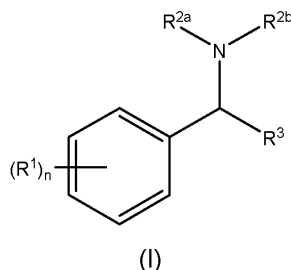


CLAIMS

1. A compound of general formula (I):



wherein:

each R^1 is independently halo, OH, cyano, nitro, $NR^{10}R^{11}$, $C(O)R^{10}$, $C(O)OR^{10}$, $C(O)NR^{10}R^{11}$, $-S(O)_qNR^{10}R^{11}$, C_{1-6} alkyl, C_{1-6} haloalkyl, $-O(C_{1-6}$ alkyl), $-O(C_{1-6}$ haloalkyl), aryl, heteroaryl, $-O$ -aryl or $-O$ -heteroaryl,

10 wherein

each R^{10} and R^{11} is independently selected from H or C_{1-6} alkyl optionally substituted with one or more substituents selected from OH, halo, cyano, NH_2 , aryl or heteroaryl;

15 alkyl and haloalkyl groups R^1 are optionally substituted with one or more substituents selected from OH, cyano, $-S(O)_pNR^4R^5$, $-C(O)NR^4R^5$, aryl, heteroaryl, $-O$ -aryl or $-O$ -heteroaryl $-O(C_{1-6}$ alkyl) optionally substituted with aryl or $-O(C_{1-6}$ haloalkyl);

20 aryl or heteroaryl groups R^1 are optionally substituted with one or more substituents selected from halo, OH, cyano, nitro, $-NR^4R^5$, $-S(O)_pNR^4R^5$, $-C(O)NR^4R^5$, $-C(O)R^4$, $-C(O)OR^4$ or $-C_{1-6}$ alkyl or $-O(C_{1-6}$ alkyl), either of which is optionally substituted with one or more substituents selected from OH, halo, aryl, heteroaryl, $-O(C_{1-6}$ alkyl), $O(C_{1-6}$ haloalkyl), $-O$ -aryl or $-O$ -heteroaryl);

p is 1 or 2;

25 each R^4 and R^5 is independently selected from H or C_{1-4} alkyl or R^4 and R^5 together with a nitrogen atom to which they are attached may form a 3- or 8-membered heterocyclic ring, optionally containing one or more additional heteroatoms selected from O, N and S;

n is 0, 1, 2, 3 4, or 5;

30

R^{2a} and R^{2b} are each independently C_{1-6} alkyl optionally substituted with one or more substituents selected from halo, OH, aryl or heteroaryl; or

R^{2a} and R^{2b} together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclic ring optionally containing one or more further heteroatoms selected from O, N or S and optionally substituted with one or more substituents R⁶;

5 each R⁶ is independently selected from aryl, heteroaryl, -O-aryl, -O-heteroaryl, carbocyclyl, heterocyclyl, -O-carbocyclyl, -O-heterocyclyl, R¹², OR¹², C(O)R¹², C(O)OR¹¹, C(O)NR¹¹R¹², CN, OH,

each R¹¹ and R¹² is independently H or C₁₋₄ alkyl, either or which may be substituted with one or more aryl or heteroaryl groups, wherein aryl and heteroaryl groups are substituted with one or more substituent selected from halo, OH, cyano, 10 nitro, -NR⁴R⁵, -S(O)_pNR⁴R⁵, -C(O)NR⁴R⁵, -C(O)R⁴, -C(O)OR⁴ or -C₁₋₆ alkyl or -O(C₁₋₆ alkyl), either of which is optionally substituted with one or more substituents selected from OH, halo, aryl, heteroaryl, -O(C₁₋₆ alkyl), O(C₁₋₆ haloalkyl), -O-aryl or -O-heteroaryl);

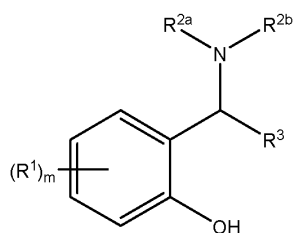
wherein R⁴ and R⁵ are as defined above; or R¹¹ and R¹² may combine with a 15 nitrogen atom to which they are attached to form a 3 to 8-membered heterocyclic ring optionally containing one or more further heteroatoms selected from N, O and S and optionally substituted with C₁₋₄ alkyl, C₁₋₄ haloalkyl or halo;

R³ is aryl, heteroaryl, carbocyclyl or heterocyclyl any of which is optionally substituted with one or more substituents R⁷ selected from halo, -C₁₋₄ alkyl optionally substituted with aryl, 20 -O(C₁₋₄ alkyl) optionally substituted with aryl, -C₁₋₄ haloalkyl, -O(C₁₋₄ haloalkyl) or -C(O)NR⁸R⁹;

each R⁸ and R⁹ is independently selected from H, C₁₋₄ alkyl or C₃₋₆ cycloalkyl or R⁸ and R⁹ together with the nitrogen atom to which they are attached may form a 5- or 6-membered heterocyclic ring, optionally containing one or more additional 25 heteroatoms selected from O, N and S;

or a pharmaceutically acceptable salt, solvate or hydrate thereof or a deuterated or tritiated variant thereof, including all stereoisomers.

30 2. compound of general formula general formula (IA):



(IA)

wherein:

each R¹ is independently halo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, aryl or heteroaryl, wherein aryl or heteroaryl groups are optionally substituted with one or more substituents selected from halo, OH, cyano, nitro, -S(O)_pNR⁴R⁵, -C(O)NR⁴R⁵, -C₁₋₆ alkyl optionally substituted with aryl, -C₁₋₆ haloalkyl, -O(C₁₋₆ alkyl) optionally substituted with aryl or -O(C₁₋₆ haloalkyl);

p is 0, 1 or 2;

each R⁴ and R⁵ is independently selected from H or C₁₋₄ alkyl or R⁴ and R⁵ together with the nitrogen atom to which they are attached may form a 5- or 6-membered heterocyclic ring, optionally containing one or more additional heteroatoms selected from O, N and S;

m is 0, 1, 2, 3 or 4;

R^{2a} and R^{2b} are each independently C₁₋₆ alkyl optionally substituted with one or more substituents selected from halo, OH, aryl or heteroaryl; or

R^{2a} and R^{2b} together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclic ring optionally containing one or more further heteroatoms selected from O, N or S and optionally substituted with one or more substituents R⁶;

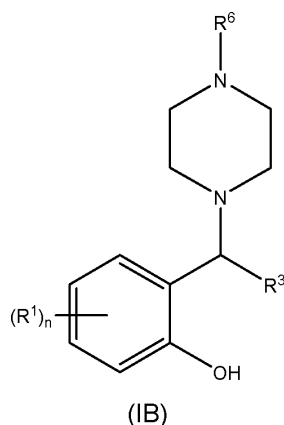
each R⁶ is independently selected from aryl, heteroaryl, -O-aryl, -O-heteroaryl or C₁₋₄ alkyl substituted with one or more aryl or heteroaryl groups, wherein aryl and heteroaryl groups are substituted with one or more substituent selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, -O(C₁₋₄ alkyl) or -O(C₁₋₄ haloalkyl);

R³ is aryl, heteroaryl, carbocyclyl or heterocyclyl any of which is optionally substituted with one or more substituents R⁷ selected from halo, -C₁₋₄ alkyl optionally substituted with aryl, -O(C₁₋₄ alkyl) optionally substituted with aryl, -C₁₋₄ haloalkyl, -O(C₁₋₄ haloalkyl) or -C(O)NR⁸R⁹;

each R⁸ and R⁹ is independently selected from H, C₁₋₄ alkyl or C₃₋₆ cycloalkyl or R⁸ and R⁹ together with the nitrogen atom to which they are attached may form a 5- or 6-membered heterocyclic ring, optionally containing one or more additional heteroatoms selected from O, N and S;

or a pharmaceutically acceptable salt, solvate or hydrate thereof or a deuterated or tritiated variant thereof, including all stereoisomers.

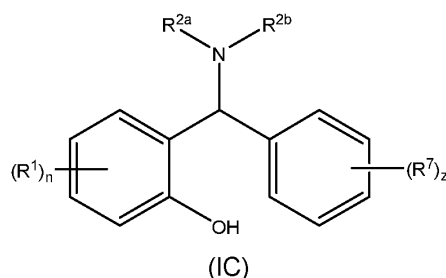
3. A compound according to claim 1 wherein n is 1 or 2 and at least one R¹ group is OH; or a compound according to claim 2 wherein m is 0 or 1.
4. A compound according to claim 2 or claim 3 wherein m is other than 0 and R¹ is
5 halo or an aryl or heteroaryl group optionally substituted as defined in claim 2.
5. A compound according to claim 4 wherein R¹ is an aryl or heteroaryl group optionally substituted with halo, OH, cyano, nitro, -SO₂NH₂, -C(O)NR⁴R⁵, -C₁₋₄ alkyl optionally substituted with aryl, -C₁₋₄ haloalkyl, -O(C₁₋₄ alkyl) optionally substituted with
10 aryl or -O(C₁₋₄ haloalkyl), where R⁴ and R⁵ together with the nitrogen atom to which they are attached form a piperidine or pyrrolidine ring.
6. A compound according to claim 5 wherein R¹ is an aryl or heteroaryl group optionally substituted with chloro, fluoro, methyl, ethyl, trifluoromethyl, benzyl, methoxy,
15 ethoxy, benzyloxy, trifluoromethoxy and piperidine-1-carbonyl.
7. A compound according to any one of claims 1 to 6 wherein R^{2a} and R^{2b} together with the nitrogen atom to which they are attached form a 6-membered heterocyclic ring optionally substituted with one or more substituents R⁶.
- 20 8. A compound according to claim 7 wherein R^{2a} and R^{2b} together with the nitrogen atom to which they are attached form a piperazine ring substituted by a single R⁶ substituent at the piperazine 4-position such that the compound of general formula (I) is a compound of general formula (IB):



wherein R¹, n, R³ and R⁶ are as defined in claim 2.

9. A compound according to any one of claims 1 to 8 wherein R^6 is phenyl, heteroaryl, -O-phenyl, -O-heteroaryl, benzyl, -CH(phenyl)₂, -CH₂-heteroaryl and -CH(heteroaryl)₂, where the heteroaryl group is selected from pyridinyl, indolyl, isoindolyl, benzoxazolyl and benzisoxazolyl and wherein any of the above R^6 groups may be substituted as defined in claim 1.

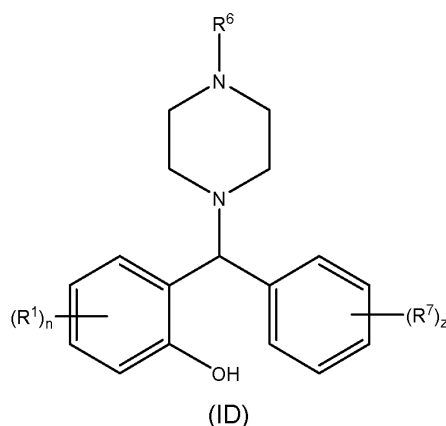
10. A compound according to any one of claims 1 to 9 wherein R^3 is phenyl optionally substituted with one or more substituents R^7 such that the compound of general formula (I) is a compound of general formula (IC):



wherein R^1 , n , R^{2a} , R^{2b} and R^7 are as defined for general formula (I) and z is 0 to 5.

11. A compound according to claim 10 wherein z is 0, 1 or 2 R^7 not present (i.e. z is 0), or R^7 is halo, -C₁₋₄ alkyl, benzyl, -O(C₁₋₄ alkyl) benzyloxy, -C₁₋₄ haloalkyl, -O(C₁₋₄ haloalkyl) or -C(O)NR⁸R⁹, where R^8 and R^9 together with the nitrogen atom to which they are attached form a piperidinyl ring or wherein R^8 is H and R^9 is C₃₋₇ cycloalkyl.

11. A compound according to any one of claims 1 to 10 which is a compound of general formula (ID):



wherein R^1 , n , R^6 , R^7 and z are as defined above.

12. A compound according to claim 1 selected from:
- 2-((2-chlorophenyl)(4-(4-methoxyphenyl)piperazin-1-yl)methyl)phenol (Compound 1);
- 2-((4-chlorophenyl)(4-(4-methoxyphenyl)piperazin-1-yl)methyl)phenol (Compound 2);
- 2-((4-(benzyloxy)-3-fluorophenyl)(4-(4-methoxyphenyl)piperazin-1-yl)methyl)phenol
- 5 (Compound 3);
- (4-((2-hydroxyphenyl)(4-(4-Methoxyphenyl)piperazinyl)methyl)phenyl)(piperidin-1-yl)methanone (Compound 4);
- 3-((5-chloro-2-hydroxyphenyl)(4-(4-methoxyphenyl)piperazin-1-yl)methyl)-N-cyclopentylbenzamide (Compound 5);
- 10 2-((4-(benzyloxy)-3-fluorophenyl)(4-(4-methoxyphenyl)piperazin-1-yl)methyl)-4-chlorophenol (Compound 6);
- 2-((4-(benzyloxy)-3-fluorophenyl)(4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl)methyl)phenol (Compound 7);
- 2-((4-(2, 3-dichlorophenyl)piperazin-1-yl)(o-tolyl)methyl)phenol (Compound 8);
- 15 N-cyclopentyl-3-((4-(2,3-dichlorophenyl)piperazin-1-yl)(2-hydroxyphenyl)methyl)benzamide (Compound 9, NPB);
- 2-((4-(benzyloxy)-3-fluorophenyl)(4-(2,3-dichlorophenyl)piperazin-1-yl)methyl)phenol (Compound 10);
- 2-((4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)(phenyl)methyl)phenol (Compound
- 20 11);
- 2-((4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)(p-tolyl)methyl)phenol (Compound 12);
- 2-((4-chlorophenyl)(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)methyl)phenol (Compound 13);
- 25 2-((4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)(4-ethylphenyl)methyl)phenol (Compound 14);
- (4-((4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)(2-hydroxyphenyl)methyl)phenyl)(piperidin-1-yl)methanone (Compound 15);
- N-cyclopentyl-3-((4-(2,3-dichlorophenyl)piperazin-1-yl)(4-hydroxy-[1,1'-biphenyl]-3-yl)methyl)benzamide (Compound 16);
- 30 N-cyclopentyl-3-((4-(2,3-dichlorophenyl)piperazin-1-yl)(4-hydroxy-2'-methyl-[1,1'-biphenyl]-3-yl)methyl)benzamide (Compound 17);
- N-cyclopentyl-3-((4-(2,3-dichlorophenyl)piperazin-1-yl)(4-hydroxy-3'-methyl-[1,1'-biphenyl]-3-yl)methyl)benzamide (Compound 18);
- 35 N-cyclopentyl-3-((4-(2,3-dichlorophenyl)piperazin-1-yl)(4-hydroxy-4'-methyl-[1,1'-biphenyl]-3-yl)methyl)benzamide (Compound 19);
- 3-((2'-chloro-4-hydroxy-[1,1'-biphenyl]-3-yl)(4-(2,3-dichlorophenyl)piperazin-1-yl)methyl)-

- N-cyclopentylbenzamide (Compound 20);
3-((3'-chloro-4-hydroxy-[1,1'-biphenyl]-3-yl)(4-(2,3-dichlorophenyl)piperazin-1-yl)methyl)-
N-cyclopentylbenzamide (Compound 21);
3-((4'-chloro-4-hydroxy-[1,1'-biphenyl]-3-yl)(4-(2,3-dichlorophenyl)piperazin-1-yl)methyl)-
5 N-cyclopentylbenzamide (Compound 22);
N-cyclopentyl-3-((4-(2,3-dichlorophenyl)piperazin-1-yl)(4'-ethyl-4-hydroxy-[1,1'-biphenyl]-
3-yl)methyl)benzamide (Compound 23);
N-cyclopentyl-3-((4-(2,3-dichlorophenyl)piperazin-1-yl)(4-hydroxy-4'-(piperidine-1-
carbonyl)-[1,1'-biphenyl]-3-yl)methyl)benzamide (Compound 24);
10 N-cyclopentyl-3-((4-(2,3-dichlorophenyl)piperazin-1-yl)(4-hydroxy-4'-methoxy-[1,1'-
biphenyl]-3-yl)methyl)benzamide (Compound 25);
N-cyclopentyl-3-((4-(2,3-dichlorophenyl)piperazin-1-yl)(2'-ethyl-4-hydroxy-[1,1'-biphenyl]-
3-yl)methyl)benzamide (Compound 26);
N-cyclopentyl-3-((4-(2,3-dichlorophenyl)piperazin-1-yl)(2'-fluoro-4-hydroxy-[1,1'-
15 biphenyl]-3-yl)methyl)benzamide (Compound 27);
N-cyclopentyl-3-((4-(2,3-dichlorophenyl)piperazin-1-yl)(3'-fluoro-4-hydroxy-[1,1'-
biphenyl]-3-yl)methyl)benzamide (Compound 28);
N-cyclopentyl-3-((4-(2,3-dichlorophenyl)piperazin-1-yl)(4'-fluoro-4-hydroxy-[1,1'-
biphenyl]-3-yl)methyl)benzamide (Compound 29);
20 N-cyclopentyl-3-((4-(2,3-dichlorophenyl)piperazin-1-yl)(4-hydroxy-3'-nitro-[1,1'-biphenyl]-
3-yl)methyl)benzamide (Compound 30);
N-cyclopentyl-3-((4-(2,3-dichlorophenyl)piperazin-1-yl)(4-hydroxy-3'-sulfamoyl-[1,1'-
biphenyl]-3-yl)methyl)benzamide (Compound 31);
N-cyclopentyl-3-((4-(2,3-dichlorophenyl)piperazin-1-yl)(4-hydroxy-2'-(trifluoromethyl)-
25 [1,1'-biphenyl]-3-yl)methyl)benzamide (Compound 32);
N-cyclopentyl-3-((4-(2,3-dichlorophenyl)piperazin-1-yl)(4-hydroxy-3'-(trifluoromethyl)-
[1,1'-biphenyl]-3-yl)methyl)benzamide (Compound 33);
N-cyclopentyl-3-((4-(2,3-dichlorophenyl)piperazin-1-yl)(4-hydroxy-4'-(trifluoromethyl)-
[1,1'-biphenyl]-3-yl)methyl)benzamide (Compound 34);
30 3-((2'-cyano-4-hydroxy-[1,1'-biphenyl]-3-yl)(4-(2,3-dichlorophenyl)piperazin-1-yl)methyl)-
N-cyclopentylbenzamide (Compound 35);
3-((3'-cyano-4-hydroxy-[1,1'-biphenyl]-3-yl)(4-(2,3-dichlorophenyl)piperazin-1-yl)methyl)-
N-cyclopentylbenzamide (Compound 36);
3-((4'-cyano-4-hydroxy-[1,1'-biphenyl]-3-yl)(4-(2,3-dichlorophenyl)piperazin-1-yl)methyl)-
35 N-cyclopentylbenzamide (Compound 37);
3-((2'-chloro-4-hydroxy-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)(4-(2,3-dichlorophenyl)
piperazin-1-yl)methyl)-N-cyclopentylbenzamide (Compound 38);

- N-cyclopentyl-3-((2',4'-dichloro-4-hydroxy-[1,1'-biphenyl]-3-yl)(4-(2,3-dichlorophenyl)piperazin-1-yl)methyl)benzamide (Compound 39);
3-((4'-chloro-2',4-dihydroxy-[1,1'-biphenyl]-3-yl)(4-(2,3-dichlorophenyl)piperazin-1-yl)methyl)-N-cyclopentylbenzamide (Compound 40);
- 5 3-((4-(4-chlorophenyl)piperazin-1-yl)(2-hydroxyphenyl)methyl)-N-cyclopentylbenzamide (Compound 41, NCK1)
2-((4-chlorophenyl)(4-(2,3-dichlorophenyl)piperazin-1-yl)methyl)phenol (Compound 42, NCK2)
2-((4-(2,3-dichlorophenyl)piperazin-1-yl)(3-methoxyphenyl)methyl)phenol (Compound 43, NCK3)
- 10 1-(5-((4-(2,3-dichlorophenyl)piperazin-1-yl)(2-hydroxyphenyl)methyl)thiophen-2-yl)ethanone (Compound 44, NCK4)
2-((4-(2,3-dichlorophenyl)piperazin-1-yl)(naphthalen-1-yl)methyl)phenol (Compound 45, NCK5)
- 15 5-((4-(2,3-dichlorophenyl)piperazin-1-yl)(2-hydroxyphenyl)methyl)furan-2-carbaldehyde (Compound 46, NCK6)
2-((4-(5,6-dichlorocyclohexa-1,5-dien-1-yl)piperazin-1-yl)(2-fluoro-3-methylpyridin-4-yl)methyl)phenol (Compound 47, NCK7)
2-((4-(2,3-dichlorophenyl)piperazin-1-yl)(4-(trifluoromethyl)phenyl)methyl)phenol (Compound 48, NCK8)
- 20 2-((6-chloro-5-methylpyridin-3-yl)(4-(2,3-dichlorophenyl)piperazin-1-yl)methyl)phenol (Compound 49, NCK9)
2-((4-(2,3-dichlorophenyl)piperazin-1-yl)(pyridin-3-yl)methyl)phenol (Compound 50, NCK10)
- 25 1-(5-((4-(4-chlorophenyl)piperazin-1-yl)(2-hydroxyphenyl)methyl)thiophen-2-yl)ethanone (Compound 51, NCK14)
3-((4-(4-chlorophenyl)piperazin-1-yl)(4-(diethylamino)-2-hydroxyphenyl)methyl)-N-cyclopentylbenzamide (Compound 52, NCK16)
N-cyclopentyl-3-((4-(2,3-dichlorophenyl)piperazin-1-yl)(4-(diethylamino)-2-hydroxyphenyl)methyl)benzamide (Compound 53, NCK18)
- 30 N-cyclopentyl-3-((4-(2,3-dichlorophenyl)piperazin-1-yl)(2-hydroxy-4,6-dimethoxyphenyl)methyl)benzamide (Compound 54, NCK19)
2-((4-chlorophenyl)(4-(4-chlorophenyl)piperazin-1-yl)methyl)phenol (Compound 55, NCK20)
- 35 2-((4-(4-chlorophenyl)piperazin-1-yl)(6-methylpyridin-3-yl)methyl)phenol (Compound 56, NCK21)
2-(o-tolyl(4-(p-tolyl)piperazin-1-yl)methyl)phenol (Compound 57, SG1)

2-((4-(p-tolyl)piperazin-1-yl)(4-(trifluoromethyl)phenyl)methyl)phenol (Compound 58, SG2)

N-cyclopentyl-4-((2-hydroxyphenyl)(4-(p-tolyl)piperazin-1-yl)methyl)benzamide (Compound 59, SG3)

5 2-((4-chlorophenyl)(4-(p-tolyl)piperazin-1-yl)methyl)phenol (Compound 60, SG4)

2-((3-methoxyphenyl)(4-(p-tolyl)piperazin-1-yl)methyl)phenol (Compound 61, SG5)

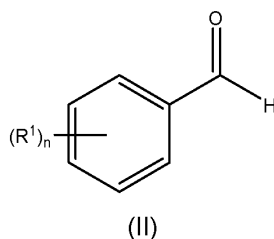
5-((2-hydroxyphenyl)(4-(p-tolyl)piperazin-1-yl)methyl)furan-2-carbaldehyde (Compound 62, SG6)

2-((6-methylpyridin-3-yl)(4-(p-tolyl)piperazin-1-yl)methyl)phenol (Compound 63, SG7);

10 or a pharmaceutically acceptable salt, solvate or hydrate thereof or a deuterated or tritiated variant thereof, including all stereoisomers.

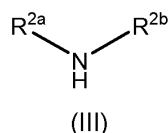
14. A process for the preparation of a compound according to any one of claims 1 to 13 which comprises either:

15 i. reacting an aldehyde of general formula (II):



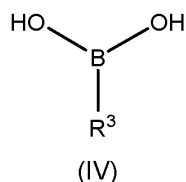
wherein R¹ and n are as defined in claim 1;

20 with a compound of general formula (III):



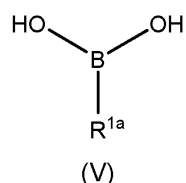
wherein R^{2a} and R^{2b} are as defined in claim 1;

25 and a boronic acid of general formula (IV):



wherein R³ is as defined in claim 1; or

- ii. reacting a compound of general formula (I) in which R¹ is halo with a compound of general formula (V):



- 5 wherein R^{1a} is aryl or heteroaryl optionally substituted as defined for R¹ in claim 1;
via a Suzuki coupling reaction in the presence of a palladium catalyst to obtain a compound
of general formula (I) in which R¹ is R^{1a}.
15. A compound according to any one of claims 1 to 13 for use in medicine.
- 10 16. A compound according to any one of claims 1 to 13 for use in the treatment of
cancer.
- 15 17. The use of a compound according to any one of claims 1 to 13 in the preparation
of an agent for the treatment of cancer.
18. A method for the treatment of cancer, the method comprising administering to a
patient in need of such treatment an effective amount of a compound according to any one
of claims 1 to 13.
- 20 19. A compound for use, use or method according to any one of claims 16 to 18
wherein the cancer is a cancer in which there is BAD phosphorylation, for example breast
cancer, endometrial cancer, ovarian cancer, liver cancer, colon cancer, prostate cancer or
pancreatic cancer or any other epithelial derived cancer in which BAD is phosphorylated.
- 25 20. A pharmaceutical composition comprising a compound according to any one of
claims 1 to 13 and a pharmaceutically acceptable excipient.
- 30 21. A pharmaceutical composition according to claim 20 which is formulated for
intraperitoneal administration, hepatoportal administration, intravenous administration,
intra articular administration, pancreatic duodenal artery administration or intramuscular
administration, or any combination thereof.