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(54) Benævnelse: **Nye kemiske molekyler, der hæmmer splejsningsmekanismen, til behandling af sygdomme, der skyldes splejsningsdefekter**

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Fortsættes ...

DESCRIPTION

[0001] The invention relates to novel compounds for the preparation of compositions useful for the treatment of diseases resulting from changes in splicing processes.

[0002] Certain indole derivative compounds such as ellipticine derivatives and azaellipticine derivatives are already known as intercalating molecules for correcting dysfunctions in gene expression, notably in DNA replication. They have been more specifically described for treating diseases such as cancer, leukemia or AIDS (see in particular patents FR 2 627 493, FR 2 645 861, FR 2 436 786).

[0003] Concerning current treatments for AIDS, the various approaches aimed at reducing viral load in patients infected by HIV utilize molecules intended to inhibit the enzymatic activity of viral reverse transcriptase or of the protease involved in virus protein maturation. Regarding reverse transcriptase inhibitors, these can be nucleosidic (NRTIs), non-nucleosidic (NNRTIs) or nucleotidic in nature. The purpose of using these compounds is to prevent a DNA copy of the retroviral genome from being produced and, consequently, from being integrated into the genome of the host cell. Protease inhibitors (PIs) interfere with the proper maturation of viral proteins and cause the production of incomplete particles with altered infectious capacities. There is another type of anti-retroviral compound used for its ability to prevent viruses from entering the cell. These entry inhibitors can be either peptides that interfere with the fusion of viral glycoproteins gp41 or gp120 with the membrane of CD4 cells or molecules that target HIV cellular co-receptors CCR5 and CXCR4. The absence of cellular proteins resembling HIV integrase has also been exploited to develop novel anti-HIV molecules that inhibit this enzymatic activity. Although a number of integrase inhibitors are in the clinical trial phase, no molecule is yet available on the market.

[0004] The intracellular splicing process consists of eliminating introns in pre-messenger RNAs to produce mature messenger RNAs that can be used by the translation mechanism of the cell (SHARP, Cell, vol. 77, p. 805-815, 1994). In the case of alternative splicing, the same precursor can be the source of messenger RNAs coding for proteins with distinct functions (BLACK, Annu. Rev. Biochem. vol. 72, p. 291-336, 2003). The precise selection of 5' and 3' splicing sites is thus a mechanism that generates diversity and that can lead to the regulation of gene expression according to the type of tissue or during the development of an organism. The factors involved in this selection include a family of proteins called SR, characterized by the presence of one or two RNA recognition motifs (RRM) and a domain rich in arginine and serine residues called an RS domain (MANLEY & TACKE, Genes Dev., vol. 10, p. 1569-1579, 1996). By binding to short exon or intron sequences of the pre-mRNA, called ESE (exonic splicing enhancer) or ISE (intronic splicing enhancer), SR proteins are able to activate, in a dose-dependant manner, suboptimal splicing sites and to enable the inclusion of exons (GRAVELEY, RNA, vol. 6, p. 1197-1211, 2000). The activity of an SR protein in alternative splicing is specific insofar as the inactivation of the corresponding gene is lethal (WANG et al., Mol. Cell, vol. 7, p. 331-342, 2001).

[0005] Sequencing of the human genome and analysis of EST (expressed sequence tag) banks has revealed that 65% of genes are expressed in the form of alternatively spliced variants (EWING & GREEN, Nat. Genet., vol. 25, p. 232-234, 2000; JOHNSON et al., Science, vol. 302, p. 2141-2144, 2003). This mechanism is thus a favored target of modifications that can affect the factors involved in regulating splicing and of mutations that affect the sequences necessary for this regulation. At present, it is estimated that roughly 50% of the point mutations responsible for genetic diseases induce aberrant splicing. These mutations can interfere with splicing by inactivating or creating splicing sites, but also by modifying or generating regulating elements such as splicing enhancers or splicing silencers in a particular gene (CARTEGNI et al., Nat. Rev. Genet., vol. 3, p. 285-298, 2002; TAZI et al., TIBS, vol. 40, p. 469-478, 2005).

[0006] The strategies currently developed to correct these splicing defects rest on the use of various types of molecules (TAZI et al., cited above, 2005).

[0007] One strategy aimed at developing novel molecules to correct or eliminate abnormal splicing, for example, rests on the overexpression of proteins that interfere with this type of splicing (NISSIM-RAFINIA et al., Hum. Mol. Genet., vol. 9, p. 1771-1778, 2000; HOFINANN et al., Proc. Natl. Acad. Sci. U.S.A., vol. 97, p. 9618-9623, 2000).

[0008] Other strategies rest on the use of antisense oligonucleotides (SAZANI et al., Nat. Biotechnol., vol. 20, p. 1228-1233, 2002; SAZANI & KOLE, Prog. Mol. Subcell. Biol., vol. 31, p. 217-239, 2003) or of PNA (CARTEGNI et al., Nat. Struct. Biol., vol. 10, p. 120-125, 2003) enabling, respectively, the inhibition or activation of a splicing event.

[0009] Yet another strategy rests on the identification of compounds that influence the splicing efficiency of the pre-mRNA of interest (ANDREASSI et al., Hum. Mol. Genet., vol. 10, p. 2841-2849, 2001).

[0010] Lastly, a strategy based on the use of trans-splicing to replace mutant exons has been described (LIU et al., Nat. Biotechnol., vol. 20, p. 47-52, 2002).

[0011] One of the disadvantages of the developed strategies cited above to correct or eliminate abnormal splicing is their production cost. Indeed, the cost of producing antisense oligonucleotides that must be modified to improve their stability, and that of PNA molecules, is high.

[0012] Another disadvantage of the developed strategies cited above is that they require the use of expression vectors, such as, for example, for the strategy based on the use of trans-splicing.

[0013] International application WO05023255, under French priority of applications FR0310460 and FR0400973, filed by the Applicant, disclosed the use of indole derivatives to treat diseases related to the pre-messenger RNA splicing process in the cell.

[0014] Thus it was recently shown that certain indole derivatives prove particularly effective in treating metastatic cancer and in treating AIDS (BAKKOUR et al., PLoS Pathogens, vol. 3, p. 1530-1539, 2007).

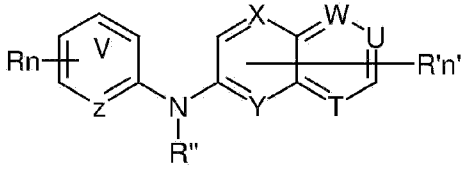
[0015] However, the compounds described have a flat structure with four rings that have the disadvantage of intercalating between DNA bases and can thus lead to cellular toxicity.

[0016] In order to minimize the risk that these indole derivatives intercalate between DNA bases, the inventors developed novel compounds that are particularly effective in treating diseases related to the splicing process, but which, in a surprising manner, have a cellular toxicity that is clearly less than the indole derivatives of the prior art. In addition, these compounds are able to selectively inhibit certain splicing events.

[0017] International application WO2009/029617 describes intermediate compounds, such as N-(3-chlorophenyl)quinolin-2-amine, of arylamine substituted quinolones which are nitric oxide synthase inhibitors.

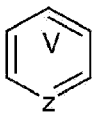
[0018] EP0394112 describes dipyrido[4,3-b][3,4-f]indoles which are useful in the treatment of AIDS.

[0019] The present text describes a compound of formula (I)



(I)

wherein:



means an aromatic ring wherein V is C or N and when V is N, V is in ortho, meta or para of Z, i.e. forms respectively a pyridazine, a pyrimidine or a pyrazine group,

R independently represent a hydrogen atom, a halogen atom or a group chosen among a -CN group, a hydroxyl group, a -$COOR_1$ group, a (C_1-C_3)fluoroalkyl group, a (C_1-C_3)fluoroalkoxy group, a -NO_2 group, a -NR_1R_2 group, a (C_1-C_4)alkoxy group, a phenoxy group and a (C_1-C_3)alkyl group, said alkyl being optionally mono-substituted by a hydroxyl group,

R_1 and R2 are independently a hydrogen atom or a (C_1-C_3)alkyl group,

n is 1, 2 or 3,

n' is 1 or 2,

R' is a hydrogen atom or a group chosen among a (C_1-C_3)alkyl group, a halogen atom, a

hydroxyl group, a -$COOR_1$ group, a -NO_2 group, a -NR_1R_2 group, a morpholinyl or a morpholino group, a N-methylpiperazinyl group, a (C_1-C_3)fluoroalkyl group, a (C_1-C_4)alkoxy group and a -CN group,

R'' is a hydrogen atom or a (C_1-C_4)alkyl group,

Z is N or C,

Y is N or C,

X is N or C,

W is N or C,

T is N or C,

U is N or C,

and wherein at most four of the groups V, T, U, Z, Y, X and W are N,

and at least one of the groups T, U, Y, X and W is N,

or anyone of its pharmaceutically acceptable salt,

for use for preventing, inhibiting or treating AIDS.

[0020] The present invention is as defined in claim 1.

[0021] The compounds of the invention may exist in the form of free bases or of addition salts with pharmaceutically acceptable acids.

[0022] Suitable physiologically acceptable acid addition salts of compounds of formula (I) include hydrobromide, tartrate, citrate, trifluoroacetate, ascorbate, hydrochloride, tartrate, triflate, maleate, mesylate, formate, acetate and fumarate.

[0023] The compounds of formula (I) and or salts thereof may form solvates (e.g. hydrates) and the invention includes all such solvates.

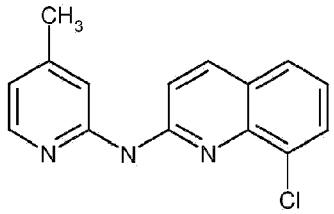
[0024] In the context of the present invention, the term:

- "halogen" is understood to mean chlorine, fluorine, bromine, or iodine, and in particular denotes chlorine, fluorine or bromine,
- "(C_1-C_3)alkyl" as used herein respectively refers to C_1-C_3 normal, secondary or tertiary saturated hydrocarbon. Examples are, but are not limited to, methyl, ethyl, 1-propyl, 2-propyl,
- "(C_1-C_3)alkoxy" as used herein respectively refers to O-(C_1-C_3)alkyl moiety, wherein alkyl

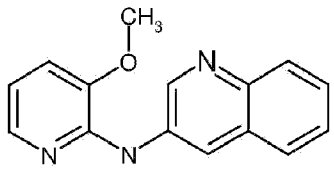
is as defined above. Examples are, but are not limited to, methoxy, ethoxy, 1-propoxy, 2-propoxy,

- "fluoroalkyl group" and "fluoroalkoxy group" refers respectively to alkyl group and alkoxy group as above-defined, said groups being substituted by at least one fluorine atom. Examples are perfluoroalkyl groups, such as trifluoromethyl or perfluoropropyl, and
- "patient" may extend to humans or mammals, such as cats or dogs.

[0025] Advantageously, the compound of formula I is chosen among the group comprising:

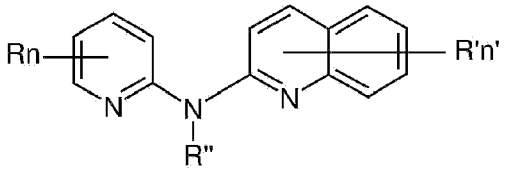


(8-Chloro-quinolin-2-yl)-(4-methyl-pyridin-2-yl)-amine; compound (6) of table I; and



(3-Methoxy-pyridin-2-yl)-quinolin-3-yl-amine; compound (10) of table I.

[0026] According to a particular embodiment, a subject-matter of the present invention is a compound of formula (Ia)



(Ia)

wherein:

R independently represent a hydrogen atom, a halogen atom or a group chosen among a (C_1-C_3)alkyl group, a -CN group, a hydroxyl group, a -$COOR_1$ group, a (C_1-C_3)fluoroalkyl group, a -NO_2 group, a -NR_1R_2 group and a (C_1-C_3)alkoxy group,

R" is a hydrogen atom or a (C_1-C_4)alkyl group and is advantageously a hydrogen atom,

n is 1, 2 or 3 and is advantageously 1,

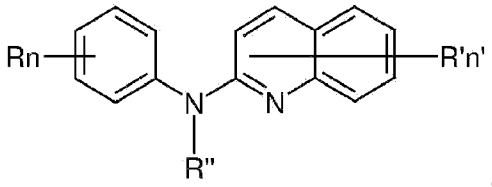
n' is 1 or 2 and is advantageously 1,

R' is a hydrogen atom, a halogen atom or a group chosen among a (C_1-C_3)alkyl group, a -NO_2 group, a (C_1-C_3)alkoxy group and a -NR_1R_2 group,

R_1 and R_2 are a hydrogen atom or a (C_1-C_3)alkyl group, or one of its pharmaceutically acceptable salt,

for use for preventing, inhibiting or treating AIDS.

[0027] According to another particular embodiment, a subject-matter of the present invention is a compound of formula (Ib)



(Ib)

wherein :

R independently represent a hydrogen atom, a halogen atom or a group chosen among a (C_1-C_3)alkyl group, a -NR_1R_2 group, a (C_1-C_3)fluoroalkoxy group, a -NO_2 group, a phenoxy group and a (C_1-C_4)alkoxy group,

R_1 and R2 are independently a hydrogen atom or a (C_1-C_3)alkyl group,

R" is a hydrogen atom or a (C_1-C_4)alkyl groupand is advantageously a hydrogen atom,

n is 1, 2 or 3 and is preferably 1 or 2,

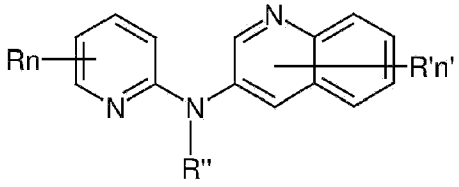
n' is 1 or 2 and is preferably 1,

R' is a hydrogen atom, a halogen atom or a group chosen among a (C_1-C_3)alkyl group and a (C_1-C_4)alkoxy group,

or one of its pharmaceutically acceptable salt,

for use for preventing, inhibiting or treating AIDS.

[0028] According to another particular embodiment, a subject-matter of the present invention is a compound of formula (Ic)



(Ic)

wherein:

R independently represent a hydrogen atom or a group chosen among a (C_1-C_3)alkyl group, a (C_1-C_3)fluoroalkyl group, a -NR_1R_2 group, a -$COOR_1$ group, a -NO_2 group and a (C_1-C_3)alkoxy group,

R'' is a hydrogen atom or a (C_1-C_4)alkyl group and is advantageously a hydrogen atom,

n is 1, 2 or 3 and is advantageously 1,

n' is 1 or 2 and is advantageously 1,

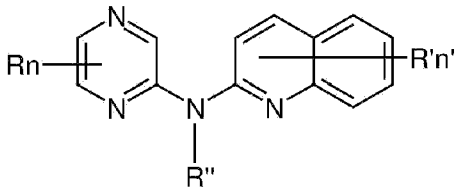
R' is a hydrogen atom,

R_1 and R_2 are independently a hydrogen atom or a (C_1-C_3)alkyl group,

or one of its pharmaceutically acceptable salt,

for use for preventing, inhibiting or treating AIDS.

[0029] According to another particular embodiment, a subject-matter of the present invention is a compound of formula (Ie)



(Ie)

wherein:

R represents a hydrogen atom,

R'' is a hydrogen atom or a (C_1-C_4)alkyl group and is advantageously a hydrogen atom,

n is 1, 2 or 3 and is advantageously 1,

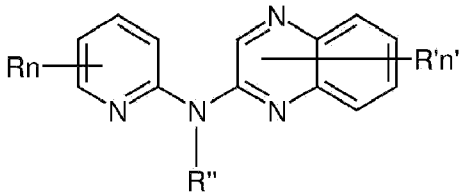
n' is 1 or 2 and is advantageously 1,

R' is a hydrogen atom, a halogen atom or a group chosen among a (C_1-C_3)alkyl group and a (C_1-C_3)alkoxy group,

or one of its pharmaceutically acceptable salt,

for use for preventing, inhibiting or treating AIDS.

[0030] According to another particular embodiment, a subject-matter of the present invention is a compound of formula (Io)



(Io)

wherein:

R independently represent a hydrogen atom or a halogen atom or a group chosen among, a -NO_2 group, a -CN group and a (C_1-C_3)alkyl group, said alkyl being optionally mono-substituted by a hydroxyl group,

R'' is a hydrogen atom or a (C_1-C_4)alkyl group and is advantageously a hydrogen atom,

n is 1, 2 or 3and is advantageously 1,

n' is 1 or 2 and is advantageously 1,

R' is a hydrogen atom, a halogen atom or a (C_1-C_3)fluoroalkyl group,

or one of its pharmaceutically acceptable salt,

for use for preventing, inhibiting or treating AIDS.

[0031] he compounds in accordance with the invention belong to formulae (Ia), (Ib), (Ic), (Ie) and (Io), as defined above or one of its pharmaceutically acceptable salts.

[0032] Thus, the present invention relates to a compound of formula (Ia), (Ib), (Ic), (Ie) and (Io), as defined above, for use for preventing, inhibiting or treating AIDS.

[0033] Thus, according to a more particular embodiment, the present invention particularly focuses on a compound of formula (Ia)
wherein:

R independently represent a hydrogen atom, a halogen atom or a group chosen among a (C_1-C_3)alkyl group, a (C_1-C_3)fluoroalkyl group, a hydroxyl group, a -CN group, a-COOH group and a (C_1-C_3)alkoxy group,

R'' is as defined above and more preferably is a hydrogen atom,

n is as defined above and more preferably is 1,

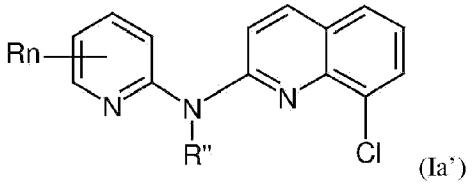
n' is as defined above,

R' is a hydrogen atom, a halogen atom, a -NO_2 group or a (C_1-C_3)alkyl group, or one of its pharmaceutically acceptable salt,

for use for preventing, inhibiting or treating AIDS.

[0034] Still according to this more particular embodiment, the present invention more

preferably focuses on compounds of formula (Ia'),



(Ia')

wherein,

R independently represent a hydrogen atom, a -CN group, a (C_1-C_3)alkyl group, a (C_1-C_3)fluoroalkyl group, a halogen atom or a hydroxyl group,

R' is as defined in formula (Ia) and is preferably a halogen, a (C_1-C_3)alkyl group or a NO_2 group,

R" is a hydrogen atom,

n is 1 or 2

or one of its pharmaceutically acceptable salt,

for use for preventing, inhibiting or treating AIDS.

[0035] According to another more particular embodiment, the present invention particularly focuses on a compound of formula (Ib) wherein:

R independently represent a hydrogen atom, a halogen atom, a group chosen among a (C_1-C_4)alkyl group, a -NR_1R_2 group, a (C_1-C_3)alkoxy group and a (C_1-C_3)fluoroalkoxy group,

R_1 and R_2 are independently a hydrogen atom or a (C_1-C_3)alkyl group,

R" is as defined above and more preferably is a hydrogen atom,

n is as defined above,

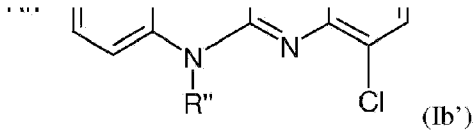
n' is as defined above,

R' is a hydrogen atom, halogen atom or a (C_1-C_3)alkyl group,

or one of its pharmaceutically acceptable salt,

for use for preventing, inhibiting or treating AIDS.

[0036] Still according to this more particular embodiment, the present invention more preferably focuses on compounds of formula (Ib'),


(Ib')

wherein:

R independently represent a hydrogen atom, a halogen atom, a group chosen among a (C_1-C_3)alkoxy group, a (C_1-C_3)fluoroalkoxy group,

R" is as defined above and more preferably is a hydrogen atom,

n is as defined above and more preferably is 1,

or one of its pharmaceutically acceptable salt,

for use for preventing, inhibiting or treating AIDS.

[0037] According to another more particular embodiment, the present invention particularly focuses on a compound of formula (Ic)
wherein:

R independently represent a hydrogen atom or a group chosen among a (C_1-C_3)fluoroalkyl group, a -NO_2 group, and a (C_1-C_3)alkoxy group,

R" is as defined above and more preferably is a hydrogen atom,

n is as defined above and more preferably is 1,

n' is as defined above,

R' is a hydrogen atom,

or one of its pharmaceutically acceptable salt,

for use for preventing, inhibiting or treating AIDS.

[0038] According to another more particular embodiment, the present invention particularly focuses on a compound of formula (Ie)
wherein:

R represents a hydrogen atom,

R" is as defined above and more preferably is a hydrogen atom,

n is as defined above and more preferably is 1,

n' is as defined above,

R' is a hydrogen atom or a halogen atom,

or one of its pharmaceutically acceptable salt,

for use for preventing, inhibiting or treating

[0039] According to another more particular embodiment, the present invention particularly focuses on a compound of formula (Io)
wherein:

R independently represent a hydrogen atom, a halogen atom or a group chosen among a (C_1-C_3)alkyl group and a -NO_2 group,

R'' is as defined above and more preferably is a hydrogen atom,

n is 1, 2 or 3,

n' is as defined above,

R' is a hydrogen atom or a (C_1-C_3)fluoroalkyl group,

or one of its pharmaceutically acceptable salt,

for use for preventing, inhibiting or treating AIDS.

[0040] In a particular embodiment, the present invention relates to a compound of formula (Ia), (Ic) or (Io) as defined above or one of its pharmaceutically acceptable salts, for use for preventing, inhibiting or treating AIDS.

[0041] According to a preferred embodiment of the present invention, the compound for use for preventing, inhibiting or treating AIDS, is chosen from:

- (1) (8-Chloro-quinolin-2-yl)-pyridin-2-yl-amine
- (2) 2-(Quinolin-2-ylamino)-isonicotinic acid
- (3) (4-Methyl-pyridin-2-yl)-quinolin-2-yl-amine
- (4) Pyridin-2-yl-quinolin-2-yl-amine
- (5) 2-(8-Chloro-quinolin-2-ylamino)-isonicotinic acid
- (6) (8-Chloro-quinolin-2-yl)-(4-methyl-pyridin-2-yl)-amine
- (7) 6-(Quinolin-2-ylamino)-nicotinonitrile
- (8) Quinolin-2-yl-(4-trifluoromethoxy-phenyl)-amine
- (9) Pyridin-2-yl-quinolin-3-yl-amine
- (10) (3-Methoxy-pyridin-2-yl)-quinolin-3-yl-amine

- (11) Quinolin-3-yl-(5-trifluoromethyl-pyridin-2-yl)-amine
- (12) (5-Nitro-pyridin-2-yl)-quinolin-3-yl-amine
- (13) (5-Methyl-pyridin-2-yl)-quinolin-3-yl-amine
- (14) 2-(Quinolin-3-ylamino)-isonicotinic acid
- (17) N-(6-methylpyridin-2-yl)quinolin-2-amine
- (18) 8-chloro-N-(6-methylpyridin-2-yl)quinolin-2-amine
- (19) 4-methyl-N-(pyridin-2-yl)quinolin-2-amine
- (20) 4-methyl-N-(4-methylpyridin-2-yl)quinolin-2-amine
- (21) 3-methyl-N-(4-methylpyridin-2-yl)quinolin-2-amine
- (22) 3-methyl-N-(pyridin-2-yl)quinolin-2-amine
- (23) 6-((4-methylquinolin-2-yl)amino)nicotinonitrile
- (24) 6-((3-methylquinolin-2-yl)amino)nicotinonitrile
- (25) 6-chloro-N-(4-methylpyridin-2-yl)quinolin-2-amine
- (26) 6-chloro-N-(6-methylpyridin-2-yl)quinolin-2-amine
- (27) 4-methyl-N-(5-nitropyridin-2-yl)quinolin-2-amine
- (28) N-(3-nitropyridin-2-yl)quinolin-2-amine
- (29) 8-chloro-N-(3-nitropyridin-2-yl)quinolin-2-amine
- (30) 2-((4-methylquinolin-2-yl)amino)nicotinonitrile
- (31) N-(3-methylpyridin-2-yl)quinolin-2-amine
- (32) N-(5-methylpyridin-2-yl)quinolin-2-amine
- (33) 2-(quinolin-2-ylamino)isonicotinonitrile
- (34) N-(5-(trifluoromethyl)pyridin-2-yl)quinolin-2-amine
- (35) 8-chloro-N-(3-methylpyridin-2-yl)quinolin-2-amine
- (36) 8-chloro-N-(5-methylpyridin-2-yl)quinolin-2-amine
- (37) 8-chloro-N-(5-(trifluoromethyl)pyridin-2-yl)quinolin-2-amine
- (38) N-(3-methoxypyridin-2-yl)quinolin-2-amine
- (39) N-(5-nitropyridin-2-yl)quinolin-2-amine
- (40) 6-((8-chloroquinolin-2-yl)amino)nicotinonitrile
- (41) N-(5-fluoropyridin-2-yl)quinolin-2-amine
- (42) N-(6-(trifluoromethyl)pyridin-2-yl)quinolin-2-amine
- (43) 8-chloro-N-(5-fluoropyridin-2-yl)quinolin-2-amine
- (44) 2-((8-chloroquinolin-2-yl)amino)nicotinic acid
- (45) 4-methyl-N-(6-methylpyridin-2-yl)quinolin-2-amine
- (46) 3-methyl-N-(6-methylpyridin-2-yl)quinolin-2-amine
- (47) 5-cyano-2-(quinolin-2-ylamino)pyridin-1-ium chloride
- (48) 2-((8-chloroquinolin-2-yl)amino)-4-methylpyridin-1-ium chloride
- (49) 8-chloro-N-(4-ethylpyridin-2-yl)quinolin-2-amine
- (50) 8-chloro-N-(6-ethylpyridin-2-yl)quinolin-2-amine
- (51) 8-chloro-N-(4,6-dimethylpyridin-2-yl)quinolin-2-amine
- (52) 6-((8-chloroquinolin-2-yl)amino)-2-methylnicotinonitrile
- (53) 8-chloro-N-(4-chloropyridin-2-yl)quinolin-2-amine
- (54) 8-methyl-N-(4-methylpyridin-2-yl)quinolin-2-amine
- (55) N-(5-bromo-4-methylpyridin-2-yl)-8-chloroquinolin-2-amine
- (56) 8-chloro-N-(3-ethyl-6-methylpyridin-2-yl)quinolin-2-amine

- (57) 8-fluoro-N-(4-methylpyridin-2-yl)quinolin-2-amine
- (58) 8-bromo-N-(4-methylpyridin-2-yl)quinolin-2-amine
- (59) methyl 6-(quinolin-2-ylamino)nicotinate
- (60) methyl 6-[(8-chloroquinolin-2-yl)amino]pyridine-3-carboxylate
- (61) methyl 6-[(3-methylquinolin-2-yl)amino]pyridine-3-carboxylate
- (62) methyl 2-[(8-chloroquinolin-2-yl)amino]pyridine-3-carboxylate
- (63) 8-methoxy-N-(4-methylpyridin-2-yl)quinolin-2-amine
- (64) N-(4-methylpyridin-2-yl)-5-nitroquinolin-2-amine
- (65) 2-N-(4-methylpyridin-2-yl)quinoline-2,8-diamine
- (67) methyl 6-[(4-methylquinolin-2-yl)amino]pyridine-3-carboxylate
- (68) 8-chloro-N-[4-(trifluoromethyl)pyridin-2-yl]quinolin-2-amine
- (69) 2-[(8-chloroquinolin-2-yl)amino]pyridin-3-ol
- (70) 8-chloro-N-[6-(trifluoromethyl)pyridin-2-yl]quinolin-2-amine
- (71) 6-chloro-N-(5-fluoropyridin-2-yl)quinolin-2-amine
- (72) N-(6-ethylpyridin-2-yl)-3-methylquinolin-2-amine
- (73) N-(5-fluoropyridin-2-yl)-3-methylquinolin-2-amine
- (74) 3-methyl-N-[5-(trifluoromethyl)pyridin-2-yllquinolin-2-amine
- (75) 4-N-(8-chloroquinolin-2-yl)-1-N,1-N-dimethylbenzene-1,4-diamine
- (76) N-(4-methoxyphenyl)quinolin-2-amine
- (77) 8-chloro-N-(4-methoxyphenyl)quinolin-2-amine
- (78) 4-methyl-N-[4-(trifluoromethoxy)phenyl]quinolin-2-amine
- (79) N-(4-methoxyphenyl)-3-methylquinolin-2-amine
- (80) 3-methyl-N-[4-(trifluoromethoxy)phenyl]quinolin-2-amine
- (81) 1-N,1-N-dimethyl-4-N-(3-methylquinolin-2-yl)benzene-1,4-diamine
- (82) N-[2-methyl-4-(trifluoromethoxy)phenyl]quinolin-2-amine
- (83) N-[3-(trifluoromethoxy)phenyl]quinolin-2-amine
- (84) N-[2-(trifluoromethoxy)phenyl]quinolin-2-amine
- (85) N-(4-nitrophenyl)quinolin-2-amine
- (86) N-(3-fluorophenyl)quinolin-2-amine
- (87) 8-chloro-N-[3-(trifluoromethoxy)phenyl]quinolin-2-amine
- (88) 8-chloro-N-(3-fluorophenyl)quinolin-2-amine
- (89) 2-{[4-(trifluoromethoxy)phenyl]amino}quinolin-1-ium chloride
- (90) 8-chloro-N-[4-(trifluoromethoxy)phenyl]quinolin-2-amine
- (91) 3-methyl-N-[2-methyl-4-(trifluoromethoxy)phenyl]quinolin-2-amine
- (92) 3-methyl-N-[3-(trifluoromethoxy)phenyl]quinolin-2-amine
- (93) 3-methyl-N-[2-(trifluoromethoxy)phenyl]quinolin-2-amine
- (95) 3-methyl-2-{[4-(trifluoromethoxy)phenyl]amino}quinolin-1-ium chloride
- (96) 6-chloro-N-(4-(trifluoromethoxy)phenyl)quinolin-2-amine
- (97) 4-methyl-2-{[4-(trifluoromethoxy)phenyl]amino}quinolin-1-ium chloride
- (98) 8-bromo-N-[4-(trifluoromethoxy)phenyl]quinolin-2-amine
- (99) 8-fluoro-N-[4-(trifluoromethoxy)phenyl]quinolin-2-amine
- (100) 8-methyl-N-[4-(trifluoromethoxy)phenyl]quinolin-2-amine
- (101) N-(4-butoxyphenyl)-8-chloroquinolin-2-amine
- (102) N-(4-phenoxyphenyl)quinolin-2-amine

- (103) 8-methoxy-N-[4-(trifluoromethoxy)phenyl]quinolin-2-amine
- (104) 8-chloro-N-[3-chloro-4-(trifluoromethoxy)phenyl]quinolin-2-amine
- (105) N-(6-methylpyridin-2-yl)quinolin-3-amine
- (106) N-(3-nitropyridin-2-yl)quinolin-3-amine
- (109) 6-chloro-N-(pyrazin-2-yl)quinolin-2-amine
- (110) 8-bromo-N-(pyrazin-2-yl)quinolin-2-amine
- (111) 8-methyl-N-(pyrazin-2-yl)quinolin-2-amine
- (112) 8-chloro-N-(pyrazin-2-yl)quinolin-2-amine
- (113) N-(pyrazin-2-yl)quinolin-2-amine
- (114) 4-methyl-N-(pyrazin-2-yl)quinolin-2-amine
- (115) 3-methyl-N-(pyrazin-2-yl)quinolin-2-amine
- (116) 8-fluoro-N-(pyrazin-2-yl)quinolin-2-amine
- (117) 8-methoxy-N-(pyrazin-2-yl)quinolin-2-amine
- (135) N-(pyridin-2-yl)quinoxalin-2-amine
- (136) N-(4-methylpyridin-2-yl)quinoxalin-2-amine
- (137) 6-(quinoxalin-2-ylamino)pyridine-3-carbonitrile
- (138) N-(6-methylpyridin-2-yl)quinoxalin-2-amine
- (139) N-(4-methylpyridin-2-yl)-3-(trifluoromethyl)quinoxalin-2-amine
- (140) N-(3,5-dichloro-4-methylpyridin-2-yl)quinoxalin-2-amine
- (141) N-(4-methyl-3-nitropyridin-2-yl)quinoxalin-2-amine
- (150) N-(4-methylpyridin-2-yl)-8-nitroquinolin-2-amine
- (151) 6-chloro-N-(6-ethylpyridin-2-yl)quinolin-2-amine
- (152) 6-chloro-N-(5-methylpyridin-2-yl)quinolin-2-amine
- (153) 6-chloro-N-[5-(trifluoromethyl)pyridin-2-yl]quinolin-2-amine
- (154) N2-(8-chloroquinolin-2-yl)-4-methylpyridine-2,3-diamine
- (155) N-(4-butoxyphenyl)-3-methylquinolin-2-amine
- (156) 4-N-(6-chloroquinolin-2-yl)-1-N,1-N-dimethylbenzene-1,4-diamine
- (157) 8-chloro-N-(3-chloro-4-methoxyphenyl)quinolin-2-amine
- (158) N1-(8-chloroquinolin-2-yl)-4-(trifluoromethoxy)benzene-1,2-diamine
- (159) 2-{4-[(8-chloroquinolin-2-yl)amino]phenoxy}ethan-1-ol
- (160) 6-chloro-N-(4-methylpyridin-2-yl)quinoxalin-2-amine
- (161) N-(4-ethylpyridin-2-yl)quinoxalin-2-amine
- (162) N-(5-bromo-4-methylpyridin-2-yl)quinoxalin-2-amine
- (163) N-(4,6-dimethylpyridin-2-yl)quinoxalin-2-amine
- (164) [2-(quinoxalin-2-ylamino)pyridin-4-yl]methanol
- (165) N-(4-methyl-5-nitropyridin-2-yl)quinoxalin-2-amine
- and their pharmaceutically acceptable salts.

[0042] Among said compounds, compounds (1), (6), (33), (34), (35), (36), (37), (38), (42), (43), (44), (45), (46), (48), (50), (64), (68), (69), (70), (71), (72), (73), (74), (75), (77), (78), (79), (80), (81), (82), (86), (87), (88), (90), (92), (96), (104), (106), (109), (112), (136), (139), (140) and (141) are of particular interest.

[0043] The present invention therefore extends to compounds (1), (6), (33), (34), (35), (36), (37), (38), (42), (43), (44), (45), (46), (48), (50), (64), (68), (69), (70), (71), (72), (73), (74), (75), (77), (78), (79), (80), (81), (82), (86), (87), (88), (90), (92), (96), (104), (106), (109), (112), (136), (139), (140) and (141) or one of its pharmaceutically acceptable salts for use for preventing, inhibiting or treating AIDS.

[0044] Some of said preceding compounds are new and form part of the present invention: (1), (6), (33), (34), (35), (36), (37), (38), (42), (43), (44), (46), (48), (50), (64), (68), (69), (70), (71), (72), (73), (74), (75), (77), (78), (79), (80), (81), (82), (86), (87), (88), (90), (92), (96), (104), (106), (109), (112), (136), (139), (140), (141) and their pharmaceutically acceptable salts, such as hydrobromide, tartrate, citrate, trifluoroacetate, ascorbate, hydrochloride, tartrate, triflate, maleate, mesylate, formate, acetate and fumarate.

[0045] The compounds of formulae (I), (Ia), (Ib), (Ic), (Ie), and (Io) can comprise one or more asymmetric carbon atoms. They can thus exist in the form of enantiomers or of diastereoisomers. These enantiomers, diastereoisomers and their mixtures, including the racemic mixtures, are encompassed within the scope of the present invention.

[0046] Among the compounds of formula (I), some of them are new and form part of the invention, as well as their pharmaceutically acceptable salts, such as hydrobromide, tartrate, citrate, trifluoroacetate, ascorbate, hydrochloride, tartrate, triflate, maleate, mesylate, formate, acetate and fumarate.

[0047] For a sake of simplification, the following compounds and their corresponding definitions are called "new compounds".

[0048] According to another particular embodiment, the present invention encompasses compounds of formula (Ia), as such,
wherein:

R" and n are as defined in formula (Ia),

n' is 1,

R independently represent a hydrogen atom, a halogen atom or a group chosen among a (C_1-C_3)alkyl group, a -CN group, a hydroxyl group, a -$COOR_1$ group, a (C_1-C_3)fluoroalkyl group, a -NO_2 group, a (C_1-C_3)fluoroalkoxy group and a (C_1-C_3)alkoxy group,

R' is a hydrogen atom or a halogen atom or a group chosen among a (C_1-C_3)alkyl group, a -$COOR_1$ group, and a -CN group,

R_1 is a hydrogen atom or a (C_1-C_3)alkyl group,

and wherein:

with the proviso that

when R and R' are not simultaneously a hydrogen atom,

when n is 1, R is not a methyl group in ortho or para position with respect to Z, Z being N,

when R' is a hydrogen atom, R is not a bromine atom or a chlorine atom,

when R is a hydrogen atom, R' is not a methyl or ethyl group, a -COOH group, a $COOC_2H_5$ group or a bromine atom, said bromine atom being in ortho position of the bond linked to NR",

or one of its pharmaceutically acceptable salt.

According to this particular embodiment, the present invention more particularly focuses on compounds of formula (Ia), as such, wherein,

R independently represent a hydrogen atom, a (C_1-C_3)fluoroalkyl group, a halogen atom, a -CN group or a (C_1-C_3) alkyl group,

R" is as defined in formula (Ia),

R' is a hydrogen atom, a halogen atom or a $-NO_2$ group,

n' is 1,

n is 1,

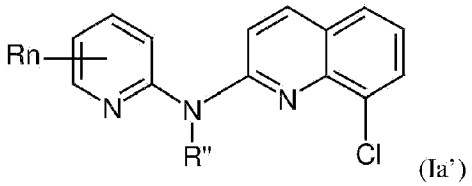
with the proviso that

when n is 1, R is not a methyl group in ortho or para position with respect to Z, Z being N,

R is not a bromine atom or a chlorine atom when R' is a hydrogen atom,

or one of its pharmaceutically acceptable salt.

[0049] Still according to this particular embodiment, the present invention more preferably focuses on compounds of formula (Ia'), as such,



(Ia')

wherein,

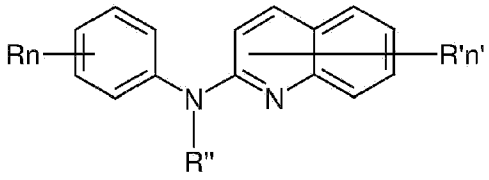
R independently represent a hydrogen atom, a (C_1-C_3) alkyl group, a (C_1-C_3)fluoroalkyl group, a halogen atom or a hydroxyl group,

R" is as defined in formula (Ia),

n is 1 or 2, and preferably 1,

or one of its pharmaceutically acceptable salt.

[0050] The present invention further relates to a compound of formula (Ib) as defined above, as such



(Ib)

wherein :

R' is a hydrogen atom, a halogen atom or a group chosen among a (C_1-C_3)alkyl group and a (C_1-C_4)alkoxy group,

R" is a hydrogen atom or a (C_1-C_4)alkyl group and is advantageously a hydrogen atom,

n' is 1 or 2,

n is 1, and

R is a (C_1-C_3)fluoroalkoxy group,
or one of its pharmaceutically acceptable salt.

[0051] According to this particular embodiment, the present invention more particularly focuses on compounds of formula (Ib)
wherein:

R is a (C_1-C_3)fluoroalkoxy group,

R' is a hydrogen atom, a halogen atom or a (C_1-C_3)alkyl group,

R" is as defined in the formula (Ib),

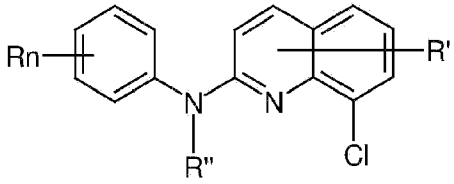
n' is 1 or 2 and is preferably 1,

n is 1 or 2 and is preferably 1,

or one of its pharmaceutically acceptable salt.

[0052] Still according to this particular embodiment, the present invention more particularly

focuses on compounds of formula (Ib')



(Ib')

wherein:

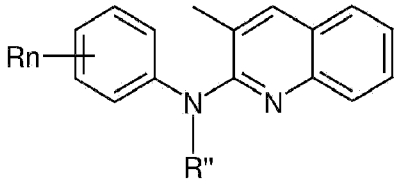
R, R" and n are as defined in formula (Ib),

R' is as defined in formula (Ib),

with the proviso that R' is different from a methyl group in position 4 on the quinoline,

or one of its pharmaceutically acceptable salt.

[0053] Still according to this particular embodiment, the present invention more particularly focuses on compounds of formula (Ib'')



(Ib'')

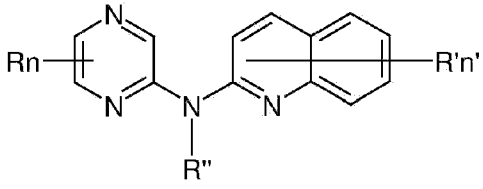
wherein:

R, R" and n are as defined in formula (Ib),

with the proviso that when n is 1, R is not a hydrogen atom, a methyl group in para of the bond linked to NR", an ethoxy group in para of the bond linked to NR", nor a fluorine atom in para of the bond linked to NR",

or one of its pharmaceutically acceptable salt.

[0054] The present invention further relates to a compound of formula (Ie) as defined above, as such



(Ie)

wherein:

R represents a hydrogen atom,

R" is a hydrogen atom or a (C_1-C_4)alkyl group and is advantageously a hydrogen atom,

n is 1, 2 or 3 and is advantageously 1,

n' is 1 or 2 and is advantageously 1,

R' is a hydrogen atom, a halogen atom or a group chosen among a a (C_1-C_3)alkyl group and a (C_1-C_3)alkoxy group,

with the proviso that

when R is a hydrogen atom, R' is not a bromine atom,

or one of its pharmaceutically acceptable salt.

[0055] Among said compounds as such, compounds (1), (2), (5)-(8), (18), (21)-(44), (46)-(65), (67)-(75), (77)-(84), (86)-(93), (95)-(104), (109)-(117), (155)-(158) and their pharmaceutically acceptable salts are of particular interest.

[0056] The present invention therefore extends to compounds (1), (2), (5)-(8), (18), (21)-(44), (46)-(65), (67)-(75), (77)-(84), (86)-(93), (95)-(104), (109)-(117), (155)-(158) and their pharmaceutically acceptable salts, as such.

[0057] More preferably, compounds (8), (75), (77)-(84), (86)-(93), (95)-(104), (109)-(117), (155)-(158) and their pharmaceutically acceptable salts are of particular interest.

[0058] The present invention therefore extends more preferably to compounds (8), (75), (77)-(84), (86)-(93), (95)-(104), (109)-(117), (155)-(158) and their pharmaceutically acceptable salts, such as hydrobromide, tartrate, citrate, trifluoroacetate, ascorbate, hydrochloride, tartrate, triflate, maleate, mesylate, formate, acetate and fumarate.

[0059] Still more preferably, the present invention extends to compounds (75), (77), (78), (79), (80), (81), (82), (86), (87), (88), (90), (92), (96), (104), (109), (112), and their pharmaceutically acceptable salts, such as hydrobromide, tartrate, citrate, trifluoroacetate, ascorbate, hydrochloride, tartrate, triflate, maleate, mesylate, formate, acetate and fumarate.

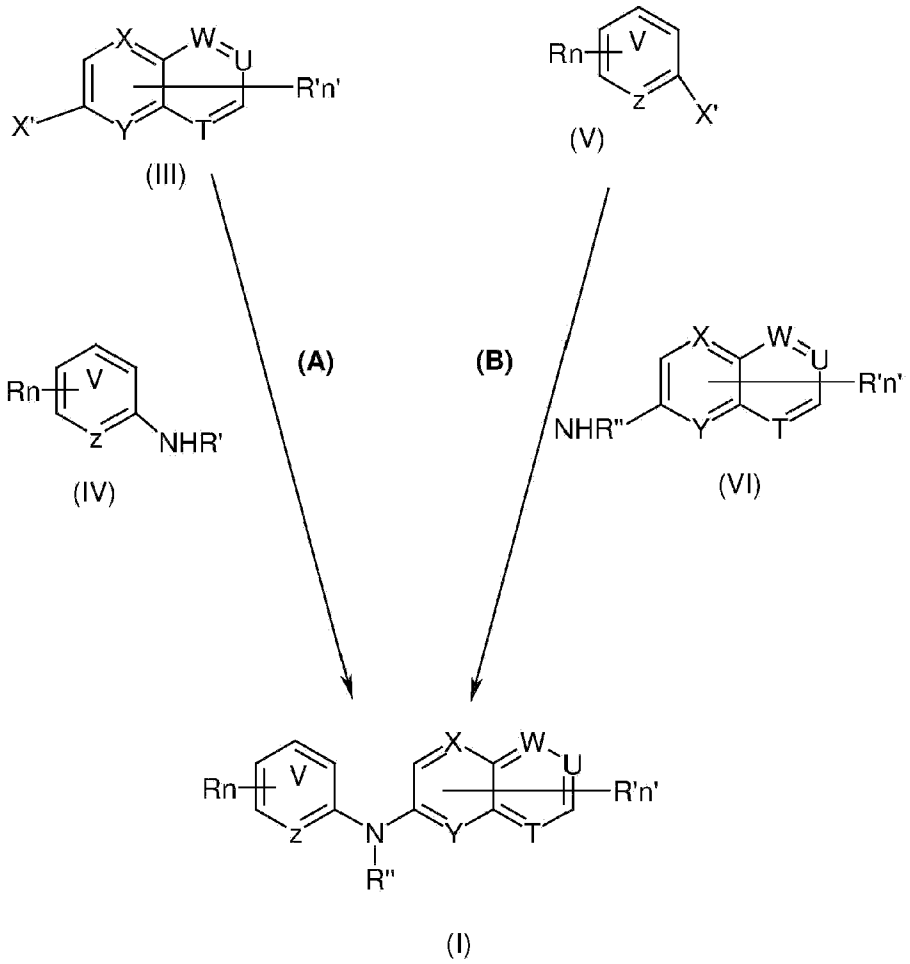
[0060] The new compounds of the present invention, i.e. compounds of formulae (Ia), (Ib), (Ib'), (Ib") and (Ie) and the specific compounds as listed above, are not only useful for inhibiting, preventing or treating AIDS but can also be useful for inhibiting, preventing or treating premature aging and for inhibiting, preventing or treating cancer, and more particularly colorectal cancer, pancreatic cancer, lung cancer including non-small cell lung cancer, breast cancer, bladder cancer, gall bladder cancer, liver cancer, thyroid cancer, melanoma, uterine/cervical cancer, oesophageal cancer, kidney cancer, ovarian cancer, prostate cancer, head and neck cancer and stomach cancer, etc.

[0061] According to an aspect of the invention said compounds may be useful to inhibit, prevent and/or treat diseases with premature aging and that are likely related to an aberrant splicing of the nuclear lamin A gene. Among all, said disease may include Hutchinson Guilford Progeria Syndrome (HGPS), progeria, premature aging associated with HIV infection, muscular dystrophy, Charcot-Marie-Tooth disorder, Werner syndrome, but also atherosclerosis, insulin resistant type II diabetes, cataracts, osteoporosis and aging of the skin such as restrictive dermopathy.

[0062] The compounds of the present invention can be prepared by conventional methods of organic synthesis practiced by those skilled in the art. The general reaction sequences outlined below represent a general method useful for preparing the compounds of the present invention and are not meant to be limiting in scope or utility.

[0063] The compounds of general formula (I) can be prepared according to scheme 1 below.

Scheme 1



[0064] As appears in said scheme two routes are available for recovering a compound of formula (I) according to the present invention.

[0065] The synthesis is based on a coupling reaction alternatively starting from a halogeno-bicycle of formula (III), wherein X, Y, W, T, U, n', R' and R" are as defined above and X' is a chlorine atom or a bromine atom or from a chloro-monocycle of formula (V), wherein Z, V, n and R are as defined above and X' is a chlorine atom or a bromine atom.

[0066] According to route (A), the compound of formula (III) is placed in a protic solvent such as tert-butanol. The compound of formula (IV) is then added in a molar ratio ranging from 1 to 1.5 with respect to the compound of formula (III) in presence of an inorganic base, such as Cs_2CO_3 or K_2CO_3 in a molar ratio ranging from 1 and 2, in the presence of a diphosphine, such as Xantphos (4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene) or X-Phos (2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl) in an amount ranging from 2mol% to 10mol% relative to the total amount of compound of formula (III), and in the presence of a catalyst, such as Pd(OAc)2 or Pd2dba3 in an amount ranging from 2mol% and 10mol% relative to the total amount of compound of formula (III). The reaction mixture can then be heated at a temperature ranging from 80 to 120°C, for example at 90°C and stirred for a time ranging form 15 to 25 hours, for example during 20 hours under inert gas and for example argon. The reaction mixture can be concentrated under reduced pressure.

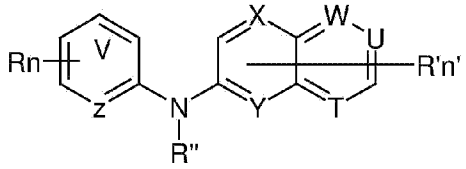
[0067] According to route (B) the compound of formula (V) is placed in a protic solvent such as tert-butanol. The compound of formula (VI) is then added in a molar ratio ranging from 1 to 1.5 with respect to the compound of formula (V) in presence of an inorganic base, such as Cs_2CO_3 or K_2CO_3 in a molar ratio ranging from 1 to 2, in the presence of a diphosphine, such as Xantphos (4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene) or X-Phos (2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl) in an amount ranging from 2 mol% to 10 mol% relative to the total amount of compound of formula (V), and in the presence of a catalyst, such as Pd(OAc)2 or Pd2dba3 in an amount ranging from 2 mol% to 10 mol% relative to the total amount of compound of formula (V). The reaction mixture can then be heated at a temperature ranging from 80 to 120°C, for example at 90°C and stirred for a time ranging form 15 to 25 hours, for example during 20 hours under inert gas and for example argon. The reaction mixture can be concentrated under reduced pressure.

[0068] The starting compounds of formula (III), (IV), (V) and (VI) are commercially available or can be prepared according to methods known to the person skilled in the art.

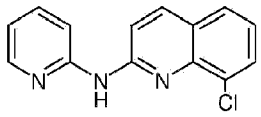
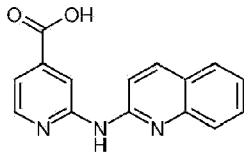
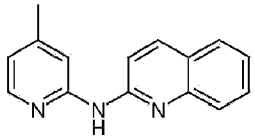
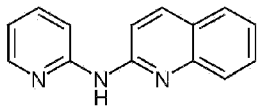
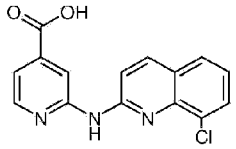
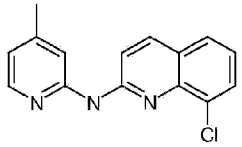
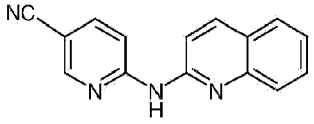
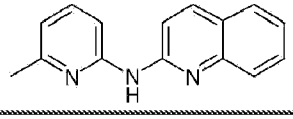
[0069] The chemical structures and spectroscopic data of some compounds of formula (I) of the invention are illustrated respectively in the following Table I and Table II.

Table I

(I)



(I)

Formula (Ia)	
1	
2	
3	
4	
5	
6	
7	
17	
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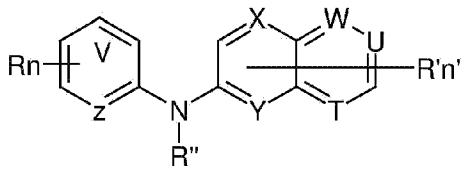

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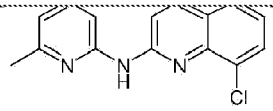
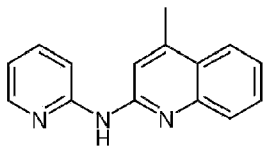
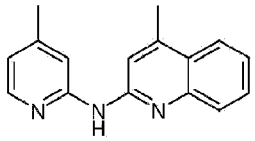
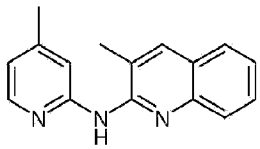
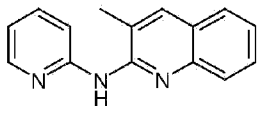
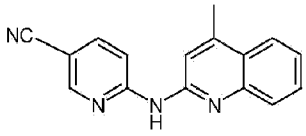
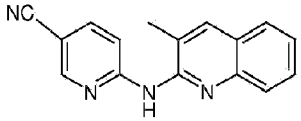
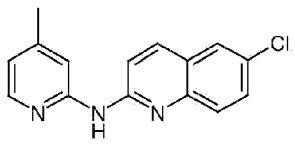
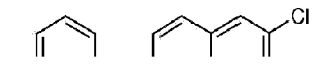
	
19	
20	
21	
22	
23	
24	
25	
26	

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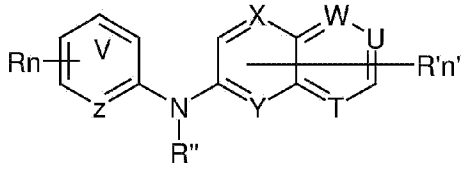

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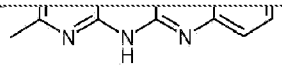
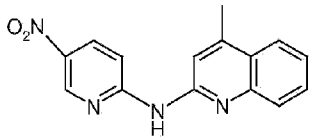
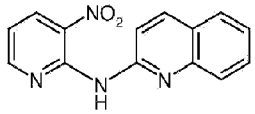
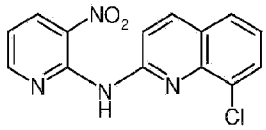
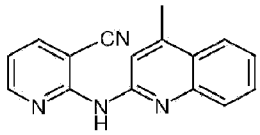
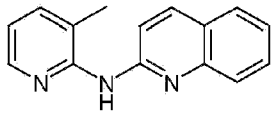
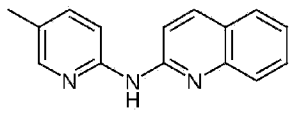
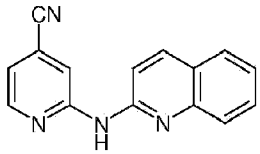
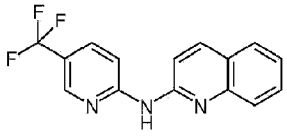
	
27	
28	
29	
30	
31	
32	
33	
34	

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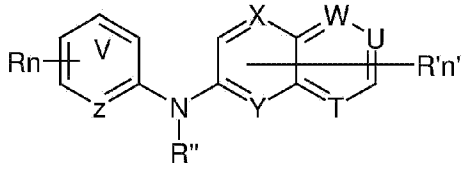

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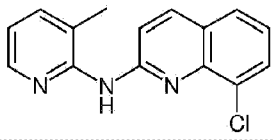
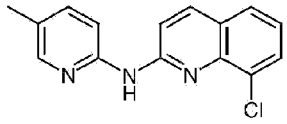
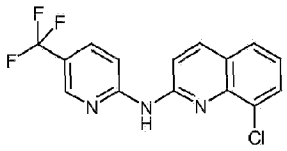
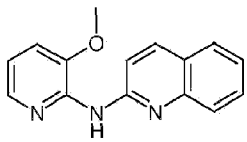
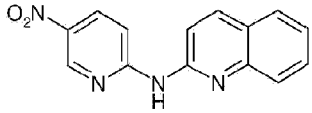
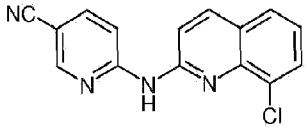
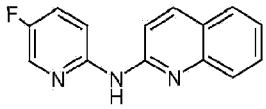
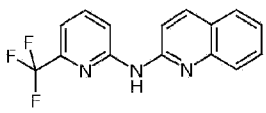
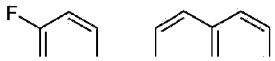
35	
36	
37	
38	
39	
40	
41	
42	
43	

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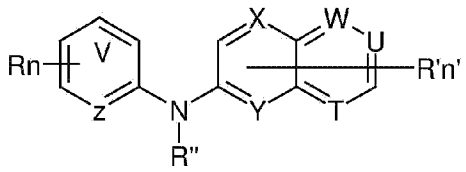

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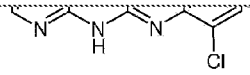
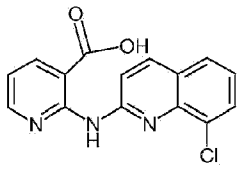
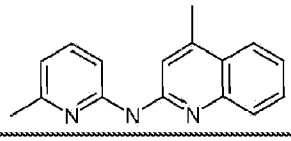
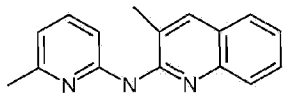
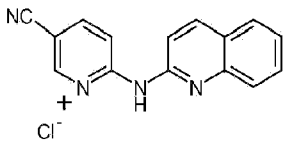
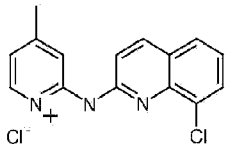
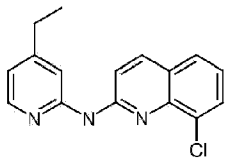
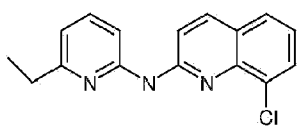
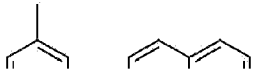
	
44	
45	
46	
47	
48	
49	
50	
51	

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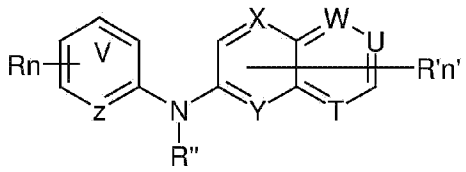

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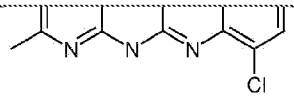
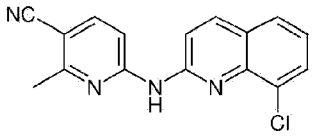
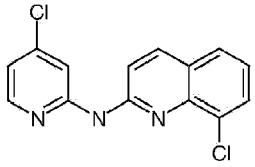
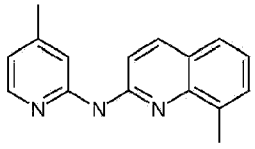
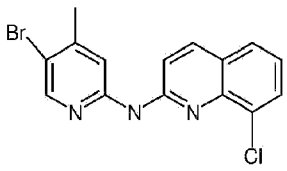
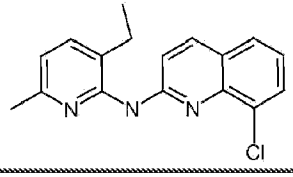
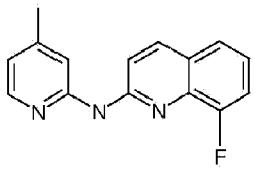
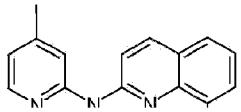
	
52	
53	
54	
55	
56	
57	
58	

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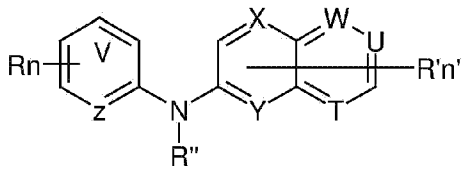

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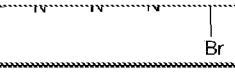
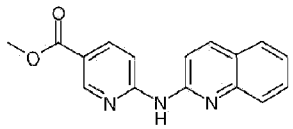
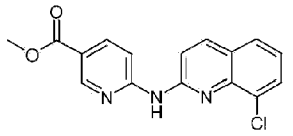
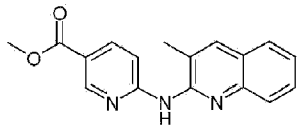
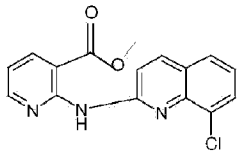
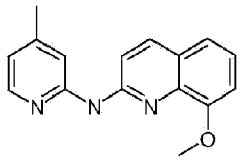
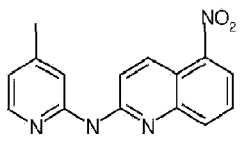
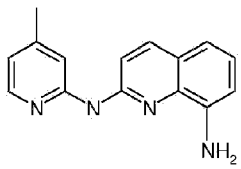
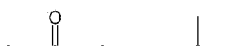
	
59	
60	
61	
62	
63	
64	
65	
67	

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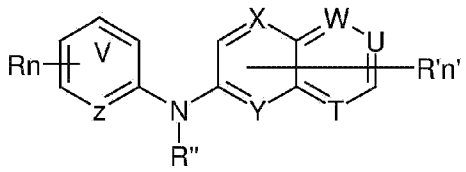

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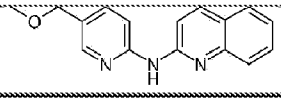
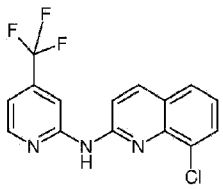
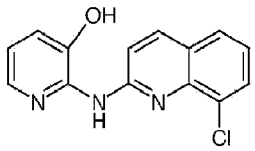
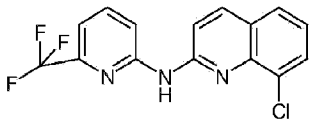
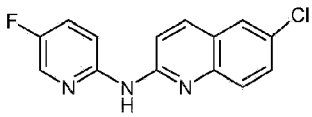
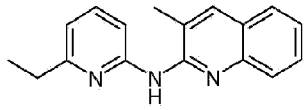
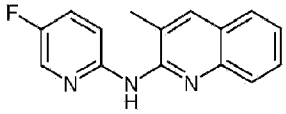
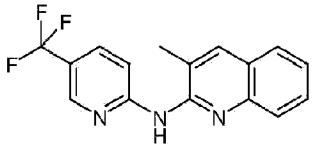
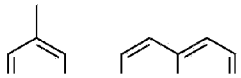
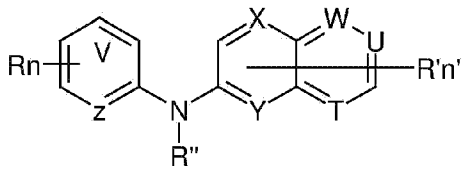
	
68	
69	
70	
71	
72	
73	
74	
150	

(I)



(I)

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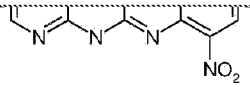
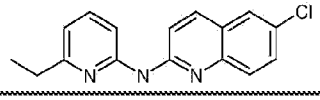
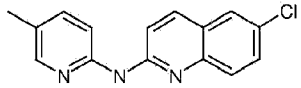
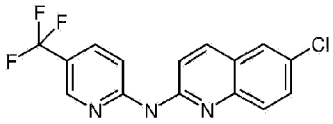
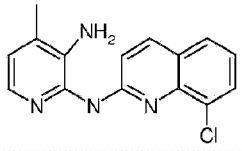
	
151	
152	
153	
154	
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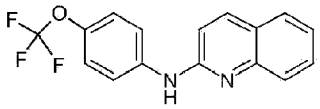
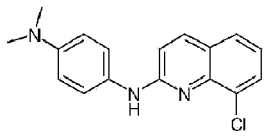
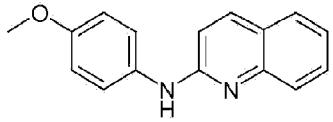
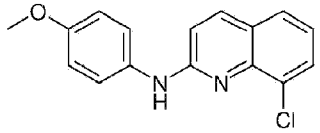
8	
75	
76	
77	

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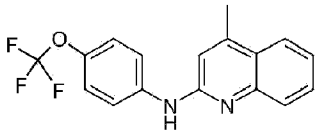
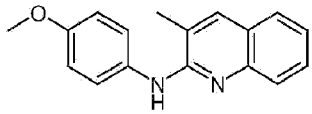
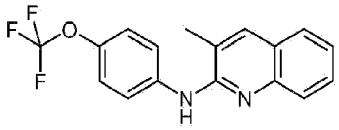
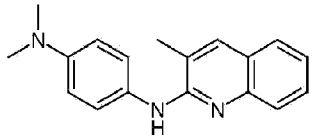
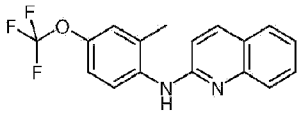
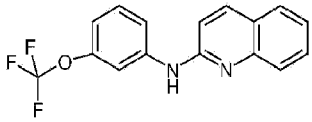
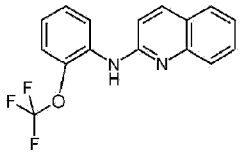
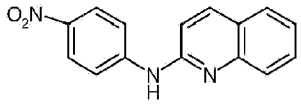
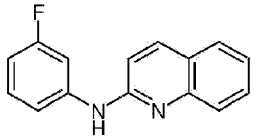
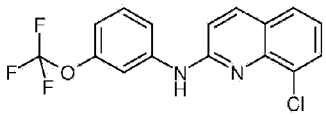
78	
79	
80	
81	
82	
83	
84	
85	
86	
87	
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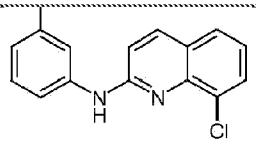
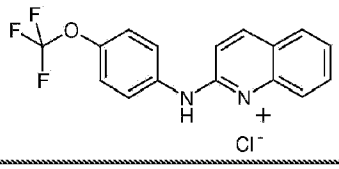
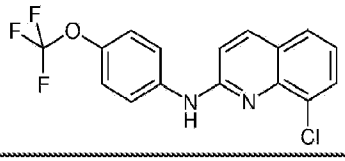
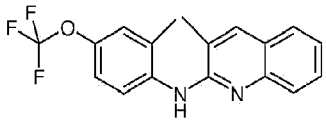
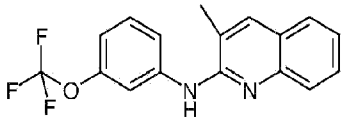
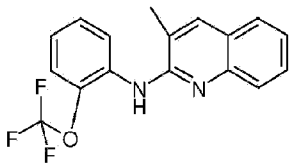
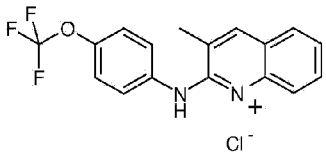
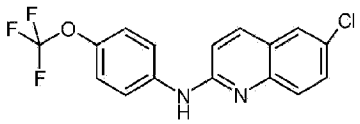
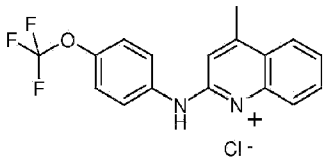
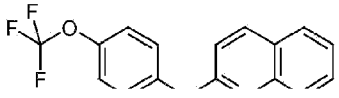
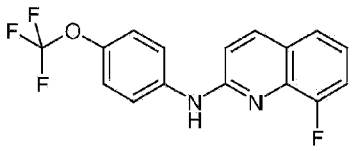
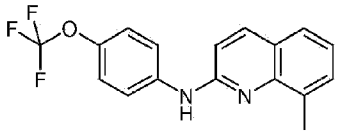
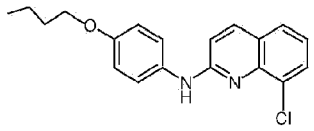
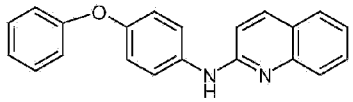
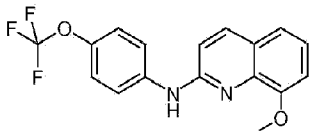
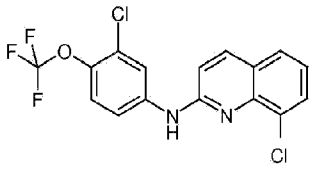
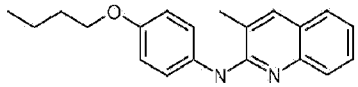
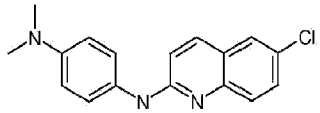
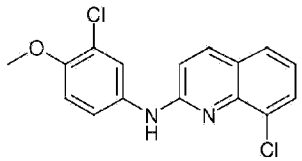
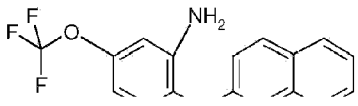
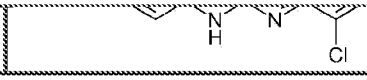
	
89	
90	
91	
92	
93	
95	
96	
97	
98	

Formula (Ib)	
	
99	
100	
101	
102	
103	
104	
155	
156	
157	
158	

Formula (Ib)	
	
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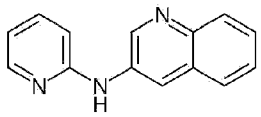
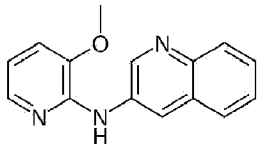
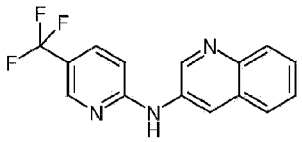
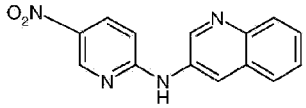
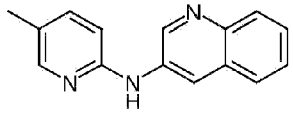
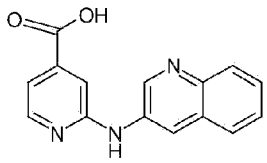
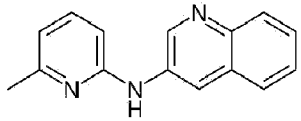
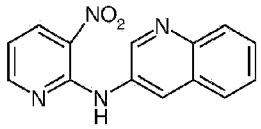
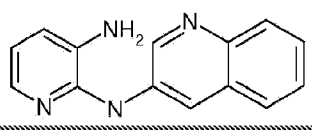
9	
10	
11	
12	
13	
14	
105	
106	
159	

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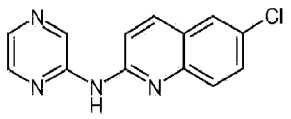
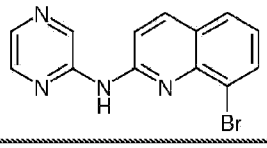
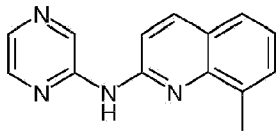
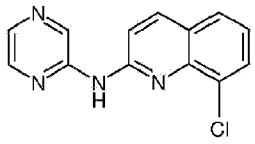
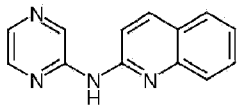
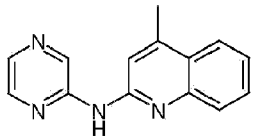
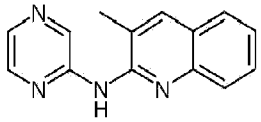
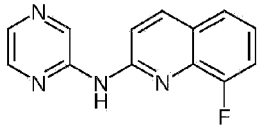
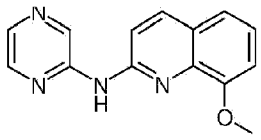
109	
110	
111	
112	
113	
114	
115	
116	
117	

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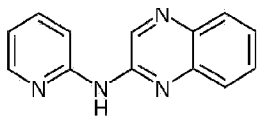
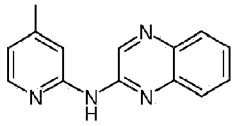
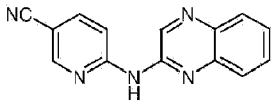
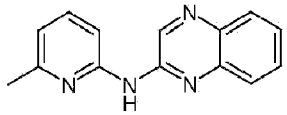
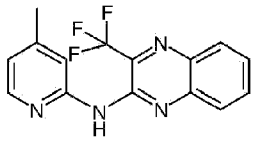
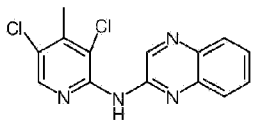
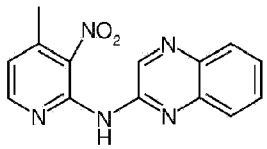
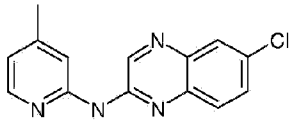
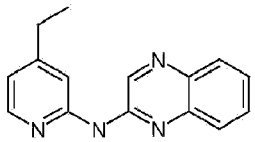
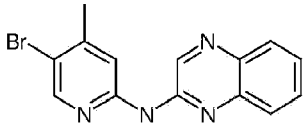
135	
136	
137	
138	
139	
140	
141	
160	
161	
162	

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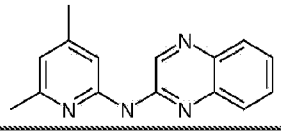
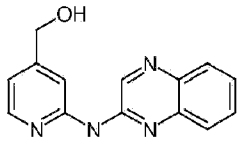
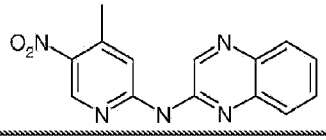
163	
164	
165	

Table II

Ex	Characterizations
1	MS (ESI) $[M+H]^+$=256
2	^{1}H NMR (300 MHz, D_2O) δ 8.31 (d, *J* = 5.1, 1H), 8.21 (d, *J* = 9.3, 1H), 7.60 (d, *J* = 7.5, 3H), 7.34 (dd, *J* = 6.2, 15.6, 2H), 7.18 (s, 1H), 6.99 (d, *J* = 9.1, 1H) MS (ESI) $[M+H]^+$=266
5	MS (ESI) $[M+H]^+$=300
6	^{1}H NMR (300 MHz, DMSO) δ 10.23 (s, 1H), 8.96 (s, 1H), 8.18 (d, *J* = 8.8, 2H), 7.78 (dd, *J* = 7.7, 13.7, 2H), 7.46 (d, *J* = 8.9, 1H), 7.31 (t, *J* = 7.8, 1H), 6.86 (d, *J* = 4.3, 1H), 2.37 (s, 3H).
	^{13}C NMR (75 MHz, DMSO) δ 153.63, 153.61, 148.37, 147.32, 142.65, 137.52, 129.68, 129.47, 126.82, 125.06, 123.26, 118.36, 115.10, 113.31, 21.24.
	MS (ESI) $[M+H]^+$=270
7	^{1}H NMR (300 MHz, DMSO) δ 10.71 (s, 1H), 8.71 (d, *J* = 1.4, 1H), 8.62 (d, *J* = 8.9, 1H), 8.24 (d, *J* = 8.9, 1H), 8.17 (dd, *J* = 1.9, 8.9, 1H), 7.89 - 7.74 (m, 2H), 7.66 (dd, *J* = 7.9, 14.2, 2H), 7.42 (t, *J* = 7.3, 1H). ^{13}C NMR (75 MHz, DMSO) δ 156.09, 152.40, 152.11, 146.24, 141.07, 137.83, 129.87, 127.67, 126.78, 124.50, 124.21, 118.04, 114.49, 111.67, 100.12.
	MS (ESI) $[M+H]^+$=247
8	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.9, 1H), 7.79 (d, *J* = 8.4, 1H), 7.65 (t, *J* = 7.7, 3H), 7.59 (dd, *J* = 7.1, 8.3, 1H), 7.31 (t, *J* = 7.0, 1H), 7.20 (d, *J* = 8.5, 2H), 6.88 (d, *J* = 8.9, 1H), 6.80 (s, 1H)
	^{13}C NMR (75 MHz, $CDCl_3$) δ 153.88, 147.62, 144.35, 139.26, 138.11, 130.13, 127.65, 127.12, 124.43, 123.70, 122.20, 120.95, 112.25.
	MS (ESI) $[M+H]^+$=305

Ex	Characterizations
10	^{1}H NMR (300 MHz, $CDCl_3$) δ 9.10 (d, *J* = 2.5, 1H), 8.83 (d, *J* = 2.6, 1H), 8.02 (d, *J* = 7.9, 1H), 7.94 (dd, *J* = 1.3, 5.0, 1H), 7.85 - 7.79 (m, 1H), 7.52 (pd, *J* = 1.5, 6.9, 2H), 7.33 (s, 1H), 7.04 (dd, *J* = 1.2, 7.9, 1H), 6.81 (dd, *J* = 5.1, 7.9, 1H), 3.95 (s, 3H)
11	MS (ESI) $[M+H]^+$=290
12	^{1}H NMR (300 MHz, $CDCl_3$) δ 9.18 (d, *J* = 2.7, 1H), 8.86 (d, *J* = 2.5, 1H), 8.56 (d, *J* = 2.3, 1H), 8.33 (dd, *J* = 2.7, 9.2, 1H), 8.08 (d, *J* = 8.5, 1H), 7.83 (d, *J* = 8.5, 1H), 7.71 - 7.63 (m, 2H), 7.57 (t, *J* = 7.4, 2H), 6.82 (d, *J* = 9.1, 1H)
13	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (d, *J* = 2.6, 1H), 8.37 (d, *J* = 2.3, 1H), 8.00 (d, *J* = 8.2, 1H), 7.71 (d, *J* = 7.7, 1H), 7.59 - 7.51 (m, 1H), 7.46 (dd, *J* = 7.3, 15.1, 2H), 6.71 (d, *J* = 8.3, 1H), 6.67 (d, *J* = 7.4, 1H), 2.49 (s, 3H)
	^{13}C NMR (75 MHz, $CDCl_3$) δ 157.13, 154.59, 145.81, 144.43, 138.78, 134.54, 129.22, 128.86, 127.41, 127.27, 121.48, 115.41, 106.50, 24.18.
	MS (ESI) $[M+H]^+$=236
14	MS (ESI) $[M+H]^+$= 266
18	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (d, *J* = 59.9, 2H), 7.76 (d, *J* = 8.6, 1H), 7.58 (t, *J* = 8.3, 2H), 7.42 (d, *J* = 7.8, 1H), 7.09 (t, *J* = 7.7, 1H), 6.95 (d, *J* = 8.7, 1H), 6.71 (d, *J* = 7.3, 1H), 2.38 (s, 3H)
21	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.13 (d, *J* = 5.1, 1H), 7.89 (d, *J* = 8.3, 1H), 7.79 (s, 1H), 7.63 (d, *J* = 8.0, 1H), 7.56 (d, *J* = 7.3, 1H), 7.38 (s, 1H), 7.33 (t, *J* = 7.5, 1H), 6.79 (d, *J* = 4.9, 1H), 2.44 (s, 6H)
22	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.95 (d, *J* = 8.4, 1H), 8.28 (d, *J* = 5.7, 1H), 7.87 (d, *J* = 8.3, 1H), 7.78 (s, 1H), 7.76 - 7.70 (m, 1H), 7.62 (d, *J* = 8.0, 1H), 7.60 - 7.52 (m, 1H), 7.42 (s, 1H), 7.32 (t, *J* = 7.4, 1H), 6.95 (dd, *J* = 5.1, 6.5, 1H), 2.45 (s, 3H)
23	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (d, *J* = 8.4, 1H), 8.55 (d, *J* = 2.1, 1H), 8.03 (s, 1H), 7.90 (d, *J* = 8.5, 4H), 7.66 (t, *J* = 7.6, 1H), 7.44 (t, *J* = 7.6, 1H), 7.06 (s, 1H), 2.67 (s, 4H)
24	^{1}H NMR (300 MHz, $CDCl_3$) δ 9.09 (d, *J* = 8.9, 1H), 8.53 (d, *J* = 1.7, 1H), 7.94 (dd, *J* = 2.2, 8.9, 1H), 7.92 - 7.84 (m, 2H), 7.67 (d, *J* = 8.6, 2H), 7.65 - 7.58 (m, 1H), 7.40 (t, *J* = 7.4, 1H), 2.49 (s, 3H)
25	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, *J* = 5.2, 1H), 8.10 (s, 1H), 7.90 (d, *J* = 8.8, 1H), 7.79 (d, *J* = 9.0, 1H), 7.66 (d, *J* = 2.2, 1H), 7.55 (dd, *J* = 2.3, 8.9, 1H), 7.39 (d, *J* = 9.0, 1H), 6.79 (d, *J* = 5.2, 1H), 2.42 (s, 3H) MS (ESI) $[M+H]^+$=270
26	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.3, 1H), 7.70 (d, *J* = 9.0, 1H), 7.64 (d, *J* = 8.9, 1H), 7.49 (t, *J* = 7.9, 2H), 7.40 (dd, *J* = 2.3, 8.9, 1H), 7.18 (d, *J* = 8.9, 1H), 6.68 (d, *J* = 7.4, 1H), 2.38 (s, 3H)

Ex	Characterizations
	MS (ESI) $[M+H]^+$=270
27	^{1}H NMR (300 MHz, $CDCl_3$) δ 9.17 (d, *J* = 2.5, 1H), 8.71 (s, 1H), 8.49 (dd, *J* = 2.6, 9.0, 1H), 7.99 (s, 1H), 7.93 (d, *J* = 8.9, 2H), 7.74 - 7.64 (m, 1H), 7.48 (dd, *J* = 4.2, 11.4, 1H), 7.09 (s, 1H), 2.71 (s, 3H)
28	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 - 8.51 (m, 3H), 8.18 (d, *J* = 9.0, 1H), 7.93 (d, *J* = 8.4, 1H), 7.79 (d, *J* = 8.1, 1H), 7.73 - 7.64 (m, 1H), 7.51 - 7.41 (m, 1H), 7.00 (dd, *J* = 4.6, 8.2, 1H), 6.75 (dd, *J* = 4.6, 8.3, 0H)
29	^{1}H NMR (300 MHz, $CDCl_3$) δ 10.77 (s, 1H), 8.60 (s, 3H), 8.19 (d, *J* = 8.2, 1H), 7.76 (dd, *J* = 6.6, 25.5, 2H), 7.38 (d, *J* = 7.2, 1H), 7.04 (d, *J* = 4.4, 1H)
30	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (dd, *J* = 1.9, 5.0, 1H), 7.87 (dd, *J* = 2.0, 7.6, 1H), 7.82 (d, *J* = 7.3, 1H), 7.60 (t, *J* = 7.3, 2H), 7.43 - 7.33 (m, 1H), 6.90 (dd, *J* = 5.0, 7.6, 1H), 2.64 (s, 3H)
31	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (d, *J* = 9.1, 1H), 8.17 (d, *J* = 4.8, 1H), 8.03 (d, *J* = 9.1, 1H), 7.78 (d, *J* = 8.4, 1H), 7.68 (d, *J* = 8.0, 1H), 7.62 - 7.54 (m, 1H), 7.39 (d, *J* = 7.3, 1H), 7.32 (t, *J* = 7.5, 1H), 6.82 (dd, *J* = 5.0, 7.3, 1H), 2.31 (s, 3H)
	MS (ESI) $[M+H]^+$=236
32	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.5, 1H), 8.10 (s, 1H), 7.91 (d, *J* = 8.9, 1H), 7.82 (d, *J* = 8.4, 1H), 7.62 (d, *J* = 8.3, 1H), 7.56 (d, *J* = 7.3, 1H), 7.50 (dd, *J* = 1.8, 8.5, 1H), 7.37 - 7.24 (m, 2H), 2.26 (s, 3H) MS (ESI) $[M+H]^+$=236
33	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.32 (d, *J* = 5.0, 1H), 7.95 (d, *J* = 8.8, 1H), 7.84 (d, *J* = 8.3, 1H), 7.60 (dd, *J* = 7.4, 14.1, 2H), 7.32 (t, *J* = 7.5, 1H), 7.04 (dd, *J* = 5.0, 9.0, 2H)
	MS (ESI) $[M+H]^+$=247
34	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.45 (d, *J* = 8.6, 1H), 8.01 (d, *J* = 8.8, 1H), 7.87 (dd, *J* = 2.5, 8.5, 2H), 7.72 - 7.56 (m, 2H), 7.39 (d, *J* = 9.0, 2H)
	MS (ESI) $[M+H]^+$=290
35	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, *J* = 9.1, 1H), 8.07 (d, *J* = 4.8, 1H), 7.93 (d, *J* = 9.1, 1H), 7.59 (t, *J* = 7.9, 1H), 7.52 (d, *J* = 8.0, 1H), 7.36 (d, *J* = 7.2, 1H), 7.14 (t, *J* = 7.8, 1H), 6.77 (dd, *J* = 5.0, 7.3, 1H), 2.29 (s, 3H)
	MS (ESI) $[M+H]^+$=270
36	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (d, *J* = 7.2, 1H), 8.01 (s, 1H), 7.82 (d, *J* = 8.9, 1H), 7.62 (d, *J* = 7.6, 1H), 7.53 (dd, *J* = 1.8, 8.6, 1H), 7.46 (d, *J* = 7.9, 1H), 7.12 (t, *J* = 7.8, 1H), 7.05 (d, *J* = 8.8, 1H), 2.21 (s, 3H)
	MS (ESI) $[M+H]^+$=270
37	^{1}H NMR (300 MHz, $CDCl_3$) δ 9.08 (d, *J* = 8.5, 1H), 8.55 (s, 1H), 8.36 (s, 1H), 8.02 (d, *J* = 8.1, 2H), 7.77 (d, *J* = 7.2, 1H), 7.62 (d, *J* = 7.6, 1H), 7.35 - 7.24

Ex	Characterizations
	(m, 1H), 7.12 (d, *J* = 8.8, 1H)
	MS (ESI) $[M+H]^+$=324
38	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (d, *J* = 9.1, 1H), 7.97 (d, *J* = 9.1, 1H), 7.80 - 7.74 (m, 1H), 7.70 (d, *J* = 8.4, 1H), 7.59 (d, *J* = 8.0, 1H), 7.54 - 7.45 (m, 1H), 7.22 (t, *J* = 7.5, 1H), 6.87 (d, *J* = 7.9, 1H), 6.68 (dd, *J* = 5.0, 7.9, 1H), 3.73 (s, 3H)
	MS (ESI) $[M+H]^+$=252
39	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (d, *J* = 29.4, 1H), 7.80 (d, *J* = 8.8, 1H), 7.66 (t, *J* = 6.7, 2H), 7.46 (d, *J* = 7.9, 1H), 7.14 (t, *J* = 7.8, 1H), 7.06 (d, *J* = 8.8, 1H), 6.79 (d, *J* = 7.3, 1H), 2.73 (dd, *J* = 7.6, 15.2, 2H), 1.28 (t, *J* = 7.7, 3H)
40	^{1}H NMR (300 MHz, DMSO) δ 9.75 (s, 1H), 9.12 (d, *J* = 2.3, 1H), 8.50 (d, *J* = 2.2, 1H), 8.48 (s, 1H), 8.13 (s, 1H), 7.83 (s, 1H), 7.80 (s, 1H), 7.64 (t, *J* = 7.7, 1H), 7.45 (t, *J* = 7.8, 1H)
41	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (dd, *J* = 2.8, 8.6, 1H), 8.35 (s, 1H), 8.15 (d, *J* = 2.3, 1H), 7.94 (d, *J* = 8.8, 1H), 7.84 (d, *J* = 8.2, 1H), 7.65 (d, *J* = 7.8, 1H), 7.59 (d, *J* = 7.2, 1H), 7.50 - 7.40 (m, 1H), 7.33 (t, *J* = 7.4, 1H), 7.11 (d, *J* = 8.9, 1H)
	MS (ESI) $[M+H]^+$=240
42	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, *J* = 6.8, 1H), 8.01 (d, *J* = 8.9, 2H), 7.82 (dd, *J* = 9.1, 17.3, 2H), 7.69 (d, *J* = 8.0, 1H), 7.63 (t, *J* = 7.6, 1H), 7.37 (t, *J* = 7.5, 1H), 7.32 - 7.18 (m, 2H)
	MS (ESI) $[M+H]^+$=290
43	^{1}H NMR (300 MHz, DMSO) δ 10.41 (s, 1H), 9.08 (dd, *J* = 4.1, 9.3, 1H), 8.31 (d, *J* = 2.9, 1H), 8.20 (d, *J* = 8.9, 1H), 7.88 - 7.70 (m, 3H), 7.44 (d, *J* = 8.9, 1H), 7.32 (t, *J* = 7.8, 1H)
	^{13}C NMR (75 MHz, DMSO) δ 156.30, 153.32, 153.04, 150.17, 142.55, 137.73, 135.06, 134.74, 129.58, 129.49, 126.86, 125.29, 125.14, 125.04, 123.36, 114.91, 113.36.
	MS (ESI) $[M+H]^+$=274
44	^{1}H NMR (300 MHz, $CDCl_3$) δ 11.09 (s, 1H), 8.78 (d, *J* = 9.0, 1H), 8.42 (dd, *J* = 1.9, 4.7, 1H), 8.28 (dd, *J* = 1.9, 7.8, 1H), 8.11 (d, *J* = 9.1, 1H), 7.73 (d, *J* = 7.5, 1H), 7.65 (d, *J* = 8.1, 1H), 7.27 (dd, *J* = 6.4, 9.2, 1H), 6.88 (dd, *J* = 4.8, 7.8, 1H)
	MS (ESI) $[M+H]^+$=300
46	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (d, *J* = 8.3, 1H), 7.73 (d, *J* = 8.3, 1H), 7.57 (s, 1H), 7.51 (t, *J* = 7.9, 1H), 7.43 (t, *J* = 9.2, 2H), 7.17 (t, *J* = 7.4, 1H), 6.67 (d, *J* = 7.4, 1H), 2.36 (s, 3H), 2.28 (s, 3H)

Ex	Characterizations
47	^{1}H NMR (300 MHz, MeOD) δ 8.99 (s, 1H), 8.76 (d, *J* = 9.2, 1H), 8.32 (d, *J* = 8.7, 1H), 8.22 (d, *J* = 8.6, 1H), 8.11 (d, *J* = 7.8, 1H), 8.01 (t, *J* = 7.1, 1H), 7.76 (t, *J* = 7.4, 1H), 7.55 - 7.43 (m, 2H)
	MS (ESI) [M+H] $^+$=247
48	^{1}H NMR (300 MHz, MeOD) δ 8.48 (d, *J* = 9.1, 1H), 8.40 (d, *J* = 6.7, 1H), 7.94 (d, *J* = 8.4, 1H), 7.90 (d, *J* = 7.8, 1H), 7.54 (t, *J* = 8.0, 1H), 7.38 (d, *J* = 8.6, 1H), 7.30 (s, 2H), 2.58 (s, 3H)
	MS (ESI) [M+H] $^+$=270
49	^{1}H NMR (300 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.95 (s, 1H), 8.21 (d, *J* = 5.1, 1H), 7.87 (d, *J* = 8.9, 1H), 7.71 (d, *J* = 7.5, 1H), 7.52 (d, *J* = 7.9, 1H), 7.19 (t, *J* = 7.8, 1H), 7.05 (d, *J* = 8.9, 1H), 6.84 (d, *J* = 5.1, 1H), 2.76 (q, *J* = 7.6, 2H), 1.37 (t, *J* = 7.6, 3H)
50	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (d, *J* = 29.4, 1H), 7.80 (d, *J* = 8.8, 1H), 7.66 (t, *J* = 6.7, 2H), 7.46 (d, *J* = 7.9, 1H), 7.14 (t, *J* = 7.8, 1H), 7.06 (d, *J* = 8.8, 1H), 6.79 (d, *J* = 7.3, 1H), 2.73 (dd, *J* = 7.6, 15.2, 2H), 1.28 (t, *J* = 7.7, 3H)
51	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.06 (s, 1H), 7.89 (d, *J* = 8.7, 1H), 7.71 (d, *J* = 7.4, 1H), 7.54 (d, *J* = 7.8, 1H), 7.20 (t, *J* = 7.7, 1H), 7.02 (d, *J* = 8.8, 1H), 6.67 (s, 1H), 2.43 (s, 3H), 2.39 (s, 3H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.15, 153.17, 152.82, 150.16, 143.70, 137.92, 131.34, 129.89, 126.49, 125.47, 123.43, 118.62, 114.47, 111.02, 24.13, 21.70.
	MS (ESI) [M+H] $^+$=284
52	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (d, *J* = 8.8, 1H), 8.05 (d, *J* = 8.8, 1H), 8.01 (s, 1H), 7.93 (d, *J* = 8.8, 1H), 7.79 (d, *J* = 7.5, 1H), 7.64 (d, *J* = 8.0, 1H), 7.32 (t, *J* = 7.8, 1H), 7.13 (d, *J* = 8.8, 1H), 2.67 (s, 3H)
53	^{1}H NMR (300 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.33 (d, *J* = 5.7, 1H), 8.13 (d, *J* = 5.2, 1H), 8.00 (d, *J* = 8.8, 1H), 7.76 (d, *J* = 7.4, 1H), 7.60 (d, *J* = 8.0, 1H), 7.29 (d, *J* = 7.9, 1H), 7.07 (d, *J* = 8.9, 1H), 6.97 (d, *J* = 4.8, 1H)
54	MS (ESI) [M+H] $^+$=250
55	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.90 (d, *J* = 9.0, 1H), 7.63 (d, *J* = 7.5, 1H), 7.52 (d, *J* = 7.9, 1H), 7.33 (d, *J* = 7.4, 1H), 7.14 (t, *J* = 7.8, 1H), 6.69 (d, *J* = 7.5, 1H), 2.70 (dd, *J* = 7.3, 14.8, 2H), 2.47 (s, 3H), 1.26 (t, *J* = 7.7, 3H)
56	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.90 (d, *J* = 9.0, 1H), 7.63 (d, *J* = 7.5, 1H), 7.52 (d, *J* = 7.9, 1H), 7.33 (d, *J* = 7.4, 1H), 7.14 (t, *J* = 7.8, 1H), 6.69 (d, *J* = 7.5, 1H), 2.70 (dd, *J* = 7.3, 14.8, 2H), 2.47 (s, 3H), 1.25 (dd, *J* = 7.5, 15.5, 3H)
57	MS (ESI) [M+H] $^+$=253
58	MS (ESI) [M+H] $^+$=314-316

Ex	Characterizations
59	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.91 (d, *J* = 1.7, 1H), 8.46 (d, *J* = 8.8, 1H), 8.28 (dd, *J* = 2.0, 8.8, 1H), 8.23 (s, 1H), 8.03 (d, *J* = 8.8, 1H), 7.88 (d, *J* = 8.3, 1H), 7.70 (d, *J* = 8.0, 1H), 7.67 - 7.58 (m, 1H), 7.38 (t, *J* = 7.4, 1H), 7.32 (d, *J* = 8.8, 2H), 3.91 (s, 3H)
60	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.94 (d, *J* = 8.9, 1H), 8.91 (d, *J* = 1.8, 1H), 8.37 (dd, *J* = 2.2, 8.8, 1H), 8.04 (d, *J* = 8.9, 2H), 7.77 (d, *J* = 7.5, 1H), 7.62 (d, *J* = 7.2, 1H), 7.30 (t, *J* = 7.8, 2H), 7.19 (d, *J* = 8.8, 2H), 3.92 (s, 3H)
61	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.96 (d, *J* = 8.8, 1H), 8.85 (d, *J* = 1.3, 1H), 8.28 (d, *J* = 9.9, 1H), 7.84 (d, *J* = 8.0, 1H), 7.77 (s, 1H), 7.65 (s, 1H), 7.59 (d, *J* = 8.4, 2H), 7.53 (d, *J* = 8.4, 1H), 7.31 (t, *J* = 7.4, 1H), 3.88 (s, 4H), 2.42 (s, 4H)
	MS (ESI) $[M+H]^+$=294
62	^{1}H NMR (300 MHz, $CDCl_3$) δ 11.02 (s, 1H), 8.75 (d, *J* = 9.2, 1H), 8.44 (d, *J* = 3.7, 1H), 8.31 (d, *J* = 7.9, 1H), 8.10 (d, *J* = 9.0, 1H), 7.72 (d, *J* = 7.5, 1H), 7.64 (d, *J* = 8.2, 1H), 7.27 (d, *J* = 8.1, 1H), 6.88 (dd, *J* = 4.7, 7.8, 1H), 3.97 (s, 3H)
	MS (ESI) $[M+H]^+$=314
63	MS (ESI) $[M+H]^+$=266
64	^{1}H NMR (300 MHz, DMSO) δ 10.38 (s, 1H), 8.56 (s, 1H), 8.28 (d, *J* = 9.1, 1H), 8.20 - 8.03 (m, 3H), 7.50 (d, *J* = 8.7, 1H), 7.45 (d, *J* = 8.0, 1H), 6.88 (d, *J* = 4.4, 1H), 2.37 (s, 3H)
65	MS (ESI) $[M+H]^+$=314-316
67	^{1}H NMR (300 MHz, DMSO) δ 10.51 (s, 1H), 8.83 (d, *J* = 2.3, 1H), 8.62 (d, *J* = 9.3, 1H), 8.24 (dd, *J* = 2.7, 9.1, 1H), 7.96 (d, *J* = 8.9, 1H), 7.81 (d, *J* = 7.8, 1H), 7.67 (t, *J* = 7.6, 1H), 7.45 (d, *J* = 11.2, 2H), 3.86 (s, 3H), 2.62 (s, 3H)
	MS (ESI) $[M+H]^+$=294
68	^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (s, 1H), 8.44 (d, *J* = 4.8, 1H), 8.05 (d, *J* = 8.8, 1H), 7.86 (s, 1H), 7.80 (d, *J* = 7.5, 1H), 7.64 (d, *J* = 8.0, 1H), 7.31 (t, *J* = 7.8, 1H), 7.19 (d, *J* = 4.3, 1H), 7.04 (d, *J* = 8.8, 1H)
69	^{1}H NMR (300 MHz, $CDCl_3$) δ 9.12 (s, 1H), 7.94 (d, *J* = 8.6, 1H), 7.71 (d, *J* = 7.5, 1H), 7.57 (d, *J* = 7.8, 1H), 7.40 (s, 1H), 7.25 (d, *J* = 10.2, 2H), 7.17 (s, 1H), 7.05 (s, 1H)
70	^{1}H NMR (300 MHz, $CDCl_3$) δ 9.07 (d, *J* = 8.5, 1H), 7.97 (d, *J* = 8.8, 1H), 7.90 (t, *J* = 8.0, 1H), 7.84 (s, 1H), 7.75 (dd, *J* = 1.1, 7.5, 1H), 7.62 - 7.55 (m, 1H), 7.31 (d, *J* = 7.6, 1H), 7.27 (t, *J* = 7.8, 1H), 7.08 (d, *J* = 8.8, 1H)
	MS (ESI) $[M+H]^+$=274
71	MS (ESI) $[M+H]^+$=274
72	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (d, *J* = 7.9, 1H), 7.83 (d, *J* = 8.3, 1H), 7.71 (s, 1H), 7.69 - 7.61 (m, 1H), 7.57 (d, *J* = 7.9, 2H), 7.52 (d, *J* = 7.1, 1H), 7.28 (t, *J* = 7.4, 1H), 2.74 (q, *J* = 7.6, 2H), 2.42 (s, 3H), 1.31 (t, *J* = 7.6, 3H)

Ex	Characterizations
	MS (ESI) $[M+H]^+$=264
73	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.91 (dd, *J* = 3.8, 9.0, 1H), 8.11 (d, *J* = 2.9, 1H), 7.81 (d, *J* = 8.3, 1H), 7.71 (s, 1H), 7.56 (dd, *J* = 7.4, 14.1, 2H), 7.51 - 7.42 (m, 1H), 7.29 (d, *J* = 7.2, 1H), 2.38 (s, 3H)
	MS (ESI) $[M+H]^+$=254
74	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.96 (d, *J* = 8.3, 1H), 8.49 (s, 1H), 7.89 (dd, *J* = 1.9, 9.0, 1H), 7.82 (d, *J* = 8.2, 1H), 7.72 (s, 1H), 7.57 (t, *J* = 8.7, 3H), 7.33 (t, *J* = 7.4, 1H), 2.37 (s, 3H)
	MS (ESI) $[M+H]^+$=304
75	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 9.0, 1H), 7.69 (dd, *J* = 1.3, 7.6, 1H), 7.53 (dd, *J* = 1.2, 8.0, 1H), 7.42 (d, *J* = 8.9, 2H), 7.15 (t, *J* = 7.8, 1H), 6.89 (d, *J* = 8.9, 2H), 6.79 (d, *J* = 8.9, 2H), 2.97 (s, 6H)
77	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.8, 1H), 7.70 (d, *J* = 7.6, 1H), 7.59 (d, *J* = 8.6, 2H), 7.52 (d, *J* = 7.3, 1H), 7.16 (t, *J* = 7.7, 1H), 6.94 (d, *J* = 8.4, 3H), 6.86 (d, *J* = 8.8, 1H), 3.82 (s, 3H)
	^{13}C NMR (75 MHz, $CDCl_3$) δ 156.40, 155.54, 144.29, 138.09, 132.96, 130.44, 129.99, 126.61, 125.22, 123.29, 122.66, 114.73, 112.16, 55.74.
	MS (ESI) $[M+H]^+$=285
78	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (t, *J* = 7.6, 2H), 7.64 (d, *J* = 8.9, 2H), 7.61 - 7.55 (m, 1H), 7.33 (t, *J* = 7.6, 1H), 7.19 (d, *J* = 8.7, 2H), 2.59 (s, 3H)
79	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4, 1H), 7.76 - 7.71 (m, 2H), 7.69 (s, 1H), 7.57 (dd, *J* = 1.1, 8.0, 1H), 7.51 (ddd, *J* = 1.5, 7.0, 8.4, 1H), 7.29 - 7.21 (m, 1H), 6.96 - 6.90 (m, 2H), 3.82 (s, 3H), 2.35 (s, 3H)
80	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.9 Hz, 2H), 7.84 (d, *J* = 8.3 Hz, 1H), 7.78 (s, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 7.7 Hz, 1H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.24 (d, *J* = 8.7 Hz, 2H), 6.53 (s, 1H), 2.42 (s, 3H)
	^{13}C NMR (75 MHz, $CDCl_3$) δ 152.46, 146.25, 143.86, 139.33, 136.83, 128.93, 126.96, 126.71, 124.75, 123.56, 121.88, 120.44, 119.95, 17.77.
	MS (ESI) $[M+H]^+$=319
81	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3, 1H), 7.66 (d, *J* = 8.5, 3H), 7.55 (d, *J* = 7.8, 1H), 7.48 (t, *J* = 7.6, 1H), 7.20 (d, *J* = 7.2, 1H), 6.80 (d, *J* = 8.8, 2H), 6.32 (s, 1H), 2.93 (s, 7H), 2.35 (s, 3H)
82	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.9, 1H), 7.82 - 7.70 (m, 2H), 7.66 (d, *J* = 7.8, 1H), 7.59 (t, *J* = 7.6, 1H), 7.30 (dd, *J* = 6.0, 13.5, 1H), 7.14 (s, 1H), 7.11 (s, 1H), 6.84 (d, *J* = 8.9, 1H), 2.32 (s, 3H)
	MS (ESI) $[M+H]^+$=319

Ex	Characterizations
83	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 - 7.86 (m, 1H), 7.85 (s, 1H), 7.82 (d, *J* = 8.4, 1H), 7.59 (dd, *J* = 8.2, 15.5, 2H), 7.44 - 7.38 (m, 1H), 7.29 (dd, *J* = 8.3, 16.8, 2H), 6.91 (d, *J* = 9.0, 1H), 6.87 (d, *J* = 8.3, 1H)
	MS (ESI) $[M+H]^+$=305
84	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (d, *J* = 8.1, 1H), 7.92 (d, *J* = 8.9, 1H), 7.85 (d, *J* = 8.4, 1H), 7.63 (d, *J* = 7.6, 1H), 7.58 (d, *J* = 7.3, 1H), 7.30 (dd, *J* = 6.8, 14.8, 3H), 7.02 (t, *J* = 7.8, 1H), 6.89 (d, *J* = 8.9, 1H)
	MS (ESI) $[M+H]^+$=305
86	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.9, 1H), 7.83 (d, *J* = 8.3, 1H), 7.70 (d, *J* = 12.0, 1H), 7.61 (dd, *J* = 7.9, 18.1, 2H), 7.32 (d, J = 7.9, 1H), 7.31 - 7.25 (m, 1H), 7.21 (t, *J* = 6.5, 1H), 6.92 (d, *J* = 8.9, 1H), 6.79 - 6.68 (m, 1H)
	MS (ESI) $[M+H]^+$=239
87	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.76 (d, *J* = 8.9, 1H), 7.67 (d, *J* = 7.5, 1H), 7.51 (d, *J* = 8.2, 1H), 7.45 (d, *J* = 7.9, 1H), 7.28 (d, *J* = 8.2, 1H), 7.14 (t, *J* = 7.8, 1H), 6.86 (d, *J* = 10.1, 1H), 6.76 (d, *J* = 8.9, 1H)
	MS (ESI) $[M+H]^+$=339
88	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (dt, *J* = 2.1, 12.1, 1H), 7.76 (d, *J* = 8.9, 1H), 7.66 (dd, *J* = 1.2, 7.6, 1H), 7.45 (dd, *J* = 1.1, 8.0, 1H), 7.22 (dd, *J* = 1.4, 7.2, 2H), 7.18 (d, *J* = 7.6, 1H), 7.12 (d, *J* = 7.8, 1H), 6.75 (d, *J* = 8.9, 1H), 6.69 (d, *J* = 7.9, 1H)
	MS (ESI) $[M+H]^+$=273
89	^{1}H NMR (300 MHz, DMSO) δ 11.38 (s, 1H), 8.41 (d, *J* = 9.1, 1H), 7.93 (d, *J* = 7.8, 1H), 7.80 (dt, *J* = 8.1, 20.9, 4H), 7.50 (d, *J* = 7.8, 3H), 7.36 (d, *J* = 9.3, 1H)
90	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 9.1, 2H), 7.79 (d, *J* = 8.9, 1H), 7.67 (dd, *J* = 1.2, 7.6, 1H), 7.48 (dd, *J* = 1.1,8.0, 1H), 7.18 (s, 3H), 6.89 (s, 1H), 6.75 (d, *J* = 8.9, 1H)
	^{13}C NMR (75 MHz, $CDCl_3$) δ 153.88, 144.30, 143.91, 139.00, 138.25, 131.13, 130.13, 126.55, 125.42, 123.45, 122.50, 122.17, 120.49, 119.10, 113.24.
	MS (ESI) $[M+H]^+$=339
91	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.54 (s, 1H), 8.46 (d, *J* = 8.8, 1H), 7.91 (dd, *J* = 5.5, 14.5, 2H), 7.79 (d, *J* = 8.9, 1H), 7.67 (d, *J* = 2.1, 1H), 7.56 (dd, *J* = 2.3, 8.9, 1H), 7.35 (d, *J* = 8.9, 1H)
92	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (d, *J* = 7.9, 1H), 7.83 (d, *J* = 8.3, 1H), 7.71 (s, 1H), 7.69 - 7.61 (m, 1H), 7.55 (dd, *J* = 7.5, 14.4, 2H), 7.29 (d, *J* = 7.8, 1H), 6.80 (d, *J* = 7.4, 1H)

Ex	Characterizations
93	^{1}H NMR (300 MHz, $CDCl_3$) δ 9.21 (dd, *J* = 1.5, 8.4, 1H), 7.85 (d, *J* = 8.4, 1H), 7.73 (s, 1H), 7.58 (d, *J* = 7.8, 1H), 7.53 (dd, *J* = 1.3, 8.3, 1H), 7.40 - 7.35 (m, 1H), 7.32 (dd, *J* = 1.1, 4.6, 1H), 7.31 - 7.24 (m, 2H), 7.04 (s, 1H), 7.02 - 6.94 (m, 1H), 2.38 (s, 3H)
95	^{1}H NMR (300 MHz, MeOD) δ 8.42 (s, 1H), 7.94 (d, *J* = 7.9, 1H), 7.83 (d, *J* = 8.1, 1H), 7.78 (d, *J* = 7.1, 1H), 7.72 (d, *J* = 8.7, 2H), 7.58 (d, *J* = 8.2, 3H), 2.60 (s, 3H) MS (ESI) $[M+H]^+$=319
96	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.9, 1H), 7.70 (d, *J* = 8.9, 1H), 7.64 (d, *J* = 8.9, 2H), 7.59 (d, *J* = 2.1, 1H), 7.50 (dd, *J* = 2.3, 8.9, 1H), 7.19 (d, *J* = 8.6, 2H), 6.85 (d, *J* = 8.9, 1H)
	MS (ESI) $[M+H]^+$=281
97	^{1}H NMR (300 MHz, MeOD) δ 8.11 (d, *J* = 8.4, 1H), 7.81 (s, 2H), 7.62 (d, *J* = 8.7, 3H), 7.51 (d, *J* = 8.3, 2H), 7.12 (s, 1H), 2.77 (s, 3H) MS (ESI) $[M+H]^+$=319
98	MS (ESI) $[M+H]^+$=383-385
99	MS (ESI) $[M+H]^+$=320
100	MS (ESI) $[M+H]^+$=316
101	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.9, 1H), 7.70 - 7.63 (m, 1H), 7.51 (dd, *J* = 5.3, 7.6, 3H), 7.14 (t, *J* = 7.8, 1H), 6.91 (d, *J* = 8.8, 3H), 6.85 (d, *J* = 9.0, 2H), 3.96 (t, *J* = 6.5, 2H), 1.84 - 1.68 (m, 3H), 1.49 (dd, *J* = 7.4, 15.0, 3H), 0.97 (t, *J* = 7.4, 3H)
	MS (ESI) $[M+H]^+$=327
102	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.9, 1H), 7.76 (d, *J* = 8.5, 1H), 7.63 (d, *J* = 8.1, 1H), 7.59 (s, 1H), 7.54 (d, *J* = 8.8, 2H), 7.38 - 7.24 (m, 3H), 7.09 (d, *J* = 7.4, 1H), 7.02 (dd, *J* = 2.4, 8.8, 4H), 6.90 (d, *J* = 8.9, 1H)
	MS (ESI) $[M+H]^+$=313
103	MS (ESI) $[M+H]^+$=334
104	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (d, *J* = 2.5, 1H), 7.89 (d, *J* = 8.8, 1H), 7.72 (d, *J* = 7.6, 1H), 7.63 (dd, *J* = 2.5, 8.9, 1H), 7.53 (d, *J* = 8.0, 1H), 7.23 (dd, *J* = 6.2, 14.0, 2H), 7.04 (s, 1H), 6.81 (d, *J* = 8.8, 1H)
	MS (ESI) $[M+H]^+$=373
105	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (d, *J* = 2.6, 1H), 8.45 (d, *J* = 2.3, 1H), 8.01 (d, *J* = 8.1, 1H), 7.71 (d, *J* = 7.8, 1H), 7.58 (s, 1H), 7.53 (d, *J* = 7.6, 1H), 7.51 - 7.45 (m, 2H), 7.45 - 7.36 (m, 1H), 6.72 - 6.62 (m, 2H), 2.48 (s, 3H) 13C NMR (75 MHz, CDCh) δ 157.18, 154.80, 145.42, 143.80, 138.17, 135.04, 128.88, 128.76, 127.17, 127.04, 120.69, 115.22, 106.73, 24.38
106	^{1}H NMR (300 MHz, DMSO) δ 10.24 (s, 1H), 9.06 (d, *J* = 2.3, 1H), 8.65 (d, *J* =

Ex	Characterizations
	1.8, 1H), 8.60 (d, *J* = 8.3, 1H), 8.56 (d, *J* = 4.5, 1H), 7.97 (dd, *J* = 8.2, 14.4, 2H), 7.69 (t, *J* = 6.9, 1H), 7.59 (t, *J* = 7.4, 1H), 7.08 (dd, *J* = 4.6, 8.3, 1H)
	MS (ESI) $[M+H]^+$=267
109	^{1}H NMR (300 MHz, $CDCl_3$) δ 9.68 (s, 1H), 8.21 (s, 2H), 7.94 (d, *J* = 8.9, 1H), 7.79 (d, *J* = 9.2, 1H), 7.67 (d, *J* = 2.3, 1H), 7.56 (dd, *J* = 2.3, 8.9, 1H), 7.34 (d, *J* = 8.9, 1H)
	MS (ESI) $[M+H]^+$=257
110	1H NMR (300 MHz, $CDCl_3$) δ 10.32 (s, 1H), 8.33 - 8.21 (m, 2H), 8.05 (d, J = 8.9, 1H), 8.00 (dd, J = 1.2, 7.6, 1H), 7.69 (dd, J = 1.1, 7.8, 1H), 7.61 (s, 1H), 7.30 - 7.22 (m, 3H), 7.16 (d, J = 8.8, 1H).
	MS (ESI) $[M+H]^+$=301-303
111	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.9, 1H), 7.70 - 7.63 (m, 1H), 7.51 (dd, *J* = 5.3, 7.6, 3H), 7.14 (t, *J* = 7.8, 1H), 6.91 (d, *J* = 8.8, 3H), 6.85 (d, *J* = 9.0, 2H), 3.96 (t, *J* = 6.5, 2H), 1.84 - 1.68 (m, 3H), 1.49 (dd, *J* = 7.4, 15.0, 3H), 0.97 (t, *J* = 7.4, 3H)
112	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.9, 1H), 7.76 (d, *J* = 8.5, 1H), 7.63 (d, *J* = 8.1, 1H), 7.59 (s, 1H), 7.54 (d, *J* = 8.8, 2H), 7.38 - 7.24 (m, 3H), 7.09 (d, *J* = 7.4, 1H), 7.02 (dd, *J* = 2.4, 8.8, 4H), 6.90 (d, *J* = 8.9, 1H)
	^{13}C NMR (75 MHz, DMSO) δ 152.94, 150.19, 142.48, 142.18, 138.20, 137.55, 135.74, 129.71, 126.99, 125.35, 123.84, 114.75.
	MS (ESI) $[M+H]^+$=255
113	^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (s, 1H), 8.20 (s, 2H), 8.03 (d, *J* = 8.6, 1H), 7.87 (d, *J* = 7.6, 1H), 7.80 (s, 1H), 7.70 (d, *J* = 8.0, 1H), 7.63 (t, *J* = 7.7, 1H), 7.37 (t, *J* = 7.4, 1H), 7.30 (d, *J* = 8.7, 1H)
114	^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (s, 1H), 8.34 - 8.12 (m, 2H), 7.84 (d, *J* = 8.0, 2H), 7.70 - 7.54 (m, 1H), 7.38 (t, *J* = 7.6, 1H), 7.17 (s, 1H), 2.61 (s, 3H)
	MS (ESI) $[M+H]^+$=237
115	^{1}H NMR (300 MHz, $CDCl_3$) δ 10.15 (s, 1H), 8.24 - 8.12 (m, 2H), 7.79 (s, 1H), 7.71 (s, 1H), 7.55 (t, *J* = 8.3, 2H), 7.30 (t, *J* = 7.9, 1H), 2.38 (s, 3H)
	MS (ESI) $[M+H]^+$=237
116	MS (ESI) $[M+H]^+$=240
117	MS (ESI) $[M+H]^+$=253
135	^{1}H NMR (300 MHz, $CDCl_3$) δ 9.09 (s, 1H), 8.71 (s, 1H), 8.54 (d, *J* = 8.4, 1H), 8.37 (dd, *J* = 1.0, 4.9, 1H), 7.96 (d, *J* = 8.2, 1H), 7.85 (d, *J* = 8.3, 1H), 7.82 - 7.74 (m, 1H), 7.66 (t, *J* = 7.6, 1H), 7.52 (dd, *J* = 7.0, 8.1, 1H), 7.02 (dd, *J* = 5.0, 7.2, 1H)
	MS (ESI) $[M+H]^+$=223

Ex	Characterizations
136	^{1}H NMR (300 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.70 (s, 1H), 8.30 (s, 1H), 8.20 (d, *J* = 5.1, 1H), 7.94 (d, *J* = 8.1, 1H), 7.84 (d, *J* = 8.2, 1H), 7.64 (t, *J* = 7.6, 1H), 7.49 (t, *J* = 8.1, 1H), 6.83 (d, *J* = 5.0, 1H), 2.43 (s, 3H)
	^{13}C NMR (75 MHz, $CDCl_3$) δ 153.28, 150.20, 148.55, 147.40, 140.93, 139.83, 138.35, 130.44, 129.16, 127.18, 126.28, 119.70, 113.75, 21.87.
	MS (ESI) $[M+H]^+$=237
137	^{1}H NMR (300 MHz, DMSO) δ 11.10 (s, 1H), 9.03 (s, 1H), 8.82 - 8.75 (m, 1H), 8.56 (d, *J* = 8.9, 1H), 8.24 (dd, *J* = 2.3, 8.9, 1H), 7.96 (dd, *J* = 1.2, 8.2, 1H), 7.87 (dd, *J* = 1.0, 8.3, 1H), 7.79 - 7.71 (m, 1H), 7.61 (ddd, *J* = 1.4, 7.0, 8.3, 1H)
	MS (ESI) $[M+H]^+$=248
138	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.53 (s, 1H), 8.20 (d, *J* = 8.3, 1H), 7.93 (d, *J* = 8.2, 1H), 7.81 (d, *J* = 8.3, 1H), 7.62 (td, *J* = 3.4, 8.1, 2H), 7.53 -7.43 (m, 1H), 6.83 (d, *J* = 7.4, 1H), 2.48 (s, 3H)
	^{13}C NMR (75 MHz, $CDCl_3$) δ 156.86, 152.27, 148.40, 140.92, 139.70, 139.00, 138.35, 130.42, 129.13, 127.14, 126.27, 117.76, 110.01, 24.15.
	MS (ESI) $[M+H]^+$=237
139	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.20 (d, *J* = 4.8, 1H), 8.04 (d, *J* = 8.3, 1H), 7.92 (d, *J* = 8.4, 1H), 7.87 (s, 1H), 7.79 (t, *J* = 7.6, 1H), 7.60 (t, *J* = 7.6, 1H), 6.88 (d, *J* = 4.7, 1H), 2.46 (s, 3H)
140	^{1}H NMR (300 MHz, $CDCl_3$) δ 9.93 (s, 1H), 8.19 (s, 1H), 8.05 (d, *J* = 8.1, 1H), 7.99 (s, 1H), 7.82 (d, *J* = 8.2, 1H), 7.69 (t, *J* = 7.6, 1H), 7.59 (t, *J* = 8.2, 1H), 2.53 (s, 4H)
141	^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (s, 1H), 9.35 (s, 1H), 8.30 (d, *J* = 5.0, 1H), 8.05 (d, *J* = 7.7, 1H), 7.87 (d, *J* = 7.0, 1H), 7.66 (dd, *J* = 7.4, 16.9, 3H), 6.92 (d, *J* = 4.9, 1H), 2.58 (s, 3H)
150	MS (ESI) $[M+H]^+$=280
151	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.04 (d, *J* = 8.3, 1H), 7.82 (d, *J* = 8.9, 1H), 7.74 (d, *J* = 8.9, 1H), 7.60 (t, *J* = 7.8, 2H), 7.50 (dd, *J* = 2.3, 8.9, 1H), 7.36 (d, *J* = 8.9, 1H), 6.79 (d, *J* = 7.4, 1H), 2.75 (q, *J* = 7.6, 2H), 1.30 (t, *J* = 7.6, 3H).
	MS (ESI) $[M+H]^+$= 284
152	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.5, 1H), 8.08 (s, 1H), 7.90 (d, *J* = 9.0, 1H), 7.77 (d, *J* = 8.9, 1H), 7.65 (d, *J* = 2.2, 1H), 7.55 (td, *J* = 2.0, 8.8, 2H), 7.39 (d, *J* = 9.0, 1H), 2.31 (s, 3H).
	MS (ESI) $[M+H]^+$= 270
153	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.54 (s, 1H), 8.46 (d, *J* = 8.8, 1H),

Ex	Characterizations
	7.91 (dd, *J* = 5.5, 14.5, 2H), 7.79 (d, *J* = 8.9, 1H), 7.67 (d, *J* = 2.1, 1H), 7.56 (dd, *J* = 2.3, 8.9, 1H), 7.35 (d, *J* = 8.9, 1H).
	MS (ESI) $[M+H]^+$= 324
154	^{1}H NMR (300 MHz, DMSO) δ 9.08 (s, 1H), 8.12 (d, *J* = 8.4, 1H), 7.73 (d, *J* = 8.2, 2H), 7.66 (d, *J* = 10.0, 1H), 7.53 (s, 1H), 7.25 (s, 1H), 6.82 (s, 1H), 5.10 (s, 2H), 2.16 (s, 4H).
	MS (ESI) $[M+H]^+$= 285
155	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.3, 1H), 7.61 (s, 1H), 7.56 (d, *J* = 11.5, 2H), 7.44 (d, *J* = 8.3, 1H), 7.38 (d, *J* = 7.8, 1H), 7.13 (t, *J* = 7.4, 1H), 6.80 (d, *J* = 8.7, 2H), 3.85 (t, *J* = 6.5, 2H), 2.18 (s, 3H), 1.73 - 1.58 (m, 2H), 1.48 - 1.31 (m, 2H), 0.88 (t, *J* = 7.3, 3H)
	MS (ESI) $[M+H]^+$= 307
156	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 9.1, 1H), 7.62 (d, *J* = 8.9, 1H), 7.58 (d, *J* = 2.2, 1H), 7.48 (dd, *J* = 2.4, 8.9, 1H), 7.30 (d, *J* = 8.9, 2H), 6.86 (d, *J* = 9.0, 1H), 6.77 (d, *J* = 8.9, 2H), 6.71 (s, 1H), 2.97 (s, 6H)
	MS (ESI) $[M+H]^+$= 298
157	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, *J* = 2.6, 1H), 7.89 (d, *J* = 8.9, 1H), 7.72 (d, *J* = 7.5, 1H), 7.62 (dd, *J* = 2.6, 8.8, 1H), 7.55 (d, *J* = 7.8, 1H), 7.20 (t, *J* = 7.8, 1H), 6.95 (d, *J* = 8.9, 1H), 6.84 (d, *J* = 8.9, 1H), 6.79 (s, 1H), 3.91 (s, 3H)
	MS (ESI) $[M+H]^+$= 319
158	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 9.0, 1H), 7.70 (dd, *J* = 1.2, 7.5, 1H), 7.56 (dd, *J* = 1.1, 8.0, 1H), 7.30 (d, *J* = 8.6, 1H), 7.20 (t, *J* = 7.8, 1H), 6.71 (t, *J* = 5.9, 2H), 6.64 (d, *J* = 9.5, 1H).
	MS (ESI) $[M+H]^+$= 354
159	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (d, *J* = 2.6, 1H), 8.37 (d, *J* = 2.6, 1H), 8.01 (d, *J* = 8.1, 1H), 7.91 (dd, *J* = 1.6, 4.9, 1H), 7.78 - 7.70 (m, 1H), 7.58 - 7.43 (m, 2H), 7.09 (dd, *J* = 1.6, 7.6, 1H), 6.84 (dd, *J* = 4.9, 7.6, 1H), 6.69 (s, 1H), 3.82 - 3.07 (m, 2H).
160	^{1}H NMR (300 MHz, $CDCl_3$) δ 9.68 - 8.90 (m, 1H), 8.77 (s, 1H), 8.35 (s, 1H), 8.14 (d, *J* = 5.0, 1H), 7.96 (s, 1H), 7.79 (d, *J* = 8.8, 1H), 7.61 (d, *J* = 8.5, 1H), 6.88 (d, *J* = 4.8, 1H), 2.46 (s, 3H)
161	^{1}H NMR (300 MHz, $CDCl_3$) δ 9.98 (s, 1H), 8.70 (s, 1H), 8.45 (s, 1H), 8.27 (d, *J* = 5.2, 1H), 7.94 (d, *J* = 8.1, 1H), 7.84 (d, *J* = 8.2, 1H), 7.63 (t, *J* = 7.5, 1H), 7.48 (t, *J* = 7.5, 1H), 6.87 (d, *J* = 5.0, 1H), 2.74 (q, *J* = 7.6, 2H), 1.34 (t, *J* = 7.6, 3H).
	MS (ESI) $[M+H]^+$= 251
162	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.70 - 8.60 (m, 1H), 8.48 (s, 1H), 8.31 (s, 1H), 7.98 (d, *J* = 8.1, 1H), 7.86 (d, *J* = 7.9, 1H), 7.68 (t, *J* = 8.2, 1H),

Ex	Characterizations
	7.54 (t, *J* = 8.1, 1H), 2.49 (s, 3H)
	MS (ESI) $[M+H]^+$= 315
163	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.68 (s, 1H), 8.01 (s, 1H), 7.95 (d, *J* = 8.2, 1H), 7.84 (d, *J* = 8.3, 1H), 7.64 (t, *J* = 8.2, 1H), 7.49 (t, *J* = 7.0, 1H), 6.69 (s, 1H), 2.45 (s, 3H), 2.38 (s, 3H)
	MS (ESI) $[M+H]^+$= 251
164	^{1}H NMR (300 MHz, DMSO) δ 10.46 (s, 1H), 9.00 (s, 1H), 8.41 (s, 1H), 8.24 (d, *J* = 3.0, 1H), 7.90 (d, *J* = 8.2, 1H), 7.79 (d, *J* = 8.3, 1H), 7.69 (t, *J* = 7.0, 1H), 7.52 (t, *J* = 7.4, 1H), 6.98 (d, *J* = 4.8, 1H), 5.45 (q, *J* = 5.6, 1H), 4.58 (d, *J* = 5.7, 2H).
	MS (ESI) $[M+H]^+$= 253
165	^{1}H NMR (300 MHz, $CDCl_3$) δ 9.07 (s, 1H), 8.79 (s, 1H), 8.51 (s, 1H), 8.18 (s, 1H), 8.09 - 8.01 (m, 1H), 7.94 (d, *J* = 8.4, 1H), 7.81 - 7.71 (m, 1H), 7.69 - 7.59 (m, 1H), 2.80 (s, 3H)
	MS (ESI) $[M+H]^+$= 282

[0070] The following examples are provided as illustrations and in no way limit the scope of this invention.

[0071] The following examples illustrate in detail the preparation of some compounds according to the invention. The structures of the products obtained have been confirmed by NMR spectra.

EXAMPLES

[0072] According to route (A), the compound of formula (III) is placed in a protic solvent such as tert-butanol. The compound of formula (IV) is then added in a 1.1 molar ratio with respect to the compound of formula (III) in presence of Cs_2CO_3, in a 2.8 molar ratio, in the presence of Xantphos (4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene), in a 2 mol% amount relative to the total amount of compound of formula (III), and in the presence of $Pd(OAc)_2$, in a 2 mol% amount relative to the total amount of compound of formula (III). The reaction mixture is then heated at 90°C, and stirred during 20 hours, under argon. The reaction mixture is concentrated under reduced pressure and the resulting residue is diluted with ethyl acetate. The organic phase is then washed twice with water, dried on magnesium sulphate, fitrered and concentrated under reduced pressure. The residue could then be purified by column chromatography on silica gel to yield pure compounds (6), (43), (77), (80), (90), (112) and (136).

[0073] According to route (B), the compound of formula (V) is placed in a protic solvent such as tert-butanol. The compound of formula (VI) is then added in a 1.1 molar ratio with respect to the compound of formula (V) in presence of Cs_2CO_3 in a 2.8 molar ratio, in the presence of Xantphos (4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene) in a 2 mol% amount relative to the total amount of compound of formula (V), and in the presence of a $Pd(OAc)_2$, in a 2 mol% amount relative to the total amount of compound of formula (V). The reaction mixture is then heated at 90°C, and stirred during 20 hours, under argon. The reaction mixture is concentrated under reduced pressure and the resulting residue is diluted with ethyl acetate. The organic phase is then washed twice with water, dried on magnesium sulphate, filtered and concentrated under reduced pressure. The residue could then be purified by column chromatography on silica gel to yield pure compound (106).

Example 1: compound (6) of the table I

[0074] According to route (A), a mixture of 2,8-dichloroquinoline (1.5g) and 2-amino-4methylpyridine (904mg), $Pd(OAc)_2$ (34mg), XantPhos (88mg) and Cs_2CO_3 (7.0g) in 30mL of t-BuOH gave compound (6) (1.3g).

[0075] ^1H NMR (300 MHz, DMSO) δ 10.23 (s, 1H), 8.96 (s, 1H), 8.18 (d, *J* = 8.8, 2H), 7.78 (dd, *J* = 7.7, 13.7, 2H), 7.46 (d, *J* = 8.9, 1H), 7.31 (t, *J* = 7.8, 1H), 6.86 (d, *J* = 4.3, 1H), 2.37 (s, 3H).

[0076] ^{13}C NMR (75 MHz, DMSO) δ 153.63, 153.61, 148.37, 147.32, 142.65, 137.52, 129.68, 129.47, 126.82, 125.06, 123.26, 118.36, 115.10, 113.31, 21.24.

[0077] MS (ESI) $[M+H]^+$= 270

Example 2: compound (43) of the table I

[0078] According to route (A), a mixture of 2,8-dichloroquinoline (394mg) and 2-amino-5fluoropyridine (246mg), $Pd(OAc)_2$ (9mg), XantPhos (23mg) and Cs_2CO_3 (1.8g) in 8mL of t-BuOH gave compound (43) (320mg).

[0079] ^1H NMR (300 MHz, DMSO) δ 10.41 (s, 1H), 9.08 (dd, *J* = 4.1, 9.3, 1H), 8.31 (d, *J* = 2.9, 1H), 8.20 (d, *J* = 8.9, 1H), 7.88 - 7.70 (m, 3H), 7.44 (d, *J* = 8.9, 1H), 7.32 (t, *J* = 7.8, 1H).

[0080] ^{13}C NMR (75 MHz, DMSO) δ 156.30, 153.32, 153.04, 150.17, 142.55, 137.73, 135.06, 134.74, 129.58, 129.49, 126.86, 125.29, 125.14, 125.04, 123.36, 114.91, 113.36.

[0081] MS (ESI) $[M+H]^+$= 274

Example 3: compound (77) of the table I

[0082] According to route (A), a mixture of 2,8-dichloroquinoline (985mg) and *p*-anisidine (677mg), $Pd(OAc)_2$ (22mg), XantPhos (58mg) and Cs_2CO_3 (4.6g) in 20mL of t-BuOH gave compound (77) (629mg).

[0083] ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.8, 1H), 7.70 (d, *J* = 7.6, 1H), 7.59 (d, *J* = 8.6, 2H), 7.52 (d, *J* = 7.3, 1H), 7.16 (t, *J* = 7.7, 1H), 6.94 (d, *J* = 8.4, 3H), 6.86 (d, *J* = 8.8, 1H), 3.82 (s, 3H).

[0084] ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.40, 155.54, 144.29, 138.09, 132.96, 130.44, 129.99, 126.61, 125.22, 123.29, 122.66, 114.73, 112.16, 55.74.

[0085] MS (ESI) $[M+H]^+$= 285

Example 4: compound (80) of the table I

[0086] According to route (A), a mixture of 2-chloro-3methylquinoline (885mg) and 4-(trifluoromethoxy)aniline (743µE), $Pd(OAc)_2$ (22mg), XantPhos (58mg) and Cs_2CO_3 (4.6g) in 20mL of t-BuOH gave compound (80) (1.3g).

[0087] ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.9 Hz, 2H), 7.84 (d, *J* = 8.3 Hz, 1H), 7.78 (s, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 7.7 Hz, 1H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.24 (d, *J* = 8.7 Hz, 2H), 6.53 (s, 1H), 2.42 (s, 3H).

[0088] ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.46, 146.25, 143.86, 139.33, 136.83, 128.93, 126.96, 126.71, 124.75, 123.56, 121.88, 120.44, 119.95, 17.77.

[0089] MS (ESI) $[M+H]^+$= 319

Example 5: compound (90) of the table I

[0090] According to route (A), a mixture of 2,8-dichloroquinoline (984mg) and 4-(trifluoromethoxy)aniline (743 µE), $Pd(OAc)_2$ (22mg), XantPhos (58mg) and Cs_2CO_3 (4.6g) in 20mL of t-BuOH gave compound (90) (1.1g).

[0091] ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 9.1, 2H), 7.79 (d, *J* = 8.9, 1H), 7.67 (dd, *J* =

1.2, 7.6, 1H), 7.48 (dd, *J* = 1.1, 8.0, 1H), 7.18 (s, 3H), 6.89 (s, 1H), 6.75 (d, *J* = 8.9, 1H).

[0092] ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.88, 144.30, 143.91, 139.00, 138.25, 131.13, 130.13, 126.55, 125.42, 123.45, 122.50, 122.17, 120.49, 119.10, 113.24.

[0093] MS (ESI) $[M+H]^+$= 339

Example 6: compound (106) of the table I

[0094] According to route (B), a mixture of 3-aminoquinoline (316mg) and 2-chloro-3nitropyridine (315mg), $Pd(OAc)_2$ (22mg), XantPhos (58mg) and Cs_2CO_3 (4.6g) in 20 mL of t-BuOH gave compound (106) (374.1mg).

[0095] ^1H NMR (300 MHz, DMSO) δ 10.24 (s, 1H), 9.06 (d, *J* = 2.3, 1H), 8.65 (d, *J* = 1.8, 1H), 8.60 (d, *J* = 8.3, 1H), 8.56 (d, *J* = 4.5, 1H), 7.97 (dd, *J* = 8.2, 14.4, 2H), 7.69 (t, *J* = 6.9, 1H), 7.59 (t, *J* = 7.4, 1H), 7.08 (dd, *J* = 4.6, 8.3, 1H).

[0096] MS (ESI) $[M+H]^+$= 267

Example 7: compound (112) of the table I

[0097] According to route (A), a mixture of 2,8-dichloroquinoline (958mg) and aminopyrazine (522mg), $Pd(OAc)_2$ (22mg), XantPhos (58mg) and Cs_2CO_3 (4.6g) in 20 mL of t-BuOH gave compound (112) (728mg).

[0098] ^1H NMR (300 MHz, DMSO) δ 10.58 (s, 1H), 10.26 (s, 1H), 8.36 (s, 1H), 8.27 (s, 2H), 7.91 - 7.74 (m, 2H), 7.50 (d, *J* = 8.8, 1H), 7.37 (t, *J* = 7.6, 1H).

[0099] ^{13}C NMR (75 MHz, DMSO) δ 152.94, 150.19, 142.48, 142.18, 138.20, 137.55, 135.74, 129.71, 126.99, 125.35, 123.84, 114.75.

[0100] MS (ESI) $[M+H]^+$= 255

Example 7: compound (136) of the table I

[0101] According to route (A), a mixture of 2-chloroquinoxaline (82.0mg) and 2-amino-4methylpyridine (59.4mg), $Pd(OAc)_2$ (2.2mg), XantPhos (5.8mg) and Cs_2CO_3 (456mg) in 2 mL of t-BuOH gave compound (136) (35.4mg).

[0102] ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.70 (s, 1H), 8.30 (s, 1H), 8.20 (d, *J* = 5.1, 1H), 7.94 (d, *J* = 8.1, 1H), 7.84 (d, *J* = 8.2, 1H), 7.64 (t, *J* = 7.6, 1H), 7.49 (t, *J* = 8.1, 1H), 6.83 (d, *J* = 5.0, 1H), 2.43 (s, 3H).

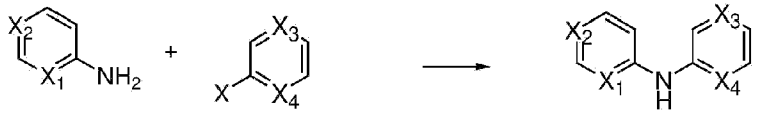
[0103] ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.28, 150.20, 148.55, 147.40, 140.93, 139.83, 138.35, 130.44, 129.16, 127.18, 126.28, 119.70, 113.75, 21.87.

[0104] MS (ESI) $[M+H]^+$= 237

Example 8: Method for synthesizing the compounds of the present invention

Typical procedure for Pd-catalysed aminations

[0105] To a solution of halogeno compound (0.5mmol, 1 equiv) in tert-butanol (2mL) were added the amino moiety (0.55mmol, 1.1 equiv), Cs_2CO_3 (456mg, 1.4mmol, 2.8 equiv), Xantphos (4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene) (5.8mg, 0.01mmol, 2 mol%), $Pd(OAc)_2$ (2.2mg, 0.01mmol, 2mol%). The reaction mixture was heated at 90°C and stirred for 20 h under argon. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to yield pure compounds.



X=Br or Cl

X=Br or Cl

[0106] For example this procedure permitted to synthetize the following compounds:
Isoquinolin-5-yl-(3-methoxy-pyridin-2-yl)-amine

[0107] ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.66 (dd, *J* = 1.7, 6.8, 1H), 8.55 (d, *J* = 6.0, 1H), 7.85 (d, *J* = 5.0, 1H), 7.76 (d, *J* = 6.0, 1H), 7.69 - 7.58 (m, 2H), 7.53 (s, 1H), 7.06 (d, *J* = 7.7, 1H), 6.78 (dd, *J* = 5.1, 7.8, 1H), 3.99 (s, 3H).

[0108] ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.23, 146.60, 142.97, 142.79, 138.53, 134.82, 129.53, 129.13, 127.95, 121.66, 119.82, 115.18, 115.05, 114.09, 100.15, 55.80.

(8-Chloro-quinolin-2-yl)-(4-methyl-pyridin-2-yl)-amine : (6) of the table I

[0109] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.17 (d, *J* = 5.1, 1H), 8.09 (s, 1H), 7.98 (d, *J* = 8.9, 1H), 7.76 (dd, *J* = 1.2, 7.6, 1H), 7.61 (dd, *J* = 1.0, 8.0, 1H), 7.26 (t, *J* = 7.8, 2H), 7.15 (d, *J* = 8.7, 1H), 6.83 (d, *J* = 5.0, 1H), 2.46 (s, 3H).

[0110] ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.52, 153.14, 149.90, 147.43, 143.68, 138.08, 131.37, 129.98, 126.56, 125.58, 123.58, 119.17, 114.52, 114.02, 21.84.

(3-Methoxy-pyridin-2-yl)-quinolin-3-yl-amine : (10) of the table I

[0111] ^{1}H NMR (300 MHz, DMSO) δ 9.17 (d, *J* = 2.5, 1H), 8.97 (d, *J* = 2.4, 1H), 8.79 (s, 1H), 7.94 - 7.79 (m, 3H), 7.58 - 7.46 (m, 2H), 7.31 (d, *J* = 7.9, 1H), 6.88 (dd, *J* = 5.0, 7.9, 1H), 3.94 (s, 3H).

Pharmalogical data

[0112] The compounds of the invention have been the subject of pharmacological tests which have demonstrated their relevance as active substances in therapy and in particular for preventing, inhibiting or treating AIDS.

Example 9: Development of IDC16 derivative compounds

[0113] The inventors have shown that compound IDC16 (BAKKOUR *et al.,* cited above, 2007) interacts functionally with the SF2/ASF complex and thus contributes to blocking alternative splicing during HIV replication, leading to the termination of the production of Tat protein.

[0114] Accordingly, the family of polycyclic indoles, to which compound IDC16 belongs, is known to exhibit the properties of DNA intercalating agents. Such compounds thus present a risk in terms of undesirable side effects.

[0115] The inventors thus sought to develop novel molecules exhibiting activity comparable to IDC16, in terms of activity inhibiting HIV splicing, but while not exhibiting the characteristics of DNA intercalating agents.

[0116] In their initial hypothesis, the inventors considered that the two polar heterocycles at the two ends of compound IDC16 were associated with its activity and that the two median rings were of less importance.

[0117] Based on this hypothesis, the inventors considered that:

- the nitrogen of the indoline and of the D ring of IDC16 might act as acceptors of hydrogen bonds;
- the N-methylated 4-pyridinone motif might be preserved in the analogues;
- the flat tetracyclic geometry was not optimal and it might be wise to replace the B and C rings by other motifs to limit DNA intercalating properties.

Example 10: Inhibition of HIV-1 production in infected peripheral blood mononuclear cells (PBMCs)

MATERIAL AND METHODS

[0118] The first determination is that of the concentration of compound that exhibits the fewest side effects in terms of cell viability and progression of the cell cycle.

[0119] Within this framework, the peripheral blood mononuclear cells (PBMCs) of healthy donors are isolated by centrifugation on a FICOLL gradient. The cells are then cultivated to a density of 2.5×10^6 cells/ml with RPMI medium supplemented with 1% inactivated human AB serum, then incubated at 37 °C, 5% CO_2 for an additional hour. The peripheral blood mononuclear cells are then recovered and cultivated for two days in RPMI medium supplemented with 10% fetal calf serum.

[0120] A standard experiment using 96 plates to test 30 molecules in triplicates including positive and negative controls, is performed as follows:

50 10^6 Ficoll purified PBMCs (10% DMSO 90% FCS) are washed with RPMI 10% FCS and resuspended in 25 ml of RPMI 10% FCS, glutamax containing 1000 U/ml of IL2 and 5 µg/ml PHA. The cells are then incubated for 3 days at 37°C before to be washed with 50 ml PBS then with 50 ml RPMI 10% FCS. The cells are resuspended in 100 µl of RPMI 10% FCS containing 100 U/ml IL2 and seeded in 96 wells (1.5 10^5 cells/well). Viral infection is performed with 1 ng of AdaM/well. 100 µl of tested molecules at concentration of 10 µM are added to each well. Virus production is determined by p24 antigen immunosorbent assays after 3 and 6 days of infection (Kit Innogenetics). Typically PBMCs are prepared from several healthy donors (around 11 different donors). Dose response curves were then established with selected compounds to determine IC_{50}.

Protocol for cytotoxicity:

[0121] To evaluate the cytoxicity of different compounds we used the same protocol as above to seed the HOS-$CD4^+$-$CCR5^+$ cells or PBMCs in a final volume of 100 µl without adding the virus. After an incubation for 48h at 37°C, the medium was removed and cells were incubated with 20µl of CellTiter96 AqueousOne solution to determine the number of viable cells in proliferation and cytotoxicity assays (Promega). CellTiter96 AqueousOne is a colorimetric assay solution that has many advantages compared to MTT assays and gives us satisfactory results.

[0122] We have also evaluated the effect of selected molecules on CD4 and CD8 proliferation using the division tracking dye carboxyfluorescein diacetate succinimidyl ester (CFSE) (In vitrogen).

RESULTS

[0123]

Compound number	**IC_{50} in nM**	**Inhibition of p24 production in HIV infected PBMCs from different donors**
Formula (Ia)		
1	nd	4 out 6 donnors
6	0.1	9 out 14 donnors
33	nd	5 out 6 donnors
34	nd	6 out 8 donnors
35	nd	6 out 8 donnors
36	nd	6 out 8 donnors
37	nd	4 out 6 donnors
38	nd	4 out 6 donnors
42	nd	4 out 6 donnors
43	0.1	8 out of 10 donnors
44	nd	4 out 6 donnors
45	nd	4 out of 4 donnors
46	nd	4 out of 4 donnors
48	nd	4 out 4 donnors
50	nd	4 out of 4 donnors
64	nd	5 out of 5 donnors
68	nd	4 out of 4 donnors
69	nd	4 out of 4 donnors
70	nd	4 out of 4 donnors

Compound number	**IC_{50} in nM**	**Inhibition of p24 production in HIV infected PBMCs from different donors**
Formula (Ia)		
71	nd	4 out of 4 donnors
72	nd	4 out of 4 donnors
73	nd	4 out of 4 donnors
74	nd	4 out of 4 donnors
Formula (Ib)		
75	nd	6 out of 7 donnors
77	0.05	11 out of 13 donnors
78	nd	7 out of 8 donnors
79	nd	7 out of 8 donnors
80	1	7 out of 8 donnors
81	nd	4 out of 4 donnors
82	nd	4 out of 4 donnors
86	nd	3 out of 4 donnors
87	nd	4 out of 4 donnors
88	nd	4 out of 4 donnors
90	0.1	8 out of 10 donnors
92	nd	3 out of 5 donnors
96	nd	5 out of 6 donnors
104	nd	4 out of 4 donnors
Formula (Ic)		
106	0.5	6 out of 6 donnors
Formula (Ie)		
109	nd	8 out of 8 donnors
112	0.1	12 out of 13 donnors
Formula (Io)		
136	nd	6 out of 8 donnors
139	nd	4 out of 4 donnors
140	nd	4 out of 4 donnors
141	nd	4 out of 4 donnors

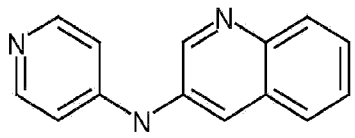
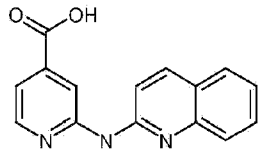
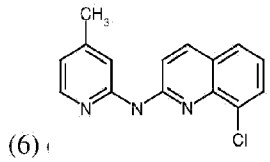
Example 11: Inhibition of HIV-1 production in infected macrophages

[0124] In order to generalize the HIV-1 replication effect of the molecules of the present invention to other cell types, we examined various steps of the viral cycle in cells treated with the various drug at a concentration of 5 µM and submitted to one-round infection.

[0125] For such experiences, macrophages can be infected by the Ada-M R5 HIV strain and treated for 18 hours with various concentrations of the compounds of the present invention. The culture medium is then eliminated and the cells washed with an abundance of PBS. The cells are then cultivated under normal conditions. The culture medium and the cells are then collected at days 4, 7 and 14. Finally, virus replication is measured indirectly by determining the level of p24 antigen in both the culture supernatant and the cellular lysate by the ELISA method. In parallel, cell viability of the macrophages in the presence of the compounds of of the present invention is measured as before.

[0126] For this purpose, we exposed HOS-$CD4^+$-$CCR5^+$ cells to defective virions obtained by cotransfecting 293T cells with a plasmid encoding the R5 envelope of the AD8 strain and another plasmid containing the entire HIV-1 genome mutated in the *envelope* gene and harbouring a *luciferase* marker gene fused to *nef* (Connor RI, Chen BK, Choe S, Landau NR. (1995) Vpr is required for efficient replication of human immunodeficiency virus type-1 in mononuclear phagocytes. Virology 206: 935-944.). The amounts of luciferase activity in cells infected with these virions reflect both the number of integrated proviruses and expression of multiply spliced species encoding nef/luc. Two days post-infection, luciferase activity in HOS-$CD4^+$-$CCR5^+$ infected cells was measured.

[0127] The results are shown below:

Compound	Results
	+
Out of the invention	
 (2) of the table I	-
 (6)	+
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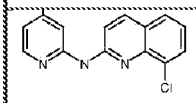
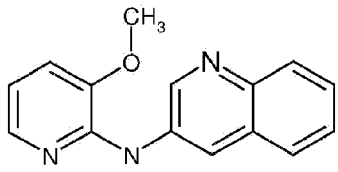
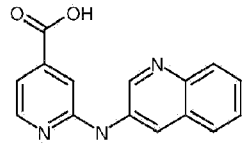
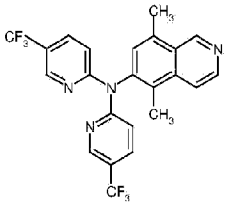
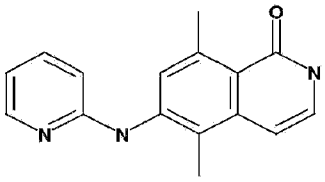
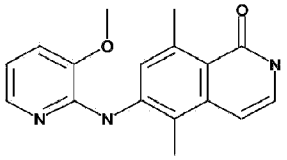
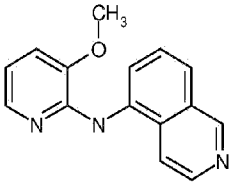
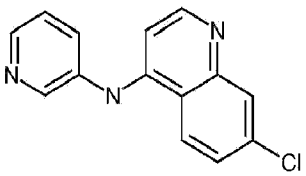
Compound	Results
 (5) of the table I	
 (10) of the table I	+
 (14) of the table I	-
	-
	-
	-
	+
	-

[0128] The results established that the compounds of the present invention show a luciferase inhibitory effect, thus showing that these compounds inhibit viral RNA splicing.

[0129] A further object of the invention consists of a pharmaceutical composition comprising at least one compound of formula (Ib) or (Ie) or anyone of compounds (8), (75), (77)-(84), (86)-(93), (95)-(104), (109)-(117), (155)-(158) and their pharmaceutically acceptable salts, such as hydrobromide, tartrate, citrate, trifluoroacetate, ascorbate, hydrochloride, tartrate, triflate, maleate, mesylate, formate, acetate and fumarate and, optionally, a pharmaceutically acceptable support.

[0130] As examples of pharmaceutically acceptable supports, the composition can include emulsions, microemulsions, oil in water emulsions, anhydrous lipids and water in oil emulsions or other types of emulsions.

[0131] The inventive composition can further include one or more additives such as diluents, excipients, stabilizers and preservatives. Such additives are well known to those skilled in the art and are described notably in "Ullmann's Encyclopedia of Industrial Chemistry, 6th Ed." (various editors, 1989-1998, Marcel Dekker) and in "Pharmaceutical Dosage Forms and Drug Delivery Systems" (ANSEL et al., 1994, WILLIAMS & WILKINS).

[0132] The aforementioned excipients are selected according to the dosage form and the desired mode of administration.

[0133] In this context they can be present in any pharmaceutical form which is suitable for enteral or parenteral administration, in association with appropriate excipients, for example in the form of plain or coated tablets, hard gelatine, soft shell capsules and other capsules, suppositories, or drinkable, such as suspensions, syrups, or injectable solutions or suspensions, in doses which enable the daily administration of from 0.1 to 1000 mg of active substance.

[0134] Still a further object consists of the use of at least one compound of formula (I), (Ia), (Ib), (Ic), (Ie), or (Io) as defined above, and compounds (1)-(14), (17)-(65), (67)-(93), (95)-(106), (109)-(117), (135)-(141), (150)-(165) as defined above, or one of its pharmaceutically acceptable salts according to the present invention in preparing a drug to treat, in a subject, a disease resulting from at least one splicing anomaly.

[0135] Therefore, the present invention relates to a compound of formula (I), (Ia), (Ib), (Ic), (Ie), or (Io) as defined above, and compounds (1)-(14), (17)-(65), (67)-(93), (95)-(106), (109)-(117), (135)-(141), (150)-(165) as defined above, or one of its pharmaceutically acceptable salts according to the present invention for preparing a drug to treat, in a subject, a disease resulting from at least one splicing anomaly.

[0136] As used in the present application, the term "subject" refers to a mammal such as a rodent, cat, dog, primate or human, preferably said subject is a human.

[0137] Preferably, the inventive compounds have the ability to inhibit pre-messenger RNA splicing processes that are either constitutive or, more specifically, dependent on regulating sequences known as an ESE (exonic splicing enhancer), ISE (intronic splicing enhancer), ESS (exonic splicing silencer) and ISS (intronic splicing silencer).

[0138] In a particularly preferred way, splicing processes are either constitutive and/or or dependent on ESE regulating sequences.

[0139] Preferably, the present invention relates to the use of the at least one compound of formula (I), (Ia), (Ib), (Ic), (Ie), or (Io) as defined above, or one of its pharmaceutically acceptable salts according to the present invention, and more particularly of formula (Ia), (Ib), (Ic), (Ie) and (Io) as described above for preparing a drug to treat, in a subject, AIDS.

[0140] Therefore, the present invention relates to a one of said compounds, and more particularly to a compound (1)-(14), (17)-(65), (67)-(93), (95)-(106), (109)-(117), (135)-(141), (150)-(165) or one of its acceptable salts for treating AIDS.

[0141] The compounds can be administered by any mode of administration such as, for example, by intramuscular, intravenous or oral route, etc.

[0142] In one embodiment according to the invention, said composition further includes an excipient making it possible to formulate the inventive compounds in such a way that said composition is provided in solid or liquid form to be prepared and administered by intravenous route.

[0143] The inventive compounds preferably will be administered by intravenous route at a concentration of 80-100 mg/m^2. The concentration will be chosen by those skilled in the art according to the organ or tissue to be treated, the state of advancement of the disease and the targeting mode used.

REFERENCES CITED IN THE DESCRIPTION

Cited references

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all

liability in this regard.

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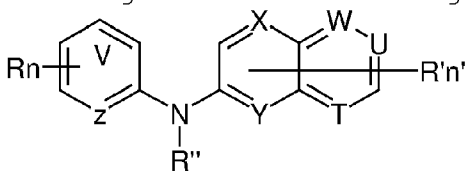
Patentkrav

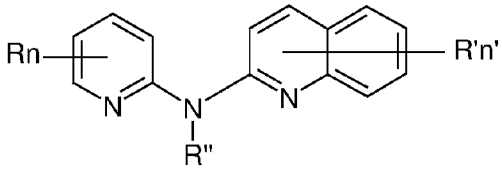
1. Forbindelse med formel (I) til anvendelse til forebyggelse, hæmning eller behandling af AIDS:



(I)

som er alternativt valgt blandt:

(1)



(Ia)

hvor:

R uafhængigt er et hydrogenatom, et halogenatom eller en gruppe valgt blandt en (C_1-C_3)alkylgruppe, en -CN-gruppe, en hydroxylgruppe, en -$COOR_1$-gruppe, en (C_1-C_3)fluoralkylgruppe, en -NO_2-gruppe, en -NR_1R_2-gruppe og en (C_1-C_3)alkoxygruppe,

R" er et hydrogenatom eller en (C_1-C_4)alkylgruppe og fortrinsvis er et hydrogenatom,

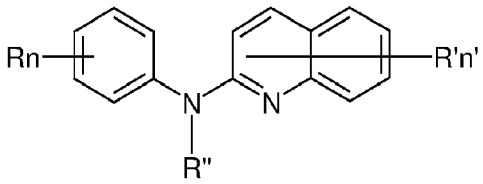
n er 1, 2 eller 3 og fortrinsvis er 1,

n' er 1 eller 2 og fortrinsvis er 1,

R' er et hydrogenatom, et halogenatom eller en gruppe valgt blandt en (C_1-C_3)alkylgruppe, en -NO_2-gruppe, en (C_1-C_3)alkoxygruppe og en -NR_1R_2-gruppe,

R_1 og R_2 er et hydrogenatom eller en (C_1-C_3)alkylgruppe,

(2)



(Ib)

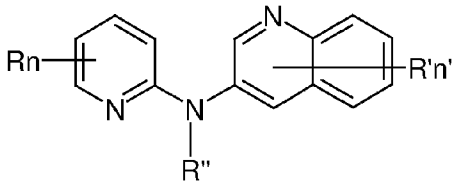
hvor:

R uafhængigt er et hydrogenatom, et halogenatom eller en gruppe valgt blandt en (C_1-C_3)alkylgruppe, en -NR_1R_2-gruppe, en (C_1-C_3)fluoralkoxygruppe, en -NO_2-gruppe, en phenoxygruppe og en (C_1-C_4)alkoxygruppe,

R_1 og R_2 uafhængigt er et hydrogenatom eller en (C_1-C_3)alkylgruppe,

R" er et hydrogenatom eller en (C_1-C_4)alkylgruppe og fortrinsvis er et hydrogenatom,
n er 1, 2 eller 3 og fortrinsvis er 1 eller 2,
n' er 1 eller 2 og fortrinsvis er 1,
R' er et hydrogenatom, et halogenatom eller en gruppe valgt blandt en (C_1-C_3)alkylgruppe og en (C_1-C_4)alkoxygruppe,

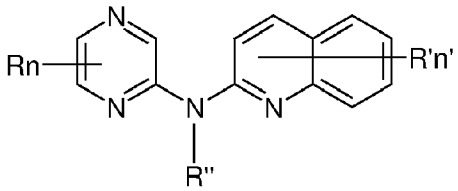
(3)



(Ic)

hvor:
R uafhængigt er et hydrogenatom eller en gruppe valgt blandt en (C_1-C_3)alkylgruppe, en (C_1-C_3)fluoralkylgruppe, en -NR_1R_2-gruppe, en -$COOR_1$-gruppe, en -NO_2-gruppe og en (C_1-C_3)alkoxygruppe,
R" er et hydrogenatom eller en (C_1-C_4)alkylgruppe og fortrinsvis er et hydrogenatom,
n er 1, 2 eller 3 og fortrinsvis er 1,
n' er 1 eller 2 og fortrinsvis er 1,
R' er et hydrogenatom,
R_1 og R_2 uafhængigt er et hydrogenatom eller en (C_1-C_3)alkylgruppe,

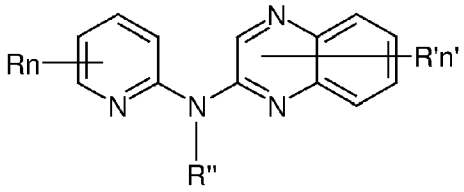
(4)



(Ie)

hvor:
R er et hydrogenatom,
R" er et hydrogenatom eller en (C_1-C_4)alkylgruppe og fortrinsvis er et hydrogenatom,
n er 1, 2 eller 3 og fortrinsvis er 1,
n' er 1 eller 2 og fortrinsvis er 1,
R' er et hydrogenatom, et halogenatom eller en gruppe valgt blandt en (C_1-C_3)alkylgruppe og en (C_1-C_3)alkoxygruppe,

(5)



(Io)

hvor:

R uafhængigt er et hydrogenatom, et halogenatom eller en gruppe valgt blandt, en -NO_2-gruppe, en -CN-gruppe og en (C_1-C_3)alkylgruppe, idet alkyl'en eventuelt er monosubstitueret med en hydroxylgruppe,

R" er et hydrogenatom eller en (C_1-C_4)alkylgruppe og fortrinsvis er et hydrogenatom,

n er 1, 2 eller 3 og fortrinsvis er 1,

n' er 1 eller 2 og fortrinsvis er 1,

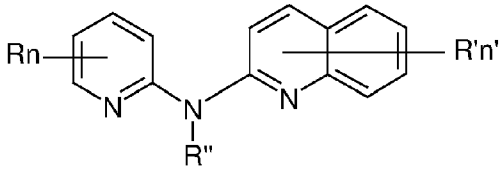
R' er et hydrogenatom, et halogenatom eller en (C_1-C_3)fluoralkylgruppe,

(6)

eller et af dets farmaceutisk acceptable salte.

2. Forbindelse med formel (I) ifølge krav 1 til anvendelse til forebyggelse, hæmning eller behandling af AIDS, som er valgt alternativt blandt:

(1)



(Ia)

hvor:

R uafhængigt er et hydrogenatom, et halogenatom eller en gruppe valgt blandt en (C_1-C_3)alkylgruppe, en (C_1-C_3)fluoralkylgruppe, en hydroxylgruppe, en -CN-gruppe, en - COOH-gruppe og en (C_1-C_3)alkoxygruppe,

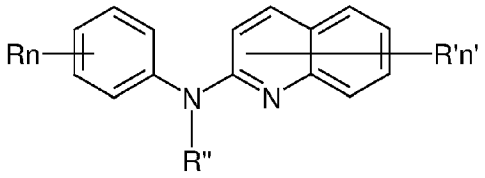
R" er som defineret i krav 1 og mere fortrinsvis er et hydrogenatom,

n er som defineret i krav 1 og mere fortrinsvis er 1,

n' er som defineret i krav 1,

R' er et hydrogenatom, et halogenatom, en -NO_2-gruppe eller en (C_1-C_3)alkylgruppe,

(2)



(Ib)

hvor:

R uafhængigt er et hydrogenatom, et halogenatom, en gruppe valgt blandt en (C_1-C_4)alkylgruppe, en -NR_1R_2-gruppe, en (C_1-C_3)alkoxygruppe og en (C_1-C_3)fluoralkoxygruppe,

R_1 og R_2 uafhængigt er et hydrogenatom eller en (C_1-C_3)alkylgruppe,

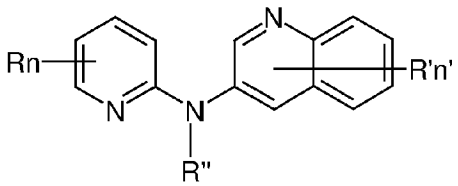
R" er som defineret i krav 1 og mere fortrinsvis er et hydrogenatom,

n er som defineret i krav 1,

n' er som defineret i krav 1,

R' er et hydrogenatom, et halogenatom eller en (C_1-C_3)alkylgruppe,

(3)



(Ic)

hvor:

R uafhængigt er et hydrogenatom eller en gruppe valgt blandt en (C_1-C_3)fluoralkylgruppe, en -NO_2-gruppe og en (C_1-C_3)alkoxygruppe,

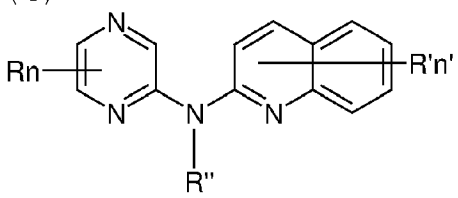
R" er som defineret i krav 1 og mere fortrinsvis er et hydrogenatom,

n er som defineret i krav 1 og mere fortrinsvis er 1,

n' er som defineret i krav 1,

R' er et hydrogenatom,

(4)

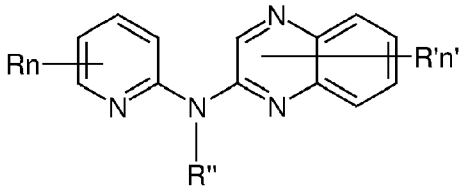


(Ie)

hvor:

R er et hydrogenatom,

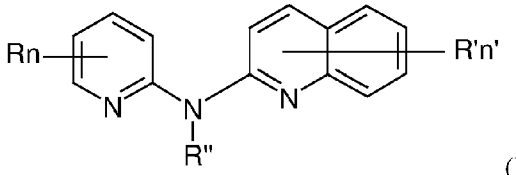
R" er som defineret i krav 1 og mere fortrinsvis er et hydrogenatom,
n er som defineret i krav 1 og mere fortrinsvis er 1,
n' er som defineret i krav 1,
R' er et hydrogenatom eller et halogenatom,
(5)



(Io)

hvor:
R uafhængigt er et hydrogenatom, et halogenatom eller en gruppe valgt blandt en (C_1-C_3)alkylgruppe og en -NO_2-gruppe,
R" er som defineret i krav 1 og mere fortrinsvis er et hydrogenatom,
n er 1, 2 eller 3,
n' er som defineret i krav 1,
R' er et hydrogenatom eller en (C_1-C_3)fluoralkylgruppe,
(6)
eller et af dets farmaceutisk acceptable salte.

3. Forbindelse med formel (Ia)

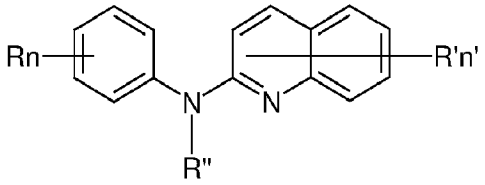


(Ia)

hvor:
R" er et hydrogenatom eller en (C_1-C_4)alkylgruppe og fortrinsvis er et hydrogenatom,
n er 1, 2 eller 3 og fortrinsvis er 1,
n' er 1,
R uafhængigt er et hydrogenatom, et halogenatom eller en gruppe valgt blandt en (C_1-C_3)alkylgruppe, en -CN-gruppe, en hydroxylgruppe, en -$COOR_1$-gruppe, en (C_1-C_3)fluoralkylgruppe, en -NO_2-gruppe, en (C_1-C_3)fluoralkoxygruppe og en (C_1-C_3)alkoxygruppe,
R' er et hydrogenatom, et halogenatom eller en gruppe valgt blandt en (C_1-C_3)alkylgruppe, en -$COOR_1$-gruppe og en -CN-gruppe,

R_1 er et hydrogenatom eller en (C_1-C_3)alkylgruppe,
med det forbehold, at
R og R' ikke samtidigt er et hydrogenatom,
når n er 1, så er R ikke en methylgruppe i orto- eller para-positionen i forhold til Z, idet Z er N,
når R' er et hydrogenatom, så er R ikke et bromatom eller et chloratom,
når R er et hydrogenatom, så er R' ikke en methyl- eller ethylgruppe, en -COOH-gruppe, en $COOC_2H_5$-gruppe eller et bromatom, idet bromatomet er i orto-positionen i bindingen, der er koblet til NR",
eller et af dets farmaceutisk acceptable salte.

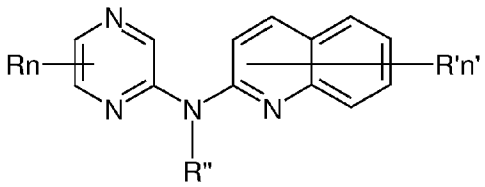
4. Forbindelse med formel (Ib)



(Ib)

hvor:
R' er et hydrogenatom, et halogenatom eller en gruppe valgt blandt en (C_1-C_3)alkylgruppe og en (C_1-C_4)alkoxygruppe,
R" er et hydrogenatom eller en (C_1-C_4)alkylgruppe og fortrinsvis er et hydrogenatom,
n' er 1 eller 2,
n er 1, og
R er en (C_1-C_3)fluoralkoxygruppe,
eller et af dets farmaceutisk acceptable salte.

5. Forbindelse med formel (Ie)

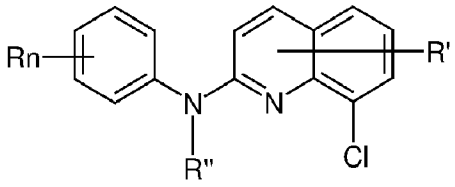


(Ie)

hvor:
R er et hydrogenatom,
R" er et hydrogenatom eller en (C_1-C_4)alkylgruppe og fortrinsvis er et hydrogenatom,
n er 1, 2 eller 3 og fortrinsvis er 1,

n' er 1 eller 2 og fortrinsvis er 1,
R' er et hydrogenatom, et halogenatom eller en gruppe valgt blandt en (C_1-C_3)alkylgruppe og en (C_1-C_3)alkoxygruppe,
med det forbehold, at
når R er et hydrogenatom, så er R' ikke et bromatom,
eller et af dets farmaceutisk acceptable salte.

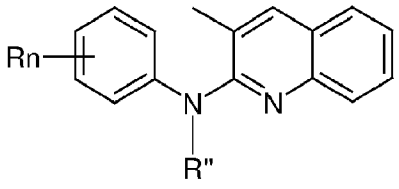
6. Forbindelse med formel (Ib')



(Ib')

hvor:
R uafhængigt er et hydrogenatom, et halogenatom eller en gruppe valgt blandt en (C_1-C_3)alkylgruppe, en -NR_1R_2-gruppe, en (C_1-C_3)fluoralkoxygruppe, en -NO_2-gruppe, en phenoxygruppe og en (C_1-C_4)alkoxygruppe,
R" er et hydrogenatom eller en (C_1-C_4)alkylgruppe og fortrinsvis er et hydrogenatom,
R' er et hydrogenatom, et halogenatom eller en gruppe valgt blandt en (C_1-C_3)alkylgruppe og en (C_1-C_4)alkoxygruppe,
n er 1, 2 eller 3,
med det forbehold, at R' er forskelligt fra en methylgruppe i position 4 på quinolinet,
eller et af dets farmaceutisk acceptable salte.

7. Forbindelse med formel (Ib")



(Ib'')

hvor:
R uafhængigt er et hydrogenatom, et halogenatom eller en gruppe valgt blandt en (C_1-C_3)alkylgruppe, en -NR_1R_2-gruppe, en (C_1-C_3)fluoralkoxygruppe, en -NO_2-gruppe, en phenoxygruppe og en (C_1-C_4)alkoxygruppe,
R" er et hydrogenatom eller en (C_1-C_4)alkylgruppe og fortrinsvis er et hydrogenatom,

n er 1, 2 eller 3,
med det forbehold, at når n er 1, så er R ikke et hydrogenatom, en methylgruppe i para i bindingen, der er koblet til NR", en ethoxygruppe i para i bindingen, der er koblet til NR", eller et fluoratom i para i bindingen, der er koblet til NR",
eller et af dets farmaceutisk acceptable salte.

8. Forbindelse til anvendelse ifølge krav 1 eller krav 2, hvilken forbindelse er valgt blandt:

- (1) (8-chlorquinolin-2-yl)-pyridin-2-ylamin
- (2) 2-(quinolin-2-ylamino)-isonicotinsyre
- (3) (4-methylpyridin-2-yl)-quinolin-2-ylamin
- (4) pyridin-2-ylquinolin-2-ylamin
- (5) 2-(8-chlorquinolin-2-ylamino)-isonicotinsyre
- (6) (8-chlorquinolin-2-yl)-(4-methylpyridin-2-yl)-amin
- (7) 6-(quinolin-2-ylamino)-nicotinonitril
- (8) quinolin-2-yl-(4-trifluormethoxyphenyl)-amin
- (9) pyridin-2-ylquinolin-3-ylamin
- (10) (3-methoxypyridin-2-yl)-quinolin-3-ylamin
- (11) quinolin-3-yl-(5-trifluormethylpyridin-2-yl)-amin
- (12) (5-nitropyridin-2-yl)-quinolin-3-ylamin
- (13) (5-methylpyridin-2-yl)-quinolin-3-ylamin
- (14) 2-(quinolin-3-ylamino)-isonicotinsyre
- (17) N-(6-methylpyridin-2-yl)quinolin-2-amin
- (18) 8-chlor-N-(6-methylpyridin-2-yl)quinolin-2-amin
- (19) 4-methyl-N-(pyridin-2-yl)quinolin-2-amin
- (20) 4-methyl-N-(4-methylpyridin-2-yl)quinolin-2-amin
- (21) 3-methyl-N-(4-methylpyridin-2-yl)quinolin-2-amin
- (22) 3-methyl-N-(pyridin-2-yl)quinolin-2-amin
- (23) 6-((4-methylquinolin-2-yl)amino)nicotinonitril
- (24) 6-((3-methylquinolin-2-yl)amino)nicotinonitril
- (25) 6-chlor-N-(4-methylpyridin-2-yl)quinolin-2-amin
- (26) 6-chlor-N-(6-methylpyridin-2-yl)quinolin-2-amin
- (27) 4-methyl-N-(5-nitropyridin-2-yl)quinolin-2-amin
- (28) N-(3-nitropyridin-2-yl)quinolin-2-amin
- (29) 8-chlor-N-(3-nitropyridin-2-yl)quinolin-2-amin
- (30) 2-((4-methylquinolin-2-yl)amino)nicotinonitril
- (31) N-(3-methylpyridin-2-yl)quinolin-2-amin

- (32) N-(5-methylpyridin-2-yl)quinolin-2-amin
- (33) 2-(quinolin-2-ylamino)isonicotinonitril
- (34) N-(5-(trifluormethyl)pyridin-2-yl)quinolin-2-amin
- (35) 8-chlor-N-(3-methylpyridin-2-yl)quinolin-2-amin
- (36) 8-chlor-N-(5-methylpyridin-2-yl)quinolin-2-amin
- (37) 8-chlor-N-(5-(trifluormethyl)pyridin-2-yl)quinolin-2-amin
- (38) N-(3-methoxypyridin-2-yl)quinolin-2-amin
- (39) N-(5-nitropyridin-2-yl)quinolin-2-amin
- (40) 6-((8-chlorquinolin-2-yl)amino)nicotinonitril
- (41) N-(5-fluorpyridin-2-yl)quinolin-2-amin
- (42) N-(6-(trifluormethyl)pyridin-2-yl)quinolin-2-amin
- (43) 8-chlor-N-(5-fluorpyridin-2-yl)quinolin-2-amin
- (44) 2-((8-chlorquinolin-2-yl)amino)nicotinsyre
- (45) 4-methyl-N-(6-methylpyridin-2-yl)quinolin-2-amin
- (46) 3-methyl-N-(6-methylpyridin-2-yl)quinolin-2-amin
- (47) 5-cyano-2-(quinolin-2-ylamino)pyridin-1-iumchlorid
- (48) 2-((8-chlorquinolin-2-yl)amino)-4-methylpyridin-1-iumchlorid
- (49) 8-chlor-N-(4-ethylpyridin-2-yl)quinolin-2-amin
- (50) 8-chlor-N-(6-ethylpyridin-2-yl)quinolin-2-amin
- (51) 8-chlor-N-(4,6-dimethylpyridin-2-yl)quinolin-2-amin
- (52) 6-((8-chlorquinolin-2-yl)amino)-2-methylnicotinonitril
- (53) 8-chlor-N-(4-chlorpyridin-2-yl)quinolin-2-amin
- (54) 8-methyl-N-(4-methylpyridin-2-yl)quinolin-2-amin
- (55) N-(5-brom-4-methylpyridin-2-yl)-8-chlorquinolin-2-amin
- (56) 8-chlor-N-(3-ethyl-6-methylpyridin-2-yl)quinolin-2-amin
- (57) 8-fluor-N-(4-methylpyridin-2-yl)quinolin-2-amin
- (58) 8-brom-N-(4-methylpyridin-2-yl)quinolin-2-amin
- (59) methyl-6-(quinolin-2-ylamino)nicotinat
- (60) methyl-6-[(8-chlorquinolin-2-yl)amino]pyridin-3-carboxylat
- (61) methyl-6-[(3-methylquinolin-2-yl)amino]pyridin-3-carboxylat
- (62) methyl-2-[(8-chlorquinolin-2-yl)amino]pyridin-3-carboxylat
- (63) 8-methoxy-N-(4-methylpyridin-2-yl)quinolin-2-amin
- (64) N-(4-methylpyridin-2-yl)-5-nitroquinolin-2-amin

- (65) 2-N-(4-methylpyridin-2-yl)quinolin-2,8-diamin
- (67) methyl-6-[(4-methylquinolin-2-yl)amino]pyridin-3-carboxylat
- (68) 8-chlor-N-[4-(trifluormethyl)pyridin-2-yl]quinolin-2-amin
- (69) 2-[(8-chlorquinolin-2-yl)amino]pyridin-3-ol
- (70) 8-chlor-N-[6-(trifluormethyl)pyridin-2-yl]quinolin-2-amin
- (71) 6-chlor-N-(5-fluorpyridin-2-yl)quinolin-2-amin
- (72) N-(6-ethylpyridin-2-yl)-3-methylquinolin-2-amin
- (73) N-(5-fluorpyridin-2-yl)-3-methylquinolin-2-amin
- (74) 3-methyl-N-[5-(trifluormethyl)pyridin-2-yllquinolin-2-amin
- (75) 4-N-(8-chlorquinolin-2-yl)-1-N,1-N-dimethylbenzen-1,4-diamin
- (76) N-(4-methoxyphenyl)quinolin-2-amin
- (77) 8-chlor-N-(4-methoxyphenyl)quinolin-2-amin
- (78) 4-methyl-N-[4-(trifluormethoxy)phenyl]quinolin-2-amin
- (79) N-(4-methoxyphenyl)-3-methylquinolin-2-amin
- (80) 3-methyl-N-[4-(trifluormethoxy)phenyl]quinolin-2-amin
- (81) 1-N,1-N-dimethyl-4-N-(3-methylquinolin-2-yl)benzen-1,4-diamin
- (82) N-[2-methyl-4-(trifluormethoxy)phenyl]quinolin-2-amin
- (83) N-[3-(trifluormethoxy)phenyl]quinolin-2-amin
- (84) N-[2-(trifluormethoxy)phenyl]quinolin-2-amin
- (85) N-(4-nitrophenyl)quinolin-2-amin
- (86) N-(3-fluorphenyl)quinolin-2-amin
- (87) 8-chlor-N-[3-(trifluormethoxy)phenyl]quinolin-2-amin
- (88) 8-chlor-N-(3-fluorphenyl)quinolin-2-amin
- (89) 2-{[4-(trifluormethoxy)phenyl]amino}quinolin-1-iumchlorid
- (90) 8-chlor-N-[4-(trifluormethoxy)phenyl]quinolin-2-amin
- (91) 3-methyl-N-[2-methyl4-(trifluormethoxy)phenyl]quinolin-2-amin
- (92) 3-methyl-N-[3-(trifluormethoxy)phenyl]quinolin-2-amin
- (93) 3-methyl-N-[2-(trifluormethoxy)phenyl]quinolin-2-amin
- (95) 3-methyl-2-{[4-(trifluormethoxy)phenyl]amino}quinolin-1-iumchlorid

- (96) 6-chlor-N-(4-(trifluormethoxy)phenyl)quinolin-2-amin
- (97) 4-methyl-2-{[4-(trifluormethoxy)phenyl]amino]quinolin-1-iumchlorid
- (98) 8-brom-N-[4-(trifluormethoxy)phenyl]quinolin-2-amin
- (99) 8-fluor-N-[4-(trifluormethoxy)phenyl]quinolin-2-amin
- (100) 8-methyl-N-[4-(trifluormethoxy)phenyl]quinolin-2-amin
- (101) N-(4-butoxyphenyl)-8-chlorquinolin-2-amin
- (102) N-(4-phenoxyphenyl)quinolin-2-amin
- (103) 8-methoxy-N-[4-(trifluormethoxy)phenyl]quinolin-2-amin
- (104) 8-chlor-N-[3-chlor-4-(trifluormethoxy)phenyl]quinolin-2-amin
- (105) N-(6-methylpyridin-2-yl)quinolin-3-amin
- (106) N-(3-nitropyridin-2-yl)quinolin-3-amin
- (109) 6-chlor-N-(pyrazin-2-yl)quinolin-2-amin
- (110) 8-brom-N-(pyrazin-2-yl)quinolin-2-amin
- (111) 8-methyl-N-(pyrazin-2-yl)quinolin-2-amin
- (112) 8-chlor-N-(pyrazin-2-yl)quinolin-2-amin
- (113) N-(pyrazin-2-yl)quinolin-2-amin
- (114) 4-methyl-N-(pyrazin-2-yl)quinolin-2-amin
- (115) 3-methyl-N-(pyrazin-2-yl)quinolin-2-amin
- (116) 8-fluor-N-(pyrazin-2-yl)quinolin-2-amin
- (117) 8-methoxy-N-(pyrazin-2-yl)quinolin-2-amin
- (135) N-(pyridin-2-yl)quinoxalin-2-amin
- (136) N-(4-methylpyridin-2-yl)quinoxalin-2-amin
- (137) 6-(quinoxalin-2-ylamino)pyridin-3-carbonitril
- (138) N-(6-methylpyridin-2-yl)quinoxalin-2-amin
- (139) N-(4-methylpyridin-2-yl)-3-(trifluormethyl)quinoxalin-2-amin
- (140) N-(3,5-dichlor-4-methylpyridin-2-yl)quinoxalin-2-amin
- (141) N-(4-methyl-3-nitropyridin-2-yl)quinoxalin-2-amin
- (150) N-(4-methylpyridin-2-yl)-8-nitroquinolin-2-amin
- (151) 6-chlor-N-(6-ethylpyridin-2-yl)quinolin-2-amin
- (152) 6-chlor-N-(5-methylpyridin-2-yl)quinolin-2-amin
- (153) 6-chlor-N-[5-(trifluormethyl)pyridin-2-yl]quinolin-2-amin
- (154) N-2-(8-chlorquinolin-2-yl)-4-methylpyridin-2,3-diamin
- (155) N-(4-butoxyphenyl)-3-methylquinolin-2-amin

- (156) 4-N-(6-chlorquinolin-2-yl)-1-N,1-N-dimethylbenzen-1,4-diamin
- (157) 8-chlor-N-(3-chlor-4-methoxyphenyl)quinolin-2-amin
- (158) N-1-(8-chlorquinolin-2-yl)-4-(trifluormethoxy)benzen-1,2-diamin
- (159) N-(3-aminopyridin-2-yl)quinolin-3-amin
- (160) 6-chlor-N-(4-methylpyridin-2-yl)quinoxalin-2-amin
- (161) N-(4-ethylpyridin-2-yl)quinoxalin-2-amin
- (162) N-(5-brom-4-methylpyridin-2-yl)quinoxalin-2-amin
- (163) N-(4,6-dimethylpyridin-2-yl)quinoxalin-2-amin
- (164) [2-(quinoxalin-2-ylamino)pyridin-4-yl]methanol
- (165) N-(4-methyl-5-nitropyridin-2-yl)quinoxalin-2-amin
- og deres farmaceutisk acceptable salte.

9. Forbindelse til anvendelse ifølge et hvilket som helst af kravene 1, 2 og 8, hvilken forbindelse er: (90) 8-chlor-N-[4-(trifluormethoxy)phenyl]quinolin-2-amin.

10. Forbindelse ifølge et hvilket som helst af kravene 3 til 7, hvilken forbindelse er valgt blandt forbindelserne: (1), (2), (5)-(7), (18), (21)-(44), (46)-(65), (67)-(74), (150)-(154), (8), (75), (77)-(84), (86)-(93), (95)-(104), (109)-(117), (155)-(158) som defineret i ovennævnte krav samt deres farmaceutisk acceptable salte, såsom hydrobromid, tartrat, citrat, trifluoracetat, ascorbat, hydrochlorid, triflat, maleat, mesylat, format, acetat og fumarat.

11. Forbindelse ifølge et hvilket som helst af kravene 4, 6 og 10, hvilken forbindelse er: (90) 8-chlor-N-[4-(trifluormethoxy)phenyl]quinolin-2-amin.

12. Farmaceutisk sammensætning, som omfatter mindst én forbindelse som defineret i et hvilket som helst af kravene 3, 4, 5, 6, 7, 10 og 11.

13. Farmaceutisk sammensætning ifølge krav 12, som omfatter et farmaceutisk acceptabelt støttemateriale.

14. Forbindelse ifølge et hvilket som helst af kravene 1 til 11 til fremstilling af et lægemiddel til behandling hos et individ af en sygdom, der skyldes mindst én splejsningsanomali.

15. Forbindelse til fremstilling af et lægemiddel ifølge krav 14, der er kendetegnet ved, at sygdommen er AIDS.