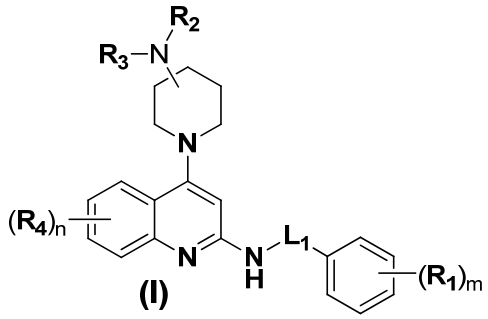
CLAIMS

1. A combination comprising

- a compound of formula (I)



(I)

wherein

- L_1 is chosen from a single bond; an optionally substituted $(CH_2)_p$ group; an optionally substituted alkylene; a carbonyl.
- R_1 , either alone or simultaneously or independently when m > 1 is selected from a hydrogen atom; a halogen atom ; an optionally substituted alkyl; a haloalkyl; a fluoroalkyl; an optionally substituted alkenyl; an optionally substituted alkynyl; an optionally substituted cycloalkyl; an optionally substituted cycloalkenyl; an optionally substituted cycloalkynyl; an optionally substituted alkoxy; -O-R_7; -O-(CO)-R_7; -O-(CO)-NR_5R_6; -NR_5-(CO)-R_7; -O-(CO)-O-R_7; -NR_5-(CO)-O-R_7; an azido; a hydroxyl; a cyano; a nitro; -NR_5R_6;
- R_2 and R_3 , simultaneously or independently, are selected from a hydrogen atom; an optionally substituted alkyl; an optionally substituted alkenyl; an optionally substituted alkynyl; an optionally substituted cycloalkyl; an optionally substituted cycloalkenyl; an optionally substituted cycloalkynyl; an optionally substituted heterocyclyl group; an optionally substituted aryl; an optionally substituted benzyl; an optionally substituted heteroaryl;

or R_2 and R_3 can be linked together with the nitrogen atom to which they are covalently linked to form an optionally substituted heterocyclyl group;

- R_4 , either alone or simultaneously or independently when n > 1, is selected from a hydrogen atom; a halogen atom; an optionally substituted alkyl; a haloalkyl; a fluoroalkyl; an optionally substituted alkenyl; an optionally substituted alkynyl; an optionally substituted cycloalkyl; an optionally substituted cycloalkenyl; an optionally substituted cycloalkynyl; an optionally substituted alkoxy; -O-R_7; -O-(CO)-R_7; -O-(CO)-NR_5R_6; -NR_5-(CO)-R_7; -O-(CO)-O-R_7; -NR_5-(CO)-O-R_7; an azido; a hydroxyl; a cyano; a nitro; -NR_5R_6.
- R_5 and R_6 , simultaneously or independently, are slected from a hydrogen atom; an optionally substituted alkyl; an optionally substituted alkenyl; an optionally substituted alkynyl; an optionally substituted cycloalkyl; an optionally substituted cycloalkenyl; an optionally

substituted cycloalkynyl; an optionally substituted heterocyclyl group; an optionally substituted aryl; an optionally substituted heteroaryl ;

or R_5 and R_6 can be linked together with the nitrogen atom to which they are covalently linked to form an optionally substituted heterocyclyl group ;

- R_7 can be selected from an optionally substituted alkyl; a haloalkyl; a fluoroalkyl; an optionally substituted alkenyl; an optionally substituted alkynyl; an optionally substituted cycloalkyl; an optionally substituted cycloalkenyl; an optionally substituted cycloalkynyl; an optionally substituted heterocyclyl group; an optionally substituted aryl; an optionally substituted heteroaryl;
- n is an integer which can have any one of the values 0, 1, 2, 3 or 4;
- m is an integer which can have any one of the values 0, 1, 2, 3, 4 or 5;
- p is an integer which can have any one of the values 0 or 1;

and pharmaceutically acceptable salts, hydrates, solvate, polymorphs, tautomers, isotopic variants, stereoisomers or mixtures of stereoisomers thereof, and

- a Mitogen-Activated Protein Kinase Kinase inhibitor (MEK inhibitor), and pharmaceutically acceptable salts or solvates thereof.

2. The combination according to claim 1, comprising a compound of formula (I) wherein R_1, either alone or simultaneously or independently when m>1, is chosen from a hydrogen atom, a halogen atom, an optionally substituted alkyl, a haloalkyl; a fluoroalkyl; an optionally substituted alkoxy; a hydroxyl.

3. The combination according to claim 1 or 2, comprising a compound of formula (I) wherein R_1, either alone or simultaneously or independently when m>1, is chosen from a hydrogen atom and a chlorine.

4. The combination according to any one of claims 1 to 3, comprising a compound of formula (I) wherein R_2 and R_3 , simultaneously or independently, are selected from a hydrogen atom; an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted heterocyclyl.

5. The combination according to any one of claims 1 to 4, comprising a compound of formula (I) wherein R_2 and R_3 , simultaneously or independently, are selected from a hydrogen atom; a methyl, an ethyl, a n-propyl, an *iso*-propyl, a n-butyl, an *iso*-butyl, a *sec*-butyl and a *tert*-butyl.

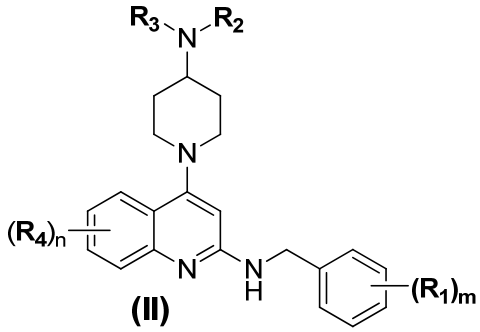
6. The combination according to any one of claims 1 to 4, comprising a compound of formula (I) wherein R_2 and R_3 simultaneously or independently, are selected from hydrogen and a *tert*-butyl .

7. The combination according to any one of claims 1 to 6, comprising a compound of formula (I) wherein R_4, either alone or simultaneously or independently when n > 1, is chosen

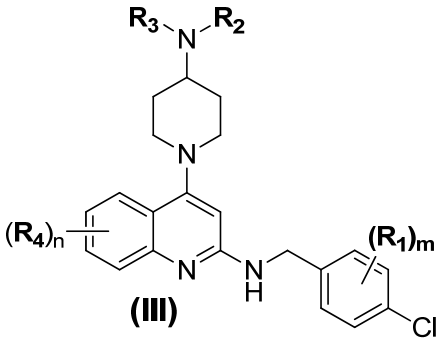
from a hydrogen atom, a halogen atom, an alkyl, a haloalkyl; a fluoroalkyl; an alkoxy, a hydroxyl.

8. The combination according to any one of claims 1 to 7, comprising a compound of formula (I) wherein $\mathbf{R_4}$, either alone or simultaneously or independently when n > 1, is chosen from a hydrogen atom, a hydroxyl, a methoxy.

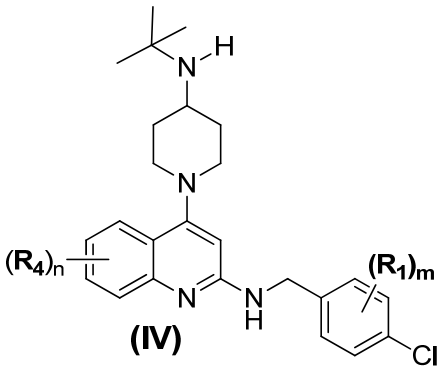
9. The combination according to any one of claims 1 to 8, in which the compound of formula (I) is chosen from compounds of formula (II), (III), and (IV) below:



(II)



(III)



(IV)

wherein

- **R_1** , either alone or simultaneously or independently when m > 1 is selected from a hydrogen atom; a halogen atom; an optionally substituted alkyl; a haloalkyl; a fluoroalkyl; an optionally substituted alkenyl; an optionally substituted alkynyl; an optionally substituted cycloalkyl; an optionally substituted cycloalkenyl; an optionally substituted cycloalkynyl; an optionally substituted alkoxy; -O-**R_7**; an azido; a hydroxyl; a cyano; a nitro; -N**R_5R_6**;
- **R_2** and **R_3** , simultaneously or independently, are selected from a hydrogen atom; an optionally substituted alkyl; an optionally substituted alkenyl; an optionally substituted alkynyl; an optionally substituted cycloalkyl; an optionally substituted cycloalkenyl; an optionally substituted cycloalkynyl; an optionally substituted heterocyclyl group; or **R_2** and **R_3** can be linked together with the nitrogen atom to which they are covalently linked to form an optionally substituted heterocyclyl group;
- **R_4** , either alone or simultaneously or independently when n > 1, is selected from a hydrogen atom; a halogen atom; an optionally substituted alkyl; a haloalkyl; a fluoroalkyl; an optionally substituted alkenyl; an optionally substituted alkynyl; an optionally substituted cycloalkyl; an optionally substituted cycloalkenyl; an optionally substituted cycloalkynyl; an optionally substituted alkoxy; -O-**R_7**; an azido; a hydroxyl; a cyano; a nitro; -N**R_5R_6**.
- **R_5** and **R_6** , simultaneously or independently, are slected from a hydrogen atom; an optionally substituted alkyl; an optionally substituted alkenyl; an optionally substituted alkynyl; an optionally substituted cycloalkyl; an optionally substituted cycloalkenyl; an optionally substituted cycloalkynyl; an optionally substituted heterocyclyl group; or **R_5** and **R_6** can be linked together with the nitrogen atom to which they are covalently linked to form an optionally substituted heterocyclyl group ;
- **R_7** can be selected from an optionally substituted alkyl; a haloalkyl; a fluoroalkyl; an optionally substituted alkenyl; an optionally substituted alkynyl; an optionally substituted cycloalkyl; an optionally substituted cycloalkenyl; an optionally substituted cycloalkynyl; an optionally substituted heterocyclyl group;
- n is an integer which can have any one of the values 0, 1, 2, 3 or 4;
- m is an integer which can have any one of the values 0, 1, 2, 3, 4 or 5 for formula (II); and m is an integer which can have any one of the values 0, 1, 2, 3 or 4 for formula (III) and (IV);

and pharmaceutically acceptable salt, hydrates, solvatepolymorphs, tautomers, isotopic variants, stereoisomers or mixtures of stereoisomers thereof.

10. The combination according to claim 9, in which **R_1**, **R_2**, **R_3** and **R_4** are as defined in any of claims 2 to 8 for formula (II) or (III) and in which **R_1**,and **R_4** are as defined in any of claims 2, 3, 7 and 8 for formula (IV).

11. The combination according to claim 1, comprising a compound of formula (I) wherein

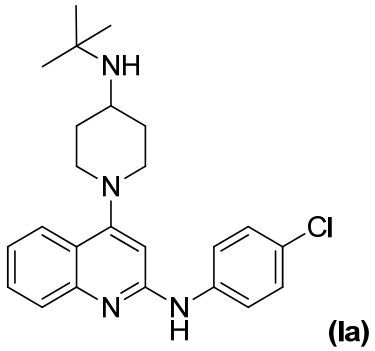
- **L_1** is chosen from a single bond and $(-CH_2-)_p$ group;
- **R_1** is a halogen atom, in particular chlorine;

- **R_2** and **R_3**, simultaneously or independently, are selected from a hydrogen atom and an optionally substituted alkyl, in particular a methyl, an ethyl, a n-propyl, an *iso*-propyl, a n-butyl, an *iso*-butyl, a *sec*-butyl or a *tert*-butyl.;
- m =1,
- n=0, and
- p=1,

and pharmaceutically acceptable salts, hydrates, solvate, polymorphs, tautomers, isotopic variants, stereoisomers or mixtures of stereoisomers thereof.

12. The combination according to claim 1, in which the compound of formula (I) is chosen from the following compounds:

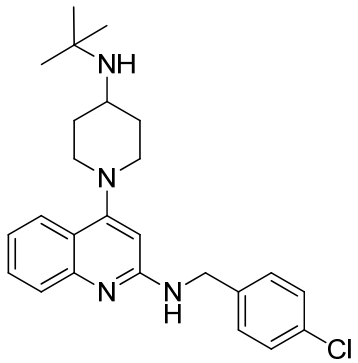
2-(4-chlorophenylamino)-4-(4-*tert*-butylaminopiperidin-1-yl)-quinoline of formula (**Ia**) (**1-5**)



(Ia)

and

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



(Ib)

or a pharmaceutically acceptable salt or solvate thereof.

13. The combination according to claim 1, in which the compound of formula (I) is chosen from 2-(4-chlorophenylamino)-4-(4-*tert*-butylaminopiperidin-1-yl)-quinoline hydrochloride salt (**1-6**) and 2-(4-chlorobenzylamino)-4-(4-*tert*-butylaminopiperidin-1-yl)-quinoline hydrochloride salt (**2-3**).

14. The combination according to any one of claims 1 to 13, in which the MEK inhibitor is chosen from the group consisting of Binimetinib [606143-89-9], Cobimetinib [934660-93-2], Selumetinib [606143-52-6], Trametinib [871700-17-3], AZD8330 [869357-68-6], BI-847325 [1207293-36-4], GDC-0623 [1168091-68-6], Mirdametinib (PD0325901) [391210-10-9], PD184352 (CI-1040) [212631-79-3], Pimasertib (AS-703026) [1236699-92-5], Refametinib [923032-37-5], TAK-733 [1035555-63-5], BIX 02188 [1094614-84-2], BIX 02189 [1265916-41-3], Honokiol [35354-74-6], Myricetin [529-44-2], PD98059 [167869-21-8], PD318088 [391210-00-7], SL-327 [305350-87-2], U0126 [109511-58-2] or a pharmaceutically acceptable salt or solvate thereof.

15. The combination according to any one of claims 1 to 14, in which the MEK inhibitor is chosen from the group consisting of Binimetinib [606143-89-9], Cobimetinib [934660-93-2], Selumetinib [606143-52-6], Trametinib [871700-17-3] or a pharmaceutically acceptable salt or a solvate thereof.

16. The combination according to any one of claims 1 to 15, which comprises 2-(4-chlorobenzylamino)-4-(4-*tert*-butylaminopiperidin-1-yl)-quinoline of formula (**Ib**) (**2-2**), or a salt, solvate thereof, and Trametinib [871700-17-3] or a pharmaceutically acceptable salt or a solvate thereof.

17. The combination according to any one of claims 1 to 15, which comprises 2-(4-chlorobenzylamino)-4-(4-*tert*-butylaminopiperidin-1-yl)-quinoline of formula (**Ib**) (**2-2**), or a salt, or a solvate thereof, and Cobimetinib [934660-93-2] or a pharmaceutically acceptable salt or a solvate thereof.

18. A pharmaceutical composition comprising a therapeutically effective amount of a combination according to any one of claims 1 to 17, comprising a compound of formula (I), (II), (III) or (IV) and pharmaceutically acceptable salts, hydrates, solvate, polymorphs, tautomers, isotopic variants, stereoisomers or mixtures of stereoisomers thereof and a MEK inhibitor or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable carrier, where each component of the combination can be either contained in a separate pharmaceutical composition or in the same pharmaceutical composition.

19. Use of a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof and a MEK inhibitor or a pharmaceutically acceptable salt or solvate thereof according to any one of claims 1 to 18, in the manufacture of a combination medicament for treatment and/or prevention and/or decrease of liver cancers related diseases.

20. The use according to claim 19, wherein the compound of formula (I) is a compound of formula (II), (III) or (IV) or a pharmaceutically acceptable salt or solvate thereof as defined in claims 9 or 10.

21. The use according to claim 19, wherein the compound of formula (I) is chosen from 2-(4-chlorophenylamino)-4-(4-*tert*-butylaminopiperidin-1-yl)-quinoline (**1-5**) and 2-(4-chlorobenzylamino)-4-(4-*tert*-butylaminopiperidin-1-yl)-quinoline (**2-2**).

22. The use according to claim 19, wherein the combination medicament comprises 2-(4-chlorobenzylamino)-4-(4-*tert*-butylaminopiperidin-1-yl)-quinoline of formula (**Ib**) (**2-2**), or a pharmaceutically acceptable salt, or solvate thereof, and Trametinib [871700-17-3] or a pharmaceutically acceptable salt or solvate thereof.

23. The use according to claim 19 wherein is the combination medicament comprises 2-(4-chlorobenzylamino)-4-(4-*tert*-butylaminopiperidin-1-yl)-quinoline of formula (**Ib**) (**2-2**), or a pharmaceutically acceptable salt or solvate thereof, and Cobimetinib [934660-93-2] or a pharmaceutically acceptable salt or solvate thereof.

24. The use according to any one of claims 19 to 22, in which each component of the combination medicament is to be for simultaneous, separate or sequential use in liver cancer therapy.

25. The use according to any one of claims 19 to 24, in which the liver cancers related disease is selected from hepatocarcinoma, hepatoblastoma and cholangiocarcinoma.

26. The use according to any one of claims 19 to 25, in which the liver cancers related disease is selected from an intrahepatic cholangiocarcinoma and an extrahepatic cholangiocarcinoma.

27. The use according to any one of claims 19 to 25, in which the liver cancers related disease is a hepatocarcinoma.

28. A kit comprising the combination of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof and a MEK inhibitor or a pharmaceutically acceptable salt or solvate thereof, as defined in any one of claims 1 to 18, in which both or either of the components of the combination, are/is in the form of a pharmaceutical composition which may be administered simultaneously, separately or sequentially.