

patient-derived cancer primary cells allowing to discover novel anticancer agents. Moreover, this class of compounds shows equally an additional activity against human cancer stem cells (CSCs) which are widely incriminated in the recurrence and the relapse of cancers after anti-cancer therapy. A well describe in the art ALDH assay was used as cancer stem cell functional marker to describe the activity against CSCs (Greve, B. *et al.* Cytometry A 2012 (81) 284-293, Liu, S. *et al.* PLoS One 2013 (25) e81050, Ran, D. *et al.* Exp. Hematol. 2009 (37) 1423-1434, Cheung, A. M. *et al.* Leukemia 2007 (21) 1423-1430, Pearce, D. J. *et al.* Stem Cells 2005 (23) 752-760).

Therefore, it is an object of the present invention to provide active agents for preventing or inhibiting cell proliferation in a variety of organisms, and to provide methods for their synthesis.

It is another object of the present invention to provide a pharmaceutical composition comprising a therapeutically effective amount of active agents of the invention, alone nor in combination with other active agents, and a pharmaceutically acceptable adjuvant, diluent or carrier.

It is another object of the present invention to provide active agents for use in therapy.

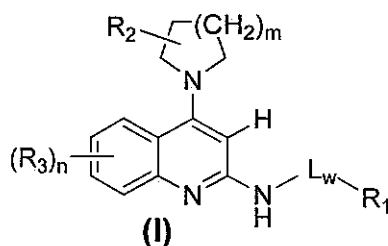
It is another object of the present invention to provide a method for the treatment and/or

prevention of a proliferative and/or neoplastic disease.

It is another object of the present invention to provide a method for inhibiting the growth or differentiation of a Cancer Stem Cell (CSC), a tumor initiating cell, a mesenchymal-like cell associated with cancer, a mesenchymal cancerous cell, or a mesenchymal cell.

▪ Summary

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



Wherein

- R_1 is chosen from a C6-C10 aryl substituted or not by R_9 ; a heteroaryl 5 to 8-membered ring comprising 1, 2, or 3 heteroatoms selected from O, N and S substituted or not by R_9 ; a fused heteroaryl as defined comprising from 8 to 13 atoms including 1, 2, 3, 4 heteroatoms selected from O, N and S and comprising at least 2 carbon atoms substituted or not by R_9 ;
- L is chosen from an optionally substituted (C1-C10) alkyl; a (C1-C10) alkyl linear or branched substituted by R_4 ; an optionally substituted (C3-C10) cycloalkyl; an optionally substituted (C5-C10) cycloalkenyl; an optionally substituted (C3-C10) alkenyl; an optionally substituted (C3-C10) alkynyl; C=O; SO; SO₂; (C=O)-NR₈; (C=O)-O; (C=O)-O-(C1-C4)alkyl; SO₂-NR₈;

NR₈; wherein R₄ is chosen from H; an optionally substituted (C1-C10) alkyl; an optionally substituted (C3-C10) alkenyl; an optionally substituted (C3-C10) alkynyl; an optionally substituted (C3-C10) cycloalkyl; an optionally substituted (C5-C10) cycloalkenyl; an optionally substituted (C8-C10) cycloalkynyl; an optionally substituted (C6-C10) aryl; an heteroaryl 5 to 8-membered ring or a fused heteroaryl as defined comprising from 8 to 13 atoms including 1, 2, 3, 4 heteroatoms selected from O, N and S and comprising at least 2 carbon atoms substituted or not with one or more substituent groups independently selected from hydrogen, halogen atom, (C1-C10) alkyl substituted with by one or more halogens atom(s), (C1-C10) alkoxy, hydroxyl, cyano, nitro, carboxy, NR₈R₈, a 4 to 9-membered ring saturated or unsaturated comprising 1, 2 or until 3 heteroatoms independently selected from O, N and S;

- R₂ is selected from NR₅R₆;
- R₃ is chosen from a hydrogen atom; a halogen atom; a (C1-C10) alkyl linear or branched substituted or not by one or more halogen atom(s), hydroxyl, alkoxy, -NR₅R₆; a (C2-C10) alkenyl; a (C2-C10) alkynyl; a (C3-C10) cycloalkyl; a (C5-C10) cycloalkenyl; a (C8-C10) cycloalkynyl; a (C1-C10) alkoxy; a hydroxyl; a nitro; a cyano; a NR₅R₆; a O-(R₇); a (CO)-R₇; a (CO)-O-R₇; a (CO)-NR₅R₆; a O-(CO)-R₇; a O-(CO)-NR₅R₆; a NR₅-(CO)-R₇; a NR₅-(CO)-OR₇; a NR₅-(CO)-NR₅R₆; a -(O-CH₂CH₂)_m-OR₁₁; a -(O-CH₂CH₂)_m-NR₁₁R₁₁; a SO₂-R₇; a NR₅-SO₂-R₇; a SO₂-NR₅R₆; a NR₅-(C2-C6)-alkyl-NR₅R₆; an optionally substituted aryl; an optionally substituted benzyl; an optionally substituted heteroaryl from 5 to 8-membered ring comprising 1, 2, or 3 heteroatoms selected from O, N and S; an optionally substituted fused heteroaryl as defined comprising from 8 to 13 atoms including 1, 2, 3, 4 heteroatoms selected from O, N and S and comprising at least 2 carbon atoms; an optionally substituted heterocyclyl from 4 to 9-membered ring saturated or unsaturated comprising 1, 2 or until 3 heteroatoms independently selected from O, N and S;
- R₅ and R₆ are independently chosen from a hydrogen; an optionally substituted (C1-C10) alkyl; an optionally substituted (C3-C10) alkenyl; an optionally substituted (C3-C10) alkynyl; an optionally substituted (C3-C10) cycloalkyl; an optionally substituted (C5-C10) cycloalkenyl; an optionally substituted (C8-C10) cycloalkynyl; a (CO)-R₇, a (CO)-O-R₇; a (CO)-NR₈R₈; a SO₂-R₇; a SO₂-NR₈R₈; a (C1-C10) alkyl substituted with NR₈R₈; a (C3-C10) cycloalkyl substituted with NR₈R₈; an optionally substituted aryl; an optionally substituted benzyl; an optionally substituted heteroaryl 5 to 8-membered ring comprising 1, 2, or 3 heteroatoms selected from O, N and S; an optionally substituted heterocyclyl from 4 to 9-membered ring saturated or unsaturated comprising 1, 2 or until 3 heteroatoms independently selected from O, N and S; or R₅ and R₆ can be linked together with the nitrogen atom to which they are covalently linked to form a heterocyclyl group forming a

4 to 9-membered ring which may contain additional 1, 2, or 3 heteroatoms selected from O, N and S;

- R_7 is chosen from a hydrogen; an optionally substituted (C1-C10) alkyl; an optionally substituted (C3-C10) alkenyl; an optionally substituted (C3-C10) alkynyl; an optionally substituted (C3-C10) cycloalkyl; an optionally substituted (C5-C10) cycloalkenyl; an optionally substituted (C8-C10) cycloalkynyl; a C1-C10 linear or branched alkyl substituted with NR_8R_8 ; an optionally substituted (C6-C10) aryl; an optionally substituted benzyl; an optionally substituted heteroaromatic 5 to 8-membered ring comprising 1, 2, or 3 heteroatoms selected from O, N and S;

- R_8 and R_8 are independently chosen from a hydrogen; an optionally substituted (C1-C10) alkyl; an optionally substituted (C3-C10) alkenyl; an optionally substituted (C3-C10) alkynyl; an optionally substituted (C3-C10) cycloalkyl; an optionally substituted (C5-C10) cycloalkenyl; an optionally substituted (C8-C10) cycloalkynyl; or R_8 and R_8 can be linked together with the nitrogen atom to which they are covalently linked to form a heterocyclyl group forming a 4 to 9-membered ring which may contain additional 1, 2, or 3 heteroatoms selected from O, N and S;

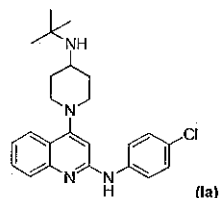
- R_9 is independently selected from a hydrogen; a halogen atom; an optionally substituted (C1-C10) alkyl; an (C1-C10) alkyl linear or branched substituted by one or more halogen atom(s), a hydroxyl, an alkoxy; an optionally substituted (C2-C10) alkenyl; an optionally substituted (C2-C10) alkynyl; an optionally substituted (C3-C10) cycloalkyl; an optionally substituted (C5-C10) cycloalkenyl; an optionally substituted (C8-C10) cycloalkynyl; an optionally substituted (C1-C10) alkoxy; a hydroxyl; a nitro; a cyano; a NR_5R_6 ; a $(CO)-R_7$; a $(CO)-O-R_7$; a $(CO)-NR_5R_6$; a $O-(CO)-R_7$; a $O-(CO)-NR_5R_6$; a $NR_5-(CO)-R_7$; a $NR_5-(CO)-OR_7$; a $NR_5-(CO)-NR_5R_6$; a SO_2-R_7 ; a $NR_5-SO_2-R_7$; a $SO_2-NR_5R_6$; a (C1-C10) alkyl substituted with NR_5R_6 ; a $NR_5-(C2-C10)-alkyl-NR_5R_6$; a $-(O-CH_2CH_2)_m-OR_{11}$; a $-(O-CH_2CH_2)_m-NR_{11}R_{11}$; an optionally substituted (C6-C10) aryl; an optionally substituted benzyl; an optionally substituted heteroaryl 5 to 8-membered ring comprising 1, 2, or 3 heteroatoms selected from O, N and S; an optionally substituted heterocyclyl group forming a 4 to 9-membered ring which may contain 1, 2, or 3 heteroatoms selected from O, N and S; a $-NR_5R_{10}$; a $-O-R_{10}$;

- R_{10} is independently chosen from a hydrogen; a (C6-C12)-aryl substituted or not by R_{12} ; a benzyl substituted or not by R_{12} ; a heteroaryl from 5 to 8-membered ring comprising 1, 2, or 3 heteroatoms selected from O, N and S substituted or not by R_{12} ; a fused heteroaryl defined as comprising from 8 to 13 atoms including 1, 2, 3, 4 heteroatoms selected from O, N and S and comprising at least 2 carbon atom substituted or not by R_{12} ; a heterocyclyl forming a 4 to 9-

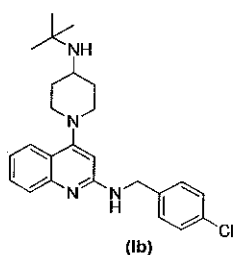
and any pharmaceutically acceptable salt, solvate, isomers, stereoisomers or mixtures of stereoisomers or solvate thereof.

In some specific embodiments, the disclosure provides a compound chosen from:

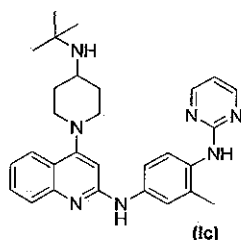
2-(4-chlorophenylamino)-4-(4-*tert*-butylaminopiperidin-1-yl)-quinoline of formula (Ia) (1-5)



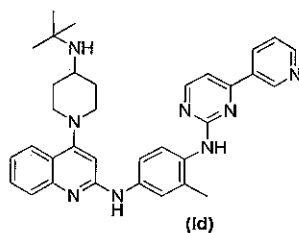
2-(4-chlorobenzylamino)-4-(4-*tert*-butylaminopiperidin-1-yl)-quinoline of formula (Ib) (2-2)



2-[3-methyl-4-(pyrimidin-2-ylamino)phenylamino]-4-(4-*tert*-butylaminopiperidin-1-yl)-quinoline (3-4) of formula (Ic)



2-{4-[4-(pyridin-3-yl)-2-pyrimidinamino]-3-methyl-phenylamino}-4-(4-*tert*-butylaminopiperidin-1-yl)-quinoline (4-2) of formula (Id)



or a pharmaceutically acceptable salt, solvate or prodrug thereof.

In some other specific embodiments, the disclosure provides a compound chosen from 2-(4-chlorophenylamino)-4-(4-*tert*-butylaminopiperidin-1-yl)-quinoline hydrochloride salt (1-6), 2-(4-chlorobenzylamino)-4-(4-*tert*-butylaminopiperidin-1-yl)-quinoline hydrochloride salt (2-3), 2-[3-methyl-4-(pyrimidin-2-ylamino)phenylamino]-4-(4-*tert*-butylaminopiperidin-1-yl)-quinoline hydrochloride salt (3-5), 2-{4-[4-(pyridin-3-yl)-2-pyrimidinamino]-3-methyl-phenylamino}-4-(4-*tert*-butylaminopiperidin-1-yl)-quinoline hydrochloride salt (4-3).

In another aspect, the disclosure provides a pharmaceutical composition comprising a therapeutically effective amount of a compound according to the above, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable adjuvant, diluent or carrier.

5 In some particular embodiments, the pharmaceutical composition of the disclosure can further comprise one or more anti-neoplastic agents.

In some particular embodiments, the pharmaceutical composition according to the above can comprise a therapeutically effective amount of the compound of the disclosure which can be formulated or co-formulated in nanoparticles.

10 In some specific embodiments of the pharmaceutical composition of the disclosure, the nanoparticles can comprise a lysosomal biodegradable composition.

In some specific embodiments of the pharmaceutical composition of the disclosure, the nanoparticles can comprise a biocompatible polymer or copolymer.

In some specific embodiments of the pharmaceutical composition of the disclosure, the nanoparticles can be associated covalently or non-covalently with a polyethylene glycol (PEG).

15 In some specific embodiments of the pharmaceutical composition of the disclosure, the nanoparticles can have an average size of from about 80 to about 600 nm.

In some specific embodiments of the pharmaceutical composition of the disclosure, the nanoparticle can be a targeted nanoparticle containing a signaling motif.

20 In some specific embodiments, the nanoparticles can comprise a polymeric biodegradable composition.

In some particular specific embodiments, the polymer can be based on Poly (DL-Lactic-co-glycolic acid) that can have a molecular weight from 7 to 240 kDa; or a copolymer of polylactic acid (PLA) and polyglycolic acid (PGA) where the molecular ratio can be between 95:5 and 50:50.

25 In some specific embodiments of the pharmaceutical composition of the disclosure, the nanoparticles can comprise an item chosen from PLGA nanoparticles, PLGA-PEG nanoparticles (block type AB, BA, ABA or BAB, where A = PLGA and B = PEG) and targeted nanoparticles.

In some specific embodiments of the pharmaceutical composition of the disclosure, the nanoparticles can comprise an item chosen from liposomes.

30 In some embodiments, the pharmaceutical composition of the disclosure can be suitable for slow- or sustained-release.

In some specific embodiments, the pharmaceutical composition of the disclosure can be suitable for oral-, parenteral-, ocular-, transdermal-, nasal-administration, or for inhalation.

In some specific embodiments of the pharmaceutical composition of the disclosure, the active compound of the disclosure can be associated with at least one therapeutically active anti-cancer agent.

In another aspect, there is provided a pharmaceutical composition comprising a combination of a therapeutically effective amount of a compound as defined herein and a therapeutically effective amount of one or more anti-neoplastic agents for use in cancer therapy.

In specific embodiments of the pharmaceutical composition of the disclosure, the anti-neoplastic agent can be chosen from the group consisting of everolimus, chloroquine, hydroxychloroquine, trabectedin, abraxane, TLK 286, AV-299, DN-101, pazopanib, GSK690693, RTA 744, ON 0910.Na, AZD 6244 (ARRY-142886), AMN-107, TKI-258, GSK461364, AZD 1152, enzastaurin, vandetanib, ARQ-197, MK-0457, MLN8054, PHA-739358, R-763, AT-9263, pemetrexed, erlotinib, dasatinib, nilotinib, decatanib, panitumumab, amrubicin, oregovomab, Lep-etu, nolatrexed, azd2171, batabulin, ofatumumab, zanolimumab, edotecarin, tetrandrine, rubitecan, tesmilifene, oblimersen, ticilimumab, ipilimumab, gossypol, Bio 111, 131-I-TM-601, ALT-110, BIO 140, CC 8490, cilengitide, gimatecan, IL13-PE38QQR, TNO 1001, IPdR1 KRX-0402, lucanthone, LY 317615, neuradiab, vitespan, Rta 744, Sdx 102, talampanel, atrasentan, Xr 311, romidepsin, ADS-100380, sunitinib, 5-fluorouracil, vorinostat, etoposide, gemcitabine, doxorubicin, irinotecan, liposomal doxorubicin, 5'-deoxy-5-fluorouridine, vincristine, temozolomide, ZK-304709, seliciclib, PD0325901, AZD-6244, capecitabine, L-Glutamic acid, N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-disodium salt heptahydrate, camptothecin, PEG-labeled irinotecan, tamoxifen, toremifene citrate, anastrozole, exemestane, letrozole, DES(diethylstilbestrol), estradiol, estrogen, conjugated estrogen, bevacizumab, IMC-1C11, CHIR-258, 3-[5-(methylsulfonylpiperadinemethyl)-indolyl]-quinolone, vatalanib, AG-013736, AVE-0005, the acetate salt of [D-Ser(But)₆, Azgly₁₀](pyro-Glu-His-Trp-Ser-Tyr-D-Ser(But)-Leu-Arg-Pro-Azgly-NH₂ acetate, goserelin acetate, leuprolide acetate, triptorelin pamoate, medroxyprogesterone acetate, hydroxyprogesterone caproate, megestrol acetate, raloxifene, bicalutamide, flutamide, nilutamide, megestrol acetate, CP-724714; TAK-165, HKI-272, erlotinib, lapatanib, canertinib, ABX-EGF antibody, erbitux, EKB-569, PKI-166, GW-572016, lonafamib, BMS-214662, tipifarnib; amifostine, NVP-LAQ824, suberoyl analog hydroxamic acid, valproic acid, trichostatin A, FK-228, SU11248, sorafenib, KRN951, aminoglutethimide, arnsacrine, anagrelide, L-asparaginase, Bacillus Calmette-Guerin (BCG) vaccine, bleomycin, buserelin, busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, clodronate, cyproterone, cytarabine, dacarbazine,

AKT inhibitor, a JAK/STAT inhibitor, a checkpoint-1 or 2 inhibitor, a focal adhesion kinase inhibitor, a Map kinase kinase (MEK) inhibitor, a VEGF trap antibody, and mixtures thereof.

In another aspect, there is provided a compound as defined herein for use in therapy.

The disclosure provides a method for the treatment and/or prevention of a proliferative and/or neoplastic disease, that can comprise the step of administering a therapeutically active amount of
5 a compound of the disclosure, or a pharmaceutical composition comprising the same, to a human being or animal in need thereof.

The disclosure provides a method for inhibiting the growth or differentiation of a Cancer Stem Cell (CSC), a tumor initiating cell, a mesenchymal-like cell associated with cancer, a mesenchymal
10 cancerous cell, or a mesenchymal cell that can comprise the step of administering a therapeutically active amount of a compound of the disclosure, or a pharmaceutical composition comprising the same, to a human being or an animal in need thereof.

The disclosure provides a compound for the treatment and/or prevention of a proliferative and/or neoplastic disease.

15 In another aspect, there is provided a compound as defined herein, for use as a therapeutically active substance for the treatment and/or prevention of a proliferative and/or neoplastic disease.

In another aspect, there is provided use of a compound as defined herein, or a pharmaceutical composition as defined above in the manufacture of a medicament for the treatment and/or prevention of a proliferative and/or neoplastic disease.

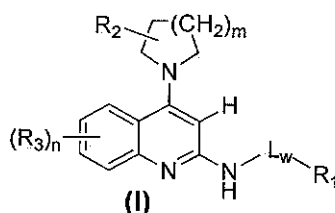
20 In another aspect, there is provided a pharmaceutical composition as defined herein for use in the treatment and/or prevention of a proliferative and/or neoplastic disease.

The disclosure provides a compound for inhibiting the growth or differentiation of a Cancer Stem Cell (CSC), a tumor initiating cell, a mesenchymal-like cell associated with cancer, a mesenchymal cancerous cell, or a mesenchymal cell.

25 In another aspect, there is provided a compound as defined herein, or a pharmaceutical composition as defined above for use in inhibiting the growth or differentiation of a Cancer Stem Cell (CSC), a tumor initiating cell, a mesenchymal-like cell associated with cancer, a mesenchymal cancerous cell, or a mesenchymal cell.

CLAIMS:

1. A compound of formula (I)



Wherein

- 5 • R_1 is chosen from a C6-C10 aryl substituted or not by R_9 ; a heteroaryl 5 to 8-membered ring comprising 1, 2, or 3 heteroatoms selected from O, N and S substituted or not by R_9 ; a fused heteroaryl as defined comprising from 8 to 13 atoms including 1, 2, 3, 4 heteroatoms selected from O, N and S and comprising at least 2 carbon atoms substituted or not by R_9 ;
- 10 • L is chosen from an optionally substituted (C1-C10) alkyl; a (C1-C10) alkyl linear or branched substituted by R_4 ; an optionally substituted (C3-C10) cycloalkyl; an optionally substituted (C5-C10) cycloalkenyl; an optionally substituted (C3-C10) alkenyl; an optionally substituted (C3-C10) alkynyl; C=O; SO; SO₂; (C=O)-NR₈; (C=O)-O; (C=O)-O-(C1-C4)alkyl; SO₂-NR₈; NR₈; wherein R_4 is chosen from H; an optionally substituted (C1-C10) alkyl; an optionally substituted (C3-C10) alkenyl; an optionally substituted (C3-C10) alkynyl; an optionally substituted (C3-C10) cycloalkyl;
- 15 an optionally substituted (C5-C10) cycloalkenyl; an optionally substituted (C8-C10) cycloalkynyl; an optionally substituted (C6-C10) aryl; a heteroaryl 5 to 8-membered ring or a fused heteroaryl as defined comprising from 8 to 13 atoms including 1, 2, 3, 4 heteroatoms selected from O, N and S and comprising at least 2 carbon atoms substituted or not with one or more substituent groups independently selected from hydrogen, halogen atom, (C1-C10) alkyl substituted with by one or
- 20 more halogens atom(s), (C1-C10) alkoxy, hydroxyl, cyano, nitro, carboxy, NR₈R₈, a 4 to 9-membered ring saturated or unsaturated comprising 1, 2 or until 3 heteroatoms independently selected from O, N and S;
- R_2 is selected from NR₅R₆;
- R_3 is chosen from a hydrogen atom; a halogen atom; a (C1-C10) alkyl linear or branched
- 25 substituted or not by one or more halogen atom(s), hydroxyl, alkoxy, -NR₅R₆; a (C2-C10) alkenyl; a (C2-C10) alkynyl; a (C3-C10) cycloalkyl; a (C5-C10) cycloalkenyl; a (C8-C10) cycloalkynyl; a (C1-C10) alkoxy; a hydroxyl; a nitro; a cyano; a NR₅R₆; a O-(R₇); a (CO)-R₇; a (CO)-O-R₇; a (CO)-NR₅R₆; a O-(CO)-R₇; a O-(CO)-NR₅R₆; a NR₅-(CO)-R₇; a NR₅-(CO)-OR₇; a NR₅-(CO)-NR₅R₆; a -(O-CH₂CH₂)_m-OR₁₁; a -(O-CH₂CH₂)_m-NR₁₁R₁₁; a SO₂-R₇; a NR₅-SO₂-R₇; a SO₂-NR₅R₆; a NR₅-(C2-C6)-alkyl-NR₅R₆; an
- 30 optionally substituted aryl; an optionally substituted benzyl; an optionally substituted heteroaryl from 5 to 8-membered ring comprising 1, 2, or 3 heteroatoms selected from O, N and S; an

optionally substituted fused heteroaryl as defined comprising from 8 to 13 atoms including 1, 2, 3, 4 heteroatoms selected from O, N and S and comprising at least 2 carbon atoms; an optionally substituted heterocyclyl from 4 to 9-membered ring saturated or unsaturated comprising 1, 2 or until 3 heteroatoms independently selected from O, N and S;

- 5 • R₅ and R₆ are independently chosen from a hydrogen; an optionally substituted (C1-C10) alkyl; an optionally substituted (C3-C10) alkenyl; an optionally substituted (C3-C10) alkynyl; an optionally substituted (C3-C10) cycloalkyl; an optionally substituted (C5-C10) cycloalkenyl; an optionally substituted (C8-C10) cycloalkynyl; a (CO)-R₇; a (CO)-O-R₇; a (CO)-NR₈R_{8'}; a SO₂-R₇; a SO₂-NR₈R_{8'}; a (C1-C10) alkyl substituted with NR₈R_{8'}; a (C3-C10) cycloalkyl substituted with NR₈R_{8'}; an
10 optionally substituted aryl; an optionally substituted benzyl; an optionally substituted heteroaryl 5 to 8-membered ring comprising 1, 2, or 3 heteroatoms selected from O, N and S; an optionally substituted heterocyclyl from 4 to 9-membered ring saturated or unsaturated comprising 1, 2 or until 3 heteroatoms independently selected from O, N and S; or R₅ and R₆ is linked together with the nitrogen atom to which they are covalently linked to form a heterocyclyl group forming a 4 to
15 9-membered ring which may contain additional 1, 2, or 3 heteroatoms selected from O, N and S;
 • R₇ is chosen from a hydrogen; an optionally substituted (C1-C10) alkyl; an optionally substituted (C3-C10) alkenyl; an optionally substituted (C3-C10) alkynyl; an optionally substituted (C3-C10) cycloalkyl; an optionally substituted (C5-C10) cycloalkenyl; an optionally substituted (C8-C10) cycloalkynyl; a C1-C10 linear or branched alkyl substituted with NR₈R_{8'}; an optionally
20 substituted (C6-C10) aryl, an optionally substituted benzyl, an optionally substituted heteroaromatic 5 to 8-membered ring comprising 1, 2, or 3 heteroatoms selected from O, N and S;
 • R₈ and R_{8'} are independently chosen from a hydrogen; an optionally substituted (C1-C10) alkyl; an optionally substituted (C3-C10) alkenyl; an optionally substituted (C3-C10) alkynyl; an
25 optionally substituted (C3-C10) cycloalkyl; an optionally substituted (C5-C10) cycloalkenyl; an optionally substituted (C8-C10) cycloalkynyl; or R₈ and R_{8'} is linked together with the nitrogen atom to which they are covalently linked to form a heterocyclyl group forming a 4 to 9-membered ring which may contain additional 1, 2, or 3 heteroatoms selected from O, N and S;
 • R₉ is independently selected from a hydrogen; a halogen atom; an optionally substituted
30 (C1-C10) alkyl; an (C1-C10) alkyl linear or branched substituted by one or more halogen atom(s), a hydroxyl, an alkoxy; an optionally substituted (C2-C10) alkenyl; an optionally substituted (C2-C10) alkynyl; an optionally substituted (C3-C10) cycloalkyl; an optionally substituted (C5-C10) cycloalkenyl; an optionally substituted (C8-C10) cycloalkynyl; an optionally substituted (C1-C10) alkoxy; a hydroxyl; a nitro; a cyano; a NR₅R₆; a (CO)-R₇; a (CO)-O-R₇; a (CO)-NR₅R₆; a O-(CO)-R₇; a O-

- n can represent an equal integer which can have any one of the values 0, 1, 2, 3 or 4;
- m can represent an equal integer which can have any one of the values 1, 2 or 3;
- w can represent an equal integer which can have any one of the values 0 or 1;

Wherein the term "optionally substituted" means optionally substituted with one or more

5 substituents independently chosen from an halogen atom, a (C1-C10) alkyl linear or branched substituted or not by one or more halogen atom(s), a (C2-C10) alkenyl linear or branched substituted or not by one or more halogen atom(s), a (C2-C10) alkynyl linear or branched substituted or not by one or more halogen atom(s), a (C3-C10) cycloalkyl substituted or not by one or more halogen atom(s), a (C5-C10) cycloalkenyl substituted or not by one or more halogen atom(s), a (C8-C10) cycloalkynyl substituted or not by one or more halogen atom(s), a (C1-C10) alkoxy, a hydroxyl, a cyano, a nitro, a NR_8R_8 (with R_8 and R_8 as described above);

and any pharmaceutically acceptable salt, solvate, isomers, stereoisomers or mixtures of stereoisomers or solvate thereof.

2. A compound according to the claim 1 chosen from 2-(4-chlorophenylamino)-4-(4-*tert*-butylaminopiperidin-1-yl)-quinoline (**1-5**); 2-(4-chlorobenzylamino)-4-(4-*tert*-butylaminopiperidin-1-yl)-quinoline (**2-2**); 2-[3-methyl-4-(pyrimidin-2-ylamino)phenylamino]-4-(4-*tert*-butylaminopiperidin-1-yl)-quinoline (**3-4**); 2-{4-[4-(pyridin-3-yl)-2-pyrimidinamino]-3-methyl-phenylamino}-4-(4-*tert*-butylaminopiperidin-1-yl)-quinoline (**4-2**) or a pharmaceutically acceptable salt or solvate thereof.

3. A compound according to the claim 1 chosen from 2-(4-chlorophenylamino)-4-(4-*tert*-butylaminopiperidin-1-yl)-quinoline hydrochloride salt (**1-6**); 2-(4-chlorobenzylamino)-4-(4-*tert*-butylaminopiperidin-1-yl)-quinoline hydrochloride salt (**2-3**); 2-[3-methyl-4-(pyrimidin-2-ylamino)phenylamino]-4-(4-*tert*-butylaminopiperidin-1-yl)-quinoline hydrochloride salt (**3-5**); 2-{4-[4-(pyridin-3-yl)-2-pyrimidinamino]-3-methyl-phenylamino}-4-(4-*tert*-butylaminopiperidin-1-yl)-quinoline hydrochloride salt (**4-3**) or a pharmaceutically acceptable solvate thereof.

4. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable adjuvant, diluent or carrier.

5. A pharmaceutical composition according to claim 4 further comprising in combination one or more anti-neoplastic agents.

6. A pharmaceutical composition according to any one of claims 4 and 5, wherein the therapeutically effective amount of the compound of any one of claims 1 to 5 is formulated or co-formulated in nanoparticles.

7. The pharmaceutical composition according to claim 6, wherein the nanoparticles comprise a polymeric biodegradable composition.
8. The pharmaceutical composition according to claim 7, wherein the polymer is based on Poly (DL-Lactic-co-glycolic acid) having molecular weight from 7 to 240 kDa; or a copolymer of
5 polylactic acid (PLA) and polyglycolic acid (PGA) where the molecular ratio is between 95:5 and 50:50.
9. The pharmaceutical composition according to claim 6, wherein the nanoparticles comprise a lysosomal biodegradable composition.
10. The pharmaceutical composition according to claim 6, wherein the nanoparticles comprise
10 a biocompatible polymer or copolymer.
11. The pharmaceutical composition according to claim 6, wherein the nanoparticles comprise a liposomal formulation.
12. The pharmaceutical composition according to any one of claims 6 to 11, wherein the nanoparticles are associated covalently or non-covalently with a polyethylene glycol (PEG).
13. The pharmaceutical composition according to any one of claims 6 to 12, wherein the
15 nanoparticles have an average size of from about 80 to about 600 nm.
14. The pharmaceutical composition according to any one of claims 6 to 13, wherein the compound of any one of claims 1 to 3 is associated with at least one therapeutically active anti-cancer agent.
15. The pharmaceutical composition according to any one of claims 4 to 14 which is suitable for
20 oral-, parenteral-, ocular-, transdermal-, nasal-administration or for inhalation.
16. A pharmaceutical composition according to claim 6, wherein the nanoparticles comprise an item chosen from poly(DL-Lactic-co-glycolic acid) (PLGA) nanoparticles, poly(DL-Lactic-co-glycolic acid)-polyethylene glycol (PLGA-PEG) nanoparticles and targeted nanoparticles.
17. The pharmaceutical composition according to claim 16, wherein the PLGA-PEG
25 nanoparticles are in the form of block type AB, BA, ABA or BAB, where A = PLGA and B = PEG.
18. A pharmaceutical composition according to claim 16 or 17, wherein the nanoparticle is a targeted nanoparticle containing a signaling motif.

19. A pharmaceutical composition comprising a combination of a therapeutically effective amount of a compound according to any one of claims 1 to 3 and a therapeutically effective amount of one or more anti-neoplastic agents for use in cancer therapy.

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20. The pharmaceutical composition of claim 19, wherein the components constituting the combination are to be used simultaneously, separately or sequentially.

21. The pharmaceutical composition of claims 5, 19 or 20, wherein the anti-neoplastic agent is
10 chosen from the group consisting of everolimus, chloroquine, hydroxychloroquine, trabectedin, abraxane, TLK 286, AV-299, DN-101, pazopanib, GSK690693, RTA 744, ON 0910.Na, AZD 6244

(ARRY-142886), AMN-107, TKI-258, GSK461364, AZD 1152, enzastaurin, vandetanib, ARQ-197, MK-0457, MLN8054, PHA-739358, R-763, AT-9263, pemetrexed, erlotinib, dasatanib, nilotinib, decatanib, panitumumab, amrubicin, oregovomab, Lep-etu, nolatrexed, azd2171, batabulin, ofatumumab, zanolimumab, edotecarin, tetrandrine, rubitecan, tesmilifene, oblimersen, ticilimumab, ipilimumab, gossypol, Bio 111, 131-I-TM-601, ALT-110, BIO 140, CC 8490, cilengitide, gimatecan. IL13-PE38QQR, TNO 1001, IPdR1 KRX-0402, lucanthone, LY 317615, neuradiab, vitespan, Sdx 102, talampanel, atrasentan, Xr 311, romidepsin, ADS-100380, sunitinib, 5-fluorouracil, vorinostat, etoposide, gemcitabine, doxorubicin, irinotecan, liposomal doxorubicin, 5'-deoxy-5-fluorouridine, vincristine, temozolomide, ZK-304709, seliciclib, PD0325901, AZD-6244, capecitabine, L-Glutamic acid, N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-disodium salt heptahydrate, camptothecin, PEG-labeled irinotecan, tamoxifen, toremifene citrate, anastrozole, exemestane, letrozole, DES(diethylstilbestrol), estradiol, estrogen, conjugated estrogen, bevacizumab, IMC-1C11, CHIR-258, 3-[5-(methylsulfonylpiperadinemethyl)-indolyl]-quinolone, vatalanib, AG-013736, AVE-0005, the acetate salt of [D-Ser(But)₆, Azgly₁₀](pyro-Glu-His-Trp-Ser-Tyr-D-Ser(But)-Leu-Arg-Pro-Azgly-NH₂ acetate, goserelin acetate, leuprolide acetate, triptorelin pamoate, medroxyprogesterone acetate, hydroxyprogesterone caproate, megestrol acetate, raloxifene, bicalutamide, flutamide, nilutamide, CP-724714, TAK-165, HKI-272, lapatanib, canertinib, ABX-EGF antibody, erbitux, EKB-569, PKI-166, GW-572016, lonafamib, BMS-214662, tipifarnib; amifostine, NVP-LAQ824, suberoyl analide hydroxamic acid, valproic acid, trichostatin A, FK-228, SU11248, sorafenib, KRN951, aminoglutethimide, arnsacrine, anagrelide, L-asparaginase, Bacillus Calmette-Guerin (BCG) vaccine, bleomycin, buserelin, busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, clodronate, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, diethylstilbestrol, epirubicin, fludarabine, fludrocortisone, fluoxymesterone, gleeevec, hydroxyurea, idarubicin, ifosfamide, imatinib, leuprolide, levamisole, lomustine, mechlorethamine, melphalan, 6-mercaptopurine, mesna, methotrexate, mitomycin, mitotane, mitoxantrone, octreotide, oxaliplatin, pamidronate, pentostatin, plicamycin, porfimer, procarbazine, raltitrexed, rituximab, streptozocin, teniposide, testosterone, thalidomide, thioguanine, thiotepa, tretinoin, vindesine, 13-cis-retinoic acid, phenylalanine mustard, uracil mustard, estramustine, altretamine, floxuridine, 5-deoxyuridine, cytosine arabinoside, deoxycoformycin, calcitriol, valrubicin, mithramycin, vinblastine, vinorelbine, topotecan, razoxin, marimastat, COL-3, neovastat, BMS-275291, squalamine, endostatin, SU5416, SU6668, EMD121974, interleukin-12, 1M862, angiostatin, vitaxin, spironolactone, finasteride, cimitidine, trastuzumab, denileukin diftitox,

gefitinib, bortezomib, paclitaxel, irinotecan, docetaxel, bevacizumab (monoclonal antibody) and erbitux, cremophor-free paclitaxel, epithilone B, BMS-247550, BMS-310705, droloxifene, 4-hydroxytamoxifen, pibendoxifene, ERA-923, arzoxifene, fulvestrant, acolbifene, lasofoxifene, idoxifene, TSE-424, HMR-3339, ZK186619, PTK787/ZK 222584, VX-745, PD 184352, rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, temsirolimus, AP-23573, RAD001, ABT-578, BC-210, LY294002, LY292223, LY292696, LY293684, LY293646, wortmannin, ZM336372, L-779,450, PEG-filgrastim, darbepoetin, erythropoietin, granulocyte colony-stimulating factor, zoledronate, prednisone, cetuximab, granulocyte macrophage colony-stimulating factor, histrelin, pegylated interferon alfa-2a, interferon alfa-2a, pegylated interferon alfa-2b, interferon alfa-2b, azacitidine, PEG-L-asparaginase, lenalidomide, gemtuzumab, hydrocortisone, interleukin-11, dexrazoxane, alemtuzumab, all-transretinoic acid, ketoconazole, interleukin-2, megestrol, nitrogen mustard, methylprednisolone, ibritumomab tiuxetan, androgens, decitabine, hexamethylmelamine, bexarotene, tositumomab, arsenic trioxide, cortisone, editronate, cyclosporine, liposomal daunorubicin, Edwina-asparaginase, strontium 89, casopitant, netupitant, an NK-1 receptor antagonists, palonosetron, aprepitant, diphenhydramine, hydroxyzine, metoclopramide, lorazepam, alprazolam, haloperidol, droperidol, dronabinol, dexamethasone, prochlorperazine, granisetron, ondansetron, dolasetron, tropisetron, pegfilgrastim, epoetin alfa and darbepoetin alfa, ipilimumab, vemurafenib, FLT-3 inhibitor, a VEGFR inhibitor, an aurora kinase inhibitor, a PIK-1 modulator, a Bcl-2 inhibitor, an HDAC inhibitor, a c-MET inhibitor, a PARP inhibitor, a Cdk inhibitor, an EGFR TK inhibitor, an IGFR-TK inhibitor, an anti-HGF antibody, a PI3 kinase inhibitors, a mTOR inhibitor, an AKT inhibitor, a JAK/STAT inhibitor, a checkpoint-1 or 2 inhibitor, a focal adhesion kinase inhibitor, a Map kinase kinase (MEK) inhibitor, a VEGF trap antibody, and mixtures thereof.

22. The pharmaceutical composition according to any one of claims 4 to 18 and 21, which is suitable for slow- or sustained-release.

23. A compound according to any one of claims 1 to 3, for use in therapy.

24. A compound according to any one of claims 1 to 3, for use as a therapeutically active substance for the treatment and/or prevention of a proliferative and/or neoplastic disease.

25. A compound for use according to claim 22, wherein the proliferative and/or neoplastic disease is chosen from the group consisting of: carcinoma; head, kidney, liver, lung, nasopharyngeal, neck, ovary, breast, cervix, pancreas, prostate, or stomach; a leukemia (e.g. acute myelogenous leukemia, acute lymphocytic leukemia, acute promyelocytic leukemia (APL), acute T-cell lymphoblastic leukemia, adult T-cell leukemia, basophilic leukemia, eosinophilic

leukemia, granulocytic leukemia, hairy cell leukemia, leukopenic leukemia, lymphatic leukemia, lymphoblastic leukemia, lymphocytic leukemia, megakaryocytic leukemia, micromyeloblastic leukemia, monocytic leukemia, neutrophilic leukemia and stem cell leukemia); a malignant lymphoma, a malignant melanoma; myeloproliferative diseases; a sarcoma; a tumor of the central nervous system; a germ-line tumor; testicular cancer; thyroid cancer; astrocytoma; esophageal cancer; colon cancer, and a mixed type of neoplasia.

26. Use of a compound according to any one of claims 1 to 3, or a pharmaceutical composition according to any one of claims 4 to 18, 21 and 22 in the manufacture of a medicament for the treatment and/or prevention of a proliferative and/or neoplastic disease.

27. The use according to claim 26, wherein the proliferative and/or neoplastic disease is chosen from the group consisting of: carcinoma; head, kidney, liver, lung, nasopharyngeal, neck, ovary, breast, cervix, pancreas, prostate, or stomach; a leukemia (e.g. acute myelogenous leukemia, acute lymphocytic leukemia, acute promyelocytic leukemia (APL), acute T-cell lymphoblastic leukemia, adult T-cell leukemia, basophilic leukemia, eosinophilic leukemia, granulocytic leukemia, hairy cell leukemia, leukopenic leukemia, lymphatic leukemia, lymphoblastic leukemia, lymphocytic leukemia, megakaryocytic leukemia, micromyeloblastic leukemia, monocytic leukemia, neutrophilic leukemia and stem cell leukemia); a malignant lymphoma, a malignant melanoma; myeloproliferative diseases; a sarcoma; a tumor of the central nervous system; a germ-line tumor; testicular cancer; thyroid cancer; astrocytoma; esophageal cancer; colon cancer, and a mixed type of neoplasia.

28. A pharmaceutical composition according to any one of claims 4 to 18, 21 and 22 for use in the treatment and/or prevention of a proliferative and/or neoplastic disease.

29. A compound according to any one of claims 1 to 3, or a pharmaceutical composition according to any one of claims 4 to 18, 21 and 22 for use in inhibiting the growth or differentiation of a Cancer Stem Cell (CSC), a tumor initiating cell, a mesenchymal-like cell associated with cancer, a mesenchymal cancerous cell, or a mesenchymal cell.