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(54) Title: SUBSTITUTED 2,3-DIHYDROIMIDAZO[1,2-C]QUINAZOLINE-CONTAINING COMBINATIONS

(57) Abstract: The present invention relates to : * combinations of : component A : one or more 2,3-dihydroimidazo[1,2-c]quinazoline compounds of general formula (A1) or (A2), or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof; component B : one or more N-(2-arylamino) aryl sulfonamide compounds of general formula (B), or Lapatinib, or Paclitaxel, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof; and, optionally, component C : one or more further pharmaceutical agents; in which optionally some or all of the components are in the form of a pharmaceutical formulation which is ready for use to be administered simultaneously, concurrently, separately or sequentially, dependently of one another by the oral, intravenous, topical, local installations, intraperitoneal or nasal route; * use of such combinations for the preparation of a medicament for the treatment or prophylaxis of a cancer; and * a kit comprising such a combination.



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SUBSTITUTED 2,3-DIHYDROIMIDAZO[1,2-C]QUINAZOLINE-CONTAINING COMBINATIONS

The present invention relates :

5

- to combinations of :

component A : one or more 2,3-dihydroimidazo[1,2-c]quinazoline compounds of general formula (A1) or (A2), or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;

10 component B : one or more N-(2-arylamino) aryl sulfonamide compounds of general formula (B), or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and, optionally,

component C : one or more further pharmaceutical agents ;

15 - to combinations of :

component A : one or more 2,3-dihydroimidazo[1,2-c]quinazoline compounds of general formula (A1) or (A2), or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;

20 component B : N-[3-chloro-4-[(3-fluorophenyl)methoxy]phenyl]-6-[5-[(2-methyl-sulfonylethylamino)methyl]-2-furyl]quinazolin-4-amine (hereinafter referred to as Lapatinib) ; and, optionally,

component C : one or more further pharmaceutical agents ;

- and to combinations of :

25 component A : one or more 2,3-dihydroimidazo[1,2-c]quinazoline compounds of general formula (A1) or (A2), or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;

30 component B : 5B,20-Epoxy-1,2 α ,4,7B,10B,13 α -hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine (hereinafter referred to as paclitaxel) ; and, optionally,

component C : one or more further pharmaceutical agents ;

in which optionally either or both of components A and B in any of the above-mentioned combinations are in the form of a pharmaceutical formulation which is ready for use to be administered simultaneously, concurrently, separately or sequentially. The components may be administered
5 independently of one another by the oral, intravenous, topical, local installations, intraperitoneal or nasal route.

Another aspect of the present invention relates to the use of such combinations as described *supra* for the preparation of a medicament for the
10 treatment or prophylaxis of a cancer, particularly lung cancer, in particular non-small cell lung carcinoma (abbreviated to and hereinafter referred to as "NSCLC"), colorectal cancer (abbreviated to and hereinafter referred to as "CRC"), melanoma, pancreatic cancer, hepatocyte carcinoma, pancreatic cancer, hepatocyte carcinoma or breast cancer.

15

Further, the present invention relates to :

a kit comprising :

20

- a combination of :

component A : one or more 2,3-dihydroimidazo[1,2-c]quinazoline compounds of general formula (A1) or (A2), or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;

25

component B : one or more N-(2-arylamino) aryl sulfonamide compounds of general formula (B), or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and, optionally,

component C : one or more further pharmaceutical agents ;

- or a combination of :

30

component A : one or more 2,3-dihydroimidazo[1,2-c]quinazoline compounds of general formula (A1) or (A2), or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;

component B : Lapatinib ; and, optionally,
component C : one or more further pharmaceutical agents ;

- or a combination of :

5 component A : one or more 2,3-dihydroimidazo[1,2-c]quinazoline compounds of general formula (A1) or (A2), or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;

component B : Paclitaxel ; and, optionally,
component C : one or more further pharmaceutical agents ;

10

in which optionally either or both of said components A) and B) in any of the above-mentioned combinations are in the form of a pharmaceutical formulation which is ready for use to be administered simultaneously, concurrently, separately or sequentially. The components may be administered
15 independently of one another by the oral, intravenous, topical, local installations, intraperitoneal or nasal route.

BACKGROUND OF THE INVENTION

20 Combinations of PI3K Inhibitors and MEK Inhibitors :

Deregulated activation of protein kinases, such as the epidermal growth factor receptor (EGFR), and downstream signalling kinases (PI3K and MAPK pathways) are associated with human cancers. Although inhibitors of such activated
25 kinases have proved to be of therapeutic benefit in individuals, some patients manifest intrinsic or acquired resistance to these drugs. Developing new agents or novel combination therapies, clearly represents therefore a long-felt need to overcome this intrinsic and acquired drug resistance.

30 Recent insights into the molecular pathogenesis of CRC and NSCLC have given rise to specific target-directed therapies, including kinase inhibitors and monoclonal antibodies (mAb) against epidermal growth factor receptor (EGFR)

and vascular endothelial growth factor (VEGF). Activating mutations of KRAS and BRAF genes are genetic events in tumorigenesis and these mutations are implicated as negative predictive factors in determining response to anti-EGFR drugs. Additional data suggest that other EGFR downstream molecules such as PI3K/PTEN/AKT are also important when considering mechanisms of EGFR antibody resistance.

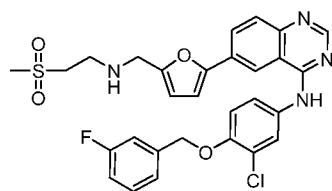
Unexpectedly, and this represents a basis of the present invention, when combinations of :

- component A : a 2,3-dihydroimidazo[1,2-c]quinazoline compound of general formula (A1) or (A2), or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, as described and defined herein; with

- component B : which is :

- either an N-(2-aryl amino) aryl sulfonamide compound of general formula (B), or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, as described and defined herein ;

- or N-[3-chloro-4-[(3-fluorophenyl)methoxy]phenyl]-6-[5-[(2-methylsulfonyl)ethylamino)methyl]-2-furyl]quinazolin-4-amine :



, (which is herein referred to as Lapatinib) ;

- or 5B,20-Epoxy-1,2 α ,4,7B,10B,13 α -hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine (which is hereinafter referred to as Paclitaxel) ;

were evaluated for the treatment of CRC, NSCLC, , pancreatic cancer, hepatocyte carcinoma and breast cancer, synergistically increased anti-tumor activities were demonstrated with these combinations compared to each

monotherapy, providing a fundamental rationale for the clinical combination therapy using PI3K inhibitors-MEK inhibitors, PI3K inhibitors-Lapatinib or PI3K inhibitors-Paclitaxel .

- 5 The same mechanism and rationale can also be applied in other cancer indications with genetic alteration in RTKs, RAS/RAF/MEK and PI3K/PTEN/AKT pathway molecules, or with activation of in RTKs, RAS/RAF/MEK and PI3K/PTEN/AKT pathway molecules through other mechanisms.
- 10 To the Applicant's knowledge, no generic or specific disclosure or suggestion in the prior art is known that either combinations of :
- component A : one or more 2,3-dihydroimidazo[1,2-c]quinazoline compounds of general formula (A1) or (A2), or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;
- 15 component B : one or more N-(2-arylamino) aryl sulfonamide compounds of general formula (B), or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and, optionally,
- component C : one or more further pharmaceutical agents ;
- or combinations of :
- 20 component A : one or more 2,3-dihydroimidazo[1,2-c]quinazoline compounds of general formula (A1) or (A2), or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;
- component B : Lapatinib ; and, optionally,
- component C : one or more further pharmaceutical agents ;
- 25 or combinations of :
- component A : one or more 2,3-dihydroimidazo[1,2-c]quinazoline compounds of general formula (A1) or (A2), or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;
- component B : Paclitaxel ; and, optionally,
- 30 component C : one or more further pharmaceutical agents ;

in which optionally either or both of said components A and B of any of the above-mentioned combinations are in the form of a pharmaceutical formulation which is ready for use to be administered simultaneously, concurrently, separately or sequentially, would be effective in the treatment
5 or prophylaxis of cancer, particularly NSCLC, CRC, melanoma, pancreatic cancer, hepatocyte carcinoma or breast cancer.

Based on the action of the testing compounds described in this invention, the combinations of the present invention as described and defined herein, show a
10 beneficial effect in the treatment of cancer, particularly NSCLC, CRC, melanoma, pancreatic cancer, hepatocyte carcinoma or breast cancer.

Accordingly, in accordance with a first aspect, the present invention relates :
to combinations of :

15 component A : one or more 2,3-dihydroimidazo[1,2-c]quinazoline compounds of general formula (A1) or (A2), or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;

component B : one or more N-(2-arylamino) aryl sulfonamide compounds of general formula (B), or a physiologically acceptable salt, solvate, hydrate or
20 stereoisomer thereof ; and, optionally,

component C : one or more further pharmaceutical agents ;

to combinations of :

component A : one or more 2,3-dihydroimidazo[1,2-c]quinazoline compounds of general formula (A1) or (A2), or a physiologically acceptable salt, solvate,
25 hydrate or stereoisomer thereof ;

component B : Lapatinib ; and, optionally,

component C : one or more further pharmaceutical agents ;

and to combinations of :

30 component A : one or more 2,3-dihydroimidazo[1,2-c]quinazoline compounds of general formula (A1) or (A2), or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;

component B : Paclitaxel ; and, optionally,
component C : one or more further pharmaceutical agents ;

in which optionally either or both of said components A and B) of any of the
5 above-mentioned combinations are in the form of a pharmaceutical
formulation which is ready for use to be administered simultaneously,
concurrently, separately or sequentially. The components may be administered
independently of one another by the oral, intravenous, topical, local
installations, intraperitoneal or nasal route.

10

In accordance with a second aspect, of the present invention relates to the use
of any of such combinations as described *supra* for the preparation of a
medicament for the treatment or prophylaxis of a cancer, particularly NSCLC,
CRC, melanoma, pancreatic cancer, hepatocyte carcinoma or breast cancer.

15

Further, in accordance with a third aspect, the present invention relates to a
kit comprising :

a combination of :

component A : one or more 2,3-dihydroimidazo[1,2-c]quinazoline compounds
20 of general formula (A1) or (A2), or a physiologically acceptable salt, solvate,
hydrate or stereoisomer thereof ;

component B : one or more N-(2-arylamino) aryl sulfonamide compounds of
general formula (B), or a physiologically acceptable salt, solvate, hydrate or
stereoisomer thereof ; and, optionally,

25 component C : one or more further pharmaceutical agents ;

or a combination of :

component A : one or more 2,3-dihydroimidazo[1,2-c]quinazoline compounds
of general formula (A1) or (A2), or a physiologically acceptable salt, solvate,
hydrate or stereoisomer thereof ;

30 component B : Lapatinib ; and, optionally,
component C : one or more further pharmaceutical agents ;
or a combination of :

component A : one or more 2,3-dihydroimidazo[1,2-c]quinazoline compounds of general formula (A1) or (A2), or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;

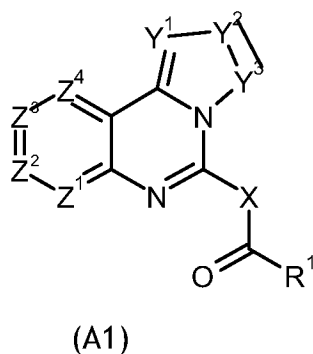
- 5 component B : Paclitaxel ; and, optionally,
component C : one or more further pharmaceutical agents ;

in which optionally either or both of components A and B in any of the above-mentioned combinations are in the form of a pharmaceutical formulation
10 which is ready for use to be administered simultaneously, concurrently, separately or sequentially. The components may be administered independently of one another by the oral, intravenous, topical, local installations, intraperitoneal or nasal route.

15 Detailed description of the Invention

In accordance with an embodiment of the above-mentioned aspects of the present invention, said combinations are of :

- 20 component A : which is one or more 2,3-dihydroimidazo[1,2-c]quinazoline compounds of general formula (A1) :



25 wherein

X represents CR⁵R⁶ or NH;

Y¹ represents CR³ or N;

Chemical bond between Y²—Y³ represents a single bond or double bond,

5

with the proviso that when the Y²—Y³ represents a double bond,

Y² and Y³ independently represent CR⁴ or N, and

10 when Y²—Y³ represents a single bond, Y² and Y³ independently represent CR³R⁴ or NR⁴;

Z¹, Z², Z³ and Z⁴ independently represent CH, CR² or N;

15 R¹ represents aryl optionally having 1 to 3 substituents selected from R¹¹, C₃₋₈ cycloalkyl optionally having 1 to 3 substituents selected from R¹¹, C₁₋₆ alkyl optionally substituted by aryl, heteroaryl, C₁₋₆ alkoxyaryl, aryloxy, heteroaryloxy or one or more halogen,

20 C₁₋₆ alkoxy optionally substituted by carboxy, aryl, heteroaryl, C₁₋₆ alkoxyaryl, aryloxy, heteroaryloxy or one or more halogen,
or

25 a 3 to 15 membered mono- or bi-cyclic heterocyclic ring that is saturated or unsaturated, and contains 1 to 3 heteroatoms selected from the group consisting of N, O and S, and optionally having 1 to 3 substituents selected from R¹¹

wherein

R¹¹ represents

30 halogen, nitro, hydroxy, cyano, carboxy, amino, N-(C₁₋₆alkyl)amino, N-(hydroxyc₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆acyl)amino, N-(formyl)-N-(C₁₋₆alkyl)amino, N-(C₁₋₆alkanesulfonyl) amino, N-(carboxyC₁₋₆-

alkyl)-N-(C₁₋₆alkyl)amino, N-(C₁₋₆alkoxycarbonyl)amino, N-[N,N-di(C₁₋₆alkyl)amino methylene]amino, N-[N,N-di(C₁₋₆alkyl)amino (C₁₋₆ alkyl)methylene]amino, N-[N,N-di(C₁₋₆alkyl)amino C₂₋₆alkenyl]amino, aminocarbonyl, N-(C₁₋₆alkyl)aminocarbonyl, N,N-di(C₁₋₆alkyl)aminocarbonyl, C₃₋₈cycloalkyl, C₁₋₆ alkylthio, C₁₋₆alkanesulfonyl, sulfamoyl, C₁₋₆alkoxycarbonyl,

N-arylamino wherein said aryl moiety is optionally having 1 to 3 substituents selected from R¹⁰¹, N-(aryl C₁₋₆alkyl)amino wherein said aryl moiety is optionally having 1 to 3 substituents selected from R¹⁰¹, aryl C₁₋₆alkoxycarbonyl wherein said aryl moiety is optionally having 1 to 3 substituents selected from R¹⁰¹,

C₁₋₆alkyl optionally substituted by

mono-, di- or tri- halogen, amino, N-(C₁₋₆alkyl)amino or N,N-di(C₁₋₆alkyl)amino,

C₁₋₆alkoxy optionally substituted by

mono-, di- or tri- halogen, N-(C₁₋₆alkyl)sulfonamide, or N-(aryl)sulfonamide,

or

a 5 to 7 membered saturated or unsaturated ring having 1 to 3 heteroatoms selected from the group consisting of O, S and N, and optionally having 1 to 3 substituents selected from R¹⁰¹

wherein

R¹⁰¹ represents

halogen, carboxy, amino, N-(C₁₋₆ alkyl)amino, N,N-di(C₁₋₆alkyl)amino, aminocarbonyl, N-(C₁₋₆alkyl)aminocarbonyl, N,N-di(C₁₋₆alkyl)aminocarbonyl, pyridyl,

C₁₋₆ alkyl optionally substituted by cyano or mono- di- or tri- halogen, or

C₁₋₆alkoxy optionally substituted by cyano, carboxy, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, aminocarbonyl, N-(C₁₋₆alkyl)aminocarbonyl, N,N-di(C₁₋₆alkyl)aminocarbonyl or mono-, di- or tri- halogen;

R^2 represents hydroxy, halogen, nitro, cyano, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(hydroxyC₁₋₆alkyl)amino, N-(hydroxyC₁₋₆alkyl)-N-(C₁₋₆alkyl)amino, C₁₋₆ acyloxy, aminoC₁₋₆ acyloxy, C₂₋₆alkenyl, aryl,

5 a 5-7 membered saturated or unsaturated heterocyclic ring having 1 to 3 heteroatoms selected from the group consisting O, S and N, and optionally substituted by

hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, amino, amino C₁₋₆alkyl, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆ acyl)amino, N-(C₁₋₆alkyl)carbonylamino, phenyl, phenyl C₁₋₆ alkyl, carboxy, C₁₋₆alkoxycarbonyl, aminocarbonyl, N-(C₁₋₆alkyl)aminocarbonyl, or N,N-di(C₁₋₆alkyl)amino, -C(O)- R^{20}

wherein

15 R^{20} represents C₁₋₆ alkyl, C₁₋₆ alkoxy, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆ acyl)amino, or a 5-7 membered saturated or unsaturated heterocyclic ring having 1 to 3 heteroatoms selected from the group consisting O, S and N, and optionally substituted by

20 C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆ acyl)amino, phenyl, or benzyl,

C₁₋₆ alkyl optionally substituted by R^{21}

or

25 C₁₋₆ alkoxy optionally substituted by R^{21}

wherein

R^{21} represents cyano, mono-, di or tri- halogen, hydroxy, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(hydroxyC₁₋₆ alkyl) amino, N-(halophenylC₁₋₆ alkyl) amino, amino C₂₋₆ alkylenyl, C₁₋₆ alkoxy, hydroxyC₁₋₆ alkoxy, -C(O)- R^{201} , -NHC(O)- R^{201} , C₃₋₈cycloalkyl, isoindolino, phthalimidyl, 2-oxo-1,3-oxazolidinyl, aryl

30 or a 5 or 6 membered saturated or unsaturated heterocyclic ring

having 1 to 4 heteroatoms selected from the group consisting O, S and N optionally substituted by

hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxycarbonyl, hydroxyC₁₋₆ alkoxy, oxo, amino, aminoC₁₋₆alkyl, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆ acyl)amino, or benzyl,

wherein

R²⁰¹ represents hydroxy, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N- (halophenylC₁₋₆ alkyl) amino, C₁₋₆alkyl, aminoC₁₋₆ alkyl, aminoC₂₋₆ alkylenyl, C₁₋₆ alkoxy, a 5 or 6 membered saturated or unsaturated heterocyclic ring having 1 to 4 heteroatoms selected from the group consisting O, S and N optionally substituted by

hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxycarbonyl, hydroxyC₁₋₆ alkoxy, oxo, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆ acyl)amino or benzyl;

R³ represents hydrogen, halogen, aminocarbonyl, or C₁₋₆ alkyl optionally substituted by aryl C₁₋₆ alkoxy or mono-, di- or tri-halogen;

R⁴ represents hydrogen or C₁₋₆ alkyl;

R⁵ represents hydrogen or C₁₋₆ alkyl; and

R⁶ represents halogen, hydrogen or C₁₋₆ alkyl ;or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;

said compounds are published as compounds of general formulae I, I-a, and I-b in International patent application PCT/EP2003/010377, published as WO 04/029055 A1 on April 08, 2004, which is incorporated herein by reference in its entirety. In WO 04/029055, said compounds of general formula I, I-a and I-b are described on pp. 6 *et seq.*, they may be synthesized according to the

methods given therein on pp. 26 *et seq.*, and are exemplified as specific compound Examples 1-1 to 1-210 on pp. 47 to 106, specific compound Examples 2-1 to 2-368 on pp. 107 to 204, specific compound Examples 3-1 to 3-2 on pp. 205 to 207, and as specific compound Examples 4-1 to 4-2 on pp. 208 to 210, therein.

Said component A may be in the form of a pharmaceutical formulation which is ready for use to be administered simultaneously, concurrently, separately or sequentially. The components may be administered independently of one another by the oral, intravenous, topical, local installations, intraperitoneal or nasal route.

In accordance with another embodiment of the above-mentioned aspects of the present invention, said combinations are of :

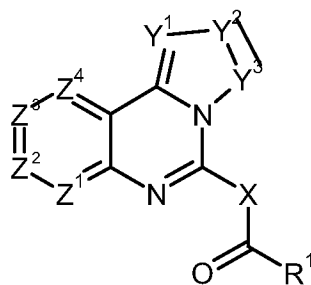
component A : which is one or more 2,3-dihydroimidazo[1,2-c]quinazoline compounds of general formula (A1), *supra*, which is selected from the list consisting of specific compound Examples 1-1 to 1-210 on pp. 47 to 106, specific compound Examples 2-1 to 2-368 on pp. 107 to 204, specific compound Examples 3-1 to 3-2 on pp. 205 to 207, and specific compound Examples 4-1 to 4-2 on pp. 208 to 210, of in International patent application PCT/EP2003/010377, published as WO 04/029055 A1 on April 08, 2004, which is incorporated herein by reference in its entirety, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof.

Said component A may be in the form of a pharmaceutical formulation which is ready for use to be administered simultaneously, concurrently, separately or sequentially. The components may be administered independently of one another by the oral, intravenous, topical, local installations, intraperitoneal or nasal route.

As mentioned *supra*, said specific compound Examples may be synthesized according to the methods given in WO 04/029055 A1 on pp. 26 *et seq.*.

In accordance with another embodiment of the above-mentioned aspects of the present invention, said combinations are of :

component A : which is one or more 2,3-dihydroimidazo[1,2-c]quinazoline compounds of general formula (A2) :



(A2)

in which :

X represents CR^5R^6 or NH ;

Y^1 represents CR^3 or N ;

the chemical bond between $\text{Y}^2\text{---}\text{Y}^3$ represents a single bond or double bond, with the proviso that when the $\text{Y}^2\text{---}\text{Y}^3$ represents a double bond, Y^2 and Y^3 independently represent CR^4 or N , and when $\text{Y}^2\text{---}\text{Y}^3$ represents a single bond, Y^2 and Y^3 independently represent CR^3R^4 or NR^4 ;

Z^1 , Z^2 , Z^3 and Z^4 independently represent CH , CR^2 or N ;

R¹ represents aryl optionally having 1 to 3 substituents selected from R¹¹, C₃₋₈ cycloalkyl optionally having 1 to 3 substituents selected from R¹¹,

5 C₁₋₆ alkyl optionally substituted by aryl, heteroaryl, C₁₋₆ alkoxyaryl, aryloxy, heteroaryloxy or one or more halogen,

C₁₋₆ alkoxy optionally substituted by carboxy, aryl, heteroaryl, C₁₋₆ alkoxyaryl, aryloxy, heteroaryloxy or one or more halogen,

or

10 a 3 to 15 membered mono- or bi-cyclic heterocyclic ring that is saturated or unsaturated, optionally having 1 to 3 substituents selected from R¹¹, and contains 1 to 3 heteroatoms selected from the group consisting of N, O and S,

wherein

15 R¹¹ represents halogen, nitro, hydroxy, cyano, carboxy, amino, N-(C₁₋₆alkyl)amino, N-(hydroxyC₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆acyl)amino, N-(formyl)-N-(C₁₋₆alkyl)amino, N-(C₁₋₆alkanesulfonyl) amino, N-(carboxyC₁₋₆alkyl)-N-(C₁₋₆alkyl)amino, N-(C₁₋₆alkoxycarbonyl)amino, N-[N,N-di(C₁₋₆alkyl)amino methylene]amino, N-[N,N-di(C₁₋₆alkyl)amino (C₁₋₆alkyl)methylene]amino, N-[N,N-di(C₁₋₆alkyl)amino C₂₋₆alkenyl]amino, aminocarbonyl, N-(C₁₋₆alkyl)aminocarbonyl, N,N-di(C₁₋₆alkyl)aminocarbonyl, C₃₋₈cycloalkyl, C₁₋₆ alkylthio, C₁₋₆alkanesulfonyl, sulfamoyl, C₁₋₆alkoxycarbonyl,

25 N-arylamino wherein said aryl moiety is optionally having 1 to 3 substituents selected from R¹⁰¹, N-(aryl C₁₋₆alkyl)amino wherein said aryl moiety is optionally having 1 to 3 substituents selected from R¹⁰¹, aryl C₁₋₆alkoxycarbonyl wherein said aryl moiety is optionally having 1 to 3 substituents selected from R¹⁰¹,

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C₁₋₆alkyl optionally substituted by mono-, di- or tri- halogen, amino, N-(C₁₋₆alkyl)amino or N,N-di(C₁₋₆alkyl)amino,

C₁₋₆alkoxy optionally substituted by mono-, di- or tri-halogen, N-(C₁₋₆alkyl)sulfonamide, or N-(aryl)sulfonamide,

or

a 5 to 7 membered saturated or unsaturated ring having 1 to 3 heteroatoms selected from the group consisting of O, S and N, and optionally having 1 to 3 substituents selected from R¹⁰¹

wherein

R¹⁰¹ represents halogen, carboxy, amino, N-(C₁₋₆ alkyl)amino, N,N-di(C₁₋₆alkyl)amino, aminocarbonyl, N-(C₁₋₆alkyl)aminocarbonyl, N,N-di(C₁₋₆alkyl)aminocarbonyl, pyridyl,

C₁₋₆ alkyl optionally substituted by cyano or mono- di- or tri- halogen,

and

C₁₋₆alkoxy optionally substituted by cyano, carboxy, amino, N-(C₁₋₆ alkyl)amino, N,N-di(C₁₋₆alkyl)amino, aminocarbonyl, N-(C₁₋₆alkyl)aminocarbonyl, N,N-di(C₁₋₆alkyl)aminocarbonyl or mono-, di- or tri- halogen;

R² represents hydroxy, halogen, nitro, cyano, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(hydroxyC₁₋₆alkyl)amino, N-(hydroxyC₁₋₆alkyl)-N-(C₁₋₆alkyl)amino, C₁₋₆ acyloxy, aminoC₁₋₆ acyloxy, C₂₋₆alkenyl, aryl,

a 5-7 membered saturated or unsaturated heterocyclic ring having 1 to 3 heteroatoms selected from the group consisting O, S and N, and optionally substituted by

hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, amino, amino C₁₋₆alkyl, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆ acyl)amino, N-

(C₁₋₆alkyl)carbonylamino, phenyl, phenyl C₁₋₆ alkyl, carboxy, C₁₋₆alkoxycarbonyl, aminocarbonyl, N-(C₁₋₆alkyl)aminocarbonyl, or N,N-di(C₁₋₆alkyl)amino, -C(O)- R²⁰

wherein

R²⁰ represents C₁₋₆ alkyl, C₁₋₆ alkoxy, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆ acyl)amino, or a 5-7 membered saturated or unsaturated heterocyclic ring having 1 to 3 heteroatoms selected from the group consisting O, S and N, and optionally substituted by C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆ acyl)amino, phenyl, or benzyl,

C₁₋₆ alkyl optionally substituted by R²¹,

or

C₁₋₆ alkoxy optionally substituted by R²¹,

wherein

R²¹ represents cyano, mono-, di or tri- halogen, hydroxy, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(hydroxyC₁₋₆ alkyl) amino, N- (halophenylC₁₋₆ alkyl) amino, amino C₂₋₆ alkylenyl, C₁₋₆ alkoxy, hydroxyC₁₋₆ alkoxy, -C(O)- R²⁰¹, -NHC(O)- R²⁰¹, C₃₋₈cycloalkyl, isoindolino, phthalimidyl, 2-oxo-1,3-oxazolidinyl, aryl or a 5 or 6 membered saturated or unsaturated heterocyclic ring having 1 to 4 heteroatoms selected from the group consisting O, S and N, and optionally substituted by hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxycarbonyl, hydroxyC₁₋₆ alkoxy, oxo, amino, aminoC₁₋₆alkyl, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆ acyl)amino, or benzyl,

wherein

R²⁰¹ represents hydroxy, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N- (halophenylC₁₋₆alkyl) amino, C₁₋₆alkyl, aminoC₁₋₆ alkyl, aminoC₂₋₆ alkylenyl, C₁₋₆ alkoxy, a 5 or 6 membered saturated or unsaturated heterocyclic ring having 1 to 4 heteroatoms selected from the group consisting O, S and N, and optionally substituted by hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxy carbonyl, hydroxyC₁₋₆ alkoxy, oxo, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆acyl)amino or benzyl;

R³ represents hydrogen, halogen, aminocarbonyl, or C₁₋₆ alkyl optionally substituted by aryl C₁₋₆ alkoxy or mono-, di- or tri-halogen;

R⁴ represents hydrogen or C₁₋₆ alkyl;

R⁵ represents hydrogen or C₁₋₆ alkyl; and

R⁶ represents halogen, hydrogen or C₁₋₆ alkyl ;
or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;
said compounds are published as compounds of general formulae I, Ia, Ib, Ic, Id and Ie in International patent application PCT/US2007/024985, published as WO 2008/070150 A1 on June 12, 2008, which is incorporated herein by reference in its entirety. In WO 2008/070150, said compounds of general formula I, Ia, Ib, Ic, Id and Ie are described on pp. 9 *et seq.*, they may be synthesized according to the methods given therein on pp. 42, *et seq.*, and are exemplified as specific compound Examples 1 to 103 therein on pp. 65 to 101.

Biological test data for certain of said compounds are given therein on pp. 101 to 107.

Said component A may be in the form of a pharmaceutical formulation which is ready for use to be administered simultaneously, concurrently, separately or sequentially. The components may be administered independently of one another by the oral, intravenous, topical, local installations, intraperitoneal or nasal route.

In accordance with another embodiment of the above-mentioned aspects of the present invention, said combinations are of :

component A : which is one or more 2,3-dihydroimidazo[1,2-c]quinazoline compounds of general formula (A2), *supra*, which is selected from the list consisting of :

Example 1 : N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide

Example 2 : N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide

Example 3 : N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2,4-dimethyl-1,3-thiazole-5-carboxamide

Example 4 : 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1,3-thiazole-5-carboxamide.

Example 5 : 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]isonicotinamide

Example 6 : 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-4-methyl-1,3-thiazole-5-carboxamide

Example 7 : 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-4-propylpyrimidine-5-carboxamide

Example 8 : N-{8-[2-(4-ethylmorpholin-2-yl)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide

Example 9 : N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-

5 c]quinazolin-5-yl}pyrimidine-5-carboxamide

Example 10 : N-(8-{3-[2-(hydroxymethyl)morpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide

Example 11 : N-(8-{3-[2-(hydroxymethyl)morpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide

10 Example 12 : N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide 1-oxide

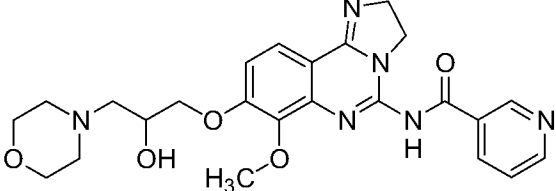
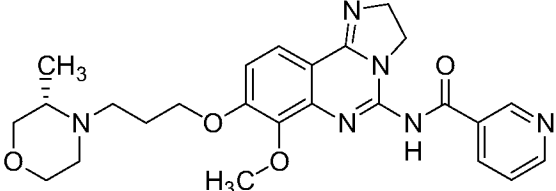
Example 13 : 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide.

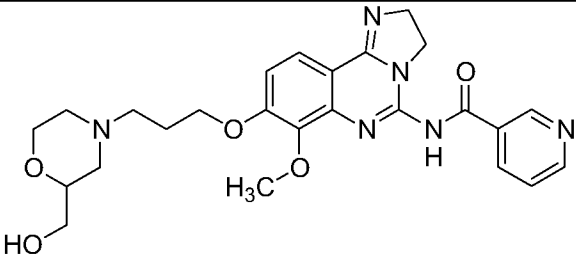
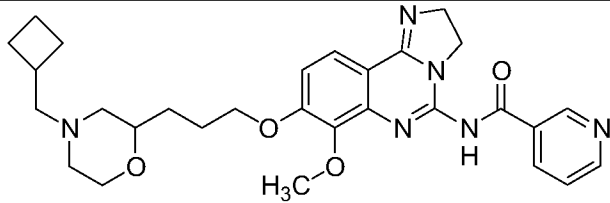
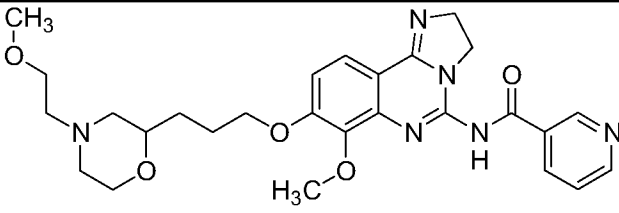
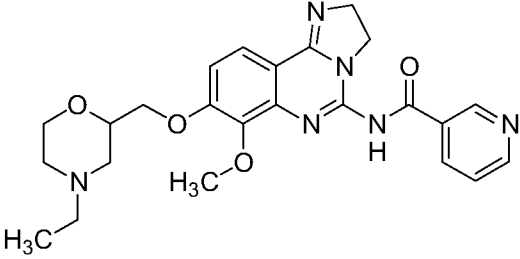
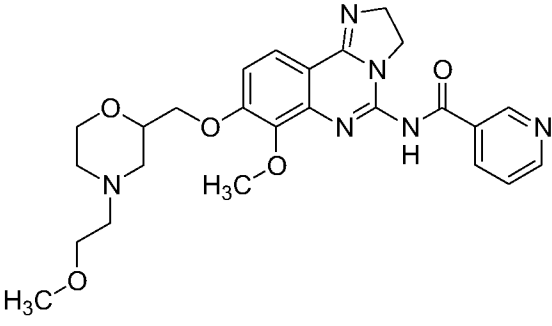
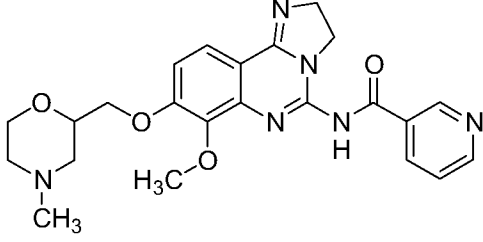
Example 14 : N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-
15 dihydroimidazo[1,2-

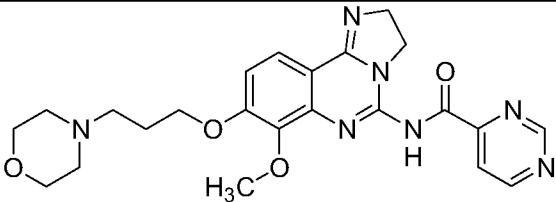
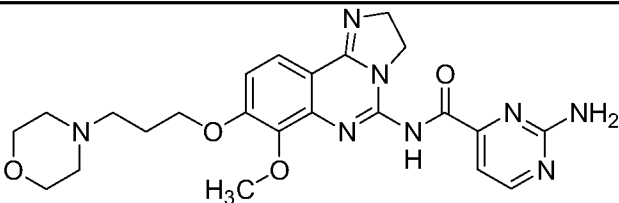
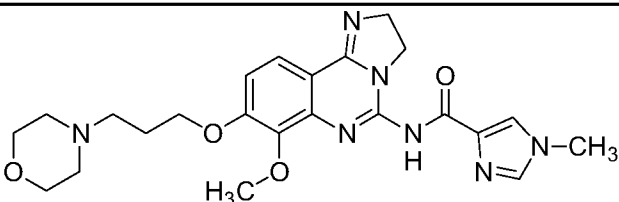
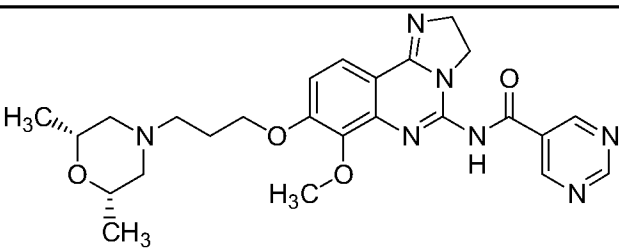
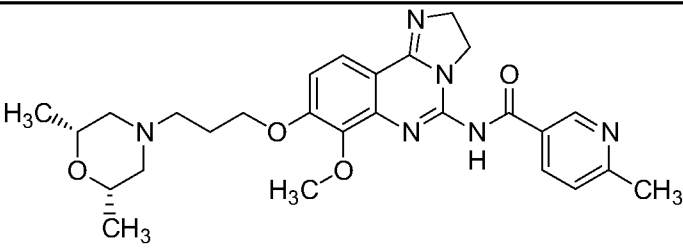
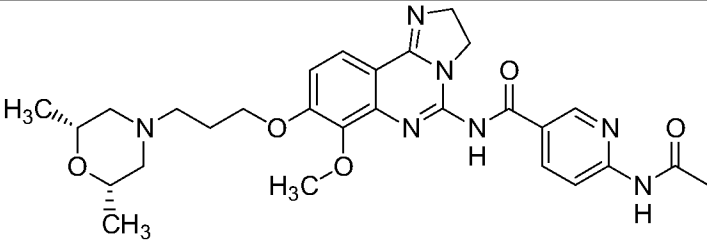
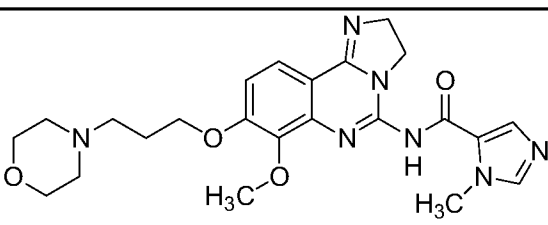
c]quinazolin-5-yl]-6-(2-pyrrolidin-1-ylethyl)nicotinamide.

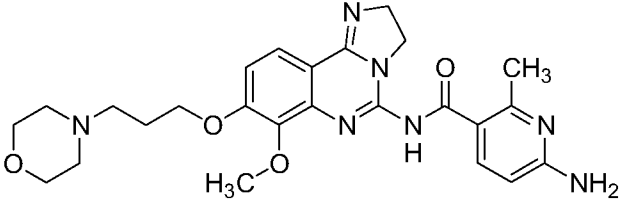
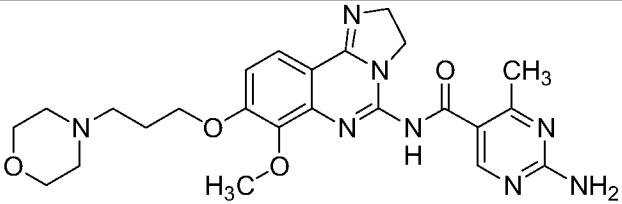
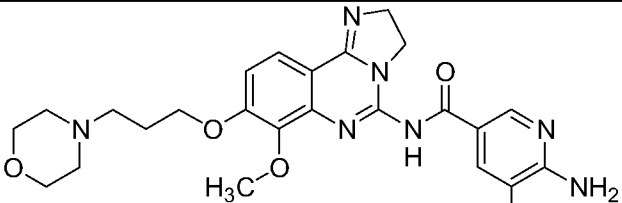
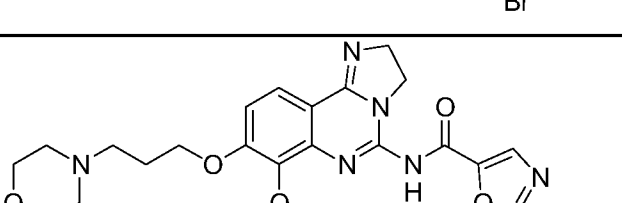
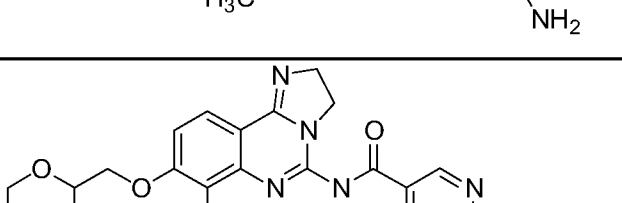
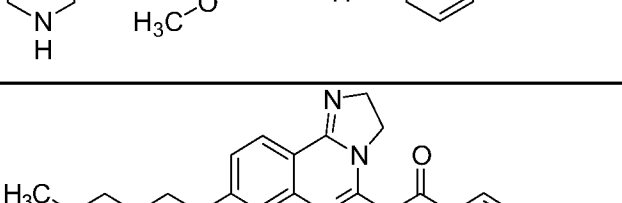
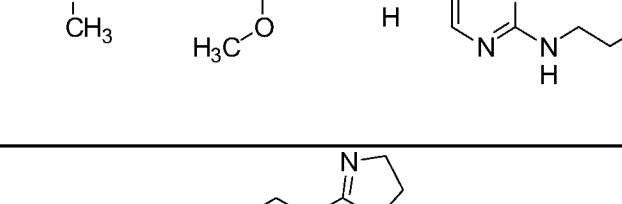
Example 15 : 6-(cyclopentylamino)-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide

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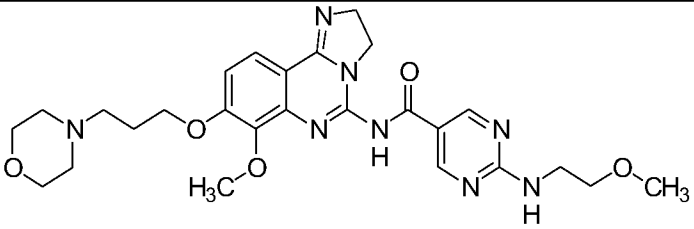
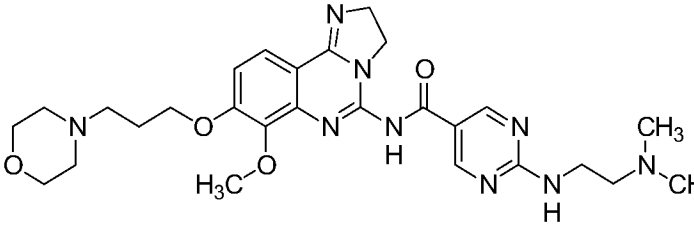
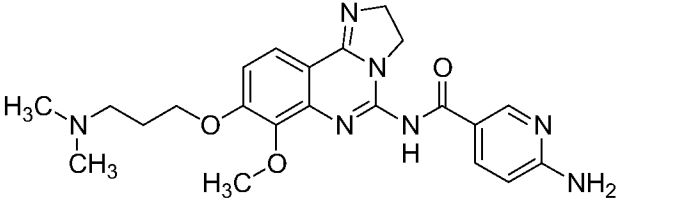
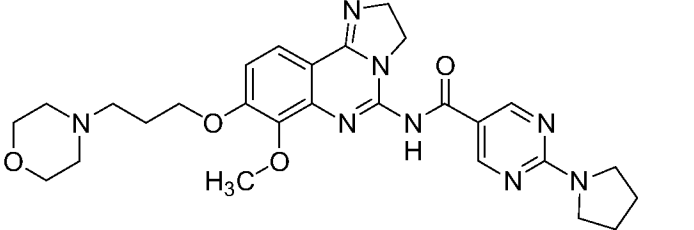
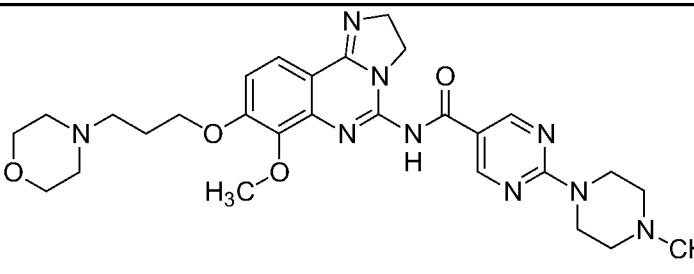
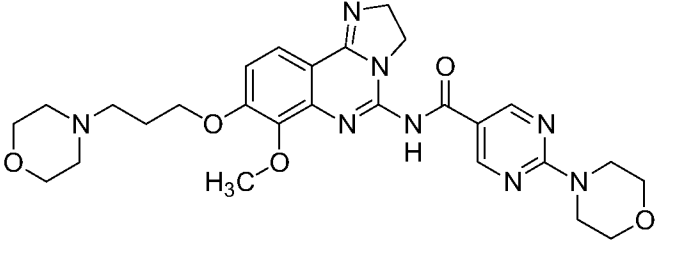
Example	Structure
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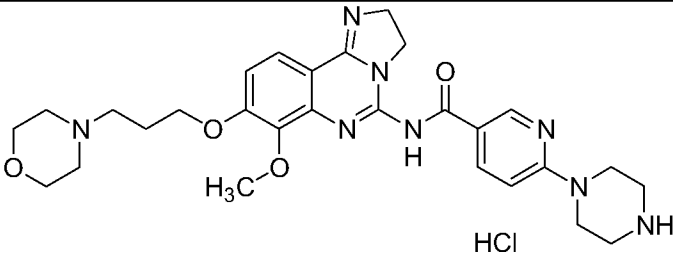
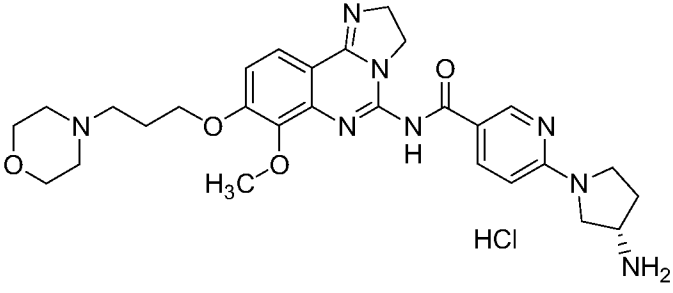
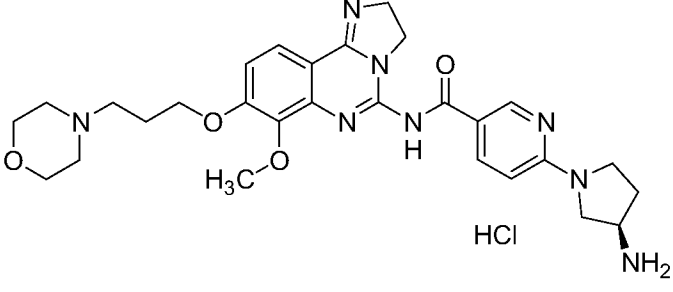
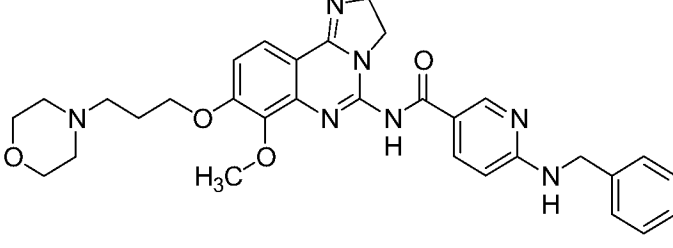
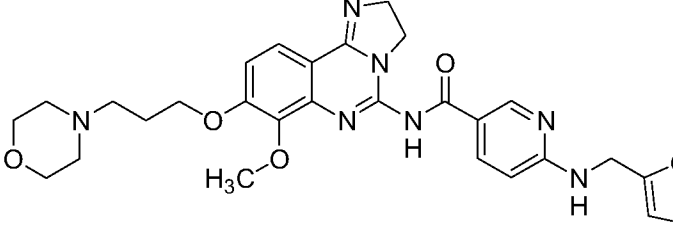
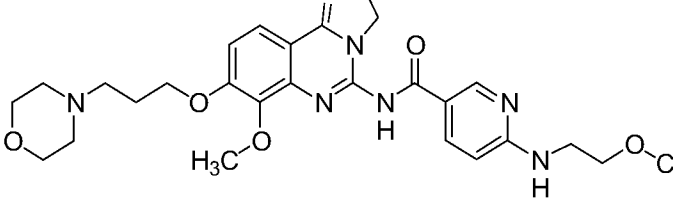
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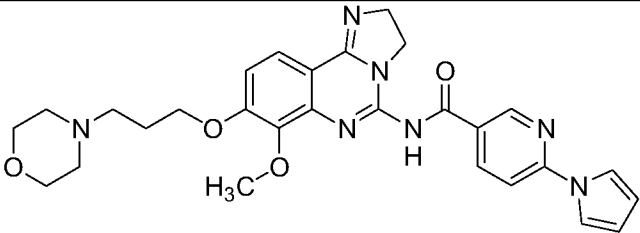
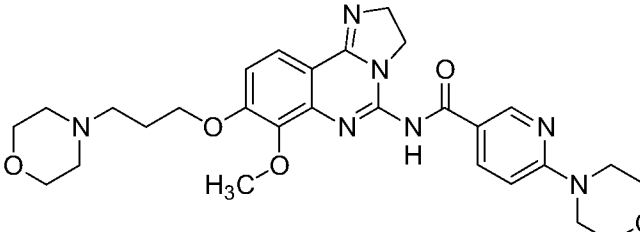
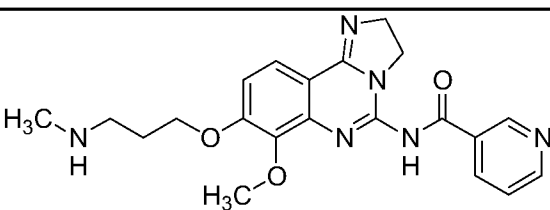
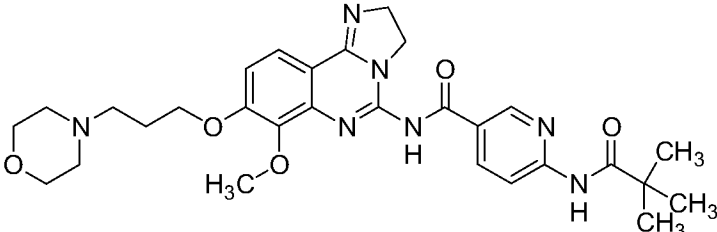
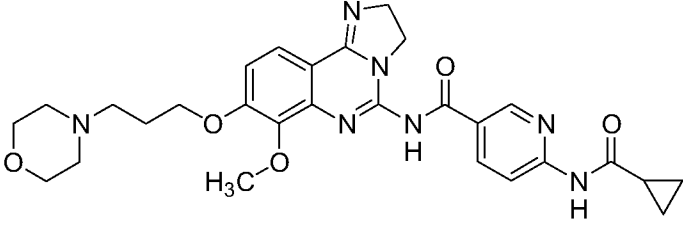
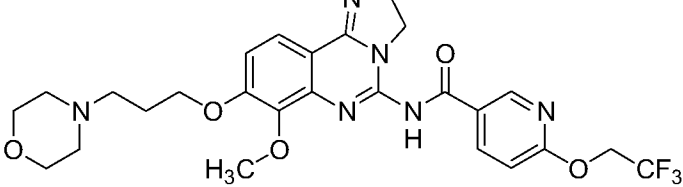
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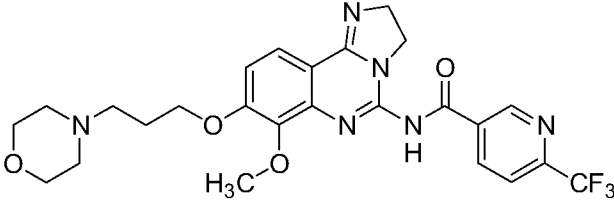
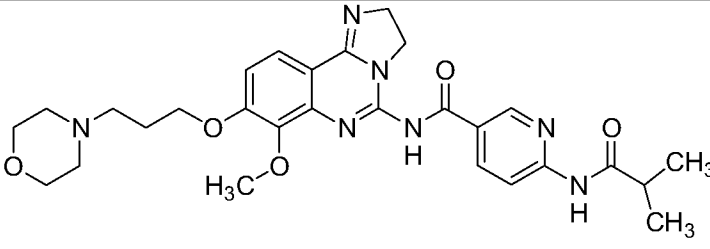
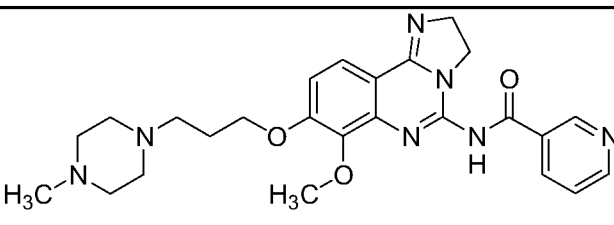
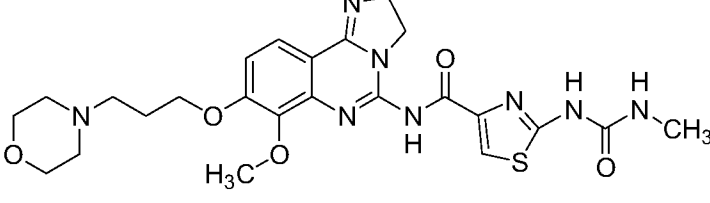
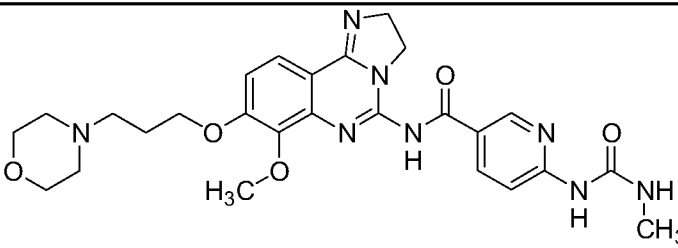
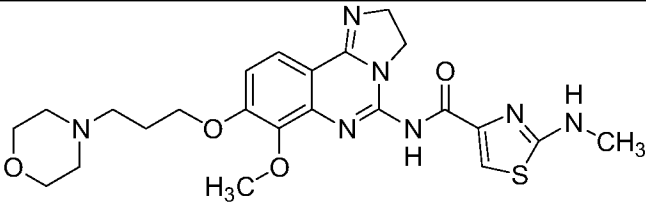
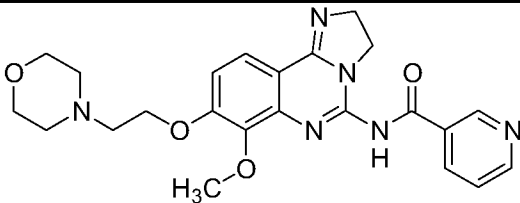
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41	 <chem>COC1=CC=C(C=C1)N2C=NC(=C2)NC(=O)C3=CC=CC=C3NCCOC</chem>
42	 <chem>CN(C)CCOC1=CC(OC)=CC=C1N2C=NC(=C2)NC(=O)C3=CC=CC=C3N</chem>
43	 <chem>COC1=CC=C(C=C1)N2C=NC(=C2)NC(=O)C3=CC=CC=C3NCCCN4CCOCC4</chem>

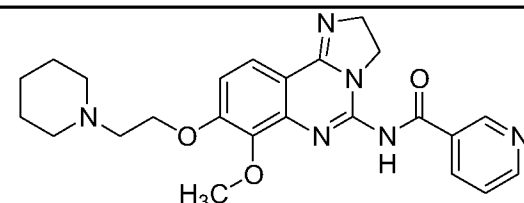
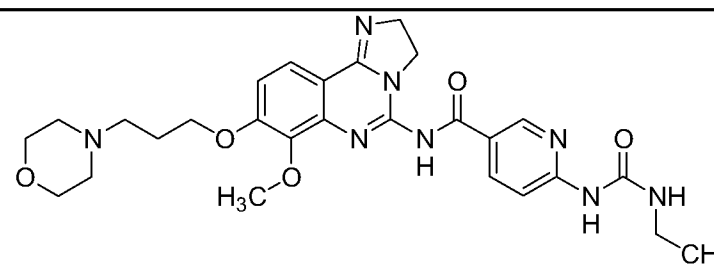
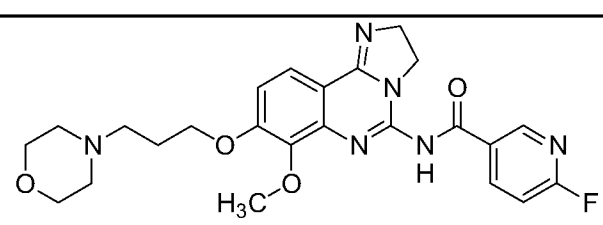
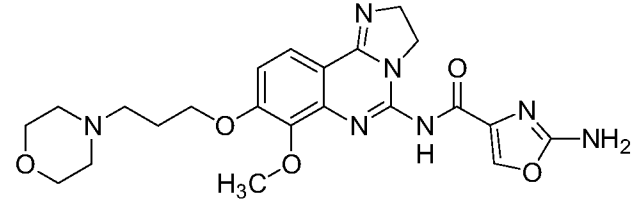
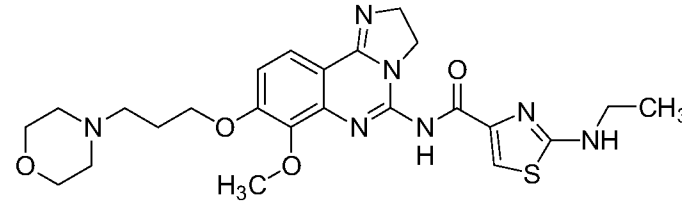
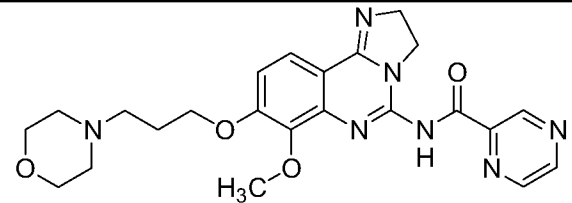
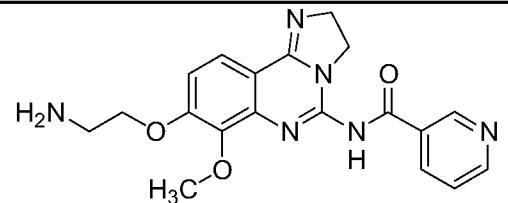
44	 <chem>COC1=CC=C(C=C1)OCCCN2CCOCC2C3=CC=C(C=C3)N4C(=N5C=CC(=N5)NC(=O)N4C6=CC=CC=C6OC)N=C3</chem>
45	 <chem>CN(C)CCN4C=NC(=C5C=CC(=N5)NC(=O)N4C6=CC=C(C=C6)OC)N=C5</chem>
46	 <chem>CN(C)CCOCC1=CC=C(C=C1)N2C(=N3C=CC(=N3)NC(=O)N2C4=CC=CC=C4N)N=C3</chem>
47	 <chem>C1CCNCC1C2=NC(=C3C=CC(=N3)NC(=O)N2C4=CC=C(C=C4)OC)N=C5</chem>
48	 <chem>CN1CCNCC1C2=NC(=C3C=CC(=N3)NC(=O)N2C4=CC=C(C=C4)OC)N=C5</chem>
49	 <chem>C1CCNCC1C2=NC(=C3C=CC(=N3)NC(=O)N2C4=CC=C(C=C4)OC)N=C5</chem>

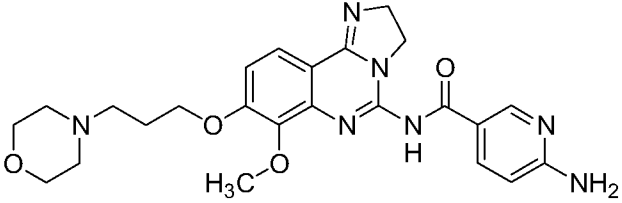
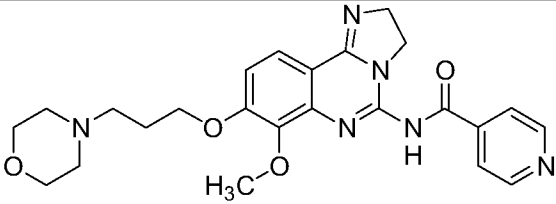
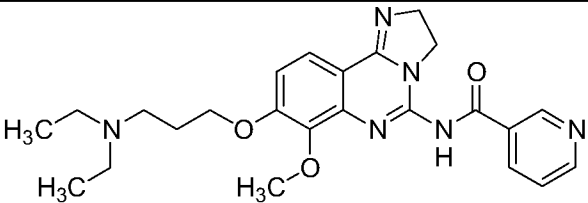
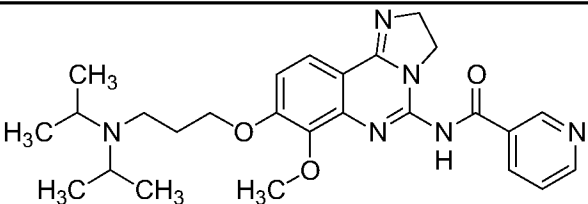
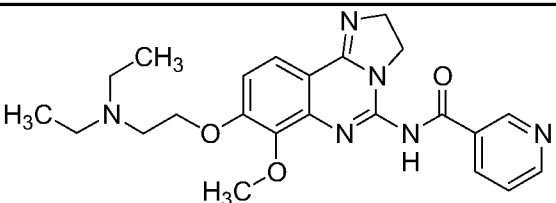
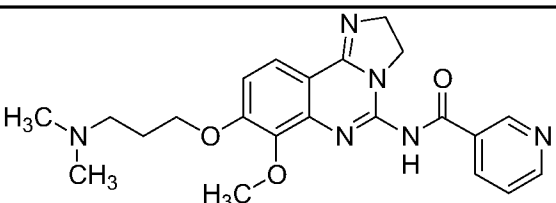
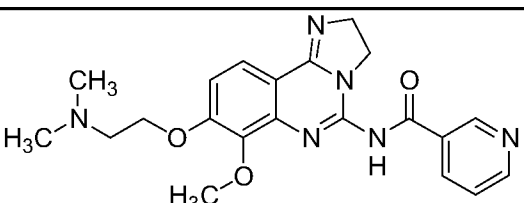
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51	 <chem>COC1=CC=C(OC)C(=C1)OCCCN2CCOCC2NC(=O)c3ccc(N4CC[C@H](N)C4)cc3</chem> HCl
52	 <chem>COC1=CC=C(OC)C(=C1)OCCCN2CCOCC2NC(=O)c3ccc(N4CC[C@@H](N)C4)cc3</chem> HCl
53	 <chem>COC1=CC=C(OC)C(=C1)OCCCN2CCOCC2NC(=O)c3ccc(NC4=CC=CC=C4F)cc3</chem> HCl
54	 <chem>COC1=CC=C(OC)C(=C1)OCCCN2CCOCC2NC(=O)c3ccc(NC4=CC=CO4)cc3</chem> HCl
55	 <chem>COC1=CC=C(OC)C(=C1)OCCCN2CCOCC2NC(=O)c3ccc(NCCOC)cc3</chem> HCl

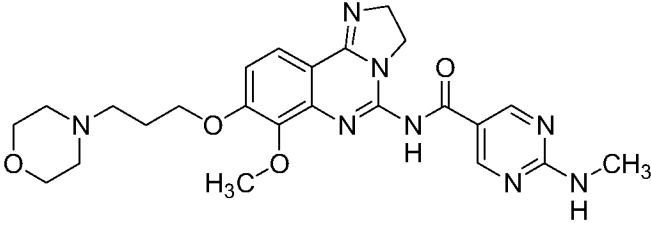
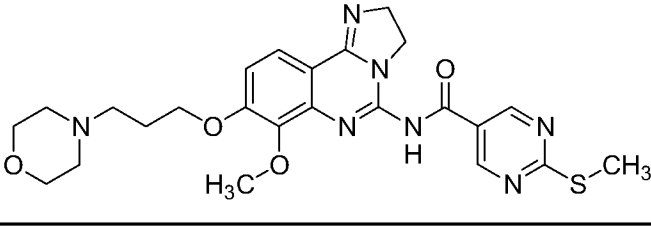
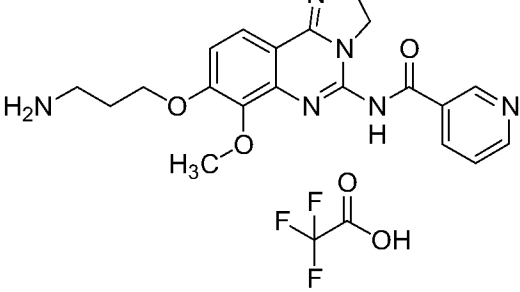
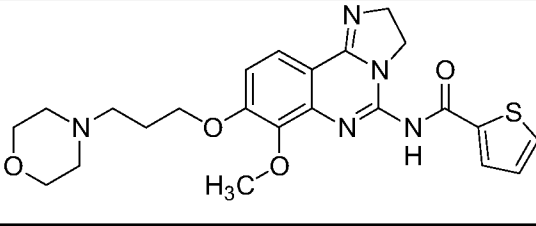
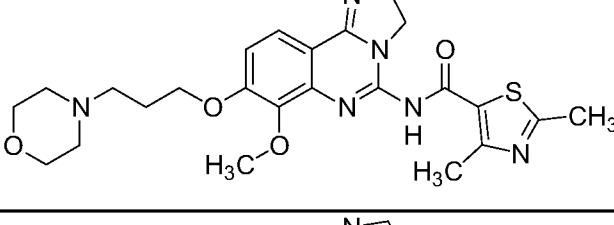
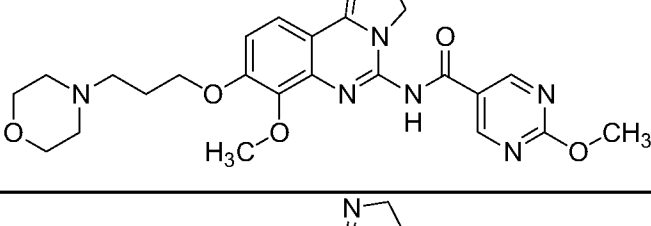
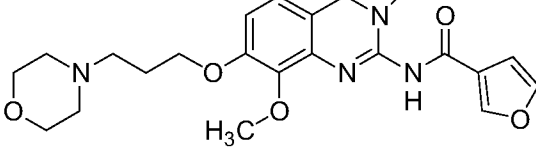
56	 <chem>COc1ccc(cc1N2C=NC(NC(=O)c3ccc(cc3n4c[nH]c4)N2CCO)CCOCCN5CCOCC5)c6ccc(cc6)N7C=CC=C7</chem>
57	 <chem>COc1ccc(cc1N2C=NC(NC(=O)c3ccc(cc3N4CCOCCO4)N2CCO)CCOCCN5CCOCC5)c6ccc(cc6)N7C=CC=C7</chem>
58	 <chem>COc1ccc(cc1N2C=NC(NC(=O)c3ccccn3)N2CCO)CCOCCN4CCOCC4</chem>
59	 <chem>CC(C)C(=O)Nc1ccc(cc1NC(=O)N2C=NC(NC(=O)c3ccc(cc3N4C=CC=CC4)N2CCO)CCOCCN5CCOCC5)c6ccccn6</chem>
60	 <chem>C1CC1C(=O)Nc1ccc(cc1NC(=O)N2C=NC(NC(=O)c3ccc(cc3N4C=CC=CC4)N2CCO)CCOCCN5CCOCC5)c6ccccn6</chem>
61	 <chem>COc1ccc(cc1N2C=NC(NC(=O)c3ccc(cc3OCCF(F)F)N2CCO)CCOCCN4CCOCC4)</chem>

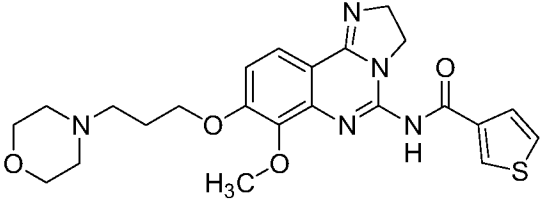
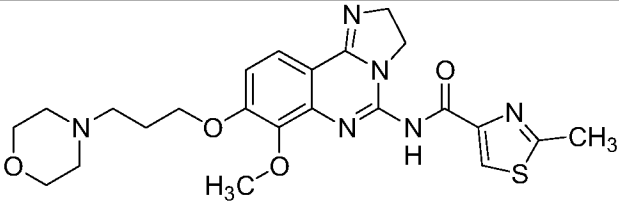
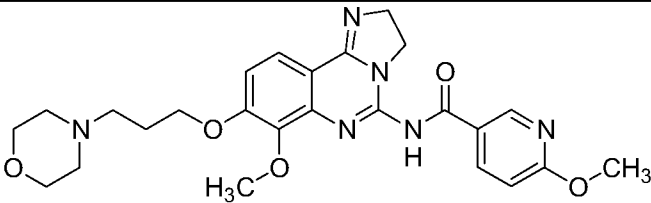
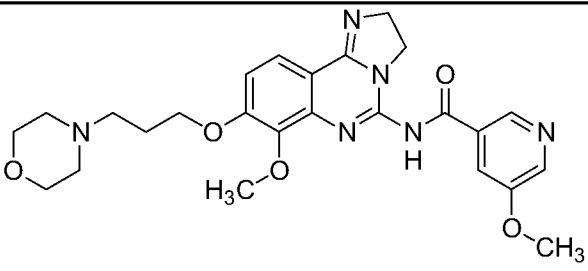
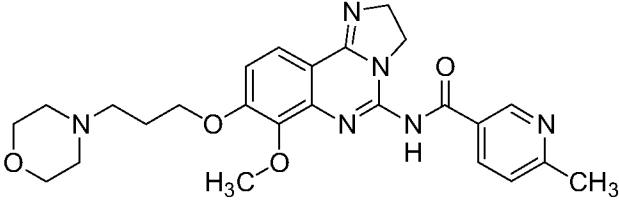
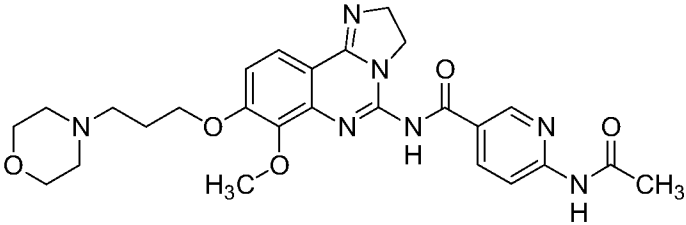
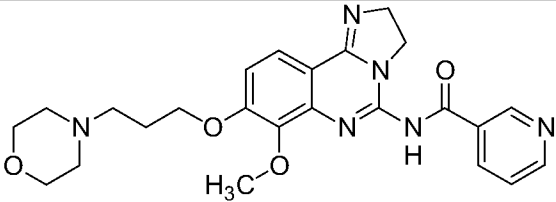
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69	<chem>CN(C)CCOC1=CC=C(C=C1OC)N2C=NC3C(=N2)C(=C3)C(=O)N4C=NC(C)=S4</chem>
70	<chem>CN(C)CCOC1=CC=C(C=C1OC)N2C=NC3C(=N2)C(=C3)C(=O)N4C=CC=C(C)N4</chem>
71	<chem>CC(C)NC(=O)Nc1ccc(cc1)C(=O)N2C=NC3C(=N2)C(=C3)C(=O)N4C=CC=C(C)N4</chem>
72	<chem>C1CCN(C1)c2ccc(cc2)C(=O)N3C=NC4C(=N3)C(=C4)C(=O)N5C=CC=C(C)N5</chem>
73	<chem>CN(C)C1=CC=C(C=C1)C(=O)N2C=NC3C(=N2)C(=C3)C(=O)N4C=CC=C(C)N4</chem>
74	<chem>C1CCN(C1)CCOC2=CC=C(C=C2OC)N3C=NC4C(=N3)C(=C4)C(=O)N5C=CC=C(C)N5</chem>
75	<chem>C1CCN(C1)CCOC2=CC=C(C=C2OC)N3C=NC4C(=N3)C(=C4)C(=O)N5C=CC=C(C)N5</chem>

76	 <chem>COc1cc(OC2CCNCC2)c3cc4c(c1)nc5c4ncn5C(=O)Nc6ccncc6</chem>
77	 <chem>CCNC(=O)Nc1ccc2c(c1)C(=O)Nc3nc4c5c2ncn4c3OC(=O)c6cc(OC7CCOCC7)c8ccccc86</chem>
78	 <chem>COc1cc(OC2CCNCC2)c3cc4c(c1)nc5c4ncn5C(=O)Nc6ccc(F)cc6</chem>
79	 <chem>NC1=NC2=C(N1)OC=C2C(=O)Nc3nc4c5c2ncn4c3OC(=O)c6cc(OC7CCOCC7)c8ccccc86</chem>
80	 <chem>CCNC1=NC2=C(N1)SC=C2C(=O)Nc3nc4c5c2ncn4c3OC(=O)c6cc(OC7CCOCC7)c8ccccc86</chem>
81	 <chem>COc1cc(OC2CCNCC2)c3cc4c(c1)nc5c4ncn5C(=O)Nc6ccncc6</chem>
82	 <chem>COc1cc(OC2CCN)cc3cc4c(c1)nc5c4ncn5C(=O)Nc6ccncc6</chem>

83	 <chem>COc1cc(ccc1N2C=NC3C(=N2)C=CC3C(=O)Nc4ccc(N)cc4)OCCCN5CCOCC5</chem>
84	 <chem>COc1cc(ccc1N2C=NC3C(=N2)C=CC3C(=O)Nc4ccc5ccncc54)OCCCN5CCOCC5</chem>
85	 <chem>COc1cc(ccc1N2C=NC3C(=N2)C=CC3C(=O)Nc4ccc5ccncc54)OCCCN(CC)CC</chem>
86	 <chem>COc1cc(ccc1N2C=NC3C(=N2)C=CC3C(=O)Nc4ccc5ccncc54)OCCCN(C(C)C)C(C)C</chem>
87	 <chem>COc1cc(ccc1N2C=NC3C(=N2)C=CC3C(=O)Nc4ccc5ccncc54)OCCN(C)CC</chem>
88	 <chem>COc1cc(ccc1N2C=NC3C(=N2)C=CC3C(=O)Nc4ccc5ccncc54)OCCN(C)C</chem>
89	 <chem>COc1cc(ccc1N2C=NC3C(=N2)C=CC3C(=O)Nc4ccc5ccncc54)OCCN(C)C</chem>

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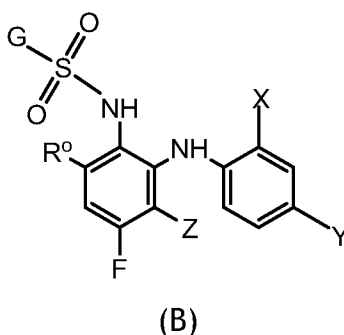
or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof,

said compounds are published as specific compound Examples 1 to 103 in International patent application PCT/US2007/024985, published as WO 2008/070150 A1 on June 12, 2008, which is incorporated herein by reference in its entirety. In WO 2008/070150, said specific compound Examples may be synthesized according to the Examples. Biological test data for certain of said compounds are given therein on pp. 101 to 107.

Said component A may be in the form of a pharmaceutical formulation which is ready for use to be administered simultaneously, concurrently, separately or sequentially. The components may be administered independently of one another by the oral, intravenous, topical, local installations, intraperitoneal or nasal route.

In accordance with an embodiment of the above-mentioned aspects of the present invention, said combinations are of :

component B : which is one or more N-(2-arylamino) aryl sulfonamide compounds of general formula (B) :



where G is R_{1a}, R_{1b}, R_{1c}, R_{1d}, R_{1e}, Ar₁, Ar₂ or Ar₃; R^o is H, halogen, C₁-C₆ alkyl, C₁-C₄ alkoxy, C₃-C₆ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, said alkyl, cycloalkyl, alkenyl, and alkynyl groups optionally substituted with 1-3 substituents selected independently from halogen, OH, CN, cyanomethyl, nitro, phenyl, and trifluoromethyl, and said C₁-C₆ alkyl and C₁-C₄ alkoxy groups also optionally substituted with OCH₃ or OCH₂CH₃; X is F, Cl or methyl; Y is I,

Br, Cl, CF₃, C₁-C₃ alkyl, C₂-C₃ alkenyl, C₂-C₃ alkynyl, cyclopropyl, phenyl, pyridyl, pyrazolyl, OMe, OEt, or SMe, where all said methyl, ethyl, C₁-C₃ alkyl, and cyclopropyl groups of X and Y are optionally substituted with OH, all said phenyl, pyridyl, pyrazolyl groups of Y are optionally substituted with halogen,
5 acetyl, methyl, and trifluoromethyl, and all said methyl groups of X and Y are optionally substituted with one, two, or three F atoms; and Z is H or F,

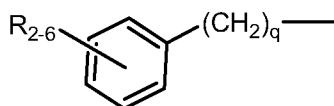
where R_{1a} is methyl, optionally substituted with 1-3 fluorine atoms or 1-3 chlorine atoms, or with OH, cyclopropoxy, or C₁-C₄ alkoxy, where the C₁-C₄ alkyl moieties of said C₁-C₄ alkoxy groups are optionally substituted with one
10 hydroxy or methoxy group, and where all C₂-C₄ alkyl groups within said C₁-C₄ alkoxy are optionally further substituted with a second OH group;

R_{1b} is CH(CH₃)-C₁₋₃ alkyl or C₃-C₆ cycloalkyl, said methyl, alkyl, and cycloalkyl groups optionally substituted with 1-3 substituents selected independently
15 from F, Cl, Br, I, OH, C₁-C₄ alkoxy, and CN;

R_{1c} is (CH₂)_nO_mR', where m is 0 or 1; where, when m is 1, n is 2 or 3, and when m is 0, n is 1 or 2; and where R' is C₁-C₆ alkyl, optionally substituted with 1-3
20 substituents selected independently from F, Cl, OH, OCH₃, OCH₂CH₃, and C₃-C₆ cycloalkyl;

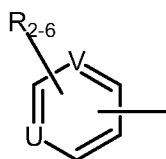
R_{1d} is C(A)(A')(B)- where B, A, and A' are, independently, H or C₁₋₄ alkyl, optionally substituted with one or two OH groups or halogen atoms, or A and A', together with the carbon atom to which they are attached, form a 3- to 6-
25 member saturated ring, said ring optionally containing one or two heteroatoms selected, independently, from O, N, and S and optionally substituted with one or two groups selected independently from methyl, ethyl, and halo;

R_{1e} is benzyl or 2-phenyl ethyl, in which the phenyl group is optionally substituted
30



where q is 1 or 2, R_2 , R_3 and R_4 are, independently, H, F, Cl, Br, CH_3 , CH_2F , CHF_2 , CF_3 , OCH_3 , OCH_2F , $OCHF_2$, OCF_3 , ethyl, *n*-propyl, isopropyl, cyclopropyl, isobutyl, *sec*-butyl, *tert*-butyl, and methylsulfonyl, and R_4 may also be nitro, acetamido, amidinyl, cyano, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, 1,3,4-oxadiazol-2-yl, 5-methyl-1,3,4-oxadiazolyl, 1,3,4-thiadiazolyl, 5-methyl-1,3,4-thiadiazol-1*H*-tetrazolyl, N-morpholinyl carbonylamino, N-morpholinylsulfonyl, and N-pyrrolidinylcarbonylamino; R_5 and R_6 are, independently, H, F, Cl, or methyl;

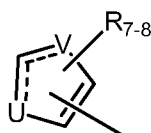
Ar_1 is



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where U and V are, independently, N, CR_2 or CR_3 ; R_2 , R_3 and R_4 are, independently, H, F, Cl, Br, CH_3 , CH_2F , CHF_2 , CF_3 , OCH_3 , OCH_2F , $OCHF_2$, OCF_3 , ethyl, *n*-propyl, isopropyl, cyclopropyl, isobutyl, *sec*-butyl, *tert*-butyl, and methylsulfonyl, and R_4 may also be nitro, acetamido, amidinyl, cyano, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, 1,3,4-oxadiazol-2-yl, 5-methyl-1,3,4-oxadiazol, 1,3,4-thiadiazol, 5-methyl-1,3,4-thiadiazol 1*H*-tetrazolyl, N-morpholinylcarbonylamino, N-morpholinylsulfonyl and N-pyrrolidinylcarbonylamino; R_5 and R_6 are, independently, H, F, Cl or methyl;

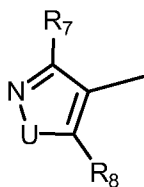
25 Ar_2 is



Ar₂

where the dashed line represents a double bond which may be located formally either between V and the carbon between U and V, or between U and the carbon between U and V; where U is -S-, -O- or -N = and where, when U is -O- or -S-, V is -CH=, -CCl= or -N =; and when U is -N =, V CH=, or -NCH₃-; R₇ and R₈ are, independently, H, methoxycarbonyl, methylcarbamoyl, acetamido, acetyl, methyl, ethyl, trifluoromethyl, or halogen.

Ar₃ is



Ar₃

where U is -NH-, -NCH₃- or -O-; and R₇ and R₈ are, independently, H, F, Cl, or methyl ;

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;

said compounds are published as compounds of general formulae I, IA-1, IA-2, IB-1, IB-2, IC-1, IC-2, ID-1, ID-2, IE-1, IE-2, IIA-1, IIA-2, IIA-3, II-B, III-A, and III-B in International patent application PCT/US2006/028326, published as WO 2007/014011 A2 on July 21, 2006, which is incorporated herein by reference in its entirety. In WO 2007/014011 A2, said compounds of general formulae I, IA-1, IA-2, IB-1, IB-2, IC-1, IC-2, ID-1, ID-2, IE-1, IE-2, IIA-1, IIA-2, IIA-3, II-B, III-A, and III-B are described on pp. 4 *et seq.*, and pp. 19 *et seq.*, they may be synthesized according to the methods given therein on pp. 39, *et seq.*, and are exemplified as specific compound Examples 1 to 71 therein on pp. 41 to 103. Biological test data for certain of said compounds are given therein on pp. 104 to 111.

Said component B may be in the form of a pharmaceutical formulation which is ready for use to be administered simultaneously, concurrently, separately or sequentially. The components may be administered independently of one

another by the oral, intravenous, topical, local installations, intraperitoneal or nasal route.

In accordance with another embodiment of the above-mentioned aspects of the present invention, said combinations are of :

component B : which is one or more 2,3-dihydroimidazo[1,2-c]quinazoline compounds of general formula (B), *supra*, which is selected from the list consisting of :

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Example 1 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-methanesulfonamide:

Example 2 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)cyclopropanesulfonamide:

15 Example 3 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)propane-2-sulfonamide:

Example 4 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)butane-1-sulfonamide:

20 Example 5 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2,2,2-trifluoro ethane sulfonamide:

Example 6 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)butane-2-sulfonamide:

Example 7 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-N-methyl cyclopropane sulfonamide:

25 Example 8 : 1-Chloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl) methane sulfonamide:

Example 9 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2-methylpropane-2-sulfonamide:

30 Example 10 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)cyclopentanesulfonamide:

Example 11 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)cyclohexanesulfonamide:

Example 12 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-methylcyclopropane-1-sulfonamide:

Example 13 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide:

5 Example 14 : (S)-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide:

Example 15 : (R)-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide:

10 Example 16 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-(2-hydroxyethyl)cyclopropane-1-sulfonamide:

Example 17 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-3-hydroxypropane-1-sulfonamide:

Example 18 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2-methyl-5-(trifluoromethyl)furan-3-sulfonamide:

15 Example 19 : N-(5-(N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)sulfamoyl)-methylthiazol-2-yl)acetamide:

Example 20 : 5-(5-Chloro-1,2,4-thiadiazol-3-yl)-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino) phenyl) thiophene-2-sulfonamide:

20 Example 21 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-3,5dimethylisoxazole-4-sulfonamide:

Example 22 : 5-Chloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1,3-dimethyl-1H-pyrazole-4-sulfonamide:

Example 23 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2,5-dimethylfuran-3-sulfonamide:

25 Example 24 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-sulfonamide:

Example 25 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2,4-dimethylthiazole-5-sulfonamide:

30 Example 26 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1,2-dimethyl-1H-imidazole-4-sulfonamide:

Example 27 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)thiophene-3-sulfonamide:

Example 28 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)furan-2-sulfonamide:

Example 29 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-5-methylthiophene-2-sulfonamide:

5 Example 30 : 5-Chloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)thiophene-2-sulfonamide:

Example 31 : 5-Bromo-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)thiophene-2-sulfonamide:

10 Example 32 : 4-Bromo-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)thiophene-3-sulfonamide:

Example 33 : 4-Bromo-5-chloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)thiophene-2-sulfonamide:

Example 34 : 3-Bromo-5-chloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)thiophene-2-sulfonamide:

15 Example 35 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2,5-dimethylthiophene-3-sulfonamide:

Example 36 : 2,5-Dichloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)thiophene-3-sulfonamide:

20 Example 37 : Methyl 3-(N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)sulfamoyl)thiophene-2-carboxylate:

Example 38 : Methyl 5-(N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)sulfamoyl)-1-methyl-1H-pyrrole-2-carboxylate:

Example 39 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-5-methylisoxazole-4-sulfonamide:

25 Example 40 : 3-Chloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)propane-1-sulfonamide:

Example 41 : N-(2-(4-chloro-2-fluorophenylamino)-3,4-difluorophenyl)cyclopropanesulfonamide:

30 Example 42 : N-(3,4-difluoro-2-(4-iodo-2-methylphenylamino)phenyl)cyclopropanesulfonamide:

Example 43 : N-(2-(4-tert-butyl-2-chlorophenylamino)-3,4-difluorophenyl)cyclopropanesulfonamide:

Example 44 : N-(2-(2,4-dichlorophenylamino)-3,4-difluorophenyl)cyclopropanesulfonamide:

Example 45 : 3-Chloro-N-(3,4-difluoro-2-(2-fluoro-4-trifluoromethyl)phenylamino)phenyl)propane-1-sulfonamide:

5 Example 46 : N-(3,4-difluoro-2-(2-chloro-4-trifluoromethyl)phenylamino)methanesulfonamide:

Example 47 : 3-Chloro-N-(3,4-difluoro-2-(2-chloro-4-trifluoromethyl)phenylamino)phenyl)propane-1-sulfonamide:

10 Example 48 : 3-Chloro-N-(3,4-difluoro-2-(2-bromo-4-trifluoromethyl)phenylamino)phenyl)propane-1-sulfonamide:

Example 49 : Cyclopropanesulfonic acid (3,4,6-trifluoro-2-(2-fluoro-4-iodophenylamino)-phenyl)-amide:

Example 50 : N-(3,4-difluoro-2-(4-fluoro-2-iodophenylamino)-6-ethoxyphenyl)cyclopropane sulfonamide:

15 Example 51 : Methylsulfonic acid (3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxy-phenyl)-amide:

Example 52 : 1-(2,3-Dihydroxy-propyl)-cyclopropanesulfonic acid [3,4,6-trifluoro-2-(4-fluoro-2-iodo-phenylamino)-phenyl]-amide:

20 Example 53 : (S)-1-(2,3-dihydroxypropyl)-N-(3,4,6-trifluoro-2-(2-fluoro-4-iodophenylamino) phenyl)cyclopropane-1-sulfonamide:

Example 54 : (R)-1-(2,3-dihydroxypropyl)-N-(3,4,6-trifluoro-2-(2-fluoro-4-iodophenylamino) phenyl)cyclopropane-1-sulfonamide:

Example 55 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide:

25 Example 56 : (S)-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide:Example

57 : (R)-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide:

30 Example 58 : 1-(2-hydroxyethyl)-N-(3,4,6-trifluoro-2-(2-fluoro-4-iodophenylamino)phenyl) cyclopropane-1-sulfonamide:

Example 59 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2-hydroxyethyl)cyclopropane-1-sulfonamide:

Example 60 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(3-hydroxy-2-(hydroxymethyl)propyl)cyclopropane-1-sulfonamide:

Example 61 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)
5 cyclobutane sulfonamide:

Example 62 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methylphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide:

Example 63 : 1-(2,3-Dihydroxypropyl)-N-(6-ethyl-3,4-difluoro-2-(2-fluoro-4-iodophenylamino) phenyl) cyclopropane-1-sulfonamide:

10 Example 64 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-(2-methoxyethoxy)phenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide:

Example 65 : 2,4-dichloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl) benzene sulfonamide:

Example 66 : 2-chloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-
15 4-(trifluoromethyl) benzenesulfonamide:

Example 67 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2-(trifluoromethoxy) benzene sulfonamide:

Example 68 : 4-(N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)sulfamoyl)benzoic acid:

20 Example 69 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)benzenesulfonamide:

Example 70 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2-fluorobenzene sulfonamide:

Example 71 : N-(3,4-difluoro-2-(2-fluoro-4-methylphenylamino)phenyl)cyclopropanesulfonamide ;
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or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof.

In accordance with an embodiment of the above-mentioned aspects of the present invention, said combinations are of :

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component B : which is Lapatinib ;

In accordance with an embodiment of the above-mentioned aspects of the present invention, said combinations are of :

component B : which is Paclitaxel ;

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In accordance with an embodiment of the above-mentioned aspects of the present invention, said combinations are of :

component A : 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide ; and

10

component B : (S)-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide.

15 In accordance with an embodiment of the above-mentioned aspects of the present invention, said combinations are of :

component A : 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide ; and

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component B : lapatinib.

In accordance with an embodiment of the above-mentioned aspects of the present invention, said combinations are of :

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component A : 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide ; and

component B : paclitaxel.

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Said component B may be in the form of a pharmaceutical formulation which is ready for use to be administered simultaneously, concurrently, separately or sequentially. The components may be administered independently of one another by the oral, intravenous, topical, local installations, intraperitoneal or
5 nasal route.

In accordance with an embodiment, the present invention relates to a combination of any component A mentioned herein with any component B mentioned herein, optionally with any component C mentioned herein.

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In a particular embodiment, the present invention relates to a combination of a component A with a component B, optionally with a component C, as mentioned in the Examples section herein.

15 **Useful forms of components A and B of the combinations of the present invention**

As mentioned *supra*, either or both of components A and B of any of the combinations of the present invention may be in a useful form, such as
20 pharmaceutically acceptable salts, co-precipitates, metabolites, hydrates, solvates and prodrugs of all the compounds of examples. The term "pharmaceutically acceptable salt" refers to a relatively non-toxic, inorganic or organic acid addition salt of a compound of the present invention. For example, see S. M. Berge, *et al.* "Pharmaceutical Salts," *J. Pharm. Sci.* 1977,
25 66, 1-19. Pharmaceutically acceptable salts include those obtained by reacting the main compound, functioning as a base, with an inorganic or organic acid to form a salt, for example, salts of hydrochloric acid, sulfuric acid, phosphoric acid, methane sulfonic acid, camphor sulfonic acid, oxalic acid, maleic acid, succinic acid and citric acid. Pharmaceutically acceptable
30 salts also include those in which the main compound functions as an acid and is reacted with an appropriate base to form, e.g., sodium, potassium, calcium, magnesium, ammonium, and chlorine salts. Those skilled in the art will further

recognize that acid addition salts of the claimed compounds may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods. Alternatively, alkali and alkaline earth metal salts of acidic compounds of the invention are prepared by reacting the compounds of the invention with the appropriate base via a variety of known methods.

Representative salts of the compounds of this invention include the conventional non-toxic salts and the quaternary ammonium salts which are formed, for example, from inorganic or organic acids or bases by means well known in the art. For example, such acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cinnamate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, chloride, bromide, iodide, 2-hydroxyethanesulfonate, itaconate, lactate, maleate, mandelate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, sulfonate, sulfate, tartrate, thiocyanate, tosylate, and undecanoate.

Base salts include alkali metal salts such as potassium and sodium salts, alkaline earth metal salts such as calcium and magnesium salts, and ammonium salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine. Additionally, basic nitrogen containing groups may be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, or butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl sulfate, or diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

A solvate for the purpose of this invention is a complex of a solvent and a compound of the invention in the solid state. Exemplary solvates would include, but are not limited to, complexes of a compound of the invention with ethanol or methanol. Hydrates are a specific form of solvate wherein the solvent is water.

Pharmaceutical formulations of components A and B of the combinations of the present invention

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As mentioned *supra*, the components A or B may, independently from one another, be in the form of a pharmaceutical formulation which is ready for use to be administered simultaneously, concurrently, separately or sequentially. The components may be administered independently of one another by the oral, intravenous, topical, local installations, intraperitoneal or nasal route.

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Said compositions can be utilized to achieve the desired pharmacological effect by administration to a patient in need thereof. A patient, for the purpose of this invention, is a mammal, including a human, in need of treatment for the particular condition or disease. Therefore, the present invention includes combinations in which components A and B, independently of one another, are pharmaceutical formulations compositions that are comprised of a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a said component. A pharmaceutically acceptable carrier is preferably a carrier that is relatively non-toxic and innocuous to a patient at concentrations consistent with effective activity of the active ingredient so that any side effects ascribable to the carrier do not vitiate the beneficial effects of component, and/or combination. A pharmaceutically effective amount of a combination is preferably that amount which produces a result or exerts an influence on the particular condition being treated. The combinations of the present invention can be administered with pharmaceutically-acceptable carriers well known in the art using any effective

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conventional dosage unit forms, including immediate, slow and timed release preparations, orally, parenterally, topically, nasally, ophthalmically, optically, sublingually, rectally, vaginally, and the like.

- 5 For oral administration, the combinations can be formulated into solid or liquid preparations such as capsules, pills, tablets, troches, lozenges, melts, powders, solutions, suspensions, or emulsions, and may be prepared according to methods known to the art for the manufacture of pharmaceutical compositions. The solid unit dosage forms can be a capsule that can be of the
10 ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers such as lactose, sucrose, calcium phosphate, and corn starch.

- In another embodiment, the combinations of this invention may be tableted
15 with conventional tablet bases such as lactose, sucrose and cornstarch in combination with binders such as acacia, corn starch or gelatin, disintegrating agents intended to assist the break-up and dissolution of the tablet following administration such as potato starch, alginic acid, corn starch, and guar gum, gum tragacanth, acacia, lubricants intended to improve the flow of tablet
20 granulation and to prevent the adhesion of tablet material to the surfaces of the tablet dies and punches, for example talc, stearic acid, or magnesium, calcium or zinc stearate, dyes, coloring agents, and flavoring agents such as peppermint, oil of wintergreen, or cherry flavoring, intended to enhance the aesthetic qualities of the tablets and make them more acceptable to the
25 patient. Suitable excipients for use in oral liquid dosage forms include dicalcium phosphate and diluents such as water and alcohols, for example, ethanol, benzyl alcohol, and polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent or emulsifying agent. Various other materials may be present as coatings or to
30 otherwise modify the physical form of the dosage unit. For instance tablets, pills or capsules may be coated with shellac, sugar or both.

Dispersible powders and granules are suitable for the preparation of an aqueous suspension. They provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example those sweetening, flavoring and coloring agents described above, may also be present.

The pharmaceutical compositions of this invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil such as liquid paraffin or a mixture of vegetable oils. Suitable emulsifying agents may be (1) naturally occurring gums such as gum acacia and gum tragacanth, (2) naturally occurring phosphatides such as soy bean and lecithin, (3) esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan monooleate, (4) condensation products of said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil such as, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as, for example, beeswax, hard paraffin, or cetyl alcohol. The suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate; one or more coloring agents; one or more flavoring agents; and one or more sweetening agents such as sucrose or saccharin.

Syrups and elixirs may be formulated with sweetening agents such as, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, and preservative, such as methyl and propyl parabens and flavoring and coloring agents.

The combinations of this invention may also be administered parenterally, that is, subcutaneously, intravenously, intraocularly, intrasynovially, intramuscularly, or interperitoneally, as injectable dosages of the compound in preferably a physiologically acceptable diluent with a pharmaceutical carrier
5 which can be a sterile liquid or mixture of liquids such as water, saline, aqueous dextrose and related sugar solutions, an alcohol such as ethanol, isopropanol, or hexadecyl alcohol, glycols such as propylene glycol or polyethylene glycol, glycerol ketals such as 2,2-dimethyl-1,1-dioxolane-4-methanol, ethers such as poly(ethylene glycol) 400, an oil, a fatty acid, a fatty
10 acid ester or, a fatty acid glyceride, or an acetylated fatty acid glyceride, with or without the addition of a pharmaceutically acceptable surfactant such as a soap or a detergent, suspending agent such as pectin, carbomers, methycellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agent and other pharmaceutical adjuvants.

15 Illustrative of oils which can be used in the parenteral formulations of this invention are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, sesame oil, cottonseed oil, corn oil, olive oil, petrolatum and mineral oil. Suitable fatty acids include oleic acid, stearic
20 acid, isostearic acid and myristic acid. Suitable fatty acid esters are, for example, ethyl oleate and isopropyl myristate. Suitable soaps include fatty acid alkali metal, ammonium, and triethanolamine salts and suitable detergents include cationic detergents, for example dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates; anionic
25 detergents, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates; non-ionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and poly(oxyethylene-oxypropylene)s or ethylene oxide or propylene oxide copolymers; and amphoteric detergents, for example, alkyl-beta-aminopropionates, and 2-
30 alkylimidazoline quarternary ammonium salts, as well as mixtures.

The parenteral compositions of this invention will typically contain from about 0.5% to about 25% by weight of the active ingredient in solution. Preservatives and buffers may also be used advantageously. In order to minimize or eliminate irritation at the site of injection, such compositions may contain a non-ionic surfactant having a hydrophile-lipophile balance (HLB) preferably of from about 12 to about 17. The quantity of surfactant in such formulation preferably ranges from about 5% to about 15% by weight. The surfactant can be a single component having the above HLB or can be a mixture of two or more components having the desired HLB.

Illustrative of surfactants used in parenteral formulations are the class of polyethylene sorbitan fatty acid esters, for example, sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol.

The pharmaceutical compositions may be in the form of sterile injectable aqueous suspensions. Such suspensions may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents such as, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents which may be a naturally occurring phosphatide such as lecithin, a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate, a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadeca-ethyleneoxycetanol, a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol such as polyoxyethylene sorbitol monooleate, or a condensation product of an ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride, for example polyoxyethylene sorbitan monooleate.

The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Diluents

and solvents that may be employed are, for example, water, Ringer's solution, isotonic sodium chloride solutions and isotonic glucose solutions. In addition, sterile fixed oils are conventionally employed as solvents or suspending media. For this purpose, any bland, fixed oil may be employed including synthetic
5 mono- or diglycerides. In addition, fatty acids such as oleic acid can be used in the preparation of injectables.

A composition of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be
10 prepared by mixing the drug with a suitable non-irritation excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are, for example, cocoa butter and polyethylene glycol.

15 Another formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in
20 the art (see, e.g., US Patent No. 5,023,252, issued June 11, 1991, incorporated herein by reference). Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Controlled release formulations for parenteral administration include
25 liposomal, polymeric microsphere and polymeric gel formulations that are known in the art.

It may be desirable or necessary to introduce the pharmaceutical composition to the patient via a mechanical delivery device. The construction and use of
30 mechanical delivery devices for the delivery of pharmaceutical agents is well known in the art. Direct techniques for, for example, administering a drug directly to the brain usually involve placement of a drug delivery catheter into

the patient's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of agents to specific anatomical regions of the body, is described in US Patent No. 5,011,472, issued April 30, 1991.

5

The compositions of the invention can also contain other conventional pharmaceutically acceptable compounding ingredients, generally referred to as carriers or diluents, as necessary or desired. Conventional procedures for preparing such compositions in appropriate dosage forms can be utilized.

10 Such ingredients and procedures include those described in the following references, each of which is incorporated herein by reference: Powell, M.F. *et al*, "Compendium of Excipients for Parenteral Formulations" *PDA Journal of Pharmaceutical Science & Technology* 1998, 52(5), 238-311; Strickley, R.G "Parenteral Formulations of Small Molecule Therapeutics Marketed in the
15 United States (1999)-Part-1" *PDA Journal of Pharmaceutical Science & Technology* 1999, 53(6), 324-349; and Nema, S. *et al*, "Excipients and Their Use in Injectable Products" *PDA Journal of Pharmaceutical Science & Technology* 1997, 51(4), 166-171.

20 Commonly used pharmaceutical ingredients that can be used as appropriate to formulate the composition for its intended route of administration include:

acidifying agents (examples include but are not limited to acetic acid, citric acid, fumaric acid, hydrochloric acid, nitric acid);

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alkalinizing agents (examples include but are not limited to ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium hydroxide, triethanolamine, trolamine);

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adsorbents (examples include but are not limited to powdered cellulose and activated charcoal);

aerosol propellants (examples include but are not limited to carbon dioxide, CCl_2F_2 , $\text{F}_2\text{ClC-CClF}_2$ and CClF_3)

5 **air displacement agents** (examples include but are not limited to nitrogen and argon);

antifungal preservatives (examples include but are not limited to benzoic acid, butylparaben, ethylparaben, methylparaben, propylparaben, sodium benzoate);

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antimicrobial preservatives (examples include but are not limited to benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate and thimerosal);

15

antioxidants (examples include but are not limited to ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorus acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite);

20

binding materials (examples include but are not limited to block polymers, natural and synthetic rubber, polyacrylates, polyurethanes, silicones, polysiloxanes and styrene-butadiene copolymers);

25

buffering agents (examples include but are not limited to potassium metaphosphate, dipotassium phosphate, sodium acetate, sodium citrate anhydrous and sodium citrate dihydrate)

30 **carrying agents** (examples include but are not limited to acacia syrup, aromatic syrup, aromatic elixir, cherry syrup, cocoa syrup, orange syrup,

syrup, corn oil, mineral oil, peanut oil, sesame oil, bacteriostatic sodium chloride injection and bacteriostatic water for injection)

5 **chelating agents** (examples include but are not limited to edetate disodium and edetic acid)

colorants (examples include but are not limited to FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel and ferric oxide red);

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clarifying agents (examples include but are not limited to bentonite);

15 **emulsifying agents** (examples include but are not limited to acacia, cetomacrogol, cetyl alcohol, glyceryl monostearate, lecithin, sorbitan monooleate, polyoxyethylene 50 monostearate);

encapsulating agents (examples include but are not limited to gelatin and cellulose acetate phthalate)

20 **flavorants** (examples include but are not limited to anise oil, cinnamon oil, cocoa, menthol, orange oil, peppermint oil and vanillin);

humectants (examples include but are not limited to glycerol, propylene glycol and sorbitol);

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levigating agents (examples include but are not limited to mineral oil and glycerin);

30 **oils** (examples include but are not limited to arachis oil, mineral oil, olive oil, peanut oil, sesame oil and vegetable oil);

ointment bases (examples include but are not limited to lanolin, hydrophilic ointment, polyethylene glycol ointment, petrolatum, hydrophilic petrolatum, white ointment, yellow ointment, and rose water ointment);

- 5 **penetration enhancers (transdermal delivery)** (examples include but are not limited to monohydroxy or polyhydroxy alcohols, mono-or polyvalent alcohols, saturated or unsaturated fatty alcohols, saturated or unsaturated fatty esters, saturated or unsaturated dicarboxylic acids, essential oils, phosphatidyl derivatives, cephalin, terpenes, amides, ethers, ketones and ureas)

10

plasticizers (examples include but are not limited to diethyl phthalate and glycerol);

- 15 **solvents** (examples include but are not limited to ethanol, corn oil, cottonseed oil, glycerol, isopropanol, mineral oil, oleic acid, peanut oil, purified water, water for injection, sterile water for injection and sterile water for irrigation);

- 20 **stiffening agents** (examples include but are not limited to cetyl alcohol, cetyl esters wax, microcrystalline wax, paraffin, stearyl alcohol, white wax and yellow wax);

suppository bases (examples include but are not limited to cocoa butter and polyethylene glycols (mixtures));

- 25 **surfactants** (examples include but are not limited to benzalkonium chloride, nonoxynol 10, octoxynol 9, polysorbate 80, sodium lauryl sulfate and sorbitan mono-palmitate);

- 30 **suspending agents** (examples include but are not limited to agar, bentonite, carbomers, carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, methylcellulose, tragacanth and veegum);

sweetening agents (examples include but are not limited to aspartame, dextrose, glycerol, mannitol, propylene glycol, saccharin sodium, sorbitol and sucrose);

5

tablet anti-adherents (examples include but are not limited to magnesium stearate and talc);

10 **tablet binders** (examples include but are not limited to acacia, alginic acid, carboxymethylcellulose sodium, compressible sugar, ethylcellulose, gelatin, liquid glucose, methylcellulose, non-crosslinked polyvinyl pyrrolidone, and pregelatinized starch);

15 **tablet and capsule diluents** (examples include but are not limited to dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sodium carbonate, sodium phosphate, sorbitol and starch);

20 **tablet coating agents** (examples include but are not limited to liquid glucose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, cellulose acetate phthalate and shellac);

25 **tablet direct compression excipients** (examples include but are not limited to dibasic calcium phosphate);

30 **tablet disintegrants** (examples include but are not limited to alginic acid, carboxymethylcellulose calcium, microcrystalline cellulose, polacrillin potassium, cross-linked polyvinylpyrrolidone, sodium alginate, sodium starch glycollate and starch);

tablet glidants (examples include but are not limited to colloidal silica, corn starch and talc);

tablet lubricants (examples include but are not limited to calcium stearate, magnesium stearate, mineral oil, stearic acid and zinc stearate);

tablet/capsule opaquants (examples include but are not limited to titanium dioxide);

tablet polishing agents (examples include but are not limited to carnuba wax and white wax);

thickening agents (examples include but are not limited to beeswax, cetyl alcohol and paraffin);

tonicity agents (examples include but are not limited to dextrose and sodium chloride);

viscosity increasing agents (examples include but are not limited to alginic acid, bentonite, carbomers, carboxymethylcellulose sodium, methylcellulose, polyvinyl pyrrolidone, sodium alginate and tragacanth); and

wetting agents (examples include but are not limited to heptadecaethylene oxycetanol, lecithins, sorbitol monooleate, polyoxyethylene sorbitol monooleate, and polyoxyethylene stearate).

Pharmaceutical compositions according to the present invention can be illustrated as follows:

Sterile IV Solution: A 5 mg/mL solution of the desired compound of this invention can be made using sterile, injectable water, and the pH is adjusted if necessary. The solution is diluted for administration to 1 - 2 mg/mL with

sterile 5% dextrose and is administered as an IV infusion over about 60 minutes.

Lyophilized powder for IV administration: A sterile preparation can be prepared with (i) 100 - 1000 mg of the desired compound of this invention as a lyophilized powder, (ii) 32- 327 mg/mL sodium citrate, and (iii) 300 - 3000 mg Dextran 40. The formulation is reconstituted with sterile, injectable saline or dextrose 5% to a concentration of 10 to 20 mg/mL, which is further diluted with saline or dextrose 5% to 0.2 - 0.4 mg/mL, and is administered either IV bolus or by IV infusion over 15 - 60 minutes.

Intramuscular suspension: The following solution or suspension can be prepared, for intramuscular injection:

50 mg/mL of the desired, water-insoluble compound of this invention

5 mg/mL sodium carboxymethylcellulose

4 mg/mL TWEEN 80

9 mg/mL sodium chloride

9 mg/mL benzyl alcohol

Hard Shell Capsules: A large number of unit capsules are prepared by filling standard two-piece hard galantine capsules each with 100 mg of powdered active ingredient, 150 mg of lactose, 50 mg of cellulose and 6 mg of magnesium stearate.

Soft Gelatin Capsules: A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into molten gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules are washed and dried. The active ingredient can be dissolved in a mixture of polyethylene glycol, glycerin and sorbitol to prepare a water miscible medicine mix.

Tablets: A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 mg of active ingredient, 0.2 mg. of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg. of starch, and 98.8 mg of lactose. Appropriate aqueous and
5 non-aqueous coatings may be applied to increase palatability, improve elegance and stability or delay absorption.

Immediate Release Tablets/Capsules: These are solid oral dosage forms made by conventional and novel processes. These units are taken orally without
10 water for immediate dissolution and delivery of the medication. The active ingredient is mixed in a liquid containing ingredient such as sugar, gelatin, pectin and sweeteners. These liquids are solidified into solid tablets or caplets by freeze drying and solid state extraction techniques. The drug compounds may be compressed with viscoelastic and thermoelastic sugars and polymers or
15 effervescent components to produce porous matrices intended for immediate release, without the need of water.

Method of treating cancer

20 Within the context of the present invention, the term “cancer” includes, but is not limited to, cancers of the breast, lung, brain, reproductive organs, digestive tract, urinary tract, liver, eye, skin, head and neck, thyroid, parathyroid and their distant metastases. Those disorders also include multiple myeloma, lymphomas, sarcomas, and leukemias.

25 Examples of breast cancer include, but are not limited to invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ, and lobular carcinoma in situ.

30 Examples of cancers of the respiratory tract include, but are not limited to small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma.

Examples of brain cancers include, but are not limited to brain stem and hypophthalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumor.

5

Tumors of the male reproductive organs include, but are not limited to prostate and testicular cancer. Tumors of the female reproductive organs include, but are not limited to endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

10

Tumors of the digestive tract include, but are not limited to anal, colon, colorectal, esophageal, gallbladder, gastric, pancreatic, rectal, small-intestine, and salivary gland cancers.

15 Tumors of the urinary tract include, but are not limited to bladder, penile, kidney, renal pelvis, ureter, urethral and human papillary renal cancers.

Eye cancers include, but are not limited to intraocular melanoma and retinoblastoma.

20

Examples of liver cancers include, but are not limited to hepatocellular carcinoma (liver cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.

25

Skin cancers include, but are not limited to squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer.

30 Head-and-neck cancers include, but are not limited to laryngeal, hypopharyngeal, nasopharyngeal, oropharyngeal cancer, lip and oral cavity cancer and squamous cell.

Lymphomas include, but are not limited to AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Burkitt lymphoma, Hodgkin's disease, and lymphoma of the central nervous system.

5

Sarcomas include, but are not limited to sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma.

10 Leukemias include, but are not limited to acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

15 The present invention relates to a method for using the combinations of the present invention, to treat cancer, as described *infra*, particularly mammalian NSCLC, CRC, melanoma, pancreatic cancer, hepatocyte or breast cancer. Combinations can be utilized to inhibit, block, reduce, decrease, etc., cell proliferation and/or cell division, and/or produce apoptosis, in the treatment
20 or prophylaxis of cancer, in particular NSCLC, CRC, melanoma, pancreatic cancer, hepatocyte carcinoma or breast cancer. This method comprises administering to a mammal in need thereof, including a human, an amount of a combination of this invention, or a pharmaceutically acceptable salt, isomer, polymorph, metabolite, hydrate, solvate or ester thereof; etc. which is
25 effective for the treatment or prophylaxis of cancer, in particular NSCLC, CRC, melanoma, pancreatic cancer, hepatocyte carcinoma or breast cancer.

The term "treating" or "treatment" as stated throughout this document is used conventionally, e.g., the management or care of a subject for the
30 purpose of combating, alleviating, reducing, relieving, improving the condition of, etc., of a disease or disorder, such as a carcinoma.

Dose and administration

Based upon standard laboratory techniques known to evaluate compounds useful for the treatment or prophylaxis of cancer, in particular NSCLC, CRC, melanoma, pancreatic cancer, hepatocyte carcinoma or breast cancer, by standard toxicity tests and by standard pharmacological assays for the determination of treatment of the conditions identified above in mammals, and by comparison of these results with the results of known medicaments that are used to treat these conditions, the effective dosage of the combinations of this invention can readily be determined for treatment of the indication. The amount of the active ingredient to be administered in the treatment of the condition can vary widely according to such considerations as the particular combination and dosage unit employed, the mode of administration, the period of treatment, the age and sex of the patient treated, and the nature and extent of the condition treated.

The total amount of the active ingredient to be administered will generally range from about 0.001 mg/kg to about 200 mg/kg body weight per day, and preferably from about 0.01 mg/kg to about 20 mg/kg body weight per day. Clinically useful dosing schedules will range from one to three times a day dosing to once every four weeks dosing. In addition, "drug holidays" in which a patient is not dosed with a drug for a certain period of time, may be beneficial to the overall balance between pharmacological effect and tolerability. A unit dosage may contain from about 0.5 mg to about 1,500 mg of active ingredient, and can be administered one or more times per day or less than once a day. The average daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily rectal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily topical dosage regimen will preferably be from 0.1 to 200 mg

administered between one to four times daily. The transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/kg. The average daily inhalation dosage regimen will preferably be from 0.01 to 100 mg/kg of total body weight.

5

Of course the specific initial and continuing dosage regimen for each patient will vary according to the nature and severity of the condition as determined by the attending diagnostician, the activity of the specific combination employed, the age and general condition of the patient, time of administration, route of administration, rate of excretion of the drug, drug combinations, and the like. The desired mode of treatment and number of doses of a combination of the present invention or a pharmaceutically acceptable salt or ester or composition thereof can be ascertained by those skilled in the art using conventional treatment tests.

10

Therapies using combinations of component A as described *supra*, component B as described *supra*, and component C : one or more further pharmaceutical agents.

15

The combinations of component A and component B of this invention can be administered as the sole pharmaceutical agent or in combination with one or more further pharmaceutical agents where the resulting combination of components A, B and C causes no unacceptable adverse effects. For example, the combinations of components A and B of this invention can be combined with component C, *i.e.* one or more further pharmaceutical agents, such as known anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhythmic, anti-hypercholesterolemia, anti-dyslipidemia, anti-diabetic or antiviral agents, and the like, as well as with admixtures and combinations thereof.

20

Component C, can be one or more pharmaceutical agents such as aldesleukin, alendronic acid, alfaferone, alitretinoin, allopurinol, aloprim, aloxi,

altretamine, aminoglutethimide, amifostine, amrubicin, amsacrine, anastrozole, anzmet, aranesp, arglabin, arsenic trioxide, aromasin, 5-azacytidine, azathioprine, BCG or tice BCG, bestatin, betamethasone acetate, betamethasone sodium phosphate, bexarotene, bleomycin sulfate, broxuridine, bortezomib, busulfan, calcitonin, campath, capecitabine, carboplatin, casodex, cefesone, celmoleukin, cerubidine, chlorambucil, cisplatin, cladribine, cladribine, clodronic acid, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, DaunoXome, decadron, decadron phosphate, delestrogen, denileukin diftitox, depo-medrol, deslorelin, dexamethasone, dexrazoxane, diethylstilbestrol, diflucan, docetaxel, doxifluridine, doxorubicin, dronabinol, DW-166HC, eligard, elitek, ellence, emend, epirubicin, epoetin alfa, epogen, eptaplatin, erlotinib (when component B is not itself erlotinib), ergamisol, estrace, estradiol, estramustine phosphate sodium, ethinyl estradiol, ethylol, etidronic acid, etopophos, etoposide, fadrozole, farston, filgrastim, finasteride, fligrastim, floxuridine, fluconazole, fludarabine, 5-fluorodeoxyuridine monophosphate, 5-fluorouracil (5-FU), fluoxymesterone, flutamide, formestane, fosteabine, fotemustine, fulvestrant, gammagard, gemcitabine, gemtuzumab, gleevec, gliadel, goserelin, granisetron HCl, histrelin, hycamtin, hydrocortone, eyrthrohydroxynonyladenine, hydroxyurea, ibritumomab tiuxetan, idarubicin, ifosfamide, interferon alpha, interferon-alpha 2, interferon alfa-2A, interferon alfa-2B, interferon alfa-n1, interferon alfa-n3, interferon beta, interferon gamma-1a, interleukin-2, intron A, iressa, irinotecan, kytril, lapatinib (when component B is not itself lapatinib), lentinan sulphate, letrozole, leucovorin, leuprolide, leuprolide acetate, lenalidomide, levamisole, levofolinic acid calcium salt, levothroid, levoxyl, lomustine, lonidamine, marinol, mechlorethamine, mecobalamin, medroxyprogesterone acetate, megestrol acetate, melphalan, menest, 6-mercaptopurine, Mesna, methotrexate, metvix, miltefosine, minocycline, mitomycin C, mitotane, mitoxantrone, Modrenal, Myocet, nedaplatin, neulasta, neumega, neupogen, nilutamide, nolvadex, NSC-631570, OCT-43, octreotide, ondansetron HCl, orapred, oxaliplatin, paclitaxel (when component B is not itself paclitaxel), pediapred, pegaspargase, Pegasys,

pentostatin, picibanil, pilocarpine HCl, pirarubicin, plicamycin, porfimer sodium, prednimustine, prednisolone, prednisone, premarin, procarbazine, procrit, raltitrexed, rebif, rhenium-186 etidronate, rituximab, roferon-A, romurtide, salagen, sandostatin, sargramostim, semustine, sizofiran, sobuzoxane, solu-medrol, sparfosic acid, stem-cell therapy, streptozocin, strontium-89 chloride, sunitinib, synthroid, tamoxifen, tamsulosin, tasonermin, tastolactone, taxotere, teceleukin, temozolomide, teniposide, testosterone propionate, testred, thioguanine, thiotepa, thyrotropin, tiludronic acid, topotecan, toremifene, tositumomab, trastuzumab, treosulfan, tretinoin, trexall, trimethylmelamine, trimetrexate, triptorelin acetate, triptorelin pamoate, UFT, uridine, valrubicin, vesnarinone, vinblastine, vincristine, vindesine, vinorelbine, virulizin, zinecard, zinostatin stimalamer, zofran, ABL-007, acolbifene, actimmune, affinitak, aminopterin, arzoxifene, asoprisnil, atamestane, atrasentan, BAY 43-9006 (sorafenib), avastin, CCI-779, CDC-501, celebrex, cetuximab, crisnatol, cyproterone acetate, decitabine, DN-101, doxorubicin-MTC, dSLIM, dutasteride, edotecarin, eflornithine, exatecan, fenretinide, histamine dihydrochloride, histrelin hydrogel implant, holmium-166 DOTMP, ibandronic acid, interferon gamma, intron-PEG, ixabepilone, keyhole limpet hemocyanin, L-651582, lanreotide, lasofoxifene, libra, lonafarnib, miproxifene, minodronate, MS-209, liposomal MTP-PE, MX-6, nafarelin, nemorubicin, neovastat, nolatrexed, oblimersen, onco-TCS, osidem, paclitaxel polyglutamate, pamidronate disodium, PN-401, QS-21, quazepam, R-1549, raloxifene, ranpirnase, 13-cis -retinoic acid, satraplatin, seocalcitol, T-138067, tarceva, taxoprexin, thalidomide, thymosin alpha 1, tiazofurine, tipifarnib, tirapazamine, TLK-286, toremifene, TransMID-107R, valspodar, vaporeotide, vatalanib, verteporfin, vinflunine, Z-100, zoledronic acid or combinations thereof.

Alternatively, said component C can be one or more further pharmaceutical agents selected from gemcitabine, paclitaxel (when component B is not itself paclitaxel), cisplatin, carboplatin, sodium butyrate, 5-FU, doxorubicin, tamoxifen, etoposide, trastumazab, gefitinib, intron A, rapamycin, 17-AAG,

U0126, insulin, an insulin derivative, a PPAR ligand, a sulfonylurea drug, an α -glucosidase inhibitor, a biguanide, a PTP-1B inhibitor, a DPP-IV inhibitor, a 11-beta-HSD inhibitor, GLP-1, a GLP-1 derivative, GIP, a GIP derivative, PACAP, a PACAP derivative, secretin or a secretin derivative.

5

Optional anti-hyper-proliferative agents which can be added as component C to the combination of components A and B of the present invention include but are not limited to compounds listed on the cancer chemotherapy drug regimens in the 11th Edition of the *Merck Index*, (1996), which is hereby
10 incorporated by reference, such as asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-
15 mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, and vindesine.

Other anti-hyper-proliferative agents suitable for use as component C with the
20 combination of components A and B of the present invention include but are not limited to those compounds acknowledged to be used in the treatment of neoplastic diseases in *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (Ninth Edition), editor Molinoff et al., publ. by McGraw-Hill, pages 1225-1287, (1996), which is hereby incorporated by reference, such as
25 aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2',2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyl adenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon,
30 medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel (when component B is not itself paclitaxel), pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide,

testosterone propionate, thiotepa, trimethylmelamine, uridine, and vinorelbine.

Other anti-hyper-proliferative agents suitable for use as component C with the
5 combination of components A and B of the present invention include but are
not limited to other anti-cancer agents such as epothilone and its derivatives,
irinotecan, raloxifen and topotecan.

Generally, the use of cytotoxic and/or cytostatic agents as component C in
10 combination with a combination of components A and B of the present
invention will serve to:

- (1) yield better efficacy in reducing the growth of a tumor or even
eliminate the tumor as compared to administration of either agent alone,
15
- (2) provide for the administration of lesser amounts of the administered
chemotherapeutic agents,
- (3) provide for a chemotherapeutic treatment that is well tolerated in the
20 patient with fewer deleterious pharmacological complications than observed
with single agent chemotherapies and certain other combined therapies,
- (4) provide for treating a broader spectrum of different cancer types in
mammals, especially humans,
25
- (5) provide for a higher response rate among treated patients,
- (6) provide for a longer survival time among treated patients compared to
standard chemotherapy treatments,
30
- (7) provide a longer time for tumor progression, and/or

(8) yield efficacy and tolerability results at least as good as those of the agents used alone, compared to known instances where other cancer agent combinations produce antagonistic effects.

Examples:

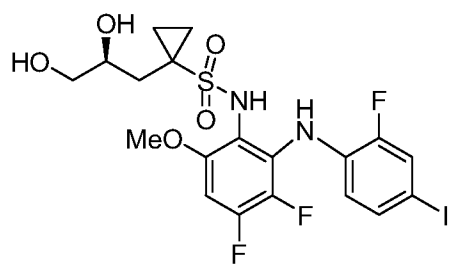
The following abbreviations are used in the Examples :

5

“cA” means compound Example 13 of WO 2008/070150 A1 as shown herein (which is an Example of component A as described and defined herein).

10

“cB” means compound Example 56 of WO 2007/014011 A2, *i.e.* (S)-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide, of structure :



(which is an Example of component B as described and defined herein).

15

“BB” means cB, Lapatinib or paclitaxel (as examples of component B).

20

The effects of combinations of the present invention were evaluated using combination index isobologram analysis for *in vitro* assessment. The efficacy parameters were the effects in a 72-hour cell proliferation assay or in a 48-hour caspase 3/7 activation assay. Briefly, cells were plated in 384-well plate with 25 μ L medium. After 24 hours, 5 μ L of experimental media containing either cA alone, or BB (such as cB, or Lapatinib, paclitaxel (example of component B) alone, etc.), or the combination of cA (as component A) plus
25 either cB, or Lapatinib, or paclitaxel, (as component B), at different ratios (0.8xcA+0.2xBB, 0.6xcA+0.4xBB, 0.4xcA+0.6xBB, 0.2xcA+0.8xBB, 0.1xcA+0.9xBB) were used to make serial three-fold dilutions to generate response curves at 7 concentrations. Experiments were conducted in

triplicates. The mapping EC50/IC50 and EC90/IC90 values were calculated using Analyze5 computer program. The corresponding component concentrations of cA and BB (either cB, or Lapatinib, or paclitaxel (as component B)) at the E(I)C50/ E(I)C90 were calculated and used for plotting isobolograms. Effects were analyzed as described by Chou (Pharmacology Reviews 2006) and the combination index was calculated using the formula :

$$\text{Combination Index} = [\text{cAx}] / \text{cA}' + [\text{BBx}] / \text{BB}'$$

[cAx] and [BBx] refer to cA and BB (either cB, or Lapatinib, or paclitaxel (as component B)), concentration at EC50/IC50 or EC90/IC90, respectively, in combination. cA' and BB' refer to the EC50/IC50 or EC90/IC90 values of cA and BB, respectively, as a single agent. Combination indices of 0-0.3, 0.3-0.6, and 0.6-0.9 were defined to indicate very strong synergy, strong synergy and synergy, respectively.

The in vivo combination effects were evaluated in tumor xenograft models in nude mice with either established human tumor cell lines or patient-derived primary tumor models at the MTD and sub-MTD dosages.

The invention is demonstrated in the following examples which are not meant to limit the invention in any way:

Example 1

To investigate if combining the PI3K inhibitor with MEK inhibitor and/or established therapies could result in synergistic or additive effects, and/or overcome the resistance to the chemotherapies in cancer (include but not limited to NSCLC, melanoma, pancreatic cancer, hepatocyte carcinoma breast, or CRC) treatment, we conducted combination studies to assess the anti-tumor activities of single agent versus combination therapy *in vitro* and *in vivo*.

The drugs having potential combinability and synergy with the 2,3-dihydroimidazo[1,2-c]quinazoline compounds are described above, particularly, but not limited to Dexamethasone, Thalidomide, Bortezomib, Melphalan, Rapalogs (temsirolimus, everolimus, and AP23573), drugs inhibiting
5 MAPK pathway, Stat1-5 pathways, IKK-NFkappaB pathways, AKT-mTOR pathway, integrin pathways, antiangiogenic drugs, etc.

The combination with 2,3-dihydroimidazo[1,2-c]quinazoline compounds can also include more than one compound : it could be two, or more compounds.

10

Table 1 shows the combination index of cA (as component A) with cB, Erlotinib, Lapatinib, and Paclitaxel (as component B), in CRC, lung and breast tumor cell lines, respectively. Very strong (combination index < 0.3) to strong synergy (combination index $0.3 < CI < 0.6$) were demonstrated in all the tumor
15 cell lines and combination drugs listed in Table1, except the combination of cA (as component A) with erlotinib (as component B) in NCI-H1975, a cell line has double EGFR mutations and resistant to erlotinib, showed moderate synergy ($CI = 0.60-0.65$). Importantly, in most of the cases, stronger synergy was observed with IC90, indicating these combinations greatly enhanced maximum tumor
20 growth inhibition compared to monotherapy.

Table 1: Summary of combination effects of cA (as component A)* with either cB, Erlotinib, Lapatinib or paclitaxel (as component B) in proliferation assays

25

Cancer Indication	Cell Line	Combination Index							
		cA/cB		cA/Erdotinib		cA/Lapatinib		cA/Paclitaxel	
		IC ₅₀	IC ₉₀	IC ₅₀	IC ₉₀	IC ₅₀	IC ₉₀	IC ₅₀	IC ₉₀
Lung	A549	0.28	0.18					0.81	0.46
	NCI-H460	0.16	0.11						
	NCI-H1975	0.38	0.08	0.62	0.65				
	NCI-H1650	0.59	0.34	0.17	0.48				
	NCI-H23	0.12	0.12						
CRC	Colo205	0.38	0.31						
	SW620	0.21	0.03						
	LoVo	0.31	0.18						
	HCT116	0.11	0.05					0.37	0.03
	DLD1	0.06	NA						
Breast	MDA-MB-231	0.23	0.09						
	MDA-MB-468			0.38	0.59				
	T47D					0.64	0.44		
	BT474					0.49	0.43		

For example, combining cA (as component A) with cB (as component B) showed not only strong synergy with respect to IC₅₀s (combination index 0.21- 0.90), but also dramatically lowered IC₉₀s, with combination indices of 0.02-0.18 across the entire tested range of concentrations. As a result, while neither cA nor cB as a **single** agent could inhibit proliferation by 90% at 5 μ M, the IC₉₀ was reached when combining e.g. 285 nM of cA (as component A) and 380 nM of cB (as component B) (see Figure 1).

Figure 1: Isobologram/combination index analysis on the combination of cA* and cB against proliferation in CRC SW620 tumor cell line.

A 72-hour proliferation assay was conducted using Cell Titer Glo (Promega). The top concentrations of cA and cB were 5 μ M and 10 μ M, respectively. MAPPING IC₅₀ and IC₉₀ refers to the IC₅₀ and IC₉₀ obtained from the dose-response curve of either cA* or cB alone, or cA* plus cB with the ratio indicated in the table, where the top relative concentration is defined as 1.

A similar result was obtained when testing for activation of caspase 3/7 as a marker of apoptosis induction in NCI-H1975 (NSCLC), NCI-H1650(NSCLC), HCT116 (CRC), Colo205 (CRC), and MDA-MB-468 (breast cancer) cell lines Table

2. For example, Neither 10 μ M of cB nor 5 μ M of cA as single agents could induce apoptosis, while the combination of the two drugs led to the activation of caspase 3/7 with combination indexes of 0.09 - 0.18 across all concentrations.

5

Table 2: Summary of combination effects of cA* and cB in caspase 3/7 assays

Cancer Indication	Cell Line	Combination Index	
		cA/cB	cA/Erlotinib
		IC50	IC50
NSCLC	NCI-H1975	0,04	
	NCI-H1650	0,85	
CRC	Colo205	0,06	
	HCT116	0,09	
Breast	MDA-MB-468	0,50	
	BT474		0,17

10

Figure 2: Activation of caspase3/7 by combined treatment of cA* and cB.

Caspase 3/7 assay was conducted at 48 h after compound exposure to HCT116 (A) and at 24 h after compound exposure to Colo205 (B). Method for compound combination and dilution were described in 3.3.1.2.1. The top concentrations of cA* and cB were 5 μ M and 10 μ M, respectively. The dose-response curve of either cA* or cB alone, or cA* (as component A) plus cB (as component B) with the ratio indicated in the figure, where the top relative concentrations are defined as 1.

15

Example 2. Synergistic combination of cA* (as component A) with cB and paclitaxel *in vivo*

20

To confirm the synergy demonstrated in the *in vitro* studies, the combination of cA with cB and paclitaxel was tested in patient-derived primary NSCLC and CRC xenografts in nude mice.

The first model was Co5841 (resistant to Cetuximab). cB was dosed daily at 12.5 (half-MTD) and 25 mg/kg (MTD) from day 6 to day 23. cA (MTD) was dosed weekly (day 6, 13, and 20) at 10 mg/kg BID (MTD) and at 14 mg/kg with Q2D

25

schedule (from day 6 to day 22). Tumor size was monitored twice weekly. cB as a single agent seemed more effective (T/C= 0.35 for 12.5 mg/kg group; T/C= 0.20 for 25 mg/kg group) than cA* (T/C = 0.49 and 0.39 for weekly and Q2D dosing schedules, respectively,

Figure 3). Clear synergistic effects were observed in the combination. The combination groups with cB at 25 mg/kg showed the best efficacy (T/C = 0.13 and 0.10 for weekly and Q2D dosing cA, respectively). More importantly, these two combination groups significantly improved the disease control rates in comparison to each monotherapy. Thus, only 0% and 20% animals showed disease progression (DP) in the groups with 25 mg/kg of cB plus 14 mg/kg (Q2D) or 10 mg/kg (BID weekly) of cA, respectively. In the corresponding monotherapy groups, 70% animals treated with 25 mg/kg of cB, and 100% and 90% of animals treated with 14 mg/kg (Q2D) or 10 mg/kg (BID weekly) of cA* exhibited DP.

Figure 3: Dose-dependent tumor growth inhibition in Co5841 primary human xenograft CRC model. Co5841 primary human tumor was derived from a patient with CRC and was xenografted in nude mice. The tumor was propagated *in vivo* and tumor tissue from one *in vivo* passage was used for s.c. implantation in the inguinal region of male nude mice. Treatment was started when the tumors were approximately 0.1 cm³ in size. Treatment was continued until progression of the tumors. Tumor diameters and body weight were monitored weekly. cA* was dosed at 14 mg/kg, Q2D x 7 from day 6 to day 22 (group C, H and I), or 10 mg/kg, BIDx1 weekly on day 6, 13, and 20. cB was dosed at either 12.5 mg/kg (group D, F and H), QD, or 25 mg/kg (group E, G and I), QD from day 6 to day 22.

The synergistic combination of cA* and cB was also confirmed in a patient-derived NSCLC xenograft model - Lu7187. This NSCLC model is resistant to erlotinib, paclitaxel, and etoposid, while Cetuximab and carboplatin (T/C = 0.21-0.35) are moderately efficacious. cB was dosed daily at 12.5 (half-MTD)

and 25 mg/kg (MTD) from day 7 to day 35. cA (MTD) was dosed weekly (day 7, 14, 21 and 28) at 10 mg/kg BID (MTD).

Similar to the CRC model described above, cB as a single agent was more effective (12.5 mg/kg: T/C= 0.46; 25 mg/kg: T/C= 0.31) than cA* (T/C = 0.88; see Figure 4). Clear synergistic effects were observed in the combination (T/C = 0.08), which resulted in effective suppression of tumor growth in this model. cA in combination with 25 mg/kg of cB resulted in 3 PR and 3 SDs while 100% of the animals in the respective monotherapy groups exhibited disease progression. Weekly dosing of cA* showed similar efficacy to the Q2D dosing schedule, but exhibited less body weight loss.

Clear synergistic effects were observed in the combination (T/C = 0.08), which resulted in effective suppression of tumor growth in this model. cA in combination with 25 mg/kg of cB resulted in 3 PR and 3 SDs while 100% of the animals in the respective monotherapy groups exhibited disease progression. Weekly dosing of cA* showed similar efficacy to the Q2D dosing schedule, but exhibited less body weight loss.

Figure 4: Dose-dependent tumor growth inhibition in Lu7187 primary human xenograft NSCLC model. Lu7187 primary human tumor was derived from a patient with NSCLC and was xenografted in nude mice. The tumor was propagated *in vivo* and tumor tissue from one *in vivo* passage was used for s.c. implantation in the inguinal region of male nude mice. Treatment was started when the tumors were approximately 0.1 cm³ in size. Treatment was continued until progression of the tumors. Tumor diameters and body weight were monitored t weekly. cA* was dosed at 14 mg/kg, Q2D x 10 from day 7 to day 25 (group C, H and I), or 10 mg/kg, BIDx1 weekly on day 7, 14, 21 and 28. cB was dosed at either 12.5 mg/kg (group D, F and H), QD, or 25 mg/kg (group E, G and I), QD from day 7 to day 35.

The synergistic combination of cA* and paclitaxel was also confirmed in a patient-derived NSCLC xenograft model - Lu7187. This NSCLC model is resistant to etoposid, Cetuximab and erlotinib (T/C > 0.5). Paclitaxel as a single agent was very efficacious at 25 mg/kg (MTD). However, 60% of the mice exhibited disease progression after stopping the treatment. In contrast, the corresponding combination group (25 mg/kg paclitaxel and 10 mg/kg cA*) demonstrated complete 100% disease control rate (30% complete tumor regression and 70% partial regression), indicating clear synergistic effects using cA in combination with paclitaxel.

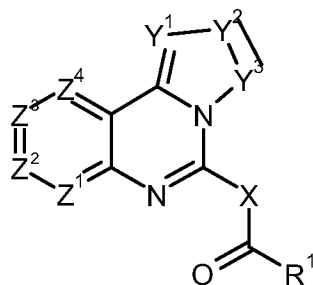
Figure 5: Dose-dependent tumor growth inhibition in Lu7343 primary human xenograft NSCLC model. Lu7343 primary human tumor was derived from a patient with NSCLC and was xenografted in nude mice. The tumor was propagated *in vivo* and tumor tissue from one *in vivo* passage was used for s.c. implantation in the inguinal region of male nude mice. Treatment was started when the tumors were approximately 0.1 cm³ in size. Treatment was continued until progression of the tumors. Tumor diameters and body weight were monitored t weekly. cA* was dosed at 10 mg/kg, BIDx1 weekly on day 15, 22, and 29. paclitaxel was dosed at either 15 mg/kg, or 25 mg/kg, once a week on day 14, 21 and day 28.

CLAIMS

1. A combination of :

component A : one or more 2,3-dihydroimidazo[1,2-c]quinazoline compounds

5 of general formula (A1) :



(A1)

wherein

10 X represents CR⁵R⁶ or NH;

Y¹ represents CR³ or N;

15 Chemical bond between Y²-----Y³ represents a single bond or double bond,

with the proviso that when the Y²-----Y³ represents a double bond,

Y² and Y³ independently represent CR⁴ or N, and

20

when Y²-----Y³ represents a single bond, Y² and Y³ independently represent CR³R⁴ or NR⁴;

Z¹, Z², Z³ and Z⁴ independently represent CH, CR² or N;

25

R¹ represents aryl optionally having 1 to 3 substituents selected from R¹¹, C₃₋₈ cycloalkyl optionally having 1 to 3 substituents selected from R¹¹,

C₁₋₆ alkyl optionally substituted by
aryl, heteroaryl, C₁₋₆ alkoxyaryl, aryloxy, heteroaryloxy or one or more
halogen,

C₁₋₆ alkoxy optionally substituted by

carboxy, aryl, heteroaryl, C₁₋₆ alkoxyaryl, aryloxy, heteroaryloxy or one
or more halogen,

or

a 3 to 15 membered mono- or bi-cyclic heterocyclic ring that is
saturated or unsaturated, and contains 1 to 3 heteroatoms selected
from the group consisting of N, O and S, and optionally having 1 to 3
substituents selected from R¹¹

wherein

R¹¹ represents

halogen, nitro, hydroxy, cyano, carboxy, amino, N-(C₁₋₆alkyl)amino, N-
(hydroxyC₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆acyl)amino, N-
(formyl)-N-(C₁₋₆alkyl)amino, N-(C₁₋₆alkanesulfonyl) amino, N-(carboxyC₁₋₆-
alkyl)-N-(C₁₋₆alkyl)amino, N-(C₁₋₆alkoxycabonyl)amino, N-[N,N-di(C₁₋₆alk-
yl)amino methylene]amino, N-[N,N-di(C₁₋₆alkyl)amino (C₁₋₆ alkyl)meth-
ylene]amino, N-[N,N-di(C₁₋₆alkyl)amino C₂₋₆alkenyl]amino, amino-
carbonyl, N-(C₁₋₆alkyl)aminocarbonyl, N,N-di(C₁₋₆alkyl)aminocarbonyl, C₃-
8cycloalkyl, C₁₋₆ alkylthio, C₁₋₆alkanesulfonyl, sulfamoyl, C₁-
6alkoxycarbonyl,

N-arylamino wherein said aryl moiety is optionally having 1 to 3
substituents selected from R¹⁰¹, N-(aryl C₁₋₆alkyl)amino wherein said aryl
moiety is optionally having 1 to 3 substituents selected from R¹⁰¹, aryl
C₁₋₆alkoxycarbonyl wherein said aryl moiety is optionally having 1 to 3
substituents selected from R¹⁰¹,

C₁₋₆alkyl optionally substituted by

mono-, di- or tri- halogen, amino, N-(C₁₋₆alkyl)amino or N,N-di(C₁₋₆alk-
yl)amino,

C₁₋₆alkoxy optionally substituted by

mono-, di- or tri- halogen, N-(C₁₋₆alkyl)sulfonamide, or N-(aryl)sulfonamide,

or

a 5 to 7 membered saturated or unsaturated ring having 1 to 3 heteroatoms selected from the group consisting of O, S and N, and optionally having 1 to 3 substituents selected from R¹⁰¹

wherein

R¹⁰¹ represents

halogen, carboxy, amino, N-(C₁₋₆ alkyl)amino, N,N-di(C₁₋₆alkyl)amino, aminocarbonyl, N-(C₁₋₆alkyl)aminocarbonyl, N,N-di(C₁₋₆alkyl)aminocarbonyl, pyridyl,

C₁₋₆ alkyl optionally substituted by cyano or mono- di- or tri- halogen,

or

C₁₋₆alkoxy optionally substituted by cyano, carboxy, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, aminocarbonyl, N-(C₁₋₆alkyl)aminocarbonyl, N,N-di(C₁₋₆alkyl)aminocarbonyl or mono-, di- or tri- halogen;

R² represents hydroxy, halogen, nitro, cyano, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(hydroxyC₁₋₆alkyl)amino, N-(hydroxyC₁₋₆alkyl)-N-(C₁₋₆alkyl)amino, C₁₋₆ acyloxy, aminoC₁₋₆ acyloxy, C₂₋₆alkenyl, aryl,

a 5-7 membered saturated or unsaturated heterocyclic ring having 1 to 3 heteroatoms selected from the group consisting O, S and N, and optionally substituted by

hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, amino, amino C₁₋₆alkyl, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆ acyl)amino, N-(C₁₋₆alkyl)carbonylamino, phenyl, phenyl C₁₋₆ alkyl, carboxy, C₁₋₆alkoxycarbonyl, aminocarbonyl, N-(C₁₋₆alkyl)aminocarbonyl, or N,N-di(C₁₋₆alkyl)amino,

-C(O)- R²⁰

wherein

5 R^{20} represents C_{1-6} alkyl, C_{1-6} alkoxy, amino, N-(C_{1-6} alkyl)amino, N,N-di(C_{1-6} alkyl)amino, N-(C_{1-6} acyl)amino, or a 5-7 membered saturated or unsaturated heterocyclic ring having 1 to 3 heteroatoms selected from the group consisting O, S and N, and optionally substituted by
 C_{1-6} alkyl, C_{1-6} alkoxy, oxo, amino, N-(C_{1-6} alkyl)amino, N,N-di(C_{1-6} alkyl)amino, N-(C_{1-6} acyl)amino, phenyl, or benzyl,

10 C_{1-6} alkyl optionally substituted by R^{21}
or
 C_{1-6} alkoxy optionally substituted by R^{21}
wherein

15 R^{21} represents cyano, mono-, di or tri- halogen, hydroxy, amino, N-(C_{1-6} alkyl)amino, N,N-di(C_{1-6} alkyl)amino, N- (hydroxy C_{1-6} alkyl) amino, N- (halophenyl C_{1-6} alkyl) amino, amino C_{2-6} alkylenyl, C_{1-6} alkoxy, hydroxy C_{1-6} alkoxy, -C(O)- R^{201} , -NHC(O)- R^{201} , C_{3-8} cycloalkyl, isoindolino, phthalimidyl, 2-oxo-1,3-oxazolidinyl, aryl or a 5 or 6 membered saturated or unsaturated heterocyclic ring having 1 to 4 heteroatoms selected from the group consisting O, S
20 and N optionally substituted by
hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, hydroxy C_{1-6} alkoxy, oxo, amino, amino C_{1-6} alkyl, N-(C_{1-6} alkyl)amino, N,N-di(C_{1-6} alkyl)amino, N-(C_{1-6} acyl)amino, or benzyl,

25 wherein
 R^{201} represents hydroxy, amino, N-(C_{1-6} alkyl)amino, N,N-di(C_{1-6} alkyl)amino, N- (halophenyl C_{1-6} alkyl) amino, C_{1-6} alkyl, amino C_{1-6} alkyl, amino C_{2-6} alkylenyl, C_{1-6} alkoxy, a 5 or 6 membered saturated or unsaturated heterocyclic ring having 1 to 4
30 heteroatoms selected from the group consisting O, S and N optionally substituted by

hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxycarbonyl, hydroxyC₁₋₆ alkoxy, oxo, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆ acyl)amino or benzyl;

5 R³ represents hydrogen, halogen, aminocarbonyl, or C₁₋₆ alkyl optionally substituted by aryl C₁₋₆ alkoxy or mono-, di- or tri-halogen;

R⁴ represents hydrogen or C₁₋₆ alkyl;

10

R⁵ represents hydrogen or C₁₋₆ alkyl; and

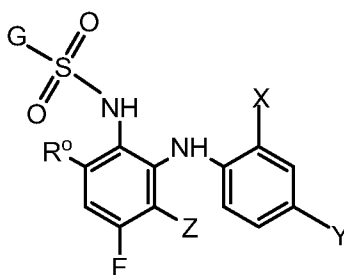
R⁶ represents halogen, hydrogen or C₁₋₆ alkyl ;

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;

15 optionally in the form of a pharmaceutical formulation which is ready for use to be administered simultaneously, concurrently, separately or sequentially ; and

component B : one or more N-(2-arylamino) aryl sulfonamide compounds of general formula (B) :

20



(B)

25

where G is R_{1a}, R_{1b}, R_{1c}, R_{1d}, R_{1e}, Ar₁, Ar₂ or Ar₃; R⁰ is H, halogen, C₁₋₆ alkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, said alkyl, cycloalkyl, alkenyl, and alkynyl groups optionally substituted with 1-3

substituents selected independently from halogen, OH, CN, cyanomethyl, nitro, phenyl, and trifluoromethyl, and said C₁-C₆ alkyl and C₁-C₄ alkoxy groups also optionally substituted with OCH₃ or OCH₂CH₃; X is F, Cl or methyl; Y is I, Br, Cl, CF₃, C₁-C₃ alkyl, C₂-C₃ alkenyl, C₂-C₃ alkynyl, cyclopropyl, phenyl, pyridyl, pyrazolyl, OMe, OEt, or SMe, where all said methyl, ethyl, C₁-C₃ alkyl, and cyclopropyl groups of X and Y are optionally substituted with OH, all said phenyl, pyridyl, pyrazolyl groups of Y are optionally substituted with halogen, acetyl, methyl, and trifluoromethyl, and all said methyl groups of X and Y are optionally substituted with one, two, or three F atoms; and Z is H or F,

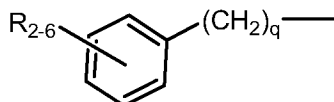
where R_{1a} is methyl, optionally substituted with 1-3 fluorine atoms or 1-3 chlorine atoms, or with OH, cyclopropoxy, or C₁-C₄ alkoxy, where the C₁-C₄ alkyl moieties of said C₁-C₄ alkoxy groups are optionally substituted with one hydroxy or methoxy group, and where all C₂-C₄ alkyl groups within said C₁-C₄ alkoxy are optionally further substituted with a second OH group;

R_{1b} is CH(CH₃)-C₁₋₃ alkyl or C₃-C₆ cycloalkyl, said methyl, alkyl, and cycloalkyl groups optionally substituted with 1-3 substituents selected independently from F, Cl, Br, I, OH, C₁-C₄ alkoxy, and CN;

R_{1c} is (CH₂)_nO_mR', where m is 0 or 1; where, when m is 1, n is 2 or 3, and when m is 0, n is 1 or 2; and where R' is C₁-C₆ alkyl, optionally substituted with 1-3 substituents selected independently from F, Cl, OH, OCH₃, OCH₂CH₃, and C₃-C₆ cycloalkyl;

R_{1d} is C(A)(A')(B)- where B, A, and A' are, independently, H or C₁₋₄ alkyl, optionally substituted with one or two OH groups or halogen atoms, or A and A', together with the carbon atom to which they are attached, form a 3- to 6-member saturated ring, said ring optionally containing one or two heteroatoms selected, independently, from O, N, and S and optionally substituted with one or two groups selected independently from methyl, ethyl, and halo;

R_{1e} is benzyl or 2-phenyl ethyl, in which the phenyl group is optionally substituted

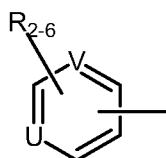


5

where q is 1 or 2, R₂, R₃ and R₄ are, independently, H, F, Cl, Br, CH₃, CH₂F, CHF₂, CF₃, OCH₃, OCH₂F, OCHF₂, OCF₃, ethyl, *n*-propyl, isopropyl, cyclopropyl, isobutyl, *sec*-butyl, *tert*-butyl, and methylsulfonyl, and R₄ may also be nitro, acetamido, amidinyl, cyano, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, 1,3,4-oxadiazol-2-yl, 5-methyl-1,3,4-oxadiazolyl, 1,3,4-thiadiazolyl, 5-methyl-1,3,4-thiadiazol-1*H*-tetrazolyl, N-morpholinyl carbonylamino, N-morpholinylsulfonyl, and N-pyrrolidinylcarbonylamino; R₅ and R₆ are, independently, H, F, Cl, or methyl;

15

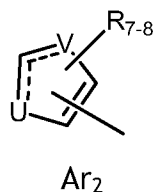
Ar₁ is



where U and V are, independently, N, CR₂ or CR₃; R₂, R₃ and R₄ are, independently, H, F, Cl, Br, CH₃, CH₂F, CHF₂, CF₃, OCH₃, OCH₂F, OCHF₂, OCF₃, ethyl, *n*-propyl, isopropyl, cyclopropyl, isobutyl, *sec*-butyl, *tert*-butyl, and methylsulfonyl, and R₄ may also be nitro, acetamido, amidinyl, cyano, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, 1,3,4-oxadiazol-2-yl, 5-methyl-1,3,4-oxadiazol, 1,3,4-thiadiazol, 5-methyl-1,3,4-thiadiazol 1*H*-tetrazolyl, N-morpholinylcarbonylamino, N-morpholinylsulfonyl and N-pyrrolidinylcarbonylamino; R₅ and R₆ are, independently, H, F, Cl or methyl;

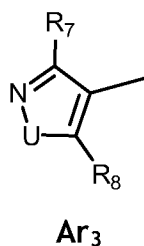
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Ar₂ is



where the dashed line represents a double bond which may be located formally either between V and the carbon between U and V, or between U and the carbon between U and V; where U is -S-, -O- or -N = and where, when U is -O- or -S-, V is -CH=, -CCl= or -N =; and when U is -N =, V CH=, or -NCH₃-; R₇ and R₈ are, independently, H, methoxycarbonyl, methylcarbamoyl, acetamido, acetyl, methyl, ethyl, trifluoromethyl, or halogen.

10 Ar_3 is



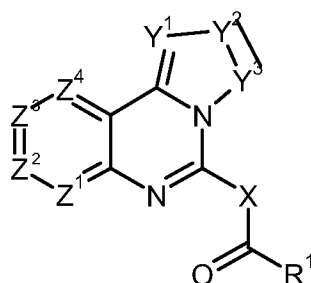
where U is -NH-, -NCH₃- or -O-; and R₇ and R₈ are, independently, H, F, Cl, or methyl ;

15 or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; optionally in the form of a pharmaceutical formulation which is ready for use to be administered simultaneously, concurrently, separately or sequentially ; and, optionally,
component C : one or more further pharmaceutical agents.

20

2. The combination according to claim 1, wherein :

said component A is one or more 2,3-dihydroimidazo[1,2-c]quinazoline compounds of general formula (A2) :



(A2)

5 in which :

X represents CR^5R^6 or NH ;

Y^1 represents CR^3 or N ;

10

the chemical bond between $\text{Y}^2\text{---}\text{Y}^3$ represents a single bond or double bond, with the proviso that when the $\text{Y}^2\text{---}\text{Y}^3$ represents a double bond, Y^2 and Y^3 independently represent CR^4 or N , and

when $\text{Y}^2\text{---}\text{Y}^3$ represents a single bond, Y^2 and Y^3 independently represent
15 CR^3R^4 or NR^4 ;

Z^1 , Z^2 , Z^3 and Z^4 independently represent CH , CR^2 or N ;

20

R^1 represents aryl optionally having 1 to 3 substituents selected from R^{11} , C_{3-8} cycloalkyl optionally having 1 to 3 substituents selected from R^{11} ,

C_{1-6} alkyl optionally substituted by aryl, heteroaryl, C_{1-6} alkoxyaryl, aryloxy, heteroaryloxy or one or more halogen,

25

C_{1-6} alkoxy optionally substituted by carboxy, aryl, heteroaryl, C_{1-6} alkoxyaryl, aryloxy, heteroaryloxy or one or more halogen,

or

a 3 to 15 membered mono- or bi-cyclic heterocyclic ring that is saturated or unsaturated, optionally having 1 to 3 substituents selected from R^{11} , and contains 1 to 3 heteroatoms selected from the group consisting of N, O and S,

5

wherein

R^{11} represents halogen, nitro, hydroxy, cyano, carboxy, amino, N-(C_{1-6} alkyl)amino, N-(hydroxy C_{1-6} alkyl)amino, N,N-di(C_{1-6} alkyl)amino, N-(C_{1-6} acyl)amino, N-(formyl)-N-(C_{1-6} alkyl)amino, N-(C_{1-6} alkanesulfonyl) amino, N-(carboxy C_{1-6} alkyl)-N-(C_{1-6} alkyl)amino, N-(C_{1-6} alkoxycarbonyl)amino, N-[N,N-di(C_{1-6} alkyl)amino methylene]amino, N-[N,N-di(C_{1-6} alkyl)amino (C_{1-6} alkyl)methylene]amino, N-[N,N-di(C_{1-6} alkyl)amino C_{2-6} alkenyl]amino, aminocarbonyl, N-(C_{1-6} alkyl)aminocarbonyl, N,N-di(C_{1-6} alkyl)aminocarbonyl, C_{3-8} cycloalkyl, C_{1-6} alkylthio, C_{1-6} alkanesulfonyl, sulfamoyl, C_{1-6} alkoxycarbonyl,

10

15

N-arylamino wherein said aryl moiety is optionally having 1 to 3 substituents selected from R^{101} , N-(aryl C_{1-6} alkyl)amino wherein said aryl moiety is optionally having 1 to 3 substituents selected from R^{101} , aryl C_{1-6} alkoxycarbonyl wherein said aryl moiety is optionally having 1 to 3 substituents selected from R^{101} ,

20

C_{1-6} alkyl optionally substituted by mono-, di- or tri- halogen, amino, N-(C_{1-6} alkyl)amino or N,N-di(C_{1-6} alkyl)amino,

25

C_{1-6} alkoxy optionally substituted by mono-, di- or tri-halogen, N-(C_{1-6} alkyl)sulfonamide, or N-(aryl)sulfonamide, or

a 5 to 7 membered saturated or unsaturated ring having 1 to 3 heteroatoms selected from the group consisting of O, S and N, and optionally having 1 to 3 substituents selected from R^{101}

30

wherein

R¹⁰¹ represents halogen, carboxy, amino, N-(C₁₋₆ alkyl)amino, N,N-di(C₁₋₆alkyl)amino, aminocarbonyl, N-(C₁₋₆alkyl)aminocarbonyl, N,N-di(C₁₋₆alkyl)aminocarbonyl, pyridyl,

5

C₁₋₆ alkyl optionally substituted by cyano or mono- di- or tri- halogen,

and

C₁₋₆alkoxy optionally substituted by cyano, carboxy, amino, N-(C₁₋₆ alkyl)amino, N,N-di(C₁₋₆alkyl)amino, aminocarbonyl, N-(C₁₋₆alkyl)aminocarbonyl, N,N-di(C₁₋₆alkyl)aminocarbonyl or mono-, di- or tri- halogen;

10

R² represents hydroxy, halogen, nitro, cyano, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(hydroxyC₁₋₆alkyl)amino, N-(hydroxyC₁₋₆alkyl)-N-(C₁₋₆alkyl)amino, C₁₋₆ acyloxy, aminoC₁₋₆ acyloxy, C₂₋₆alkenyl, aryl,

15

a 5-7 membered saturated or unsaturated heterocyclic ring having 1 to 3 heteroatoms selected from the group consisting O, S and N, and optionally substituted by

20

hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, amino, amino C₁₋₆alkyl, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆ acyl)amino, N-(C₁₋₆alkyl)carbonylamino, phenyl, phenyl C₁₋₆ alkyl, carboxy, C₁₋₆alkoxycarbonyl, aminocarbonyl, N-(C₁₋₆alkyl)aminocarbonyl, or N,N-di(C₁₋₆alkyl)amino, -C(O)- R²⁰

25

wherein

R²⁰ represents C₁₋₆ alkyl, C₁₋₆ alkoxy, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆ acyl)amino, or a 5-7 membered saturated or unsaturated heterocyclic ring having 1 to 3 heteroatoms selected from the group

30

consisting O, S and N, and optionally substituted by C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆ acyl)amino, phenyl, or benzyl,

5 C₁₋₆ alkyl optionally substituted by R²¹,
or
C₁₋₆ alkoxy optionally substituted by R²¹,
wherein

10 R²¹ represents cyano, mono-, di or tri- halogen, hydroxy, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(hydroxyC₁₋₆ alkyl) amino, N- (halophenylC₁₋₆ alkyl) amino, amino C₂₋₆ alkylene, C₁₋₆ alkoxy, hydroxyC₁₋₆ alkoxy, -C(O)- R²⁰¹, -NHC(O)- R²⁰¹, C₃₋₈cycloalkyl,
15 isoindolino, phthalimidyl, 2-oxo-1,3-oxazolidinyl, aryl or a 5 or 6 membered saturated or unsaturated heterocyclic ring having 1 to 4 heteroatoms selected from the group consisting O, S and N , and optionally substituted by hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxycarbonyl, hydroxyC₁₋₆ alkoxy, oxo, amino, aminoC₁₋₆alkyl, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆ acyl)amino, or benzyl,
20

wherein

25 R²⁰¹ represents hydroxy, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N- (halophenylC₁₋₆ alkyl) amino, C₁₋₆alkyl, aminoC₁₋₆ alkyl, aminoC₂₋₆ alkylene, C₁₋₆ alkoxy, a 5 or 6 membered saturated or unsaturated heterocyclic ring having 1 to 4 heteroatoms selected from the group consisting O, S and N,
30

and optionally substituted by hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxycarbonyl, hydroxyC₁₋₆ alkoxy, oxo, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆acyl)amino or benzyl;

5

R³ represents hydrogen, halogen, aminocarbonyl, or C₁₋₆ alkyl optionally substituted by aryl C₁₋₆ alkoxy or mono-, di- or tri-halogen;

10

R⁴ represents hydrogen or C₁₋₆ alkyl;

R⁵ represents hydrogen or C₁₋₆ alkyl; and

15

R⁶ represents halogen, hydrogen or C₁₋₆ alkyl ;

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; optionally in the form of a pharmaceutical formulation which is ready for use to be administered simultaneously, concurrently, separately or sequentially.

20

3. The combination according to claim 1, wherein :

said component A is one or more 2,3-dihydroimidazo[1,2-c]quinazoline compounds of general formula (A1) according to claim 1, which is selected from the list consisting of specific compound Examples 1-1 to 1-210 on pp. 47 to 106, specific compound Examples 2-1 to 2-368 on pp. 107 to 204, specific compound Examples 3-1 to 3-2 on pp. 205 to 207, and specific compound Examples 4-1 to 4-2 on pp. 208 to 210, of in International patent application PCT/EP2003/010377, published as WO 04/029055 A1 on April 08, 2004 ;

25

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;

30

optionally in the form of a pharmaceutical formulation which is ready for use to be administered simultaneously, concurrently, separately or sequentially.

4. The combination according to claim 2, wherein :

Said component A is one or more 2,3-dihydroimidazo[1,2-c]quinazoline compounds of general formula (A2) according to claim 2, which is selected from the list consisting of :

5 Example 1 : N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide

Example 2 : N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide

10 Example 3 : N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2,4-dimethyl-1,3-thiazole-5-carboxamide

Example 4 : 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1,3-thiazole-5-carboxamide.

15 Example 5 : 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]isonicotinamide

Example 6 : 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-4-methyl-1,3-thiazole-5-carboxamide

20 Example 7 : 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-4-propylpyrimidine-5-carboxamide

Example 8 : N-{8-[2-(4-ethylmorpholin-2-yl)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide

25 Example 9 : N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyrimidine-5-carboxamide

Example 10 : N-(8-{3-[2-(hydroxymethyl)morpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide

Example 11 : N-(8-{3-[2-(hydroxymethyl)morpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide

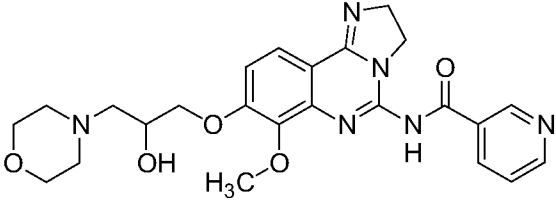
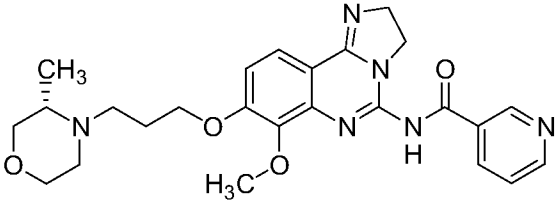
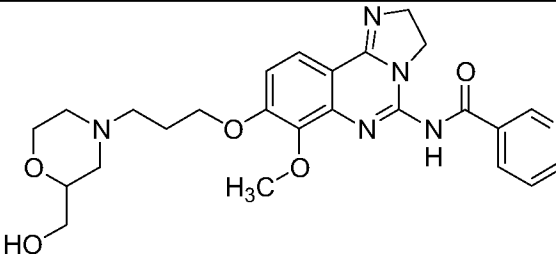
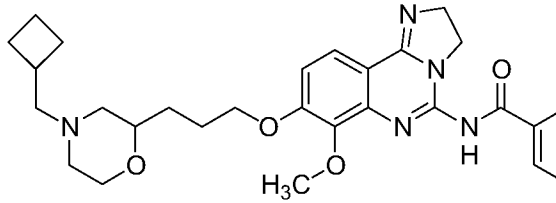
Example 12 : N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide 1-oxide

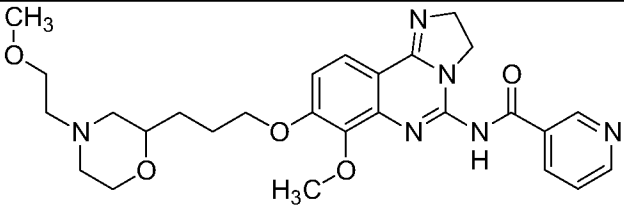
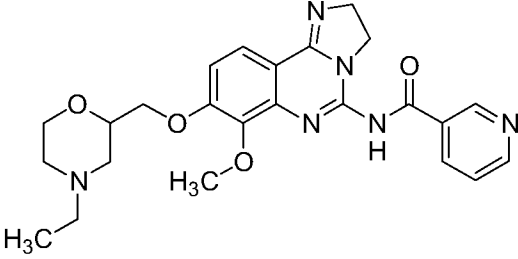
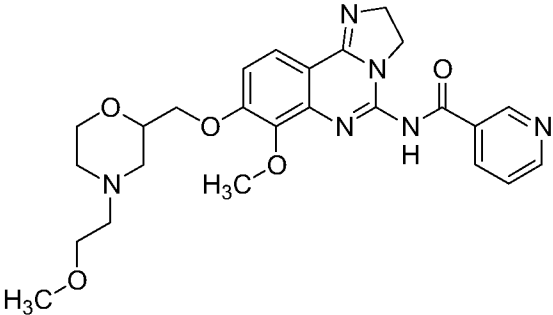
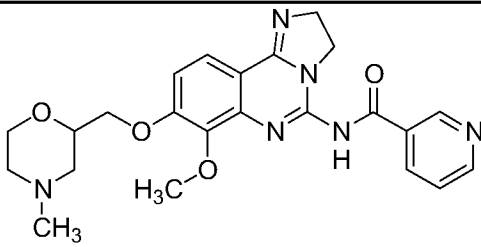
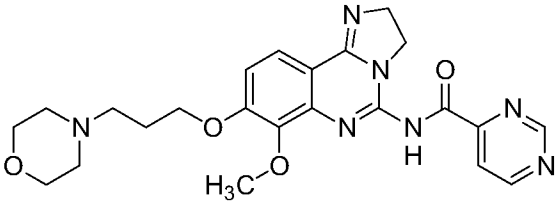
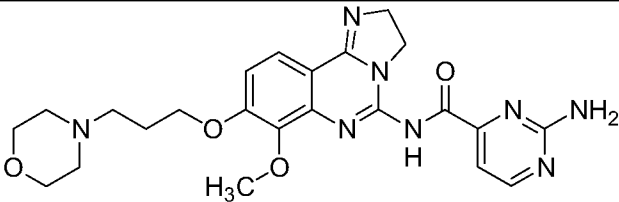
Example 13 : 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide.

5 Example 14 : N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-(2-pyrrolidin-1-ylethyl)nicotinamide.

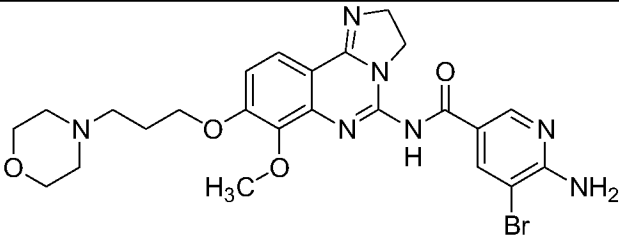
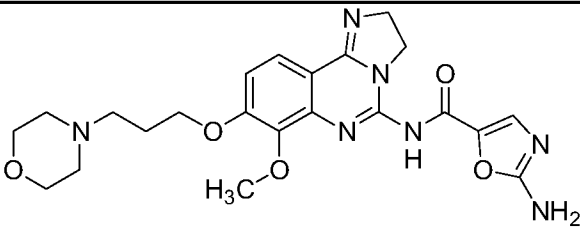
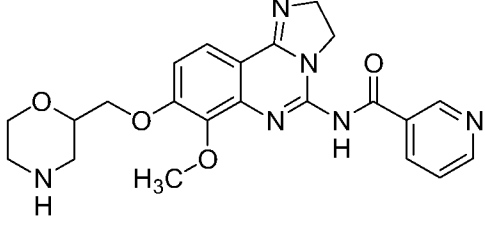
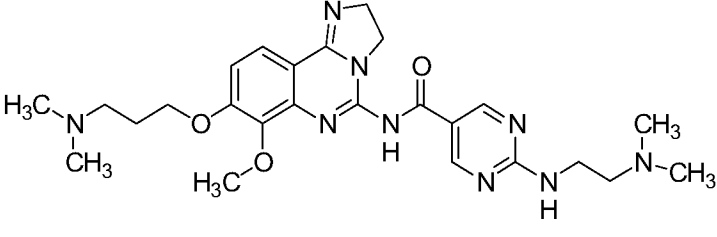
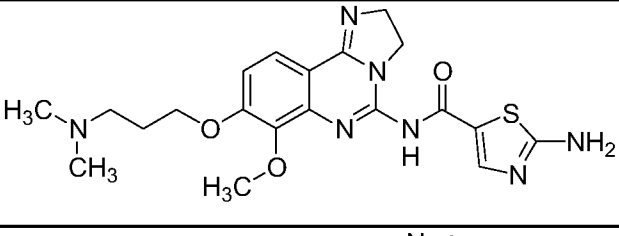
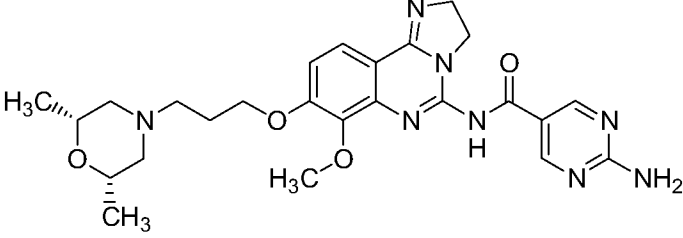
Example 15 : 6-(cyclopentylamino)-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide

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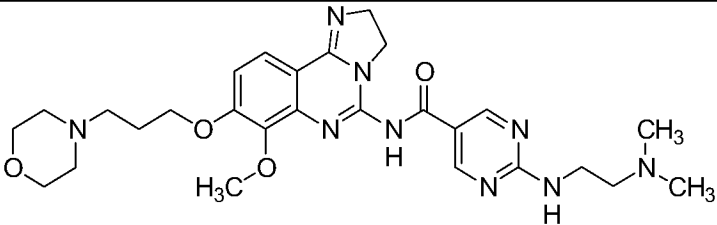
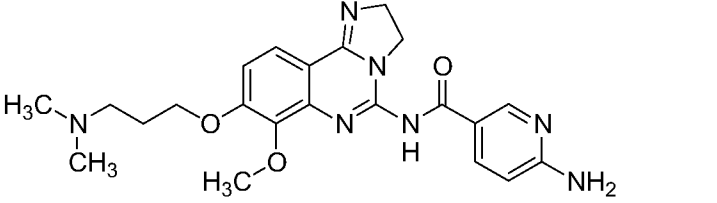
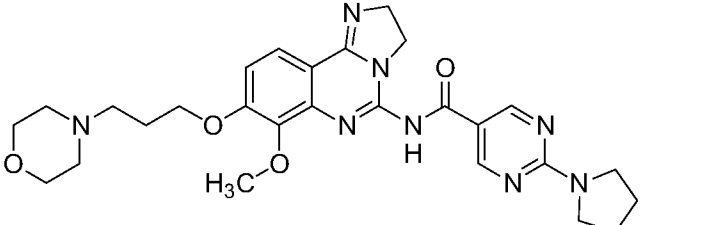
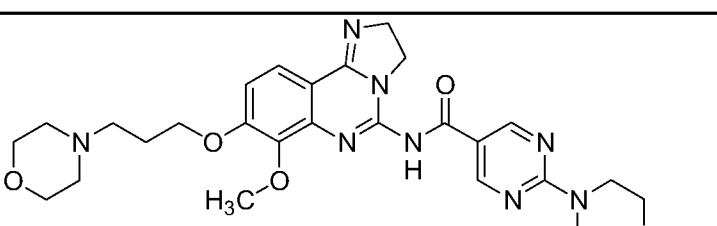
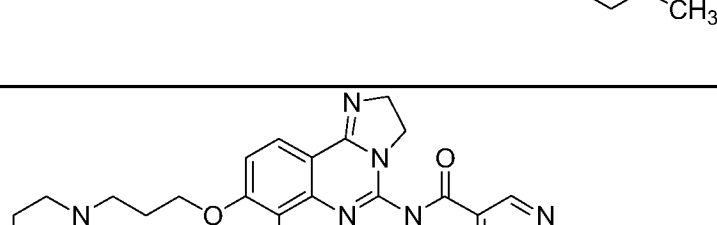
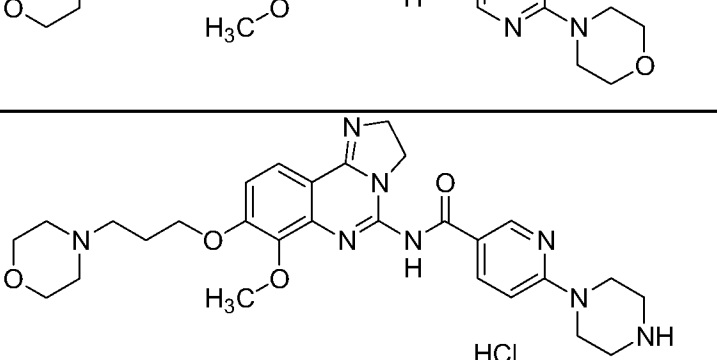
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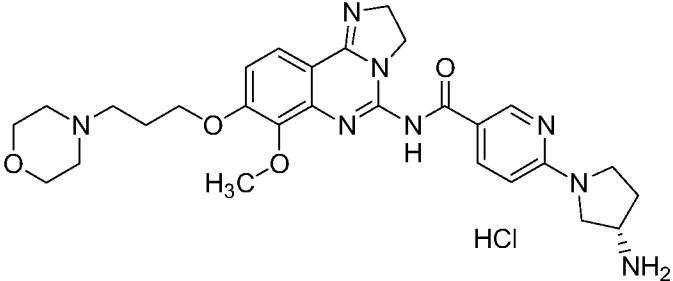
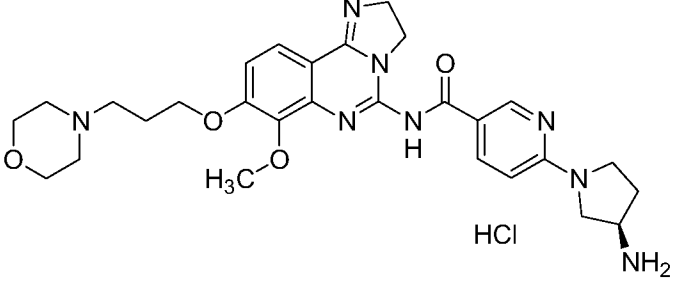
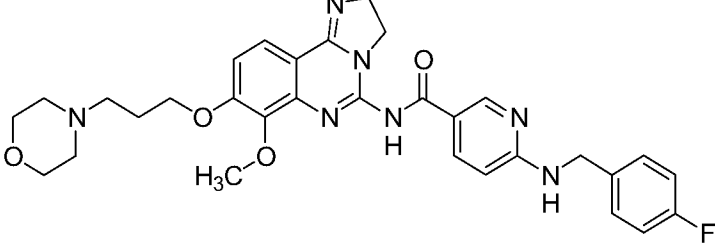
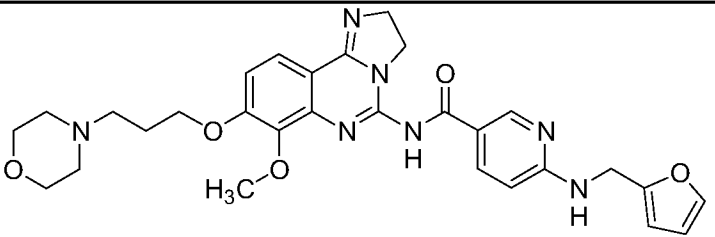
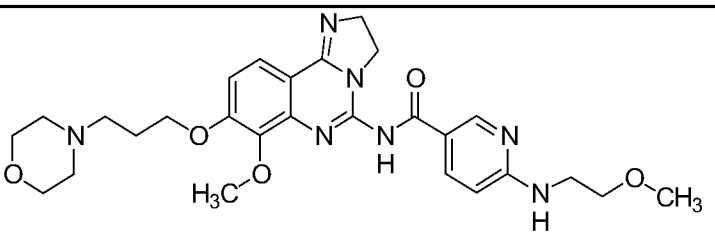
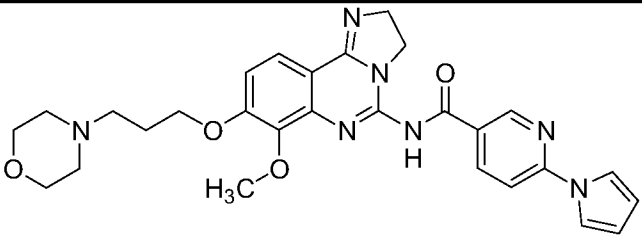
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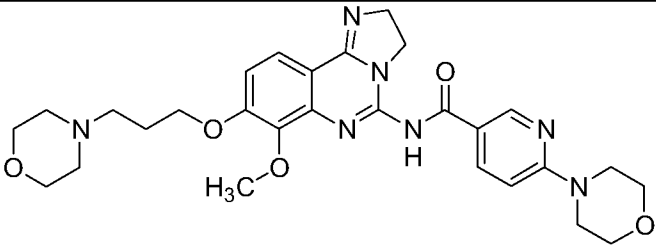
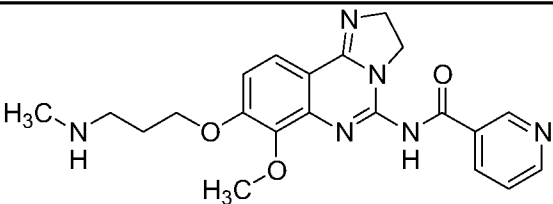
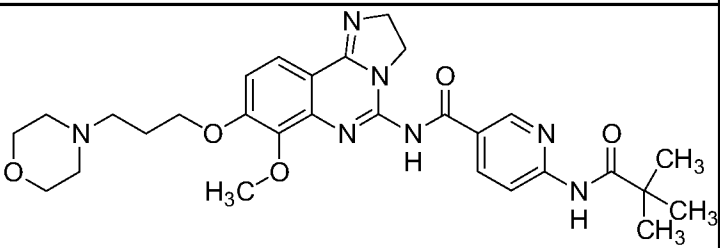
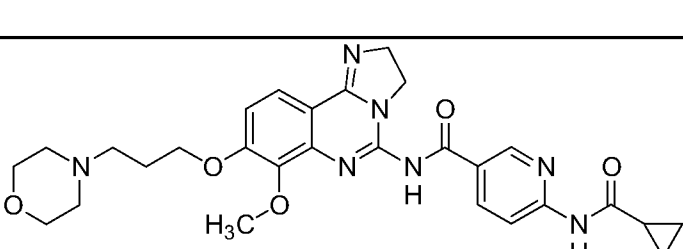
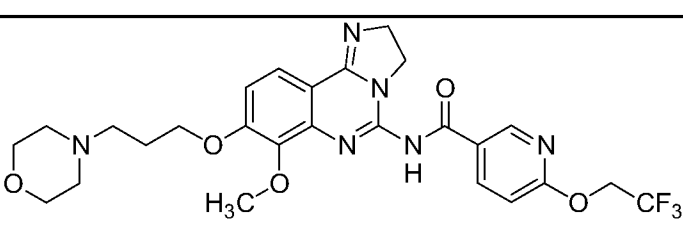
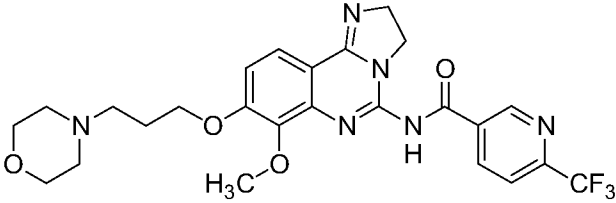
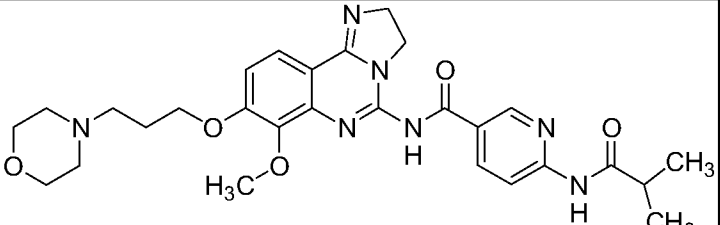
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27	 <chem>CN1C=NC(=C1)C(=O)NC2=NC=CC=C2C(=O)NC3=CC=C(C=C3)COC4=CC(=C(C=C4)OC)COC5CCN(CCC5)C[C@H]6C[C@@H](C)OC6</chem>
28	 <chem>CN1C=NC(=C1)C(=O)NC2=CC=C(C=C2)C(=O)NC3=CC=C(C=C3)COC4=CC(=C(C=C4)OC)COC5CCN(CCC5)C[C@H]6C[C@@H](C)OC6</chem>
29	 <chem>CC(=O)NC1=CC=C(C=C1)C(=O)NC2=CC=C(C=C2)C(=O)NC3=CC=C(C=C3)COC4=CC(=C(C=C4)OC)COC5CCN(CCC5)C[C@H]6C[C@@H](C)OC6</chem>
30	 <chem>CN1C=NC(=C1)C(=O)NC2=CC=C(C=C2)C(=O)NC3=CC=C(C=C3)COC4=CC(=C(C=C4)OC)COC5CCN(CCC5)CO6</chem>
31	 <chem>CN1C=NC(=C1)C(=O)NC2=CC=C(C=C2)C(=O)NC3=CC=C(C=C3)COC4=CC(=C(C=C4)OC)COC5CCN(CCC5)CO6</chem>
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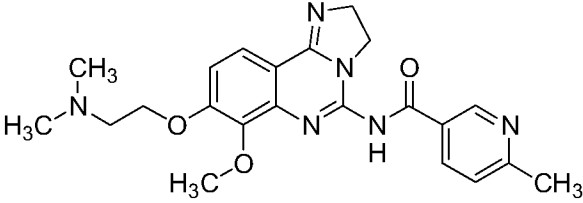
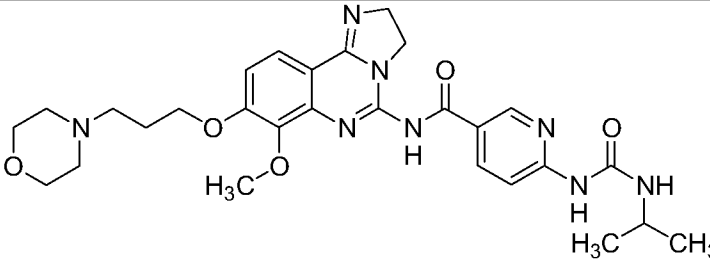
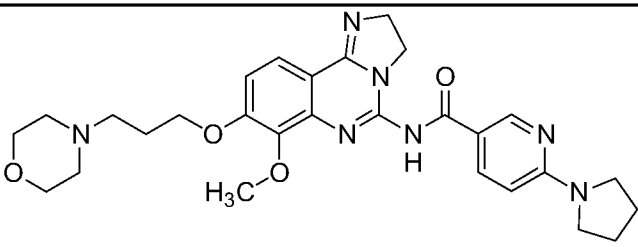
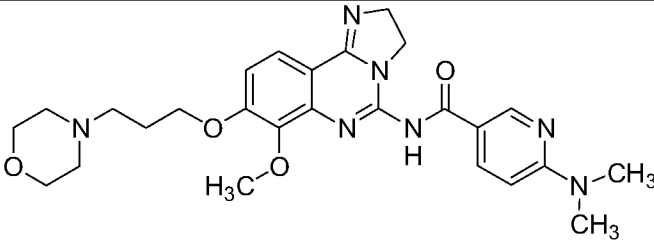
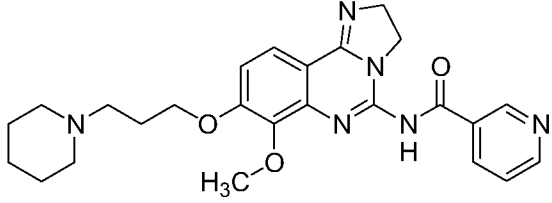
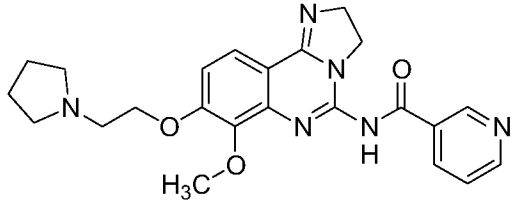
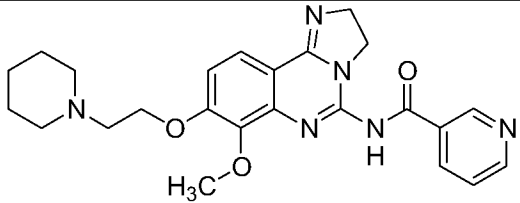
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40	 <chem>OCCNc1nc2c(ncn2)cc(OC)c1OCCN3CCN(C3)C</chem>
41	 <chem>COCNc1nc2c(ncn2)cc(OC)c1OCCN3CCN(C3)C</chem>
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43	 <chem>C1CCN(C1)CCNc2nc3c(ncn3)cc(OC)c2OCCN4CCN(C4)C</chem>
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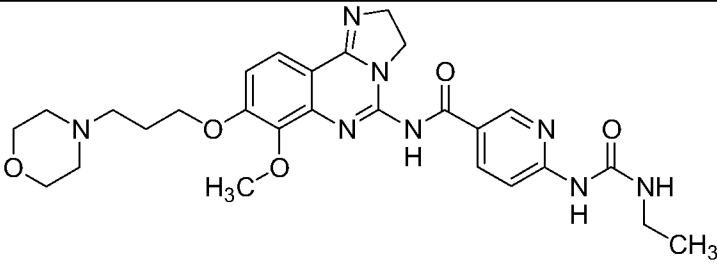
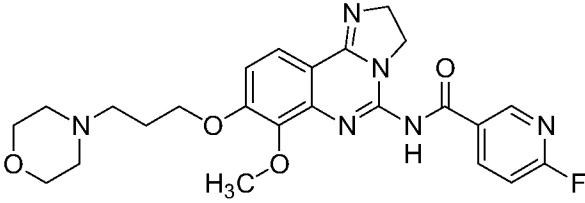
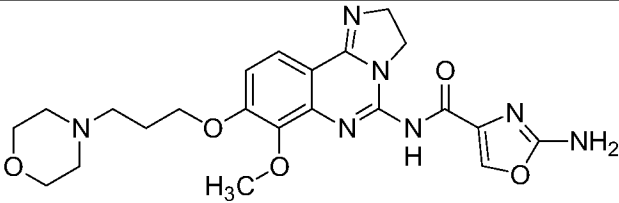
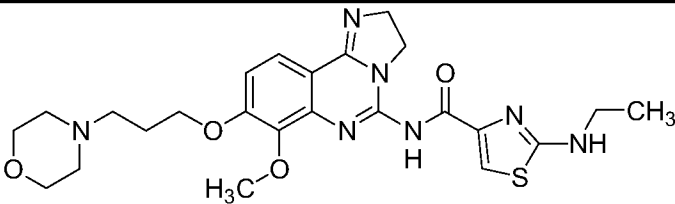
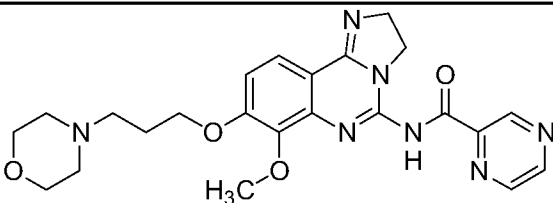
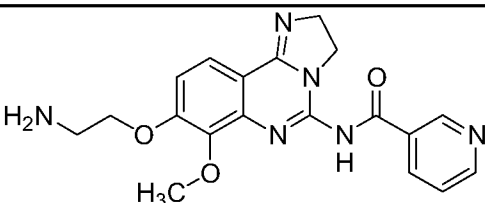
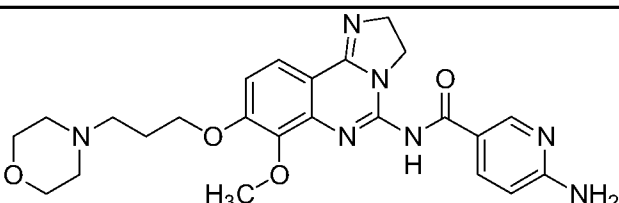
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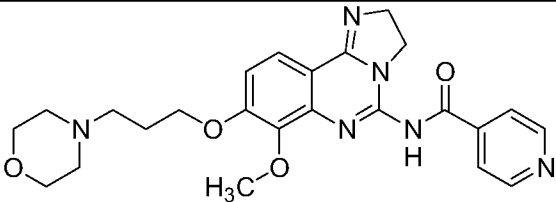
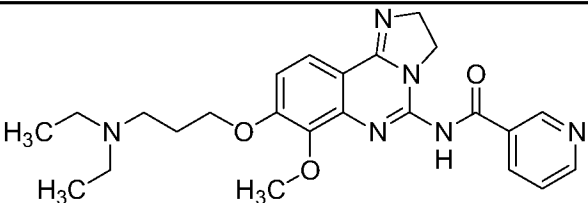
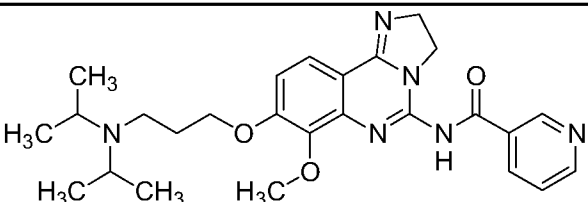
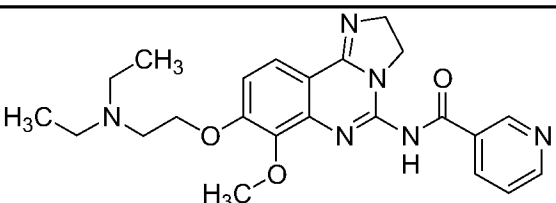
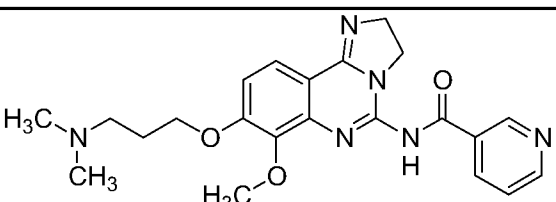
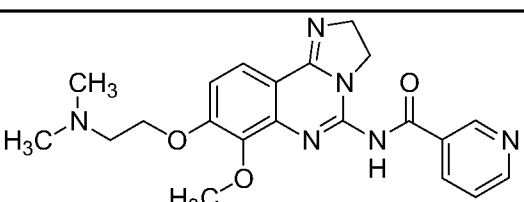
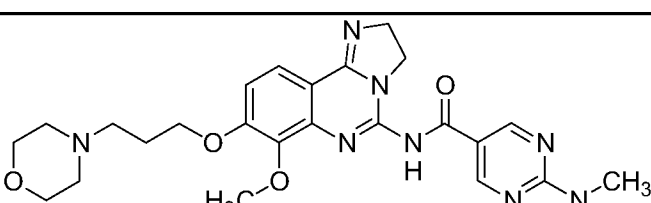
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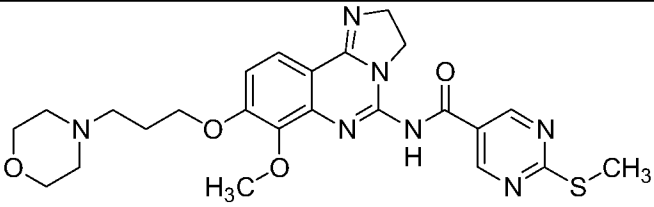
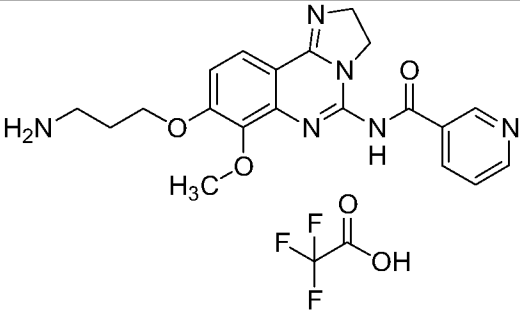
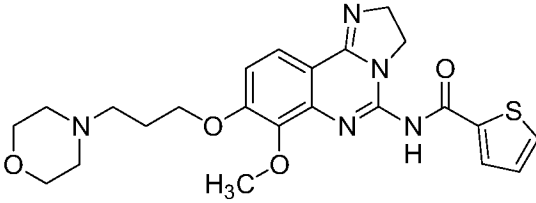
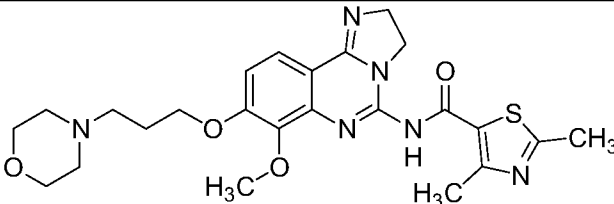
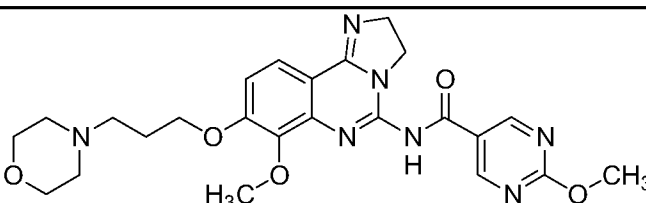
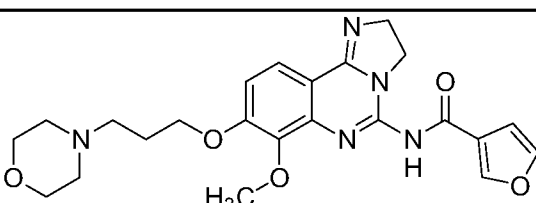
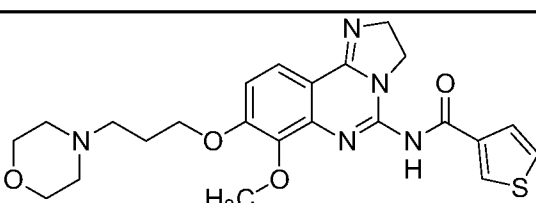
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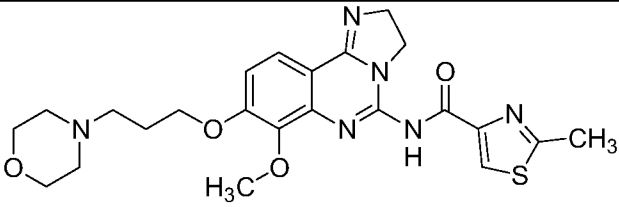
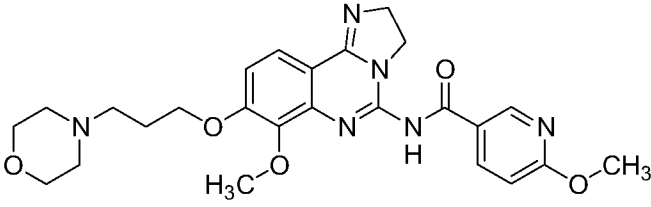
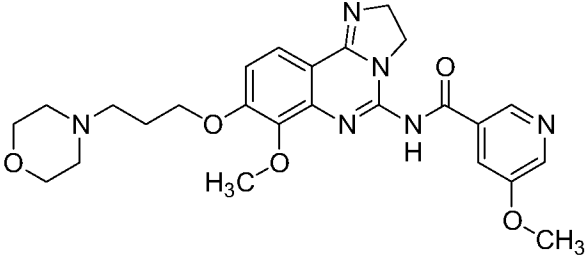
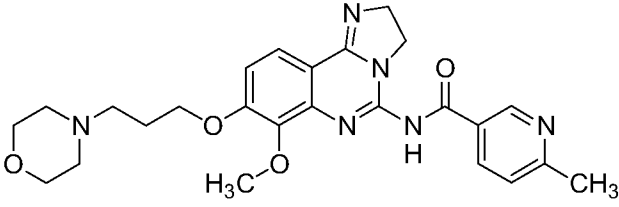
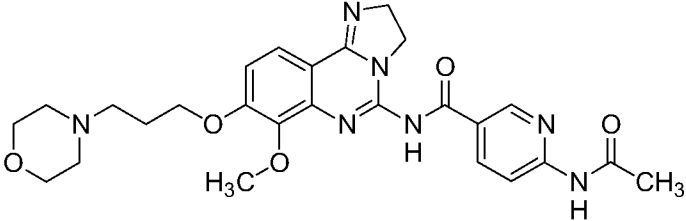
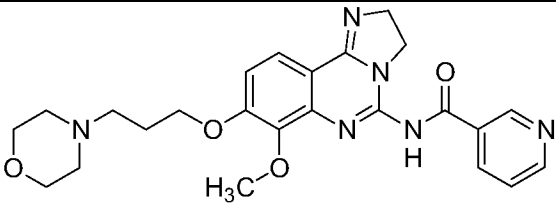
64	<chem>CN1CCN(CCCOC2=CC=C(OC)C=C2N3C=NC4C(=N3)C=CC5C4=NC(=N5)NC(=O)c6ccncc6)C1</chem>
65	<chem>CN(C)C(=O)Nc1ccsc1NC(=O)Nc2nc3c(ncn3C)nc2NC4=CC=C(OC)C=C4OC5CCOCC5</chem>
66	<chem>CN(C)C(=O)Nc1ccc2nc3c(ncn3C)nc21NC(=O)Nc4cc5c(ncn5)nc4OC6=CC=C(OC)C=C6OC7CCOCC7</chem>
67	<chem>CN(C)C(=O)Nc1ccsc1NC(=O)Nc2nc3c(ncn3C)nc2NC4=CC=C(OC)C=C4OC5CCOCC5</chem>
68	<chem>CN1CCOCC1OC2=CC=C(OC)C=C2N3C=NC4C(=N3)C=CC5C4=NC(=N5)NC(=O)c6ccncc6</chem>
69	<chem>CN(C)CCOC1=CC=C(OC)C=C1N2C=NC3C(=N2)C=CC4C3=NC(=N4)NC(=O)c5c6c(ncn6)sc5C</chem>

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77	 <chem>CCNC(=O)Nc1ccc(cc1)C(=O)Nc2nc3c(ncn3)c4cc(OC)c(OCCN5CCOCC5)c4</chem>
78	 <chem>Fc1ccc(cc1)C(=O)Nc2nc3c(ncn3)c4cc(OC)c(OCCN5CCOCC5)c4</chem>
79	 <chem>Nc1cc2oc(cc2n1)C(=O)Nc3nc4c(ncn4)c5cc(OC)c(OCCN6CCOCC6)c5</chem>
80	 <chem>CCNC(=O)Nc1cc2sc(cc2n1)C(=O)Nc3nc4c(ncn4)c5cc(OC)c(OCCN6CCOCC6)c5</chem>
81	 <chem>c1cc2nc(ccn2)C(=O)Nc3nc4c(ncn4)c5cc(OC)c(OCCN6CCOCC6)c5</chem>
82	 <chem>c1ccc(cc1)C(=O)Nc2nc3c(ncn3)c4cc(OC)c(OCCN5CCOCC5)c4</chem>
83	 <chem>Nc1ccc(cc1)C(=O)Nc2nc3c(ncn3)c4cc(OC)c(OCCN5CCOCC5)c4</chem>

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91	 <chem>CN1CCN(C1)c2nc(NC(=O)c3nc(CS)nc3)c3cc(OC)c(OCCCN4CCOCC4)c3</chem>
92	 <chem>NCCCOc1cc(OC)c2nc(NC(=O)c3ccncc3)c4ccnnc24</chem> <chem>OC(=O)C(F)(F)F</chem>
93	 <chem>CN1CCN(C1)c2nc(NC(=O)c3ccsc3)c3cc(OC)c(OCCCN4CCOCC4)c3</chem>
94	 <chem>CN1CCN(C1)c2nc(NC(=O)c3c(C)n(C)s3)c3cc(OC)c(OCCCN4CCOCC4)c3</chem>
95	 <chem>CN1CCN(C1)c2nc(NC(=O)c3nc(OC)nc3)c3cc(OC)c(OCCCN4CCOCC4)c3</chem>
96	 <chem>CN1CCN(C1)c2nc(NC(=O)c3ccoc3)c3cc(OC)c(OCCCN4CCOCC4)c3</chem>
97	 <chem>CN1CCN(C1)c2nc(NC(=O)c3ccsc3)c3cc(OC)c(OCCCN4CCOCC4)c3</chem>

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or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; optionally in the form of a pharmaceutical formulation which is ready for use to be administered simultaneously, concurrently, separately or sequentially.

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4. The combination according to any one of claims 1 to 3, wherein :

said component B is one or more 2,3-dihydroimidazo[1,2-c]quinazoline compounds of general formula (B) according to claim 1, which is selected from the list consisting of :

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Example 1 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-methanesulfonamide:

Example 2 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)cyclopropanesulfonamide:

10 Example 3 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)propane-2-sulfonamide:

Example 4 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)butane-1-sulfonamide:

15 Example 5 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2,2,2-trifluoro ethane sulfonamide:

Example 6 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)butane-2-sulfonamide:

Example 7 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-N-methyl cyclopropane sulfonamide:

20 Example 8 : 1-Chloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl) methane sulfonamide:

Example 9 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2-methylpropane-2-sulfonamide:

25 Example 10 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)cyclopentanesulfonamide:

Example 11 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)cyclohexanesulfonamide:

Example 12 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-methylcyclopropane-1-sulfonamide:

30 Example 13 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide:

Example 14 : (S)-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide:

Example 15 : (R)-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide:

5 Example 16 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-(2-hydroxyethyl)cyclopropane-1-sulfonamide:

Example 17 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-3-hydroxypropane-1-sulfonamide:

10 Example 18 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2-methyl-5-(trifluoromethyl)furan-3-sulfonamide:

Example 19 : N-(5-(N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)sulfamoyl)-methylthiazol-2-yl)acetamide:

Example 20 : 5-(5-Chloro-1,2,4-thiadiazol-3-yl)-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)thiophene-2-sulfonamide:

15 Example 21 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-3,5-dimethylisoxazole-4-sulfonamide:

Example 22 : 5-Chloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1,3-dimethyl-1H-pyrazole-4-sulfonamide:

20 Example 23 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2,5-dimethylfuran-3-sulfonamide:

Example 24 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-sulfonamide:

Example 25 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2,4-dimethylthiazole-5-sulfonamide:

25 Example 26 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1,2-dimethyl-1H-imidazole-4-sulfonamide:

Example 27 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)thiophene-3-sulfonamide:

30 Example 28 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)furan-2-sulfonamide:

Example 29 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-5-methylthiophene-2-sulfonamide:

Example 30 : 5-Chloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)thiophene-2-sulfonamide:

Example 31 : 5-Bromo-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)thiophene-2-sulfonamide:

5 Example 32 : 4-Bromo-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)thiophene-3-sulfonamide:

Example 33 : 4-Bromo-5-chloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)thiophene-2-sulfonamide:

10 Example 34 : 3-Bromo-5-chloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)thiophene-2-sulfonamide:

Example 35 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2,5-dimethylthiophene-3-sulfonamide:

Example 36 : 2,5-Dichloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)thiophene-3-sulfonamide:

15 Example 37 : Methyl 3-(N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)sulfamoyl)thiophene-2-carboxylate:

Example 38 : Methyl 5-(N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)sulfamoyl)-1-methyl-1H-pyrrole-2-carboxylate:

20 Example 39 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-5-methylisoxazole-4-sulfonamide:

Example 40 : 3-Chloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)propane-1-sulfonamide:

Example 41 : N-(2-(4-chloro-2-fluorophenylamino)-3,4-difluorophenyl)cyclopropanesulfonamide:

25 Example 42 : N-(3,4-difluoro-2-(4-iodo-2-methylphenylamino)phenyl)cyclopropanesulfonamide:

Example 43 : N-(2-(4-tert-butyl-2-chlorophenylamino)-3,4-difluorophenyl)cyclopropanesulfonamide:

30 Example 44 : N-(2-(2,4-dichlorophenylamino)-3,4-difluorophenyl)cyclopropanesulfonamide:

Example 45 : 3-Chloro-N-(3,4-difluoro-2-(2-fluoro-4-trifluoromethyl)phenylamino)phenyl)propane-1-sulfonamide:

Example 46 : N-(3,4-difluoro-2-(2-chloro-4-trifluoromethyl)phenylamino)methanesulfonamide:

Example 47 : 3-Chloro-N-(3,4-difluoro-2-(2-chloro-4-trifluoromethyl)phenylamino)phenyl)propane-1-sulfonamide:

5 Example 48 : 3-Chloro-N-(3,4-difluoro-2-(2-bromo-4-trifluoromethyl)phenylamino)phenyl)propane-1-sulfonamide:

Example 49 : Cyclopropanesulfonic acid (3,4,6-trifluoro-2-(2-fluoro-4-iodophenylamino)-phenyl)-amide:

10 Example 50 : N-(3,4-difluoro-2-(4-fluoro-2-iodophenylamino)-6-ethoxyphenyl)cyclopropane sulfonamide:

Example 51 : Methylsulfonic acid (3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxy-phenyl)-amide:

Example 52 : 1-(2,3-Dihydroxy-propyl)-cyclopropanesulfonic acid [3,4,6-trifluoro-2-(4-fluoro-2-iodo-phenylamino)-phenyl]-amide:

15 Example 53 : (S)-1-(2,3-dihydroxypropyl)-N-(3,4,6-trifluoro-2-(2-fluoro-4-iodophenylamino) phenyl)cyclopropane-1-sulfonamide:

Example 54 : (R)-1-(2,3-dihydroxypropyl)-N-(3,4,6-trifluoro-2-(2-fluoro-4-iodophenylamino) phenyl)cyclopropane-1-sulfonamide:

20 Example 55 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide:

Example 56 : (S)-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide:

Example 57 : (R)-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide:

25 Example 58 : 1-(2-hydroxyethyl)-N-(3,4,6-trifluoro-2-(2-fluoro-4-iodophenylamino)phenyl) cyclopropane-1-sulfonamide:

Example 59 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2-hydroxyethyl)cyclopropane-1-sulfonamide:

30 Example 60 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(3-hydroxy-2-(hydroxymethyl)propyl)cyclopropane-1-sulfonamide:

Example 61 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl) cyclobutane sulfonamide:

Example 62 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methylphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide:

5 Example 63 : 1-(2,3-Dihydroxypropyl)-N-(6-ethyl-3,4-difluoro-2-(2-fluoro-4-iodophenylamino) phenyl) cyclopropane-1-sulfonamide:

Example 64 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-(2-methoxyethoxy)phenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide:

10 Example 65 : 2,4-dichloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl) benzene sulfonamide:

Example 66 : 2-chloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-4-(trifluoromethyl) benzenesulfonamide:

Example 67 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2-(trifluoromethoxy) benzene sulfonamide:

15 Example 68 : 4-(N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)sulfamoyl)benzoic acid:

Example 69 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)benzenesulfonamide:

20 Example 70 : N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2-fluorobenzene sulfonamide:

Example 71 : N-(3,4-difluoro-2-(2-fluoro-4-methylphenylamino)phenyl)cyclopropanesulfonamide ;

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; optionally in the form of a pharmaceutical formulation which is ready for use
25 to be administered simultaneously, concurrently, separately or sequentially.

5. The combination according to any one of claims 1 to 4, wherein said component A is (S)-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide.

6. The combination according to any one of claims 1 to 5, wherein said component B is 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide.

5 7. The combination according to any one of claims 1 to 6, wherein said component A is (S)-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide and said component B is 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide.

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8. Use of a combination according to any one of claims 1 to 7 for the preparation of a medicament for the treatment or prophylaxis of a cancer, particularly lung cancer, in particular non-small cell lung carcinoma, colorectal cancer, melanoma, pancreatic cancer, hepatocyte carcinoma or breast cancer.

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9. A method of treatment or prophylaxis of a cancer, particularly lung cancer, in particular non-small cell lung carcinoma, colorectal cancer, melanoma, pancreatic cancer, hepatocyte carcinoma or breast cancer, in subject, comprising administering to said subject a therapeutically effective amount of
20 a combination according to any one of claims 1 to 7.

10. A kit comprising a combination of :

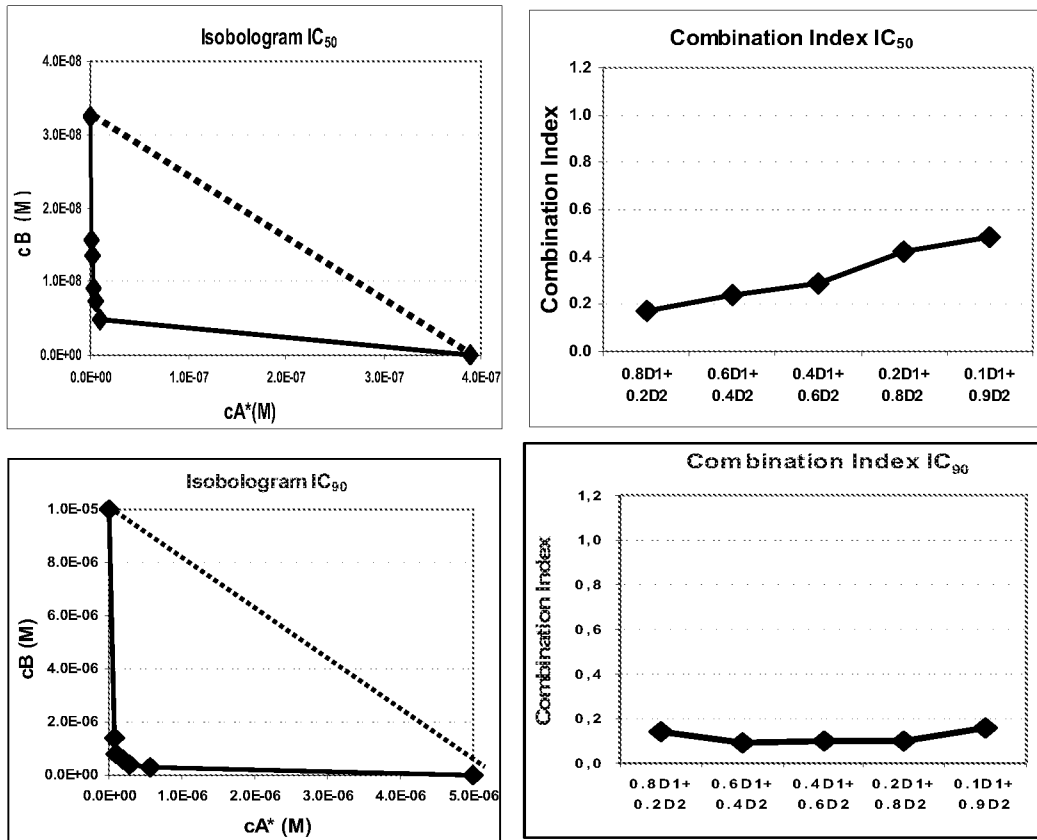
component A : one or more 2,3-dihydroimidazo[1,2-c]quinazoline compounds of general formula (A1) or (A2), or a physiologically acceptable salt, solvate,
25 hydrate or stereoisomer thereof, according to any one of claims 1 to 7 ;

component B : one or more N-(2-arylamino) aryl sulfonamide compounds of general formula (B), or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, according to any one of claims 1 to 7 ; and, optionally,
component C : one or more further pharmaceutical agents, according to any
30 one of claims 1 to 7 ;

in which optionally both or either of said components A) and B) are in the form of a pharmaceutical formulation which is ready for use to be administered simultaneously, concurrently, separately or sequentially.

- 5 11. The kit according to claim 10, wherein said component A is (S)-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide and said component B is 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide.

FIGURE 1/5



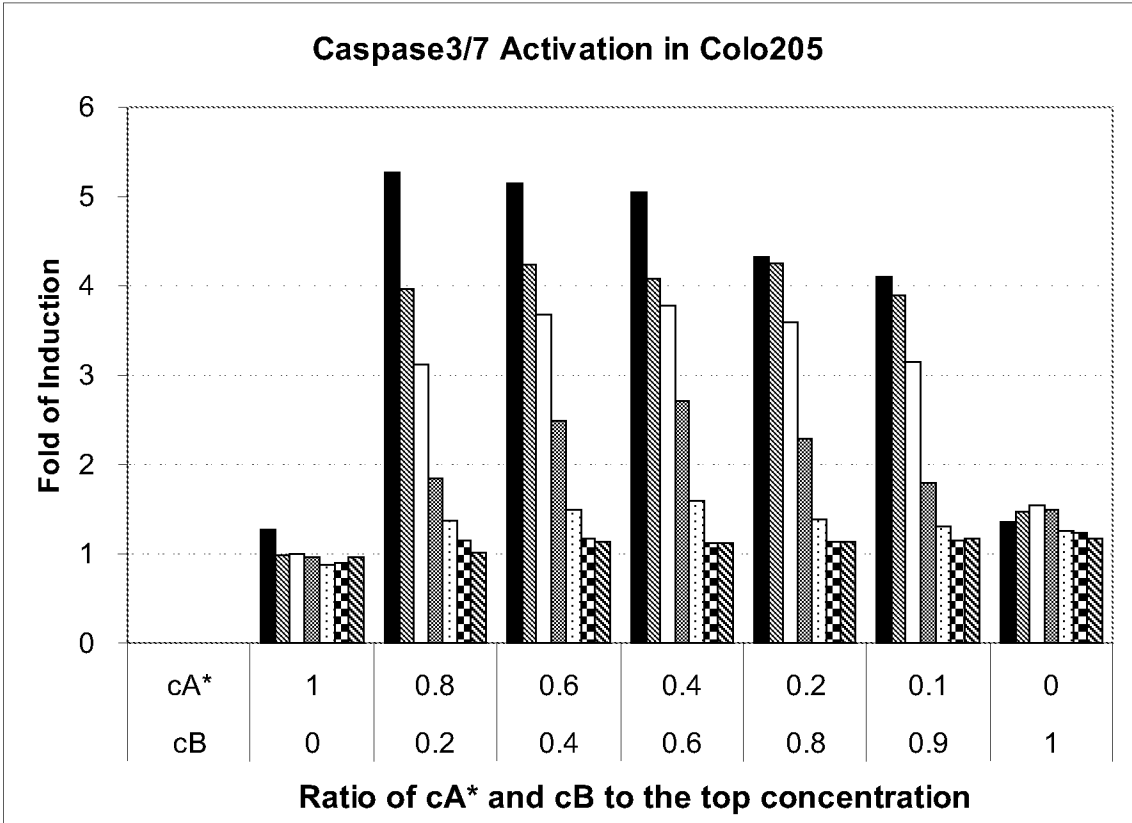
Isobologram IC₅₀ for Combination of cA* and cB

	D1_only	0.8D1+ 0.2D2	0.6D1+ 0.4D2	0.4D1+ 0.6D2	0.2D1+ 0.8D2	0.1D1+ 0.9D2	D2_only
MAPPING IC ₅₀	7.78E-02	2.38E-03	1.83E-03	1.52E-03	1.70E-03	1.73E-03	3.24E-03
cA* Con	3.89E-07	9.52E-09	5.49E-09	3.04E-09	1.70E-09	8.65E-10	0
cB Con	0	4.76E-09	7.32E-09	9.12E-09	1.36E-08	1.56E-08	3.24E-08

Isobologram IC₉₀ for Combination of cA* and cB

	D1_only	0.8D1+ 0.2D2	0.6D1+ 0.4D2	0.4D1+ 0.6D2	0.2D1+ 0.8D2	0.1D1+ 0.9D2	D2_only
MAPPING IC ₅₀	1.00E+00	1.43E-01	9.49E-02	9.66E-02	9.77E-02	1.58E-01	1.00E+00
cA* Con	5.00E-06	5.72E-07	2.85E-07	1.93E-07	9.77E-08	7.90E-08	0
cB Con	0	2.86E-07	3.80E-07	5.80E-07	7.82E-07	1.42E-06	1.00E-05

FIGURE 2/5



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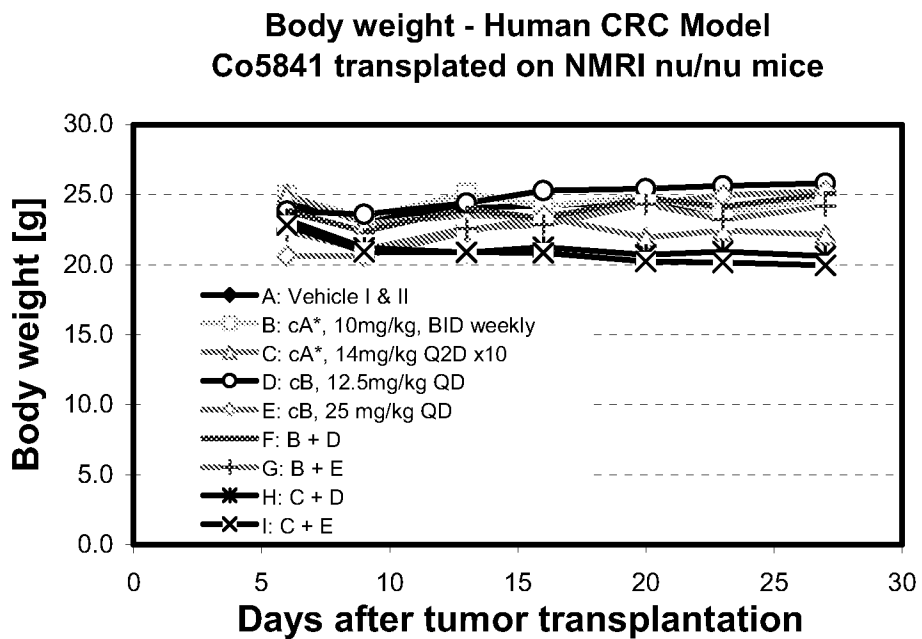
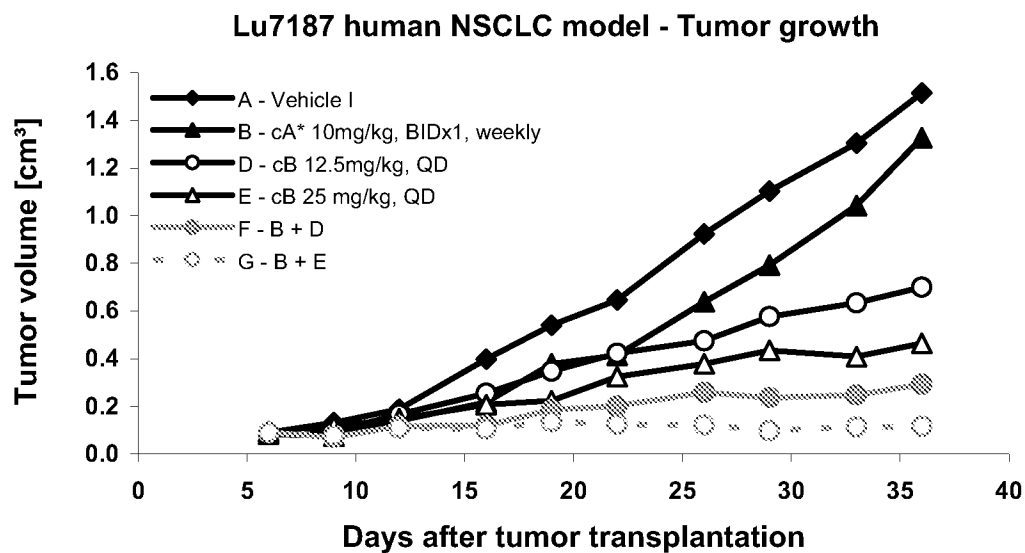


FIGURE 4/5

A



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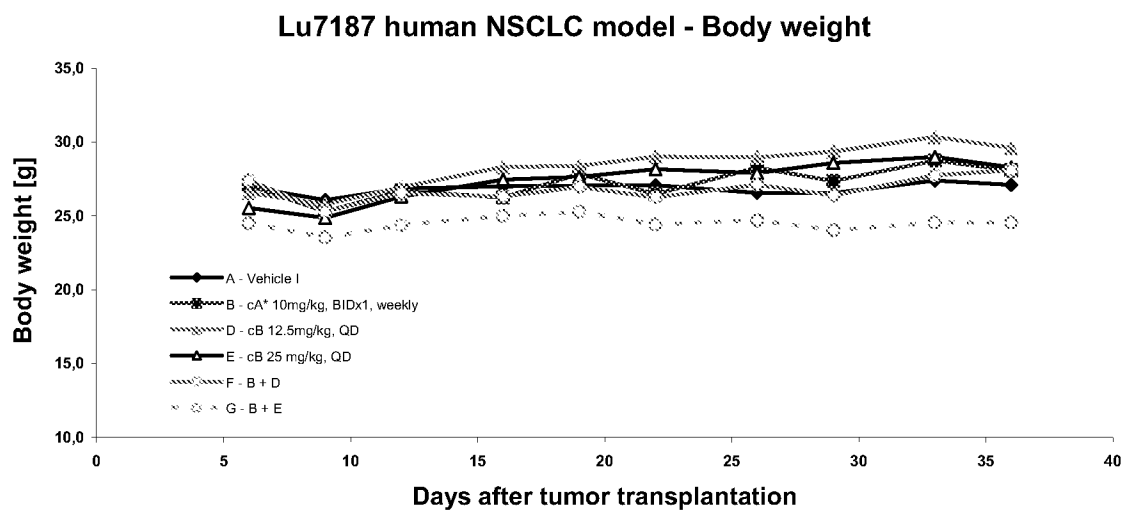


FIGURE 5/5

Lu7343 human NSCLC model - Tumor growth