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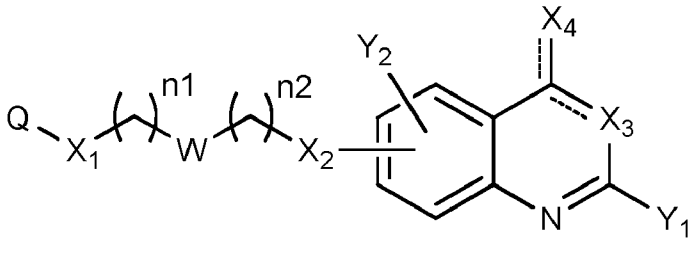
(54) Title: SUBSTITUTED QUINAZOLINE DERIVATIVES AS DNA METHYLTRANSFERASE INHIBITORS



(I)

(57) Abstract: The present invention relates to compounds of the following formula (I) and pharmaceutically acceptable salts and solvates thereof, their methods of preparation, their use as a drug, notably in the treatment of cancer, and pharmaceutical compositions containing such compounds.

SUBSTITUTED QUINAZOLINE DERIVATIVES AS DNA METHYLTRANSFERASE INHIBITORS

The present invention relates to substituted quinazoline derivatives useful as DNA methyltransferase (DNMT) inhibitors, notably in the treatment of cancer.

Gene expression is modulated by epigenetic modifications. Methylation of deoxycytidines (dC) in the DNA was shown to play a key role in epigenetic regulation in mammals (Berger *et al. Genes Dev.* 2009, 23, 781; Kelly *et al. Biotechnol.* 2010, 28, 1069). It is the most stable epigenetic mark and occurs at CpG sites, which are regrouped in island and essentially located in promoters, repeated sequences and CpG island shores (Gros *et al. Biochimie* 2012, 94, 2280). Hypermethylation of promoters' CpG islands induces gene silencing while hypomethylation induces gene expression (Sharma *et al. Carcinogenesis* 2010, 31, 27; Esteller *N. Engl. J. Med.* 2008, 358, 1148).

The enzymes responsible for DNA methylation are DNA methyltransferases (DNMTs). Two families of catalytically active DNMTs have been identified: DNMT1, responsible for DNA methylation maintenance during replication, and DNMT3A and 3B, responsible for *de novo* DNA methylation. DNMTs add a methyl group on the carbon-5 position of the deoxycytosine at the CpG site in the DNA by using *S*-adenosyl-L-methionine (AdoMet) as methyl donor (Jurkowska *et al. ChemBioChem* 2011, 12, 206).

Alteration of DNA methylation patterns lead to various diseases such as cancer (Baylin and Jones *Nat. Rev. Cancer* 2011, 11, 726). Cancerous cells often present aberrant DNA methylation, in particular a specific hypermethylation of tumour suppressor genes is observed. Restoring their expression by specific inhibition of DNA methylation represents an attractive therapeutic strategy (Fahy *et al. Expert Opin. Ther. Pat.* 2012, 22, 1427; Ahuja *et al. J. Clin. Invest.* 2014, 124, 56-63).

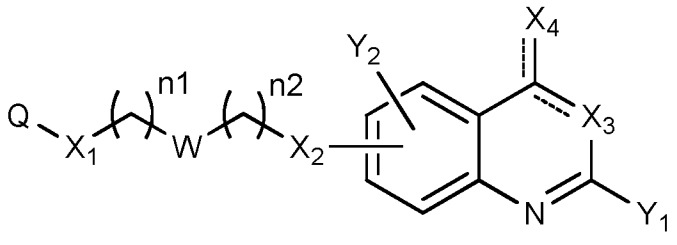
DNMT inhibitors can be divided into two families: nucleoside analogues and non-nucleosides. The first are the most active ones. Two of them were FDA approved: 5-azacytidine (Vidaza®) and 5-azadeoxycytidine (Dacogene®) (Gros *et al. Biochimie* 2012, 94, 2280). Despite their high efficiency, their poor bioavailability, their instability

in physiologic media and their little selectivity restrict their use (Erdmann *et al. J. Med. Chem.* Article ASAP, DOI: 10.1021/jm500843d, Publication Date (Web): November 19, 2014). Non-nucleoside analogues present various structures and mechanisms of action. Many of them were shown to target the catalytic site but suffer from high toxicity, lack of specificity and weak activity.

There exists thus a need for novel DNMT inhibitors.

The inventors of the present invention have thus discovered that substituted quinazoline derivatives can be used as DNA methyltransferase (DNMT) inhibitors.

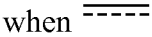
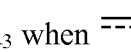
The present invention concerns thus a compound of the following formula (I):



(I)

or a pharmaceutically acceptable salt or solvate thereof,

wherein:

- ------ represents a single bond or a double bond on the condition that the two bonds ------ do not represent a double bond at the same time,
- n1 and n2 represent, independently of each other, an integer comprised between 0 and 8, notably between 1 and 8,
- Q represents an optionally substituted aryl or an optionally substituted nitrogen-containing heterocycle,
- W represents a bond, a divalent monoglycosyl, NR_0, a piperidinediyl, a piperazinediyl or a pyrrolidinediyl, and preferably a divalent monoglycosyl, NR_0, a piperidinediyl, a piperazinediyl or a pyrrolidinediyl,
- X_1 represents O or NR_1,
- X_2 represents O, NR_2 or a bond,
- X_3 represents:
  - N when  represents a double bond  , and
  - NR_3 when  represents a single bond  ,

- X_4 represents:
  - O or NR_4 when represents a double bond , and
  - OR_4 or NR_4R_5 when represents a single bond ,
- Y_1 and Y_2 represent, independently of each other, a halogen atom, R_{100}, OR_{101} or $NR_{102}R_{103}$, provided that at least one of Y_1 and Y_2 represent a group other than H,
- R_0 represents H; CHO; CO_2-($(C_1$-$C_6)$alkyl); or a $(C_1$-$C_6)$alkyl optionally substituted with CHO, CO_2H or CO_2-($(C_1$-$C_6)$alkyl),
- R_1 and R_2 represent, independently of each other, H or a $(C_1$-$C_6)$alkyl,
- R_3 and R_4 represent, independently of each other, H, $(C_1$-$C_6)$alkyl, aryl, heterocycle, -($(C_1$-$C_6)$alkyl)-X_5-aryl or -($(C_1$-$C_6)$alkyl)-X_5-heterocycle, with X_5 representing a bond, O, S or NR_6 and each aryl or heterocycle moiety being optionally substituted,
- R_5 and R_6 represent, independently of each other, H or a $(C_1$-$C_6)$alkyl, and notably H,
- R_{100}, R_{101}, R_{102} and R_{103} represent, independently of one another, H, optionally substituted aryl, optionally substituted heterocycle, or -($(C_1$-$C_6)$alkyl)-X_6-A_1, with X_6 representing a bond, O, S or NR_{104} and A_1 representing H, $(C_1$-$C_6)$alkyl, optionally substituted aryl or optionally substituted heterocycle, or, for the R_{102} and R_{103} groups, R_{102} and R_{103} form together, with the nitrogen carrying them, an optionally substituted heterocycle, and
- R_{104} represents H or a $(C_1$-$C_6)$alkyl.

For the purpose of the invention, the term "pharmaceutically acceptable" is intended to mean what is useful to the preparation of a pharmaceutical composition, and what is generally safe and non-toxic, for a pharmaceutical use.

The term "pharmaceutically acceptable salt or solvate" is intended to mean, in the framework of the present invention, a salt or solvate of a compound which is pharmaceutically acceptable, as defined above, and which possesses the pharmacological activity of the corresponding compound.

The pharmaceutically acceptable salts comprise:

(1) acid addition salts formed with inorganic acids such as hydrochloric, hydrobromic, sulfuric, nitric and phosphoric acid and the like; or formed with organic acids such as acetic, benzenesulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, hydroxynaphtoic, 2-hydroxyethanesulfonic, lactic, maleic, malic, mandelic, methanesulfonic, muconic, 2-naphtalenesulfonic, propionic, succinic, dibenzoyl-L-tartaric, tartaric, p-toluenesulfonic, trimethylacetic, and trifluoroacetic acid and the like, and

(2) base addition salts formed when an acid proton present in the compound is either replaced by a metal ion, such as an alkali metal ion, an alkaline-earth metal ion, or an aluminium ion; or coordinated with an organic or inorganic base. Acceptable organic bases comprise diethanolamine, ethanolamine, N-methylglucamine, triethanolamine, tromethamine and the like. Acceptable inorganic bases comprise aluminium hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate and sodium hydroxide.

Acceptable solvates for the therapeutic use of the compounds of the present invention include conventional solvates such as those formed during the last step of the preparation of the compounds of the invention due to the presence of solvents. As an example, mention may be made of solvates due to the presence of water (these solvates are also called hydrates) or ethanol.

The term "(C_1-C_6)alkyl", as used in the present invention, refers to a straight or branched saturated hydrocarbon chain containing from 1 to 6 carbon atoms including, but not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, n-hexyl, and the like.

The term "(C_2-C_6)alkenyl", as used in the present invention, refers to a straight or branched unsaturated hydrocarbon chain containing from 2 to 6 carbon atoms and comprising at least one double bond, notably one double bond, including, but not limited to, ethenyl, propenyl, butenyl, pentenyl, hexenyl and the like. It can be in particular an allyl group.

The term "aryl", as used in the present invention, refers to an aromatic hydrocarbon group comprising preferably 6 to 10 carbon atoms and comprising one or more, notably 1 or 2, fused rings, such as, for example, a phenyl or naphtyl group. Advantageously, it will be a phenyl group.

The term "aryl-(C_1-C_6)alkyl", as used in the present invention, refers to an aryl group as defined above bound to the molecule via a (C_1-C_6)alkyl group as defined above. In particular, the aryl-(C_1-C_6)alkyl group is a benzyl group.

The term "(C_1-C_6)alkyl-aryl", as used in the present invention, refers to a (C_1-C_6)alkyl group as defined above bound to the molecule via an aryl group as defined above. In particular, it can be a tolyl group (-$PhCH_3$).

The term "heterocycle" as used in the present invention refers to a saturated, unsaturated or aromatic hydrocarbon monocycle or polycycle (comprising fused, bridged or spiro rings), such as a bicycle, in which one or more, advantageously 1 to 4, and more advantageously 1 or 2, carbon atoms have each been replaced with a heteroatom selected from nitrogen, oxygen and sulphur atoms, and notably being a nitrogen atom. Advantageously, the heterocycle comprises 5 to 15, notably 5 to 10 atoms in the ring(s). Each ring of the heterocycle has advantageously 5 or 6 members.

According to a particular embodiment, the heterocycle is a saturated, unsaturated or aromatic hydrocarbon monocycle or bicycle (comprising fused, bridged or spiro rings, notably fused rings), each cycle having 5 or 6 members and 1 to 4, notably 1 or 2, carbon atoms having each been replaced with a nitrogen or oxygen atom, notably a nitrogen atom.

A heterocycle can be notably thiophene, furan, pyrrole, imidazole, pyrazole, oxazole, isoxazole, thiazole, isothiazole, triazoles (1,2,3-triazole and 1,2,4-triazole), benzofuran, indole, benzothiophene, benzimidazole, indazole, benzoxazole, benzisoxazole, benzothiazole, benzisothiazole, pyridine, pyrimidine, pyridazine, pyrazine, triazine, quinoline, isoquinoline, quinoxaline, quinazoline, piperidine, piperazine, triazinane, morpholine, pyrrolidine, dihydropyridines, dihydropyrimidines (notably 1,2-dihydropyrimidine), dihydropyridazines, dihydropyrazines, dihydrotriazines, tetrahydropyridines, tetrahydropyrimidines, tetrahydropyridazines, tetrahydropyrazines, tetrahydrotriazines, etc.

The term "nitrogen-containing heterocycle" as used in the present invention refers to a heterocycle as defined above containing at least one nitrogen atom.

Such a nitrogen-containing heterocycle is thus a saturated, unsaturated or aromatic hydrocarbon monocycle or polycycle (comprising fused, bridged or spiro rings), such as a bicycle, in which one or more, advantageously 1 to 4, and more

advantageously 1 or 2, carbon atoms have each been replaced with a heteroatom selected from nitrogen, oxygen and sulphur atoms, at least one of the heteroatom(s) being a nitrogen atom, and notably all the heteroatoms are nitrogen. Advantageously, the heterocycle comprises 5 to 15, notably 5 to 10 atoms in the ring(s). Each ring of the heterocycle has advantageously 5 or 6 members.

According to a particular embodiment, the heterocycle is a saturated, unsaturated or aromatic hydrocarbon monocycle or bicycle (comprising fused, bridged or spiro rings, notably fused rings), each cycle having 5 or 6 members, in which one carbon atom has been replaced with a nitrogen atom and optionally 1 to 3, notably 1, additional carbon atom(s) has/have each been replaced with a nitrogen or oxygen atom, notably a nitrogen atom.

A nitrogen-containing heterocycle can be notably pyrrole, imidazole, pyrazole, oxazole, isoxazole, thiazole, isothiazole, triazoles (1,2,3-triazole and 1,2,4-triazole), indole, benzimidazole, indazole, benzoxazole, benzisoxazole, benzothiazole, benzisothiazole, pyridine, pyrimidine, pyridazine, pyrazine, triazine, quinoline, isoquinoline, quinoxaline, quinazoline, piperidine, piperazine, triazinane, morpholine, pyrrolidine, dihydropyridines, dihydropyrimidines (notably 1,2-dihydropyrimidine), dihydropyridazines, dihydropyrazines, dihydrotriazines, tetrahydropyridines, tetrahydropyrimidines, tetrahydropyridazines, tetrahydropyrazines, tetrahydrotriazines, etc.

The term “heterocycle-(C_1-C_6)alkyl”, as used in the present invention, refers to a heterocycle group as defined above bound to the molecule via a (C_1-C_6)alkyl group as defined above.

The term “heteroaryl” as used in the present invention refers to an aromatic heterocycle as defined above.

According to a particular embodiment, the heteroaryl is an aromatic hydrocarbon monocycle or bicycle (i.e. comprising two fused rings), each cycle having 5 or 6 members, notably 6 members, and 1 to 4, notably 1 or 2, carbon atoms having each been replaced with a nitrogen or oxygen atom, notably a nitrogen atom.

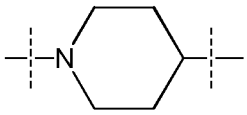
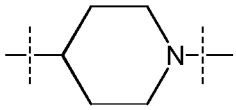
A heteroaryl can be notably thiophene, furan, pyrrole, imidazole, pyrazole, oxazole, isoxazole, thiazole, isothiazole, triazoles (1,2,3-triazole and 1,2,4-triazole), benzofuran, indole, benzothiophene, benzimidazole, indazole, benzoxazole,

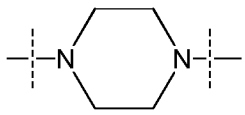
benzisoxazole, benzothiazole, benzisothiazole, pyridine, pyrimidine, pyridazine, pyrazine, triazine, quinoline, isoquinoline, quinoxaline, quinazoline, etc.

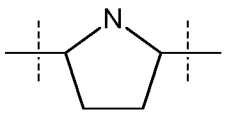
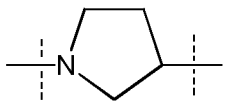
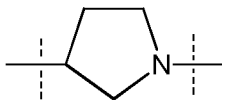
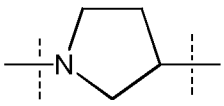
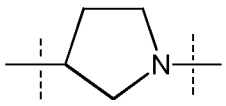
The term "nitrogen-containing heteroaryl" as used in the present invention refers to an aromatic nitrogen-containing heterocycle as defined above.

According to a particular embodiment, the nitrogen-containing heteroaryl is an aromatic hydrocarbon monocycle or bicycle (i.e. comprising two fused rings), each cycle having 5 or 6 members, notably 6 members, in which one carbon atom has been replaced with a nitrogen atom and optionally 1 to 3, notably 1, additional carbon atom(s) has/have each been replaced with a nitrogen or oxygen atom, notably a nitrogen atom.

A nitrogen-containing heteroaryl can be notably pyrrole, imidazole, pyrazole, oxazole, isoxazole, thiazole, isothiazole, triazoles (1,2,3-triazole and 1,2,4-triazole), indole, benzimidazole, indazole, benzoxazole, benzisoxazole, benzothiazole, benzisothiazole, pyridine, pyrimidine, pyridazine, pyrazine, triazine, quinoline, isoquinoline, quinoxaline, quinazoline, etc.

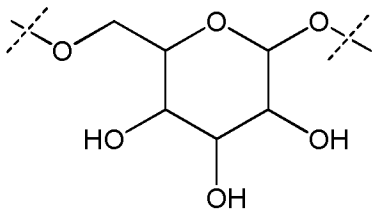
The term "piperidinediyl", as used in the present invention, refers to a divalent piperidine moiety. It can be in particular  or  .

The term "piperazinediyl", as used in the present invention, refers to a divalent piperazine moiety. It can be in particular  .

The term "pyrrolidinediyl", as used in the present invention, refers to a divalent pyrrolidine moiety. It can be in particular  ,  or  , such as  or  .

The term "divalent monoglycosyl", as used in the present invention, refers to a divalent monosaccharide moiety in its cyclic form. This monosaccharide will be advantageously linked by two of its oxygen atoms. Advantageously, the monosaccharide is a pentose (deoxyribose, ribose, arabinose, xylose, lyxose, ribulose, xylulose), a hexose (allose, altrose, galactose, glucose, gulose, idose, mannose, talose,

fructose, psicose, sorbose, tagatose), fucose or rhamnose, in their D or L forms. The monosaccahride is advantageously a hexose in its pyranose form such as allose, altrose, galactose, glucose, gulose, idose, mannose, talose, fructose, psicose, sorbose or tagatose, notably allose, altrose, galactose, glucose, gulose, idose, mannose or talose, and in particular glucose. The divalent monoglycosylwill be advantageously a group



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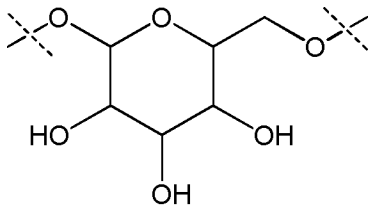

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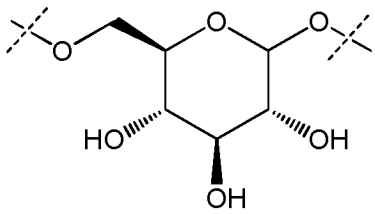
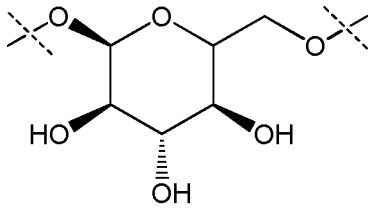


or



(glucose moieties).

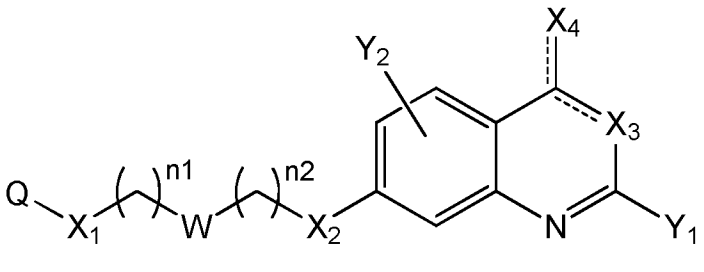
An "optionally substituted" radical, as used in the present invention, refers to a radical optionally substituted with one or several groups selected from halogen; oxo (=O); NO_2; OR_{11}; $NR_{12}R_{13}$; $C(O)R_{14}$; CO_2R_{15}; $OC(O)R_{16}$; $C(O)NR_{17}R_{18}$; $NR_{19}C(O)R_{20}$; $S(O)R_{50}$; $S(O)_2R_{51}$; $S(O)_2NR_{52}R_{53}$; $(C_1\text{-}C_6)$alkyl optionally substituted with one or several groups selected from halogen, OR_{21}, $NR_{22}R_{23}$, $C(O)R_{24}$, CO_2R_{25}, $OC(O)R_{26}$, $C(O)NR_{27}R_{28}$, $NR_{29}C(O)R_{30}$, $S(O)R_{54}$, $S(O)_2R_{55}$, and $S(O)_2NR_{56}R_{57}$; and aryl or aryl-$(C_1\text{-}C_6)$alkyl optionally substituted with one or several groups selected from halogen, OR_{31}, $NR_{32}R_{33}$, $C(O)R_{34}$, CO_2R_{35}, $OC(O)R_{36}$, $C(O)NR_{37}R_{38}$, $NR_{39}C(O)R_{40}$, $S(O)R_{58}$, $S(O)_2R_{59}$, and $S(O)_2NR_{60}R_{61}$,

with R_{11} to R_{40} and R_{50} to R_{61} representing, independently of one another, H or $(C_1\text{-}C_6)$alkyl.

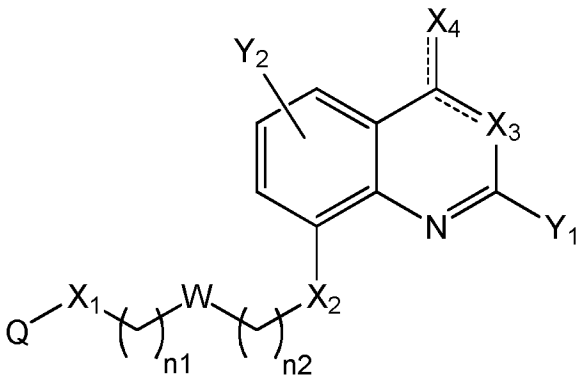
The person skilled in the art will understand however that oxo (=O) cannot represent a substituent of an aryl moiety.

The term "halogen", as used in the present invention, refers to a fluorine, bromine, chlorine or iodine atom.

According to a particular embodiment of the present invention, the compound of the present invention is a compound of the following formula (I-1) or (I-2), in particular of the following formula (I-1):



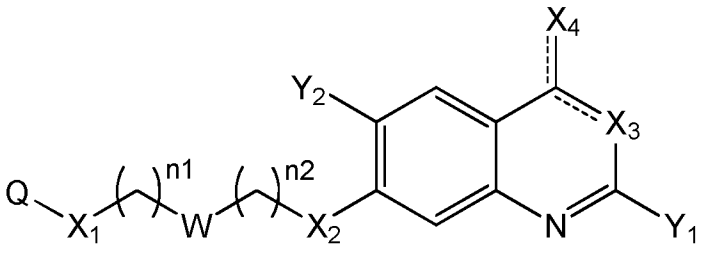
(I-1)



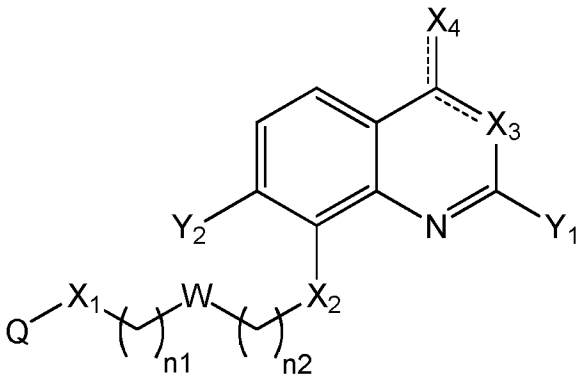
(I-2)

or a pharmaceutically acceptable salt or solvate thereof.

According to another particular embodiment of the present invention, the compound of the present invention is a compound of the following formula (I-3) or (I-4), in particular of the following formula (I-3):



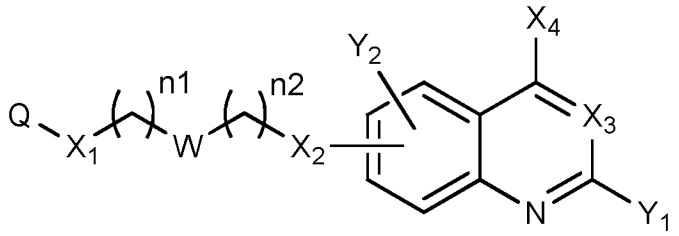
(I-3)



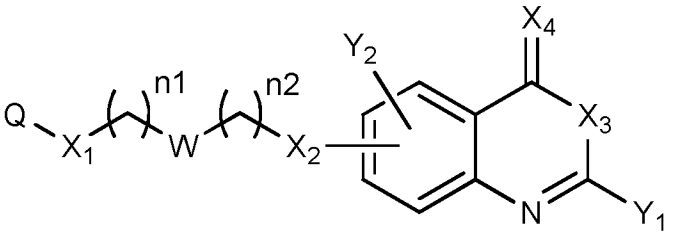
(I-4)

or a pharmaceutically acceptable salt or solvate thereof.

The formula (I) of the present invention comprises two bonds ------. According to a particular embodiment, one of them is a single bond and the other is a double bond. Thus the compound of the present invention can correspond to a compound of the following formula (Ia) or (Ib), preferably of the following formula (Ia):



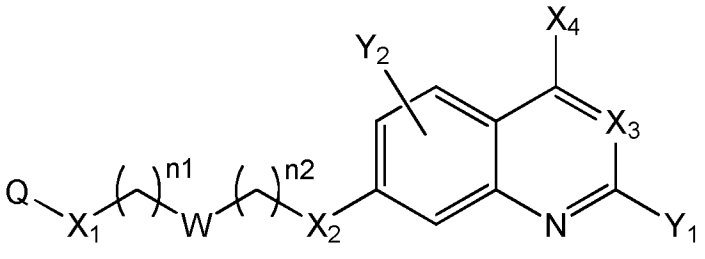
(Ia)



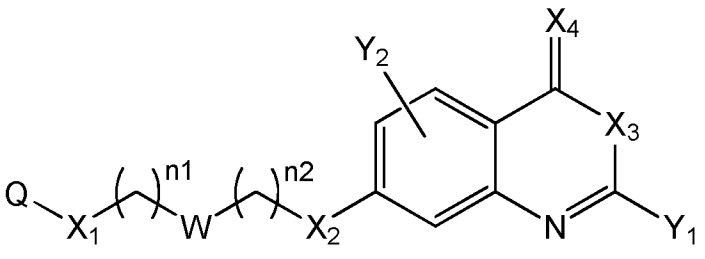
(Ib),

or a pharmaceutically acceptable salt or solvate thereof.

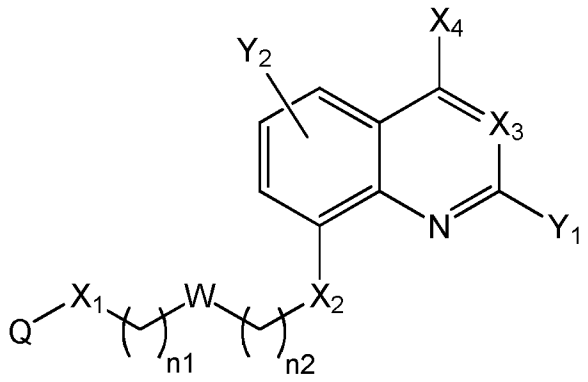
According to another particular embodiment of the present invention, the compound of the present invention is a compound of the following formula (I-1a), (I-1b), (I-2a) or (I-2b), preferably of the following formula (I-1a) or (I-2a), in particular of the following formula (I-1a):



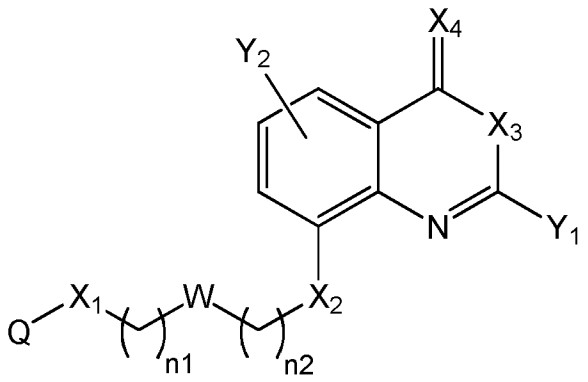
(I-1a)



(I-1b)



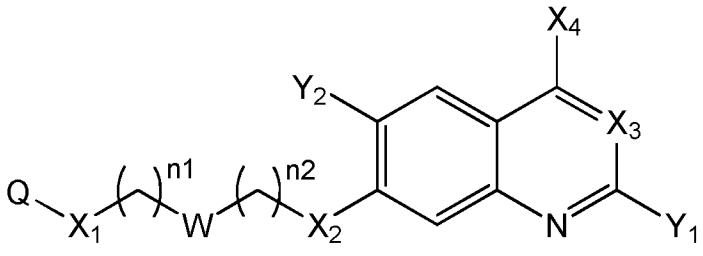
(I-2a)



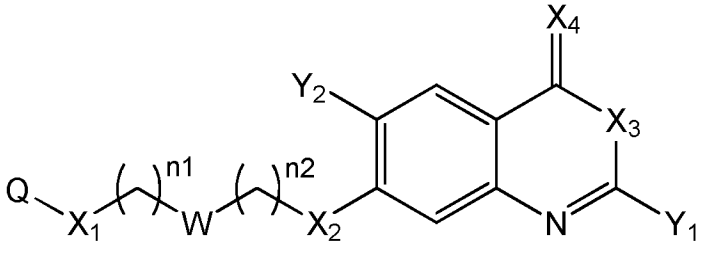
(I-2b)

or a pharmaceutically acceptable salt or solvate thereof.

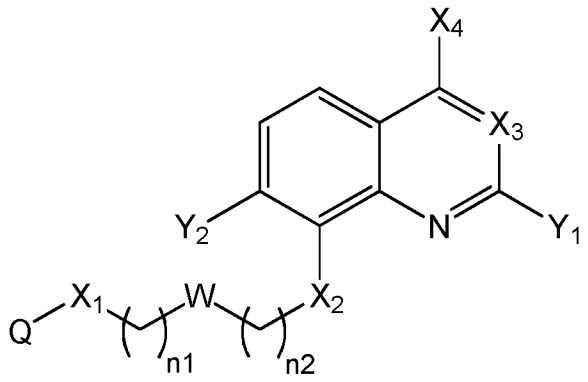
According to another particular embodiment of the present invention, the compound of the present invention is a compound of the following formula (I-3a), (I-3b), (I-4a) or (I-4b), preferably of the following formula (I-3a) or (I-4a), in particular of the following formula (I-3a):



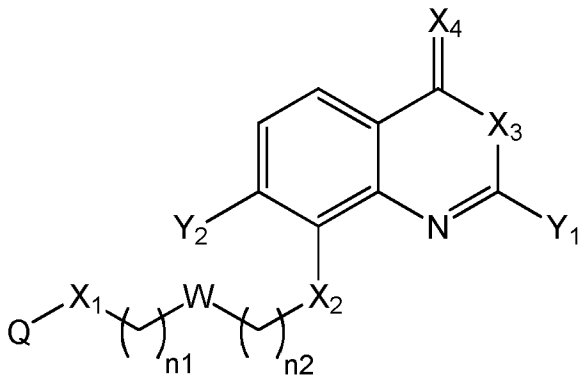
(I-3a)



(I-3b)



(I-4a)



(I-4b)

or a pharmaceutically acceptable salt or solvate thereof.

In particular, n1 can represent 0, 1, 2, 3 or 4, notably 0, 1 or 2.

n1 can represent also 1, 2, 3 or 4, notably 1 or 2.

In particular, n2 can represent 0, 1, 2, 3 or 4, notably 0, 1 or 2.

n2 can represent also 1, 2, 3 or 4, notably 1 or 2.

According to a preferred embodiment, n1 represents 1, 2, 3 or 4, notably 1 or 2, and n2 represents 0, 1, 2, 3 or 4, notably 0, 1 or 2, provided that $n2 \neq 0$ when $X_2 = O$ or NR_2.

X_1 represents advantageously NH or O, in particular NH.

X_2 represents advantageously a bond, NH or O, in particular a bond or O, such as O.

According to a particular embodiment, X_1 represents NR_1 and X_2 represents a bond or O, such as O; notably X_1 represents NH and X_2 represents a bond or O, such as O.

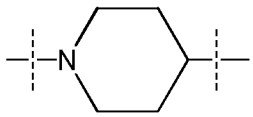
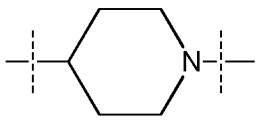
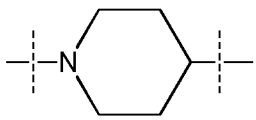
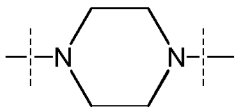
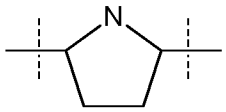
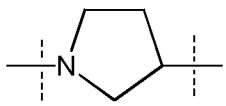
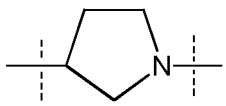
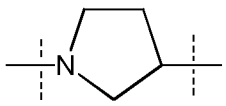
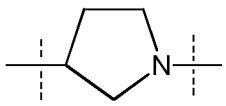
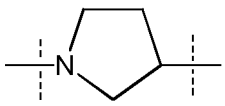
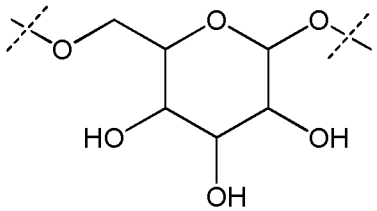
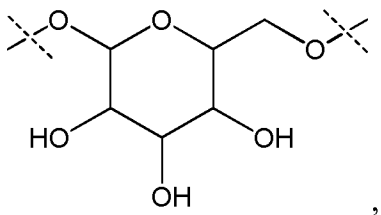
According to a first embodiment, W represents a bond, a divalent monoglycosyl, NR_0, a piperidinediyl, a piperazinediyl or a pyrrolidinediyl.

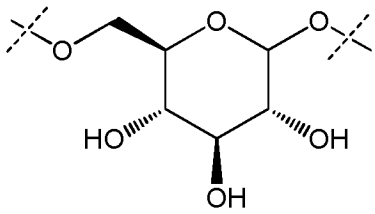
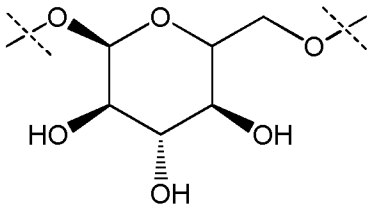
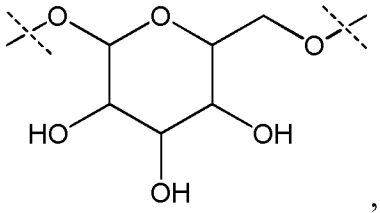
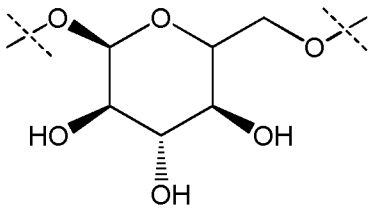
According to a second embodiment, W represents a bond, a divalent monoglycosyl, a piperidinediyl, a piperazinediyl or a pyrrolidinediyl. Advantageously, W represents a bond, a piperidinediyl or a piperazinediyl.

According to a third embodiment, W represents NR_0, a divalent monoglycosyl, a piperidinediyl, a piperazinediyl or a pyrrolidinediyl, notably NR_0, a piperidinediyl or a piperazinediyl.

According to a fourth embodiment, W represents a divalent monoglycosyl, a piperidinediyl, a piperazinediyl or a pyrrolidinediyl, notably a divalent monoglycosyl, a piperidinediyl or a piperazinediyl. Advantageously, W represents a piperidinediyl or a piperazinediyl.

According to sixth embodiment, W represents a divalent monoglycosyl.

In these six embodiments, the piperidinediyl group can be  or  , and in particular is  , the nitrogen atom being linked to $(CH_2)_{n1}$. The piperazinediyl group is in particular  . The pyrrolidinediyl group can be  ,  or  , such as  or  , and in particular is  , the nitrogen atom being linked to $(CH_2)_{n1}$. The divalent monoglycosyl group can be  or  , such as



or . In particular, the divalent monoglycosyl group can be  , such as  , the oxygen atom of the CH_2O moiety being linked to $(CH_2)_{n1}$. R_0 represents notably H; CHO; or a $(C_1$-$C_6)$alkyl optionally substituted with CO_2H or CO_2-$((C_1$-$C_6)$alkyl) (e.g. CO_2Me). According to a first particular embodiment, R_0 represents H. According to a second particular embodiment, R_0 represents CHO or CO_2-$((C_1$-$C_6)$alkyl), such as CHO. According to a third particular embodiment, R_0 represents a $(C_1$-$C_6)$alkyl optionally substituted with CHO, CO_2H or CO_2-$((C_1$-$C_6)$alkyl); notably a $(C_1$-$C_6)$alkyl optionally substituted with CO_2H or CO_2-$((C_1$-$C_6)$alkyl) (e.g. CO_2Me); in particular an unsubstituted $(C_1$-$C_6)$alkyl. According to a fourth particular embodiment, R_0 represents H or a $(C_1$-$C_6)$alkyl.

Q represents notably an aryl or nitrogen-containing heterocycle, notably a nitrogen-containing heterocycle, optionally substituted with one or several groups selected from halogen; oxo (=O); NO_2; OR_{11}; $NR_{12}R_{13}$; $C(O)R_{14}$; CO_2R_{15}; $OC(O)R_{16}$; $C(O)NR_{17}R_{18}$; $NR_{19}C(O)R_{20}$; $S(O)R_{50}$; $S(O)_2R_{51}$; $S(O)_2NR_{52}R_{53}$; $(C_1$-$C_6)$alkyl optionally substituted with one or several groups selected from halogen, OR_{21}, $NR_{22}R_{23}$, $C(O)R_{24}$, CO_2R_{25}, $OC(O)R_{26}$, $C(O)NR_{27}R_{28}$, $NR_{29}C(O)R_{30}$, $S(O)R_{54}$, $S(O)_2R_{55}$, and $S(O)_2NR_{56}R_{57}$; and aryl or aryl-$(C_1$-$C_6)$alkyl optionally substituted with one or several groups selected from halogen, OR_{31}, $NR_{32}R_{33}$, $C(O)R_{34}$, CO_2R_{35}, $OC(O)R_{36}$, $C(O)NR_{37}R_{38}$, $NR_{39}C(O)R_{40}$, $S(O)R_{58}$, $S(O)_2R_{59}$, and $S(O)_2NR_{60}R_{61}$,

with R_{11} to R_{40} and R_{50} to R_{61} representing, independently of one another, H or $(C_1$-$C_6)$alkyl.

Q represents notably an aryl or nitrogen-containing heterocycle, notably a nitrogen-containing heterocycle, optionally substituted with one or several groups selected from halogen; oxo (=O); OR_{11}; $NR_{12}R_{13}$; $C(O)R_{14}$; CO_2R_{15}; $OC(O)R_{16}$; $C(O)NR_{17}R_{18}$; $NR_{19}C(O)R_{20}$; $(C_1\text{-}C_6)$alkyl optionally substituted with one or several groups selected from halogen, OR_{21}, $NR_{22}R_{23}$, $C(O)R_{24}$, CO_2R_{25}, $OC(O)R_{26}$, $C(O)NR_{27}R_{28}$, and $NR_{29}C(O)R_{30}$; and aryl optionally substituted with one or several groups selected from halogen, OR_{31}, $NR_{32}R_{33}$, $C(O)R_{34}$, CO_2R_{35}, $OC(O)R_{36}$, $C(O)NR_{37}R_{38}$, and $NR_{39}C(O)R_{40}$,

with R_{11} to R_{40} representing, independently of one another, H or $(C_1\text{-}C_6)$alkyl.

Q represents in particular an aryl or nitrogen-containing heterocycle, notably a nitrogen-containing heterocycle, optionally substituted with one or several groups selected from halogen; oxo (=O); $(C_1\text{-}C_6)$alkyl optionally substituted with one or several groups selected from halogen, OR_{21}, $NR_{22}R_{23}$, $C(O)R_{24}$, CO_2R_{25}, $OC(O)R_{26}$, $C(O)NR_{27}R_{28}$, and $NR_{29}C(O)R_{30}$; and aryl optionally substituted with one or several groups selected from halogen, OR_{31}, $NR_{32}R_{33}$, $C(O)R_{34}$, CO_2R_{35}, $OC(O)R_{36}$, $C(O)NR_{37}R_{38}$, and $NR_{39}C(O)R_{40}$.

Q can also represent an aryl or nitrogen-containing heterocycle, notably a nitrogen-containing heterocycle, optionally substituted with one or several groups selected from halogen; oxo (=O); OR_{11}; $NR_{12}R_{13}$; $C(O)R_{14}$; CO_2R_{15}; $OC(O)R_{16}$; $C(O)NR_{17}R_{18}$; $NR_{19}C(O)R_{20}$; and $(C_1\text{-}C_6)$alkyl optionally substituted with one or several groups selected from halogen, OR_{21}, $NR_{22}R_{23}$, $C(O)R_{24}$, CO_2R_{25}, $OC(O)R_{26}$, $C(O)NR_{27}R_{28}$, and $NR_{29}C(O)R_{30}$.

Q can represent in particular an aryl or nitrogen-containing heterocycle, notably a nitrogen-containing heterocycle, optionally substituted with one or several groups selected from halogen; oxo (=O); OR_{11}; $NR_{12}R_{13}$; and $(C_1\text{-}C_6)$alkyl optionally substituted with one or several groups selected from halogen, OR_{21} and$NR_{22}R_{23}$.

Q represents particularly an aryl or nitrogen-containing heterocycle, notably a nitrogen-containing heterocycle, optionally substituted with one or several groups selected from halogen; oxo (=O); and $(C_1\text{-}C_6)$alkyl optionally substituted with one or several groups selected from halogen, OR_{21} and $NR_{22}R_{23}$.

Q represents more particularly an aryl or nitrogen-containing heterocycle, notably a nitrogen-containing heterocycle, optionally substituted with one or several

groups selected from halogen, oxo (=O), and (C_1-C_6)alkyl. Q can represent also an aryl or nitrogen-containing heterocycle, notably a nitrogen-containing heterocycle.

In the definitions of Q above, the aryl is preferably a phenyl or a naphtyl, in particular a phenyl.

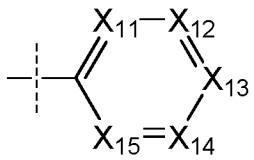
In the definitions of Q above, the nitrogen-containing heterocycle is notably a saturated, unsaturated or aromatic hydrocarbon monocycle or bicycle (comprising fused, bridged or spiro rings, notably fused rings), each cycle having 5 or 6 members, in which one carbon atom has been replaced with a nitrogen atom and optionally 1 to 3, notably 1, additional carbon atom(s) has/have each been replaced with a nitrogen or oxygen atom, notably a nitrogen atom. The heterocycle can be notably chosen among pyrrole, imidazole, pyrazole, triazoles, indole, benzimidazole, indazole, pyridine, pyrimidine, pyridazine, pyrazine, triazine, quinoline, isoquinoline, quinoxaline, quinazoline, piperidine, piperazine, triazinane, pyrrolidine, dihydropyridines, dihydropyrimidines (notably 1,2-dihydropyrimidine), dihydropyridazines, dihydropyrazines, dihydrotriazines, tetrahydropyridines, tetrahydropyrimidines, tetrahydropyridazines, tetrahydropyrazines and tetrahydrotriazines. In particular, the heterocycle can be chosen among pyridine, pyrimidine, pyridazine, pyrazine, quinoline, isoquinoline, quinoxaline, quinazoline, piperidine, piperazine, dihydropyridines, dihydropyrimidines (notably 1,2-dihydropyrimidine), dihydropyridazines, dihydropyrazines, tetrahydropyridines, tetrahydropyrimidines, tetrahydropyridazines and tetrahydropyrazines. More particularly, the heterocycle can be chosen among quinoline, quinazoline, pyridine, pyrimidine and dihydropyrimidines (notably 1,2-dihydropyrimidine). Notably, the heterocycle can be chosen among quinoline, pyridine and dihydropyrimidines (notably 1,2-dihydropyrimidine).

In the definitions of Q above, the nitrogen-containing heterocycle is preferably a nitrogen-containing heteroaryl, such as an aromatic hydrocarbon monocycle or bicycle (i.e. comprising fused rings), each cycle having 5 or 6 members, notably 6 members, in which one carbon atom has been replaced with a nitrogen atom and optionally 1 to 3, notably 1, additional carbon atom(s) has/have each been replaced with a nitrogen or oxygen atom, notably a nitrogen atom. Preferably, the nitrogen-containing hereoaryl is an aromatic hydrocarbon monocycle or bicycle (i.e. comprising fused rings), each cycle having 6 members, in which one carbon atom has been replaced with a nitrogen atom

and optionally one additional carbon atom has been replaced with a nitrogen or oxygen atom, notably a nitrogen atom. The nitrogen-containing heteroaryl can be notably chosen among pyrrole, imidazole, pyrazole, oxazole, isoxazole, thiazole, isothiazole, triazoles (1,2,3-triazole and 1,2,4-triazole), indole, benzimidazole, indazole, benzoxazole, benzisoxazole, benzothiazole, benzisothiazole, pyridine, pyrimidine, pyridazine, pyrazine, triazine, quinoline, isoquinoline, quinoxaline and quinazoline. In particular, the nitrogen-containing heteroaryl can be chosen among pyridine, pyrimidine, pyridazine, pyrazine, quinoline, isoquinoline, quinoxaline, and quinazoline. Notably, the nitrogen-containing heteroaryl can be chosen among quinoline, quinazoline, pyridine and pyrimidine. In particular, it is quinoline or pyridine.

In the definitions of Q above, the nitrogen-containing heterocycle can be in particular a quinoline.

According to a preferred embodiment, Q represents a cycle of the following formula:

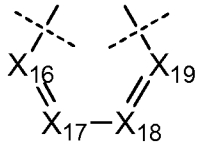


wherein:

- X_{11} represents N or CR_{41},
- X_{12} represents N or CR_{42},
- X_{13} represents N or C-$NR_{43a}R_{43b}$, notably N,
- X_{14} represents N or CR_{44},
- X_{15} represents N or CR_{45},
- R_{43a} and R_{43b} each represent, independently of each other, H or (C_1-C_6)alkyl (such as methyl),
- R_{41}, R_{42}, R_{44} and R_{45} each represent, independently of each other, hydrogen; halogen; NO_2; OR_{11}; $NR_{12}R_{13}$; $C(O)R_{14}$; CO_2R_{15}; $OC(O)R_{16}$; $C(O)NR_{17}R_{18}$; $NR_{19}C(O)R_{20}$; $S(O)R_{50}$; $S(O)_2R_{51}$; $S(O)_2NR_{52}R_{53}$; (C_1-C_6)alkyl optionally substituted with one or several groups selected from halogen, OR_{21}, $NR_{22}R_{23}$, $C(O)R_{24}$, CO_2R_{25}, $OC(O)R_{26}$, $C(O)NR_{27}R_{28}$, $NR_{29}C(O)R_{30}$, $S(O)R_{54}$, $S(O)_2R_{55}$, and $S(O)_2NR_{56}R_{57}$; or aryl or aryl-(C_1-C_6)alkyl optionally substituted with one or

several groups selected from halogen, OR_{31}, $NR_{32}R_{33}$, $C(O)R_{34}$, CO_2R_{35}, $OC(O)R_{36}$, $C(O)NR_{37}R_{38}$, $NR_{39}C(O)R_{40}$, $S(O)R_{58}$, $S(O)_2R_{59}$, and $S(O)_2NR_{60}R_{61}$, or

in the case of R_{44} and R_{45}, R_{44} and R_{45} form together a chain of the following formula:



wherein:

- X_{16} represents N or CR_{46},
- X_{17} represents N or CR_{47},
- X_{18} represents N or CR_{48},
- X_{19} represents N or CR_{49}, and
- R_{46}, R_{47}, R_{48} and R_{49} each represent, independently of one another, hydrogen; halogen; NO_2; OR_{11}; $NR_{12}R_{13}$; $C(O)R_{14}$; CO_2R_{15}; $OC(O)R_{16}$; $C(O)NR_{17}R_{18}$; $NR_{19}C(O)R_{20}$; $S(O)R_{50}$; $S(O)_2R_{51}$; $S(O)_2NR_{52}R_{53}$; $(C_1\text{-}C_6)$alkyl optionally substituted with one or several groups selected from halogen, OR_{21}, $NR_{22}R_{23}$, $C(O)R_{24}$, CO_2R_{25}, $OC(O)R_{26}$, $C(O)NR_{27}R_{28}$, $NR_{29}C(O)R_{30}$, $S(O)R_{54}$, $S(O)_2R_{55}$, and $S(O)_2NR_{56}R_{57}$; or aryl or aryl-$(C_1\text{-}C_6)$alkyl optionally substituted with one or several groups selected from halogen, OR_{31}, $NR_{32}R_{33}$, $C(O)R_{34}$, CO_2R_{35}, $OC(O)R_{36}$, $C(O)NR_{37}R_{38}$, $NR_{39}C(O)R_{40}$, $S(O)R_{58}$, $S(O)_2R_{59}$, and $S(O)_2NR_{60}R_{61}$,

on the proviso that no more than three, notably two, and preferably one, of X_{11}, X_{12}, X_{14}, X_{15}, X_{16}, X_{17}, X_{18} and X_{19} represent N.

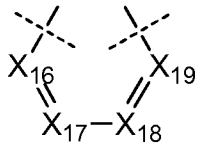
In particular, none of X_{11}, X_{12}, X_{14}, X_{15}, X_{16}, X_{17}, X_{18} and X_{19} represents N.

In particular, none of X_{11}, X_{12}, X_{14}, X_{15}, X_{16}, X_{17}, X_{18} and X_{19} represents N and X_{13} represents N.

Advantageously, R_{41}, R_{42}, R_{44} and R_{45} each represent, independently of each other, hydrogen; halogen; OR_{11}; $NR_{12}R_{13}$; $C(O)R_{14}$; CO_2R_{15}; $OC(O)R_{16}$; $C(O)NR_{17}R_{18}$; $NR_{19}C(O)R_{20}$; $(C_1\text{-}C_6)$alkyl optionally substituted with one or several groups selected from halogen, OR_{21}, $NR_{22}R_{23}$, $C(O)R_{24}$, CO_2R_{25}, $OC(O)R_{26}$, $C(O)NR_{27}R_{28}$, and $NR_{29}C(O)R_{30}$; or aryl or aryl-$(C_1\text{-}C_6)$alkyl optionally substituted with one or several

groups selected from halogen, OR_{31}, $NR_{32}R_{33}$, $C(O)R_{34}$, CO_2R_{35}, $OC(O)R_{36}$, $C(O)NR_{37}R_{38}$, and $NR_{39}C(O)R_{40}$, or

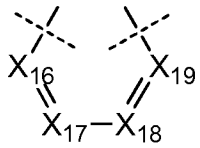
in the case of R_{44} and R_{45}, R_{44} and R_{45} form together a chain of the following formula:



with R_{46}, R_{47}, R_{48} and R_{49} each representing, independently of one another, hydrogen; halogen; OR_{11}; $NR_{12}R_{13}$; $C(O)R_{14}$; CO_2R_{15}; $OC(O)R_{16}$; $C(O)NR_{17}R_{18}$; $NR_{19}C(O)R_{20}$; $(C_1\text{-}C_6)$alkyl optionally substituted with one or several groups selected from halogen, OR_{21}, $NR_{22}R_{23}$, $C(O)R_{24}$, CO_2R_{25}, $OC(O)R_{26}$, $C(O)NR_{27}R_{28}$, and $NR_{29}C(O)R_{30}$; or aryl or aryl-$(C_1\text{-}C_6)$alkyl optionally substituted with one or several groups selected from halogen, OR_{31}, $NR_{32}R_{33}$, $C(O)R_{34}$, CO_2R_{35}, $OC(O)R_{36}$, $C(O)NR_{37}R_{38}$, and $NR_{39}C(O)R_{40}$.

In particular, R_{41}, R_{42}, R_{44} and R_{45} each represent, independently of each other, hydrogen; halogen; OR_{11}; $NR_{12}R_{13}$; $C(O)R_{14}$; CO_2R_{15}; $OC(O)R_{16}$; $C(O)NR_{17}R_{18}$; $NR_{19}C(O)R_{20}$; or $(C_1\text{-}C_6)$alkyl optionally substituted with one or several groups selected from halogen, OR_{21}, $NR_{22}R_{23}$, $C(O)R_{24}$, CO_2R_{25}, $OC(O)R_{26}$, $C(O)NR_{27}R_{28}$, and $NR_{29}C(O)R_{30}$, or

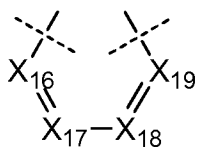
in the case of R_{44} and R_{45}, R_{44} and R_{45} form together a chain of the following formula:



with R_{46}, R_{47}, R_{48} and R_{49} each representing, independently of one another, hydrogen; halogen; OR_{11}; $NR_{12}R_{13}$; $C(O)R_{14}$; CO_2R_{15}; $OC(O)R_{16}$; $C(O)NR_{17}R_{18}$; $NR_{19}C(O)R_{20}$; or $(C_1\text{-}C_6)$alkyl optionally substituted with one or several groups selected from halogen, OR_{21}, $NR_{22}R_{23}$, $C(O)R_{24}$, CO_2R_{25}, $OC(O)R_{26}$, $C(O)NR_{27}R_{28}$, and $NR_{29}C(O)R_{30}$.

Notably, R_{41}, R_{42}, R_{44} and R_{45} each represent, independently of each other, hydrogen; halogen; OR_{11}; $NR_{12}R_{13}$; or $(C_1\text{-}C_6)$alkyl optionally substituted with one or several groups selected from halogen, OR_{21}, and $NR_{22}R_{23}$, or

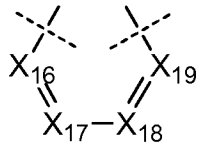
in the case of R_{44} and R_{45}, R_{44} and R_{45} form together a chain of the following formula:



with R_{46}, R_{47}, R_{48} and R_{49} each representing, independently of one another, hydrogen; halogen; OR_{11}; $NR_{12}R_{13}$; or $(C_1\text{-}C_6)$alkyl optionally substituted with one or several groups selected from halogen, OR_{21}, and $NR_{22}R_{23}$.

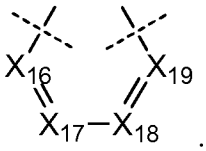
In particular, R_{41}, R_{42}, R_{44} and R_{45} each represent, independently of each other, hydrogen; halogen; OR_{11}; or $NR_{12}R_{13}$; and notably hydrogen, or

in the case of R_{44} and R_{45}, R_{44} and R_{45} form together a chain of the following formula:



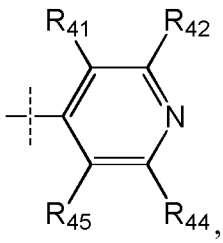
with R_{46}, R_{47}, R_{48} and R_{49} each representing, independently of one another, hydrogen; halogen; OR_{11}; or $NR_{12}R_{13}$.

Preferably, R_{44} and R_{45} form together a chain of the following formula

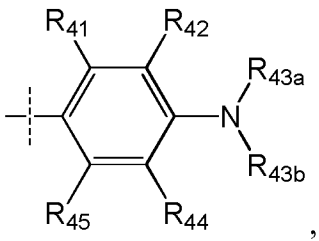


.

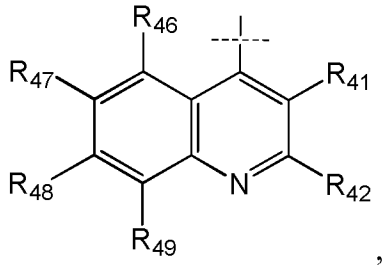
According to a most preferred embodiment, Q represents one of the following cycles:



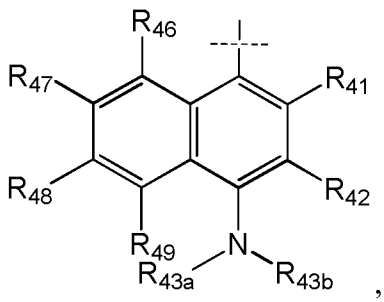
,



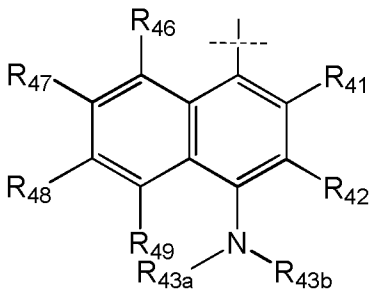
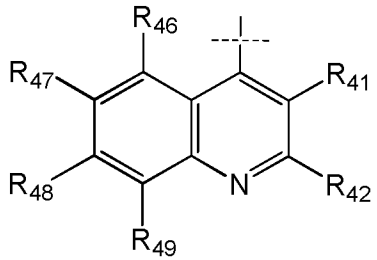
,

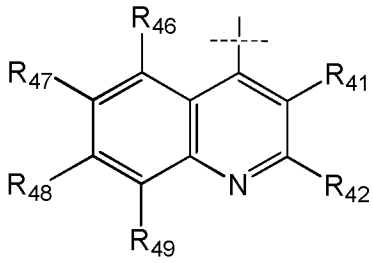


, or



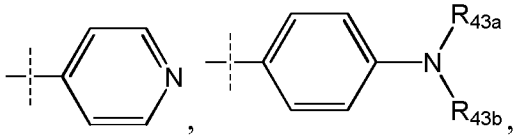
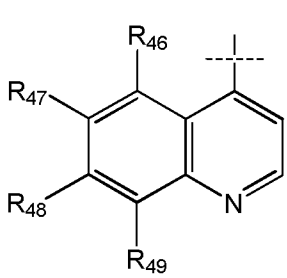
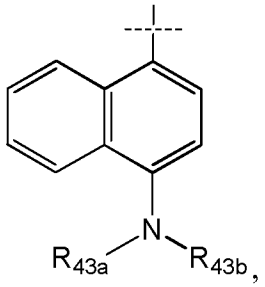
,

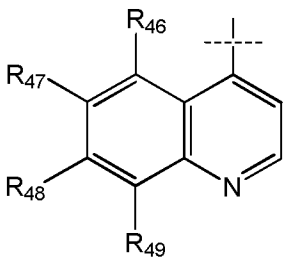
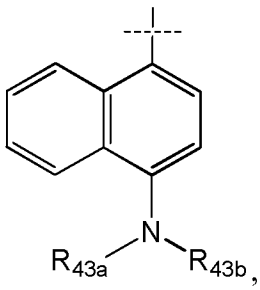
notably,  or  ,

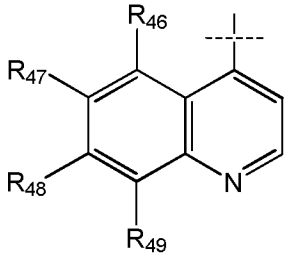
and preferably represents the cycle  ,

with R_{43a} and R_{43b} as defined above and with R_{41}, R_{42} and R_{44} to R_{49} as defined according to one of the definitions above, and in particular with R_{41}, R_{42} and R_{44} to R_{49} each representing, independently of one another, hydrogen; halogen; OR_{11}; or $NR_{12}R_{13}$.

In particular, Q represents one of the following cycles:

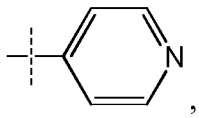
 ,  ,  ,

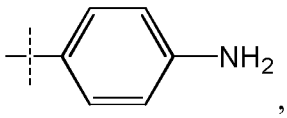
notably  , or  ,

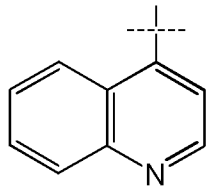
and preferably represents the cycle  ,

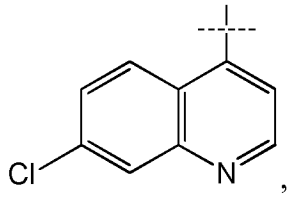
with R_{43a} and R_{43b} as defined above and with R_{46} to R_{49} as defined according to one of the definitions above, and in particular with R_{46} to R_{49} each representing, independently of one another, hydrogen; halogen; OR_{11}; or $NR_{12}R_{13}$.

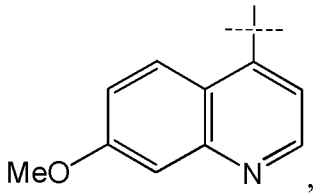
Q can be for example one of the following cycles:

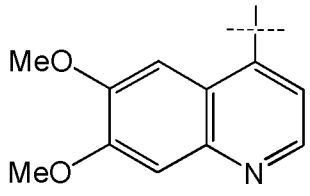


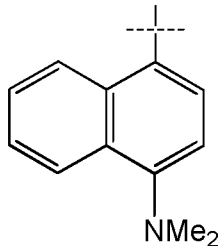
,


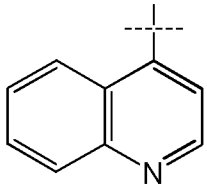
,


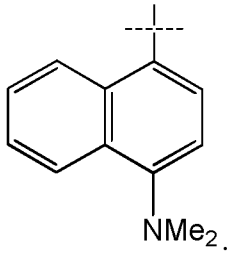
,


,


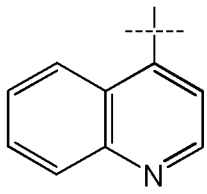
,


or


, such as


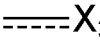
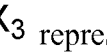
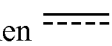
or


.

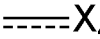
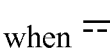
Q can be in particular


.

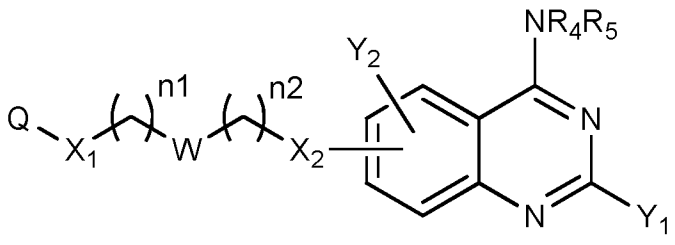
According to a particular embodiment, X_3 represents:

- N when  represents a double bond  , and
- NR_3 when  represents a single bond  ,

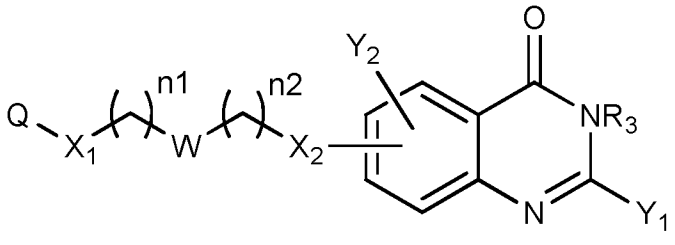
According to another particular embodiment, X_4 represents:

- O when  represents a double bond  , and
- NR_4R_5 when  represents a single bond  ,

The compound of the present invention can correspond in particular to a compound of the following formula (Ic) or (Id), preferably of the following formula (I-c):



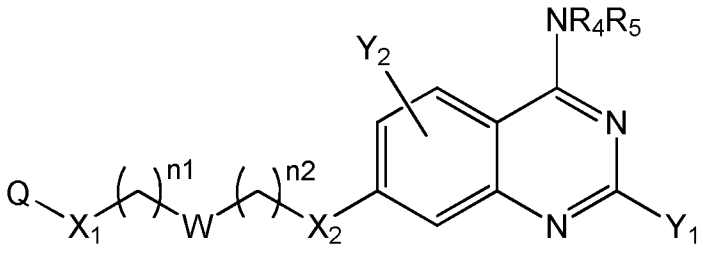
(Ic)



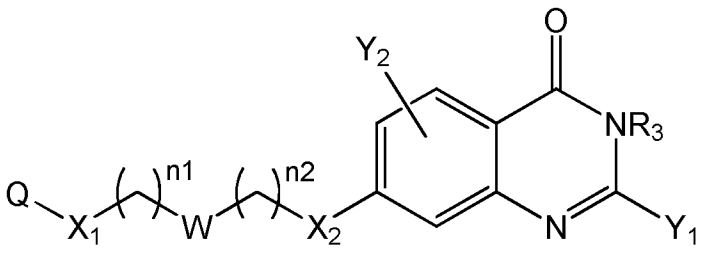
(Id)

or a pharmaceutically acceptable salt or solvate thereof.

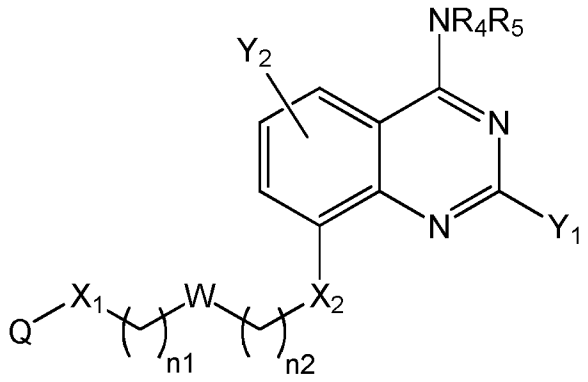
According to another particular embodiment of the present invention, the compound of the present invention is a compound of the following formula (I-1c), (I-1d), (I-2c) or (I-2d), preferably of the following formula (I-1c) or (I-2c), in particular of the following formula (I-1c):



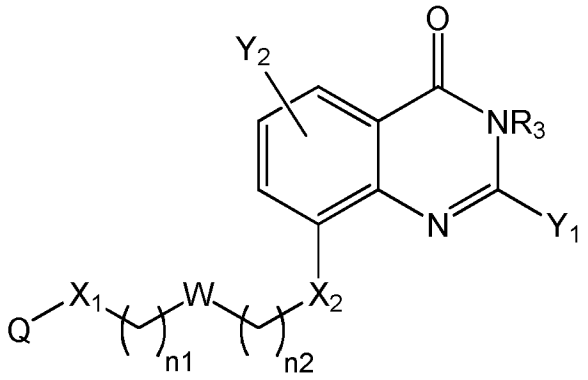
(I-1c)



(I-1d)



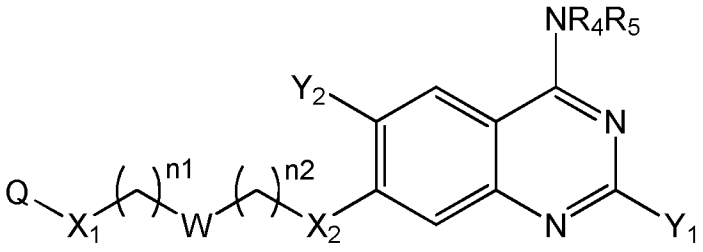
(I-2c)



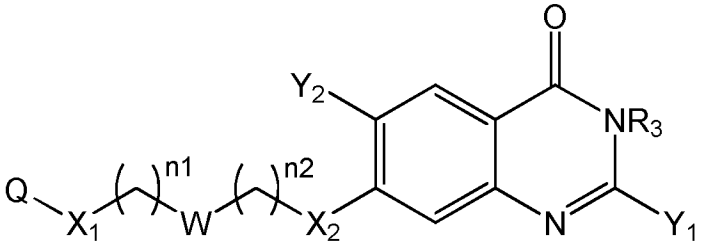
(I-2d)

or a pharmaceutically acceptable salt or solvate thereof.

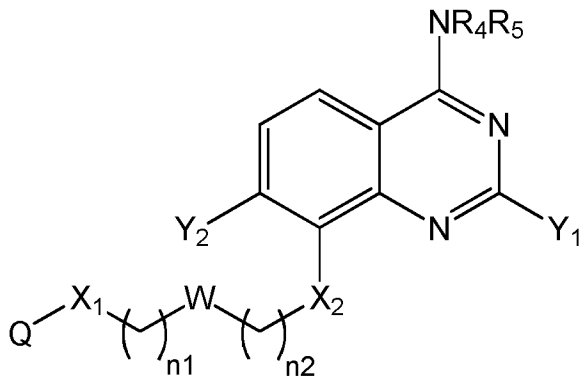
According to another particular embodiment of the present invention, the compound of the present invention is a compound of the following formula (I-3c), (I-3d), (I-4c) or (I-4d), preferably of the following formula (I-3c) or (I-4c), in particular of the following formula (I-3c):



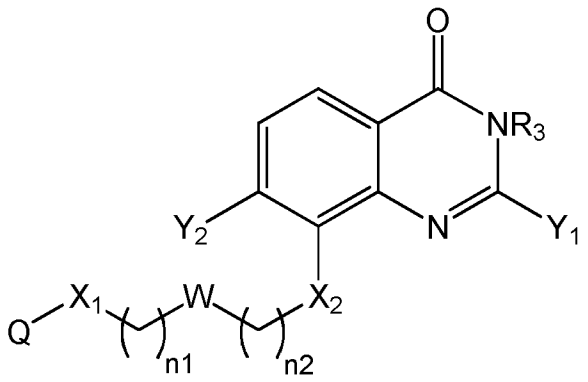
(I-3c)



(I-3d)



(I-4c)



(I-4d)

or a pharmaceutically acceptable salt or solvate thereof.

More particularly, R_3 and R_4 will represent, independently of each other, H, (C_1-C_6)alkyl, aryl, heterocycle, -((C_1-C_6)alkyl)-X_5-aryl or -((C_1-C_6)alkyl)-X_5-heterocycle; such as H, (C_1-C_6)alkyl, aryl, heterocycle, aryl-(C_1-C_6)alkyl, heterocycle-(C_1-C_6)alkyl, -((C_1-C_6)alkyl)-NH-aryl or -((C_1-C_6)alkyl)-NH-heterocycle; notably aryl, heterocycle, aryl-(C_1-C_6)alkyl, heterocycle-(C_1-C_6)alkyl, -((C_1-C_6)alkyl)-NH-aryl or -((C_1-C_6)alkyl)-NH-heterocycle; more particularly heterocycle, aryl-(C_1-C_6)alkyl or -((C_1-C_6)alkyl)-NH-aryl,

each aryl or heterocycle moiety being optionally substituted with one or several groups selected from halogen; oxo (=O); NO_2; OR_{11}; $NR_{12}R_{13}$; $C(O)R_{14}$; CO_2R_{15}; $OC(O)R_{16}$; $C(O)NR_{17}R_{18}$; $NR_{19}C(O)R_{20}$; $S(O)R_{50}$; $S(O)_2R_{51}$; $S(O)_2NR_{52}R_{53}$; (C_1-C_6)alkyl optionally substituted with one or several groups selected from halogen, OR_{21}, $NR_{22}R_{23}$, $C(O)R_{24}$, CO_2R_{25}, $OC(O)R_{26}$, $C(O)NR_{27}R_{28}$, $NR_{29}C(O)R_{30}$, $S(O)R_{54}$, $S(O)_2R_{55}$, and $S(O)_2NR_{56}R_{57}$; and aryl or aryl-(C_1-C_6)alkyl optionally substituted with one or several groups selected from halogen, OR_{31}, $NR_{32}R_{33}$, $C(O)R_{34}$, CO_2R_{35}, $OC(O)R_{36}$, $C(O)NR_{37}R_{38}$, $NR_{39}C(O)R_{40}$, $S(O)R_{58}$, $S(O)_2R_{59}$, and $S(O)_2NR_{60}R_{61}$,

with R_{11} to R_{40} and R_{50} to R_{61} representing, independently of one another, H or (C_1-C_6)alkyl.

R_3 and R_4 represent notably, independently of each other, H, (C_1-C_6)alkyl, aryl, heterocycle, -((C_1-C_6)alkyl)-X_5-aryl or -((C_1-C_6)alkyl)-X_5-heterocycle; such as H, (C_1-C_6)alkyl, aryl, heterocycle, aryl-(C_1-C_6)alkyl, heterocycle-(C_1-C_6)alkyl, -((C_1-C_6)alkyl)-NH-aryl or -((C_1-C_6)alkyl)-NH-heterocycle; notably aryl, heterocycle, aryl-(C_1-C_6)alkyl, heterocycle-(C_1-C_6)alkyl, -((C_1-C_6)alkyl)-NH-aryl or -((C_1-C_6)alkyl)-NH-heterocycle; more particularly heterocycle, aryl-(C_1-C_6)alkyl or -((C_1-C_6)alkyl)-NH-aryl,

each aryl or heterocycle moiety being optionally substituted with one or several groups selected from halogen; oxo (=O); NO_2; OR_{11}; $NR_{12}R_{13}$; $C(O)R_{14}$; $S(O)_2R_{51}$; $S(O)_2NR_{52}R_{53}$; (C_1-C_6)alkyl optionally substituted with one or several groups selected from halogen, OR_{21}, $NR_{22}R_{23}$, $C(O)R_{24}$, $S(O)_2R_{55}$, and $S(O)_2NR_{56}R_{57}$; and aryl or aryl-(C_1-C_6)alkyl optionally substituted with one or several groups selected from halogen, OR_{31}, $NR_{32}R_{33}$, $C(O)R_{34}$, $S(O)_2R_{59}$, and $S(O)_2NR_{60}R_{61}$.

R_3 and R_4 represent notably, independently of each other, H, (C_1-C_6)alkyl, aryl, heterocycle, -((C_1-C_6)alkyl)-X_5-aryl or -((C_1-C_6)alkyl)-X_5-heterocycle; such as H, (C_1-C_6)alkyl, aryl, heterocycle, aryl-(C_1-C_6)alkyl, heterocycle-(C_1-C_6)alkyl, -((C_1-C_6)alkyl)-NH-aryl or -((C_1-C_6)alkyl)-NH-heterocycle; notably aryl, heterocycle, aryl-(C_1-C_6)alkyl, heterocycle-(C_1-C_6)alkyl, -((C_1-C_6)alkyl)-NH-aryl or -((C_1-C_6)alkyl)-NH-heterocycle; more particularly heterocycle, aryl-(C_1-C_6)alkyl or -((C_1-C_6)alkyl)-NH-aryl,

each aryl or heterocycle moiety being optionally substituted with one or several groups selected from halogen; oxo (=O); NO_2; OR_{11}; $NR_{12}R_{13}$; $C(O)R_{14}$; (C_1-C_6)alkyl optionally substituted with one or several groups selected from halogen, OR_{21} and $NR_{22}R_{23}$; and aryl or aryl-(C_1-C_6)alkyl optionally substituted with one or several groups selected from halogen, OR_{31} and $NR_{32}R_{33}$.

R_3 and R_4 represent notably, independently of each other, H, (C_1-C_6)alkyl, aryl, heterocycle, -((C_1-C_6)alkyl)-X_5-aryl or -((C_1-C_6)alkyl)-X_5-heterocycle; such as H, (C_1-C_6)alkyl, aryl, heterocycle, aryl-(C_1-C_6)alkyl, heterocycle-(C_1-C_6)alkyl, -((C_1-C_6)alkyl)-NH-aryl or -((C_1-C_6)alkyl)-NH-heterocycle; notably aryl, heterocycle, aryl-(C_1-C_6)alkyl, heterocycle-(C_1-C_6)alkyl, -((C_1-C_6)alkyl)-NH-aryl or -((C_1-C_6)alkyl)-NH-

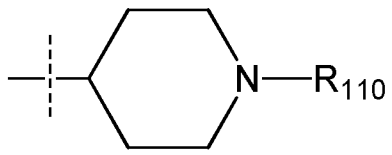
heterocycle; more particularly heterocycle, aryl-(C_1-C_6)alkyl or -((C_1-C_6)alkyl)-NH-aryl,

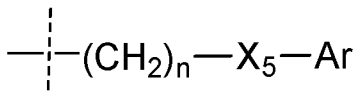
each aryl or heterocycle moiety being optionally substituted with one or several groups selected from halogen; oxo (=O); NO_2; OR_{11}; $NR_{12}R_{13}$; $S(O)_2R_{51}$; $S(O)_2NR_{52}R_{53}$; C_1-C_6)alkyl optionally substituted with one or several groups selected from halogen, OR_{21} and $NR_{22}R_{23}$; and aryl or aryl-(C_1-C_6)alkyl optionally substituted with one or several groups selected from halogen, OR_{31} and $NR_{32}R_{33}$.

R_3 and R_4 represent notably, independently of each other, H, (C_1-C_6)alkyl, aryl, heterocycle, -((C_1-C_6)alkyl)-X_5-aryl or -((C_1-C_6)alkyl)-X_5-heterocycle; such as H, (C_1-C_6)alkyl, aryl, heterocycle, aryl-(C_1-C_6)alkyl, heterocycle-(C_1-C_6)alkyl, -((C_1-C_6)alkyl)-NH-aryl or -((C_1-C_6)alkyl)-NH-heterocycle; notably aryl, heterocycle, aryl-(C_1-C_6)alkyl, heterocycle-(C_1-C_6)alkyl, -((C_1-C_6)alkyl)-NH-aryl or -((C_1-C_6)alkyl)-NH-heterocycle; more particularly heterocycle, aryl-(C_1-C_6)alkyl or -((C_1-C_6)alkyl)-NH-aryl,

each aryl or heterocycle moiety being optionally substituted with one or several groups selected from halogen; OR_{11}; $NR_{12}R_{13}$; (C_1-C_6)alkyl optionally substituted with one or several groups selected from halogen, OR_{21} and $NR_{22}R_{23}$; and aryl or aryl-(C_1-C_6)alkyl optionally substituted with one or several groups selected from halogen, OR_{31} and $NR_{32}R_{33}$.

R_3 and R_4 represent advantageously, independently of each other, a group:

- 

, or
- 

,

where R_{110} represents an aryl or aryl-(C_1-C_6)alkyl group, such as an aryl-(C_1-C_6)alkyl group, optionally substituted with one or several halogen atoms, n is an integer comprised between 1 and 6, X_5 is as defined above and notably is a bond or NH, and Ar is an aryl group such as phenyl or naphtyl,

in particular where R_{110} represents a benzyl or naphtylmethyl group optionally substituted with one or several halogen atoms, n is an integer comprised between 1 and 6, X_5 is a bond or NH, and Ar is phenyl or naphtyl.

In the definitions of R_3 and R_4 above, the aryl preferably is a phenyl or a naphtyl.

In the definitions of R_3 and R_4 above, the heterocycle is notably a saturated, unsaturated or aromatic (notably aromatic) hydrocarbon monocycle or bicycle (comprising fused, bridged or spiro rings, notably fused rings), notably a monocycle, each cycle having 5 or 6 members and 1 to 4, notably 1 or 2, carbon atoms having each been replaced with a nitrogen or oxygen atom, notably a nitrogen atom. The heterocycle can be a heteroaryl. The heterocycle can be notably chosen among pyrrole, imidazole, pyrazole, triazoles, indole, benzimidazole, indazole, pyridine, pyrimidine, pyridazine, pyrazine, triazine, quinoline, isoquinoline, quinoxaline, quinazoline, piperidine, piperazine, triazinane, pyrrolidine, dihydropyridines, dihydropyrimidines (notably 1,2-dihydropyrimidine), dihydropyridazines, dihydropyrazines, dihydrotriazines, tetrahydropyridines, tetrahydropyrimidines, tetrahydropyridazines, tetrahydropyrazines and tetrahydrotriazines. According to a first embodiment, the heterocycle is chosen among pyrrole, imidazole, pyrazole, triazoles, indole, benzimidazole, indazole, pyridine, pyrimidine, pyridazine, pyrazine, triazine, quinoline, isoquinoline, quinoxaline and quinazoline; notably chosen among pyridine, pyrimidine, pyridazine, pyrazine, triazine, quinoline, isoquinoline, quinoxaline and quinazoline. According to a second embodiment, the heterocycle is chosen among piperidine, piperazine, triazinane or pyrrolidine; and in particular is piperidine.

In the definitions of R_3 and R_4 above, X_5 represents in particular a bond or NR_6, notably a bond or NH.

According to a preferred embodiment, R_5 represents H.

Y_1 and Y_2 represent, independently of each other, a halogen atom, R_{100}, OR_{101} or $NR_{102}R_{103}$; notably H, a halogen atom, OR_{101} or $NR_{102}R_{103}$, provided that at least one of Y_1 and Y_2 represent a group other than H.

According to a particular embodiment, Y_1 represents H, a halogen atom, OR_{101} or $NR_{102}R_{103}$; notably H, a halogen atom or $NR_{102}R_{103}$, provided that Y_2 does not represent a hydrogen atom when Y_1 = H.

According to a particular embodiment, Y_2 represents H, a halogen atom, OR_{101} or $NR_{102}R_{103}$; notably H, a halogen atom or OR_{101}; in particular H or OR_{101}, provided that Y_1 does not represent a hydrogen atom when Y_2 = H.

According to another particular embodiment, Y_1 represents H, a halogen atom or $NR_{102}R_{103}$, and Y_2 represents H or OR_{101}, provided that at least one of Y_1 and Y_2 represent a group other than H.

Advantageously, R_{100}, R_{101}, R_{102} and R_{103} represent, independently of one another, H, optionally substituted aryl, optionally substituted heterocycle, or -((C_1-C_6)alkyl)-X_6-A_1,

with X_6 representing a bond, O or NR_{104}, for ex. a bond or NR_{104}, and A_1 representing H, (C_1-C_6)alkyl, optionally substituted aryl or optionally substituted heterocycle,

or, for the R_{102} and R_{103} groups, R_{102} and R_{103} form together, with the nitrogen carrying them, an optionally substituted heterocycle, and

where the optionally substituted aryl and optionally substituted heterocycle are optionally substituted with one or several groups selected from halogen; oxo (=O); NO_2; OR_{11}; $NR_{12}R_{13}$; $C(O)R_{14}$; CO_2R_{15}; $OC(O)R_{16}$; $C(O)NR_{17}R_{18}$; $NR_{19}C(O)R_{20}$; $S(O)R_{50}$; $S(O)_2R_{51}$; $S(O)_2NR_{52}R_{53}$; (C_1-C_6)alkyl optionally substituted with one or several groups selected from halogen, OR_{21}, $NR_{22}R_{23}$, $C(O)R_{24}$, CO_2R_{25}, $OC(O)R_{26}$, $C(O)NR_{27}R_{28}$, $NR_{29}C(O)R_{30}$, $S(O)R_{54}$, $S(O)_2R_{55}$, and $S(O)_2NR_{56}R_{57}$; and aryl or aryl-(C_1-C_6)alkyl optionally substituted with one or several groups selected from halogen, OR_{31}, $NR_{32}R_{33}$, $C(O)R_{34}$, CO_2R_{35}, $OC(O)R_{36}$, $C(O)NR_{37}R_{38}$, $NR_{39}C(O)R_{40}$, $S(O)R_{58}$, $S(O)_2R_{59}$, and $S(O)_2NR_{60}R_{61}$,

with R_{11} to R_{40} and R_{50} to R_{61} representing, independently of one another, H or (C_1-C_6)alkyl.

Notably, R_{100}, R_{101}, R_{102} and R_{103} represent, independently of one another, H, optionally substituted aryl, optionally substituted heterocycle, or -((C_1-C_6)alkyl)-X_6-A_1,

with X_6 representing a bond, O or NR_{104}, for ex. a bond or NR_{104}, and A_1 representing H, (C_1-C_6)alkyl, optionally substituted aryl or optionally substituted heterocycle,

or, for the R_{102} and R_{103} groups, R_{102} and R_{103} form together, with the nitrogen carrying them, an optionally substituted heterocycle, and

where the optionally substituted aryl and optionally substituted heterocycle are optionally substituted with one or several groups selected from halogen; oxo (=O); NO_2; OR_{11}; $NR_{12}R_{13}$; $C(O)R_{14}$; CO_2R_{15}; $OC(O)R_{16}$; $C(O)NR_{17}R_{18}$; $NR_{19}C(O)R_{20}$; $(C_1$-$C_6)$alkyl optionally substituted with one or several groups selected from halogen, OR_{21} or $NR_{22}R_{23}$; and aryl or aryl-$(C_1$-$C_6)$alkyl optionally substituted with one or several groups selected from halogen, OR_{31} or $NR_{32}R_{33}$.

Notably, R_{100}, R_{101}, R_{102} and R_{103} represent, independently of one another, H, optionally substituted aryl, optionally substituted heterocycle, or -$((C_1$-$C_6)$alkyl$)$-X_6-A_1, with X_6 representing a bond, O or NR_{104}, for ex. a bond or NR_{104}, and A_1 representing H, $(C_1$-$C_6)$alkyl, optionally substituted aryl or optionally substituted heterocycle,

or, for the R_{102} and R_{103} groups, R_{102} and R_{103} form together, with the nitrogen carrying them, an optionally substituted heterocycle, and

where the optionally substituted aryl and optionally substituted heterocycle are optionally substituted with one or several groups selected from halogen; oxo (=O); NO_2; OR_{11}; $NR_{12}R_{13}$; $(C_1$-$C_6)$alkyl optionally substituted with one or several groups selected from halogen, OR_{21} or $NR_{22}R_{23}$; and aryl or aryl-$(C_1$-$C_6)$alkyl optionally substituted with one or several groups selected from halogen, OR_{31} or $NR_{32}R_{33}$.

In particular, R_{100}, R_{101}, R_{102} and R_{103} represent, independently of one another, H, $(C_1$-$C_6)$alkyl, aryl, heterocycle, aryl-$(C_1$-$C_6)$alkyl, heterocycle-$(C_1$-$C_6)$alkyl or -$((C_1$-$C_6)$alkyl$)$-NR_{104}-A_1, with A_1 representing H, $(C_1$-$C_6)$alkyl, aryl or heterocycle,

or, for the R_{102} and R_{103} groups, R_{102} and R_{103} form together, with the nitrogen carrying them, a heterocycle, and

where each aryl and heterocycle moiety is optionally substituted with one or several groups selected from halogen; oxo (=O); $(C_1$-$C_6)$alkyl; aryl; and aryl-$(C_1$-$C_6)$alkyl.

According to a particular embodiment, R_{101} represents H, $(C_1$-$C_6)$alkyl, aryl, aryl-$(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$alkyl-aryl; notably H or $(C_1$-$C_6)$alkyl.

According to a particular embodiment, R_{102} and R_{103} represent, independently of one another, H, $(C_1$-$C_6)$alkyl, aryl, heterocycle, aryl-$(C_1$-$C_6)$alkyl, heterocycle-$(C_1$-$C_6)$alkyl or -$((C_1$-$C_6)$alkyl$)$-NR_{104}-A_1; notably heterocycle, heterocycle-$(C_1$-$C_6)$alkyl or -$((C_1$-$C_6)$alkyl$)$-NR_{104}-A_1,

with A_1 representing H, $(C_1$-$C_6)$alkyl, aryl or heterocycle,

or, for the R_{102} and R_{103} groups, R_{102} and R_{103} form together, with the nitrogen carrying them, a heterocycle, and

where each aryl and heterocycle moiety is optionally substituted with one or several groups selected from halogen, oxo (=O), $(C_1\text{-}C_6)$alkyl, aryl, and aryl-$(C_1\text{-}C_6)$alkyl; notably selected from $(C_1\text{-}C_6)$alkyl, aryl, and aryl-$(C_1\text{-}C_6)$alkyl.

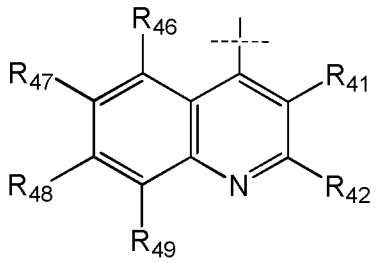
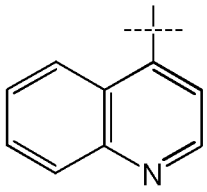
In the above definitions of R_{100}, R_{101}, R_{102} and R_{103}, the aryl preferably is a phenyl or a naphtyl, notably a phenyl.

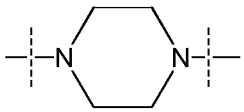
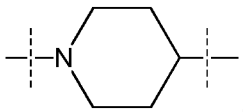
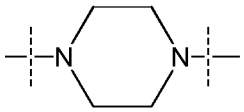
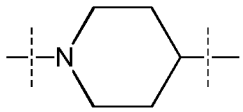
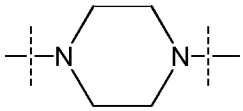
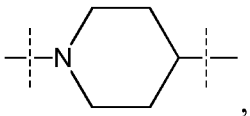
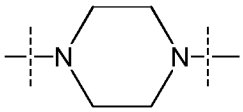
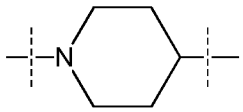
In the above definitions of R_{100}, R_{101}, R_{102} and R_{103}, the heterocycle is notably a saturated, unsaturated or aromatic (notably aromatic) hydrocarbon monocycle or bicycle (comprising fused, bridged or spiro rings, notably fused rings), notably a monocycle, each cycle having 5 or 6 members and 1 to 4, notably 1 or 2, carbon atoms having each been replaced with a nitrogen or oxygen atom, notably a nitrogen atom. The heterocycle can be notably chosen among pyrrole, imidazole, pyrazole, triazoles, indole, benzimidazole, indazole, pyridine, pyrimidine, pyridazine, pyrazine, triazine, quinoline, isoquinoline, quinoxaline, quinazoline, piperidine, piperazine, triazinane, pyrrolidine, dihydropyridines, dihydropyrimidines (notably 1,2-dihydropyrimidine), dihydropyridazines, dihydropyrazines, dihydrotriazines, tetrahydropyridines, tetrahydropyrimidines, tetrahydropyridazines, tetrahydropyrazines and tetrahydrotriazines. According to a first embodiment, the heterocycle is chosen among pyrrole, imidazole, pyrazole, triazoles, indole, benzimidazole, indazole, pyridine, pyrimidine, pyridazine, pyrazine, triazine, quinoline, isoquinoline, quinoxaline and quinazoline; notably chosen among pyridine, pyrimidine, pyridazine, pyrazine, triazine, quinoline, isoquinoline, quinoxaline and quinazoline. According to a second embodiment, the heterocycle is chosen among piperidine, piperazine, triazinane or pyrrolidine; and in particular is piperazine.

According to a particular embodiment, the compounds according to the present invention are compounds of formula (I-3c) or (I-4c), such as (I-3c), or a pharmaceutically acceptable salt or solvate thereof,

wherein:

- n1 and n2 represent, independently of each other, 0, 1, or 2,

– Q represents  where R_{41}, R_{42}, R_{46}, R_{47}, R_{48} and R_{49} each represent, independently of each other, hydrogen, halogen, OR_{11}, or $NR_{12}R_{13}$; and notably Q represents  ,

– W represents a bond,  or  , the nitrogen atom being linked to $(CH_2)_{n1}$; notably  or  , the nitrogen atom being linked to $(CH_2)_{n1}$, and preferably  or  , the nitrogen atom being linked to $(CH_2)_{n1}$; notably  or  , the nitrogen atom being linked to $(CH_2)_{n1}$,

– X_1 represents NH,

– X_2 represents a bond or O, notably O,

– Y_1 and Y_2 represent, independently of each other, H, a halogen atom, OR_{101} or $NR_{102}R_{103}$; notably Y_1 represents H, a halogen atom or $NR_{102}R_{103}$ and Y_2 represents H or OR_{101}, provided that at least one of Y_1 and Y_2 represent a group other than H,

where R_{101} represents H, $(C_1\text{-}C_6)$alkyl, aryl or aryl-$(C_1\text{-}C_6)$alkyl; such as H or $(C_1\text{-}C_6)$alkyl,

R_{102} and R_{103} represent, independently of one another, H, $(C_1\text{-}C_6)$alkyl, aryl, heterocycle, aryl-$(C_1\text{-}C_6)$alkyl, heterocycle-$(C_1\text{-}C_6)$alkyl or -$((C_1\text{-}C_6)$alkyl)-NR_{104}-A_1, with A_1 representing H, $(C_1\text{-}C_6)$alkyl, aryl or heterocycle; notably H or -$((C_1\text{-}C_6)$alkyl)-NR_{104}-A_1, with A_1 representing H, $(C_1\text{-}C_6)$alkyl or aryl, such as H or $(C_1\text{-}C_6)$alkyl,

or R_{102} and R_{103} form together, with the nitrogen carrying them, a heterocycle,

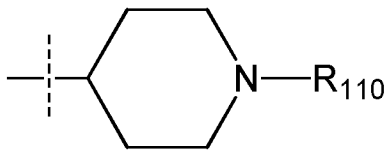
where each aryl and heterocycle moiety is optionally substituted with one or several groups selected from halogen, oxo (=O), $(C_1\text{-}C_6)$alkyl, aryl and aryl-$(C_1\text{-}C_6)$alkyl,

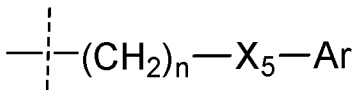
- R_4 represent, independently of each other, aryl heterocycle, aryl-$(C_1\text{-}C_6)$alkyl, heterocycle-$(C_1\text{-}C_6)$alkyl, -$((C_1\text{-}C_6)$alkyl)-NH-aryl or -$((C_1\text{-}C_6)$alkyl)-NH-heterocycle; notably heterocycle, aryl-$(C_1\text{-}C_6)$alkyl, or -$((C_1\text{-}C_6)$alkyl)-NH-aryl, each aryl or heterocycle moiety being optionally substituted with one or several groups selected from halogen, oxo (=O), $(C_1\text{-}C_6)$alkyl, aryl and aryl-$(C_1\text{-}C_6)$alkyl, and
- R_5 represents H,

wherein:

- the aryl is phenyl or naphtyl,
- the heterocycle is a saturated hydrocarbon monocycle having 5 or 6 members and 1 to 3, notably 1 or 2, carbon atoms having each been replaced with a nitrogen or oxygen atom, notably a nitrogen atom; such as piperidine, piperazine, triazinane or pyrrolidine; and in particular piperidine or piperazine.

In the above particular embodiment, R_4 represents advantageouslya group:

- 

, or
- 

,

where R_{110} represents an aryl or aryl-$(C_1\text{-}C_6)$alkyl group, such as an aryl-$(C_1\text{-}C_6)$alkyl group, optionally substituted with one or several halogen atoms, n is an integer comprised between 1 and 6, X_5 is as defined above and notably is a bond or NH, and Ar is an aryl group such as phenyl or naphtyl,

in particular where R_{110} represents a benzyl or naphtylmethyl group optionally substituted with one or several halogen atoms, n is an integer comprised between 1 and 6, X_5 is a bond or NH, and Ar is phenyl or naphtyl.

The compounds of the present invention can be selected from compounds A to H, notably from compounds A to G, described in the experimental part below and the pharmaceutically acceptable salts and solvates thereof (notably the hydrochloride thereof).

The present invention relates also to a compound of formula (I) as defined above, for use as a drug, notably intended for the treatment of cancer.

The present invention also relates to the use of a compound of formula (I) as defined above, for the manufacture of a drug, notably intended for the treatment of cancer.

The present invention also relates to a method for the treatment of cancer comprising the administration to a person in need thereof of an effective dose of a compound of formula (I) as defined above.

The cancer may be more particularly colon cancer, breast cancer, kidney cancer, liver cancer, pancreatic cancer, prostate cancer, glioblastoma, non-small cell lung cancer, neuroblastoma, inflammatory myofibroblastic tumor, leukemia (acute myeloid leukemia, myelodysplastic syndrome, chronic myelomonocytic leukemia), melanoma, diffuse B-cell lymphoma or anaplastic large-cell lymphoma.

The present invention relates also to a compound of formula (I) as defined above, for use as a DNA methylation inhibitor, in particular as a DNMT inhibitor.

According to the invention, the expression “DNA methylation inhibitor” and “DNMT inhibitor” refers to molecules that are able to reduce or inhibit the DNA methylation and the DNA methyltransferase activity respectively. Preferentially, the use of a DNMT inhibitor according to the invention makes it possible to suppress the activity of said DNMT.

The present invention also relates to a pharmaceutical composition comprising at least one compound of formula (I) as defined above and at least one pharmaceutically acceptable excipient.

The pharmaceutical compositions according to the invention may be formulated notably for oral administration or for injection, wherein said compositions are intended for mammals, including humans.

The pharmaceutical composition can be administered orally by means of tablets and gelatin capsules.

When a solid composition is prepared in the form of tablets, the main active ingredient is mixed with a pharmaceutical vehicle such as gelatin, starch, lactose, magnesium stearate, talc, gum arabic and the like. The tablets may be coated with sucrose or with other suitable materials, or they may be treated in such a way that they have a prolonged or delayed activity and they continuously release a predetermined amount of active principle.

A preparation in gelatin capsules is obtained by mixing the active ingredient with a diluent and pouring the mixture obtained into soft or hard gelatin capsules.

For administration by injection, aqueous suspensions, isotonic saline solutions or sterile and injectable solutions which contain pharmacologically compatible dispersing agents and/or wetting agents are used.

The active ingredient may be administered in unit dosage forms of administration, in mixture with standard pharmaceutical carriers, to animals or to humans. The compounds of the invention as active ingredients may be used in doses ranging between 0.01 mg and 1000 mg per day, given in a single dose once per day or administered in several doses throughout the day, for example twice a day in equal doses. The dose administered per day advantageously is between 5 mg and 500 mg, even more advantageously between 10 mg and 200 mg. It may be necessary to use doses outside these ranges as determined by the person skilled in the art.

The pharmaceutical compositions according to the invention may further comprise at least one other active ingredient, such as an anticancer agent.

The present invention relates also to a pharmaceutical composition comprising:

(i) at least one compound of formula (I) as defined above, and

(ii) at least one other active ingredient, such as an anticancer agent,

as a combination product for simultaneous, separate or sequential use.

The present invention also relates to a pharmaceutical composition as defined above for use as a drug, notably intended for the treatment of cancer.

The present invention also relates to methods for the preparation of the compounds of formula (I) according to the invention.

A first method is a method to prepare a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, in which W = NR_0 with $R_0 \neq H$, comprising:

(a) reacting a compound of formula (I) in which W = NH with:

- a compound of formula R_0-LG where R_0 represents a (C_1-C_6)alkyl optionally substituted with CHO, CO_2H or CO_2-((C_1-C_6)alkyl) and LG represents a leaving group to give a compound of formula (I) in which W = NR_0 with R_0 representing a (C_1-C_6)alkyl optionally substituted with CHO, CO_2H or CO_2-((C_1-C_6)alkyl),
- dimethylformamide (DMF) to give a compound of formula (I) in which W = NR_0 with R_0 = CHO, or
- a compound of formula R_0-A_1 where R_0 represents CO_2-((C_1-C_6)alkyl) and A_1 represents a (C_1-C_6)alkoxy group or a halogen atom (such as Cl or Br) to give a compound of formula (I) in which W = NR_0 with R_0 representing CO_2-((C_1-C_6)alkyl), and

(b) optionally salifying or solvating the compound obtained in step (a) to give a pharmaceutically acceptable salt or solvate of a compound of formula (I) in which W = NR_0 with R_0 as defined above.

Step (a):

When R_0 represents a (C_1-C_6)alkyl optionally substituted with CHO, CO_2H or CO_2-((C_1-C_6)alkyl):

The term "leaving group", as used in the present invention, refers to a chemical group which can be easily replaced with a nucleophile during a nucleophile substitution reaction, the nucleophile being in the case of step (a) a secondary amine, i.e. a molecule carrying a group NH. Such a leaving group can be in particular a halogen atom or a

sulfonate. The sulfonate is in particular a group $-OSO_2-R_7$ with R_7 representing a (C_1-C_6)alkyl, aryl, aryl-(C_1-C_6)-alkyl or (C_1-C_6)-alkyl-aryl group. The sulfonate can be in particular a mesylate (CH_3-$S(O_2)O$-), a triflate (CF_3-$S(O)_2O$-) or a tosylate (*p*-Me-C_6H_4-$S(O)_2O$-).

The LG group can be in particular a halogen atom such as a bromine.

Step (a) is advantageously carried out in the presence of a base such as triethylamine.

When R_0 represents a substituted (C_1-C_6)alkyl group, the (C_1-C_6)alkyl group will be advantageously substituted with a CO_2-((C_1-C_6)alkyl) group. This group can then be hydrolysed, notably in the presence of NaOH or KOH, to give a CO_2H group (R_0 represents then a (C_1-C_6)alkyl substituted with CO_2H). A reduction step in conditions well known to the one skilled in the art allows obtaining a CHO group (R_0 represents then a (C_1-C_6)alkyl substituted with CHO).

When R_0 represents CHO:

The reaction is advantageously performed using DMF as solvent, notably in the presence of a base such as triethylamine.

When R_0 represents CO_2-((C_1-C_6)alkyl):

This reaction can be carried out in conditions to prepare carbamates well known to the one skilled in the art.

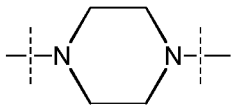
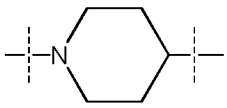
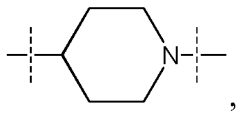
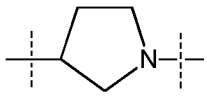
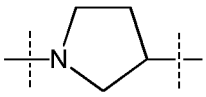
Step (b):

The salification or solvatation step can be carried out by methods well known to the one skilled in the art, in particular by reaction of the compound of formula (I) obtained in step (a) with a pharmaceutically acceptable acid (organic or inorganic acid), base (organic or inorganic acid) or solvent, as defined previously.

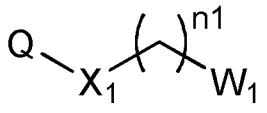
The solvent can be notably the solvent used in the last step of the preparation of the compound according to the invention, in particular the solvent used in step (a).

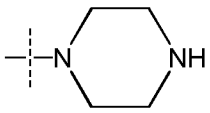
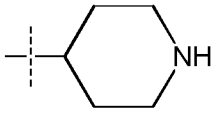
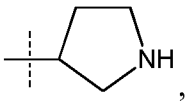
Thus steps (a) and (b) can be carried out in a single step, without isolating intermediate compounds.

A second method is a method to prepare a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, in which W represents NR_0, a

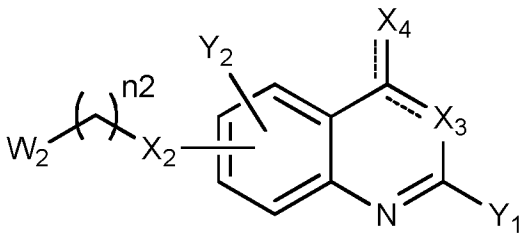
divalent monoglycosyl,  ,  ,  ,  or  , comprising:

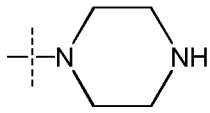
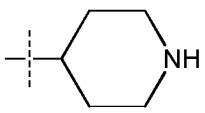
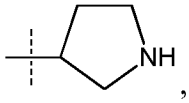
(1) reacting a compound of the following formula (II):


(II)

in which Q, X_1 and n1 are as defined above and W_1 represents LG_1, NHR_8, a monovalent monoglycosyl,  ,  or  ,

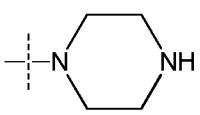
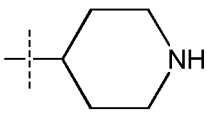
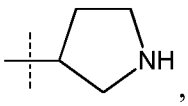
with a compound of the following formula (III):

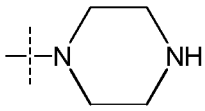
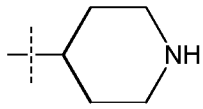
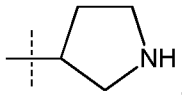

(III)

in which X_2, X_3, X_4, Y_1, Y_2 and n2 are as defined above and W_2 represents LG_2, NHR_8, a monovalent monoglycosyl,  ,  or  ,

wherein LG_1 and LG_2 represent, independently of each other, a leaving group and R_8 represents R_0 or a N-protecting group,

on the condition that:

- when W_1 represents LG_1, then W_2 represents NHR_8, a monovalent monoglycosyl,  ,  or  , and

- when W_1 represents NHR_8, a monovalent monoglycosyl,  ,  or  , then W_2 represents LG_2,

and, when W_1 or W_2 represents NHR_8 with R_8 representing a N-protecting group, deprotecting the nitrogen atom bearing the N-protecting group,

to give a compound of formula (I) as defined above, and

(2) optionally salifying or solvating the compound obtained in step (1) to give a pharmaceutically acceptable salt or solvate of a compound of formula (I) as defined above.

Step (1):

The LG_1 and LG_2 groups can be in particular a halogen atom such as a bromine or chlorine.

The reaction between the compounds of formula (II) and (III) can be carried out in the presence of a base, such as K_2CO_3. A catalytic amount of KI can also be added to the reaction medium.

R_8 can represent in particular H or a N-protecting group, notably a N-protecting group. When W_1 or W_2 represents NHR_8 with R_8 representing H or a N-protecting group, it is possible to prepare compounds of formula (I) with W = NH.

The term “protecting group”, as used in the present invention, refers to a chemical group which selectively blocks a reactive site in a multifunctional compound so as to allow selectively performing a chemical reaction on another unprotected reactive site.

The term “N-protecting group”, as used in the present invention, refers to those groups intended to protect an amine function (notably a primary amine function) against undesirable reactions (such as a disubstitution of the primary amine function) during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York (1981)). An amine function protected by a N-protecting group can be a carbamate, an amide, a sulfonamide, an N-alkyl derivative, an amino acetal derivative, a N-benzyl derivative,

an imine derivative, an enamine derivative or a N-heteroatom derivative. In particular, N-protecting groups include formyl; benzyl (Bn); -CO-R_9 such as acetyl (Ac), pivaloyl (Piv or Pv) or benzoyl (Bz); -CO_2-R_9 such as *t*butyloxycarbonyl (Boc), trichloroethoxycarbonyl (TROC), allyloxycarbonyl (Alloc) or benzyloxycarbonyl (Cbz or Z); -SO_2-R_9 such as phenylsulfonyl or 2-nitrobenzenesulfonyl (Nos or Ns); and the like, with R_9 representing a (C_1-C_6)alkyl optionally substituted with one or several halogen atoms such as F or Cl; a (C_2-C_6)alkenyl such as an allyl; an aryl, such as a phenyl, optionally substituted with NO_2; or an aryl-(C_1-C_6)alkyl such as a benzyl.

The step of deprotecting the nitrogen atom bearing the N-protecting group can be carried out by methods well known to the one skilled in the art, notably as disclosed in Greene, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York (1981)).

The N-protecting group will be in particular 2-nitrobenzenesulfonyl (Nos or Ns). It can be deprotected in the presence of thiophenol.

The compounds of formulas (II) and (III) are either commercially available or prepared by methods well known to the one skilled in the art, notably as illustrated in the examples below.

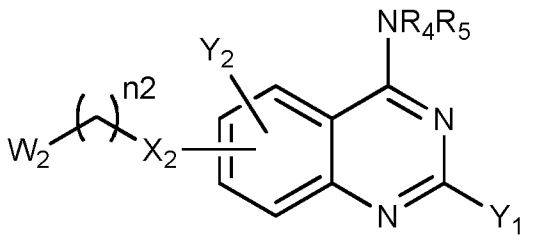
In particular, the compound of formula (II) can be prepared by reacting a compound of formula Q-Hal with a compound of formula HX_1-$(CH_2)_{n1}$-W_3 where:

- Q, X_1 and n1 are as defined above,
- Hal represents a halogen atom such as Cl or Br, and
- W_3 represents a group W_1, optionally in a protected form (W_3 can represent notably OH).

This reaction can be performed optionally in the presence of a base.

Further steps of protection(s), deprotection(s) and/or functionalization(s) well known to the one skilled in the art can be carried out, in particular a deprotection step of the W_3 group can be carried out to introduce the W_1 function on the molecule.

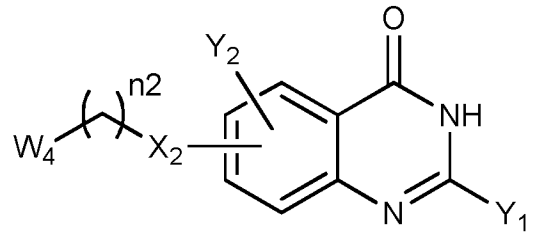
When the compound of formula (III) is a compound of the following formula (IIIc):



(IIIc)

with W_2, X_2, Y_1, Y_2, R_4, R_5 and n2 as defined above,

this compound can be prepared by reacting a compound of the following formula (IV):



(IV)

with X_2, Y_1, Y_2 and n2 as defined above and W_4 representing a group W_2, optionally in a protected form,

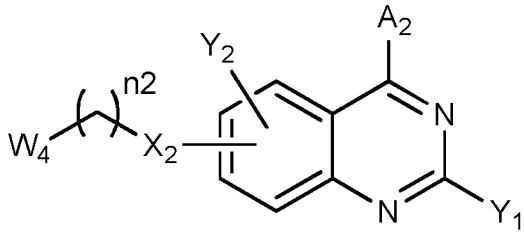
with an amine of formula R_4R_5NH with R_4 and R_5 as defined above.

This reaction can be performed in the presence of a base such as K_2CO_3, DIPEA or triethylamine.

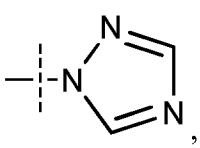
The carbonyl function of the compound of formula (IV) can be activated in the form of a triazole, notably by reaction with $POCl_3$ and triazole (more particularly 1,2,3-triazole) preferably in the presence of a base such as triethylamine, or also in the form of a halogen, such as a chlorine, notably by reaction with $POCl_3$.

Thus the compound of formula (IIIc) can be prepared by:

- activating the compound of formula (IV) in the form of a triazole or a halogen atom of the following formula (V):



(V)

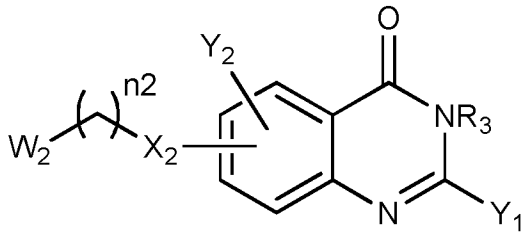
with W_4, X_2, Y_1, Y_2 and n2 as defined above and A_2 represents a halogen atom such as Cl or 

,

– reacting the compound of formula (V) with the amine of formula R_4R_5NH.

Further steps of protection(s), deprotection(s) and/or functionalization(s) well known to the one skilled in the art can be carried out, in particular a deprotection step of the W_4 group can be carried out to introduce the W_2 function on the molecule.

When the compound of formula (III) is a compound of the following formula (IIId):



(IIId)

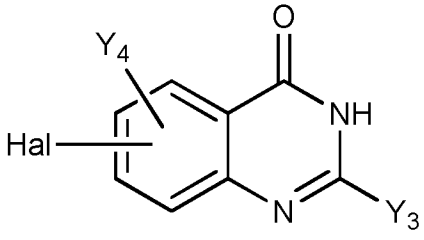
with W_2, X_2, Y_1, Y_2, R_3 and n2 as defined above, and $R_3 \neq H$,

this compound can be prepared by reacting a compound of formula (IV) as defined above with a compound of formula R_3-LG_3 with R_3 as defined above and LG_3 representing a leaving group, such as a halogen atom (e.g. Cl or Br).

This reaction can be carried out in the presence of a base, such as K_2CO_3. A catalytic amount of KI can also be added to the reaction medium.

Further steps of protection(s), deprotection(s) and/or functionalization(s) well known to the one skilled in the art can be carried out, in particular a deprotection step of the W_4 group can be carried out to introduce the W_2 function on the molecule.

The compound of formula (IV) can be prepared by reacting a compound of the following formula (VI):



(VI)

where Hal represents a halogen atom such as F, and Y_3 and Y_4 represent respectively a Y_1 or Y_2 group optionally in a protected form,

with a compound of formula W_4-$(CH_2)_{n2}$-X_2H where W_4, X_2 and n2 are as defined above and X_2 is not a bond.

This reaction can be carried out in the presence of a base such as NaH.

Further steps of protection(s), deprotection(s) and/or functionalization(s) well known to the one skilled in the art can be carried out, in particular a deprotection step of the Y_3 and Y_4 groups can be carried out to introduce the Y_1 and Y_2 functions on the molecule.

Step (2):

The salification or solvatation step can be carried out by methods well known to the one skilled in the art, in particular by reaction of the compound of formula (I) obtained in step (1) with a pharmaceutically acceptable acid (organic or inorganic acid), base (organic or inorganic acid) or solvent, as defined previously.

The solvent can be notably the solvent used in the last step of the preparation of the compound according to the invention, in particular the solvent used in step (1).

Thus steps (1) and (2) can be carried out in a single step, without isolating intermediate compounds.

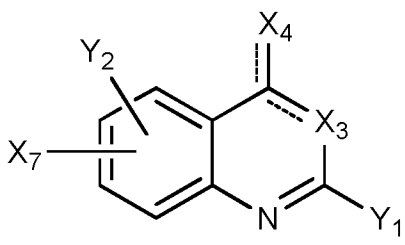
A third method is a method to prepare a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, comprising:

(A) reacting a compound of the following formula (VII):

(VII)

in which Q is as defined above and X_6 represents a halogen atom (e.g. Cl or Br) or $-X_1-(CH_2)_{n1}-W-(CH_2)_{n2}-X_2H$ with W, X_1, X_2, n1 and n2 as defined above and X_2 is not a bond,

with a compound of the following formula (VIII):



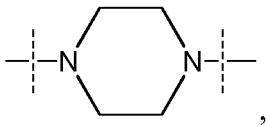
(VIII)

in which Y_1, Y_2, X_3 and X_4 are as defined above and X_7 represents a halogen atom (e.g. F) or $-X_2-(CH_2)_{n2}-W-(CH_2)_{n1}-X_1H$ with W, X_1, X_2, n1 and n2 as defined above (and can be a bond),

on the condition that:

- when X_6 represents a halogen atom, then X_7 represents $-X_2-(CH_2)_{n2}-W-(CH_2)_{n1}-X_1H$, and
- when X_6 represents $-X_1-(CH_2)_{n1}-W-(CH_2)_{n2}-X_2H$, then X_7 represents a halogen atom,

to give a compound of formula (I) in which W represents NR_0,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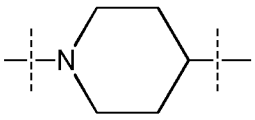
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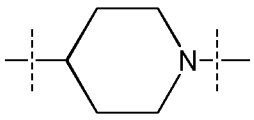
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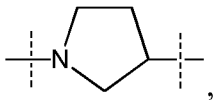
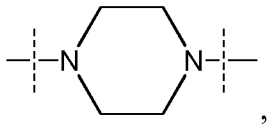

, and

(B) optionally salifying or solvating the compound obtained in step (A) to give a pharmaceutically acceptable salt or solvate of a compound of formula (I) as defined above in which W represents NR_0,

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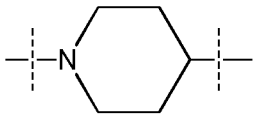
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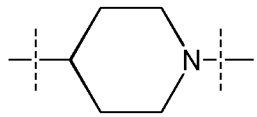
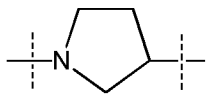

or

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Step (A):

The reaction between the compounds of formula (VII) and (VIII) can be carried out in the presence of a base, such as K_2CO_3. A catalytic amount of KI can also be added to the reaction medium.

The compounds of formulas (VII) and (VIII) are either commercially available or prepared by methods well known to the one skilled in the art, notably as illustrated in the examples below.

In particular, the compound of formula (VII), when X_6 represents $-X_1-(CH_2)_{n1}-W-(CH_2)_{n2}-X_2H$, can be prepared by reacting a compound of formula Q-Hal with a compound of formula $HX_1-(CH_2)_{n1}-W-(CH_2)_{n2}-X_8$ where:

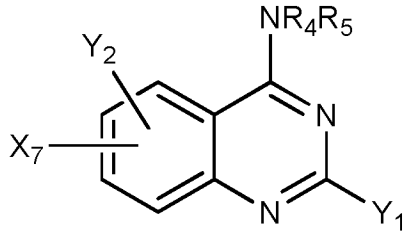
- Q, X_1, W, n1 and n2 are as defined above,
- Hal represents a halogen atom such as Cl or Br, and

– X_8 represents a group X_2H, optionally in a protected form.

This reaction can be performed optionally in the presence of a base.

Further steps of protection(s), deprotection(s) and/or functionalization(s) well known to the one skilled in the art can be carried out, in particular a deprotection step of the X_8 group can be carried out to introduce the X_2H function on the molecule.

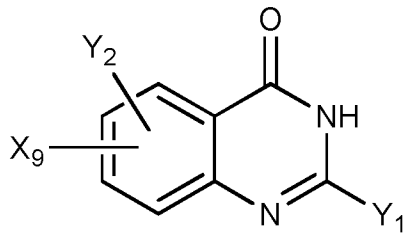
When the compound of formula (VIII) is a compound of the following formula (VIIIc):



(VIIIc)

with Y_1, Y_2, X_7, R_4 and R_5 as defined above,

this compound can be prepared by reacting a compound of the following formula (IX):



(IX)

with Y_1 and Y_2 as defined above and X_9 representing a group X_7, optionally in a protected form,

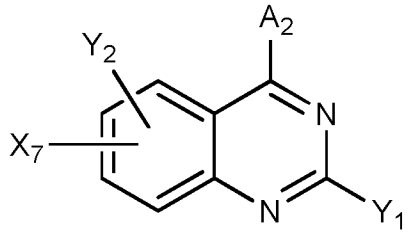
with an amine of formula R_4R_5NH with R_4 and R_5 as defined above.

This reaction can be performed in the presence of a base such as K_2CO_3 or triethylamine.

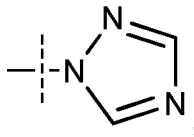
The carbonyl function of the compound of formula (IX) can be activated in the form of a triazole, notably by reaction with $POCl_3$ and triazole (more particularly 1,2,3-triazole) preferably in the presence of a base such as triethylamine, or also in the form of a halogen, such as a chlorine, notably by reaction with $POCl_3$.

Thus the compound of formula (VIIIc) can be prepared by:

– activating the compound of formula (IX) in the form of a triazole or a halogen atom of the following formula (X):



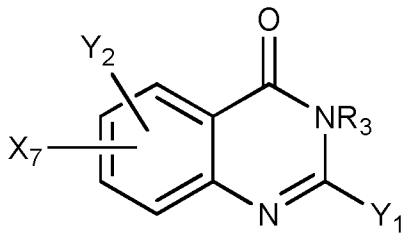
(X)

with Y_1, Y_2 and X_9 as defined above and A_2 represents a halogen atom such as Cl or  , and

- reacting the compound of formula (X) with the amine of formula R_4R_5NH.

Further steps of protection(s), deprotection(s) and/or functionalization(s) well known to the one skilled in the art can be carried out, in particular a deprotection step of the X_9 group can be carried out to introduce the X_7 group on the molecule.

When the compound of formula (VIII) is a compound of the following formula (VIIId):



(VIIId)

with Y_1, Y_2, X_7 and R_3 as defined above, and $R_3 \neq H$,

this compound can be prepared by reacting a compound of formula (IX) as defined above with a compound of formula R_3-LG_3 with R_3 as defined above and LG_3 representing a leaving group, such as a halogen atom (e.g. Cl or Br).

This reaction can be carried out in the presence of a base, such as K_2CO_3. A catalytic amount of KI can also be added to the reaction medium.

Further steps of protection(s), deprotection(s) and/or functionalization(s) well known to the one skilled in the art can be carried out, in particular a deprotection step of the X_9 group can be carried out to introduce the X_7 group on the molecule.

The compound of formula (IX), when X_9 represents $-X_2-(CH_2)_{n2}-W-(CH_2)_{n1}-X_{10}$ where X_{10} represents X_1H optionally in a protected form, can be prepared by reacting a

compound of the formula (VI) with a compound of formula HX_2-$(CH_2)_{n2}$-W-$(CH_2)_{n1}$-X_{10} where W, X_2, X_{10}, n1 and n2 are as defined above.

This reaction can be carried out in the presence of a base such as NaH.

Step (B):

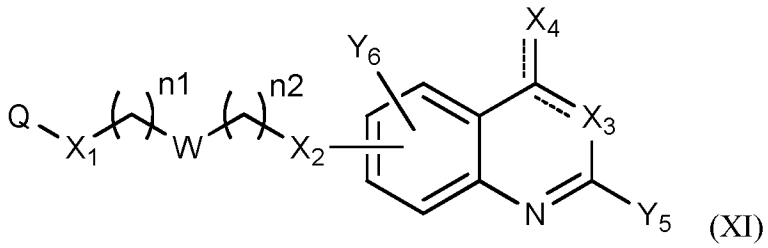
The salification or solvatation step can be carried out by methods well known to the one skilled in the art, in particular by reaction of the compound of formula (I) obtained in step (A) with a pharmaceutically acceptable acid (organic or inorganic acid), base (organic or inorganic acid) or solvent, as defined previously.

The solvent can be notably the solvent used in the last step of the preparation of the compound according to the invention, in particular the solvent used in step (A).

Thus steps (A) and (B) can be carried out in a single step, without isolating intermediate compounds.

A fourth method is a method to prepare a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, in which at least one of Y_1 and Y_2 represents a OR_{101} or $NR_{102}R_{103}$ group, comprising:

(i) reacting a compound of the following formula (XI):



(XI)

in which Y_5 represents Y_1 as defined above or a halogen atom such as a chlorine, and Y_6 represents Y_2 as defined above or a halogen atom such as a chlorine, provided that at least one of Y_5 and Y_6, and notably Y_5, represents a halogen atom such as a chlorine,

with HOR_{101} or $HNR_{102}R_{103}$,

to give a compound of formula (I) as defined above where at least one of Y_1 and Y_2 represents a OR_{101} or $NR_{102}R_{103}$ group, and

(ii) optionally salifying or solvating the compound obtained in step (i) to give a pharmaceutically acceptable salt or solvate of a compound of formula (I) as

defined above in which at least one of Y_1 and Y_2 represents a OR_{101} or $NR_{102}R_{103}$ group.

Step (i):

The reaction between the compounds of formula (XI) and HOR_{101} or $HNR_{102}R_{103}$ can be carried out in the presence of sodium.

The compounds of formulas (XI), HOR_{101} and $HNR_{102}R_{103}$ are either commercially available or prepared by methods well known to the one skilled in the art, notably as illustrated in the examples below.

Step (ii):

The salification or solvatation step can be carried out by methods well known to the one skilled in the art, in particular by reaction of the compound of formula (I) obtained in step (i) with a pharmaceutically acceptable acid (organic or inorganic acid), base (organic or inorganic acid) or solvent, as defined previously.

The solvent can be notably the solvent used in the last step of the preparation of the compound according to the invention, in particular the solvent used in step (i).

Thus steps (i) and (ii) can be carried out in a single step, without isolating intermediate compounds.

Further steps of protection(s), deprotection(s) and/or functionalization(s) well known to the one skilled in the art can be carried out to obtain the compounds of formula (I).

The compound according to the present invention obtained by one of the methods described above can be separated from the reaction medium by methods well known to the one skilled in the art, such as by extraction, evaporation of the solvent or by precipitation or crystallisation (followed by filtration).

This compound can also be purified if necessary by methods well known to the one skilled in the art, such as by recrystallization, by distillation, by chromatography on a column of silica gel or by high performance liquid chromatography (HPLC).

The examples which follow illustrate the invention without limiting its scope in any way.

EXAMPLES

The following abbreviations have been used in the following examples.

a.a.	: Amino acid
AdoMet	: *S*-Adenosyl-L-methionine
ATP	: Adenosine triphosphate
BSA	: Bovine Serum Albumin
CMV	: *Cytomegalovirus*
DCM	: Dichloromethane
DIAD	: Diisopropyl azodicarboxylate
DiPEA	: *N,N*-Diisopropylethylamine
DMF	: Dimethylformamide
DMSO	: Dimethylsulfoxide
DNA	: Deoxyribonucleic acid
EDTA	: Ethylenediaminetetraacetic acid
ESI	: Electrospray ionisation
HEPES	: 4-(2-Hydroxyethyl)-1-piperazineethanesulfonic acid
HPLC	: High Performance Liquid Chromatography
HRMS	: High Resolution Mass Spectrometry
MS	: Mass Spectrometry
MW	: Microwave
ND	: Not determined
NMR	: Nuclear Magnetic Resonance
PBS	: Phosphate buffered saline
PBST	: Phosphate buffered saline + Tween-20
RPMI	: Roswell Park Memorial Institute medium
RT	: Room temperature
SAH	: *S*-Adenosyl-L-homocysteine
SAM	: *S*-Adenosyl-L-methionine

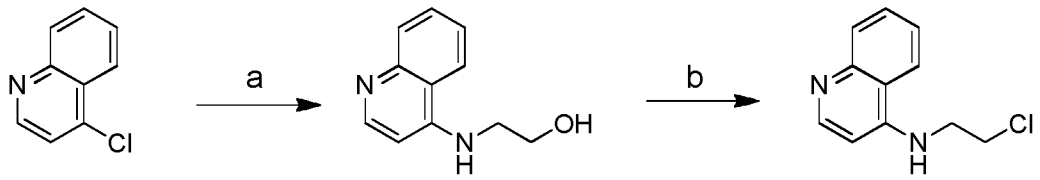
TEA : Triethylamine

TFA : Trifluoroacetic acid

Tris : Tris(hydroxymethyl)aminomethane

I. Synthesis of the compounds according to the invention

Example 1: Compound A

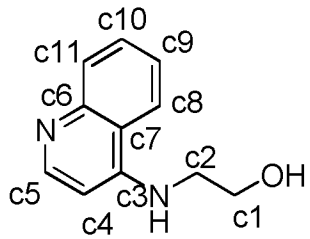


1 2 3

a) Ethanolamine, 125°C, 4h, quantitative yield. b) $SOCl_2$, DMF cat., Flash boiling, quantitative yield.

4-((2-Hydroxyethyl)amino)quinoline (2)

A mixture of 4-chloroquinoline (360mg; 2.21mmol) in ethanolamine (1.5mL; 22mmol) was stirred at 110°C for 3h. The solvent was removed and the residue was purified by silica gel flash chromatography using a linear gradient of methanol (0→10% MeOH) in dichloromethane to afford **2** as a white powder (414mg; 2.20mmol; quantitative yield).



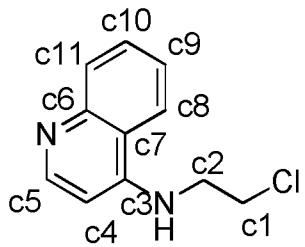
^{1}H NMR (500MHz, $CDCl_3$) δ 8.38 (d, J=5.4Hz, 1H, Hc5), 8.19 (dd, J=0.9, 8.3Hz, 1H, Hc8), 7.77 (dd, J=0.9, 8.3Hz, 1H, Hc11), 7.59 (ddd, J=1.3, 6.7, 8.3Hz, 1H, Hc10), 7.40 (ddd, J=1.3, 6.7, 8.3Hz, 1H, Hc9), 7.07 (brt, J=5.2Hz, 1H, HOH), 6.46 (d, J=5.4Hz, 1H, Hc4), 4.83 (brt, J=5.5Hz, 1H, HNHc), 3.66 (q, J=6.0Hz, 2H, Hc1), 3.35 (q, J=5.4Hz, 2H, Hc2).

^{13}C NMR (125MHz, $CDCl_3$) δ 151.1 (Cc5), 150.5 (Cc3), 148.8 (Cc6), 129.5 (Cc8), 129.1 (Cc10), 124.2 (Cc9), 122.1 (Cc11), 119.3 (Cc7), 98.6 (Cc4), 59.3 (Cc1), 45.5 (Cc2).

HRMS-ESI (m/z) calculated for $C_{11}H_{13}N_2O$ $[M+H]^+$: 189.1022; found: 189.1031.

4-((2-chloroethyl)amino)quinoline hydrochloride (3)

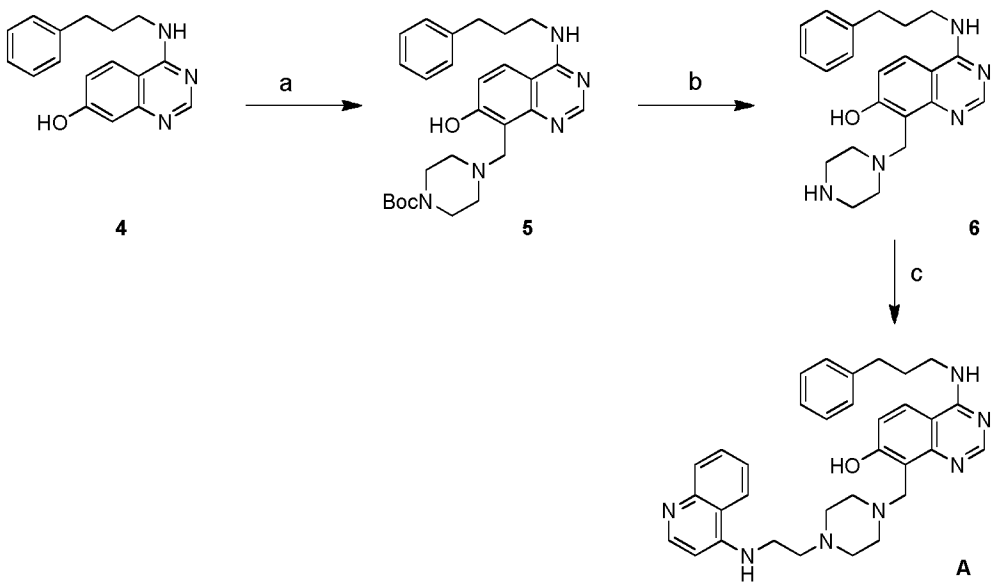
2 (360mg; 1.92mmol) was solubilized in thionyl chloride (3ml). The mixture was flash boiled and the solvent was removed. Toluene was added to remove the residual thionyl chloride by co-evaporation. The residue was triturated in dichloromethane and the solid was filtrated to afford **3** as a white solid (360mg; 1.75mmol; 91%).



^{1}H NMR (500MHz; $CDCl_3$) δ 8.59 (d, J=5.2Hz, 1H, Hc5), 8.00 (dd, J=0.7, 8.3Hz, 1H, Hc8), 7.79 (d, J=8.3Hz, 1H, Hc11), 7.65 (ddd, J=1.3, 7.9, 8.3Hz, 1H, Hc10), 7.45 (ddd, J=1.3, 7.0, 8.3Hz, 1H, Hc9), 6.43 (d, J=5.3Hz, 1H, Hc4), 5.51 (brs, 1H, HNHc), 3.84 (t, J=5.8Hz, 2H, Hc1), 3.70 (q, J=5.8Hz, 2H, Hc1).

^{13}C NMR (125MHz, $CDCl_3$) δ 151.0 (Cc5), 148.9 (Cc3), 148.5 (Cc6), 130.0 (Cc8), 129.2 (Cc10), 125.0 (Cc9), 119.3 (Cc11), 118.9 (Cc7), 99.0 (Cc4), 44.4 (Cc2), 42.6 (Cc1).

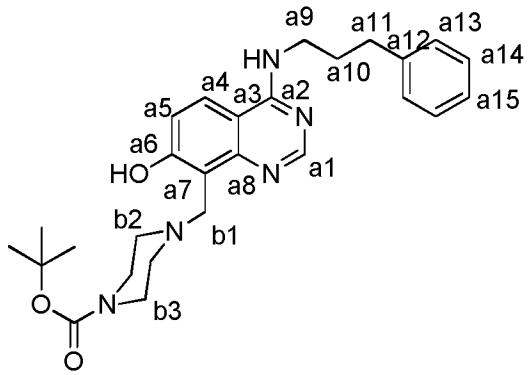
HRMS-ESI (m/z) calculated for $C_{11}H_{13}N_2Cl$ $[M+H]^+$: 207.0684; found: 207.0678.



a) *N*-Boc-piperazine, formaldehyde, isopropanol, 110°C, 1h, 94%. b) TFA, DCM, RT, 1h. 97% c) **3**, K_2CO_3, KI, DMF, 65°C, 12h, 23%.

4-((3-phenylpropyl)amino)-8-((*N*-Boc)piperazin-*N*4-ylmethy)quinazolin-7-ol (5)

To a solution of compound **4** (purchased from Pharmaron) (195 mg; 0.70 mmol) and *N*-Boc-piperazine (715 mg; 3.84 mmol) in 6 mL of isopropanol was added paraformaldehyde (160 mg). The reaction mixture was stirred at 110°C for 1h. and the solvents were removed and the residue was purified by silica gel flash chromatography using a linear gradient of ethylacetate (0→100% AcOEt) in cyclohexane to afford **5** as a white powder (314 mg; 0.66 mmol; 94%).



^{1}H NMR (500MHz; $CDCl_3$) δ 8.37 (s, 1H, Ha1), 8.05 (d, 1H, *J*=9.1Hz, Ha4), 8.02 (t, 1H, *J*= 5.7Hz, HNH), 7.31-7.22 (m, 4H, Ha13 and Ha14), 7.18 (dt, 1H, *J*= 1.4, 7.1Hz, Ha15), 6.95 (d, *J*=9.0Hz, 1H, Ha5), 4.23 (s, 2H, Hb1), 3.51 (q, *J*=6.8Hz, 2H,

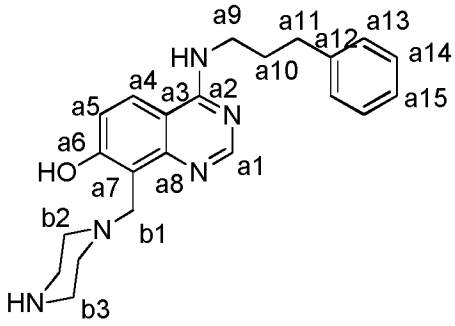
Ha9), 3.37 (m, 4H, Hb3), 2.67 (t, 2H, *J*=7.7Hz, Ha11), 2.49 (m, 4H, Hb2), 1.93 (quint, *J*=7.3Hz, 2H, Ha10), 1.40 (s, 9H, HBoc).

^{13}C NMR (125MHz; $CDCl_3$) δ 162.2 (Ca6), 159.8 (Ca2), 155.3 (Ca1), 154.2 (CBoc), 149.5 (Ca8), 142.2 (Ca12), 128.8 (Ca13), 128.7 (Ca14), 126.2 (Ca15), 122.5 (Ca4), 116.7 (Ca5), 114.0 (Ca7), 108.4 (Ca3), 79.4 (CBoc), 55.7(Cb1), 54.0 (Cb2), 52.4 (Cb2), 40.5 (Ca9), 33.2 (Ca11), 30.9 (Ca10), 28.5 (CBoc).

HRMS-ESI (m/z) calculated for $C_{27}H_{35}N_5O_3$ $[M+Na]^+$: 500.2632 ; found: 500.2661.

4-((3-phenylpropyl)amino)-8-(piperazin-*1*-ylmethyl))quinazoline-7ol (6)

A mixture of **5** (314 mg; 0.67 mmol) in TFA was stirred for 1h at room temperature. TFA was removed. The residue was diluted with dichloromethane and the organic phase was washed with saturated Na_2CO_3. The solvent was removed and **6** was obtained as pale yellow foam (245mg; 0.65 mmol; 97%).



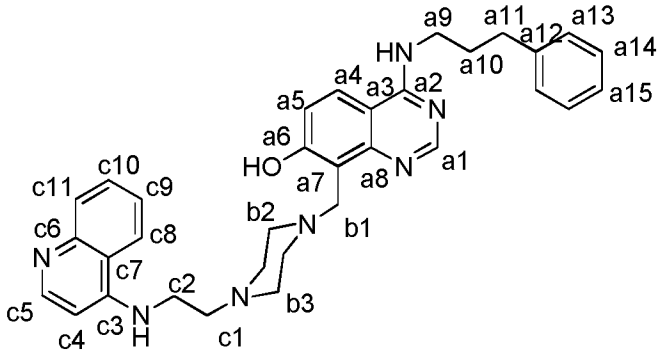
^{1}H NMR (500MHz; $CDCl_3$) δ 8.36 (s, 1H, Ha1), 8.02 (d, 1H, *J*=9.0Hz, Ha4), 8.00 (t, 1H, *J*=5.4Hz, HNH), 7.32-7.221 (m, 4H, Ha13 and Ha14), 7.18 (dt, 1H, *J*= 1.3, 7.2Hz, Ha15), 6.90 (d, *J*=9.0Hz, 1H, Ha5), 4.25 (s, 2H, Hb1), 3.51 (q, *J*=7.0Hz, 2H, Ha9), 2.75 (m, 4H, Hb3), 2.67 (t, 2H, *J*=7.6Hz, Ha11), 2.48 (m, 4H, Hb2), 1.93 (quint, *J*=7.2Hz, 2H, Ha10).

^{13}C NMR (125MHz; $CDCl_3$) δ 161.9 (Ca6), 159.8 (Ca2), 155.2 (Ca1), 149.3 (Ca8), 142.2 (Ca12), 128.8 (Ca13), 128.7 (Ca14), 126.2 (Ca15), 123.3 (Ca4), 116.8 (Ca5), 113.6 (Ca7), 108.2 (Ca3), 55.6 (Cb1), 53.8 (Cb2), 45.9 (Cb3), 40.6 (Ca9), 33.2 (Ca11), 30.9 (Ca10),.

HRMS-ESI (m/z) calculated for $C_{22}H_{28}N_5O_1$ $[M+H]^+$: 378.2288; found:378.2294

4-((3-phenylpropyl)amino)-8-((1-(2-(quinolin-4-ylamino)ethyl)piperazin-*1*-ylmethyl))quinazoline-7-ol (A)

To a solution of **6** (40mg; 0.11 mmol), K_2CO_3 (45mg; 0.33 mmol) and a catalytic amount of KI in DMF (1mL) was added **3** (57mg; 0.27µmol). The mixture was stirred at 65°C overnight. The solvent was removed and the residue was purified by silica gel flash chromatography using a linear gradient of ammonia 1N in methanol (0→10% MeOH/NH_3) in dichloromethane or by reversed phase HPLC using a linear acetonitrile gradient with 0.01% of TEA (0→80% CH_3CN) to afford **Compound A** as a white pale yellow foam (14mg; 25 µmol; 23%).

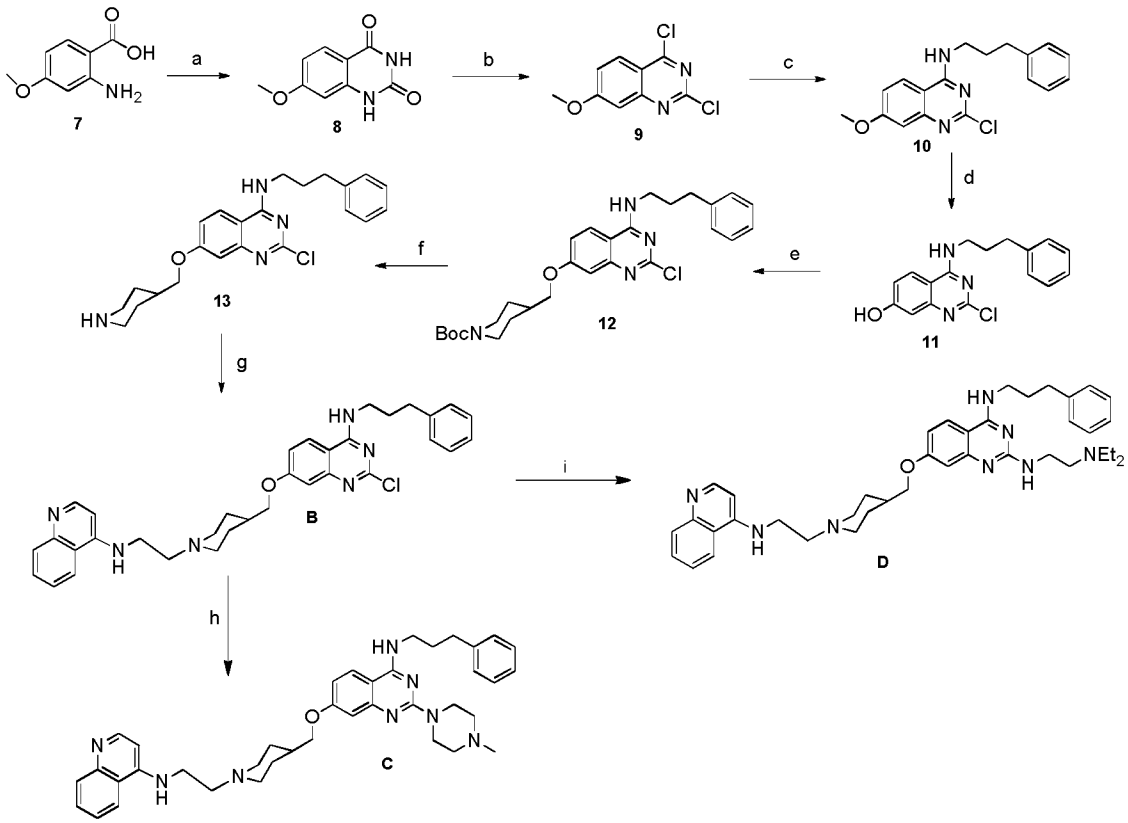


^{1}H NMR (500MHz; $CDCl_3$) δ 8.40 (d, *J*=5.4Hz, 1H, Hc5), 8.36 (s, 1H, Ha1), 8.16 (d, 1H, *J*=8.6Hz, Hc8), 8.02 (d, 1H, *J*=9.0Hz, Ha4), 8.00 (m, 1H, HNH), 7.78 (d, *J*= 8.5Hz, 1H, Hc11), 7.61 (dd, *J*=0.9, 8.0Hz, 1H, Hc10), 7.42 (dd, *J*=0.9, 8.1Hz, 1H, Hc9), 7.32-7.22 (m, 4H, Ha13 and Ha14), 7.18 (t, 1H, *J*= 7.2Hz, Ha15), 6.91 (d, *J*=8.9Hz, 1H, Ha5), 6.47 (d, *J*=5.4Hz, 1H, Hc4), 4.25 (s, 2H, Hb1), 3.86 (brt, *J*=7.1Hz, 1H, HNH), 3.52 (q, *J*=6.2Hz, 2H, Ha9), 3.40 (q, 2H, *J*=6.0Hz, Hc2), 2.71-2.55 (m, 10H, Hc1 and Hb2 and Hb3 and Ha11), 1.93 (quint, *J*=7.3Hz, 2H, Ha10).

^{13}C NMR (125MHz; $CDCl_3$) δ 161.2 (Ca6), 159.8 (Ca2), 155.2 (Ca1), 151.1 (Cc5), 150.2 (Ca8), 149.4 (Cc3), 148.7 (Cc6),142.2 (Ca12), 129.5 (Cc8), 129.1 (Cc10), 128.8 (Ca13), 128.7 (Ca14), 126.2 (Ca15), 124.3 (Cc9), 123.4 (Ca4), 121.9 (Cc11), 119.3 (Cc7), 117.0 (Ca5), 113.7 (Ca7), 108.2 (Ca3), 98.7 (Cc4), 55.6 (Cb1), 56.0 (Cc1), 54.6 (Cb2), 52.7 (Cb3), 40.5 (Ca9), 40.1 (Cc2), 33.2 (Ca11), 30.9 (Ca10).

HRMS-ESI (m/z) calculated for $C_{33}H_{38}N_7O1$ $[M+H]^+$: 548.3132; found:548.3139.

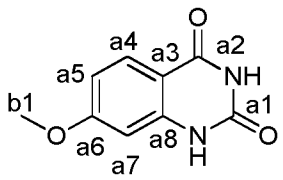
Example 2: Compounds B, C and D



a) Urea, 155 °C, 16 h, 48 %. b) $POCl_3$, MeCN, 135 °C, 8 h, 54 %. c) 3-Phenylpropylamine, DIPEA, DMF, RT, 12 h, 86 %. d) BBr_3, DCM, RT, 12 h, 87 %. e) *N*-Boc-piperidine-4-methanol, DIAD, PPh_3, DCM, RT, 18 h, 98 %. f) TFA, RT, 1 h, quantitative. g) **3**, K_2CO_3, KI, DMF, 65 °C, 12 h, 32 %. h) 1-methyl-piperazine, 90°C, 2h, 37%. i) *1.* *N*-diethylethylene diamine, Na, 70°C, 12h. *2.* TFA, MeOH, 36%.

7-methoxyquinazoline-2,4(1*H*,3*H*)dione (8)

A mixture of 2-amino-4-methoxybenzoic acid (1 g; 5.98 mmol) and urea (7.18 g; 120 mmol) was stirred at 155°C for 16 h. The reaction mixture was cooled to 100°C and then 3 mL of water was added. The mixture was cooled to room temperature and was filtered. 30 mL of 1 mol/L NaOH aqueous solution was added to dissolve the precipitate. After one hour, 4.2 mL of acetic acid was added dropwise and the resulting light brown precipitate was filtered and dried. **8** was obtained as a light brown powder (0.55 g; 2.9 mmol; 48 %).



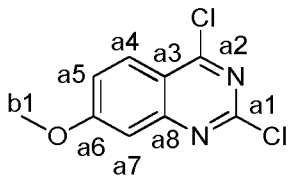
^{1}H NMR (500 MHz; DMSO) δ 11.10 (brs, 1H, HNH), 10.55 (brs, 1H, HNH), 7.8 (d, J=8.63 Hz, 1H, Ha4), 6.77 (dd, J=2.44, 8.84 Hz, 1H, Ha5), 6.64 (d, J=2.43 Hz, 1H, Ha7), 3.82 (s, 3H, Hb1).

^{13}C NMR (125 MHz; DMSO) δ 164.8 (Ca6), 162.8 (Ca2), 151 (Ca1), 143.3 (Ca8), 129.3 (Ca4), 111 (Ca5), 108.2 (Ca3), 98.8 (Ca7), 56.1 (Cb1).

HRMS-ESI (m/z) calculated for $C_9H_8N_2O_3$: 193.0489 $[M+H]^+$; found: 193.0511

2,4-dichloro-7-methoxyquinazoline (9)

7-methoxyquinazoline-2,4(1*H*,3*H*)dione (0.31 g; 1.6 mmol) was added to a solution of $POCl_3$(10 mL; 107 mmol) in 3 mL of acetonitrile and the mixture was heated to reflux for 8 h. The mixture was poured into ice water and was vigorously stirred and the resulting precipitate was filtered and dried. The precipitate was filtered through silica using dichloromethane to afford **9** as a white powder (0.201 g; 0.88 mmol; 54 %).



^{1}H NMR (500 MHz; DMSO) δ 8.1 (d, J=9.21 Hz, 1H, Ha4), 7.44 (dd, J=2.08, 9.26 Hz, 1H, Ha5), 7.38 (d, J=2.07 Hz, 1H, Ha7), 3.99 (s, 3H, Hb1).

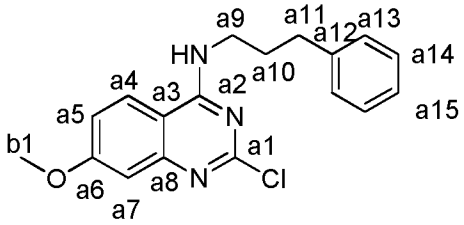
^{13}C NMR (125 MHz; DMSO) δ 166.2 (Ca6), 162.17 (Ca2), 158 (Ca1), 154.9 (Ca8), 127.7 (Ca4), 122.95 (Ca5), 117.2 (Ca3), 106.5 (Ca7), 57 (Cb1).

HRMS-ESI (m/z) calculated for $C_9H_6Cl_2N_2O$: 227.9918 $[M+H]^+$; found: 227.9935

4-((3-phenylpropyl)amino)-2-chloro-7-methoxyquinazoline (10).

3-Phenyl-1-propylamine (154 µL; 1.1 mmol) was added to a solution of 2,4-dichloro-7-methoxyquinazoline (247 mg; 1.1 mmol) in DMF (3.5 mL) with DIPEA (226 µL; 1.3 mmol). The reaction mixture was stirred at room temperature for 12 h under argon. The resulting mixture was concentrated under vacuum, 1 mL of 1 mol/L

NaOH aqueous solution was added to the residue. The residue was taken off with dichloromethane and washed with water and brine, and dried over sodium sulphate. The solvent was removed and the residue was purified by silica gel flash chromatography using a linear gradient of ethyl acetate (0→100 % AcOEt) in cyclohexane to afford **10** as a white powder (302 mg; 0.92 mmol; 86 %).



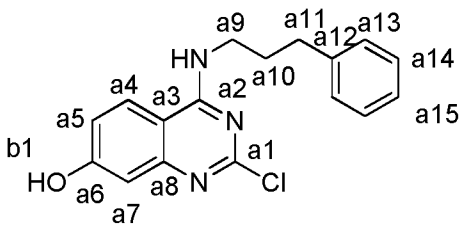
^{1}H NMR (500 MHz; DMSO) δ 8.54 (brt, J=5.28 Hz, 1H, HNH), 8.17 (d, J= 9.14 Hz, 1H, Ha4), 7.31-7.24 (m, 4H, Ha13 and Ha14), 7.20-7.16 (m, 1H, Ha15), 7.13 (dd, J=2.49, 8.95 Hz, 1H, Ha5), 7.05 (d, J=2.55 Hz, 1H, Ha7), 3.88 (s, 3H, Hb1), 3.50 (q, J=6.7 Hz, 2H, Ha9), 2.68 (t, J=7.77 Hz, 2H, Ha11), 1.96 (q, J=7.4 Hz, 2H, Ha10),

^{13}C NMR (125 MHz; DMSO) δ 163.6 (Ca6), 161.2 (Ca2), 157.9 (Ca1), 153.1 (Ca8), 142 (Ca12), 128.8 (Ca13), 128.7 (Ca14), 126.2 (Ca15), 125 (Ca4), 117.2 (Ca5), 108 (Ca3), 107 (Ca7), 56.1 (Cb1), 40.8 (Ca9), 32.9 (Ca11), 30.4 (Ca10).

HRMS-ESI (m/z) calculated for $C_{18}H_{18}ClN_3O$: 327.1105 $[M+H]^+$; found: 327.1149

4-((3-phenylpropyl)amino)-2-chloroquinazolin-7-ol (11).

10 (260 mg; 0.83 mmol) was added to a solution of 0.6 mol/L of boron tribromide in dichloromethane (5.6 mL). The reaction mixture was stirred at room temperature for 12h under argon. The resulting mixture was quenched with H_2O and concentrated under vacuum. The residue was diluted with ammonia 7N in methanol and the solvent was removed. The crude product was purified by silica gel flash chromatography using a linear gradient of ethyl acetate (0→70 % AcOEt) in cyclohexane to afford **11** as a white powder (217 mg; 0.69 mmol; 87 %)



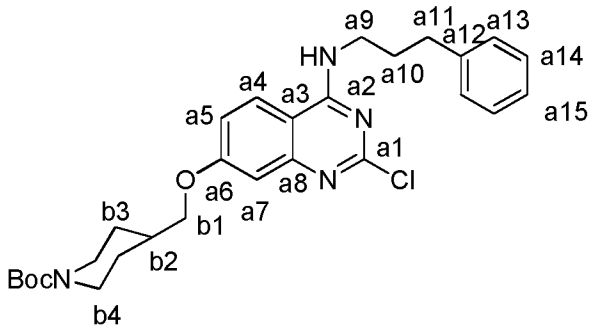
^{1}H NMR (500 MHz; DMSO) δ 10.5 (s, 1H, Hb1), 8.44 (brt, J=5.43Hz, 1H, HNH), 8.10 (d, J= 9.14Hz, 1H, Ha4), 7.31-7.23 (m, 4H, Ha13 and Ha14), 7.20-7.16 (m, 1H, Ha15), 6.99 (dd, J=2.44, 8.56Hz, 1H, Ha5), 6.85 (d, J=2.53Hz, 1H, Ha7), 3.48 (q, J=6.06Hz, 2H, Ha9), 2.67 (t, J=7.51Hz, 2H, Ha11), 1.94 (q, J=7.42Hz, 2H, Ha10),

^{13}C NMR (125 MHz; DMSO) δ 162.3 (Ca6), 161.1 (Ca2), 157.8 (Ca1), 153 (Ca8), 142 (Ca12), 128.8 (Ca13), 128.7 (Ca14), 126.2 (Ca15), 125.3 (Ca4), 117.3 (Ca5), 109.4 (Ca3), 107 (Ca7), 40.7 (Ca9), 32.9 (Ca11), 30.4 (Ca10).

HRMS-ESI (m/z) calculated for $C_{17}H_{16}ClN_3O$: 313.1035 $[M+H]^+$; found: 313.1012

4-((3-phenylpropyl)amino)-2-chloro-7-(*O*-((*N*-Boc)piperidin-4-ylmethoxy)) quinazoline (12).

To a solution of **11** (200 mg ; 0.64 mmol) in dichloromethane (2.1 mL), triphenylphosphine (185 mg; 0.7 mmol), (N-Boc)piperidin-4-ylmethanol (145 mg; 0.67 mmol) were added under argon. Diisopropylazodicarboxylate (139 µL; 0.7 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 18 h. The residue was diluted with dichloromethane and washed with water and brine, and dried over sodium sulphate. The solvent was removed and the residue was purified by silica gel flash chromatography using a linear gradient of ethyl acetate (0→50 % AcOEt) in cyclohexane to afford **12** as a yellow oil (320 mg; 0.63 mmol; 98 %).



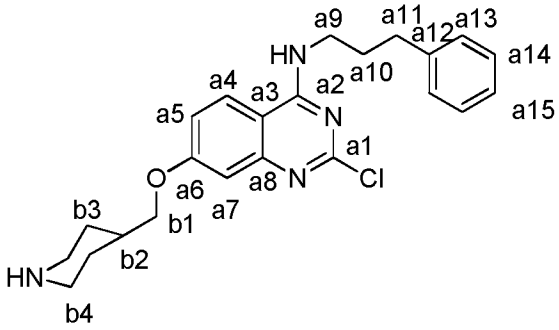
^{1}H NMR (500 MHz; DMSO) δ 8.52 (brt, J=5.69 Hz, 1H, HNH), 8.17 (d, J=9.17 Hz, 1H, Ha4), 7.32-7.24 (m, 4H, Ha13 and Ha14), 7.20-7.16 (m, 1H, Ha15), 7.13 (dd, J=2.72, 9.25 Hz, 1H, Ha5), 7.03 (d, J=2.8 Hz, 1H, Ha7), 4.03-3.93 (m, 4H, Hb1 and Hb4eq), 3.5 (q, J=6.37 Hz, 2H, Ha9), 2.81-2.7 (m, 2H, Hb4ax), 2.68 (t, J=7.68 Hz, 2H, Ha11), 1.99-1.91 (m, 1H, Hb2), 1.96 (q, J=7.17 Hz, 2H, Ha10), 1.8-1.73 (m, 2H, Hb3eq), 1.40 (s, 9H, HBoc), 1.22-1.13 (m, 2H, Hb3ax).

^{13}C NMR (125 MHz; DMSO) δ 162.9 (Ca6), 161.1 (Ca2), 157.9 (Ca1), 154.3 (Ca8), 142 (Ca12), 128.7 (Ca13), 128.6 (Ca14), 126.2 (Ca15), 125.2 (Ca4), 117.4 (Ca5), 107.8 (Ca7), 107.6 (Ca3), 78.9 (CBoc), 72.5 (Cb1), 55.3 (Cb4), 40.8 (Ca9), 35.6 (Cb2), 32.9 (Ca11), 30.4 (Ca10), 28.6 (Cb3), 28.5 (CBoc).

HRMS-ESI (m/z) calculated for $C_{28}H_{35}ClN_4O_3$: 511.1810 $[M+H]^+$; found: 511.1824

4-((3-phenylpropyl)amino)-2-chloro-7-*O*-(1*H*-*N*-piperidin-4-ylmethoxy) quinazoline (13).

12 (320 mg; 0.63 mmol) in TFA (5 mL) was stirred at room temperature for 1 h. TFA was removed and the resulting mixture was solubilized in ammonia 7N in methanol. The solvent was removed and the residue was diluted with ethyl acetate and the organic phase was washed with saturated K_2CO_3 and dried over sodium sulphate. The solvent was removed and **13** was obtained as a white power (260 mg; 0.63 mmol; quantitative).



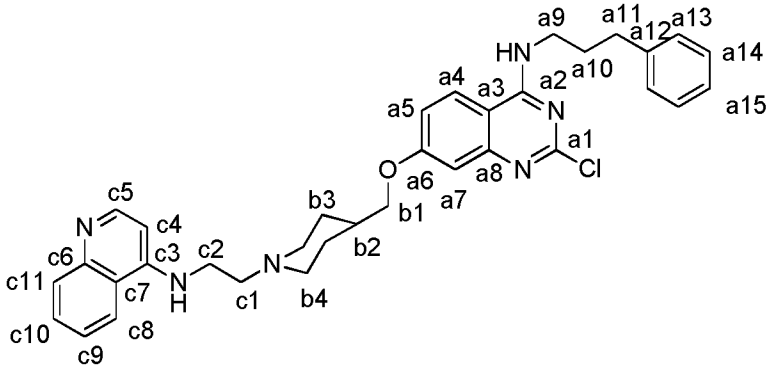
^{1}H NMR (500 MHz; DMSO) δ 8.5 (brt, J=5.45Hz, 1H, HNH), 8.12 (d, J=9.10Hz, 1H, Ha4), 7.35-7.22 (m, 4H, Ha13 and Ha14), 7.21-7.15 (m, 1H, Ha15), 7.11 (dd, J=2.65, 9.3Hz, 1H, Ha5), 7.01 (d, J=2.75Hz, 1H, Ha7), 3.97 (d, J=5.65Hz, 2H, Hb1), 3.47 (q, J=6.1Hz, 2H, Ha9), 3.00 (brd, 2H, Hb4eq), 2.15 (m, 2H, Hb4ax), 2.68 (t, J=7.68Hz, 2H, Ha11), 2.05 (q, J=7.25Hz, 2H, Ha10), 1.92-1.73 (m, 3H, Hb3eq and Hb2), 1.28-1.19 (m, 2H, Hb3ax).

^{13}C NMR (125 MHz; DMSO) δ 162.8 (Ca6), 161 (Ca2), 157.7 (Ca1), 154.3 (Ca8), 142.1 (Ca12), 128.7 (Ca13), 128.6 (Ca14), 126.1 (Ca15), 125.3 (Ca4), 117.4 (Ca5), 107.8 (Ca7), 107.6 (Ca3), 72.3 (Cb1), 53.2 (Cb4), 40.8 (Ca9), 35.6 (Cb2), 32.9 (Ca11), 30.6 (Ca10), 28.5 (Cb3).

HRMS-ESI (m/z) calculated for $C_{23}H_{27}ClN_4O$: 411.1914 $[M+H]^+$; found: 411.1938

4-((3-phenylpropyl)amino)-2-chloro-7-((1-(2-(quinolin-4-ylamino)ethyl) piperidin-4-yl)methoxy)quinazoline (B)

To a solution of **13** (250 mg; 0.6 mmol), K_2CO_3 (168 mg; 1.22 mmol) and a catalytic amount of KI in DMF (3.3 mL) was added **3** (251 mg; 1.22 mmol). The mixture was stirred at 65°C overnight then was diluted with ethyl acetate. The organic phase was washed with water and brine and dried over sodium sulfate. The solvent was removed and the residue was purified by silica gel flash chromatography using a linear gradient of ammonia 1N in methanol (0→10 % MeOH/NH_3) in dichloromethane or by reversed phase HPLC using a linear acetonitrile gradient with 0.01 % of TEA (0→80 % CH_3CN) to afford **Compound B** as a white powder (113 mg; 0.19 mmol; 32 %).



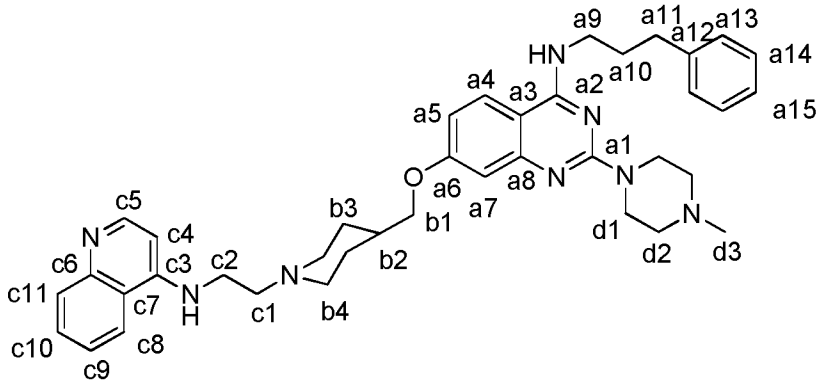
^{1}H NMR (500 MHz; DMSO) δ 8.53 (brt, J=5.4 Hz, 1H, HNH), 8.4 (d, J=5.58 Hz, 1H, Hc5), 8.19-8.1 (m, 2H, Hc8 and Ha4), 7.78 (dd, J=1.13, 8.56 Hz, 1H, Hc11), 7.61 (m, 1H, Hc10), 7.43 (m, 1H, Hc9), 7.32-7.17 (m, 5H, Ha13, Ha14 and Ha15), 7.15 (dd, J=2.52, 9 Hz, 1H, Ha5), 7.03 (d, J=2.55 Hz, 1H, Ha7), 7.02 (brt, 1H, HNH), 6.48 (d, J=5.58 Hz, 1H, Hc4), 3.99 (d, J=6.12 Hz, 2H, Hb1), 3.5 (q, J=6.12 Hz, 2H, Ha9), 3.41(q, J=6.66 Hz, 2H, Hc2), 3.00 (brd, J=11.7 Hz, 2H, Hb4eq), 2.68 (t, J=7.92 Hz, 2H, Ha11), 2.63 (t, J=7.02 Hz, 2H, Hc1), 2.06 (m, 2H, Hb4ax), 1.96 (m, 2H, Ha10), 1.85-1.75 (m, 3H, Hb3eq and Hb2), 1.29-1.2 (m, 2H, Hb3ax).

^{13}C NMR (125 MHz; DMSO) δ 163.1 (Ca6), 161.2 (Ca2), 157.9 (Ca1), 156.6 (Cc3), 153.1 (Ca8), 151.2 (Cc5), 150.2 (Cc7), 148.7 (Cc6), 142 (Ca12), 129.5 (Cc11), 129.2 (Cc10), 128.8 (Ca13), 128.7 (Ca14), 126.2 (Ca15), 125.1 (Ca4), 124.3 (Cc9), 121.9 (Cc8), 117.4 (Ca5), 107.9 (Ca7), 107.6 (Ca3), 98.7 (Cc4), 72.8 (Cb1), 56.6 (Cc1), 53.5 (Cb4), 40.8 (Ca9), 40.5 (Cc2), 35.6 (Cb2), 32.9 (Ca11), 30.4 (Ca10), 29 (Cb3).

HRMS-ESI (m/z) calculated for $C_{34}H_{37}ClN_6O$: 581.1932 $[M+H]^+$; found: 581.1929

4-((3-phenylpropyl)amino)-7-((1-(2-(quinolin-4-ylamino)ethyl)piperidin-4-yl)methoxy)-2-(4-methylpiperazin-1-yl)quinazoline (C).

A solution of **13** (7 mg; 12 µmol) in 1-methylpiperazine (100 µL, 0.9 mmol) was heated at 90 °C for 2 h. The resulting mixture was concentrated under vacuum and the residue was purified by reversed phase HPLC using a linear acetonitrile gradient with 0.01 % of TEA (0→80 % CH_3CN) to afford **Compound C** as a white powder (2.9 mg; 4.5 µmol; 37 %).



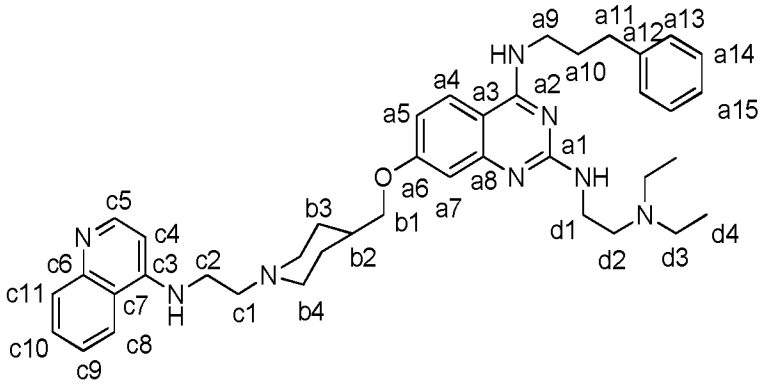
^{1}H NMR (500 MHz; DMSO) δ 8.4 (d, J=5.31 Hz, 1H, Hc5), 8.15 (dd, J=1.1,8.65 Hz, 1H, Hc8), 7.9(d, J=9.58 Hz, 1H, Ha4), 7.8 (brt, J=5.63 Hz, 1H, HNH), 7.78 (dd, J=1.15, 8.57 Hz, 1H, Hc11), 7.61 (m, 1H, Hc10), 7.43 (m, 1H, Hc9), 7.31-7.16 (m, 5H, Ha13, Ha14 and Ha15), 7.05 (brt, 1H, HNH), 6.68-6.6 (m, 2H, Ha5 and Ha7), 6.48 (d, J=5.3 Hz, 1H, Hc4), 3.99 (d, J=5.96 Hz, 2H, Hb1), 3.72-3.65 (m, 4H, Hd1), 3.45 (q, J=5.84 Hz, 2H, Ha9), 3.41(q, J=6.31 Hz, 2H, Hc2), 3.00 (brd, J=11.26 Hz, 2H, Hb4eq), 2.66 (t, J=7.28 Hz, 2H, Ha11), 2.63 (t, J=7.02 Hz, 2H, Hc1), 2.33-2.28 (m, 4H, Hd2), 2.21 (s, 3H, Hd3), 2.05 (m, 2H, Hb4ax), 1.92 (m, 2H, Ha10), 1.81-1.74 (m, 3H, Hb3eq and Hb2), 1.4-1.29 (m, 2H, Hb3ax).

^{13}C NMR (125 MHz; DMSO) δ 162.3 (Ca6), 159.9 (Ca2), 159.4 (Ca1), 154.3 (Cc3), 153.5 (Ca8), 151.2 (Cc5), 150.2 (Cc7), 148.7 (Cc6), 142 (Ca12), 129.5 (Cc11), 129.1 (Cc10), 128.8 (Ca13), 128.6 (Ca14), 126.1 (Ca15), 124.6 (Ca4), 124.3 (Cc9), 121.9 (Cc8), 111.9 (Ca5), 105.9 (Ca7), 105.2 (Ca3), 98.7 (Cc4), 72.4 (Cb1), 56.5 (Cc1), 55.1 (Cd2), 53.4 (Cb4), 46.5 (Cd3), 43.6 (Cd1), 40.3 (Ca9), 40.6 (Cc2), 35.7 (Cb2), 33.2 (Ca11), 30.7 (Ca10), 29.1 (Cb3).

HRMS-ESI (m/z) calculated for $C_{39}H_{48}N_8O$: 645.4024 $[M+H]^+$; found: 645.4015

4-((3-phenylpropyl)amino)-N^2-(2-(diethylamino)ethylenediamine)-7-((1-(2-(quinolin-4-ylamino)ethyl)piperidin-4-yl)methoxy)quinazoline (D).

To dry *N,N*-diethylethylenediamine (200 µL; 1.4 mmol) was added sodium (5 mg; 0.22mmol) and the mixture was stirred under utrasonication until complete disparition of sodium fragments (10 to 15min) then **13** (9 mg; 15 µmol) in *N,N*-diethylethylenediamine (50 µL) was added and the reaction mixture was stirred at 70°C for 12 h. The mixture was diluted with methanol (1ml) and TFA (17µL, 022mmol) was added. The solution was purified by reversed phase HPLC using a linear acetonitrile gradient with 0.02% of TFA (0→50 % CH_3CN) to afford **Compound D** as a white powder (3.6 mg; 5.5 µmol; 36 %).

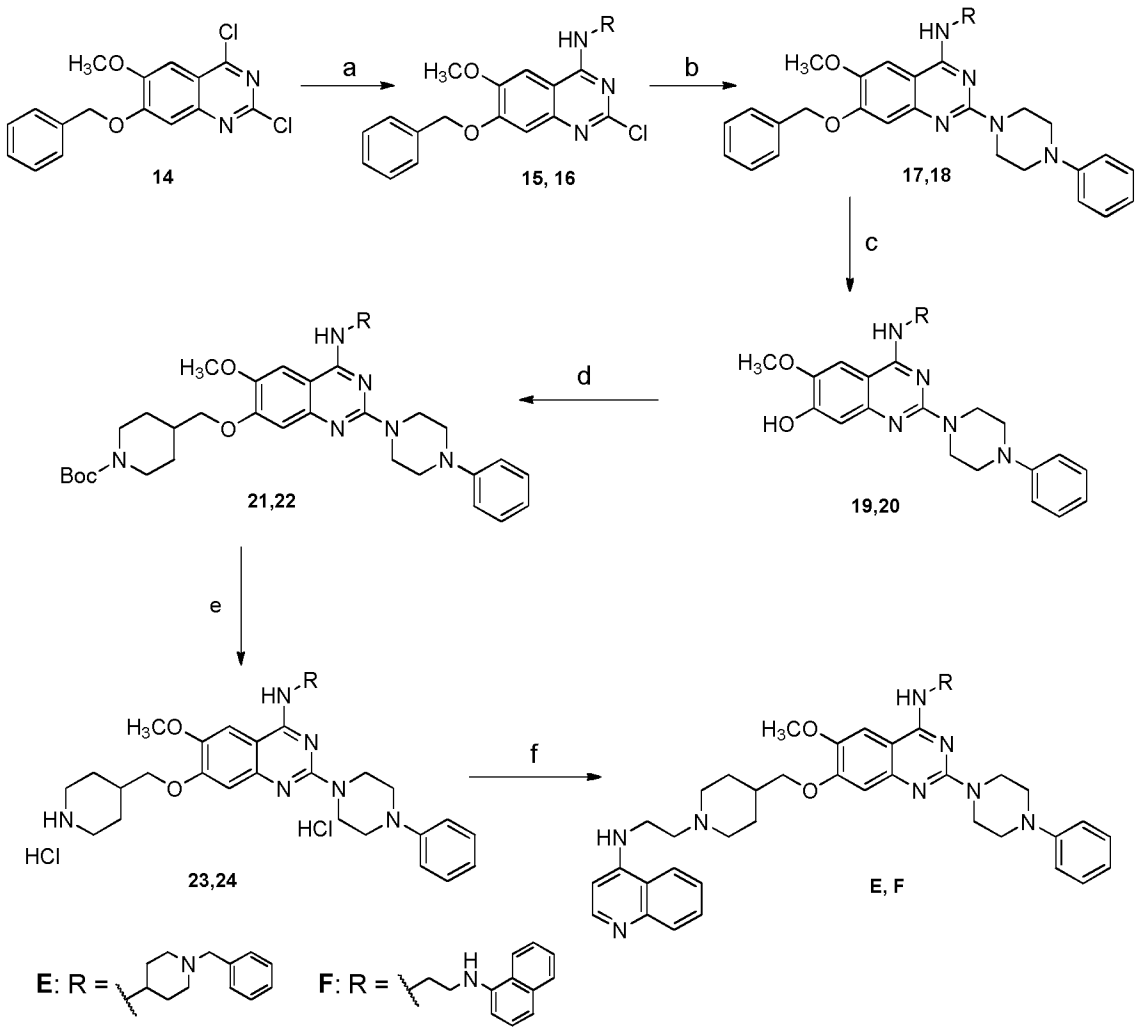


^{1}H NMR (500 MHz; DMSO) δ 8.40 (d, J=5.34 Hz, 1H, Hc5), 8.15 (dd, J=1.04,8.4 Hz, 1H, Hc8), 7.9(d, J=9.18 Hz, 1H, Ha4), 7.78 (dd, J=1.09, 8.25 Hz, 1H, Hc11), 7.61 (m, 1H, Hc10), 7.43 (m, 1H, Hc9), 7.32-7.20 (m, 5H, Ha13, Ha14 and Ha15), 7.05 (brt, 1H, HNH), 6.69-6.59 (m, 2H, Ha5 and Ha7), 6.48 (d, J=5.39 Hz, 1H, Hc4), 3.94-3.87 (m, 2H, Hb1), 3.68 (m, 2H, Hd1), 3.49-3.42 (m, 4H, Ha9 and Hc2), 3.00 (brd, J=11 Hz, 2H, Hb4eq), 2.66 (t, J=7.12 Hz, 2H, Ha11), 2.63 (t, J=7.32 Hz, 2H, Hc1), 2.3 (brt, 2H, Hd2), 2.05 (m, 2H, Hb4ax), 1.92 (m, 2H, Ha10), 1.81-1.74 (m, 3H, Hb3eq and Hb2), 1.4-1.33 (m, 2H, Hb3ax), 0.97 (m, 6H, Hd4).

^{13}C NMR (125 MHz; DMSO) δ 162.2 (Ca6), 159.9 (Ca2), 159.4 (Ca1), 154.3 (Cc3), 153.5 (Ca8), 151.3 (Cc5), 150.2 (Cc7), 148.7 (Cc6), 142 (Ca12), 129.5 (Cc11), 129.1 (Cc10), 128.8 (Ca13), 128.6 (Ca14), 126.1 (Ca15), 124.4 (Ca4), 124.3 (Cc9), 122 (Cc8), 111.9 (Ca5), 105.9 (Ca7), 105.2 (Ca3), 98.7 (Cc4), 72.3 (Cb1), 56.6 (Cc1), 55.2 (Cd2), 53.5 (Cb4), 43.7 (Cd1), 40.3 (Ca9), 40.6 (Cc2), 35.7 (Cb2), 33.2 (Ca11), 30.9 (Ca10), 29.1 (Cb3), 12.4 (Cd4).

HRMS-ESI (m/z) calculated for $C_{40}H_{52}N_8O$: 661.4321 $[M+H]^+$; found: 661.4317

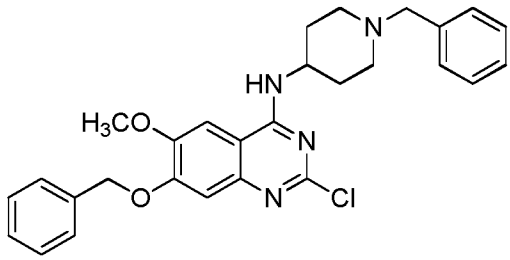
Example 3: Compounds E and F



a) R-NH_2, TEA, dry THF, 0°C to RT, 71h, 90-94%. b) *N*-phenylpiperazine, 110°C, sealed tube, 4h, 80-83%. c) TFA, 0°C to 115°C, 35min, quantitative yield. d) *N*-Boc-4-(hydroxymethyl)piperidine, PPh_3, DIAD, dry THF, 0°C to RT, N_2, 26h, 75-95%. e) HCl 4N in dioxane, dry MeOH, dry THF, 0°C, to RT, 23-49h, quantitative yield. f) *N*-(2-bromoethyl)quinoline-4-amine, NaI, K_2CO_3, dry DMF, 65°C, 27-29h, 60-65%.

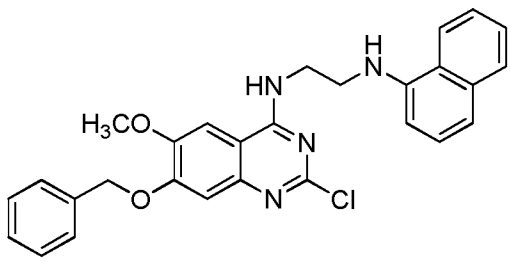
General procedure for the preparation of the intermediates 15 and 16. 7-(benzyloxy)-*N*-(1-benzylpyperidin-4-yl)-2-chloro-6-methoxyquinazolin-4-amine (15).

To a solution of **14** (1.79 mmol, 600 mg, 1 eq.) in dry THF (11.5 mL) were added in sequence TEA (5.37 mmol, 543.4 mg, 0.748 mL, 3 eq.) and 4-amine-1-benzylpiperidine (2.33 mmol, 442.8 mg, 0.438 mL, 1.3 eq.) and the resulting reaction mixture was stirred at room temperature for 23h. After three further additions of 4-amine-1-benzylpiperidine at 24h (0.3 eq., 0.1 mL), 48h (0.3 eq., 0.1 mL), and 55h (0.75 eq., 0.25 mL) the mixture was filtered after 71h. The filtrate and the washings were concentrated in vacuum and the crude solid triturated with petroleum ether, collected by filtration, washed with petroleum ether and dried under vacuum. The crude was finally purified by a silica gel column eluting with AcOEt to get **15** as a white powder (822 mg, 94%).



M.p. : 155-158°C. **^{1}H-NMR** (400MHz; DMSO) δ 1.63-1.72 (m, 2H, 2 x C*H* piperidine ring), 1.89-1.91 (m, 2H, 2 x C*H* piperidine ring), 2.05-2.10 (m, 2H, 2 x C*H* piperidine ring), 2.87-2.89 (m, 2H, 2 x C*H* piperidine ring), 3.51 (s, 2H, NCH_2Ph), 3.90 (s, 3H, OCH_3), 4.09-4.13 (broad, 1H, NHC$_4$-*H*-piperidine ring), 5.23 (s, 2H, OCH_2Ph), 7.15 (s, 1H, C*H* quinazoline ring), 7.26-7.28 (m, 1H, N*H*), 7.31-7.38 (m, 5H, C*H* phenyl rings), 7.40-7.43 (t, 2H, C*H* phenyl rings), 7.47-7.49 (d, 2H, C*H* phenyl rings) 7.67 (s, 1H, C*H* quinazoline ring), 8.03-8.05 (d, 1H, C*H* phenyl ring).

N^1-(7-(benzyloxy)-2-chloro-6-methoxyquinazolin-4-yl)-N^2-(naphtalen-1-yl)ethane-1,2-diamine (16)



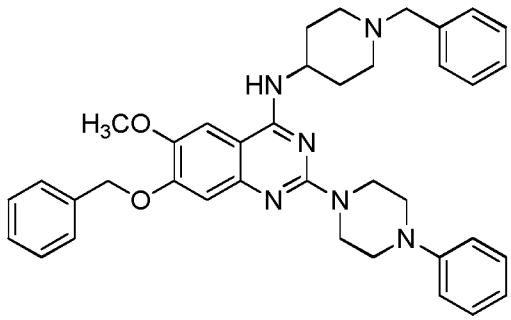
M.p.: 110-111°C. **^{1}H-NMR** (400MHz; $CDCl_3$) δ 3.67-3.70 (t, 2H, NHCH_2CH$_2$NH-napht), 3.89 (s, 3H, OCH_3), 4.09-4.12 (m, 2H, NHCH$_2$CH_2NH-napht), 5.22 (s, 2H, OCH_2Ph), 6.04 (bt, 1H, N*H*), 6.69 (d, 1H, C*H* aromatic rings), 6.78 (s,1H,

C*H* quinazoline ring), 7.18 (s, 1H, C*H* quinazoline ring), 7.26-7.29 (m, 2H, N*H* and C*H* aromatic rings), 7.30-7.36 (m, 4H, C*H* aromatic rings), 7.38-7.44 (m, 4H, C*H* aromatic rings), 7.78-7.80 (m, 1H, *CH* aromatic rings), 7.89-7.91 (m, 1H, *CH* aromatic rings).

General procedure for the preparation of the intermediates 17 and 18.

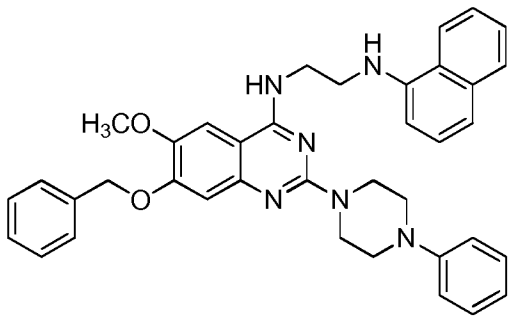
7-(benzyloxy)-*N*-(1-benzylpyperidin-4-yl)-6-methoxy-2-(4-phenylpiperazin-1-yl)quinazolin-4-amine (17).

To the intermediate **15** (0.818 mmol, 400 mg, 1 eq.) was added *N*-phenylpiperazine (6.543 mmol, 1.061 g, 0.99 mL, 8 eq.) and isoamyl alcohol (3.5 mL). The reaction was stirred in a sealed tube at 110°C for 4h and 45min. The reaction mixture was then cooled at room temperature, filtered, and washed over the filter with diethyl ether and petroleum ether. The crude solid was then triturated with water, collected by filtration and purified by crystallization from AcOEt to afford **17** as a white powder (400 mg, 80%).



M.p.: 199-200°C. **^{1}H-NMR** (400MHz; DMSO) δ 1.63-1.68 (m, 2H, 2 x C*H* piperidine ring), 1.97-1.99 (m, 2H, 2 x C*H* piperidine ring), 2.06-2.12 (m, 2H, 2 x C*H* piperidine ring), 2.89-2.91 (d, 2H, 2 x C*H* piperidine ring), 3.18 (m, 4H, 2 x CH_2 piperazine ring), 3.52 (s, 2H, NCH_2Ph), 3.83 (m, 7H, 2 x CH_2 piperazine ring and OCH_3), 4.07 (bm, 1H, NHC$_4$-*H*-piperidine ring), 5.18 (s, 2H, OCH_2Ph), 6.78-6.82 (m, 1H, C*H* phenyl rings), 6.85 (s, 1H, C*H* quinazoline ring), 6.99-7.01 (m, 2H, C*H* phenyl rings), 7.21-7.25 (m, 3H, C*H* phenyl rings and N*H*), 7.33-7.50 (m, 11H, C*H* phenyl and quinazoline rings).

N^1-(7-(benzyloxy)-6-methoxy-2-(4-phenylpiperazin-1-yl)quinazolin-4-yl)-N^2-(naphtalen-1-yl)ethane-1,2-diamine (18)

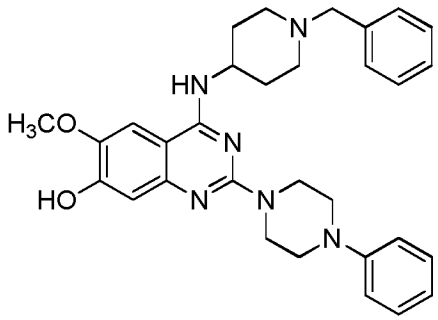


M.p.: 124°C. **^{1}H-NMR** (400MHz; DMSO) δ 3.20 (m, 4H, 2 x CH_2 piperazine ring), 3.53-3.56 (m, 2H, NHCH_2CH$_2$NH-napht), 3.83 (s, 3H, OCH_3), 3.87-3.92 (m, 6H, 2 x CH_2 piperazine ring and NHCH$_2$CH_2NH-napht), 5.20 (s, 2H, OCH_2Ph), 6.40 (t, 1H, N*H*), 6.65 (d, 1H, C*H* aromatic rings), 6.78-6.82 (t, 1H, C*H* aromatic rings), 6.90 (s, 1H, C*H* quinazoline ring), 6.98 (d, 2H, C*H* aromatic rings), 7.12 (d, 1H, C*H* aromatic rings), 7.23 (t, 2H, C*H* aromatic rings), 7.29-7.48 (m, 9H, C*H* aromatic rings), 7.76 (d, 1H, C*H* aromatic rings), 8.00-8.04 (m, 2H, C*H* aromatic rings and N*H*).

General procedure for the preparation of the intermediates 19 and 20.

4-((1-benzylpiperidin-4-yl)amino)-6-methoxy-7-hydroxy-2-(4-phenylpiperazin-1-yl)quinazoline (19).

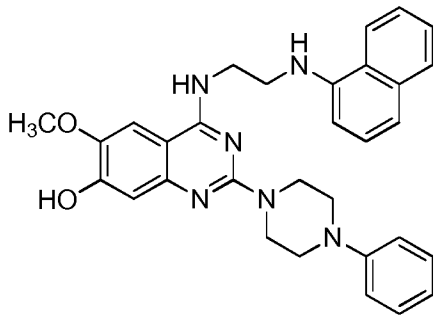
Trifluoroacetic acid (50.75 mmol, 5.78 g, 3.90 mL, 78 eq.) was added at 0°C to **17** (0.65 mmol, 400 mg, 1 eq.). The resulting solution was stirred at 115°C for 30 min, then TFA was removed under vacuum providing a crude that was suspended in H_2O at 0°C. The resulting suspension was basified with saturated solutions of Na_2CO_3 and $NaHCO_3$ until pH 9-10, and then the suspension was filtrated to give a crude product that was purified by a silica gel column eluting with a mixture AcOEt/MeOH/NH_3 (95:5:0.5) to get **19** as a white powder (quantitative yield).



M.p.: 131°C. **^{1}H-NMR** (400MHz; DMSO) δ 1.59-1.66 (m, 2H, 2 x C*H* piperidine ring), 1.96-1.99 (m, 2H, 2 x C*H* piperidine ring), 2.06-2.12 (m, 2H, 2 x C*H* piperidine ring), 2.88-2.91 (m, 2H, 2 x C*H* piperidine ring), 3.18 (m, 4H, 2 x CH_2

piperazine ring), 3.52 (s, 2H, NCH_2Ph), 3.83-3.86 (m, 7H, 2 x CH_2 piperazine ring and OCH_3), 4.06-4.09 (bm, 1H, NHC$_4$-*H*-piperidine ring), 6.65 (s, 1H, C*H* quinazoline ring), 6.80 (m, 1H, C*H* phenyl rings), 6.99-7.01 (m, 2H, C*H* phenyl rings), 7.23-7.45 (m, 9H, C*H* phenyl rings, C*H* quinazoline ring and N*H*), 9.70 (bs, 1H, O*H*).

6-Methoxy-4-((2-(naphtalen-1-ylamino)ethyl)amino)-2-(4-phenylpiperazin-1-yl)quinazolin-7-ol (20).

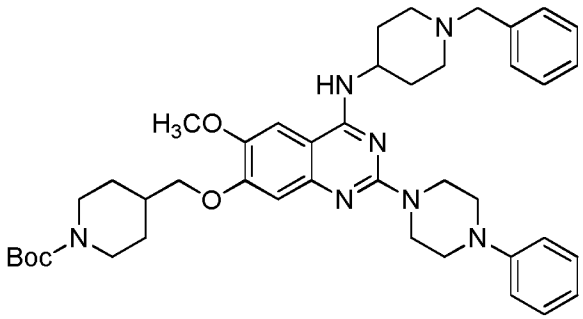


M.p.: 147-150°C. **^{1}H-NMR** (400MHz; DMSO) δ 3.16-3.26 (m, 4H, 2 x CH_2 piperazine ring), 3.52-3.55 (m, 2H, NHCH_2CH$_2$NH-napht), 3.87 (s, 3H, OCH_3), 3.89-3.90 (m, 6H, 2 x CH_2 piperazine ring and NHCH$_2$CH_2NH-napht), 6.39-6.41 (t, 1H, N*H*), 6.64-6.66 (d, 1H, C*H* aromatic rings), 6.68-6.70 (s, 1H, C*H* aromatic rings), 6.78-6.82 (t, 1H, C*H* aromatic rings), 6.98-7.00 (d, 2H, C*H* aromatic rings), 7.11-7.13 (d, 1H, C*H* aromatic rings), 7.22-7.26 (m, 2H, C*H* aromatic rings), 7.29-7.31 (m, 1H, C*H* aromatic rings), 7.33-7.43 (m, 3H, C*H* aromatic rings), 7.75-7.77 (m, 1H, C*H* aromatic rings), 7.93 (bm, 1H, N*H*), 8.02-8.04 (m, 1H, C*H* aromatic rings), 9.76-9.79 (bs, 1H, O*H*).

General procedure for the preparation of the intermediates 21 and 22.

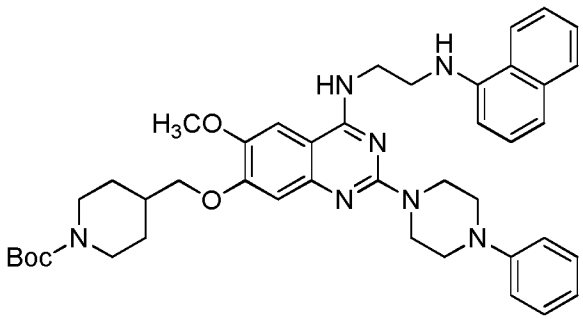
4-((1-Benzylpiperidine-4-yl)amino)-6-methoxy-2-(4-phenylpiperazin-1-yl)-7-(*O*-((*N*-Boc)piperidin-4-ylmethoxy))quinazoline (21).

To a solution of **20** (0.414 mmol, 217.6 mg, 1 eq.), *N*-Boc-4-(hydroxymethyl)piperidine (2.486 mmol, 535.4 mg, 6 eq.) and PPh_3 (3.42 mmol, 896.9 mg, 8.25 eq.) in dry THF (8.0 mL) was added DIAD (3.10 mmol, 628.6 mg, 0.611 mL, 7.5 eq.) cooling at 0°C under a nitrogen atmosphere. The resulting reaction mixture was then stirred at RT for 28h. After the completion of the reaction, the solvent was evaporated under vacuum and the crude product was purified by a silica gel flash chromatography (SNAP 100, Biotage Isolera One™) using a linear gradient of MeOH (0% to 40%) in AcOEt to give **21** as a white powder (283.4 mg, 95%).



M.p.: 225-226°C. **^{1}H-NMR** (400MHz; DMSO) δ 1.13-1.23 (m, 2H, 2 x C*H* piperidine ring), 1.40 (s, 9H, 3 x CH_3 *t*-Bu), 1.63-1.65 (m, 2H, 2 x C*H* piperidine ring), 1.74-1.77 (m, 2H, 2 x C*H* piperidine ring), 1.96-1.99 (m, 3H, 2 x C*H* piperidine ring and OCH_2CH), 2.06-2.12 (m, 2H, 2 x C*H* piperidine ring), 2.77 (bm, 2H, 2 x C*H* piperidine ring), 2.88-2.91 (d, 2H, 2 x C*H* piperidine ring), 3.18 (m, 4H, 2 x CH_2 piperazine ring), 3.51 (s, 2H, NCH_2Ph), 3.82-3.84 (m, 7H, 2 x CH_2 piperazine and OCH_3), 3.90 (m, 2H, OCH_2) 3.96-3.99 (m, 3H, NHC_4-*H*-piperidine ring and 2 x C*H* piperidine ring), 6.75 (s, 1H, C*H* quinazoline ring), 6.80 (m, 1H, C*H* phenyl ring), 7.00 (d, 2H, C*H* phenyl rings), 7.21-7.25 (m, 3H, C*H* phenyl rings and N*H*), 7.33-7.37 (m, 5H, C*H* phenyl rings), 7.47 (s, 1H, C*H* quinazoline ring).

4-(((2-Naphtalen-1-ylamino)ethyl)amino)-6-methoxy-2-(4-phenylpiperazin-1-yl)-7-(*O*-((*N*-Boc)piperidin-4-ylmethoxy))quinazoline (22).

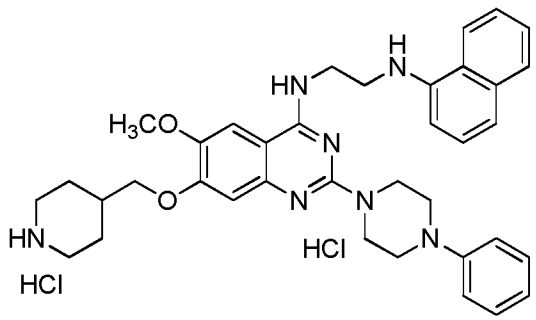


M.p.: 174°C. **^{1}H-NMR** (400MHz; DMSO) δ 1.14-1.24 (m, 2H, 2 x C*H* piperidine ring), 1.41 (s, 9H, 3 x CH_3 *t*-Bu), 1.75-1.78 (m, 2H, 2 x C*H* piperidine ring), 1.96-2.05 (m, 1H, OCH_2CH), 2.76 (bm, 2H, 2 x C*H* piperidine ring), 3.20-3.21 (m, 4H, 2 x CH_2 piperazine ring), 3.51-3.56 (m, 2H, $NHCH_2CH_2NH$-napht), 3.82 (s, 3H, OCH_3), 3.86-4.00 (m, 10H, $NHCH_2CH_2NH$-napht, 2 x CH_2 piperazine ring, OCH_2 and 2 x C*H* piperidine ring), 6.38-6.41 (m, 1H, N*H*), 6.65 (d, 1H, aromatic rings), 6.79-6.82 (m, 2H, C*H* aromatic rings), 6.98-7.00 (d, 2H, C*H* aromatic rings), 7.11-7.13 (d, 1H, C*H* aromatic rings), 7.21-7.29 (m, 2H, C*H* aromatic rings), 7.31-7.37 (m, 1H, C*H*

aromatic rings), 7.39-7.45 (m, 3H, C*H* aromatic rings), 7.76 (d, 1H, C*H* aromatic rings), 7.96-7.98 (t, 1H, N*H*), 8.02-8.06 (d, 1H, C*H* aromatic rings).

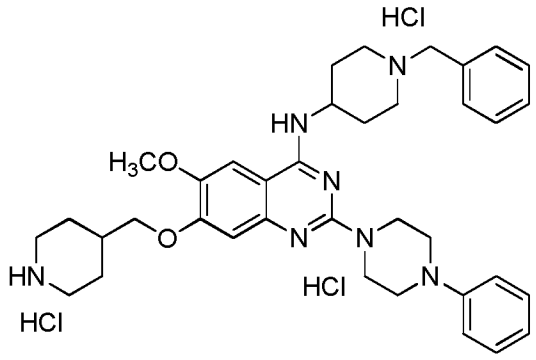
General procedure for the preparation of the intermediates 23 and 24. *N*^{1}-(6-methoxy-2-(4-phenylpiperazin-1-yl)-7-(piperidin-4-ylmethoxy)quinazolin-4-yl)-*N*^{2}-(naphtalen-1-yl)ethane-1,2-diamine dihydrochloride (24).

A solution of HCl 4N in dioxane (5.85 mmol, 1.46 mL, 55 eq.) was added dropwise at 0°C to a solution of **22** (0.106 mmol, 76.5 mg, 1 eq.) in a mixture of dry MeOH (4 mL) and dry THF (4 mL). The resulting reaction mixture was then stirred at RT for 49h and half. After the completion of the reaction, the resulting suspension was filtrated and washed with dry THF and dry Et_2O to get **23** as a white hygroscopic salt (quantitative yield).



M.p.: 215°C. **^{1}H-NMR** (400MHz; DMSO) δ 1.51-1.54 (m, 2H, 2 x C*H* piperidine ring), 1.94-1.97 (m, 2H, 2 x C*H* piperidine ring), 2.18-2.19 (m, 1H, OCH_2CH), 2.92-2.97 (m, 2H, 2 x C*H* piperidine ring), 3.25 (m, 4H, 2 x CH_2 piperazine ring), 3.31-3.34 (m, 2H, 2 x C*H* piperidine ring), 3.61-3.64 (m, 2H, $NHCH_2CH_2NH$-napht), 3.90 (s, 3H, OCH_3), 3.97 (m, 8H, $NHCH_2CH_2NH$-napht, 2 x CH_2 piperazine ring and OCH_2), 6.68 (d, 1H, C*H* aromatic rings), 6.84-6.87 (m, 1H, C*H* aromatic rings), 7.00-7.03 (m, 2H, C*H* aromatic rings), 7.14-7.16 (m, 1H, C*H* aromatic rings), 7.25-7.45 (m, 5H, C*H* aromatic rings and piperidine N*H*·*H*Cl), 7.53 (s, 1H, C*H* quinazoline ring), 7.76 (d, 1H, C*H* aromatic rings), 7.94 (s, 1H, C*H* quinazoline ring), 8.17-8.18 (d, 1H, C*H* aromatic rings), 8.56 (bm, 2H, C*H* aromatic rings and N*H*), 8.87 (m, 1H, C*H* aromatic rings), 9.73 (s, 1H, N*H*), 12.18 (s, 1H, *H*Cl).

***N*-(1-benzylpiperidin-4-yl)-6-methoxy-2-(4-phenylpiperazin-1-yl)-7-(piperidin-4-ylmethoxy)quinazolin-4-amine trihydrochloride (23).**



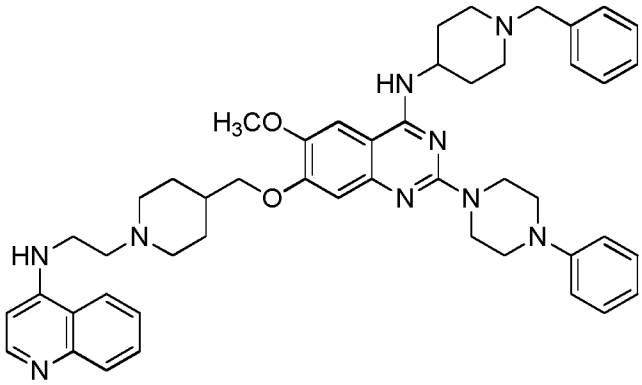
M.p.: 247-250°C. **^{1}H-NMR** (400MHz; DMSO) δ 1.51-1.54 (m, 2H, 2 x C*H* piperidine ring), 1.94-1.97 (m, 2H, 2 x C*H* piperidine ring), 2.15-2.26 (m, 5H, 4 x C*H* piperidine ring and OCH_2CH), 2.91-2.93 (m, 2H, 2 x C*H* piperidine ring), 3.16-3.19 (m, 2H, 2 x CH piperidine ring), 3.34-3.43 (m, 8H, 2 x CH_2 piperazine ring and 4 x C*H* piperidine ring), 3.90 (s, 3H, OCH_3), 3.98-4.0 (m, 2H, OCH_2), 4.07 (m, 4H, 2 x CH_2 piperazine ring), 4.29-4.31 (d, 2H, NCH_2Ph), 4.40 (bs, 1H, NHC_4-*H*-piperidine ring), 6.85-6.89 (m, 1H, C*H* aromatic rings), 7.05 (d, 2H, C*H* aromatic rings), 7.26-7.30 (m, 2H, C*H* aromatic rings), 7.48-7.49 (m, 3H, C*H* aromatic rings and piperidine N*H*·*H*Cl), 7.68-7.69 (m, 3H, C*H* aromatic rings), 8.03 (s, 1H, C*H* quinazoline ring), 8.64-8.67 (bm, 1H, C*H* aromatic rings), 8.96-9.00 (m, 1H, C*H* aromatic rings), 9.33-9.35 (d, 1H, N*H*), 11.25 (bs, 1H, $PhCH_2N$·*H*Cl), 12.52 (s, 1H, *H*Cl).

General procedure for the preparation of compounds E and F.

***N*-(1-benzylpiperidin-4-yl)-6-methoxy-2-(4-phenylpiperazin-1-yl)-7-((1-(2-(quinolin-4-ylamino)ethyl)piperidin-4-yl)methoxy)quinazolin-4-amine (E).**

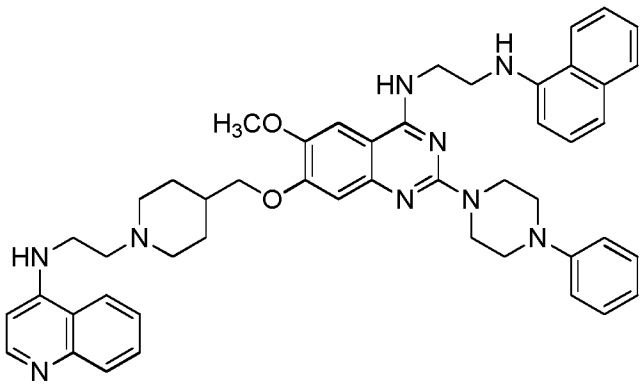
23 (0.123 mmol, 90 mg) was stirred for 20min in 20 mL of Na_2CO_3 saturated solution, then extracted with $CHCl_3$/*i*PrOH (4:1) (6 x 20 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated under reduced pressure to obtain the free amine. NaI (0.110 mmol, 19.27 mg, 1.25 eq.), K_2CO_3 (0.122 mmol, 19.91 mg, 1.4 eq.) and *N*-(2-bromoethyl)quinoline-4-amine (0.110 mmol, 32.29 mg, 1.25 eq.) were then added in sequence to the free amine of compound **23** (0.102 mmol, 64 mg, 1 eq.) and the resulting mixture was stirred in dry DMF (2 mL) at 65°C for 29h. After the completion of the reaction, the medium was quenched with NaCl saturated solution (10 mL) and the product was extracted with AcOEt (7 x 10 mL). The organic phase was then dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to

give a crude that was purified by a silica gel column eluting with a mixture AcOEt:MeOH:NH_3 (95:5:0.5) to obtain **E** as a white powder (50 mg, 62.5%).



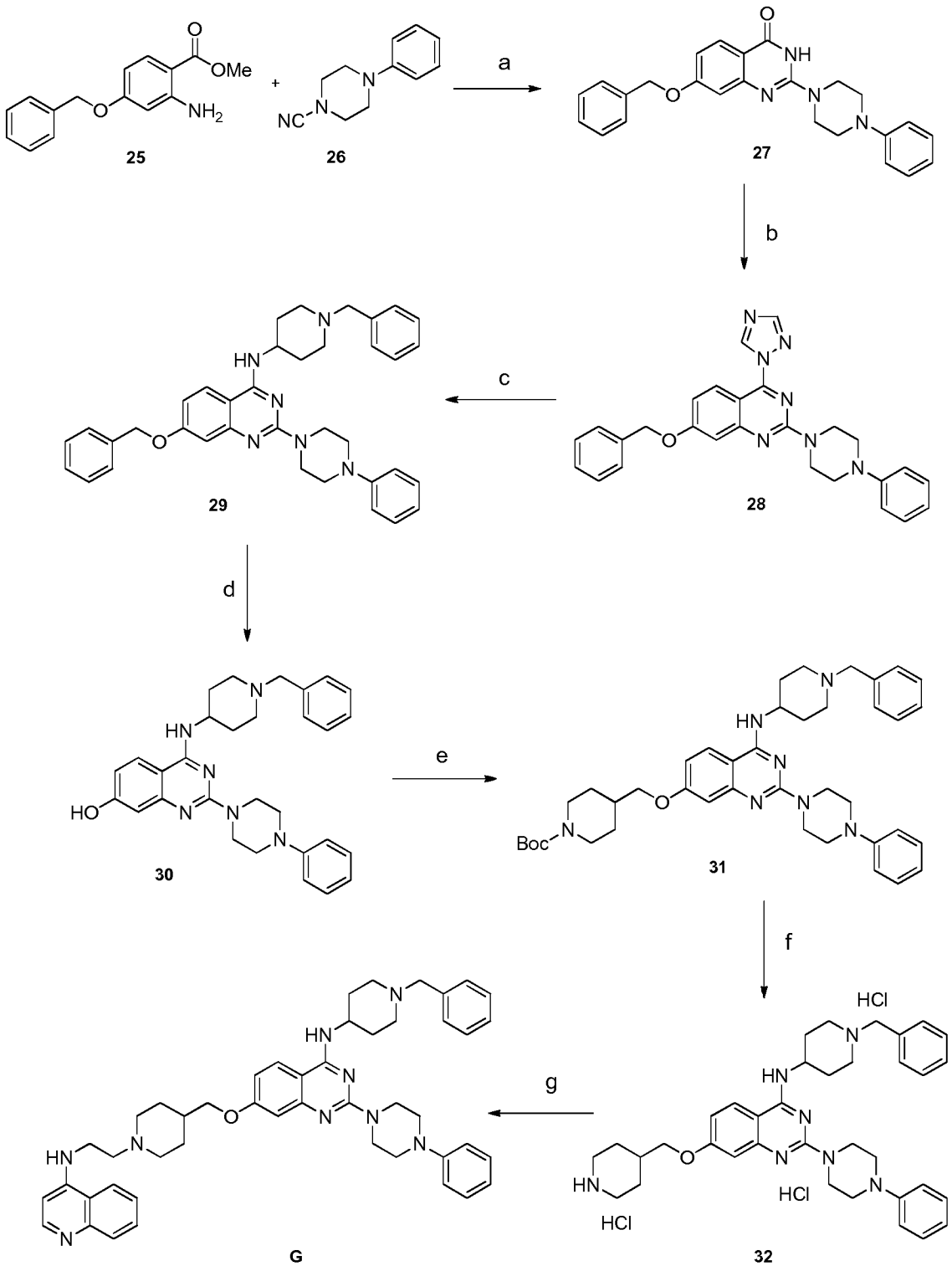
M.p.: 124-126°C. **^{1}H-NMR** (400MHz; DMSO) δ 1.35-1.43 (m, 2H, 2 x C*H* piperidine ring), 1.59-1.70 (m, 2H, 2 x C*H* piperidine ring), 1.76-1.78 (m, 3H, 2 x C*H* piperidine ring and OCH_2CH), 1.97-1.99 (m, 2H, 2 x C*H* piperidine ring), 2.07-2.10 (m, 4H, 4 x C*H* piperidine ring), 2.64-2.66 (m, 2H, CH_2CH_2NH-quinoline), 2.89-2.92 (m, 2H, 2 x C*H* piperidine ring), 3.00-3.08 (m, 2H, 2 x C*H* piperidine ring), 3.19 (m, 4H, 2 x CH_2 piperazine ring), 3.42 (m, 2H, CH_2CH_2NH-quinoline), 3.52 (s, 2H, NCH_2Ph), 3.83-3.85 (m, 7H, OCH_3 and 2 x CH_2 piperazine ring), 3.90-3.92 (m, 2H, CH_2O), 4.05 (bm, 1H, NHC_4-*H*-piperidine ring), 6.49-6.51 (d, 1H, C*H* quinoline ring), 6.75 (s, 1H, C*H* quinazoline ring), 6.78-6.80 (t, 1H, C*H* phenyl rings), 7.00 (d, 2H, C*H* phenyl rings), 7.07 (bs, 1H, N*H* quinoline), 7.21-7.25 (m, 3H, C*H* phenyl rings and N*H*), 7.33-7.36 (m, 5H, C*H* phenyl rings), 7.43-7.45 (m, 1H, C*H* quinoline ring), 7.47 (s, 1H, quinazoline ring), 7.62 (t, 1H, C*H* quinoline ring), 7.80 (d, 1H, C*H* quinoline ring), 8.17 (d, 1H, C*H* quinoline ring), 8.40 (d, 1H, C*H* quinoline ring).

N^1-(6-methoxy-2-(4-phenylpiperazin-1-yl)-7-((1-(2-(quinolin-4-ylamino)ethyl)piperidin-4-yl)methoxy)quinazolin-4-yl)-N^2-(naphtalen-1-yl)ethane-1,2-diamine (F).



M.p.: 180-181°C. **^{1}H-NMR** (400MHz; DMSO) δ 1.36-1.39 (m, 2H, 2 x C*H* piperidine ring), 1.78-1.80 (m, 3H, 2 x C*H* piperidine ring and OCH_2CH), 2.04-2.09 (m, 2H, 2 x C*H* piperidine ring), 2.63-2.65 (m, 2H, CH_2CH_2NH-quinoline), 2.99-3.01 (m, 2H, 2 x C*H* piperidine ring), 3.20 (m, 4H, 2 x CH_2 piperazine ring), 3.40 (m, 2H, CH_2CH_2NH-quinoline), 3.53-3.54 (m, 2H, NHCH_2CH_2-napht), 3.82 (s, 3H, OCH_3), 3.88-3.93 (m, 8H, CH_2O, 2 x CH_2 piperazine ring and $NHCH_2CH_2$-napht), 6.40 (m, 1H, N*H*), 6.47-6.49 (d, 1H, C*H* quinoline ring), 6.65 (m, 1H, C*H* aromatic rings), 6.79-6.82 (m, 2H, C*H* aromatic rings), 6.98-7.04 (m, 3H, aromatic rings and N*H* quinoline), 7.11-7.13 (d, 1H, C*H* aromatic rings), 7.22-7.45 (m, 7H, C*H* aromatic and quinoline ring), 7.59-7.63 (t, 1H, C*H* quinoline ring), 7.75-7.79 (t, 2H, C*H* aromatic and quinoline rings), 7.98-8.04 (m, 2H, C*H* aromatic rings and N*H*), 8.16 (d, 1H, C*H* quinoline ring), 8.39 (d, 1H, C*H* quinoline ring).

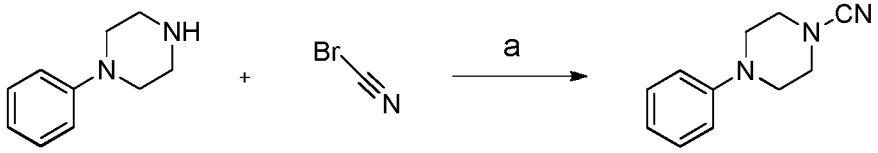
Example 4: Compound G



a) NaH, xylene, N_2, 140°C, 3h30min, 65%. b) *1.* $POCl_3$, TEA, 1,2,4-triazole, dry CH_3CN, 0°C for 40min then RT for 30min. *2.* Addition of a solution of **27** in dry $CHCl_3$, N_2, RT overnight then 100°C, 5h, 70%. c) 1-benzylpiperidin-4-amine, sealed tube, 125°C, 4h, 74%. d) TFA, 0°C to 115°C, 30min, quantitative yield. e) *N*-Boc-4-(hydroxymethyl)piperidine, DIAD, PPh_3, dry THF, 0°C to RT, N_2, 26h, 69%. f) HCl 4N

in dioxane, dry MeOH, dry THF, 0°C to RT, 76h, quantitative yield. g) **35**, NaI, K_2CO_3, dry DMF, 65°C, 51h, 75%.

Preparation of some reagents:

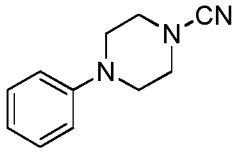


33 **34** **26**

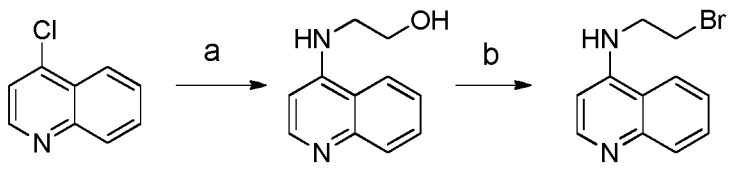
a) DIPEA, dry DCM, 0°C to RT, 1h, 96%.

Preparation of 4-phenylpiperazine-1-carbonitrile (26).

A 3M solution of BrCN in DCM (15.37 mmol, 5.125 mL, 1.25 eq.) was added dropwise at 0°C to a solution of DIPEA (36.9 mmol, 6.43 mL, 3 eq.) and *N*-phenylpiperazine (**33**) (12.3 mmol, 2 g, 1.88 mL, 1 eq.) in dry DCM (22 mL). The resulting reaction mixture was then stirred at room temperature for 1h. After the completion of the reaction, the medium was quenched with H_2O (30 mL) and the aqueous phase extracted with DCM (4 x 20 mL). The organic phases were then combined, washed with brine (7 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated under vacuum to give the desired product **26** as a white solid (96%), that was used in the subsequent step without further purification.



M.p.: 52-53°C. **^{1}H-NMR** (400MHz; $CDCl_3$) δ 3.23 (t, 4H, 2 x C*H*$_2$ piperazine ring), 3.39 (t, 4H, 2 x C*H*$_2$ piperazine ring), 6.90-6.97 (m, 3H, C*H* phenyl ring), 7.26-7.33 (m, 2H, C*H* phenyl ring).

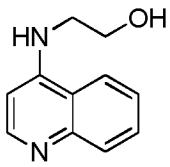


36 **37** **35**

a) Ethanolamine, MW, 140°C, 22 min, 95%. b) HBr 48%, conc. H_2SO_4, 0°C to 165°C, 7h, 60%.

Preparation of 2-(quinolin-4-ylamino)ethanol (37).

A mixture of 4-chloroquinoline (**36**) (2.44 mmol, 400 mg, 1 eq.) and ethanolamine (9.78 mmol, 597.3 mg, 0.588 mL, 4 eq.) was placed in a 2.5 mL microwave reaction vessel equipped with a magnetic stirrer. The reaction vessel was then placed in the cavity of the microwave reactor. The temperature was raised to 140°C and the vessel was irradiated for 22 min at the same temperature (the reaction temperature was modulated through the power switch and measured through the internal infrared sensor of the microwave apparatus). After the completion of the reaction, the mixture was cooled at room temperature and transferred with methanol in a flask of 50 mL. After the evaporation of the solvent under vacuum, a saturated solution of Na_2CO_3 was added and the aqueous phase was extracted with AcOEt (5 x 20 mL) and with $CHCl_3$/iPrOH (4:1) (2 x 20 mL). The crude product was then triturated with a mixture AcOEt/diethyl ether (1:1) and the desired pure product **37** was finally collected by filtration as a white powder (437.2 mg, 95%).



M.p.: 148-151°C. **^{1}H-NMR** (400MHz; DMSO) δ 3.35-3.37 (m, 2H, NHC*H*$_2$CH$_2$OH), 3.67 (m, 2H, NHCH$_2$C*H*$_2$OH), 4.86 (bs, 1H, O*H*), 6.48 (m, 1H, C*H* quinoline ring), 7.09 (m, 1H, N*H*), 7.41 (m, 1H, C*H* quinoline ring), 7.60 (m, 1H, C*H* quinoline ring), 7.77 (d, 1H, C*H* quinoline ring), 8.20 (d, 1H, C*H* quinoline ring), 8.38 (m, 1H, C*H* quinoline ring).

Preparation of *N*-(2-bromoethyl)quinolin-4-amine (35).

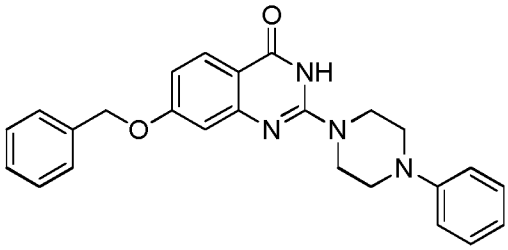
HBr 48% (27 mmol, 2.182 g, 1.467 mL, 27 eq.) and concentrated H_2SO_4 (9.9 mmol, 945.3 mg, 0.513 mL, 9.9 eq.) were added in sequence at 0°C to the previously obtained 2-(quinolin-4-ylamino)ethanol (**37**) (1 mmol, 188.2 mg, 1 eq.). The reaction mixture was then stirred for 7h at 165°C, then it was cooled down at room temperature and transferred with methanol in a flask of 50 mL. After the evaporation of the solvent under vacuum, ice (2.5 mL) and Na_2CO_3 saturated solution (2.5 mL) were added to the residue, that was cooled at 0°C and made basic (up to pH 10) with NaOH 2N. The aqueous layer was then extracted with AcOEt (8 x 20 mL), and the organic phase dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product

was finally purified by a silica gel flash chromatography (SNAP 50, Biotage Isolera Spektra One™) using a linear gradient of MeOH (1 to 10%) in $CHCl_3$ to give **35** as a white powder (150 mg, 60%).

M.p.: 138-140°C. **^{1}H-NMR** (400MHz; DMSO) δ 3.73-3.77 (m, 4H, NHC*H*$_2$C*H*$_2$Br), 6.57-6.58 (d, 1H, C*H* quinoline ring), 7.47-7.49 (t, 1H, C*H* quinoline ring), 7.52 (m 1H, N*H*), 7.63-7.67 (t, 1H, C*H* quinoline ring), 7.80-7.82 (d, 1H, C*H* quinoline ring), 8.19-8.21 (d, 1H, C*H* quinoline ring), 8.42-8.43 (d, 1H, C*H* quinoline ring).

7-(benzyloxy)-2-(4-phenylpiperazin-1-yl)quinazolin-4-ol (27)

26 (2.67 mmol, 500 mg, 1 eq.) and dry sodium hydride (9.346 mmol, 224.3 mg, 3.5 eq.) were added in sequence under nitrogen atmosphere to a solution of methyl 7-benzyloxy-2-aminobenzoate **25** (4.005 mmol, 1.03 g, 1.5 eq.) in xylenes (mixture of isomers) (17 mL). The resulting mixture was then heated at 140°C for 3h and 30 min. After the completion of the reaction, the medium was quenched with water (23 mL) and the product was extracted with AcOEt (5 x 23 mL) and with $CHCl_3$/*i*PrOH (4:1) (5 x 23 mL). The organic phases were combined and dried over Na_2SO_4. After filtration, the solvent was removed under vacuum and the product was purified by a silica gel column eluting with a mixture $CHCl_3$:MeOH (99.5:0.5) to afford **27** as a white powder (715 mg, 65%).

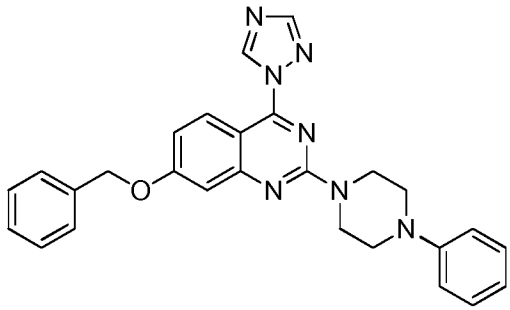


M.p.: >250°C. **^{1}H-NMR** (400MHz; DMSO) δ 3.20-3.23 (m, 4H, 2 x C*H*$_2$ piperazine ring), 3.76-3.78 (m, 4H, 2 x C*H*$_2$ piperazine ring), 5.21 (s, 2H, OC*H*$_2$Ph), 6.79-6.83 (m, 3H, C*H* aromatic rings), 6.98-7.00 (d, 2H, C*H* aromatic rings), 7.22-7.26 (t, 2H, C*H* aromatic rings), 7.34-7.37 (m, 1H, C*H* aromatic rings), 7.39-7.43 (t, 2H, C*H*

aromatic rings), 7.46-7.48 (d, 2H, C*H* aromatic rings), 7.82 (d, 1H, C*H* aromatic rings), 11.05-11.36 (bs, 1H, N*H*).

7-benzyloxy-2-(4-phenylpiperazin-1-yl)-4-(1*H*-1,2,4-triazol-1-yl)quinazoline (28).

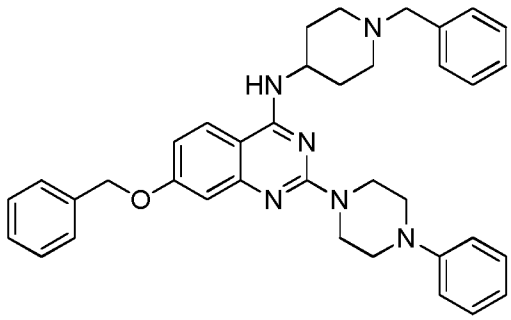
To a solution of triazole (2.959 mmol, 198.5 mg, 6.7 eq.) in dry acetonitrile (5.5 mL) at 0°C under nitrogen atmosphere, were added phosphorous oxychloride (0.972 mmol, 149 mg, 0.091 mL, 2.2 eq.) in one portion and triethylamine (2.959 mmol, 299 mg, 0.412 mL, 6.7 eq.) dropwise. The mixture was vigourously stirred at 0°C for 40 min. and then at room temperature for 30 min. A solution of **27** (0.442 mmol, 182.2 mg, 1 eq.) in dry $CHCl_3$ (5.5 mL) was then added and the resulting mixture was stirred at room temperature overnight. To get the complete disappearance of the starting material, the temperature of the reaction was raised up to 100°C and furtherly stirred for 5h. After completion of the reaction, the medium was quenched with water (12 mL) and the product was extracted with AcOEt (5 x 12 mL) and with $CHCl_3$/*i*PrOH (4:1) (5 x 12 mL). The organic phases were combined and dried over Na_2SO_4. After filtration, the solvent was removed under vacuum and the product was purified by a silica gel column eluting with a mixture $CHCl_3$:hexane (85:15) to obtain the desired product **28** as a yellow powder (143 mg, 70%).



M.p.: 196-197°C. **^{1}H-NMR** (400MHz; $CDCl_3$) δ 3.33-3.35 (m, 4H, 2 x CH_2 piperazine ring), 4.13-4.16 (m, 4H, 2 x CH_2 piperazine ring), 5.23 (s, 2H, OCH_2Ph), 6.94 (t, 1H, C*H* aromatic rings), 7.01-7.04 (m, 3H, C*H* aromatic rings), 7.09 (d, 1H, C*H* aromatic rings), 7.31-7.51 (m, 7H, C*H* aromatic rings), 8.25 (s, 1H, C*H* triazole ring), 8.88 (d, 1H, C*H* aromatic rings), 9.27 (s, 1H, C*H* triazole ring).

7-benzyloxy-*N*-(1-benzylpiperidin-1-yl)-2-(4-phenylpiperazin-1-yl)quinazolin-4-amine (29).

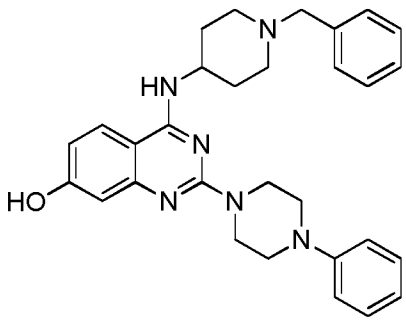
A mixture of **28** (0.235 mmol, 109 mg, 1 eq.) and *N*-benzylpiperidine-4-amine (3.53 mmol, 671 mg, 0.72 mL, 15 eq.) was stirred in sealed tube at 125°C for 4h. The reaction was diluted with AcOEt and the organic phase was washed with NaCl saturated solution (12 x 3 mL) to remove the amine in excess. The organic phase was then dried over Na_2SO_4. After filtration, the solvent was removed under vacuum and the crude product was purified on a silica gel column eluting with a mixture AcOEt/hexane/MeOH/NH_3 (20:80:1:0.1) to afford **29** as a white powder (101.5 mg, 74%).



M.p.: 104-105°C. **^{1}H-NMR** (400MHz; DMSO) δ 1.59-1.67 (m, 2H, 2 x C*H* piperidine ring), 1.93-1.96 (m, 2H, 2 x C*H* piperidine ring), 2.06-2.11 (m, 2H, 2 x C*H* piperidine ring), 2.86-2.89 (m, 2H, 2 x C*H* piperidine ring), 3.19 (m, 4H, 2 x CH_2 piperazine ring), 3.50 (s, 2H, NCH_2Ph), 3.89 (m, 4H, 2 x CH_2 piperazine ring), 4.02-4.07 (bm, 1H, NHC_4-*H*-piperidine ring), 5.19 (s, 2H, OCH_2Ph), 6.75-6.82 (m, 3H, C*H* aromatic rings), 6.99-7.01 (d, 2H, C*H* aromatic rings), 7.21-7.27 (m, 3H, C*H* aromatic rings and N*H*), 7.33-7.36 (m, 5H, C*H* aromatic rings), 7.39-7.43 (t, 2H, C*H* aromatic rings), 7.46-7.48 (m, 3H, C*H* aromatic rings), 8.00 (d, 1H, C*H* aromatic rings).

4-((1-Benzylpiperidin-4-yl)amino)-2-(4-phenylpiperazin-1-yl)quinazolin-7-ol (30).

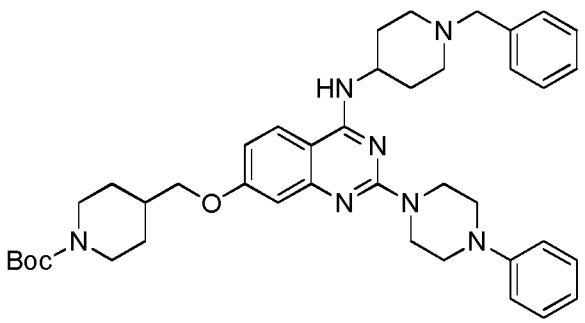
Prepared according to the general procedure for preparing intermediates 19 and 20.



M.p.: 158-160°C. **^{1}H-NMR** (400MHz; DMSO) δ 1.58-1.66 (m, 2H, 2 x C*H* piperidine ring), 1.92-1.95 (m, 2H, 2 x C*H* piperidine ring), 2.05-2.11 (m, 2H, 2 x C*H* piperidine ring), 2.86-2.88 (m, 2H, 2 x C*H* piperidine ring), 3.18 (m, 4H, 2 x CH_2 piperazine ring), 3.50 (s, 2H, NCH_2Ph), 3.87 (m, 4H, 2 x CH_2 piperazine ring), 4.03-4.08 (bm, 1H, NHC$_4$-*H*-piperidine ring), 6.55-6.57 (m, 2H, C*H* aromatic rings), 6.78-6.82 (t, 1H, C*H* aromatic rings), 6.99-7.01 (m, 2H, C*H* aromatic rings), 7.21-7.36 (m, 8H, C*H* aromatic rings and N*H*), 7.90 (d, 1H, C*H* quinazoline ring), 9.85 (s, 1H, O*H*).

4-((1-benzylpiperidine-4-yl)amino)-2-(4-phenylpiperazin-1-yl)-7-(*O*-((*N*-Boc)piperidin-4-ylmethoxy))quinazoline (31).

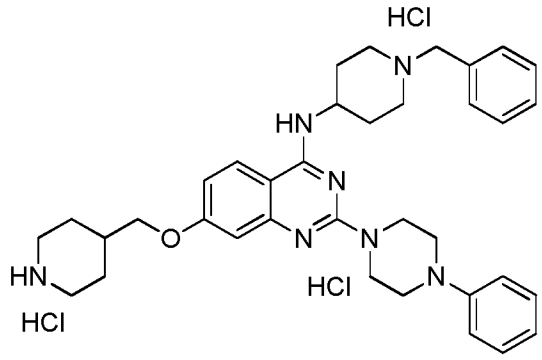
Prepared according to the general procedure for preparing intermediates 21 and 22.



M.p.: 186-187°C. **^{1}H-NMR** (400MHz; DMSO) δ 1.13-1.24 (m, 2H, 2 x C*H* piperidine ring), 1.40 (s, 9H, 3 x CH_3 *t*-Bu), 1.61-1.66 (m, 2H, 2 x C*H* piperidine ring), 1.75-1.77 (m, 2H, 2 x C*H* piperidine ring), 1.93-1.99 (m, 3H, 2 x C*H* piperidine ring and OCH$_2$C*H*), 2.05-2.11 (m, 2H, 2 x C*H* piperidine ring), 2.71-2.80 (bm, 2H, 2 x C*H* piperidine ring), 2.86-2.89 (m, 2H, 2 x C*H* piperidine ring), 3.18- 3.19 (m, 4H, 2 x CH_2 piperazine ring), 3.50 (s, 2H, NCH_2Ph), 3.89-3.92 (m, 6H, 2 x CH_2 piperazine and OCH_2), 3.97-4.02 (bm, 3H, NHC$_4$-*H*-piperidine ring and 2 x C*H* piperidine ring), 6.66-6.70 (m, 2H, C*H* aromatic rings), 6.78-6.82 (t, 1H, C*H* aromatic rings), 7.00 (d, 2H, C*H* aromatic rings), 7.21-7.28 (m, 3H, C*H* aromatic rings and N*H*), 7.31-7.34 (m, 4H, C*H* aromatic rings), 7.45-7.46 (d, 1H, C*H* aromatic rings), 7.96 (d, 1H, C*H* quinazoline ring).

***N*-(1-benzylpiperidin-4-yl)-2-(4-phenylpiperazin-1-yl)-7-(piperidin-4-ylmethoxy)quinazolin-4-amine trihydrochloride (32).**

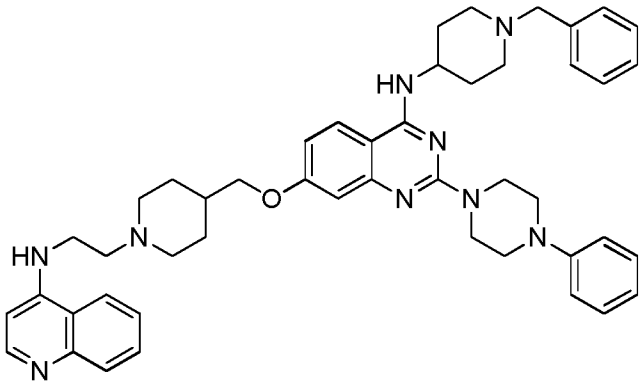
Prepared according to the general procedure for preparing intermediates 23 and 24.



M.p.: >250°C. **^{1}H-NMR** (400MHz; DMSO) δ 1.45-1.62 (m, 2H, 2 x C*H* piperidine ring), 1.91-1.98 (m, 2H, 2 x C*H* piperidine ring), 2.19-2.22 (m, 5H, 4 x C*H* piperidine ring and OCH_2CH), 2.89-2.92 (m, 2H, 2 x C*H* piperidine ring), 3.17-3.18 (m, 2H, 2 x C*H* piperidine ring), 3.29-3.4 (m, 8H, 2 x CH_2 piperazine ring and 4 x C*H* piperidine ring), 3.98-4.00 (m, 2H, OCH_2), 4.15 (m, 4H, 2 x CH_2 piperazine ring), 4.28-4.30 (d, 2H, NCH_2Ph), 4.40-4.42 (bs, 1H, NHC_4-*H*-piperidine ring), 6.88-6.92 (m, 1H, C*H* aromatic rings), 7.04-7.10 (m, 3H, C*H* aromatic rings), 7.28-7.31 (m, 2H, C*H* aromatic rings), 7.47 (m, 3H, C*H* aromatic rings and piperidine N*H*·*H*Cl), 7.66-7.69 (m, 3H, C*H* aromatic rings), 8.45 (d, 1H, C*H* aromatic rings), 8.81-8.83 (m, 1H, C*H* aromatic rings), 9.06-9.08 (m, 1H, C*H* aromatic rings), 9.34-9.36 (m, 1H, N*H*), 11.28 (bs, 1H, $PhCH_2N$·*H*Cl), 12.70 (bs, 1H, *H*Cl).

***N*-(1-benzylpiperidin-4-yl)-2-(4-phenylpiperazin-1-yl)-7-((1-(2-(quinolin-4-ylamino)ethyl)piperidin-4-yl)methoxy)quinazolin-4-amine (G).**

Prepared according to the general procedure for preparing compounds E and F.



M.p.: 122-124°C. **^{1}H-NMR** (400MHz; DMSO) δ 1.34-1.37 (m, 2H, 2 x C*H* piperidine ring), 1.62-1.67 (m, 2H, 2 x C*H* piperidine ring), 1.76-1.79 (m, 3H, 2 x C*H* piperidine ring and OCH_2CH), 1.93-1.96 (m, 2H, 2 x C*H* piperidine ring), 2.03-2.11 (m, 4H, 4 x C*H* piperidine ring), 2.62-2.65 (m, 2H, CH_2CH_2NH-quinoline), 2.86-2.89 (m,

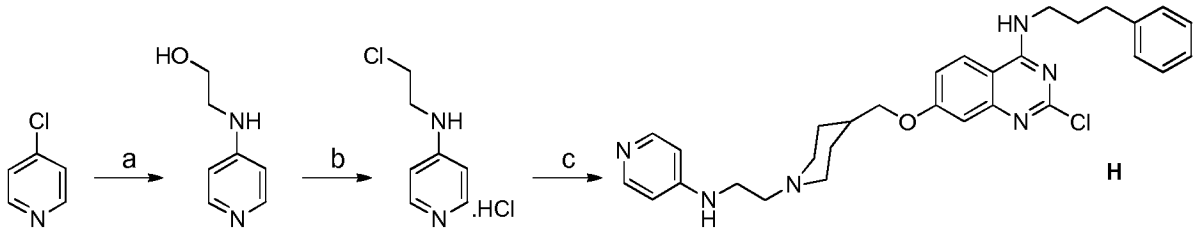
2H, 2 x C*H* piperidine ring), 2.98-3.01 (m, 2H, 2 x C*H* piperidine ring), 3.19 (m, 4H, 2 x CH_2 piperazine ring), 3.44 (m, 2H, CH_2CH_2NH-quinoline), 3.50 (s, 2H, NCH_2Ph), 3.90 (m, 6H, CH_2O and 2 x CH_2 piperazine ring), 4.04-4.05 (bm, 1H, NHC_4-*H*-piperidine ring), 6.48-6.49 (d, 1H, C*H* quinoline ring), 6.67-6.70 (m, 2H, C*H* aromatic rings), 6.78-6.82 (m, 1H, C*H* aromatic rings), 7.00 (d, 2H, C*H* aromatic rings), 7.07 (s, 1H, N*H* quinoline), 7.21-7.27 (m, 3H, C*H* aromatic rings and N*H*), 7.33 (m, 4H, C*H* aromatic rings), 7.45-7.46 (m, 2H, C*H* aromatic and quinoline ring), 7.59-7.63 (t, 1H, C*H* quinoline ring), 7.77-7.79 (d, 1H, C*H* quinoline ring), 7.97-7.99 (d, 1H, C*H* aromatic rings), 8.15-8.17 (d, 1H, C*H* quinoline ring), 8.39 (d, 1H, C*H* quinoline ring).

Example 5: Hydrochlorides of compounds E, F and G

General procedure to obtain the hydrochloride of the final free amine compounds E, F, and G.

To a solution of the final free amine compound in dry THF was added HCl 4N in dioxane (15 eq. every salt convertible position) at 0°C. The reaction mixture was then stirred for about 1h at 0°C. Finally, the white suspension was filtered and the solid washed in sequence with dry THF and dry diethyl ether and dried under vacuum.

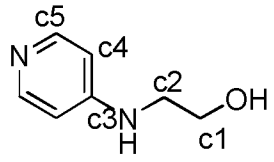
Example 6: Compound H



a) Ethanolamine, 125°C, 4h, quantitative yield. b) $SOCl_2$, DMF, Flash boiling, quantitative yield. c) **13**, K_2CO_3, KI, DMF, 90°C, 12h, 20%.

4-((2-Hydroxyethyl)amino)pyridine (33)

A mixture of 4-chloropyridine (500mg; 4.41mmol) in ethanolamine (2.6mL; 44mmol) was stirred at 110°C for 3h. The solvent was removed and the residue was purified by silica gel flash chromatography using a linear gradient of ethyl acetate (0→100% AcOEt) in cyclohexane to afford **33** as a white powder (607mg; 4.40mmol; quantitative yield).



33

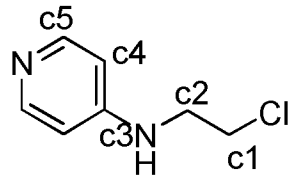
^{1}H NMR (500MHz, DMSO) δ 8.00 (d, J=6.1Hz, 1H, Hc5), 6.49 (m, 3H, Hc4 and HNH), 4.77 (brs, 1H, HOH), 3.53 (t, J=6.0Hz, 2H, Hc1), 3.13 (q, J=5.9Hz, 2H, Hc2).

^{13}C NMR (125MHz, DMSO) δ: 154.1 (Cc3), 149.7(Cc5), 107.5 (Cc4), 59.7 (Cc1), 40.6 (Cc2).

HRMS-ESI (m/z) calculated for $C_7H_{10}N_2NaO$ $[M+Na]^+$: 161.0685; found: 161.0650.

4-((2-chloroethyl)amino)quinoline hydrochloride (34)

33 (300mg; 1.92mmol) was solubilized in thionyl chloride (2ml). The mixture was flash boiled and the solvent was removed. Toluene was added to remove the residual thionyl chloride by co-evaporation. The residue was triturated in dichloromethane and the solid was filtrated to afford the hydrochloride **34** as a white solid (360mg; 1.87mmol; 97%).



34

^{1}H NMR (500MHz, DMSO) δ 8.22 (brs, 1H, HNH), 8.11 (d, J=6.8Hz, 2H, Hc5), 6.81 (d, J=6.8Hz, 2H, Hc4), 3.76 (t, J=6.0Hz, 2H, Hc1), 3.58 (q, J=5.6Hz, 2H, Hc2).

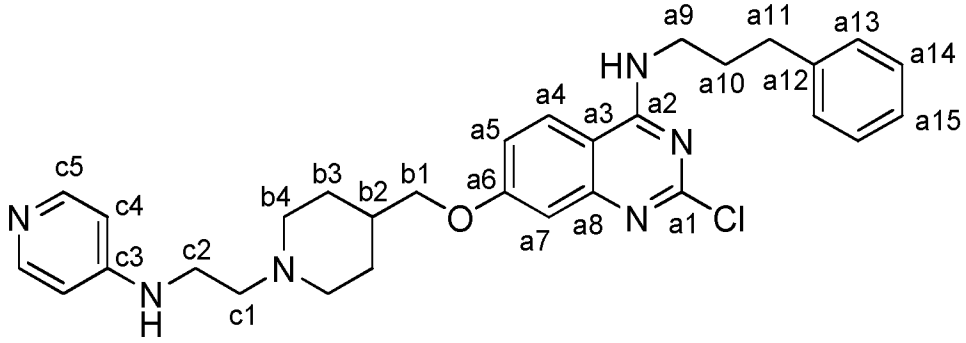
^{13}C NMR (125MHz, DMSO) δ: 156.6 (Cc3), 143.9(Cc5), 107.8 (Cc4), 44.1(Cc1), 43.5 (Cc2).

HRMS-ESI(m/z) calculated for $C_7H_{10}N_2Cl$ $[M+H]^+$: 157.0527; found: 157.0541.

1-Chloro-4-(3-phenylpropylamino)-7-((1-(2-(pyridin-4-ylamino)ethyl)piperidin-4-yl)methoxy)quinazoline (Compound H)

To a solution of **13** (15mg; 36μmol), K_2CO_3 (10mg; 72μmol) and a catalytic amount of KI in DMF (0.5mL) was added **34** (11mg; 72μmol). The mixture was stirred at 65°C overnight. The mixture was diluted with ethyl acetate. The organic phase was

washed with water and brine and dried over sodium sulfate. The solvent was removed and the residue was purified by silica gel flash chromatography using a linear gradient of ammonia 1N in methanol (0→10% MeOH/NH_3) in dichloromethane or by reversed phase HPLC using a linear acetonitrile gradient with 0.01% of TEA (0→80% CH_3CN) to afford **Compound H** (4.0mg; 7.5µmol; 20%) as a white powder.



H

^{1}H NMR (500MHz; DMSO) δ 8.55 (m, 1H, HNH), 8.19 (d, J=9.1Hz, 2H, Hc4), 7.33-7.22 (m, 4H, Ha4, Ha15 and Ha13), 7.22-7.10 (m, 2H, Ha14), 7.02 (d, J=2.5Hz, 1H, Ha5), 6.57-5.54 (m, 1H, HNH), 6.34 (m, 2H, Hc4), 3.92 (d, J=5.5Hz, 2H,Hb1), 3.92-3.82 (m, 2H, Ha9), 3.54-355 (m, 2H, Hc2), 3.21-3.10 (m, 2H, Hb4eq), 2.98-2.89 (m, 2H, Ha11), 2.68 (t, J=7.2Hz, 2H, Hc1), 2.05-1.89 (m, 4H, Ha10 and Hb4ax), 1.86-1.71 (m, 3H, Hb2 and Hb3eq), 1.43-1.41 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.5 (Ca6), 160.6 (Ca2), 157.4 (Ca1), 153.4 (Cc3), 152.6 (Ca8), 152.3 (Cc5), 141.5 (Ca12), 128.3 (Ca13), 128.2 (Ca14), 125.7 (Ca15), 124.6 (Ca4), 116.9 (Ca5), 107.4 (Ca3), 107.1 (Ca7), 94.7 (Cc4), 72.4 (Cb1), 56.7 (Cc1), 53.0 (Cb4), 40.4 (Ca9), 35.1 (Cb2), 32.4 (Ca11), 31.3 (Ca10), 29.0 (Cb3).

MS-ESI (m/z) calculated for $C_{30}H_{36Cl}N_6O$ $[M+H]^+$: 421.263; found: 421.265.

II. Biological tests of the compounds according to the invention

DNMT3A Assay.

DNMT3A enzyme inhibition was adapted from the restriction-based fluorescence assay protocol described in Ceccaldi *et al. (ChemBioChem* **2011,** *12*, 1337-45). Briefly, a 5'-labelled biotin oligonucleotide is hybridized to its complementary strand labelled with 6-carboxyfluorescein at the 3'-end into a 384 well microplate (black Optiplates; Perkin Elmer) pre-coated with avidin. The duplex contains a unique CpG site overlapping with a restriction site of a methylation sensitive restriction enzyme. The

human C-terminal DNMT3A (a.a. 623-908), produced as described in Gros et al. (*Nucleic Acids Research* 2013 41(19):e185), was added in each well (200 ng/well) and mixed with the chemical compounds at desired concentrations and freshly prepared AdoMet (20 µM final concentration) to start the reaction in a total volume of 50 µL. After 1 hour incubation at 37°C each well were washed three times with PBS, Tween-20 0.05%, NaCl (500 mM) and three more times with PBST. Specific fluorescent signals were detected with the methylation-sensitive restriction enzyme HpyCH4IV (NEB) as described and measured on a Perkin Elmer Envision detector. The percentage of inhibition is reported. The formula used to calculate the percentage of inhibition is [(X-Y) / X] x 100, where X is the signal determined in the absence of the inhibitor and Y is the signal obtained in the presence of the inhibitor. The concentration at which 50 % of efficacy of inhibition is observed (EC50) was determined by analysis of a concentration range of the tested compound in triplicates. The non-linear regression fittings with sigmoidal dose-response (variable slope) were performed with GraphPad Prism 4.03 (GraphPad Software).

DNMT1 Assay.

His-DNMT1 (182kDa, human) was cloned, expressed and purified as described in Halby *et al.* (*ChemBioChem* **2012,** *13*, 157-65). The reaction was performed in a 10µL total reaction volume in low volume NBS™ 384-well microplates (Corning), containing the tested compound (up to 1% DMSO), 1µM of a SAM/[methyl-^{3}H] SAM (3TBq/mmol, PerkinElmer) mix in a ratio of 3-to-1 (isotopic dilution 1*:3), 0.3µM of biotinylated hemimethylated DNA duplex (5'-GAT*mC*GC*mC*GATG*mC*G*mC*GAAT*mC*G*mC*GAT*mC*GATG*mC*GAT-3' and BIOT-5'-ATCGCATCGATCGCGATTCGCGCATCGGCGATC-3'), and 90nM of DNMT1 in methylation buffer (20mM HEPES pH 7.2, 1mM EDTA, 50mM KCl, 25µg/mL BSA). The reaction was incubated at 37°C for 2 hours. 8µL are then transferred into a streptavidin 96-well scintillant coated Flashplate™ (PerkinElmer) containing 190µL of 20µM SAH in 50mM Tris-HCl pH 7.4. The Flashplate™ was agitated at room temperature for 1 hour, washed three times with 200µL of 0.05% Tween®-20 in 50mM Tris-HCl pH 7.4, and read in 200µL of 50mM Tris-HCl pH 7.4 on TopCount NXT™ (PerkinElmer).

The results of these tests obtained with the compounds of the invention are indicated below:

Compound	DNMT1 (% of inhibition)			DNMT3A (% of inhibition)		
	32µM	10µM	EC_{50} µM	3.2µM	1µM	EC_{50} µM
A	0	0	-	18	0	ND
B	93	5	19	73	0	ND
C	94	0	23	43	0	ND
D	98	35	13	81	52	ND
E	100	59	10	100	74	0.6
F	93	45	11.7	84	75	ND
G	100	54	10	95	57	ND
H	-	-	-	32	0	ND

Anti-proliferative activity. (on KG-1)

KG-1 human leukemia cells were obtained from the ATCC (USA) and cultivated in RPMI 1640 medium (with HEPES and Glutamine, BE12-115F, Lonza, France) supplemented with, respectively, 20% and 15% foetal calf serum (Lonza, France), at 37°C and under 5% CO_2. To measure the anti-proliferative properties of tested molecules, $2x10^4$ cells are seeded at day 0 in a 96 wells plate. The compounds to be tested, stored at -20°C as 10^{-2} M stock solution in 100% DMSO, are freshly diluted on day 1 in RPMI 1640 medium, before adding a dose range of 3.2 nM to 10 µM to the cells. This treatment is repeated on day 2 and 3, and on day 4 cell viability is assessed using the ATPLite™ kit from Perkin (ATPlite™ 1 Step Luminescence Assay System, ref 3016739), following the provider instructions. The raw data are analyzed with GraphPad Prism software (v4.03) to generate EC_{50} values corresponding to the compound concentrations giving 50% reduction in cell viability. The values presented are the mean results of at least two independent experiments. The 95% confidence intervals for these EC_{50} values are also indicated.

Cells were then incubated for 72 h at 37°C in humidified 5% CO_2 atmosphere.

At the end of the experiment, cell viability was evaluated by determining the level of ATP released by viable cells.

EC_{50} values were determined with curve fitting analysis method (non linear regression model with a sigmoid dose response, variable Hill slope coefficient) provided by the Prism Software (GraphPad). Results were expressed as average EC_{50} values (concentration of tested compound that inhibits 50% of the maximum effect for the considered compound).

The results of these tests obtained with the compounds of the invention are indicated below:

Compound	EC_{50} (µM)	% proliferation inhibition			
	KG-1	10µM	5µM	1µM	0.1µM
A	ND	84.5	29.7	6.1	-0.8
B	ND	99.9	95.9	3.8	-1.7
C	ND	99.7	99.1	5.7	-3.1
D	ND	99.5	79.7	13.2	-2.3
E	2.5	99.8	92.1	15.4	-2.3
F	ND	99.9	99.6	31.9	2.0
G	ND	99.8	99.6	32.2	-2.2

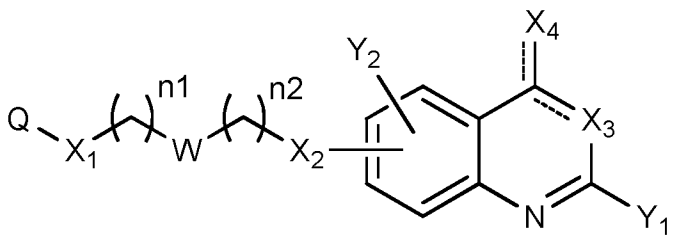
Gene expression. (CMV-luc reactivation)

KG-1 cell line, stably transfected with the luciferase Firefly (Luc+ from pGL3 by Promega) reporter gene under the control of the CMV promoter (from pEGFP-N1 by Clontech) partially methylated (50%), is seeded at 20,000 cell per well in 96-well plate. After 24 h of incubation in the presence of the compounds or the solvant DMSO, the induction of the promoter is measured by quantification of luciferase with the Brite-lite™ assay system (Perkin Elmer) according to the manufacturer protocol. The luminescence is measured on *EnVision*™ Multilabel Plate Reader (Perkin Elmer) and the data are expressed in induction factor compared to the DMSO control condition. The mean of 3 experiments and its standard error is reported in the table below.

Compound	Reactivation fold of luciferase gene reporter			
	Concentration (μM)			
	10	5	1	0.1
A	6.0 ± 0.6	4.4 ± 0.5	1.2 ± 0.1	1.1 ± 0.1
B	0.0 ± 0.0	5.8 ± 1.6	1.4 ± 0.0	1.1 ± 0.0
C	0.0 ± 0.0	0.1 ± 0.0	1.7 ± 0.1	1.1 ± 0.0
D	1.1 ± 1.0	12.7 ± 0.6	1.7 ± 0.0	1.1 ± 0.0
E	0.0 ± 0.0	1.3 ± 1.2	3.5 ± 0.0	1.1 ± 0.0
F	0.0 ± 0.0	1.0 ± 0.8	4.4 ± 0.4	1.1 ± 0.0
G	0.0 ± 0.0	0.2 ± 0.1	5.3 ± 0.4	1.1 ± 0.0

CLAIMS

1. A compound of the following formula (I):



(I)

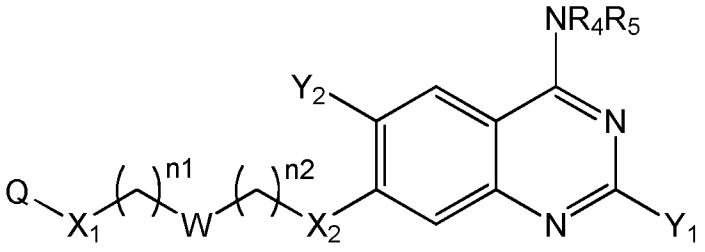
or a pharmaceutically acceptable salt or solvate thereof,

wherein:

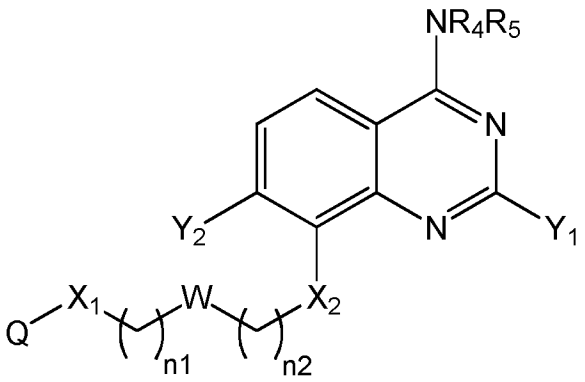
- ====== represents a single bond or a double bond on the condition that the two bonds ====== do not represent a double bond at the same time,
- n1 and n2 represent, independently of each other, an integer comprised between 0 and 8,
- Q represents an optionally substituted aryl or an optionally substituted nitrogen-containing heterocycle,
- W represents NR_0, a divalent monoglycosyl, a piperidinediyl, a piperazinediyl or a pyrrolidinediyl,
- X_1 represents O or NR_1,
- X_2 represents O, NR_2 or a bond,
- X_3 represents:
  - N when =====X_3 represents a double bond ===X_3, and
  - NR_3 when =====X_3 represents a single bond ——X_3,
- X_4 represents:
  - O or NR_4 when =====X_4 represents a double bond ===X_4, and
  - OR_4 or NR_4R_5 when =====X_4 represents a single bond ——X_4,
- Y_1 and Y_2 represent, independently of each other, a halogen atom, R_{100}, OR_{101} or $NR_{102}R_{103}$, provided that at least one of Y_1 and Y_2 represent a group other than H,
- R_0 represents H; CHO; CO_2-((C_1-C_6)alkyl); or a (C_1-C_6)alkyl optionally substituted with CHO, CO_2H or CO_2-((C_1-C_6)alkyl),

- R_1 and R_2 represent, independently of each other, H or a $(C_1\text{-}C_6)$alkyl,
- R_3 and R_4 represent, independently of each other, H, $(C_1\text{-}C_6)$alkyl, aryl, heterocycle, -$((C_1\text{-}C_6)$alkyl)-X_5-aryl or -$((C_1\text{-}C_6)$alkyl)-X_5-heterocycle,
  with X_5 representing a bond, O, S or NR_6 and each aryl or heterocycle moiety being optionally substituted,
- R_5 and R_6 represent, independently of each other, H or a $(C_1\text{-}C_6)$alkyl, and notably H,
- R_{100}, R_{101}, R_{102} and R_{103} represent, independently of one another, H, optionally substituted aryl, optionally substituted heterocycle, or -$((C_1\text{-}C_6)$alkyl)-X_6-A_1,
  with X_6 representing a bond, O, S or NR_{104} and A_1 representing H, $(C_1\text{-}C_6)$alkyl, optionally substituted aryl or optionally substituted heterocycle,
  or, for the R_{102} and R_{103} groups, R_{102} and R_{103} form together, with the nitrogen carrying them, an optionally substituted heterocycle, and
- R_{104} represents H or a $(C_1\text{-}C_6)$alkyl.

2. The compound according to claim 1, wherein it is a compound of the following formula (I-3c) or (I-4c):



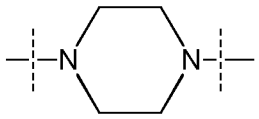
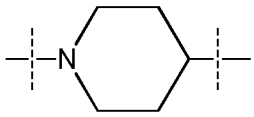
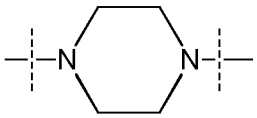
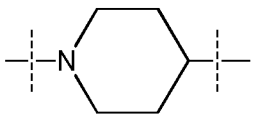
(I-3c)



(I-4c)

or a pharmaceutically acceptable salt or solvate thereof.

3. The compound according to any one of claims 1 and 2, wherein:

- n1 and n2 represent, independently of each other, an integer comprised between 0 and 4, notably between 0 and 2, such as 1 or 2,
- X_1 represents NH and X_2 represents a bond or O, notably O, and
- W represents  or  , the nitrogen atom being linked to $(CH_2)_{n1}$; notably  or  , the nitrogen atom being linked to $(CH_2)_{n1}$.

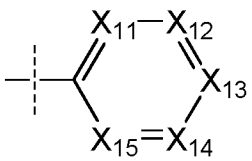
4. The compound according to any one of claims 1 to 3, wherein Q represents an aryl or nitrogen-containing heterocycle optionally substituted with one or several groups selected from halogen; oxo (=O); OR_{11}; $NR_{12}R_{13}$; $C(O)R_{14}$; CO_2R_{15}; $OC(O)R_{16}$; $C(O)NR_{17}R_{18}$; $NR_{19}C(O)R_{20}$; $(C_1\text{-}C_6)$alkyl optionally substituted with one or several groups selected from halogen, OR_{21}, $NR_{22}R_{23}$, $C(O)R_{24}$, CO_2R_{25}, $OC(O)R_{26}$, $C(O)NR_{27}R_{28}$, and $NR_{29}C(O)R_{30}$; and aryl optionally substituted with one or several groups selected from halogen, OR_{31}, $NR_{32}R_{33}$, $C(O)R_{34}$, CO_2R_{35}, $OC(O)R_{36}$, $C(O)NR_{37}R_{38}$, and $NR_{39}C(O)R_{40}$,

with R_{11} to R_{40} representing, independently of one another, H or $(C_1\text{-}C_6)$alkyl,

the aryl being in particular a phenyl or a naphtyl, and

the nitrogen-containing heterocycle being in particular a saturated, unsaturated or aromatic hydrocarbon monocycle or bicycle, each cycle having 5 or 6 members, in which one carbon atom has been replaced with a nitrogen atom and optionally 1 to 3, notably 1, additional carbon atom(s) has/have each been replaced with a nitrogen or oxygen atom, notably a nitrogen atom.

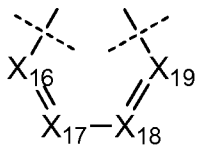
5. The compound according to claim 4, wherein Q represents a cycle of the following formula:



wherein:

- X_{11} represents N or CR_{41},
- X_{12} represents N or CR_{42},
- X_{13} represents N or C-$NR_{43a}R_{43b}$, notably N,
- X_{14} represents N or CR_{44},
- X_{15} represents N or CR_{45},
- R_{43a} and R_{43b} each represent, independently of each other, H or (C_1-C_6)alkyl, and in particular H,
- R_{41}, R_{42}, R_{44} and R_{45} each represent, independently of each other, hydrogen; halogen; OR_{11}; $NR_{12}R_{13}$; $C(O)R_{14}$; CO_2R_{15}; $OC(O)R_{16}$; $C(O)NR_{17}R_{18}$; $NR_{19}C(O)R_{20}$; (C_1-C_6)alkyl optionally substituted with one or several groups selected from halogen, OR_{21}, $NR_{22}R_{23}$, $C(O)R_{24}$, CO_2R_{25}, $OC(O)R_{26}$, $C(O)NR_{27}R_{28}$, and $NR_{29}C(O)R_{30}$; or aryl or aryl-(C_1-C_6)alkyl optionally substituted with one or several groups selected from halogen, OR_{31}, $NR_{32}R_{33}$, $C(O)R_{34}$, CO_2R_{35}, $OC(O)R_{36}$, $C(O)NR_{37}R_{38}$, and $NR_{39}C(O)R_{40}$; notably hydrogen; halogen; OR_{11}; $NR_{12}R_{13}$; (C_1-C_6)alkyl optionally substituted with one or several groups selected from halogen, OR_{21}, and $NR_{22}R_{23}$; or aryl optionally substituted with one or several groups selected from halogen, OR_{31}, and $NR_{32}R_{33}$, or

  in the case of R_{44} and R_{45}, R_{44} and R_{45} form together a chain of the following formula:



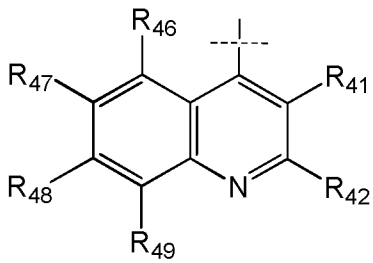
  wherein:

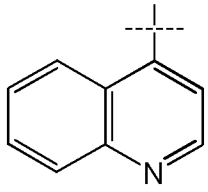
  - X_{16} represents N or CR_{46},
  - X_{17} represents N or CR_{47},
  - X_{18} represents N or CR_{48},
  - X_{19} represents N or CR_{49}, and
  - R_{46}, R_{47}, R_{48} and R_{49} each represent, independently of one another, hydrogen; halogen; OR_{11}; $NR_{12}R_{13}$; $C(O)R_{14}$; CO_2R_{15}; $OC(O)R_{16}$; $C(O)NR_{17}R_{18}$; $NR_{19}C(O)R_{20}$; (C_1-C_6)alkyl optionally substituted with one or several groups selected from halogen, OR_{21}, $NR_{22}R_{23}$, $C(O)R_{24}$, CO_2R_{25}, $OC(O)R_{26}$,

$C(O)NR_{27}R_{28}$, and $NR_{29}C(O)R_{30}$; or aryl or aryl-$(C_1$-$C_6)$alkyl optionally substituted with one or several groups selected from halogen, OR_{31}, $NR_{32}R_{33}$, $C(O)R_{34}$, CO_2R_{35}, $OC(O)R_{36}$, $C(O)NR_{37}R_{38}$, and $NR_{39}C(O)R_{40}$; notably hydrogen; halogen; OR_{11}; $NR_{12}R_{13}$; $(C_1$-$C_6)$alkyl optionally substituted with one or several groups selected from halogen, OR_{21}, and $NR_{22}R_{23}$; or aryl optionally substituted with one or several groups selected from halogen, OR_{31}, and $NR_{32}R_{33}$,

on the proviso that no more than three, notably two, and preferably one, of X_{11}, X_{12}, X_{14}, X_{15}, X_{16}, X_{17}, X_{18} and X_{19} represent N.

6. The compound according to claim 5, wherein Q represents



where R_{41}, R_{42}, R_{46}, R_{47}, R_{48} and R_{49} each represent, independently of each other, hydrogen, halogen, OR_{11}, or $NR_{12}R_{13}$; and notably represents 

.

7. The compound according to any one of claims 1 to 6, wherein R_3 and R_4 represent, independently of each other, H, $(C_1$-$C_6)$alkyl, aryl, heterocycle, -$((C_1$-$C_6)$alkyl)-X_5-aryl or -$((C_1$-$C_6)$alkyl)-X_5-heterocycle,

each aryl or heterocycle moiety being optionally substituted with one or several groups selected from halogen; oxo (=O); NO_2; OR_{11}; $NR_{12}R_{13}$; $C(O)R_{14}$; CO_2R_{15}; $OC(O)R_{16}$; $C(O)NR_{17}R_{18}$; $NR_{19}C(O)R_{20}$; $S(O)R_{50}$; $S(O)_2R_{51}$; $S(O)_2NR_{52}R_{53}$; $(C_1$-$C_6)$alkyl optionally substituted with one or several groups selected from halogen, OR_{21}, $NR_{22}R_{23}$, $C(O)R_{24}$, CO_2R_{25}, $OC(O)R_{26}$, $C(O)NR_{27}R_{28}$, $NR_{29}C(O)R_{30}$, $S(O)R_{54}$, $S(O)_2R_{55}$, and $S(O)_2NR_{56}R_{57}$; and aryl or aryl-$(C_1$-$C_6)$alkyl optionally substituted with one or several

groups selected from halogen, OR_{31}, $NR_{32}R_{33}$, $C(O)R_{34}$, CO_2R_{35}, $OC(O)R_{36}$, $C(O)NR_{37}R_{38}$, $NR_{39}C(O)R_{40}$, $S(O)R_{58}$, $S(O)_2R_{59}$, and $S(O)_2NR_{60}R_{61}$,

with R_{11} to R_{40} and R_{50} to R_{61} representing, independently of one another, H or (C_1-C_6)alkyl,

the aryl being in particular a phenyl or a naphtyl, and

the heterocycle being in particular a saturated, unsaturated or aromatic hydrocarbon monocycle or bicycle, each cycle having 5 or 6 members and 1 to 4 carbon atoms having each been replaced with a nitrogen or oxygen atom.

8. The compound according to claim 7, wherein R_3 and R_4 represent notably, independently of each other, H, (C_1-C_6)alkyl, aryl, heterocycle, -((C_1-C_6)alkyl)-X_5-aryl or -((C_1-C_6)alkyl)-X_5-heterocycle; such as H, (C_1-C_6)alkyl, aryl, heterocycle, aryl-(C_1-C_6)alkyl, heterocycle-(C_1-C_6)alkyl, -((C_1-C_6)alkyl)-NH-aryl or -((C_1-C_6)alkyl)-NH-heterocycle; notably aryl, heterocycle, aryl-(C_1-C_6)alkyl, heterocycle-(C_1-C_6)alkyl, -((C_1-C_6)alkyl)-NH-aryl or -((C_1-C_6)alkyl)-NH-heterocycle; more particularly heterocycle, aryl-(C_1-C_6)alkyl or -((C_1-C_6)alkyl)-NH-aryl,

each aryl or heterocycle moiety being optionally substituted with one or several groups selected from halogen; OR_{11}; $NR_{12}R_{13}$; (C_1-C_6)alkyl optionally substituted with one or several groups selected from halogen, OR_{21} and $NR_{22}R_{23}$; and aryl or aryl-(C_1-C_6)alkyl optionally substituted with one or several groups selected from halogen, OR_{31} and $NR_{32}R_{33}$,

the aryl being in particular a phenyl or a naphtyl, and

the heterocycle being in particular a saturated hydrocarbon monocycle or bicycle, each cycle having 5 or 6 members and 1 to 4 carbon atoms having each been replaced with a nitrogen or oxygen atom, such as piperidine, piperazine, triazinane or pyrrolidine, and in particular piperidine.

9. The compound according to any one of claims 1 to 8, wherein Y_1 and Y_2 represent, independently of each other, H, a halogen atom, OR_{101} or $NR_{102}R_{103}$, provided that at least one of Y_1 and Y_2 represent a group other than H,

where R_{100}, R_{101}, R_{102} and R_{103} represent, independently of one another, H, optionally substituted aryl, optionally substituted heterocycle, or -((C_1-C_6)alkyl)-X_6-A_1,

with X_6 representing a bond, O or NR_{104}, for ex. a bond or NR_{104}, and A_1 representing H, (C_1-C_6)alkyl, optionally substituted aryl or optionally substituted heterocycle,

or, for the R_{102} and R_{103} groups, R_{102} and R_{103} form together, with the nitrogen carrying them, an optionally substituted heterocycle, and

where the optionally substituted aryl and optionally substituted heterocycle are optionally substituted with one or several groups selected from halogen; oxo (=O); NO_2; OR_{11}; $NR_{12}R_{13}$; $C(O)R_{14}$; CO_2R_{15}; $OC(O)R_{16}$; $C(O)NR_{17}R_{18}$; $NR_{19}C(O)R_{20}$; $S(O)R_{50}$; $S(O)_2R_{51}$; $S(O)_2NR_{52}R_{53}$; (C_1-C_6)alkyl optionally substituted with one or several groups selected from halogen, OR_{21}, $NR_{22}R_{23}$, $C(O)R_{24}$, CO_2R_{25}, $OC(O)R_{26}$, $C(O)NR_{27}R_{28}$, $NR_{29}C(O)R_{30}$, $S(O)R_{54}$, $S(O)_2R_{55}$, and $S(O)_2NR_{56}R_{57}$; and aryl or aryl-(C_1-C_6)alkyl optionally substituted with one or several groups selected from halogen, OR_{31}, $NR_{32}R_{33}$, $C(O)R_{34}$, CO_2R_{35}, $OC(O)R_{36}$, $C(O)NR_{37}R_{38}$, $NR_{39}C(O)R_{40}$, $S(O)R_{58}$, $S(O)_2R_{59}$, and $S(O)_2NR_{60}R_{61}$,

with R_{11} to R_{40} and R_{50} to R_{61} representing, independently of one another, H or (C_1-C_6)alkyl,

the aryl being in particular a phenyl or a naphtyl, and

the heterocycle being in particular a saturated, unsaturated or aromatic hydrocarbon monocycle or bicycle, each cycle having 5 or 6 members and 1 to 4 carbon atoms having each been replaced with a nitrogen or oxygen atom.

10. The compound according to claim 9, wherein Y_1 represents H, a halogen atom or $NR_{102}R_{103}$, and Y_2 represents H or OR_{101}, provided that at least one of Y_1 and Y_2 represent a group other than H, with

R_{101} representing H, (C_1-C_6)alkyl, aryl, aryl-(C_1-C_6)alkyl or (C_1-C_6)alkyl-aryl; notably H or (C_1-C_6)alkyl, and

R_{102} and R_{103} representing, independently of one another, H, (C_1-C_6)alkyl, aryl, heterocycle, aryl-(C_1-C_6)alkyl, heterocycle-(C_1-C_6)alkyl or -((C_1-C_6)alkyl)-NR_{104}-A_1; notably heterocycle, heterocycle-(C_1-C_6)alkyl or -((C_1-C_6)alkyl)-NR_{104}-A_1, with A_1 representing H, (C_1-C_6)alkyl, aryl or heterocycle,

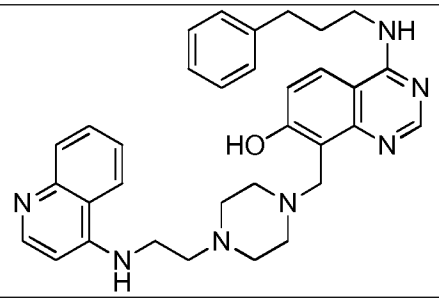
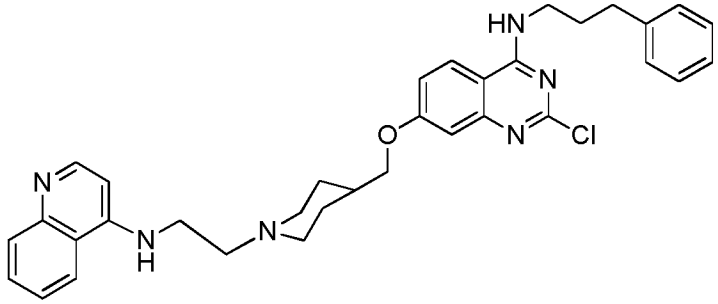
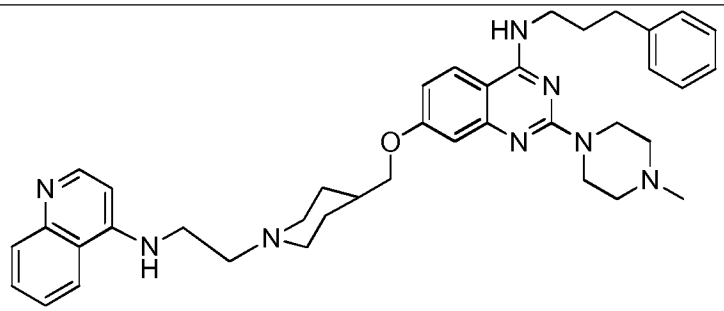
or R_{102} and R_{103} forming together, with the nitrogen carrying them, a heterocycle, and

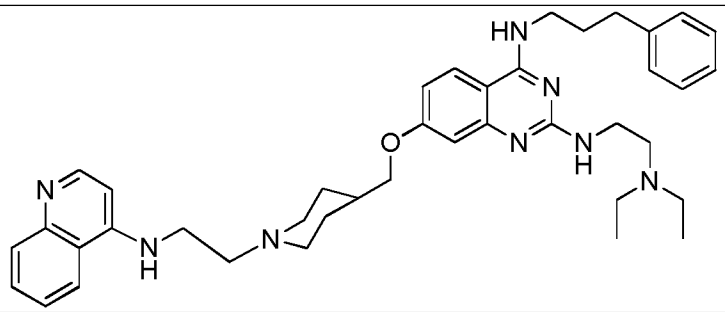
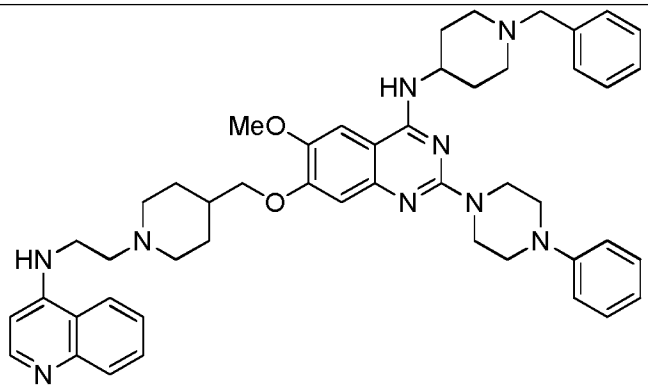
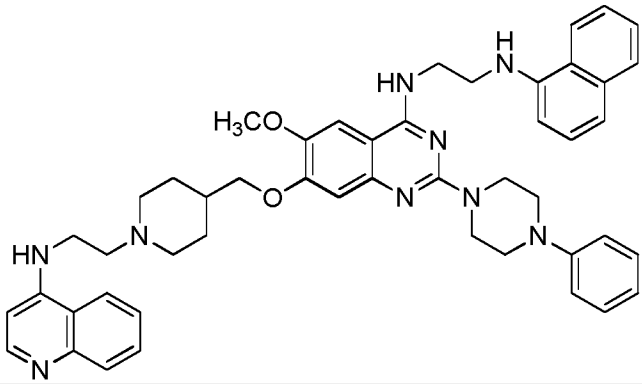
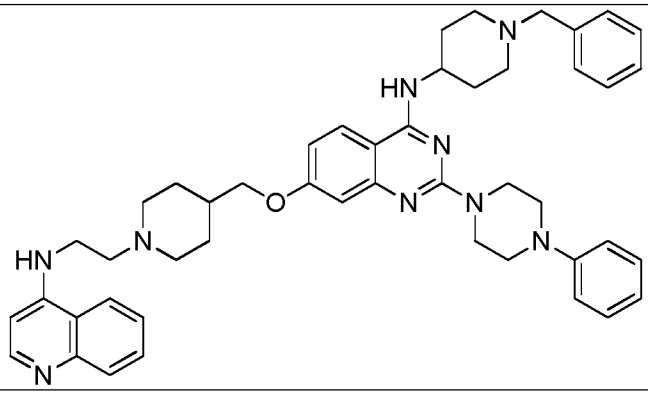
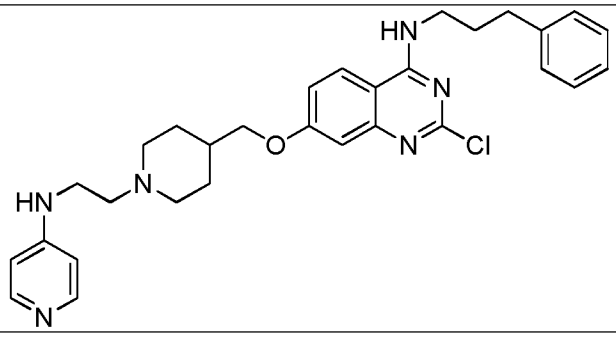
where each aryl and heterocycle moiety is optionally substituted with one or several groups selected from halogen, oxo (=O), (C_1-C_6)alkyl, aryl, and aryl-(C_1-C_6)alkyl; notably selected from (C_1-C_6)alkyl, aryl, and aryl-(C_1-C_6)alkyl,

the aryl being in particular a phenyl, and

the heterocycle in particular a saturated hydrocarbon monocycle or bicycle, each cycle having 5 or 6 members and 1 to 4, notably 1 or 2, carbon atoms having each been replaced with a nitrogen or oxygen atom, such as piperidine, piperazine, triazinane or pyrrolidine, and in particular piperazine.

11. The compound according to any one of claims 1 to 10, wherein it is selected from the following compounds:

A	
B	
C	

D	
E	
F	
G	
H	

and the pharmaceutically acceptable salts and solvates thereof.

12. A compound according to any one of claims 1 to 11 for use as a drug.

13. A compound according to any one of claims 1 to 11 for use in the treatment of cancer.

14. A compound according to any one of claims 1 to 11 for use as a DNA methylation inhibitor, in particular as a DNA methyltransferase (DNMT) inhibitor.

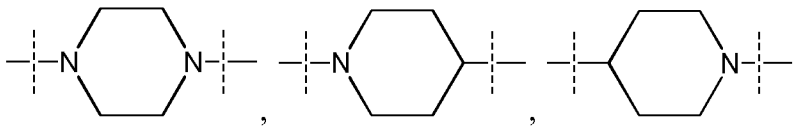
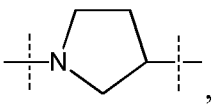
15. A pharmaceutical composition comprising at least one compound of formula (I) according to any one of claims 1 to 11 and at least one pharmaceutically acceptable excipient.

16. A pharmaceutical composition comprising:

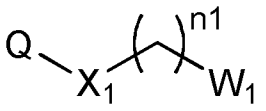
(i) at least one compound of formula (I) according to any one of claims 1 to 11, and

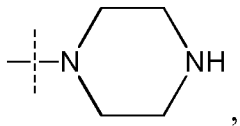
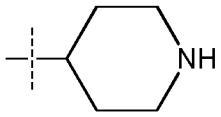
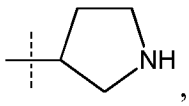
(ii) at least one other active ingredient, such as an anticancer agent,

as a combination product for simultaneous, separate or sequential use.

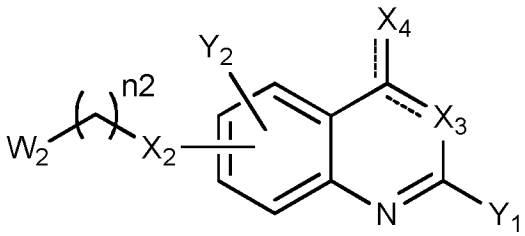
17. A method to prepare a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt or solvate thereof, in which W represents NR_0, a divalent monoglycosyl,  ,  , comprising:

(1) reacting a compound of the following formula (II):

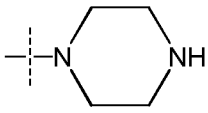
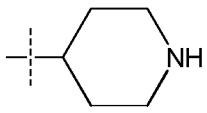
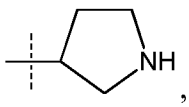
 (II)

in which Q, X_1 and n1 are as defined in claim 1 and W_1 represents LG_1, NHR_8, a monovalent monoglycosyl,  ,  or  ,

with a compound of the following formula (III):

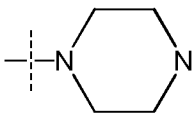
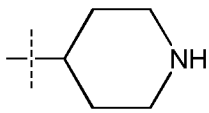
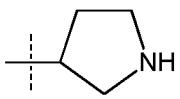
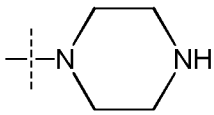
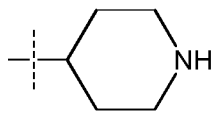
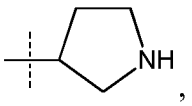


(III)

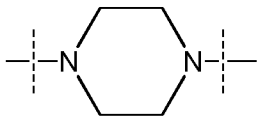
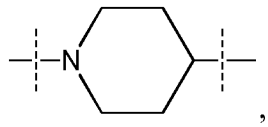
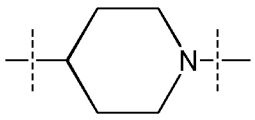
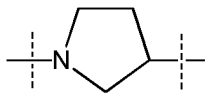
in which X_2, X_3, X_4, Y_1, Y_2 and n2 are as defined in claim 1 and W_2 represents LG_2, NHR_8, a monovalent monoglycosyl,  ,  or  ,

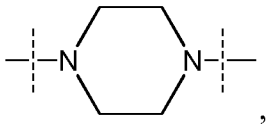
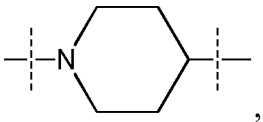
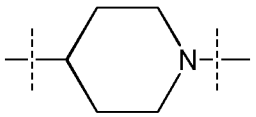
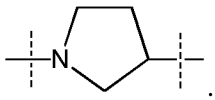
wherein LG_1 and LG_2 represent, independently of each other, a leaving group and R_8 represents R_0 as defined in claim 1 or a N-protecting group,

on the condition that:

- when W_1 represents LG_1, then W_2 represents NHR_8, a monovalent monoglycosyl,  ,  or  , and
- when W_1 represents NHR_8, a monovalent monoglycosyl,  ,  or  , then W_2 represents LG_2,

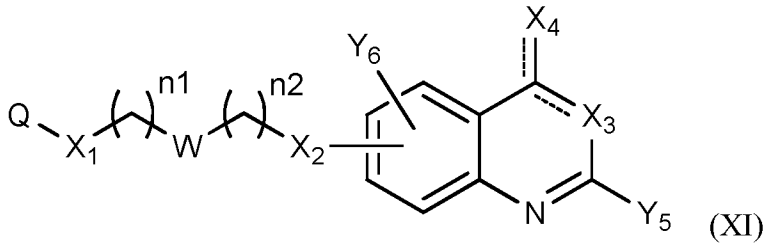
and, when W_1 or W_2 represents NHR_8 with R_8 representing a N-protecting group, deprotecting the nitrogen atom bearing the N-protecting group,

to give a compound of formula (I) as defined in claim 1 in which W represents NR_0, a divalent monoglycosyl,  ,  ,  or  ,, and

(2) optionally salifying or solvating the compound obtained in step (1) to give a pharmaceutically acceptable salt or solvate of a compound of formula (I) as defined in claim 1 in which W represents NR_0, a divalent monoglycosyl,  ,  ,  or  .

18. A method to prepare a compound of formula (I) according to claim 1, in which at least one of Y_1 and Y_2 represents a OR_{101} or $NR_{102}R_{103}$ group, or a pharmaceutically acceptable salt or solvate thereof, comprising:

(i) reacting a compound of the following formula (XI):



(XI)

in which Y_5 represents Y_1 as defined in claim 1 or a halogen atom such as a chlorine, and Y_6 represents Y_2 as defined in claim 1 or a halogen atom such as a chlorine, provided that at least one of Y_5 and Y_6 represents a halogen atom,

with HOR_{101} or $HNR_{102}R_{103}$,

to give a compound of formula (I) as defined in claim 1 in which at least one of Y_1 and Y_2 represents a OR_{101} or $NR_{102}R_{103}$ group, and

(ii) optionally salifying or solvating the compound obtained in step (i) to give a pharmaceutically acceptable salt or solvate of a compound of formula (I) as

defined in claim 1 in which at least one of Y_1 and Y_2 represents a OR_{101} or $NR_{102}R_{103}$ group.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/056734

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 A61K31/517 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2015/040169 A1 (PF MEDICAMENT [FR]; CENTRE NAT RECH SCIENT [FR]) 26 March 2015 (2015-03-26) page 1, line 6 - line 33 claim 1 claim 10; compounds A-AS	1-18
X	EP 0 602 851 A1 (ZENECA LTD [GB]) 22 June 1994 (1994-06-22) abstract claim 1	1,3,4, 15,16
X	WO 2008/020302 A2 (PFIZER PROD INC [US]; HELAL CHRISTOPHER JOHN [US]) 21 February 2008 (2008-02-21) abstract claim 1	1,3,4, 15,16

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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Date of the actual completion of the international search	Date of mailing of the international search report
28 April 2016	06/05/2016

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

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ELSLAGER E F ET AL: "FOLATE ANTAGONISTS. 16. ANTIMALARIAL AND ANTIBACTERIAL EFFECTS OF 2,4-DIAMINO-6- not (HETERCYCLIC)THIO, SULFINYL, AND SULFONY 3/4 QUINAZOLINES (1-3)", JOURNAL OF HETEROCYCLIC CHEMISTRY, WILEY-BLACKWELL PUBLISHING, INC, US, vol. 17, no. 1, 1 January 1980 (1980-01-01), pages 129-136, XP000881095, ISSN: 0022-152X, DOI: 10.1002/JHET.5570170127 compounds IVa, IVb	1,3,4
X	JOHN THURMOND ET AL: "Synthesis and Biological Evaluation of Novel 2,4-Diaminoquinazoline Derivatives as SMN2 Promoter Activators for the potential Treatment of spinal Muscular Atrophy", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 51, no. 3, 1 February 2008 (2008-02-01), pages 449-469, XP008143736, ISSN: 0022-2623, DOI: 10.1021/JM061475P [retrieved on 2008-01-19] page 452; table 1; compounds 1a-1i	1,3,4, 15,16
Y	MASOUD VEDADI ET AL: "A chemical probe selectively inhibits G9a and GLP methyltransferase activity in cells", NATURE CHEMICAL BIOLOGY, NATURE PUB. GROUP, vol. 7, no. 8, 1 August 2011 (2011-08-01), pages 566-574, XP002667515, ISSN: 1552-4450, DOI: 10.1038/NCHEMBIO.599 [retrieved on 2011-07-10] page 567; table 1	1-16
Y	NITIPOL SRIMONGKOLPITHAK ET AL: "Identification of 2,4-diamino-6,7-dimethoxyquinoline derivatives as G9a inhibitors", MEDCHEMCOMM, vol. 5, no. 12, 26 August 2014 (2014-08-26), pages 1821-1828, XP055188664, ISSN: 2040-2503, DOI: 10.1039/C4MD00274A page 1821; figure 1	1-16

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2016/056734

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