collection, aliquots were immediately transferred into micronic tubes to perform protein precipitation online using acetonitrile containing 1% formic acid and rolipram as internal standard. Samples were then stored at -80°C until analysis. After SC administration, a skin sample was also collected at the last time point from the site of injection. About 2 cm² of hairless skin samples from the site of injection was cut and collected into vials and stored frozen at -80°C until analysis. On the day of the analysis the skin was thawed, weighted and diluted to allow homogenization.

Calibration standards (CS) and quality control samples (QC) were prepared on the day of dosing by adding standard solution (test compound and brexpiprazole separately) to blank matrix (blood and skin homogenate) and stored in the same conditions as the study samples. Study samples were analyzed together with CS, QC and blank samples on an LC-MS/MS system. In each sample, the test compound and brexpiprazole were quantified. The results for test compounds and brexpiprazole in blood were subjected to non-compartmental pharmacokinetic analysis and area under the curve (AUC) was calculated using Phoenix WinNonlin 6.3. % Blood conversion to brexpiprazole after IV administration was calculated as the ratio of AUC of brexpiprazole when the test compound was administered to the value when brexpiprazole was administered. % Brexpiprazole in the skin after SC administration was calculated as the ratio of brexpiprazole concentration to the concentration of a test compound in the skin tissue.

[0211] The results of Test 3 are shown in the following table.

[Table 17]

Table 17				
Examples	IV		SC	
	AUClast (h*ng/mL)	% Blood conversion to brexpiprazole	AUClast (h*ng/mL)	% brexpiprazole in rat skin
5	141	>100%	-	3.8%
10	117	83%	1110	8.5%
19	171	>100%	394	2.2%
22	97	74%	639	30.2
24	285	>100%	342	9.47%
31	88	68%	-	0.8%
45	109	83%	-	2.7%
63	82	73%	377	19.5

The dose of test compounds by IV administration was 1 mg/kg. The dose of test compounds by SC administration other than Example 24 was 30 mg/kg. Example 24 was administered 45 mg/kg by SC administration.

[0212] Test 4: Long Term Rat PK Study

Preparation of 16.3% Example 10 aqueous suspension

A medium was prepared containing 1% sodium carboxymethyl cellulose, 3.4% D(-)-mannitol, 0.14% sodium dihydrogen phosphate monohydrate, and adjusting the pH to 6 with sodium hydroxide was prepared. This medium was sterilized by filtration through a 0.22 µm poly ether sulfone (PES) membrane. 3348 mg of the medium and 652 mg of Example 10 were added to two glass vials and suspended. Then, zirconia beads (1.5 mm in diameter) and a stir bar were added, and the suspension was milled by stirring for a few minutes or 3 hours with a magnetic stirrer. The mean particle sizes of Example 10 after milling were measured using a laser diffraction particle size distribution measuring device SALD-3100 (Shimadzu Corporation) under condition of ultrasonic irradiation and a refractive index of 2.00-0.20i, and they were found to be 3.4 µm and 1.9 µm. The suspensions were separated from the zirconia beads using a pipette and placed in separate vials, sterilized by irradiating with 25 kGy of gamma ray, and used as test formulations.

[0213] Preparation of 17.8% Example 19 aqueous suspension

A medium was prepared containing 2% D-α-tocopherol polyethylene glycol succinate, 3.4% D(-)-mannitol, 0.14% sodium dihydrogen phosphate monohydrate, and adjusted to a pH of 6 with sodium hydroxide. This medium was sterilized by filtration through a 0.22 µm polyvinylidene fluoride (PVDF) membrane. 4150 mg of medium and 890 mg of Example 19 were added to two glass vials and suspended. Then, zirconia beads (1 mm in diameter) and a stir bar were added, and the suspension was milled by stirring for 17 or 65 hours with a magnetic stirrer at 5°C. After milling, the suspensions were separated from the zirconia beads using a pipette and transferred to separate vials, then sterilized by irradiation with 25 kGy of gamma ray to prepare the test formulations. The mean particle sizes of Example 19 in the test formulations were measured under condition of ultrasonic irradiation and a refractive index of 1.70-0.20i using SALD-3100, and they were found to be 1.5 µm and 0.8 µm.

[0214] Method

The test formulations were subcutaneously administered to male rats, and the plasma concentrations of the prodrug compounds and brexpiprazole were measured.

Rats were purchased at 7 weeks of age from Japan SLC, Inc. and used in the experiment after acclimatization. The breeding environment was as follows: feeding/watering: unlimited, number of rats per cage: 3, temperature: 21-25°C, humidity: 50-70%, lighting time: 7:00-19:00. Under isoflurane anesthesia, Example 10 and 19

formulations were subcutaneously administered to the rats at doses of 34 mg/kg and 37 mg/kg (equivalent to 25 mg/kg brexpiprazole), respectively, using a plastic syringe. Blood was collected approximately 0.5 mL from the rats' jugular vein using heparinized syringes at 2 hours, and 1, 3, 6, 9, 14, 21, 28 days after administration. To prevent the hydrolysis of the prodrug compounds, blood samples were mixed with 2-thenoyltrifluoroacetone at a final concentration of 10 mM and were quickly chilled. The plasma was separated by centrifugation, and the concentrations of the prodrug compounds and brexpiprazole were measured by LC-MS/MS. Based on the obtained plasma brexpiprazole concentration - time profile, the cumulative absorption rate at each blood collection point was calculated by the deconvolution method.

[0215] Results and Discussion

When the suspensions of Example 10 or 19 were subcutaneously administered to rats, brexpiprazole was detected in the blood continuously for 28 days after administration. From these results, it was considered that these compounds have suitable characteristics as the active pharmaceutical ingredient for brexpiprazole long-acting injectable preparation. PK profiles of Examples 10 and 19 are shown in Figures 8 and 9, respectively.

[0216] Test 5: Dog irritation study

Aqueous suspensions of Example 10 and Example 19 prepared for Test 4 were used as the test formulations. Each of the test formulations was subcutaneously administered to male and female beagle dogs, and after observation for 7 or 28 days, histopathological examination was performed on the injection site after dissection.

Beagle dogs were purchased at the age of 6-8 months from Kitayama Labes Co., Ltd. and used in the experiment after acclimatization. The breeding environment was as follows: feeding: 300 g of solid feed once a day, water intake: unlimited, number of animals per cage: 1, temperature: 20-26°C, humidity: 30-70%, lighting time: 7:00-19:00. Each test formulation was subcutaneously administered to dogs anesthetized with 1 mg/kg xylazine hydrochloride and 15 mg/kg ketamine hydrochloride, using a plastic syringe at a dose of 10 mg/kg per formulation at different sites in the dorso-lumbar area. After administration, dogs were observed for 7 or 28 days, then sacrificed by bleeding under anesthesia with 0.08 mg/kg medetomidine hydrochloride, 0.5 mg/kg butorphanol tartrate, and 20 mg/kg thiopental sodium, and tissues of injection sites were collected. The collected tissues were fixed in 10% neutral buffered formalin, and hematoxylin and eosin-stained specimens were prepared for histopathological examination.

[0217] Results and Discussion

During the observation period, edema and induration were observed at the injection sites of each test formulation. On histopathological examination, the main finding at

the injection sites was granulomatous inflammation, characterized by infiltration of macrophages and foreign body giant cells. This histological change was a physiological response to foreign bodies and was not considered indicative of irritation. From these results, it was concluded that Examples 10 and 19 do not have limited irritative properties.

Industrial Applicability

[0218] Compounds of Formulas (I) and (II), or pharmaceutically acceptable salts thereof, may have antipsychotic activity and may be of use in medicine, for example in the treatment and/or prophylaxis of subjects with diseases and conditions that are antipsychotic related.

R¹ is optionally substituted linear or branched C₂₋₁₆ alkylene, wherein one or more methylene groups can be replaced with a functional group selected from -O- or -NH-, or one or more methylene groups can be

replaced with a spiro cyclopentane, or a divalent piperidine, or one or more methylene groups can be replaced with a divalent 1,3,5-triazole cycle; ethylene; optionally substituted divalent cyclohexyl; optionally substituted divalent azetidine; or optionally substituted divalent piperidine;

R² is -C(O)-, -O-C(O)-, -C(O)-N(CH₃)-CH₂-, -C(O)-NH-CH₂-, -O-, -NH-C(O)-, -CH₂-, or a direct bond;

R³ is optionally substituted divalent or trivalent piperazine, optionally substituted divalent or trivalent 2,5-diazabicyclo[2.2.2]octane, optionally substituted divalent or trivalent 2,5-diazabicyclo[2.2.1]heptane, optionally substituted divalent or trivalent octahydro-*pyrrolo*[3,4-*c*]pyrrole, optionally substituted divalent or trivalent pyrazine, optionally substituted divalent or trivalent 3,9-diazaspiro[5,5]undecane, optionally substituted divalent or trivalent 1,4,7-triazonane, optionally substituted divalent or trivalent 2,6-diazaspiro[3.3]heptane, optionally substituted divalent or trivalent 1,3,5-triazine, optionally substituted divalent or trivalent 1,3-thiazol, or optionally substituted linear or branched C₂₋₆ alkylene;

when a is 2, R³ is divalent; and

when a is 3, R³ is trivalent.

[Claim 3]

A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

a is 2;

R¹ is optionally substituted linear or branched C₂₋₁₆ alkylene, wherein one or more methylene groups can be replaced with an oxygen or amino group, or one or more methylene groups can be replaced with a spiro cyclopentane, or a divalent piperidine, or one or more methylene groups can be replaced with a divalent 1,3,5-triazole cycle; ethylene; optionally substituted divalent cyclohexyl; optionally substituted divalent azetidine; or optionally substituted divalent piperidine;

R² is -C(O)-, -O-C(O)-, -C(O)-N(CH₃)-CH₂-, -C(O)-NH-CH₂-, -CH₂-, -NH-C(O)-, or a direct bond; and

R³ is optionally substituted divalent piperazine, optionally substituted divalent 2,5-diazabicyclo[2.2.2]octane, optionally substituted divalent 2,5-diazabicyclo[2.2.1]heptane, optionally substituted divalent octahydro-*pyrrolo*[3,4-*c*]pyrrole, optionally substituted divalent pyrazine, optionally substituted divalent 3,9-diazaspiro[5,5]undecane, optionally substituted divalent 2,6-diazaspiro[3.3]heptane, optionally substituted

divalent 1,3-thiazol, or optionally substituted linear or branched C₂₋₆ alkylene.

[Claim 4]

A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

a is 3;

R¹ is optionally substituted linear or branched C₂₋₆ alkylene, wherein one or more methylene groups can be replaced with a divalent piperidine;

R² is -C(O)-, -O-, or a direct bond; and

R³ is optionally substituted trivalent 1,4,7-triazonane, or optionally substituted trivalent 1,3,5-triazine.

[Claim 5]

A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

a is 2;

R¹ is -CH=CH-, -(CH₂)₂-, -(CH₂)₄-, -(CH₂)₅-, -(CH₂)₆-, -(CH₂)₇-, -(CH₂)₈-, -(CH₂)₉-, -(CH₂)₁₂-, -(CH₂)₁₆-, -NH-(CH₂)₇-,

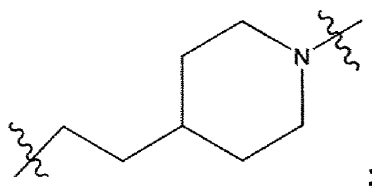
Chemical structures 1-14 are defined as follows:

- 1: 1,4-disubstituted cyclohexane.
- 2: 1,2-disubstituted cyclopentane.
- 3: 1,1-disubstituted ethane.
- 4: 2,2-disubstituted propane.
- 5: 2,2,3-trisubstituted propane.
- 6: 1,3-disubstituted butane.
- 7: 1,3-disubstituted isobutane.
- 8: 1,4-disubstituted piperidine.
- 9: 1,1-disubstituted ethane-1,2-diol derivative.
- 10: 1,1-disubstituted ethane-1,2-diol derivative.
- 11: 1,2-disubstituted ethane-1,2-diol derivative.
- 12: 1,3-disubstituted isobutane derivative.
- 13: 1,3-disubstituted piperidine.
- 14: 1,3-disubstituted pyrrolidine.

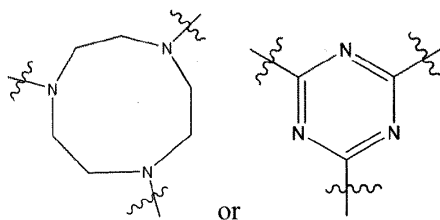
R² is -C(O)-, -O-C(O)-, -C(O)-N(CH₃)-CH₂-, -C(O)-NH-CH₂-, -CH₂-, -NH-C(O)-, or a direct bond; and
R³ is -(CH₂)₄-

The image displays a collection of chemical structures, likely representing various bicyclic and heterocyclic compounds. The structures are arranged in three rows, separated by commas. The first row includes a piperidine ring, a morpholine ring, a bicyclic amine (possibly a decalin derivative), a bicyclic amine (possibly a decalin derivative), and a bicyclic amine (possibly a decalin derivative). The second row includes a bicyclic amine (possibly a decalin derivative), a bicyclic amine (possibly a decalin derivative), a pyridine ring, and a bicyclic amine (possibly a decalin derivative). The third row includes a bicyclic amine (possibly a decalin derivative), a pyrimidine ring, and a thiophene ring. Each structure is shown with wavy lines indicating substituents.

[Chem.4]



[Chem.5]



A compound according to claim 1, or a pharmaceutically acceptable

salt thereof, wherein the compound is selected from the group consisting of:

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-6-(4-{6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexanoyl}piperazin-1-yl)-6-oxohexanoate;

(7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-8-[(2R,5S)-4-{8-[(7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanoyl}-2,5-dimethylpiperazin-1-yl]-8-oxooctanoate;

(7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-8-(5-{8-[(7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanoyl}-2,5-diazabicyclo[2.2.2]octan-2-yl)-8-oxooctanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-8-[(1S,4S)-5-{8-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanoyl}-2,5-diazabicyclo[2.2.1]heptan-2-yl]-8-oxooctanoate;

tris(trifluoroacetic acid);

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-8-(5-{8-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanoyl}-octahydropyrrolo[3,4-c]pyrrol-2-yl)-8-oxooctanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-8-(6-{8-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanoyl}-2,6-diazaspiro[3.3]heptan-2-yl)-8-oxooctanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-8-(9-{8-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanoyl}-3,9-diazaspiro[5.5]undecan-3-yl)-8-oxooctanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-7-([5-([8-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanamido)methyl]pyrazin-2-yl)methyl]carbamoyl]heptanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-7-([5-([8-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-N-met

hyl-8-oxooctanamido)methyl]pyrazin-2-yl)methyl}(methyl)carbamoyl)heptanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutanoyl}piperazin-1-yl)-4-oxobutanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-[(2S,5R)-4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutanoyl}-2,5-dimethylpiperazin-1-yl)-4-oxobutanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-(9-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutanoyl}-3,9-diazaspiro[5.5]undecan-3-yl)-4-oxobutanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl

4-[(3ar,6ar)-5-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutanoyl}-octahydropyrrolo[3,4-c]pyrrol-2-yl)-4-oxobutanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-[4,7-bis({4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutanoyl})-1,4,7-triazonan-1-yl]-4-oxobutanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-10-(4-{10-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-10-oxodecanoyl}piperazin-1-yl)-10-oxodecanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-10-[(2R,5S)-4-{10-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-10-oxodecanoyl}-2,5-dimethylpiperazin-1-yl)-10-oxodecanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-10-(5-{10-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-10-oxodecanoyl}-2,5-diazabicyclo[2.2.2]octan-2-yl)-10-oxodecanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-9-({[5-({10-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-N-m

ethyl-10-oxodecanamido)methylpyrazin-2-yl)methyl}(methyl)carbamoyl)nonanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-8-(4-{8-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanoyl}piperazin-1-yl)-8-oxooctanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-6-[(2S,5R)-4-{6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexanoyl}-2,5-dimethylpiperazin-1-yl]-6-oxohexanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-6-(6-{6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexanoyl}-2,6-diazaspiro[3.3]heptan-2-yl)-6-oxohexanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-6-[(3ar,6ar)-5-{6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexanoyl}-octahydropyrrolo[3,4-c]pyrrol-2-yl]-6-oxohexanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-6-(5-{6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexanoyl}-octahydropyrrolo[3,4-c]pyrrol-2-yl)-6-oxohexanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-5-([5-([6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-N-methyl-6-oxohexanamido)methylpyrazin-2-yl)methyl}(methyl)carbamoyl)pentanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-5-([5-([6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexanamido)methylpyrazin-2-yl)methyl}carbamoyl)pentanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-5-([5-([6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexanamido)methylpyrazin-2-yl)methyl}carbamoyl)pentanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-14-(4-{14-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-14-oxo-

tetradecanoyl}piperazin-1-yl)-14-oxotetradecanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-14-[(2S,5R)-4-{14-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-14-oxotetradecanoyl}-2,5-dimethylpiperazin-1-yl]-14-oxotetradecanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-18-(4-{18-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-18-oxooctadecanoyl}piperazin-1-yl)-18-oxooctadecanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-18-[(2S,5R)-4-{18-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-18-oxooctadecanoyl}-2,5-dimethylpiperazin-1-yl]-18-oxooctadecanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-(1r,4r)-4-{4-[(1r,4r)-4-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}cyclohexanecarbonyl]piperazine-1-carbonyl}cyclohexane-1-carboxylate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-(1r,4r)-4-[(2S,5R)-2,5-dimethyl-4-[(1r,4r)-4-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}cyclohexanecarbonyl]piperazine-1-carbonyl}cyclohexane-1-carboxylate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-(1s,4s)-4-{4-[(1s,4s)-4-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}cyclohexanecarbonyl]piperazine-1-carbonyl}cyclohexane-1-carboxylate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-(1s,4s)-4-[(2S,5R)-2,5-dimethyl-4-[(1s,4s)-4-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}cyclohexanecarbonyl]piperazine-1-carbonyl}cyclohexane-1-carboxylate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl
 1-[4-(1-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-ox

o-1,2-dihydroquinolin-1-yl)methoxy]carbonyl)cyclopentanecarbonyl)piperazine-1-carbonyl)cyclopentane-1-carboxylate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-1-[(3ar,6ar)-5-(1-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl)cyclopentanecarbonyl]-octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)cyclopentane-1-carboxylate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-3-(4-{3-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-2,2-dimethyl-3-oxopropanoyl}piperazin-1-yl)-2,2-dimethyl-3-oxopropanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl
 4-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-2,2-dimethyl-4-oxobutanoyl}piperazin-1-yl)-3,3-dimethyl-4-oxobutanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-3,3-dimethyl-4-oxobutanoyl}piperazin-1-yl)-2,2-dimethyl-4-oxobutanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-5-(4-{5-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-3,3-dimethyl-5-oxopentanoyl}piperazin-1-yl)-3,3-dimethyl-5-oxopentanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-2-{2-[4-(2-{2-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-2-oxoethoxy}acetyl)piperazin-1-yl]-2-oxoethoxy}acetate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-N-(8-{4-[8-({[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}amino)octanoyl]piperazin-1-yl}-8-oxooctyl)carbamate;
 (7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-N-[(2S)-1-{4-[(2S)-2-({[(7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}amino)-3-methylbutanoyl]piperazin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-1-[(3ar,6ar)-5-(1-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl)cyclopentanecarbonyl]-octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)cyclopentane-1-carboxylate;

droquinolin-1-yl)methyl-4-[4-(1-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl]piperidine-4-carbonyl)piperazine-1-carbonyl]piperidine-1-carboxylate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-1-[5-(4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl]piperidine-1-carbonyl)pyrazine-2-carbonyl]piperidine-4-carboxylate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-3-{1-[4-(4-{3-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-3-oxopropyl]piperidin-1-yl)-1,3,5-triazin-2-yl]piperidin-4-yl}propanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-3-{1-[4,6-bis(4-{3-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-3-oxopropyl]piperidin-1-yl)-1,3,5-triazin-2-yl]piperidin-4-yl}propanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-3-[1-({5-[(4-{3-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-3-oxopropyl]piperidin-1-yl)methyl}pyrazin-2-yl)methyl]piperidin-4-yl}propanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-3-{1-[5-(4-{3-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-3-oxopropyl]piperidine-1-carbonyl)pyrazine-2-carbonyl]piperidin-4-yl}propanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-1-[5-(3-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl]azetidine-1-carbonyl)pyrazine-2-carbonyl]azetidine-3-carboxylate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-5-{[5-({5-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-5-oxopentyl}carbamoyl)-1,3-thiazol-2-yl]formamido}pentanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-5-{[5-({5-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-5-oxopentyl}carbamoyl)pyrazin-2-yl]formamido}pentanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-10-{[5-({10-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-10-oxodecyl}carbamoyl)pyrazin-2-yl]formamido}decanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-6-(4-{6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexyl}piperazin-1-yl)hexanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-6-{4-[(6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexyl}oxy)carbonyl]piperazine-1-carbonyloxy}hexanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-(1r,4r)-4-[(4-{[(1r,4r)-4-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}cyclohexyl)methyl}piperazin-1-yl)methyl]cyclohexane-1-carboxylate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-6-{[4,6-bis({6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexyl}oxy)-1,3,5-triazin-2-yl]oxy}hexanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-5-{1-[4-(4-{5-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-5-oxopentyl]-1H-1,2,3-triazol-1-yl)butyl]-1H-1,2,3-triazol-4-yl}pentanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-{1-[4-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutyl]-1H-1,2,3-triazol-1-yl)butyl]-1H-1,2,3-triazol-4-yl}butanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-[1-(5-{4-[5-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutyl]-1H-1,2,3-triazol-1-yl)pentanoyl]piperazin-1-yl]-5-oxopentyl)-1H-1,2,3-triazol-4-yl]butanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-(1-{5-[(2S,5R)-4-[5-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)

)methoxy]-4-oxobutyl]-1H-1,2,3-triazol-1-yl)pentanoyl]-2,5-dimethylpiperazin-1-yl]-5-oxopentyl]-1H-1,2,3-triazol-4-yl)butanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-[1-(5-{5-[5-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutyl]-1H-1,2,3-triazol-1-yl)pentanoyl]-2,5-diazabicyclo[2.2.2]octan-2-yl]-5-oxopentyl]-1H-1,2,3-triazol-4-yl]butanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-[1-(6-{4-[6-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutyl]-1H-1,2,3-triazol-1-yl)hexanoyl]piperazin-1-yl]-6-oxohexyl]-1H-1,2,3-triazol-4-yl]butanoate; and
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-(1-{6-[(2S,5R)-4-[6-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutyl]-1H-1,2,3-triazol-1-yl)hexanoyl]-2,5-dimethylpiperazin-1-yl]-6-oxohexyl]-1H-1,2,3-triazol-4-yl)butanoate.

[Claim 8]

A compound according to claim 6, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-[4,7-bis({4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutanoyl})-1,4,7-triazonan-1-yl]-4-oxobutanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-3-{1-[4,6-bis(4-{3-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-3-oxopropyl}piperidin-1-yl)-1,3,5-triazin-2-yl]piperidin-4-yl}propanoate; and
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-6-{[4,6-bis({6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexyl}oxy)-1,3,5-triazin-2-yl]oxy}hexanoate.

[Claim 9]

A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

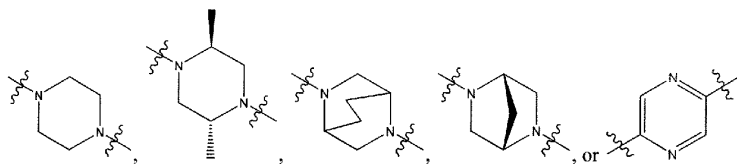
a is 2;

R¹ is -(CH₂)₂-, -(CH₂)₄-, -(CH₂)₅-, -(CH₂)₆-, -(CH₂)₇-, -(CH₂)₈-, -(CH₂)₉-, -(CH₂)₁₂-, or -(CH₂)₁₆-;

R² is -C(O)-, -CH₂-, or a direct bond; and

R³ is

[Chem.6]



[Claim 10]

A compound according to claim 9, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-6-(4-{6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexanoyl}piperazin-1-yl)-6-oxohexanoate;

(7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-8-[(2R,5S)-4-{8-[(7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanoyl}-2,5-dimethylpiperazin-1-yl]-8-oxooctanoate;

(7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-8-(5-{8-[(7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanoyl}-2,5-diazabicyclo[2.2.2]octan-2-yl)-8-oxooctanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-8-[(1S,4S)-5-{8-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanoyl}-2,5-diazabicyclo[2.2.1]heptan-2-yl]-8-oxooctanoate; tris(trifluoroacetic acid);

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutanoyl}piperazin-1-yl)-4-oxobutanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-[(2S,5R)-4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutanoyl}-2,5-dimethylpiperazin-1-yl)-4-oxobutanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-oxobutanoate;

droquinolin-1-yl)methyl-10-(4-{10-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-10-oxodecanoyl}piperazin-1-yl)-10-oxodecanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-10-[(2R,5S)-4-{10-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-10-oxodecanoyl]-2,5-dimethylpiperazin-1-yl]-10-oxodecanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-10-(5-{10-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-10-oxodecanoyl]-2,5-diazabicyclo[2.2.2]octan-2-yl)-10-oxodecanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-8-(4-{8-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanoyl}piperazin-1-yl)-8-oxooctanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-6-[(2S,5R)-4-{6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexanoyl]-2,5-dimethylpiperazin-1-yl]-6-oxohexanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-14-(4-{14-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-14-oxotetradecanoyl}piperazin-1-yl)-14-oxotetradecanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-14-[(2S,5R)-4-{14-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-14-oxotetradecanoyl]-2,5-dimethylpiperazin-1-yl]-14-oxotetradecanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-18-(4-{18-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-18-oxooctadecanoyl}piperazin-1-yl)-18-oxooctadecanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-18-[(2S,5R)-4-{18-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-18-oxooctadecanoyl]-2,5-dimethylpiperazin-1-yl]-18-oxooctadecanoate;

e;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-18-[(2S,5R)-4-{18-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-18-oxooctadecanoyl]-2,5-dimethylpiperazin-1-yl]-18-oxooctadecanoate;

droquinolin-1-yl)methyl-N-(8-{4-[8-({[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}amino)octanoyl]piperazin-1-yl}-8-oxooctyl)carbamate; and (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-6-(4-{6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexyl}piperazin-1-yl)hexanoate.

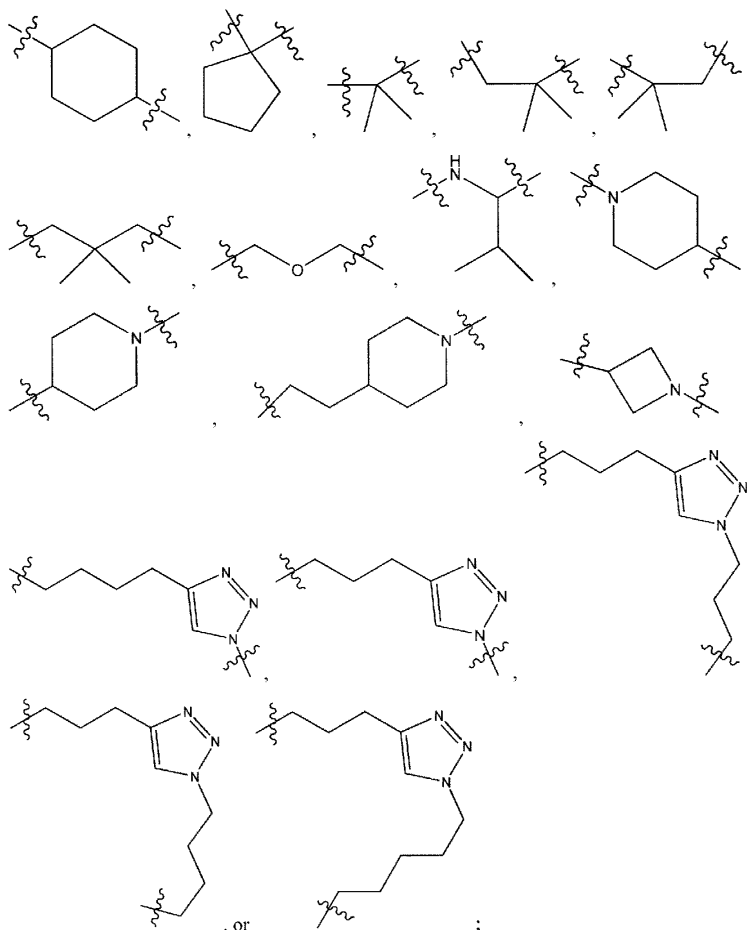
[Claim 11]

A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

a is 2;

R¹ is

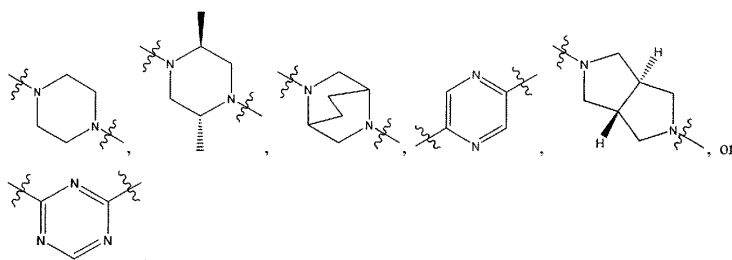
[Chem.7]



R² is -C(O)-, -CH₂-, or a direct bond; and

R³ is -(CH₂)₄-

[Chem.8]



[Claim 12]

A compound according to claim 11, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-(1r,4r)-4-{4-[(1r,4r)-4-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}cyclohexanecarbonyl]piperazine-1-carbonyl}cyclohexane-1-carboxylate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-(1r,4r)-4-[(2S,5R)-2,5-dimethyl-4-[(1r,4r)-4-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}cyclohexanecarbonyl]piperazine-1-carbonyl]cyclohexane-1-carboxylate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-(1s,4s)-4-{4-[(1s,4s)-4-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}cyclohexanecarbonyl]piperazine-1-carbonyl}cyclohexane-1-carboxylate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-(1s,4s)-4-[(2S,5R)-2,5-dimethyl-4-[(1s,4s)-4-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}cyclohexanecarbonyl]piperazine-1-carbonyl]cyclohexane-1-carboxylate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl

1-[4-(1-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}cyclopentanecarbonyl)piperazine-1-carbonyl]cyclopentane-1-carboxylate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-1-[(3ar,6ar)-5-(1-{[(7-{4-[4-(1-benzothiophen

-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}cyclopentanecarbonyl)-octahydropyrrolo[3,4-c]pyrrole-2-carbonyl}cyclopentane-1-carboxylate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-3-(4-{3-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-2,2-dimethyl-3-oxopropanoyl}piperazin-1-yl)-2,2-dimethyl-3-oxopropanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl

4-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-2,2-dimethyl-4-oxobutanoyl}piperazin-1-yl)-3,3-dimethyl-4-oxobutanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-3,3-dimethyl-4-oxobutanoyl}piperazin-1-yl)-2,2-dimethyl-4-oxobutanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-5-(4-{5-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-3,3-dimethyl-5-oxopentanoyl}piperazin-1-yl)-3,3-dimethyl-5-oxopentanoate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-2-{2-[4-(2-{2-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-2-oxoethoxy}acetyl)piperazin-1-yl]-2-oxoethoxy}acetate;

(7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-N-[(2S)-1-{4-[(2S)-2-[(7-{5-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}amino)-3-methylbutanoyl]piperazin-1-yl)-3-methyl-1-oxobutan-2-yl]carbamate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-[4-(1-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}piperidine-4-carbonyl)piperazine-1-carbonyl]piperidine-1-carboxylate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-1-[5-(4-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}piperidine-1-carbonyl)pyrazine-2-carbonyl]piperidine-4-carboxylate;

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-1-[5-(4-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}piperidine-1-carbonyl)pyrazine-2-carbonyl]piperidine-4-carboxylate;

droquinolin-1-yl)methyl-3-{1-[4-(4-{3-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-3-oxopropyl}piperidin-1-yl)-1,3,5-triazin-2-yl]piperidin-4-yl}propanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-3-[1-({5-[(4-{3-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-3-oxopropyl}piperidin-1-yl)methyl]pyrazin-2-yl)methyl}piperidin-4-yl}propanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-3-{1-[5-(4-{3-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-3-oxopropyl}piperidine-1-carbonyl)pyrazine-2-carbonyl]piperidin-4-yl}propanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-1-[5-(3-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}azetidine-1-carbonyl)pyrazine-2-carbonyl]azetidine-3-carboxylate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-(1r,4r)-4-[(4-{[(1r,4r)-4-{[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]carbonyl}cyclohexyl)methyl}piperazin-1-yl)methyl]cyclohexane-1-carboxylate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-5-{1-[4-(4-{5-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-5-oxopentyl]-1H-1,2,3-triazol-1-yl)butyl]-1H-1,2,3-triazol-4-yl}pentanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-{1-[4-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutyl]-1H-1,2,3-triazol-1-yl)butyl]-1H-1,2,3-triazol-4-yl}butanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-[1-(5-{4-[5-(4-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutyl]-1H-1,2,3-triazol-1-yl)pentanoyl]piperazin-1-yl}-5-oxopentyl)-1H-1,2,3-triazol-4-yl]butanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-(1-{5-[(2S,5R)-4-[5-(4-{4-[(7-{4-[4-(1-benz

othiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl
)methoxy]-4-oxobutyl]-1H-1,2,3-triazol-1-yl)pentanoyl]-2,5-dimethylp
iperazin-1-yl]-5-oxopentyl]-1H-1,2,3-triazol-4-yl)butanoate;
(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihy
droquinolin-1-yl)methyl-4-[1-(5-{5-[5-(4-{4-[(7-{4-[4-(1-benzothiophe
n-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methox
y]-4-oxobutyl]-1H-1,2,3-triazol-1-yl)pentanoyl]-2,5-diazabicyclo[2.2.2
]octan-2-yl}-5-oxopentyl)-1H-1,2,3-triazol-4-yl]butanoate;
(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihy
droquinolin-1-yl)methyl-4-[1-(6-{4-[6-(4-{4-[(7-{4-[4-(1-benzothiophe
n-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methox
y]-4-oxobutyl]-1H-1,2,3-triazol-1-yl)hexanoyl]piperazin-1-yl]-6-oxoh
exyl)-1H-1,2,3-triazol-4-yl]butanoate; and
(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihy
droquinolin-1-yl)methyl-4-(1-{6-[(2S,5R)-4-[6-(4-{4-[(7-{4-[4-(1-benz
othiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl
)methoxy]-4-oxobutyl]-1H-1,2,3-triazol-1-yl)hexanoyl]-2,5-dimethylpi
perazin-1-yl]-6-oxohexyl)-1H-1,2,3-triazol-4-yl)butanoate.

[Claim 13]

A compound according to claim 1, or a pharmaceutically acceptable
salt thereof, wherein:

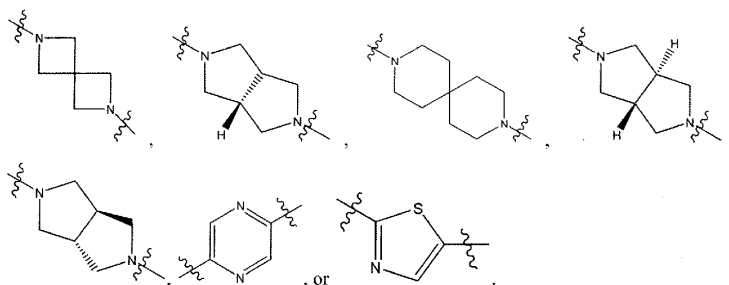
a is 2;

R¹ is -(CH₂)₂-, -(CH₂)₄-, -(CH₂)₆-, or -(CH₂)₉-;

R² is -C(O)-, -C(O)-N(CH₃)-CH₂-, -C(O)-NH-CH₂-, or -NH-C(O)-; and

R³ is

[Chem.9]



[Claim 14]

A compound according to claim 13, or a pharmaceutically acceptable
salt thereof, wherein the compound is selected from:

(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihy
droquinolin-1-yl)methyl-8-(5-{8-[(7-{4-[4-(1-benzothiophen-4-yl)piper
azin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxoocta

noyl]-octahydropyrrolo[3,4-c]pyrrol-2-yl)-8-oxooctanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-8-(6-{8-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanoyl}-2,6-diazaspiro[3.3]heptan-2-yl)-8-oxooctanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-8-(9-{8-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-8-oxooctanoyl}-3,9-diazaspiro[5.5]undecan-3-yl)-8-oxooctanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-(9-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutanoyl}-3,9-diazaspiro[5.5]undecan-3-yl)-4-oxobutanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-4-[(3ar,6ar)-5-{4-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-4-oxobutanoyl}-octahydropyrrolo[3,4-c]pyrrol-2-yl]-4-oxobutanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-6-(6-{6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexanoyl}-2,6-diazaspiro[3.3]heptan-2-yl)-6-oxohexanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-6-[(3ar,6ar)-5-{6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexanoyl}-octahydropyrrolo[3,4-c]pyrrol-2-yl]-6-oxohexanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-6-(5-{6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxohexanoyl}-octahydropyrrolo[3,4-c]pyrrol-2-yl)-6-oxohexanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-5-([5-([6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-N-methyl-6-oxohexanamido)methyl]pyrazin-2-yl)methyl)(methyl)carbamoyl)pentanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-5-([5-([6-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-6-oxoh

exanamido)methyl)pyrazin-2-yl)methyl}carbamoyl)pentanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-5-{[5-({5-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-5-oxopentyl}carbamoyl)-1,3-thiazol-2-yl]formamido}pentanoate;
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-5-{[5-({5-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-5-oxopentyl}carbamoyl)pyrazin-2-yl]formamido}pentanoate; and
 (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methyl-10-{[5-({10-[(7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-2-oxo-1,2-dihydroquinolin-1-yl)methoxy]-10-oxodecyl}carbamoyl)pyrazin-2-yl]formamido}decanoate.

- [Claim 15] A compound according to claim 1, or a pharmaceutically acceptable salt thereof, having the mean particle size measured by laser diffractometry ranging from 0.05 to 10 μm .
- [Claim 16] A pharmaceutical composition comprising a compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
- [Claim 17] A medicament for treating and/or preventing a central nervous system disorder, comprising a compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof.
- [Claim 18] The medicament according to claim 17, wherein the central nervous system disorder is selected from the group consisting of schizophrenia; refractory, intractable or chronic schizophrenia; emotional disturbance; psychotic disorder; mood disorder; bipolar I type disorder; bipolar II type disorder; depression; endogenous depression; major depressive disorder (MDD); melancholy and refractory depression; dysthymic disorder; cyclothymic disorder; panic attack; panic disorder; agoraphobia; social phobia; obsessive-compulsive disorder; post-traumatic stress disorder; generalized anxiety disorder; acute stress disorder; hysteria; somatization disorder; conversion disorder; pain disorder; hypochondriasis; factitious disorder; dissociative disorder; sexual dysfunction; sexual desire disorder; sexual arousal disorder; erectile dysfunction; anorexia nervosa; bulimia nervosa; sleep disorder; adjustment disorder; alcohol abuse; alcohol intoxication; drug addiction; stimulant intoxication; narcotism; anhedonia; iatrogenic anhedonia; anhedonia of a psychic or mental cause; anhedonia associated with depression;

anhedonia associated with schizophrenia; delirium; cognitive impairment; cognitive impairment associated with Alzheimer's disease, Parkinson's disease and other neurodegenerative diseases; cognitive impairment caused by Alzheimer's disease; Parkinson's disease and associated neurodegenerative diseases; cognitive impairment of schizophrenia; cognitive impairment caused by refractory, intractable or chronic schizophrenia; vomiting; motion sickness; obesity; migraine; pain (ache); mental retardation; autism disorder (autism); Tourette's disorder; tic disorder; attention-deficit/hyperactivity disorder; conduct disorder; Down's syndrome; impulsive symptoms associated with dementia (e.g., agitation associated with Alzheimer's disease); and borderline personality disorder.

[Claim 19] Use of a compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating and/or preventing a central nervous system disorder.

[Claim 20] The use according to claim 19, wherein the central nervous system disorder is selected from the group consisting of schizophrenia; refractory, intractable or chronic schizophrenia; emotional disturbance; psychotic disorder; mood disorder; bipolar I type disorder; bipolar II type disorder; depression; endogenous depression; major depressive disorder (MDD); melancholy and refractory depression; dysthymic disorder; cyclothymic disorder; panic attack; panic disorder; agoraphobia; social phobia; obsessive-compulsive disorder; post-traumatic stress disorder; generalized anxiety disorder; acute stress disorder; hysteria; somatization disorder; conversion disorder; pain disorder; hypochondriasis; factitious disorder; dissociative disorder; sexual dysfunction; sexual desire disorder; sexual arousal disorder; erectile dysfunction; anorexia nervosa; bulimia nervosa; sleep disorder; adjustment disorder; alcohol abuse; alcohol intoxication; drug addiction; stimulant intoxication; narcotism; anhedonia; iatrogenic anhedonia; anhedonia of a psychic or mental cause; anhedonia associated with depression; anhedonia associated with schizophrenia; delirium; cognitive impairment; cognitive impairment associated with Alzheimer's disease, Parkinson's disease and other neurodegenerative diseases; cognitive impairment caused by Alzheimer's disease; Parkinson's disease and associated neurodegenerative diseases; cognitive impairment of schizophrenia; cognitive impairment caused by refractory, intractable

or chronic schizophrenia; vomiting; motion sickness; obesity; migraine; pain (ache); mental retardation; autism disorder (autism); Tourette's disorder; tic disorder; attention-deficit/hyperactivity disorder; conduct disorder; Down's syndrome; impulsive symptoms associated with dementia (e.g., agitation associated with Alzheimer's disease); and borderline personality disorder.

[Claim 21]

A method for treating and/or preventing a central nervous system disorder, comprising administering a compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

[Claim 22]

The method according to claim 21, wherein the central nervous system disorder is selected from the group consisting of schizophrenia; refractory, intractable or chronic schizophrenia; emotional disturbance; psychotic disorder; mood disorder; bipolar I type disorder; bipolar II type disorder; depression; endogenous depression; major depressive disorder (MDD); melancholy and refractory depression; dysthymic disorder; cyclothymic disorder; panic attack; panic disorder; agoraphobia; social phobia; obsessive-compulsive disorder; post-traumatic stress disorder; generalized anxiety disorder; acute stress disorder; hysteria; somatization disorder; conversion disorder; pain disorder; hypochondriasis; factitious disorder; dissociative disorder; sexual dysfunction; sexual desire disorder; sexual arousal disorder; erectile dysfunction; anorexia nervosa; bulimia nervosa; sleep disorder; adjustment disorder; alcohol abuse; alcohol intoxication; drug addiction; stimulant intoxication; narcotism; anhedonia; iatrogenic anhedonia; anhedonia of a psychic or mental cause; anhedonia associated with depression; anhedonia associated with schizophrenia; delirium; cognitive impairment; cognitive impairment associated with Alzheimer's disease, Parkinson's disease and other neurodegenerative diseases; cognitive impairment caused by Alzheimer's disease; Parkinson's disease and associated neurodegenerative diseases; cognitive impairment of schizophrenia; cognitive impairment caused by refractory, intractable or chronic schizophrenia; vomiting; motion sickness; obesity; migraine; pain (ache); mental retardation; autism disorder (autism); Tourette's disorder; tic disorder; attention-deficit/hyperactivity disorder; conduct disorder; Down's syndrome; impulsive symptoms associated with dementia (e.g., agitation associated with Alzheimer's disease); and borderline personality disorder.

- [Claim 23] A compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, for use in treating and/or preventing a central nervous system disorder.
- [Claim 24] The compound for use according to claim 23, wherein the central nervous system disorder is selected from the group consisting of schizophrenia; refractory, intractable or chronic schizophrenia; emotional disturbance; psychotic disorder; mood disorder; bipolar I type disorder; bipolar II type disorder; depression; endogenous depression; major depressive disorder (MDD); melancholy and refractory depression; dysthymic disorder; cyclothymic disorder; panic attack; panic disorder; agoraphobia; social phobia; obsessive-compulsive disorder; post-traumatic stress disorder; generalized anxiety disorder; acute stress disorder; hysteria; somatization disorder; conversion disorder; pain disorder; hypochondriasis; factitious disorder; dissociative disorder; sexual dysfunction; sexual desire disorder; sexual arousal disorder; erectile dysfunction; anorexia nervosa; bulimia nervosa; sleep disorder; adjustment disorder; alcohol abuse; alcohol intoxication; drug addiction; stimulant intoxication; narcotism; anhedonia; iatrogenic anhedonia; anhedonia of a psychic or mental cause; anhedonia associated with depression; anhedonia associated with schizophrenia; delirium; cognitive impairment; cognitive impairment associated with Alzheimer's disease, Parkinson's disease and other neurodegenerative diseases; cognitive impairment caused by Alzheimer's disease; Parkinson's disease and associated neurodegenerative diseases; cognitive impairment of schizophrenia; cognitive impairment caused by refractory, intractable or chronic schizophrenia; vomiting; motion sickness; obesity; migraine; pain (ache); mental retardation; autism disorder (autism); Tourette's disorder; tic disorder; attention-deficit/hyperactivity disorder; conduct disorder; Down's syndrome; impulsive symptoms associated with dementia (e.g., agitation associated with Alzheimer's disease); and borderline personality disorder.