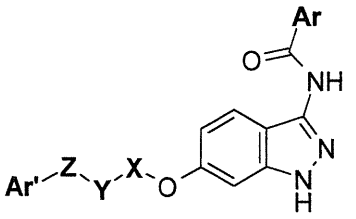
CLAIMS

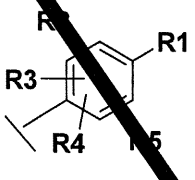
1. A compound of formula (I):



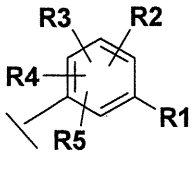
(I)

wherein:

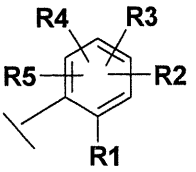
Ar is a group selected from



Ar1



Ar2



Ar3

wherein:

R1 is A, NR6R7, OR8, SO_nR9, COR10, nitro, cyano or an optionally substituted group selected from C_3-C_6 cycloalkyl, heterocyclyl and heteroaryl;

R2, **R3**, **R4** and **R5** are independently hydrogen, halogen, nitro, cyano, SO_nR9, COR10, NR11R12, OR13 or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, straight or branched C_2-C_6 alkenyl, straight or branched C_2-C_6 alkynyl, C_3-C_6 cycloalkyl and heterocyclyl wherein:

A is a straight or branched C_1-C_6 alkyl substituted with a group selected from an optionally substituted heterocyclyl, an optionally substituted heteroaryl, SO_nR9, COR10, NR11R12 and OR13;

R6 is hydrogen or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, straight or branched C_2-C_6 alkenyl, straight or branched C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, heterocyclyl, aryl and heteroaryl;

R7 is hydrogen, SO_nR9, COR10, a substituted straight or branched C_1-C_6 alkyl or an optionally substituted group selected from straight or branched C_2-C_6 alkenyl, straight or branched C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, heterocyclyl, aryl and heteroaryl or

R6 and **R7**, taken together with the nitrogen atom to which they are bound, may form an optionally substituted heterocyclyl group;

R8 is hydrogen, A, COR10 or an optionally substituted group selected from straight or branched C_2-C_6 alkenyl, straight or branched C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein A is as defined above;

R9 is NR11R12 or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, straight or branched C_2-C_6 alkenyl, straight or branched C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, heterocyclyl, aryl and heteroaryl;

R10 is hydrogen, NR11R12, OR13 or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, straight or branched C_2-C_6 alkenyl, straight or branched C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, heterocyclyl, aryl and heteroaryl;

R11 and **R12** are independently hydrogen, SO_nR9, COR10 or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, straight or branched C_2-C_6 alkenyl, straight or branched C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein R9 and R10 are as defined above, or

R11 and **R12**, taken together with the nitrogen atom to which they are bound, may form an optionally substituted heterocyclyl group;

R13 is hydrogen, COR10 or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, straight or branched C_2-C_6 alkenyl, straight or branched C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein R10 is as defined above;

n is 0,1 or 2;

X is a bond or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, heterocycly and aryl;

Y is a bond, oxygen, or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, straight or branched C_2-C_6 alkenyl, straight or branched C_2-C_6 alkynyl, heterocyclyl and aryl;

Z is a bond, oxygen or an optionally substituted straight or branched C_1-C_6 alkyl;

Ar' is an optionally substituted aryl or an optionally substituted heteroaryl;

or a pharmaceutically acceptable salt thereof.

2. A compound of formula (I) as defined in claim 1 wherein:

R1 is A, NR6R7, OR8 or an optionally substituted heterocyclyl, wherein A, R6, R7 and R8 are as defined in claim 1.

3. A compound of formula (I) as defined in claims 1 or 2 wherein:

Ar is Ar1 or Ar2; and R2, R3, R4, R5 are each independently hydrogen, halogen, NR11R12 or OR13, wherein R11, R12 and R13 are as defined in claim 1.

4. A compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in claim 1 which is selected from the group consisting of:

N-(6-Benzyloxy-1H-indazol-3-yl)-4-(4-methyl-piperazin-1-yl)-benzamide,

4-(4-Methyl-piperazin-1-yl)-N-(6-phenoxy-1H-indazol-3-yl)-benzamide,

N-[6-(3-Fluoro-phenoxy)-1H-indazol-3-yl]-4-(4-methyl-piperazin-1-yl)-benzamide,

N-[6-(4-Benzyloxy-phenoxy)-1H-indazol-3-yl]-4-(4-methyl-piperazin-1-yl)-benzamide,

4-(4-Methyl-piperazin-1-yl)-N-[6-(3-phenoxy-benzyloxy)-1H-indazol-3-yl]-benzamide,

N-[6-(1-Benzyl-piperidin-4-yloxy)-1H-indazol-3-yl]-4-(4-methyl-piperazin-1-yl)-benzamide,

4-(4-Methyl-piperazin-1-yl)-N-[6-(3-phenyl-prop-2-ynyloxy)-1H-indazol-3-yl]-benzamide,

4-(4-Methyl-piperazin-1-yl)-N-[6-(4-phenoxy-phenoxy)-1H-indazol-3-yl]-benzamide,

N-[6-(3-Benzyloxy-phenoxy)-1H-indazol-3-yl]-4-(4-methyl-piperazin-1-yl)-benzamide,

4-(4-Methyl-piperazin-1-yl)-N-[6-(2-phenoxy-ethoxy)-1H-indazol-3-yl]-benzamide,

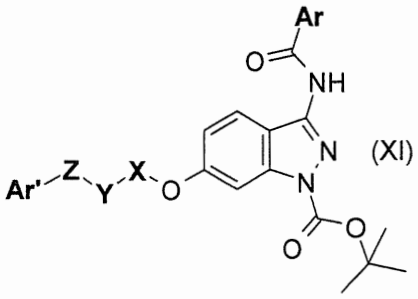
N-[6-(2-Benzyloxy-ethoxy)-1H-indazol-3-yl]-4-(4-methyl-piperazin-1-yl)-benzamide,

N-[6-(1-Benzyl-piperidin-3-yloxy)-1H-indazol-3-yl]-4-(4-methyl-piperazin-1-yl)-benzamide,

N-[6-(1-Benzyl-pyrrolidin-2-ylmethoxy)-1H-indazol-3-yl]-4-(4-methyl-piperazin-1-yl)-benzamide,
N-[6-(2-Benzyloxy-ethoxy)-1H-indazol-3-yl]-4-(4-methyl-4-oxy-piperazin-1-yl)-benzamide,
N-[6-(2-Benzyloxy-ethoxy)-1H-indazol-3-yl]-4-(4-dimethylamino-piperidin-1-yl)-benzamide,
N-[6-(2-Benzyloxy-ethoxy)-1H-indazol-3-yl]-4-[(2-dimethylamino-ethyl)-methyl-amino]-benzamide,
N-[6-(2-Benzyloxy-ethoxy)-1H-indazol-3-yl]-4-[(3-dimethylamino-propyl)-methyl-amino]-benzamide,
4-{4-[6-(2-Benzyloxy-ethoxy)-1H-indazol-3-ylcarbamoyl]-phenyl}-piperazine-1-carboxylic acid tert-butyl ester,
N-[6-(2-Benzyloxy-ethoxy)-1H-indazol-3-yl]-4-(1-methyl-piperidin-4-ylamino)-benzamide,
N-[6-(2-Benzyloxy-ethoxy)-1H-indazol-3-yl]-4-piperazin-1-yl-benzamide,
N-[6-(2-Benzyloxy-ethoxy)-1H-indazol-3-yl]-4-dimethylaminomethyl-benzamide,
N-[6-(2-Benzyloxy-ethoxy)-1H-indazol-3-yl]-4-(1-methyl-piperidin-4-yloxy)-benzamide,
N-[6-(2-Benzyloxy-ethoxy)-1H-indazol-3-yl]-4-[methyl-(1-methyl-piperidin-4-yl)-amino]-benzamide,
N-[6-(2-Benzyloxy-ethoxy)-1H-indazol-3-yl]-4-morpholin-4-yl-benzamide,
N-[6-(2-Benzyloxy-ethoxy)-1H-indazol-3-yl]-4-(2-morpholin-4-yl-ethylamino)-benzamide,
N-[6-(2-Benzyloxy-ethoxy)-1H-indazol-3-yl]-4-(tetrahydro-pyran-4-ylamino)-benzamide,
N-[6-(2-Benzyloxy-ethoxy)-1H-indazol-3-yl]-4-[(1-methyl-piperidin-4-ylmethyl)-amino]-benzamide,
N-[6-(2-Benzyloxy-ethoxy)-1H-indazol-3-yl]-4-(3-pyrrolidin-1-yl-azetidin-1-yl)-benzamide,
N-[6-(2-Benzyloxy-ethoxy)-1H-indazol-3-yl]-3-(4-methyl-piperazin-1-yl)-benzamide,
N-{6-[2-(2-Fluoro-benzyloxy)-ethoxy]-1H-indazol-3-yl}-4-(4-methyl-piperazin-1-yl)-benzamide,
N-{6-[2-(3-Fluoro-benzyloxy)-ethoxy]-1H-indazol-3-yl}-4-(4-methyl-piperazin-1-yl)-benzamide,
N-{6-[2-(4-Fluoro-benzyloxy)-ethoxy]-1H-indazol-3-yl}-4-(4-methyl-piperazin-1-yl)-benzamide,
4-(4-Methyl-piperazin-1-yl)-N-{6-[2-(4-trifluoromethyl-benzyloxy)-ethoxy]-1H-indazol-3-yl}-benzamide,
4-(4-Methyl-piperazin-1-yl)-N-{6-[2-(3-trifluoromethyl-benzyloxy)-ethoxy]-1H-indazol-3-yl}-benzamide,
4-(4-Methyl-piperazin-1-yl)-N-{6-[2-(pyridin-4-ylmethoxy)-ethoxy]-1H-indazol-3-yl}-benzamide,
4-(4-Methyl-piperazin-1-yl)-N-{6-[2-(pyridin-3-ylmethoxy)-ethoxy]-1H-indazol-3-yl}-benzamide,
4-(4-Methyl-piperazin-1-yl)-N-{6-[2-(pyridin-2-ylmethoxy)-ethoxy]-1H-indazol-3-yl}-benzamide,
N-[6-(2-Benzyloxy-ethoxy)-1H-indazol-3-yl]-2-fluoro-4-(4-methyl-piperazin-1-yl)-benzamide,
4-(4-Methyl-piperazin-1-yl)-N-[6-((E)-3-phenyl-allyloxy)-1H-indazol-3-yl]-benzamide,
N-{6-[2-(4-Methoxy-benzyloxy)-ethoxy]-1H-indazol-3-yl}-4-(4-methyl-piperazin-1-yl)-benzamide,
N-[6-(2-Benzyloxy-ethoxy)-1H-indazol-3-yl]-4-[methyl-(1-methyl-1-oxy-piperidin-4-yl)-amino]-benzamide,
4-(4-Methyl-4-oxy-piperazin-1-yl)-N-{6-[2-(4-trifluoromethyl-benzyloxy)-ethoxy]-1H-indazol-3-yl}-benzamide and
N-[6-(2-Benzyloxy-ethoxy)-1H-indazol-3-yl]-2,4-bis-(4-methyl-piperazin-1-yl)-benzamide.

5. A process for preparing a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt thereof, characterized in that the process comprises the following steps:

F) cleaving the tert-butoxy-carbonyl group of the compound of formula (XI)

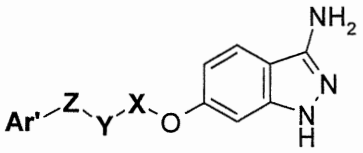


(XI)

wherein Ar, Ar', X, Y and Z are as defined in claim 1, so as to obtain a compound of formula (I), as defined above;

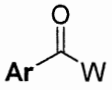
or in alternative

L) acylating the compound of formula (XVI)



(XVI)

wherein Ar', X, Y and Z are as defined in claim 1, with a compound of formula (V)

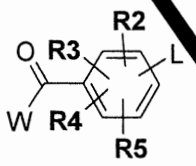


(V)

wherein Ar is as defined in claim 1 and W is hydroxy, halogen or a suitable leaving group; so as to obtain a compound of formula (I), as defined above;

or in alternative

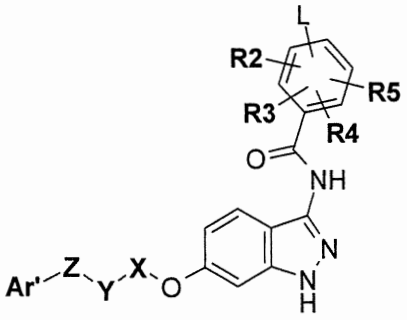
M) acylating the compound of formula (XVI), as defined above, with a compound of formula (XVII)



(XVII)

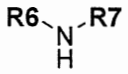
wherein R2, R3, R4 and R5 are as defined in claim 1, W is as defined above and L is a suitable leaving group, such as halogen, methanesulfonyloxy, trifluoromethanesulfonyloxy or p-toluenesulfonyloxy;

N) coupling the resultant compound of formula (XVIII)



(XVIII)

wherein Ar', X, Y, Z, R2, R3, R4 and R5 are as defined in claim 1 and L is as defined above, with a compound of formula (XIX)



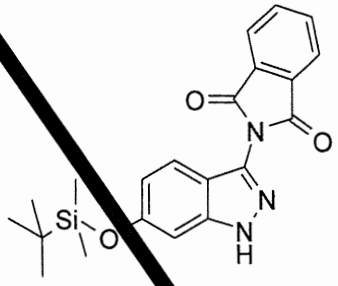
(XIX)

wherein R6 is as defined in claim 1 and R7 is hydrogen, a substituted straight or branched C_1-C_6 alkyl or an optionally substituted group selected from straight or branched C_2-C_6 alkenyl, straight or branched C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, heterocyclyl, aryl and heteroaryl, so as to obtain a compound of formula (I), wherein R1 is NR6R7, wherein R6 is as defined in formula (I) and R7 is hydrogen, a substituted straight or branched C_1-C_6 alkyl or an optionally substituted group selected from straight or branched C_2-C_6 alkenyl, straight or branched C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, heterocyclyl, aryl and heteroaryl, and Ar, Ar', X, Y, Z are as defined in claim 1;

optionally separating the resultant compound of formula (I) into the single isomers; optionally converting the resultant compound of formula (I) into a different compound of formula (I), and/or into a pharmaceutically acceptable salt.

6. A process according to claim 5, characterized in that the compound of formula (XI) as defined in claim 5 is prepared according to the following steps:

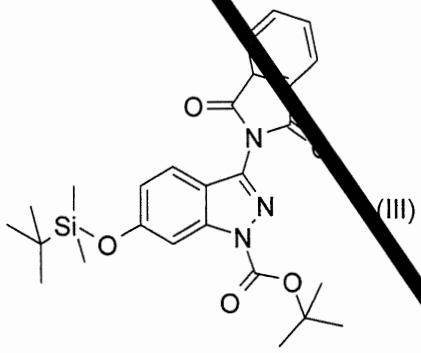
A) introducing the tert-butoxy-carbonyl group into the compound of formula (II)



(II)

;

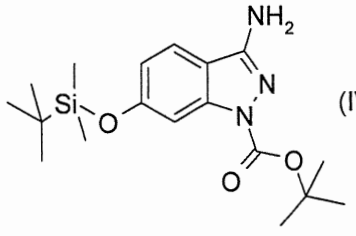
B) cleaving the phthalimido group of the resultant compound of formula (III)



(III)

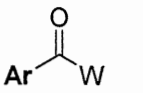
;

C) acylating the resultant compound of formula (IV)



(IV)

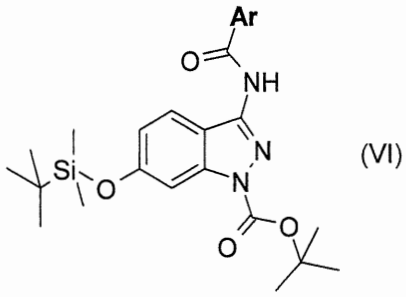
by reaction with a compound of formula (V)



(V)

wherein Ar is as defined in claim 1 and W is hydroxy, halogen or a suitable leaving group;

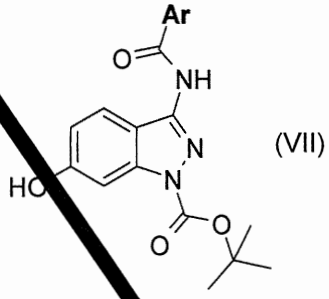
D) selectively cleaving the tert-butyldimethylsilyl ether of the resultant compound of formula (VI)



(VI)

wherein Ar is as defined above;

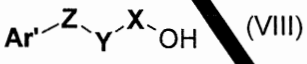
E) coupling the resultant compound of formula (VII)



(VII)

wherein Ar is as defined in claim 1, alternatively with:

Ea) a compound of formula (VIII)

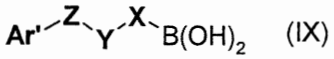


(VIII)

wherein Ar', Z and Y are as defined in claim 1 and X is an optionally substituted group selected from straight or branched C_1-C_6 alkyl and heterocyclyl;

or

Eb) a compound of formula (IX)



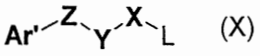
(IX)

wherein Ar', Z and Y are as defined in claim 1 and X is an optionally substituted aryl or

wherein Ar' is as defined in claim 1 and X, Y and Z are a bond;

or

Ec) a compound of formula (X)



(X)

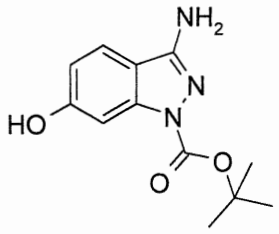
wherein Ar', Z and Y are as defined in claim 1, X is an optionally substituted group selected from straight or branched C_1-C_6 alkyl or heterocyclyl and L is a suitable leaving group such as halogen, methanesulfonyloxy,

trifluoromethanesulfonyloxy or p-toluenesulfonyloxy; so as to obtain a compound of formula (XI), as defined in claim 5.

7. A process according to claim 5, characterized in that the compound of formula (XI) as defined in claim 5 is prepared according to the following steps:

G) selectively cleaving the tert-butyldimethylsilyl ether of the compound of formula (IV), as defined in claim 6;

H) coupling the resultant compound of formula (XII)



(XII)

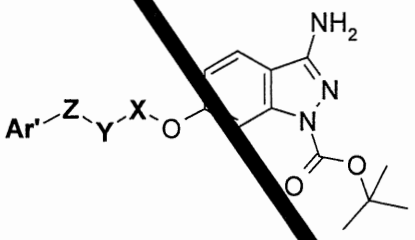
alternatively with:

Ha) a compound of formula (VIII), as defined in claim 6;

or

Hb) a compound of formula (X), as defined in claim 6;

I) acylating the resultant compound of formula (XIII)

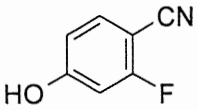


(XIII)

wherein Ar, Ar', Y and Z are as defined in claim 1 and X is an optionally substituted group selected from straight or branched C_1-C_6 alkyl and heterocyclyl, with a compound of formula (V), as defined in claim 6, so as to obtain a compound of formula (XI), wherein Ar, Ar', Y and Z are as defined in claim 1 and X is an optionally substituted group selected from straight or branched C_1-C_6 alkyl and heterocyclyl.

8. A process according to claim 5, characterized in that the compound of formula (XVI) as defined in claim 5 is prepared according to the following steps:

J) coupling the compound of formula (XIV)



(XIV)

alternatively with:

Ja) a compound of formula (VIII), as defined in claim 6;

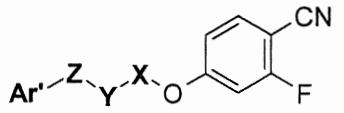
or

Jb) a compound of formula (IX), as defined in claim 6;

or

Jc) a compound of formula (X), as defined in claim 6;

K) converting the resultant compound of formula (XV)



(XV)

wherein Ar', X, Y and Z are as defined in claim 1; so as to obtain a compound of formula (XVI), as defined in claim 5.

9. An *in vitro* method for inhibiting FLT3 or KIT protein kinase activity which comprises contacting the said protein with an effective amount of a compound of formula (I) as defined in claim 1.

10. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in claim 1, and at least one pharmaceutically acceptable excipient, carrier and/or diluent.

11. A pharmaceutical composition according to claim 10 further comprising one or more chemotherapeutic agents.

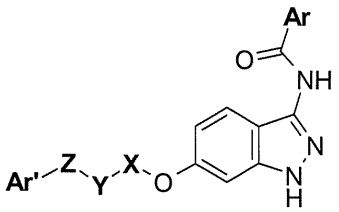
12. A product comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in claim 1, and one or more chemotherapeutic agents, as a combined preparation for simultaneous, separate or sequential use in anticancer therapy.

13. A compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in claim 1, for use as a medicament.

14. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in claim 1, in the manufacture of a medicament with anticancer activity.

CLAIMS:

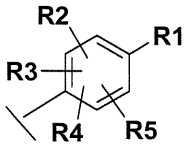
1. A compound of formula (I):



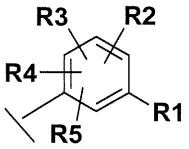
(I)

wherein:

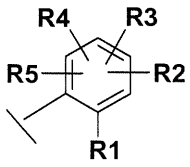
Ar is a group selected from



Ar1



Ar2



Ar3

wherein:

R1 is an optionally substituted heterocyclyl;

R2, R3, R4 and R5 are independently hydrogen, halogen, nitro, cyano, SO_nR9, COR10, NR11R12, OR13 or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, straight or branched C_2-C_6 alkenyl, straight or branched C_2-C_6 alkynyl, and C_3-C_6 cycloalkyl wherein:

R9 is NR11R12 or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, straight or branched C_2-C_6 alkenyl, straight or branched C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, heterocyclyl, aryl and heteroaryl;

R10 is hydrogen, NR11R12, OR13 or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, straight or branched C_2-C_6 alkenyl, straight or branched C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, heterocyclyl, aryl and heteroaryl;

R11 and R12, taken together with the nitrogen atom to which they are bound, may form an optionally substituted heterocyclyl group;

R13 is hydrogen, COR10 or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, straight or branched C_2-C_6 alkenyl, straight or branched C_2-C_6

alkynyl, C_3-C_6 cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein R10 is as defined above;

n is 0,1 or 2;

X is an optionally substituted straight or branched C_1-C_6 alkyl;

Y is a bond or;

Z is an optionally substituted straight or branched C_1-C_6 alkyl;

Ar' is an optionally substituted aryl or an optionally substituted heteroaryl;

or a pharmaceutically acceptable salt thereof.

2. The compound of formula (I) as defined in claim 1 wherein:

Ar is Ar1 or Ar2; and R2, R3, R4, R5 are each independently hydrogen, halogen, NR11R12 or OR13, wherein R11, R12 and R13 are as defined in claim 1.

3. A compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in claim 1 which is selected from the group consisting of:

N-[6-(2-Benzyloxy-ethoxy)-1H-indazol-3-yl]-4-(4-methyl-piperazin-1-yl)-benzamide,

N-[6-(2-Benzyloxy-ethoxy)-1H-indazol-3-yl]-4-(4-methyl-4-oxy-piperazin-1-yl)-benzamide,

N-[6-(2-Benzyloxy-ethoxy)-1H-indazol-3-yl]-4-(4-dimethylamino-piperidin-1-yl)-benzamide,

4-{4-[6-(2-Benzyloxy-ethoxy)-1H-indazol-3-ylcarbamoyl]-phenyl}-piperazine-1-carboxylic acid tert-butyl ester,

N-[6-(2-Benzyloxy-ethoxy)-1H-indazol-3-yl]-4-piperazin-1-yl-benzamide,

N-[6-(2-Benzyloxy-ethoxy)-1H-indazol-3-yl]-4-morpholin-4-yl-benzamide,

N-[6-(2-Benzyloxy-ethoxy)-1H-indazol-3-yl]-4-(3-pyrrolidin-1-yl-azetidin-1-yl)-benzamide,

N-[6-(2-Benzyloxy-ethoxy)-1H-indazol-3-yl]-3-(4-methyl-piperazin-1-yl)-benzamide,

N-{6-[2-(2-Fluoro-benzyloxy)-ethoxy]-1H-indazol-3-yl}-4-(4-methyl-piperazin-1-yl)-benzamide,

N-{6-[2-(3-Fluoro-benzyloxy)-ethoxy]-1H-indazol-3-yl}-4-(4-methyl-piperazin-1-yl)-benzamide,

N-{6-[2-(4-Fluoro-benzyloxy)-ethoxy]-1H-indazol-3-yl}-4-(4-methyl-piperazin-1-yl)-benzamide,

4-(4-Methyl-piperazin-1-yl)-N-{6-[2-(4-trifluoromethyl-benzyloxy)-ethoxy]-1H-indazol-3-yl}-benzamide,
4-(4-Methyl-piperazin-1-yl)-N-{6-[2-(3-trifluoromethyl-benzyloxy)-ethoxy]-1H-indazol-3-yl}-benzamide,
4-(4-Methyl-piperazin-1-yl)-N-{6-[2-(pyridin-4-ylmethoxy)-ethoxy]-1H-indazol-3-yl}-benzamide,
4-(4-Methyl-piperazin-1-yl)-N-{6-[2-(pyridin-3-ylmethoxy)-ethoxy]-1H-indazol-3-yl}-benzamide,
4-(4-Methyl-piperazin-1-yl)-N-{6-[2-(pyridin-2-ylmethoxy)-ethoxy]-1H-indazol-3-yl}-benzamide,
N-[6-(2-Benzyloxy-ethoxy)-1H-indazol-3-yl]-2-fluoro-4-(4-methyl-piperazin-1-yl)-benzamide,
N-{6-[2-(4-Methoxy-benzyloxy)-ethoxy]-1H-indazol-3-yl}-4-(4-methyl-piperazin-1-yl)-benzamide, and
4-(4-Methyl-4-oxy-piperazin-1-yl)-N-{6-[2-(4-trifluoromethyl-benzyloxy)-ethoxy]-1H-indazol-3-yl}-benzamide.

4. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in claim 1, and at least one pharmaceutically acceptable excipient, carrier and/or diluent.

5. A pharmaceutical composition according to claim 4 further comprising one or more chemotherapeutic agents.

6. A product comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in claim 1, and one or more chemotherapeutic agents, as a combined preparation for simultaneous, separate or sequential use in anticancer therapy.