CLAIMS

1. Use of a serotonin receptor 5-HT_{2A} inhibitor in the manufacture of a medicament for treating a liver cancer in a subject in need thereof,

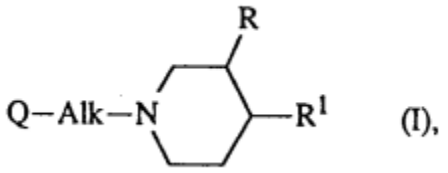
wherein the serotonin receptor 5-HT_{2A} inhibitor ameliorates the suppression of an immune system.

2. The use of claim 1, wherein the serotonin receptor 5-HT_{2A} inhibitor ameliorates the suppression of CD8 T cell function.

3. The the use of claim 1 or 2, wherein the 5-HT_{2A} inhibitor is a selective antagonist of 5-HT_{2A}.

4. The use of claim 1 or any one of claims 2 to 3, wherein the 5-HT_{2A} inhibitor is an agent that targets the serotonin receptor 5-HT_{2A} by disrupting its function in enhancing CD8 T cell activation and/or an agent that targets the serotonin receptor 5-HT_{2A} overall function and therefore disrupts its function in enhancing CD8 T cell activation.

5. The use of claim 1 or any one of claims 2 to 4, wherein the 5-HT_{2A} inhibitor is a compound having the formula:



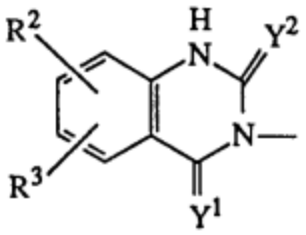
(I),

the pharmaceutically acceptable acid-addition salts thereof and the possible stereoisomeric forms thereof; wherein

R is hydrogen or C_{1-6}alkyl;

Alk is C_{1-4}alkanediyl;

Q is a radical of formula



(a)

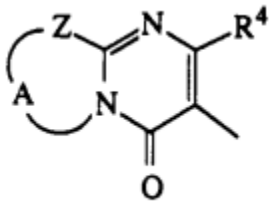
wherein Y^1 and Y^2 are each independently O or S;

R^2 is hydrogen, halo, C_{1-6}alkyl or C_{1-6}alkyloxy;

R^3 is hydrogen or halo;

or

Q is a radical of formula



(b),

wherein R^4 is hydrogen or C_{1-6}alkyl;

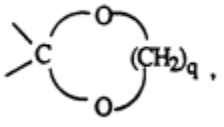
Z is -S-, $-CH_2-$ or $-CR^5=CR^6-$; said R^5 and R^6 each independently being hydrogen or C_{1-6}alkyl; and A is a bivalent radical $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$ or $-CR^7=CR^8-$, said R^7 and R^8 each independently being hydrogen, halo, amino or C_{1-6}alkyl;

R^1 is a radical of formula

-X-Ar (c),

wherein Ar is phenyl or substituted phenyl, said substituted phenyl bearing an amino group and/or 1, 2 or 3 halo atoms; and

wherein X is 〉C=O, 〉CH-OH, 〉CH-O-C(O)-R^9, 〉CH_2, 〉$C(OC_{1-6}alkyl)_2$,



,

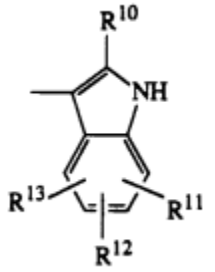
〉C=N-OH or 〉$C=N-NH_2$;

said R^9 being hydrogen or C_{1-6} alkyl and

said q being the integer 2 or 3;

or

R^1 is a radical of formula

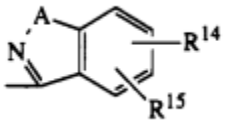


(d),

wherein R^{10} is hydrogen or C_{1-6}alkyl; R^{11}, R^{12} and R^{13} are each independently hydrogen or halo;

or

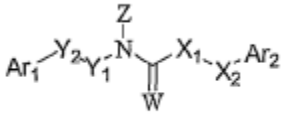
R^1 is a radical of formula



(e),

wherein A is O or S; R^{14} and R^{15} are each independently hydrogen, halo, hydroxy, C_{1-6}alkyloxy or C_{1-6}alkyl.

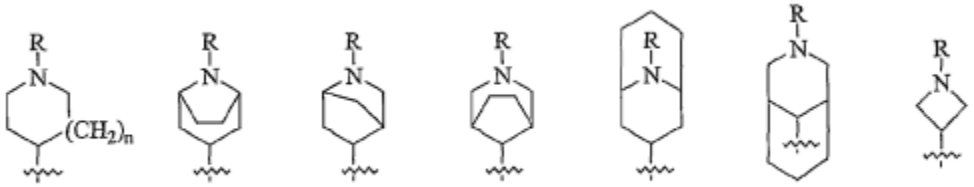
6. The use of claim 1 or any one of claims 2 to 5, wherein the 5-HT_{2A} inhibitor is a compound having the formula:



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Wherein

Z is a group selected from



, , , , , or

R is hydrogen, a cyclic or straight-chained or branched acyclic organyl group, a lower hydroxyalkyl group, a lower aminoalkyl group, or an aralkyl or heteroaralkyl group;

n is 0, 1, or 2;

X_1 is methylene, vinylene, or an NH or N(lower alkyl) group; and

X_2 is methylene , or, when X_1 is methylene or vinylene, X_2 is methylene or a bond; or when X_1 is methylene, X_2 is O, S, NH, or N(lower alkyl) or a bond;

Y_1 is methylene and Y_2 is methylene, vinylene, ethylene, propylene, or a bond; or

Y_1 is a bond and Y_2 is vinylene; or

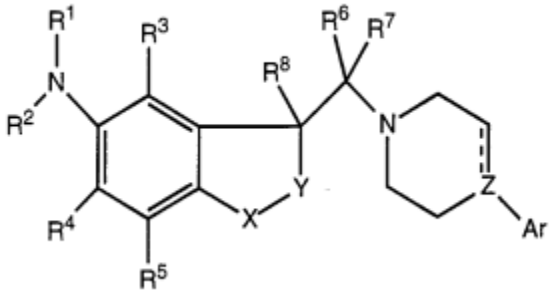
Y_1 is ethylene and Y_2 is O, S, NH, or N(lower alkyl);

Ar_1 and Ar_2 independently are unsubstituted or substituted aryl or heteroaryl groups;

W is oxygen or sulfur; or

a pharmaceutically acceptable salt, ester, or prodrug thereof.

7. The use of claim 1 or any one of claims 2 to 6, wherein the 5-HT_{2A} inhibitor is a compound having the formula:



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wherein one of X and Y is CH_2 and the other one is selected from the group consisting of CH_2, O, and S;

the dotted line, emanating from Z, indicates an optional bond; when it does not indicate a bond Z is N, CH or COH; and when it indicates a bond Z is C;

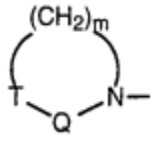
Ar is phenyl, 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, 2-pyrimidyl, 1-indolyl, 2-indolyl, 3-indolyl,1-indol-2-onyl, 3-indol-2-onyl, 2- or 3-benzofuranyl, 2- or 3-benzothiophenyl, 1 -naphthyl or 2-naphthyl, each optionally substituted with halogen, lower alkyl, lower alkoxy, lower alkylthio, hydroxy, lower alkylsulfonyl, cyano, trifluoromethyl, trifluromethylsulfonyloxy, cycloalkyl, cycloalkyl-lower-alkyl, nitro, amino, lower alkylamino, di-lower alkylamino, acylamino or C_{1-2} alkylenedioxy;

R^1 is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, cycloalk(en)yl, cycloalk(en)yl-lower alk(en/yn)yl, aryl, aryl-lower alkyl, acyl, thioacyl, lower alkylsulfonyl, trifluoromethylsulfonyl, arylsulfonyl,

R^1 is a group R^9VCO- where V is O or S and R^9 is lower alkyl, cycloalkyl, cycloalkyllower-alkyl or aryl, or R^1 is a group $R^{10}R^{11}NCO$- or $R^{10}R^{11}NCS$- wherein R^{10} and R^{11} are independently hydrogen, lower alkyl, cycloalkyl, cycloalkyl-lower-alkyl or aryl, or R^{10} and R^{11} together with the N-atom to which they are linked, form a pyrrolidinyl, piperidinyl or perhydroazepin group;

R^2 is hydrogen, lower alkyl, cycloalkyl or cycloalkyl-lower-alkyl;

or R^1 and R^2 together with the N-atom to which they are linked form a group,



wherein Q is C=O, C=S or CH_2; T is NH, S, O or CH_2; and m is 1-4, inclusive;

R^3 - R^5 are independently hydrogen, halogen, lower alkyl, lower alkylcarbonyl, phenylcarbonyl, halogen substituted phenylcarbonyl, lower alkoxy, lower alkylthio, hydroxy, lower alkylsulfonyl, cyano, trifluoromethyl, cycloalkyl, cycloalkyl-lower-alkyl or nitro;

R^6 and R^7 are each hydrogen or lower alkyl or they are linked together to constitute a 3 - 7-membered carbocyclic ring;

R^8 is hydrogen or lower alkyl;

any alkyl, cycloalkyl or cycloalkylalkyl group present being optionally substituted with one or two hydroxy groups, which again are optionally esterified with an aliphatic or aromatic carboxylic acid; and any aryl substituent present being optionally substituted with halogen, lower alkyl, lower alkoxy, lower alkylthio, hydroxy, lower alkylsulfonyl, cyano, trifluoromethyl, trifluoromethylsulfonyloxy, cycloalkyl, cycloalkyl-lower-alkyl or nitro;

and pharmaceutically acceptable acid addition salts thereof.

8. The use of claim 1 or any one of claims 2 to 7, wherein the 5-HT_{2A} inhibitor is [3-[2-[4-(4-fluorobenzoyl)piperidin-1-yl]ethyl]-1*H*-quinazoline-2,4-dione] (ketanserin), 2,3-dihydroxybutanedioic acid;3-[2-[4-(4-fluorobenzoyl)piperidin-1-yl]ethyl]-1H-quinazoline-2,4-dione (ketanserin tartrate), 1-[(4-fluorophenyl)methyl]-1-(1-methylpiperidin-4-yl)-3-[[4-(2-methylpropoxy)phenyl]methyl]urea (Pimavanserin), (*R*)-(2,3-dimethoxyphenyl)-[1-[2-(4-fluorophenyl)ethyl]piperidin-4-yl]methanol (Volinanserin) or pharmaceutical acceptable salt or solvate thereof, or pharmaceutically functional derivatives of such compounds.

9. The use of claim 1 or any one of claims 2 to 8, wherein the proliferative disease is a hepatocellular carcinoma.

10. The use of claim 1 or any one of claims 2 to 9 further comprising one or more combination therapy selected from the group consisting of an immunotherapy, a chemotherapy, an ablative therapy, and a transplantation.

11. The use of any claim 1 or any one of claims 2 to 10 further comprising an immunotherapy such as, but not limited to, an immune checkpoint blockade (ICB) therapy comprising an administration of monoclonal antibodies, optionally the immunotherapy may include the use of one or more of anti-PD-L1 (such as atezolizumab or nivolumab), anti-VEGFA (such as bevacizumab), anti-CTLA4 (such as ipilimumab), or anti-PD-1 (such as nivolumab) plus anti-CTLA4 (such as ipilimumab), and/or combination thereof.

12. The use of any claim 1 or any one of claims 2 to 11 wherein the combination therapy is to be administered to the subject concurrently, sequentially, or separately from the serotonin receptor 5-HT_{2A} inhibitor.

13. The use of claim 1 or any one of claims 2 to 12, wherein the inhibitor is to be administered intravenously, subcutaneously, orally, sublingually, or intraperitoneally.

14. A pharmaceutical composition comprising a serotonin receptor 5-HT_{2A} inhibitor and an immune checkpoint blockade/ICB therapy,

wherein the serotonin receptor 5-HT_{2A} inhibitor ameliorates the suppression of an immune system in liver cancer.

15. The pharmaceutical composition of claim 14, wherein the serotonin receptor inhibitor is [3-[2-[4-(4-fluorobenzoyl)piperidin-1-yl]ethyl]-1*H*-quinazoline-2,4-dione] (ketanserin), 2,3-dihydroxybutanedioic acid;3-[2-[4-(4-fluorobenzoyl)piperidin-1-yl]ethyl]-1H-quinazoline-2,4-dione (ketanserin tartrate), 1-[(4-fluorophenyl)methyl]-1-(1-methylpiperidin-4-yl)-3-[[4-(2-methylpropoxy)phenyl]methyl]urea (Pimavanserin), (*R*)-(2,3-dimethoxyphenyl)-[1-[2-(4-

fluorophenyl)ethyl]piperidin-4-yl]methanol (Volinanserin) or pharmaceutical acceptable salt or solvate thereof, or pharmaceutically functional derivatives of such compounds.

16. Use of a serotonin receptor 5-HT_{2A} inhibitor and an immune checkpoint blockade/ICB therapy in the manufacture of a medicament for combination therapy for treating a liver cancer in a subject, wherein the serotonin receptor inhibitor is [3-[2-[4-(4-fluorobenzoyl)piperidin-1-yl]ethyl]-1*H*-quinazoline-2,4-dione] (ketanserin), 2,3-dihydroxybutanedioic acid;3-[2-[4-(4-fluorobenzoyl)piperidin-1-yl]ethyl]-1H-quinazoline-2,4-dione (ketanserin tartrate), 1-[(4-fluorophenyl)methyl]-1-(1-methylpiperidin-4-yl)-3-[[4-(2-methylpropoxy)phenyl]methyl]urea (Pimavanserin), (*R*)-(2,3-dimethoxyphenyl)-[1-[2-(4-fluorophenyl)ethyl]piperidin-4-yl]methanol (Volinanserin) or pharmaceutical acceptable salt or solvate thereof, or pharmaceutically functional derivatives of such compounds,

wherein the serotonin receptor 5-HT_{2A} inhibitor ameliorates the suppression of an immune system.