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(54) Title: COMBINATIONS OF COPANLISIB

(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 substituted 5-(1-benzothiophen-2-yl)pyrrolo[2,1- f][1,2,4]-triazin-4-amine compounds of general formula (B), or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof; 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, independently of one another by the oral, subcutaneous, intravenous, topical, local, intraperitoneal or nasal route, for use in treating bladder cancer, head & neck cancer, particularly head & neck squamous cell carcinoma, or liver cancer; * use of such combinations for the preparation of a medicament for the treatment or prophylaxis of a cancer, particularly bladder cancer, head & neck cancer, particularly head & neck squamous cell carcinoma, liver cancer; * a kit comprising such combinations.

COMBINATIONS OF COPANLISIB

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 substituted 5-(1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-4-amine 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 ;

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 independently of one another by the oral, subcutaneous, intravenous, topical, local, 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 treatment or prophylaxis of a cancer, particularly bladder cancer, head & neck cancer, particularly head & neck squamous cell carcinoma, liver cancer.

Further, the present invention relates to :

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, hydrate or stereoisomer thereof ;

component B : one or more substituted 5-(1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-4-amine compounds of general formula (B), or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;

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 independnently of one another by the oral, subcutaneous, intravenous, topical, local, intraperitoneal or nasal route.

BACKGROUND OF THE INVENTION

Cancer is a complex disease arising after a selection process for cells with acquired functional capabilities like enhanced survival / resistance towards apoptosis and a limitless proliferative potential. Thus, it is preferred to develop drugs for cancer therapy addressing distinct features of established tumors.

The PI3K signaling pathway is one of the prominent pathways that promote tumor cell survival. PI3K is activated by many cancer related receptor tyrosine kinases (e.g. PDGFR, EGFR, HER2/3, or IGF-1R), cell adhesion molecules, GPCR, and oncogenic proteins (such as Ras). The PI3K pathway activation by genetic alteration of PI3K (activation mutation and/or amplification) and/or loss-of-function of the tumour suppressor PTEN are frequently found in many tumors. Furthermore, activation of PI3K is one of the major mechanisms causing the resitance of tumors to radio-, chemo- and targeted therapeutics.

Once PI3K is activated, it catalyzes the generation of PIP3 from PIP2. The biological active PIP3 binds to the pleckstrin homology (PH) domains of PDK-1, AKT, and other PH-domain containing proteins, such as Rho and PLC. As the consequence of binding to

PIP3, these proteins are translocated to the cell membrane and are subsequently activated to induce tumor cell proliferation, survival, invasion and migration.

Fibroblast growth factors (FGFs) and their receptors (FGFRs) drive crucial developmental signaling pathways, which are responsible for many functions of the tumor cells, including cell proliferation, survival and migration through downstream signalling pathways mediated by PLCγ/PKC, RAS/MAPK, PI3K/AKT, and STATs. FGFR signalling pathways also regulate tumor stromal cells as well as tumor angiogenesis. There are several types of genetic evidence that support an oncogenic function of FGFRs: gene amplifications, activating mutations, chromosomal translocations and aberrant splicing at the post-transcriptional level.

Urothelial bladder carcinoma (UBC) has a high incidence with approximately 429700 new cases per year and a related mortality of 165000 worldwide (Gerullis et al. 2017 (Ref. 1)). It is a heterogeneous disease that can be classified as either non-muscle-invasive bladder cancer (NMIBC) with stages Ta, carcinoma in situ and T1 or muscle-invasive bladder cancer (MIBC) with stages ≥T2. At diagnosis, the majority of patients (~70%) present with NMIBC while 25-30% of the patients have muscle invasions. Although with NMIBC the 5 year survival is >90%, the recurrence rate is high (>50%), often on multiple occasions over many years leading to high prevalence, and a about 15–20% of patients progress to muscle-invasive disease. Therefore, costly long-term surveillance with invasive cystoscopies and surgery is required and makes this one of the most expensive of all cancers to treat (di Martino et al. 2016 (Ref. 2)).

Patients with MIBC have a much less favorable prognosis with 5 year overall survival after radical cystectomy and lymph node dissection ranging from 49% to 74% depending on tumor stage. Cisplatin-based chemotherapy is the current standard of care for metastatic disease. However, many patients demonstrate intrinsic resistance and while about half of the patients initially respond to chemotherapy, duration of response is usually short and effective second-line treatments are lacking. Therefore, a clear unmet medical need for new effective therapies in both NMIBC and MIBC exists.

The successful management of these patients depends on the identification and understanding of molecular mechanisms underlying the initiation and progression of UBC to achieve a more tailored therapy, based on the biological tumor profile.

Molecular studies of bladder cancers have identified several oncogenic targets that hold promise for therapy including FGFR receptors which are implicated as oncogenes (Knowles & Hurst 2015 (Ref. 3)).

As described in the present text, the anti-tumor efficacy of the PI3K inhibitor copanlisib was investigated in preclinical tumor models in vitro in combination. The combination of the PI3K inhibitor copanlisib with the FGFR inhibitor rogaratinib was found to be synergistic, which led to decreased viability and reduced proliferation compared to single agent treatment.

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: a substituted 5-(1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-4-amine compounds of general formula (B), or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, as described and defined herein ;

were evaluated for the treatment of bladder cancer, head & neck cancer, particularly head & neck squamous cell carcinoma, liver 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-FGFR inhibitors. Surprisingly, synergism was not only observed in models with increased PI3K activation such as J82 cells but in several models (RT112, SW780, JMSU1) with no known activating genetic aberrations of the PI3K pathway.

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 ;

component B: one or more substituted 5-(1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-4-amine compounds of general formula (B), or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;

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 or prophylaxis of cancer, particularly bladder cancer, head & neck cancer, particularly head & neck squamous cell carcinoma, liver 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 beneficial effect in the treatment of cancer, particularly bladder cancer, head & neck cancer, particularly head & neck squamous cell carcinoma, liver cancer.

Accordingly, in accordance with a first aspect, 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 substituted 5-(1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-4-amine compounds of general formula (B), or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;

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. The components may be administered independnently of one another by the oral, subcutaneous, intravenous, topical, local, intraperitoneal or nasal route.

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 bladder cancer, head & neck cancer, particularly head & neck squamous cell carcinoma, liver cancer.

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 of general formula (A1) or (A2), or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;

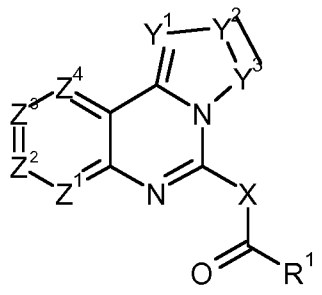
component B : one or more substituted 5-(1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-4-amine compounds of general formula (B), or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;

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 independnently of one another by the oral, subcutaneous, intravenous, topical, local, intraperitoneal or nasal route.

Detailed description of the Invention

In accordance with an 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) :



(A1)

wherein

X represents CR^5R^6 or NH;

Y^1 represents CR^3 or N;

Chemical bond between Y^2-----Y^3 represents a single bond or double bond,

with the proviso that when theY^2-----Y^3 represents a double bond,

Y^2 and Y^3 independently represent CR^4 or N, and

when Y^2-----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;

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,
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, 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 R^{11}
wherein
R^{11} represents
halogen, nitro, hydroxy, cyano, carboxy, amino, N-(C_{1-6}alkyl)amino, N-(hydroxyC_{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-(carboxyC_{1-6}alkyl)-N-(C_{1-6}alkyl)amino, N-(C_{1-6}alkoxycabonyl)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,

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},

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,

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}

wherein

R^{101} represents

halogen, carboxy, amino, N-(C_{1-6} alkyl)amino, N,N-di(C_{1-6}alkyl)amino, aminocarbonyl, N-(C_{1-6}alkyl)aminocarbonyl, N,N-di(C_{1-6}alkyl)aminocarbonyl, pyridyl,

C_{1-6} alkyl optionally substituted by cyano or mono- di- or tri- halogen,

or

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

R^2 represents hydroxy, halogen, nitro, cyano, amino, N-(C_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, N-(hydroxyC_{1-6}alkyl)amino, N-(hydroxyC_{1-6}alkyl)-N-(C_{1-6}alkyl)amino, C_{1-6} acyloxy, aminoC_{1-6} acyloxy, C_{2-6}alkenyl, aryl,

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

hydroxy, C_{1-6} alkyl, 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, N-(C_{1-6}alkyl)carbonylamino, phenyl, phenyl C_{1-6} alkyl, carboxy, C_{1-6}alkoxycarbonyl, aminocarbonyl, N-(C_{1-6}alkyl)aminocarbonyl, or N,N-di(C_{1-6}alkyl)amino,

-C(O)- R^{20}

wherein

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,

C_{1-6} alkyl optionally substituted by R^{21}

or

C_{1-6} alkoxy optionally substituted by R^{21}

wherein

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- (hydroxyC_{1-6} alkyl) amino, N-(halophenylC_{1-6} alkyl) amino, amino C_{2-6} alkylenyl, C_{1-6} alkoxy, hydroxyC_{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 and N optionally substituted by

hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, hydroxyC_{1-6} alkoxy, oxo, amino, aminoC_{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,

wherein

R^{201} represents hydroxy, amino, N-(C_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, N- (halophenylC_{1-6} alkyl) amino, C_{1-6}alkyl, aminoC_{1-6} alkyl, aminoC_{2-6} alkylenyl, C_{1-6} 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, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, hydroxyC_{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 or benzyl;

R^3 represents hydrogen, halogen, aminocarbonyl, or C_{1-6} alkyl optionally substituted by aryl C_{1-6} alkoxy or mono-, di- or tri- halogen;

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

R^5 represents hydrogen or C_{1-6} alkyl; and

R^6 represents halogen, hydrogen or C_{1-6} 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 independnently of one another by the oral, subcutaneous, intravenous, topical, local, intraperitoneal or nasal route.

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

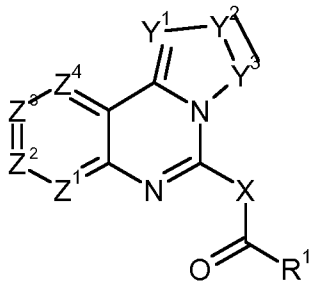
component A : which is one or more 2,3-dihydroimidazo[1,2-c]quinazoline compounds of general formula (A1), *supra*, which is selected from the list consisting of specific compound Examples 1-1 to 1-210 on pp. 47 to 106, specific compound Examples 2-1 to 2-368 on pp. 107 to 204, specific compound Examples 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 independnently of one another by the oral, subcutaneous, intravenous, topical, local, 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 Y^2-----Y^3 represents a single bond or double bond,

with the proviso that when theY^2-----Y^3 represents a double bond, Y^2 and Y^3 independently represent CR^4 or N, and

when Y^2-----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;

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,

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,

wherein

R^{11} represents halogen, nitro, hydroxy, cyano, carboxy, amino, N-(C_{1-6}alkyl)amino, N-(hydroxyC_{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-(carboxyC_{1-6}alkyl)-N-(C_{1-6}alkyl)amino, N-(C_{1-6}alkoxycabonyl)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,

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},

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,

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}

wherein

R^{101} represents halogen, carboxy, amino, N-(C_{1-6} alkyl)amino, N,N-di(C_{1-6}alkyl)amino, aminocarbonyl, N-(C_{1-6}alkyl)aminocarbonyl, N,N-di(C_{1-6}alkyl)aminocarbonyl, pyridyl,

C_{1-6} alkyl optionally substituted by cyano or mono- di- or tri-halogen,

and

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

R^2 represents hydroxy, halogen, nitro, cyano, amino, N-(C_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, N-(hydroxyC_{1-6}alkyl)amino, N-(hydroxyC_{1-6}alkyl)-N-(C_{1-6}alkyl)amino, C_{1-6} acyloxy, aminoC_{1-6} acyloxy, C_{2-6}alkenyl, 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, C_{1-6} alkyl, 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, N-(C_{1-6}alkyl)carbonylamino, phenyl, phenyl C_{1-6} alkyl, carboxy, C_{1-6}alkoxycarbonyl, aminocarbonyl, N-(C_{1-6}alkyl)aminocarbonyl, or N,N-di(C_{1-6}alkyl)amino, -C(O)- R^{20}

wherein

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,

C_{1-6} alkyl optionally substituted by R^{21},

or

C_{1-6} alkoxy optionally substituted by R^{21},

wherein

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-(hydroxyC_{1-6} alkyl) amino, N- (halophenylC_{1-6} alkyl) amino, amino C_{2-6} alkylenyl, C_{1-6} alkoxy, hydroxyC_{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 and N , and optionally substituted by hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, hydroxyC_{1-6} alkoxy, oxo, amino, aminoC_{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,

wherein

R^{201} represents hydroxy, amino, N-(C_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, N- (halophenylC_{1-6} alkyl) amino, C_{1-6}alkyl, aminoC_{1-6} alkyl, aminoC_{2-6} alkylenyl, C_{1-6} 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, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, hydroxyC_{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 or benzyl;

R^3 represents hydrogen, halogen, aminocarbonyl, or C_{1-6} alkyl optionally substituted by aryl C_{1-6} alkoxy or mono-, di- or tri- halogen;

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

R^5 represents hydrogen or C_{1-6} alkyl; and

R^6 represents halogen, hydrogen or C_{1-6} 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.

The definitions used in relation to the structure (A) in this text are as follows :

The term `alkyl` refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing solely of carbon and hydrogen atoms, containing no unsaturation, having from one to eight carbon atoms, and which is

attached to the rest of the molecule by a single bond, such as illustratively, methyl, ethyl, n-propyl 1-methylethyl (isopropyl), n-butyl, n-pentyl, and 1,1-dimethylethyl (t-butyl).

The term "alkenyl " refers to an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be a straight or branched or branched chain having about 2 to about 10 carbon atoms, e.g., ethenyl, 1-propenyl, 2-propenyl (allyl), iso-propenyl, 2-methyl-I-propenyl, 1-butenyl, 2-and butenyl.

The term "alkynyl" refers to a straight or branched chain hydrocarbonyl radicals having at least one carbon-carbon triple bond, and having in the range of about 2 up to 12 carbon atoms (with radicals having in the range of about 2 up to 10 carbon atoms presently being preferred) e.g., ethynyl.

The term "alkoxy" denotes an alkyl group as defined herein attached via oxygen linkage to the rest of the molecule. Representative examples of those groups are methoxy and ethoxy.

The term "alkoxyakyl" denotes an alkoxy group as defined herein attached via oxygen linkage to an alkyl group which is then attached to the main structure at any carbon from alkyl group that results in the creation of a stable structure the rest of the molecule. Representative examples of those groups are $–CH_2OCH_3$, $--CH_2OC_2H_5$.

The term "cycloalkyl" denotes a non-aromatic mono or multicyclic ring system of about 3 to 12 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and examples of multicyclic cycloalkyl groups include perhydronaphthyl, adamantyl and norbornyl groups bridged cyclic group or sprirobicyclic groups e.g sprio (4,4) non-2-yl.

The term "cycloalkylalkyl" refers to cyclic ring-containing radicals containing in the range of about about 3 up to 8 carbon atoms directly attached to alkyl group which is

then also attached to the main structure at any carbon from the alkyl group that results in the creation of a stable structure such as cyclopropylmethyl, cyclobuyylethyl, cyclopentylethyl.

The term "aryl" refers to aromatic radicals having in the range of 6 up to 14 carbon atoms such as phenyl, naphthyl, tetrahydronapthyl, indanyl, biphenyl .

The term "arylalkyl" refers to an aryl group as defined herein directly bonded to an alkyl group as defined herein which is then attached to the main structure at any carbon from alkyl group that results in the creation of a stable structure the rest of the molecule. e.g., --$CH_2C_6H_5$, --$C_2H_5C_6H_5$.

The term "heterocyclic ring" refers to a stable 3- to 15 membered ring radical which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, phosphorus, oxygen and sulfur. For purposes of this invention, the heterocyclic ring radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused, bridged or spiro ring systems, and the nitrogen, phosphorus, carbon, oxygen or sulfur atoms in the heterocyclic ring radical may be optionally oxidized to various oxidation states. In addition, the nitrogen atom may be optionally quaternized; and the ring radical may be partially or fully saturated (i.e., heteroaromatic or heteroaryl aromatic). Examples of such heterocyclic ring radicals include, but are not limited to, azetidinyl, acridinyl, benzodioxolyl, benzodioxanyl, benzofurnyl, carbazolyl cinnolinyl dioxolanyl, indolizinyl, naphthyridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazil, pyridyl, pteridinyl, purinyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrazoyl, imidazolyl tetrahydroisouinolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazinyl, pyrimidinyl pyridazinyl, oxazolyl oxazolinyl oxasolidinyl, triazolyl, indanyl, isoxazolyl, isoxasolidinyl, morpholinyl, thiazolyl, thiazolinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl,

octahydroisoindolyl quinolyl, isoquinolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzooxazolyl, furyl, tetrahydrofurtyl, tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide thiamorpholinyl sulfone, dioxaphospholanyl, oxadiazolyl, chromanyl, isochromanyl .

The term "heteroaryl" refers to heterocyclic ring radical as defined herein which are aromatic. The heteroaryl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The heterocyclic ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term "heteroarylalkyl" refers to heteroaryl ring radical as defined herein directly bonded to alkyl group. The heteroarylalkyl radical may be attached to the main structure at any carbon atom from alkyl group that results in the creation of a stable structure.

The term "heterocyclyl" refers to a heterocylic ring radical as defined herein. The heterocylyl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term "heterocyclylalkyl" refers to a heterocylic ring radical as defined herein directly bonded to alkyl group. The heterocyclylalkyl radical may be attached to the main structure at carbon atom in the alkyl group that results in the creation of a stable structure.

The term "carbonyl" refers to an oxygen atom bound to a carbon atom of the molecule by a double bond.

The term "halogen" refers to radicals of fluorine, chlorine, bromine and iodine.

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 independnently of one another by the oral, subcutaneous, intravenous, topical, local, 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-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.

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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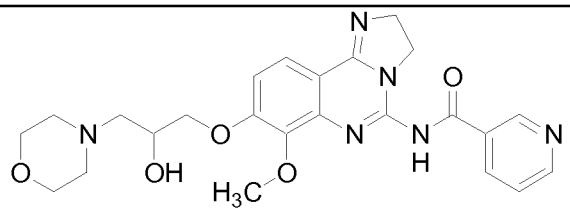
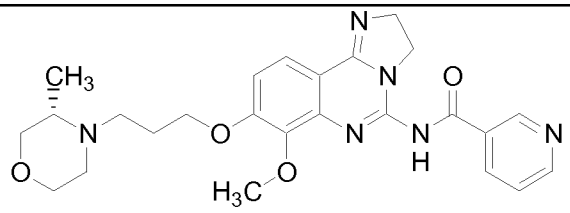
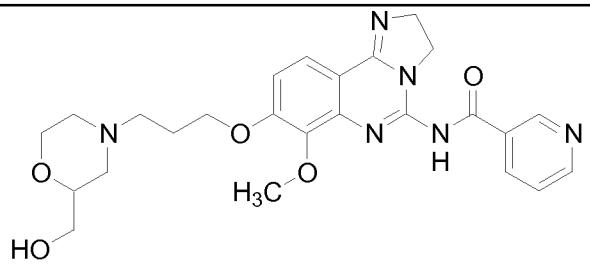
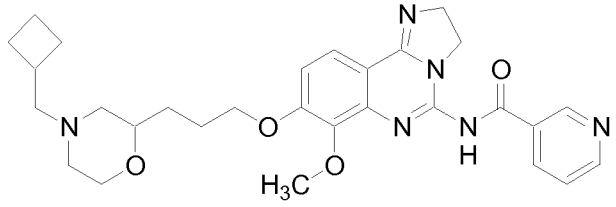
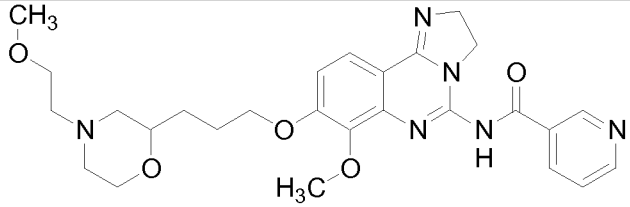
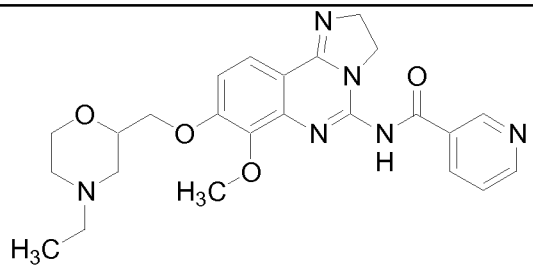
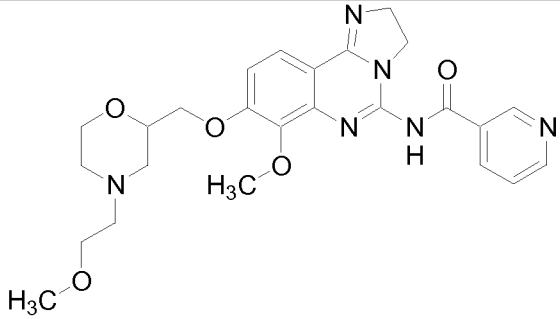
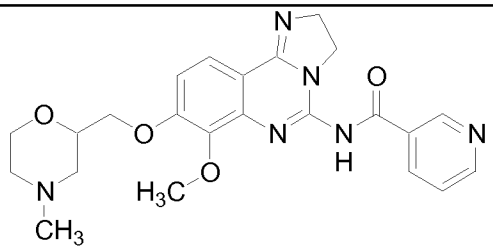
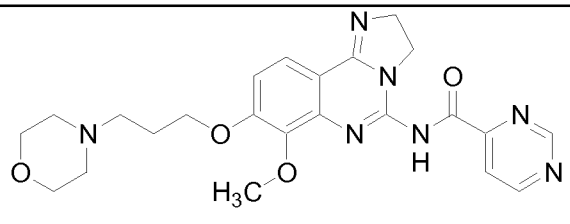
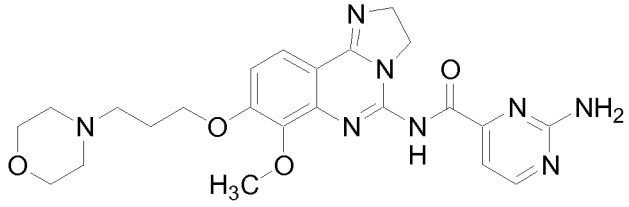
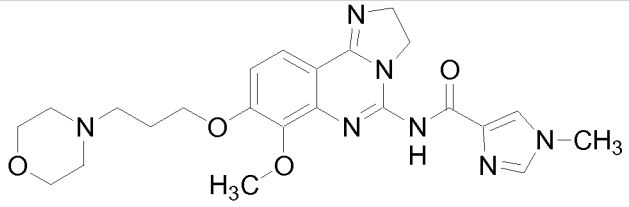
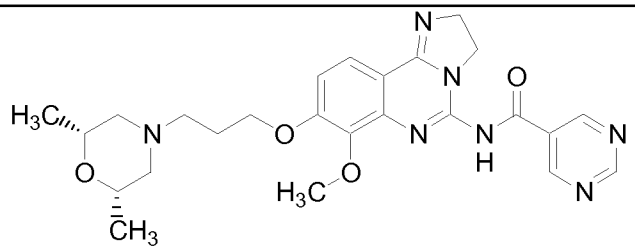
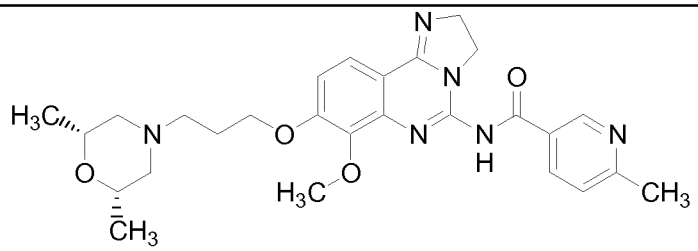
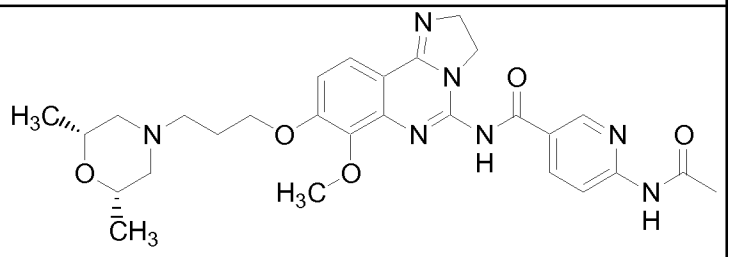
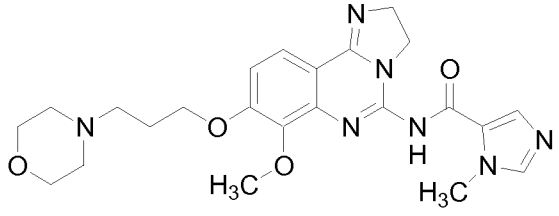
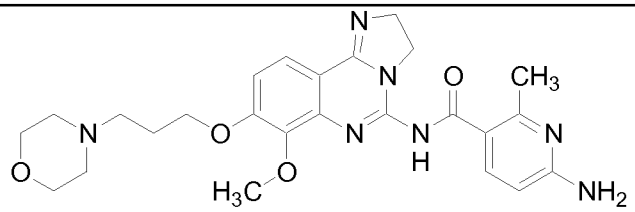
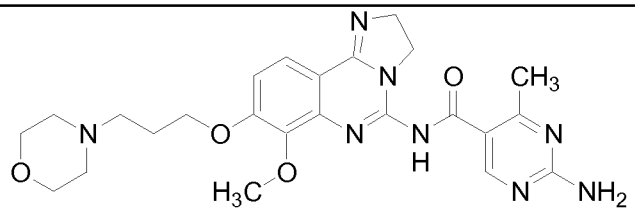
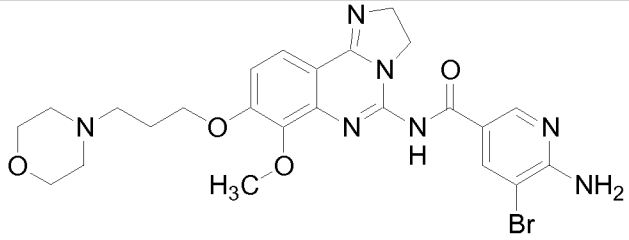
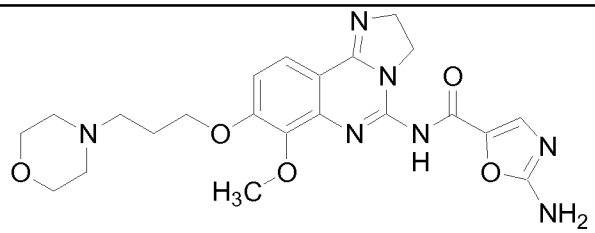
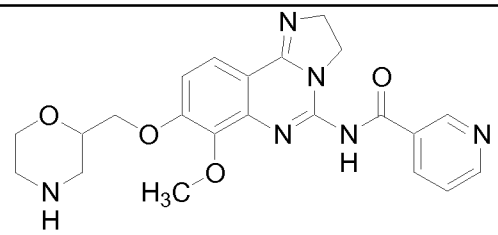
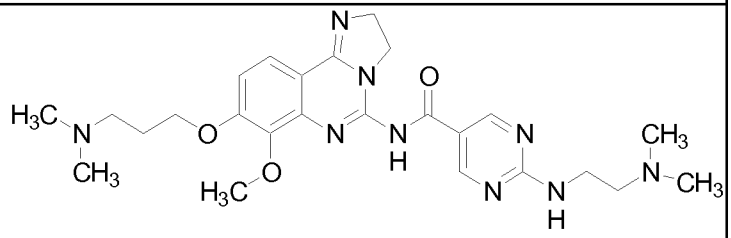
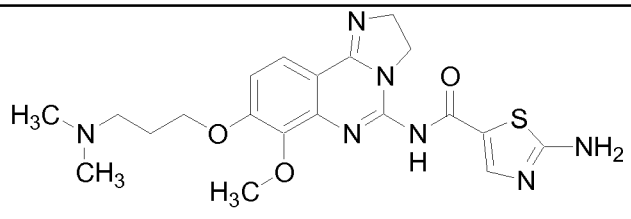
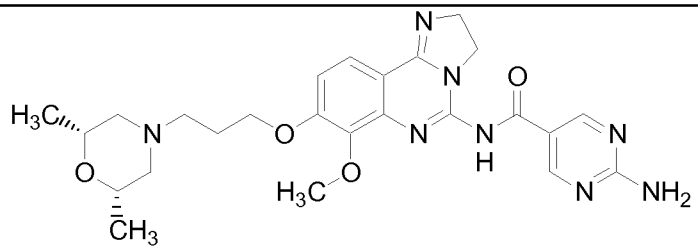
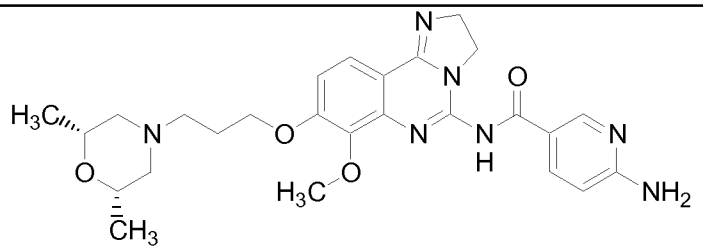
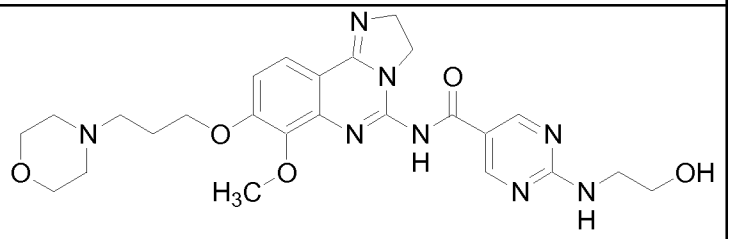
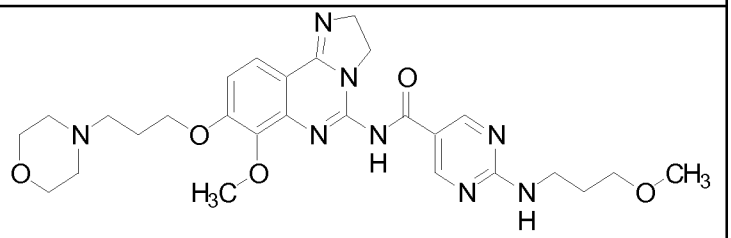
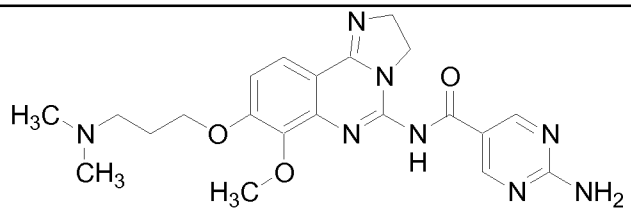
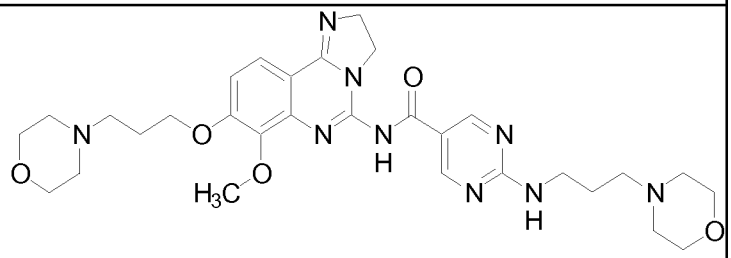
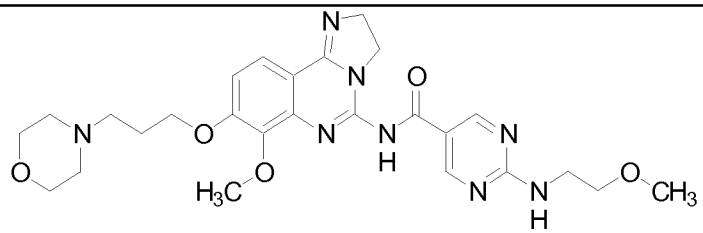
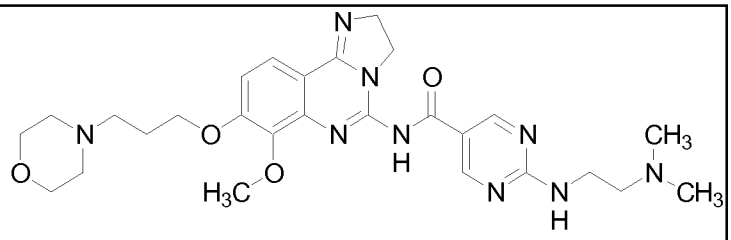
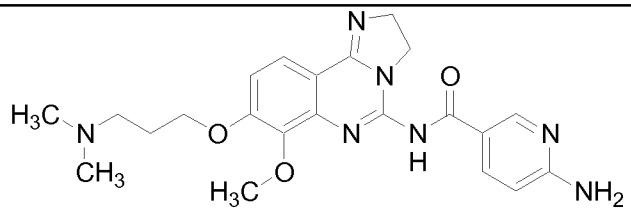
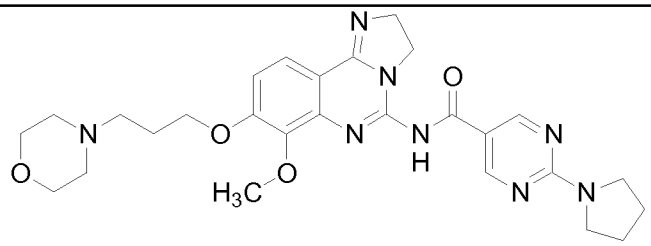
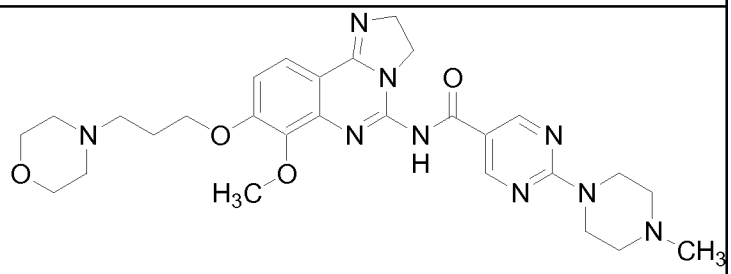
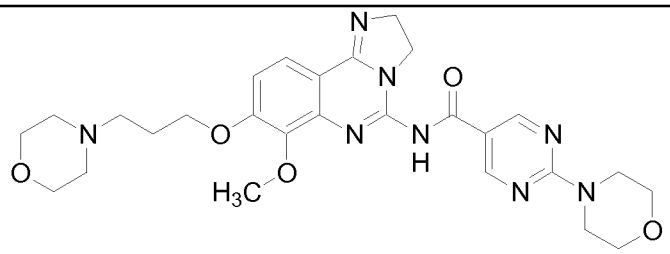
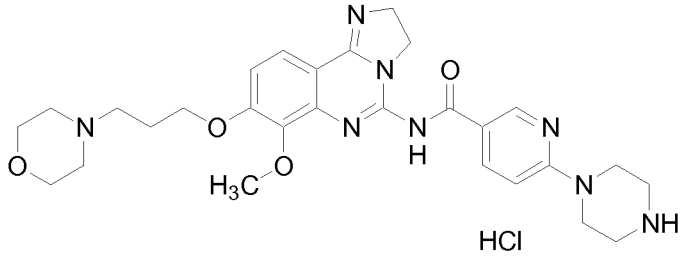
Example	Structure
16	
17	
18	

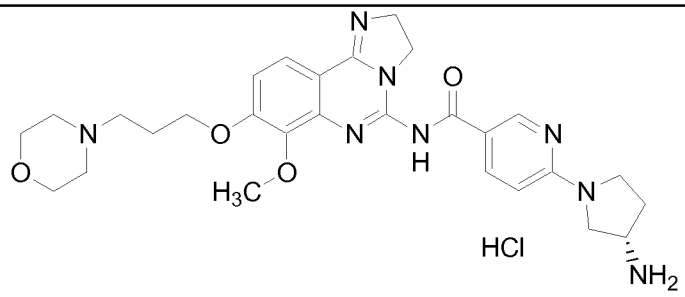
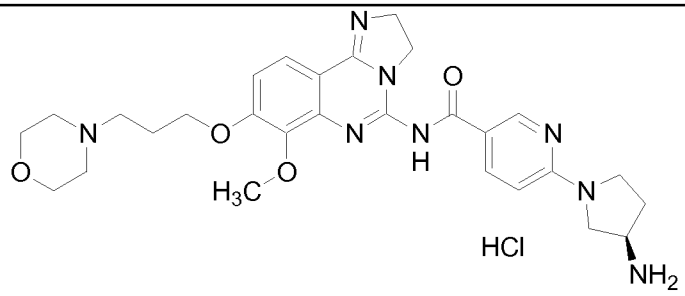
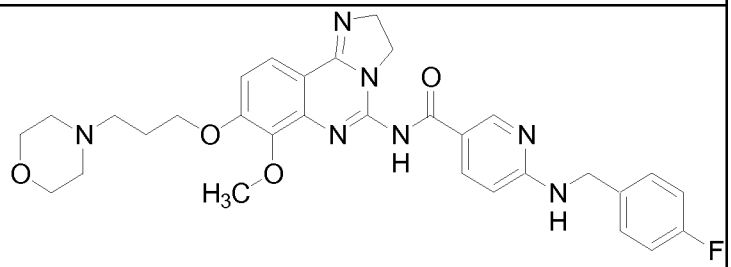
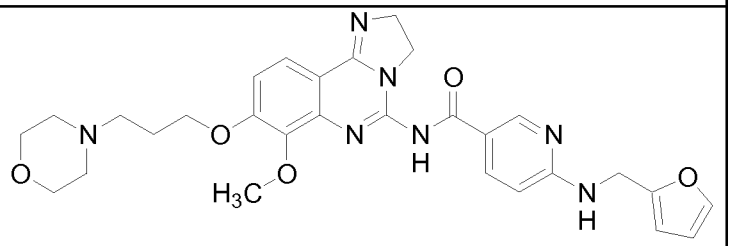
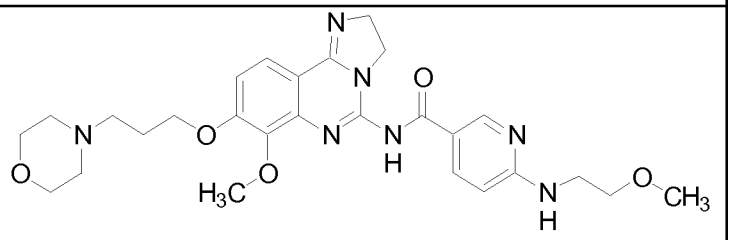
19	
20	
21	
22	
23	
24	

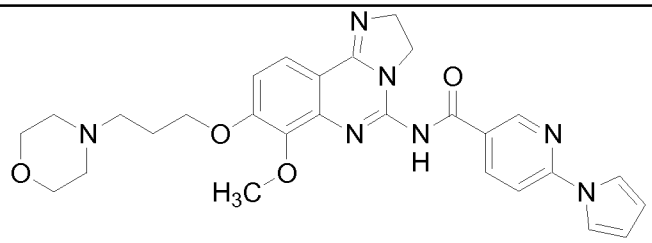
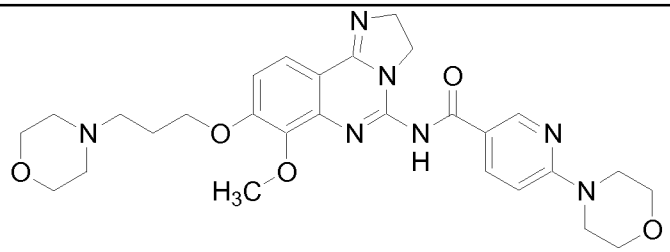
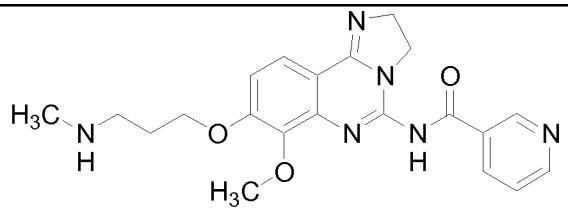
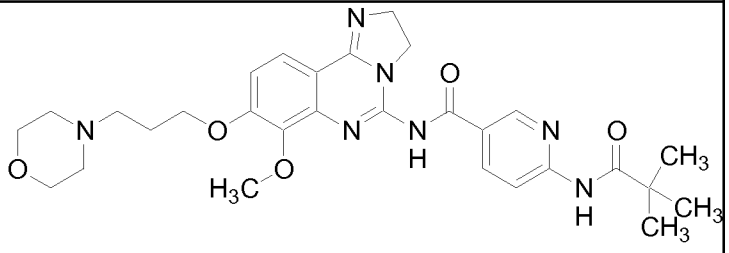
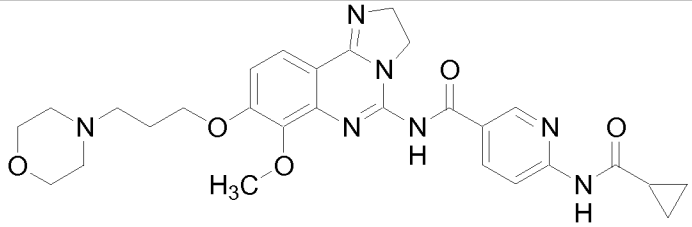
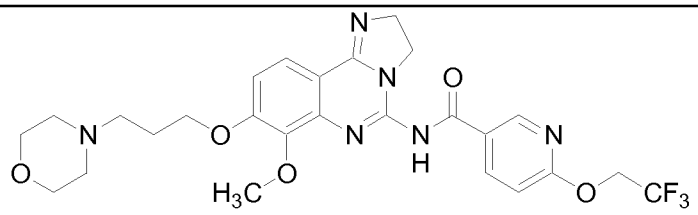
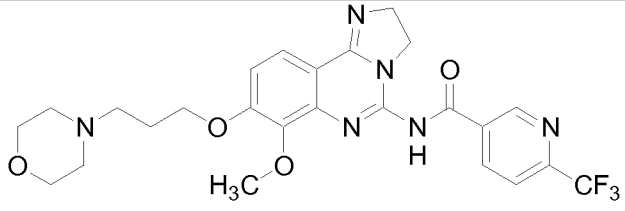
25	
26	
27	
28	
29	
30	
31	

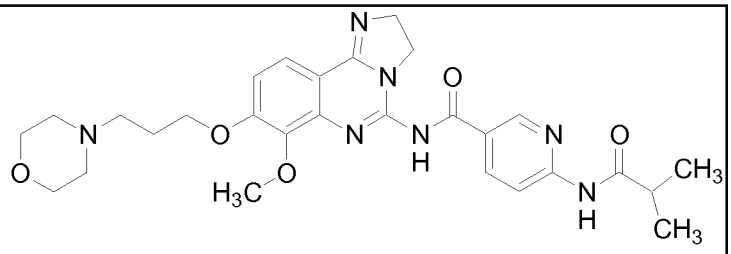
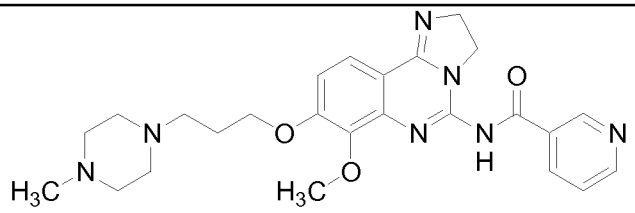
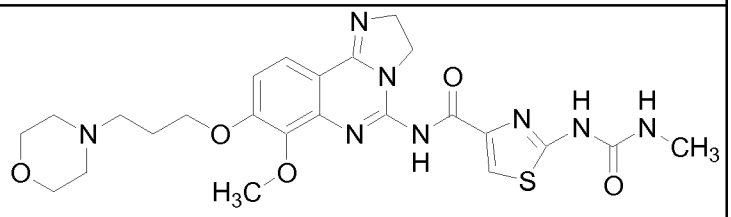
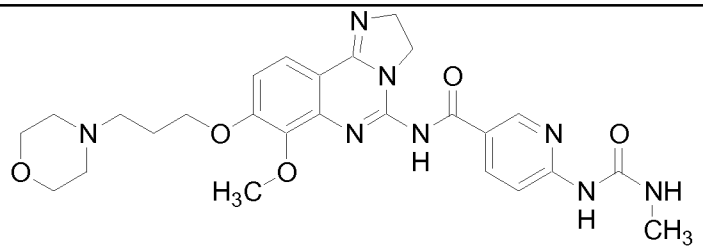
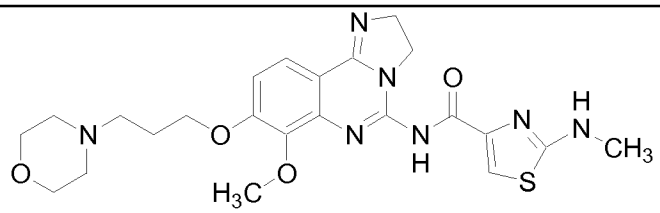
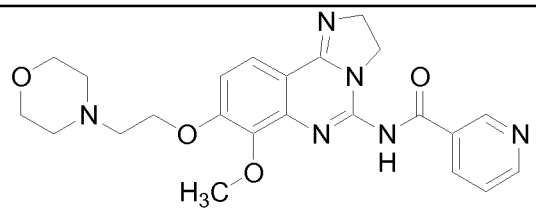
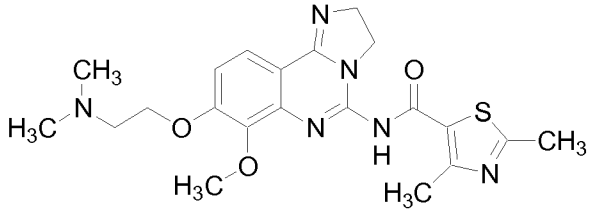
32	
33	
34	
35	
36	
37	
38	

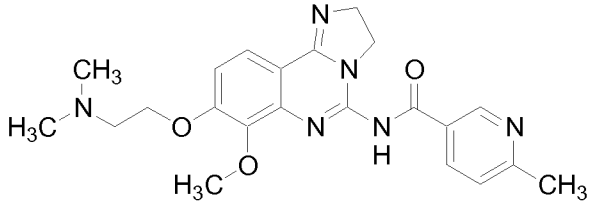
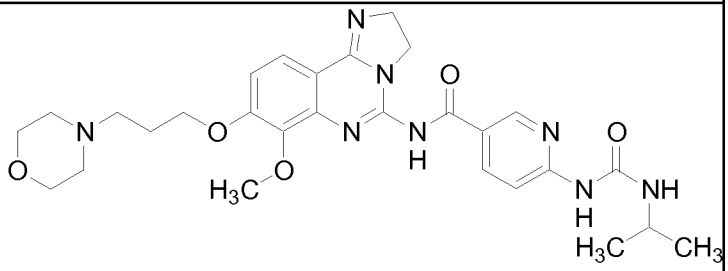
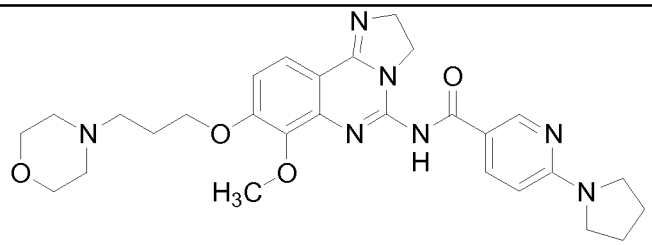
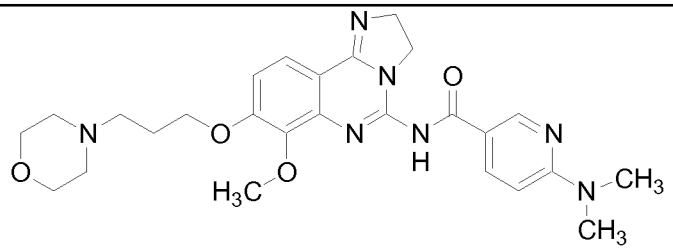
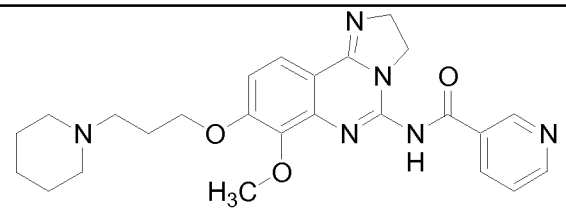
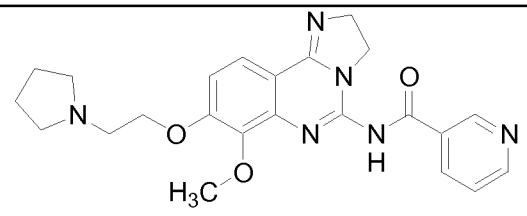
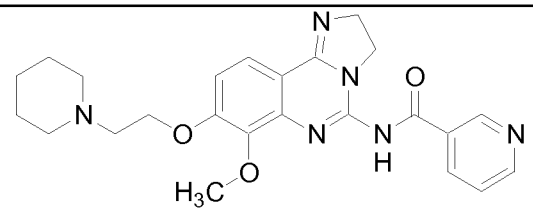
39	
40	
41	
42	
43	
44	

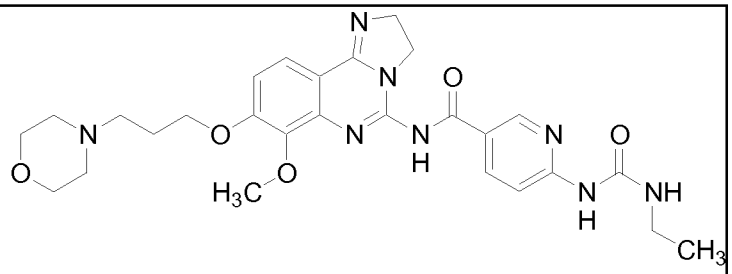
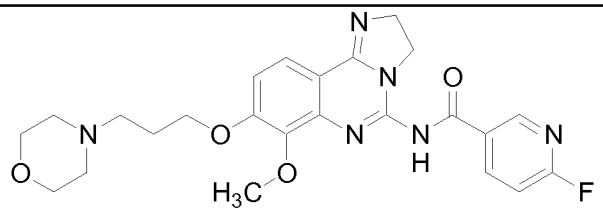
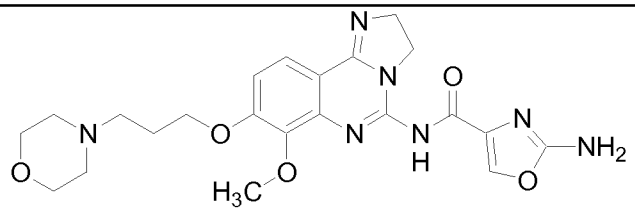
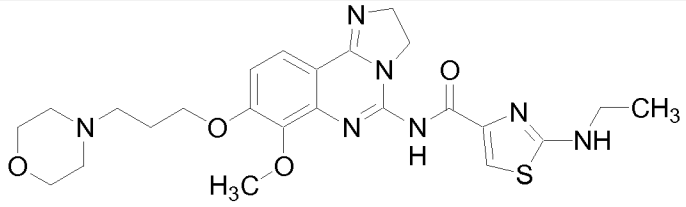
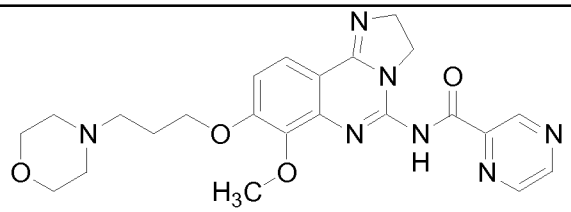
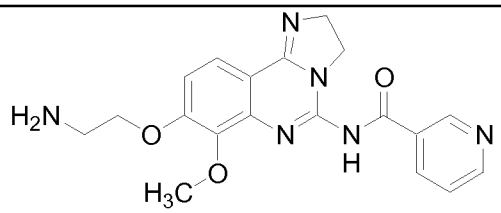
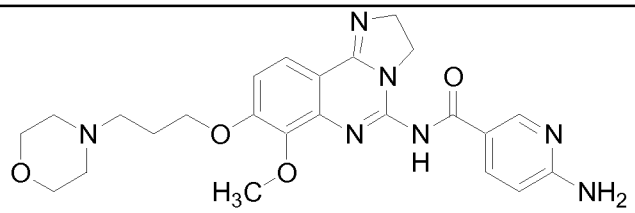
45	
46	
47	
48	
49	
50	

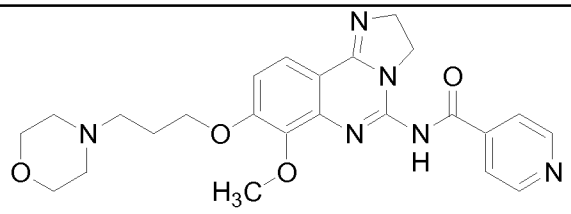
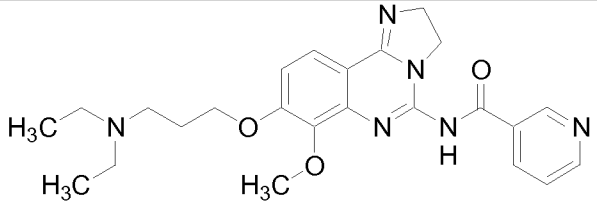
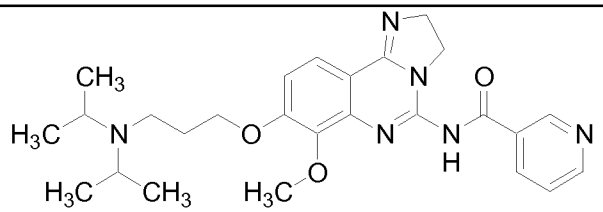
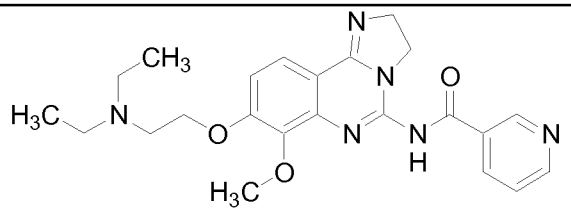
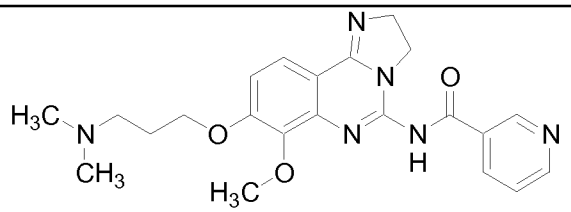
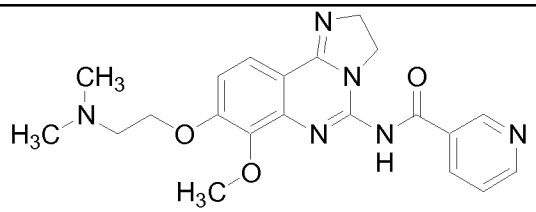
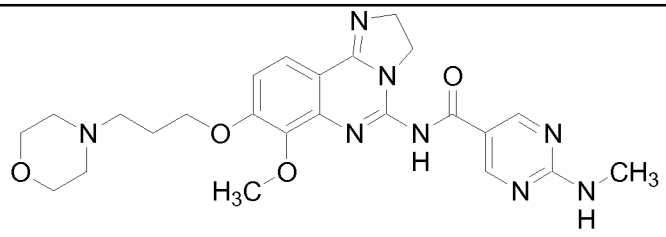
51	
52	
53	
54	
55	

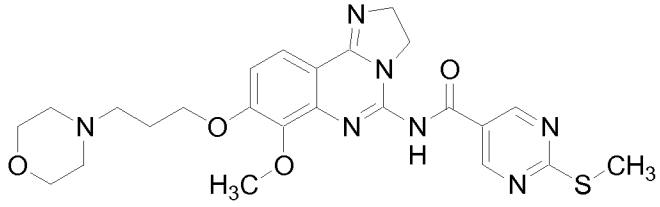
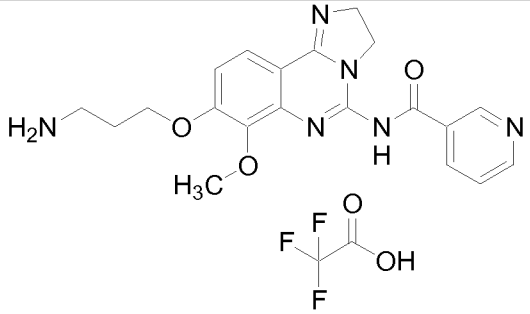
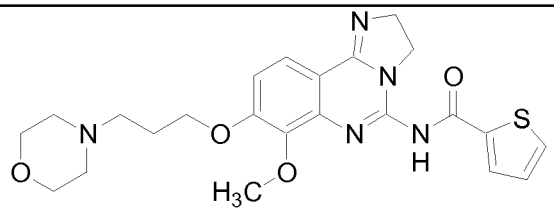
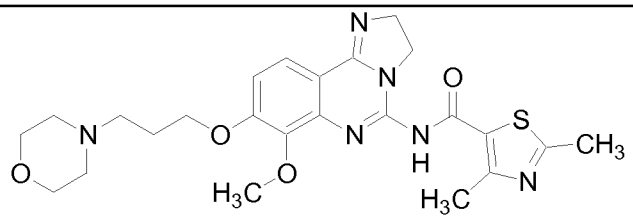
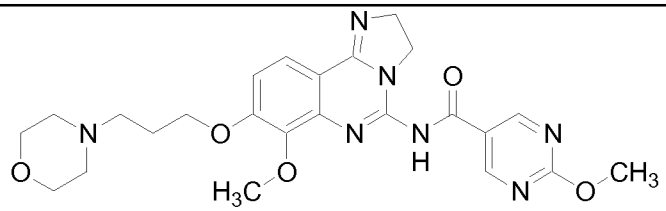
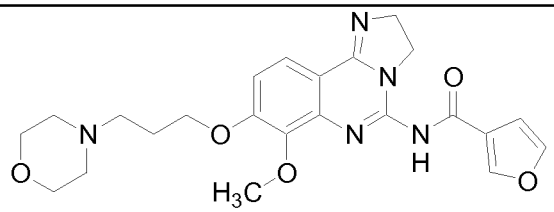
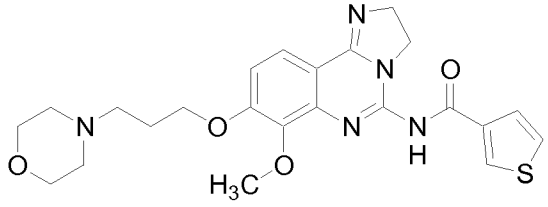
56	
57	
58	
59	
60	
61	
62	

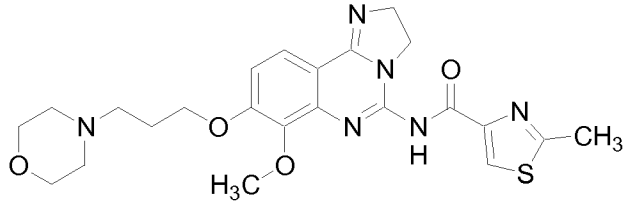
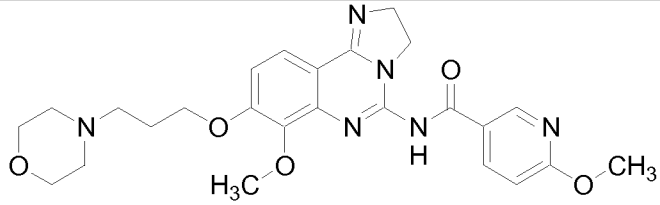
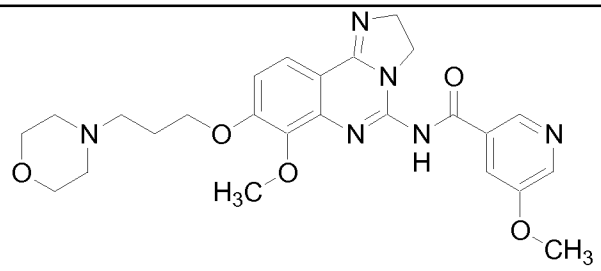
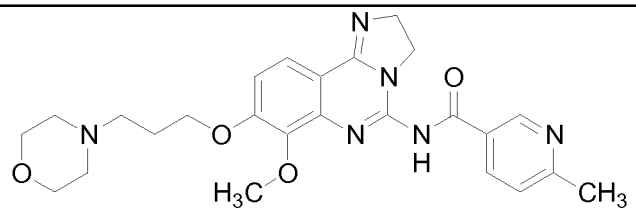
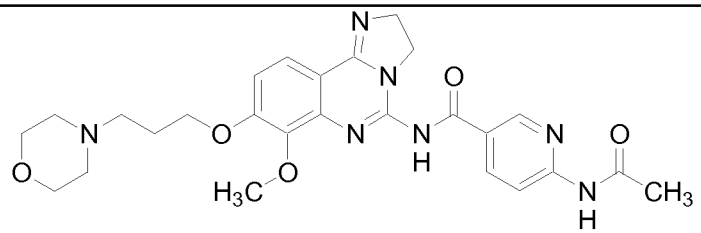
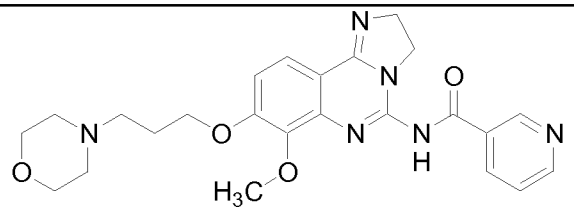
63	
64	
65	
66	
67	
68	
69	

70	
71	
72	
73	
74	
75	
76	

77	
78	
79	
80	
81	
82	
83	

84	
85	
86	
87	
88	
89	
90	

91	
92	
93	
94	
95	
96	
97	

98	
99	
100	
101	
102	
103	

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

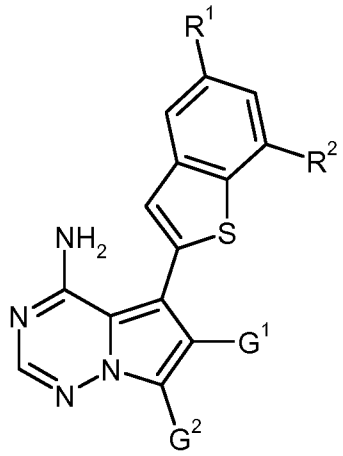
said compounds are published as specific compound Examples 1 to 103 in International patent application PCT/US2007/024985, published as WO 2008/070150 A1 on June 12, 2008, which is incorporated herein by reference in its entirety. In WO 2008/070150,

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 independnently of one another by the oral, subcutaneous, intravenous, topical, local, 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 substituted 5-(1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-4-amine compounds of general formula (B) :



(B),

wherein

R^1 is hydrogen, chloro, methyl or methoxy,

R^2 is hydrogen or methoxy,

with the proviso that at least one of R^1 and R^2 is other than hydrogen,

G^1 represents chloro, $(C_1\text{-}C_4)$-alkyl, $(C_1\text{-}C_4)$-alkoxycarbonyl, 5-membered aza-heteroaryl, or the group $-CH_2\text{-}OR^3$, $-CH_2\text{-}NR^4R^5$ or $-C(=O)\text{-}NR^4R^6$, wherein

R^3 is hydrogen, $(C_1\text{-}C_4)$-alkyl, $(C_3\text{-}C_6)$-cycloalkyl or phenyl,

(*i*) said $(C_1\text{-}C_4)$-alkyl is optionally substituted with hydroxy, $(C_1\text{-}C_4)$-alkoxy, hydroxycarbonyl, $(C_1\text{-}C_4)$-alkoxycarbonyl, amino, aminocarbonyl, mono-$(C_1\text{-}C_4)$-alkylaminocarbonyl, di-$(C_1\text{-}C_4)$-alkylaminocarbonyl, $(C_3\text{-}C_6)$-cycloalkyl or up to three fluoro atoms,

and

(*ii*) said (C_3-C_6)-cycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy and amino,

and

(*iii*) said phenyl is optionally substituted with one or two substituents independently selected from the group consisting of fluoro, chloro, bromo, cyano, trifluoromethyl, trifluoromethoxy, (C_1-C_4)-alkyl and (C_1-C_4)-alkoxy,

R^4 is hydrogen or (C_1-C_4)-alkyl,

R^5 is hydrogen, (C_1-C_4)-alkyl, (C_1-C_4)-alkylcarbonyl, (C_3-C_6)-cycloalkyl or 4- to 6-membered heterocycloalkyl, wherein

(*i*) said (C_1-C_4)-alkyl is optionally substituted with hydroxy, (C_1-C_4)-alkoxy, hydroxycarbonyl, (C_1-C_4)-alkoxycarbonyl, aminocarbonyl, mono-(C_1-C_4)-alkylaminocarbonyl, di-(C_1-C_4)-alkylaminocarbonyl or (C_3-C_6)-cycloalkyl,

and

(*ii*) said (C_3-C_6)-cycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy and amino,

and

(*iii*) said 4- to 6-membered heterocycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy, oxo and amino,

R^6 is hydrogen, (C_1-C_4)-alkyl, (C_3-C_6)-cycloalkyl or 4- to 6-membered heterocycloalkyl, wherein

(*i*) said (C_1-C_4)-alkyl is optionally substituted with hydroxy, (C_1-C_4)-alkoxy, hydroxycarbonyl, (C_1-C_4)-alkoxycarbonyl, amino, aminocarbonyl, mono-(C_1-C_4)-alkylaminocarbonyl, di-(C_1-C_4)-alkylaminocarbonyl or (C_3-C_6)-cycloalkyl,

and

(*ii*) said (C_3-C_6)-cycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy and amino,

and

(*iii*) said 4- to 6-membered heterocycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy, oxo and amino,

or

R^4 and R^5, or R^4 and R^6, respectively, are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic, saturated 4- to 7-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from N(R^7) and O, and

which may be substituted on ring carbon atoms with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, oxo, hydroxy, amino and aminocarbonyl, and wherein

R^7 is hydrogen, (C_1-C_4)-alkyl, formyl or (C_1-C_4)-alkylcarbonyl,

and

G^2 represents chloro, cyano, (C_1-C_4)-alkyl, or the group $-CR^{8A}R^{8B}$-OH, $-CH_2$-NR^9R^{10}, -C(=O)-$NR^{11}R^{12}$ or $-CH_2$-OR^{15}, wherein

R^{8A} and R^{8B} are independently selected from the group consisting of hydrogen, (C_1-C_4)-alkyl, cyclopropyl and cyclobutyl,

R^9 is hydrogen or (C_1-C_4)-alkyl,

R^{10} is hydrogen, (C_1-C_4)-alkyl, (C_1-C_4)-alkylcarbonyl, (C_3-C_6)-cycloalkyl or 4- to 6-membered heterocycloalkyl, wherein

(*i*) said (C_1-C_4)-alkyl is optionally substituted with hydroxy, amino, aminocarbonyl, mono-(C_1-C_4)-alkylaminocarbonyl or di-(C_1-C_4)-alkylaminocarbonyl,

and

(*ii*) said (C_3-C_6)-cycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy and amino,

and

(*iii*) said 4- to 6-membered heterocycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy, oxo and amino,

R^{11} is hydrogen or (C_1-C_4)-alkyl,

R^{12} is hydrogen, (C_1-C_4)-alkyl, (C_3-C_6)-cycloalkyl or 4- to 6-membered heterocycloalkyl, wherein

(*i*) said (C_1-C_4)-alkyl is optionally substituted with hydroxy, amino, aminocarbonyl, mono-(C_1-C_4)-alkylaminocarbonyl or di-(C_1-C_4)-alkylaminocarbonyl,

and

(*ii*) said (C_3-C_6)-cycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy and amino,

and

(*iii*) said 4- to 6-membered heterocycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy, oxo and amino,

or

R^9 and R^{10}, or R^{11} and R^{12}, respectively, are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic, saturated 4- to 7-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from

$N(R^{13})$, O, S and $S(O)_2$, and which may be substituted on ring carbon atoms with up to three substituents independently selected from the group consisting of fluoro, (C_1-C_4)-alkyl, oxo, hydroxy, amino and aminocarbonyl, and wherein

R^{13} is hydrogen, (C_1-C_4)-alkyl, (C_3-C_6)-cycloalkyl, formyl or (C_1-C_4)-alkylcarbonyl,

and

R^{15} is (C_1-C_4)-alkyl,

with the proviso that G^1 is not chloro when G^2 is chloro or cyano,

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

said compounds are published as compounds of general formula (I) in International patent application PCT/EP2012/074977, published as WO 2013/087578 on June 20, 2013, which is incorporated herein by reference in its entirety. In WO 2013/087578, said compounds of general formula (I) are described on pp. 5 *et seq.*, pp. 13 *et seq.* and pp. 109 *et seq.*, they may be synthesized according to the methods given therein on pp. 19, *et seq*. and pp. 53 *et seq.*, and are exemplified as specific compound Examples 1 to 127 therein on pp. 109 to 205. Biological test data for certain of said compounds are given therein on pp. 206 to 226.

The definitions used in relation to the structure (B) in this text are as follows :

(C_1-C_4)-Alkyl in the context of the invention represents a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. There may be mentioned by way of example and preferably: methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *iso*-butyl, *sec*-butyl, and *tert*-butyl.

(C_1-C_4)-Alkoxy in the context of the invention represents a straight-chain or branched alkoxy radical having 1 to 4 carbon atoms. There may be mentioned by way of example and preferably: methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *iso*-butoxy, *sec*-butoxy, and *tert*-butoxy.

Mono-(C_1-C_4)-alkylamino in the context of the invention represents an amino group with a straight-chain or branched alkyl substituent which contains 1 to 4 carbon atoms. There may be mentioned by way of example and preferably: methylamino, ethylamino, *n*-propylamino, isopropylamino, *n*-butylamino, and *tert*-butylamino.

Di-(C_1-C_4)-alkylamino in the context of the invention represents an amino group with two identical or different straight-chain or branched alkyl substituents which each contain 1 to 4 carbon atoms. There may be mentioned by way of example and preferably: *N,N*-dimethylamino, *N,N*-diethylamino, *N*-ethyl-*N*-methylamino, *N*-methyl-*N*-*n*-propylamino, *N*-isopropyl-*N*-methylamino, *N*-isopropyl-*N*-*n*-propylamino, *N,N*-diisopropylamino, *N*-*n*-butyl-*N*-methylamino, and *N*-*tert*-butyl-*N*-methylamino.

$(C_1$-$C_4)$-Alkylcarbonyl in the context of the invention represents a straight-chain or branched alkyl radical having 1 to 4 carbon atoms which is bonded to the rest of the molecule via a carbonyl group [-C(=O)-]. There may be mentioned by way of example and preferably: acetyl, propionyl, *n*-butyryl, *iso*-butyryl, *n*-pentanoyl, and pivaloyl.

$(C_1$-$C_4)$-Alkoxycarbonyl in the context of the invention represents a straight-chain or branched alkoxy radical having 1 to 4 carbon atoms which is bonded to the rest of the molecule via a carbonyl group [-C(=O)-]. There may be mentioned by way of example and preferably: methoxycarbonyl, ethoxycarbonyl, *n*-propoxycarbonyl, isopropoxycarbonyl, *n*-butoxycarbonyl, and *tert*-butoxycarbonyl.

Mono-$(C_1$-$C_4)$-alkylaminocarbonyl in the context of the invention represents an amino group which is bonded to the rest of the molecule via a carbonyl group [-C(=O)-] and which has a straight-chain or branched alkyl substituent having 1 to 4 carbon atoms. There may be mentioned by way of example and preferably: methylaminocarbonyl, ethylaminocarbonyl, *n*-propylaminocarbonyl, isopropylaminocarbonyl, *n*-butylaminocarbonyl, and *tert*-butylaminocarbonyl.

Di-$(C_1$-$C_4)$-alkylaminocarbonyl in the context of the invention represents an amino group which is bonded to the rest of the molecule via a carbonyl group [-C(=O)-] and which has two identical or different straight-chain or branched alkyl substituents having in each case 1 to 4 carbon atoms. There may be mentioned by way of example and preferably: *N,N*-dimethylaminocarbonyl, *N,N*-diethylaminocarbonyl, *N*-ethyl-*N*-methylaminocarbonyl, *N*-methyl-*N*-*n*-propylaminocarbonyl, *N*-isopropyl-*N*-methylaminocarbonyl, *N,N*-diisopropylaminocarbonyl, *N*-*n*-butyl-*N*-methylaminocarbonyl, and *N*-*tert*-butyl-*N*-methylaminocarbonyl.

$(C_3$-$C_6)$-Cycloalkyl in the context of the invention represents a monocyclic, saturated carbocycle having 3 to 6 ring carbon atoms. There may be mentioned by way of example: cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Preferred are cyclopropyl and cyclobutyl.

4- to 7-membered heterocycloalkyl and 4- to 6-membered heterocycloalkyl in the context of the invention represent a monocyclic, saturated heterocycle with 4 to 7 or, respectively, 4 to 6 ring atoms in total, which contains one or two identical or different ring heteroatoms from the series N, O, S and $S(O)_2$, and which can be bonded via a ring carbon atom or via a ring nitrogen atom (if present). 4- to 6-membered heterocycloalkyl containing one ring nitrogen atom and optionally one further ring heteroatom from the series N, O or $S(O)_2$ is preferred. 5- or 6-membered heterocycloalkyl containing one ring nitrogen atom and optionally one further ring heteroatom from the series N or O is particularly preferred. There may be mentioned by way of example: azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, tetrahydrofuranyl, thiolanyl, 1,1-dioxidothiolanyl, 1,2-oxazolidinyl, 1,3-oxazolidinyl, 1,3-thiazolidinyl, piperidinyl, piperazinyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,2-oxazinanyl, morpholinyl, thiomorpholinyl, 1,1-dioxidothiomorpholinyl, azepanyl, 1,4-diazepanyl, and 1,4-oxazepanyl. Preferred are azetidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, 1,2-oxazolidinyl, 1,3-oxazolidinyl, piperidinyl, piperazinyl, 1,2-oxazinanyl, morpholinyl, and thiomorpholinyl. Particularly preferred are pyrrolidinyl, piperidinyl, piperazinyl, and morpholinyl.

5-membered aza-heteroaryl in the context of the invention represents an aromatic heterocyclic radical (heteroaromatic) having 5 ring atoms in total, which contains at least one ring nitrogen atom and optionally one or two further ring heteroatoms from the series N, O and/or S, and which is bonded via a ring carbon atom or optionally via a ring nitrogen atom (when allowed by valency). 5-membered aza-heteroaryl containing one ring nitrogen atom and one or two further ring heteroatoms from the series N and/or O is preferred. There may be mentioned by way of example: pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, and thiadiazolyl. Preferred are pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, and oxadiazolyl.
An oxo substituent in the context of the invention represents an oxygen atom, which is bonded to a carbon atom via a double bond.

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 independnently of one another by the oral, subcutaneous, intravenous, topical, local, 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 substituted 5-(1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-4-amine compounds of general formula (B), *supra*, which is selected from the list consisting of :

Example 1

4-{[4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-2-one

Example 2

4-{[4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-2-one dihydrochloride

Example 3

(*3R*)-3-({[4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}amino)pyrrolidin-2-one dihydrochloride

Example 4

(*3R*)-3-({[4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}amino)pyrrolidin-2-one

Example 5

4-{[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-2-one

Example 6

4-{[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo-[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-2-one dihydrochloride

Example 7

(*3R*)-3-({[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}amino)pyrrolidin-2-one dihydrochloride

Example 8

(*3R*)-3-({[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}amino)pyrrolidin-2-one

Example 9

N^2-{[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}glycinamide dihydrochloride

Example 10

6-(Ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine

Example 11

1-(4-{[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-1-yl)ethanone dihydrochloride

Example 12

[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methanol bis(formiate)

Example 13

4-{[4-Amino-6-(hydroxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-2-one

Example 14

7-{[(*3S*)-3-Amino-3-methylpyrrolidin-1-yl]methyl}-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride

Example 15

7-{[(*3S*)-3-Amino-3-methylpyrrolidin-1-yl]methyl}-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine

Example 16

1-(4-{[4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-1-yl)ethanone dihydrochloride

Example 17

6-(Methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine formiate

Example 18

6-(Ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine

Example 19

6-(Ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine dihydrochloride

Example 20

1-(4-{[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo-[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-1-yl)ethanone

Example 21

4-({4-Amino-6-[(2-hydroxyethoxy)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl}methyl)piperazin-2-one formiate

Example 22

2-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methoxy}ethanol dihydrochloride

Example 23

6-(Butoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine formiate

Example 24

5-(7-Methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)-6-(propoxy-methyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine bis(formiate)

Example 25

6-[(Cyclopropylmethoxy)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine bis(formiate)

Example 26

6-[(Cyclobutyloxy)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine

Example 27

6-(Isopropoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-yl-methyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine formiate

Example 28

6-[(2-Methoxyethoxy)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine formiate

Example 29

5-(7-Methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)-6-[(2,2,2-trifluoroethoxy)methyl]pyrrolo[2,1-f][1,2,4]triazin-4-amine formiate

Example 30

6-[(2-Aminoethoxy)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride

Example 31

Methyl {[4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-yl-methyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methoxy}acetate

Example 32

{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methoxy}acetic acid

Example 33

2-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methoxy}acetamide

Example 34

2-({7-[(4-Acetylpiperazin-1-yl)methyl]-4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl}methoxy)acetamide

Example 35

5-(7-Methoxy-5-methyl-1-benzothiophen-2-yl)-6-(phenoxymethyl)-7-(piperazin-1-yl-methyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine bis(formiate)

Example 36

5-(7-Methoxy-5-methyl-1-benzothiophen-2-yl)-6-[(methylamino)methyl]-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride

Example 37

6-[(Dimethylamino)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride

Example 38

6-[(Ethylamino)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride

Example 39

2-({[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}amino)ethanol trihydrochloride

Example 40

rac-1-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}piperidin-3-ol trihydrochloride

Example 41

1-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}piperidin-4-ol trihydrochloride

Example 42

rac-1-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}pyrrolidin-3-ol trihydrochloride

Example 43

6-[(Diethylamino)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride

Example 44

6-[(Cyclobutylamino)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride

Example 45

5-(7-Methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)-6-(pyrrolidin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride

Example 46

6-[(Cyclopropylamino)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride

Example 47

6-{[(Cyclopropylmethyl)amino]methyl}-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride

Example 48

N-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}glycine trihydrochloride

Example 49

4-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}piperazin-2-one trihydrochloride

Example 50

[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methanol

Example 51

(*3S*)-3-({[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}amino)pyrrolidin-2-one

Example 52

4-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}piperazin-2-one

Example 53

rac-1-({[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}amino)propan-2-ol

Example 54

1-({[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(morpholin-4-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}amino)-2-methylpropan-2-ol

Example 55

1-(4-{[4-Amino-6-(hydroxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-1-yl)ethanone

Example 56

(*3R*)-3-[({7-[(4-Acetylpiperazin-1-yl)methyl]-4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl}methyl)amino]pyrrolidin-2-one

Example 57

1-(4-{[4-Amino-6-{[(2-hydroxy-2-methylpropyl)amino]methyl}-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-1-yl)ethanone

Example 58

4-({4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-6-[(3-oxopiperazin-1-yl)-methyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}methyl)piperazine-1-carbaldehyde formiate

Example 59

4-({7-[(4-Acetylpiperazin-1-yl)methyl]-4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl}methyl)piperazin-2-one

Example 60

Methyl 4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylcarbonyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate bis(formiate)

Example 61

5-(7-Methoxy-5-methyl-1-benzothiophen-2-yl)-6-(1,3-oxazol-5-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride

Example 62

6-(Aminomethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride

Example 63

N-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}acetamide bis(trifluoroacetate)

Example 64

N-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}acetamide dihydrochloride

Example 65

N-({4-Amino-7-[(4-formylpiperazin-1-yl)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl}methyl)acetamide formiate

Example 66

N-({7-[(4-Acetylpiperazin-1-yl)methyl]-4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl}methyl)acetamide

Example 67

N-({4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-[(3-oxopiperazin-1-yl)methyl]pyrrolo[2,1-f][1,2,4]triazin-6-yl}methyl)acetamide

Example 68

4-Amino-6-(hydroxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazine-7-carbonitrile

Example 69

4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazine-7-carbonitrile

Example 70

4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazine-7-carbonitrile

Example 71

4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-6-[(3-oxopiperazin-1-yl)methyl]pyrrolo[2,1-f][1,2,4]triazine-7-carbonitrile

Example 72

N,N'-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazine-6,7-diyl]bis(methylene)}diacetamide

Example 73

2-[4-Amino-6-(hydroxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]propan-2-ol

Example 74

4-{[4-Amino-7-(2-hydroxypropan-2-yl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}piperazin-2-one

Example 75

[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-methylpyrrolo[2,1-f][1,2,4]triazin-6-yl]methanol

Example 76

4-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-methylpyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}piperazin-2-one

Example 77

1-({[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-methylpyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}amino)-2-methylpropan-2-ol formiate

Example 78

1-({[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-methylpyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}amino)-2-methylpropan-2-ol

Example 79

[4-Amino-7-chloro-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methanol

Example 80

4-{[4-Amino-7-chloro-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}piperazin-2-one

Example 81

1-({[4-Amino-7-chloro-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}amino)-2-methylpropan-2-ol formiate

Example 82

1-({[4-Amino-7-chloro-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}amino)-2-methylpropan-2-ol

Example 83

7-Chloro-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-4-amine

Example 84

5-(7-Methoxy-5-methyl-1-benzothiophen-2-yl)-6-methyl-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine formiate

Example 85

6-Chloro-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride

Example 86

[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methanol

Example 87

1-{[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}imidazolidin-2-one

Example 88

4-{[4-Amino-5-(7-methoxy-1-benzothiophen-2-yl)-6-(methoxymethyl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-2-one

Example 89

4-{[4-Amino-6-(methoxymethyl)-5-(5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-2-one

Example 90

1-[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]ethanol

Example 91

[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl](cyclopropyl)methanol

Example 92

(*3S*)-3-({[4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}amino)pyrrolidin-2-one

Example 93

(*3S*)-3-({[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}amino)pyrrolidin-2-one

5

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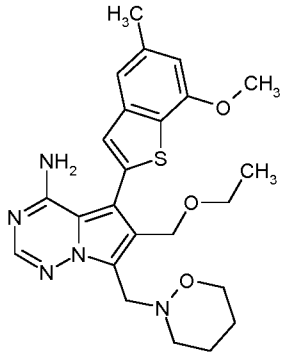
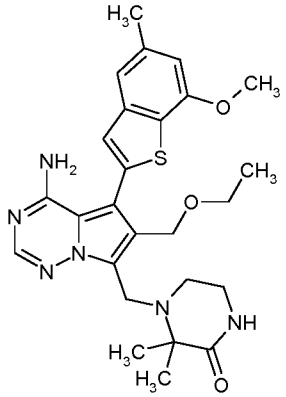
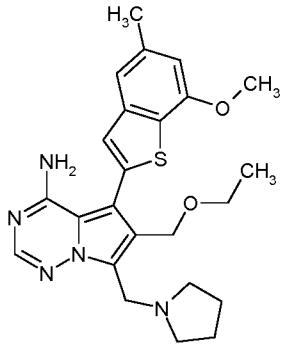
94	
95	
96	

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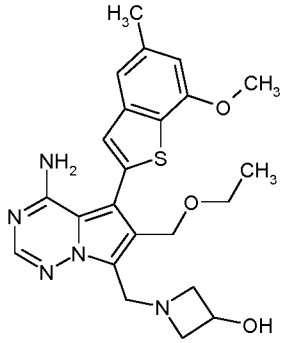
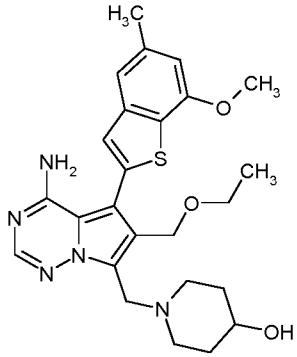
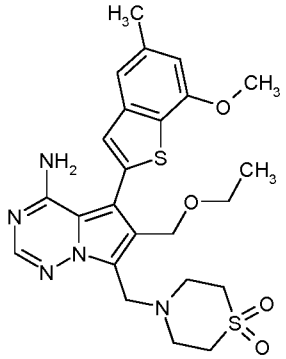
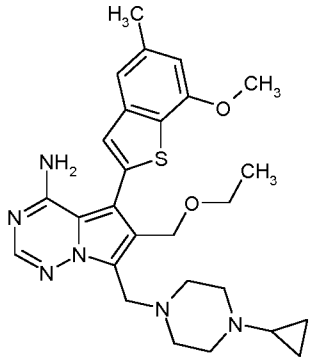
97	
98	
99	
100	

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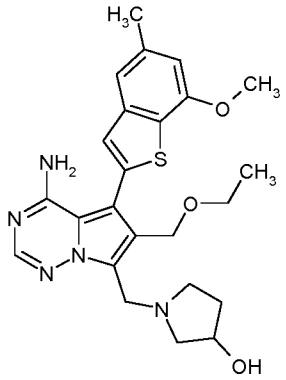
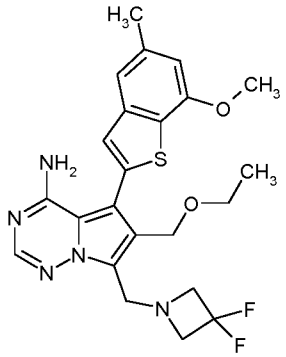
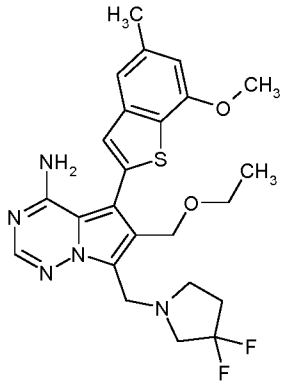
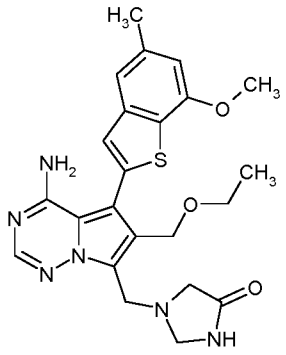
101	
102	
103	
104	

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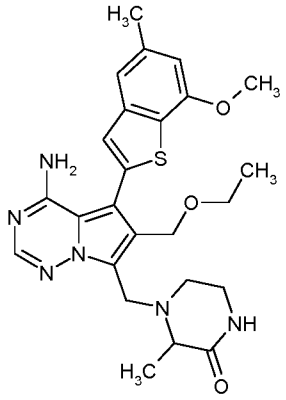
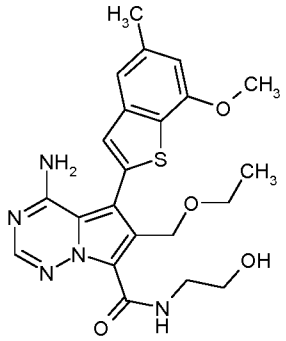
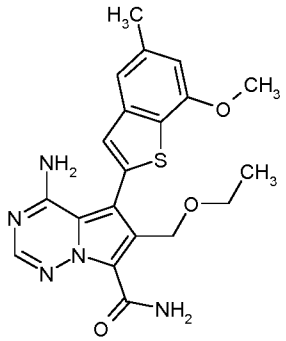
105	

Example 106

4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-*N*-[(*3R*)-2-oxopyrrolidin-3-yl]pyrrolo[2,1-f][1,2,4]triazine-7-carboxamide

Example 107

4-{[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]carbonyl}piperazin-2-one

Example No.	Structure
108	
109	

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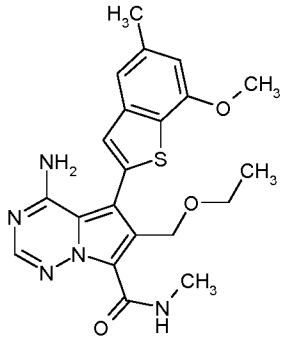
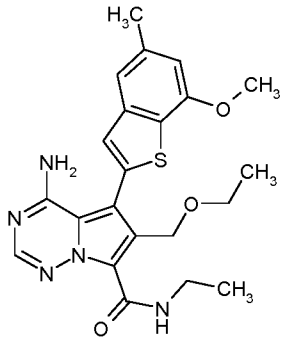
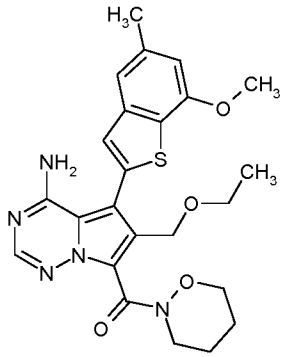
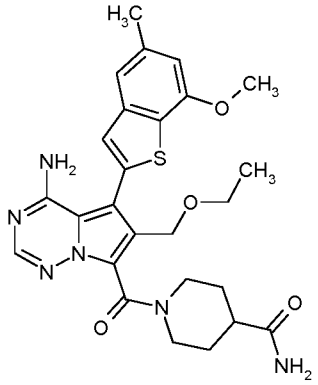
110	
111	
112	
113	

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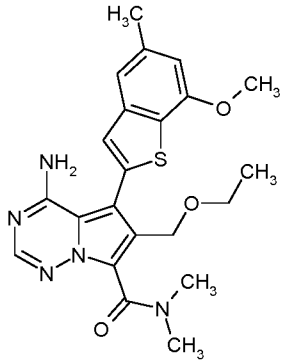
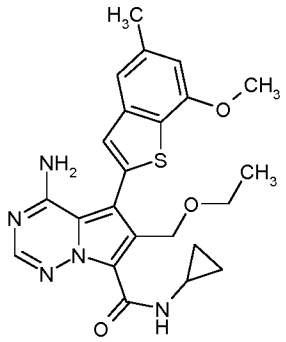
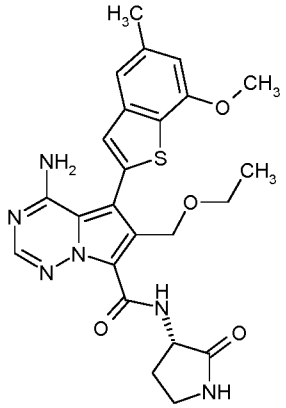
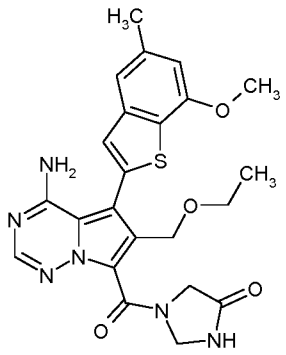
114	
115	
116	
117	

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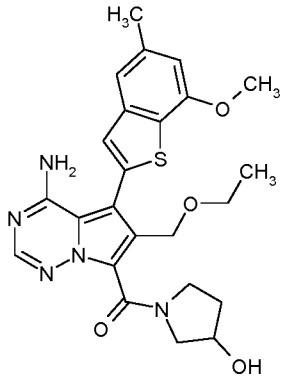
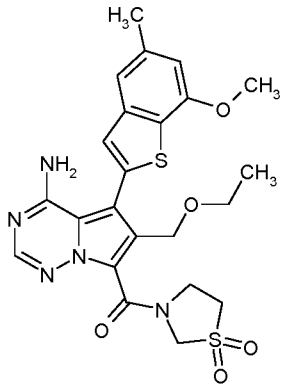
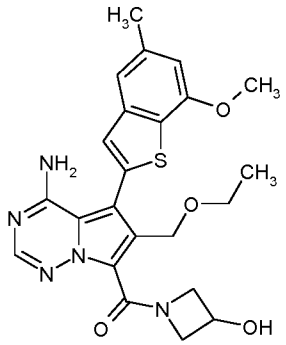
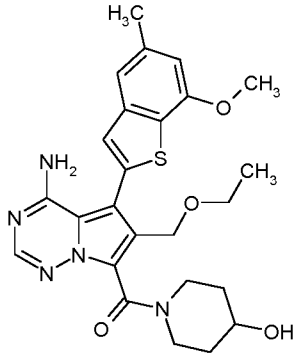
118	
119	
120	
121	

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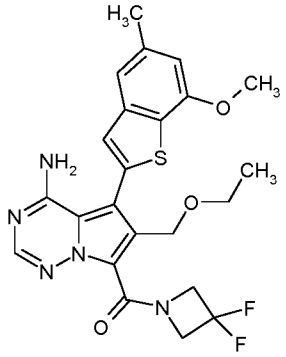
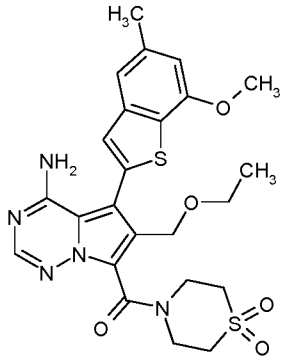
122	
123	

Example 124

4-{[4-Amino-5-(5,7-dimethoxy-1-benzothiophen-2-yl)-6-(methoxymethyl)pyrrolo[2,1-f]-[1,2,4]triazin-7-yl]methyl}piperazin-2-one

Example 125

4-{[4-Amino-7-(hydroxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}piperazin-2-one

Example 126

4-{[4-Amino-7-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}piperazin-2-one

Example 127

4-{[4-Amino-7-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}piperazin-2-one

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

component B : 4-{[4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-2-one.

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 independnently of one another by the oral, subcutaneous, intravenous, topical, local, intraperitoneal or 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.

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

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 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, 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 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 chorine 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 strearyl 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

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 independnently of one another by the oral, subcutaneous, intravenous, topical, local, intraperitoneal or nasal route.

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 conventional dosage unit forms, including immediate, slow and timed release

preparations, orally, parenterally, topically, nasally, ophthalmically, optically, sublingually, rectally, vaginally, and the like.

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 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 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 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 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 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 form 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 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 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.

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 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 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-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 form 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 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 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.

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 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 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 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.

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. 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 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.

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);

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);

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, $F_2ClC\text{-}CClF_2$ and $CClF_3$)

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);

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);

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);

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

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

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)

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);

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

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)

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);

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

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);

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)

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

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);

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));

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

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);

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

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);

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);

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);

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

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 lypholized 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 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 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 effervescent components to produce porous matrices intended for immediate release, without the need of water.

Method of treating cancer

Within the context of the present invention, the term "cancer" includes, but is not limited to, cancers of the endometrium, 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.

Examples of endometrial cancer include, but not limited to type I EC (estrogen-dependent and/or progesterone-dependent with endometrioid histology) and type II EC, or endometriosis (hormone-independent poorly differentiated endometrioid, clear cell and serous carcinomas).

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.

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 hypophtalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumor.

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.

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.

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.

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.

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.

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.

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

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

The present invention relates to a method for using the combinations of the present invention, in the treatment or prophylaxis of a cancer, particularly bladder cancer, head & neck cancer, particularly head & neck squamous cell carcinoma, liver cancer. The combinations of the present invention can be utilized to inhibit, block, reduce, decrease, etc., cell proliferation and/or cell division, and/or produce apoptosis, in the treatment or prophylaxis of cancer, in particular bladder cancer, head & neck cancer, particularly head & neck squamous cell carcinoma, liver 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 effective for the treatment or prophylaxis of cancer, in particular bladder cancer, head & neck cancer, particularly head & neck squamous cell carcinoma, liver 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 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 bladder cancer, head & neck cancer, particularly head & neck squamous cell carcinoma, liver 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.

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.

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

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, antiarrhytmic, anti-hypercholsterolemia, anti-dyslipidemia, anti-diabetic or antiviral agents, and the like, as well as with admixtures and combinations thereof.

Component C, can be one or more pharmaceutical agents such as 131I-chTNT, abarelix, abiraterone, aclarubicin, ado-trastuzumab emtansine, afatinib, aflibercept, aldesleukin, alemtuzumab, Alendronic acid, alitretinoin, altretamine, amifostine, aminoglutethimide, Hexyl aminolevulinate,amrubicin, amsacrine, anastrozole, ancestim, anethole dithiolethione, angiotensin II, antithrombin III, aprepitant, arcitumomab, arglabin, arsenic trioxide, asparaginase, axitinib, azacitidine, basiliximab, belotecan, bendamustine, belinostat, bevacizumab, bexarotene, bicalutamide, bisantrene, bleomycin, bortezomib, buserelin, bosutinib, brentuximab vedotin, busulfan, cabazitaxel, cabozantinib, calcium folinate, calcium levofolinate, capecitabine, capromab, carboplatin, carfilzomib, carmofur, carmustine, catumaxomab, celecoxib, celmoleukin, ceritinib, cetuximab, chlorambucil, chlormadinone, chlormethine,

cidofovir, cinacalcet, cisplatin, cladribine, clodronic acid, clofarabine, crisantaspase, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, darbepoetin alfa, dabrafenib, dasatinib, daunorubicin, decitabine, degarelix, denileukin diftitox, denosumab, depreotide, deslorelin, dexrazoxane, dibrospidium chloride, dianhydrogalactitol, diclofenac, docetaxel, dolasetron, doxifluridine, doxorubicin, doxorubicin + estrone, dronabinol, eculizumab, edrecolomab, elliptinium acetate, eltrombopag, endostatin, enocitabine, enzalutamide, epirubicin, epitiostanol, epoetin alfa, epoetin beta, epoetin zeta, eptaplatin, eribulin, erlotinib, esomeprazole, estradiol, estramustine, etoposide, everolimus, exemestane, fadrozole, fentanyl, filgrastim, fluoxymesterone, floxuridine, fludarabine, fluorouracil, flutamide, folinic acid, formestane, fosaprepitant, fotemustine, fulvestrant, gadobutrol, gadoteridol, gadoteric acid meglumine, gadoversetamide, gadoxetic acid, gallium nitrate, ganirelix, gefitinib, gemcitabine, gemtuzumab, Glucarpidase, glutoxim, GM-CSF, goserelin, granisetron, granulocyte colony stimulating factor, histamine dihydrochloride, histrelin, hydroxycarbamide, I-125 seeds, lansoprazole, ibandronic acid, ibritumomab tiuxetan, ibrutinib, idarubicin, ifosfamide, imatinib, imiquimod, improsulfan, indisetron, incadronic acid, ingenol mebutate, interferon alfa, interferon beta, interferon gamma, iobitridol, iobenguane (123I), iomeprol, ipilimumab, irinotecan, Itraconazole, ixabepilone, lanreotide, lapatinib, Iasocholine, lenalidomide, lenograstim, lentinan, letrozole, leuprorelin, levamisole, levonorgestrel, levothyroxine sodium, lisuride, lobaplatin, lomustine, lonidamine, masoprocol, medroxyprogesterone, megestrol, melarsoprol, melphalan, mepitiostane, mercaptopurine, mesna, methadone, methotrexate, methoxsalen, methylaminolevulinate, methylprednisolone, methyltestosterone, metirosine, mifamurtide, miltefosine, miriplatin, mitobronitol, mitoguazone, mitolactol, mitomycin, mitotane, mitoxantrone, mogamulizumab, molgramostim, mopidamol, morphine hydrochloride, morphine sulfate, nabilone, nabiximols, nafarelin, naloxone + pentazocine, naltrexone, nartograstim, nedaplatin, nelarabine, neridronic acid, nivolumabpentetreotide, nilotinib, nilutamide, nimorazole, nimotuzumab, nimustine, nitracrine, nivolumab, obinutuzumab, octreotide, ofatumumab, omacetaxine mepesuccinate, omeprazole, ondansetron, oprelvekin,

orgotein, orilotimod, oxaliplatin, oxycodone, oxymetholone, ozogamicine, p53 gene therapy, paclitaxel, palifermin, palladium-103 seed, palonosetron, pamidronic acid, panitumumab, pantoprazole, pazopanib, pegaspargase, PEG-epoetin beta (methoxy PEG-epoetin beta), pembrolizumab, pegfilgrastim, peginterferon alfa-2b, pemetrexed, pentazocine, pentostatin, peplomycin, Perflubutane, perfosfamide, Pertuzumab, picibanil, pilocarpine, pirarubicin, pixantrone, plerixafor, plicamycin, poliglusam, polyestradiol phosphate, polyvinylpyrrolidone + sodium hyaluronate, polysaccharide-K, pomalidomide, ponatinib, porfimer sodium, pralatrexate, prednimustine, prednisone, procarbazine, procodazole, propranolol, quinagolide, rabeprazole, racotumomab, radium-223 chloride, radotinib, raloxifene, raltitrexed, ramosetron, ramucirumab, ranimustine, rasburicase, razoxane, refametinib , regorafenib, risedronic acid, rhenium-186 etidronate, rituximab, romidepsin, romiplostim, romurtide, roniciclib , samarium (153Sm) lexidronam, sargramostim, satumomab, secretin, sipuleucel-T, sizofiran, sobuzoxane, sodium glycididazole, sorafenib, stanozolol, streptozocin, sunitinib, talaporfin, tamibarotene, tamoxifen, tapentadol, tasonermin, teceleukin, technetium (99mTc) nofetumomab merpentan, 99mTc-HYNIC-[Tyr3]-octreotide, tegafur, tegafur + gimeracil + oteracil, temoporfin, temozolomide, temsirolimus, teniposide, testosterone, tetrofosmin, thalidomide, thiotepa, thymalfasin, thyrotropin alfa, tioguanine, tocilizumab, topotecan, toremifene, tositumomab, trabectedin, tramadol, trastuzumab, trastuzumab emtansine, treosulfan, tretinoin, trifluridine + tipiracil, trilostane, triptorelin, trametinib, trofosfamide, thrombopoietin, tryptophan, ubenimex, valrubicin, vandetanib, vapreotide, vemurafenib, vinblastine, vincristine, vindesine, vinflunine, vinorelbine, vismodegib, vorinostat, vorozole, yttrium-90 glass microspheres, zinostatin, zinostatin stimalamer, zoledronic acid, zorubicin, 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, doxirubicin, 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.

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 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-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 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 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, 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 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 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,

(2) provide for the administration of lesser amounts of the administered chemo-therapeutic agents,

(3) provide for a chemotherapeutic treatment that is well tolerated in the 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,

(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,

(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.

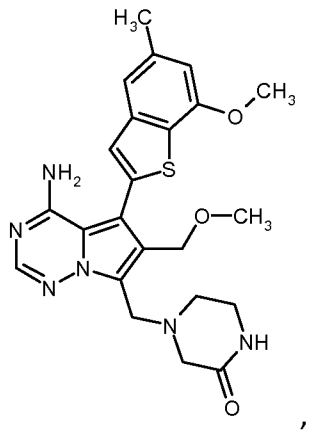
EXAMPLES

The following abbreviations are used in the Examples :

- Component A :
  - "copanlisib" or "compound A" means compound Example 13 of WO 2008/070150 A1 as shown herein (which is an example of component A as described and defined herein) ;
  - "copanlisib dihydrochloride" or "compound A*" means compound Example 1 of European patent application number EP 11 161 111.7, and in PCT application number PCT/EP2012/055600 published under WO 2012/136553, both of which are hereby incorporated herein in their entirety by reference (which is an example of component A as described and defined herein).

- Component B :

"FGFRi" or "compound B" means compound Example 1 of WO 2013/087578, *i.e.* a compound of structure :



,

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

Materials and methods:

In vitro combination assessment: 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 growth assay. Briefly, cells were plated at the indicated cell density in 384-well plates in 30 µL respective medium with 10% FCS and incubated in a humidified 37°C incubator. After 24 hours, baseline cell growth respective viability was measured in a control plate using the CellTiter-Glo® Luminescent Cell Viability Assay (Promega), while the cells in parallel plates were treated by adding 5 µL of experimental media containing:

- either A alone (concentration range 1.0E-05 M to 8.6E-12 M or 3E-05 to 8.6E-11), or
- B alone (concentration range 1.0E-05 M to 8.6E-12 M or 3E-05 to 8.6E-11), or
- the combination of A (as component A) plus B (as component B) at nine different fixed-ratio combinations (0.9xA+0.1xB, 0.8xA+0.2xB, 0.7xA+0.3xB, 0.6xA+0.4xB, 0.5xA+0.5xB, 0.4xA+0.6xB, 0.3xA+0.7xB, 0.2xA+0.8xB, 0.1xA+0.9xB).

Test compounds were added to the wells using a Tecan-HP Digital Dispenser. CellTiter-Glo® Luminescent Cell Viability Assay was conducted at 72 hours after compound exposure. Data were analyzed for effects on proliferation and on viability. IC50 values (inhibitory concentration at 50% of maximal effect) were determined by means of a 4 parameter fit on measurement data which were normalized to vehicle (DMSO) treated cells (=100%) and either the signal obtained in wells with medium but without cells (viability) or measurement readings of the control plate taken immediately before compound exposure (proliferation) (=0%). IC50 isobolograms were plotted with the actual concentrations of the two compounds on the x- and y-axis, and the combination index (CI) was calculated according to the median-effect model of Chou-Talalay (Chou 2006 (Ref. 4)). A CI of ≤0.8 was defined as more than additive (or synergistic) interaction, and a CI of ≥1.2 was defined as antagonistic interaction.

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

Table 1. Molecular features of cell line models used

Cell Line	Tumor type	Molecular features
RT112	UBC	**FGFR3-TACC3, FGFR3$^{K652E, K560E}$**
SW780	UBC	**FGFR3-BAIAP2L1, FGFR3^{S773F}**
JMSU1	UBC	**FGFR1 overexpression**
J82	UBC	**FGFR1 overexpression, PIK3CA^{P124L}, PTEN$^{p.N212fs*1}$, FGFR3^{K652E},** ERBB2
Hep3B	HCC	**FGFR2+FGFR3+FGFR4 overexpression**
HUH7	HCC	**FGFR3+FGFR4 overexpression**
SNU387	HCC	**FGFR1 overexpression, NRAS^{Q61K}**
SNU449	HCC	**FGFR1+FGFR4 overexpression, PTEN^{F241L}**

In vivo combination assessment: The in vivo efficacy was evaluated at maximal tolerated dose (MTD) or sub-MTD dose in tumor xenograft models in SCID mice (CB-17/Icr-Prkdc$^{scid/scid}$/Rj). Tumor cells were cultivated according to suppliers' recommendation in media containing 10% FCS. Cells were harvested for transplantation in a subconfluent (70%) state and were subcutaneously injected in 100 µl RPMI-1640 containing 50% matrigel (see Table 2). When tumors were approximately the size of 65 mm^3, the animals were randomized to treatment and control groups, and treatment was started. Treatment of each animal was based on individual body weight. The optimal formulation, application route and schedule were used for each compound (see Table 3). Oral administration (p.o.) was carried out via gavage. The oral application volumes were 10 ml/kg. Tumors were measured using a caliper at least twice a week. Tumor volume was calculated using the following formula: (length × width^2)/2. The animal body weight was monitored at least twice a week as a measure for treatment-

related toxicity. T/C ratios (Treatment / Control) were calculated on mean tumor volumes at the last day of the vehicle group (%T/C>50 is considered inactive). Statistical analysis between the monotherapy and combination groups was performed using tumor volumes or weights on the indicated day using a Mann-Whitney U test.

The efficacy of combination of compound A (copanlisib) and compound B (FGFRi rogaratinib) was further evaluated in a mouse-clinical-trial design study in xenografts from patient-derived models of squamous head and neck cancer. The study was performed in 20 models engrafted subcutaneously into the left flank of female NMRI nu/nu mice, with one mouse per treatment group and two mice in the control group.

Mice with a tumor size of more than 200 mm^3 have been randomized to the control (n=2) and treatment groups (n=1) according to the study design. Treatment was performed for a period of 28 days. Efficacy of the monotherapy as well as the combination treatment was evaluated by measurement of two perpendicular diameters of the subcutaneous tumors twice a week.

Measurement of body weight of the control and treatment groups was used for assessing the tolerability of the treatments. Animals were sacrificed when the tumour size reached more than 1 cm^3 or the intended duration of treatment had been reached. Tumor measurements were used for calculation of tumor volume (TV) and relative tumor volume (RTV; change relative to TV at start of treatment). The treatment effects on tumor growth was calculated based on fitting an exponential growth curve into the RTV data and calculation of doubling times (DT) and growth rate (k) (GraphPad Prism 7.0) according to Hafner et.al. 2016 (5). Statistics on treatment effects have been calculated on ranks using Dunn's multiple comparisons test, on the relative tumor volumes along the time (GraphPad Prism 7.0).

Table 2. Tumor model used for assessment of compound A (copanlisib) and compound B (FGFRi rogaratinib) in bladder tumor models in vivo.

Tumor model	Mode of Implantation
RT112	s.c. implantation of 1.5 x 10^6 cells suspended in RPMI-1640/Matrigel (50/50, V/V) on the right flank of female mice

Table 3: Formulations, route and schedule of compounds for in vivo experiments.

Table 1: Formulations, route and schedule of compounds for in vivo experiments.			
Compound	Formulation	Route	Schedule
A (PI3Ki, Copanlisib)	0.9% NaCl in water	i.v.	2days on/5 days off
B (FGFRi, Rogaratinib)	Ethanol/Solutol/Water 10/40/50 (v/v/v)	p.o.	2QD->QD

Example 1. Synergistic combination of PI3K inhibitor compound A (copanlisib) and FGFR inhibitor compound B (rogaratinib) in urothelial bladder tumor models.

As indicated in table 1, FGFR receptors are often overexpressed or mutated in UBC leading to increased pathway activity which often results in increased MAPK signaling. In only one of the UBC cell lines shown in table 1, the PI3K pathway is affected by a slightly activating PI3K mutation and loss-of-function of PTEN. The antiproliferative activity and effect on viability of compound A (Copanlisib) and FGFR inhibitor compound B was evaluated in combination and compared to the single agent activity in human cell lines derived from urothelial bladder cancers using the CellTiter-Glo® Luminescent Cell Viability Assay as described in the Materials and Methods section. Surprisingly, combining compound A (Copanlisib) and FGFR inhibitor compound B for treating UBC cells results in synergistic inhibition of proliferation and reduced viability compared to single agent treatment in cell lines with and without aberrations in the PI3K pathway as demonstrated in figures 1-4. Data are summarized in tables 2 and 3.

Table 4. Calculated combination indices at IC_{50} (CI_{50}) from proliferation analysis of bladder cancer cell lines treated with combinations of compound A (Copanlisib) and FGFR inhibitor compound B. In case of synergism lowest CI50 along with corresponding compound concentrations is presented.

Cell Line	$IC_{50, mono}$ [M] compound A	$IC_{50, mono}$ [M] compound B	Combination (proliferation) A [M]	plus B [M]	CI_{50}
RT112	1.4E-08	8.1E-08	2.7E-09	2.5E-08	0.51
SW780	2.2E-08	9.2E-08	4.1E-09	3.7E-08	0.59
JMSU1	3.3E-08	2.8E-08	6.0E-09	9.1E-09	0.50
J82	5.7E-08	4.3E-06	1.8E-08	1.6E-07	0.35

Table 5. Calculated combination indices at IC_{50} (CI_{50}) from viability analysis of bladder cancer cell lines treated with combinations of compound A (Copanlisib) and FGFR inhibitor compound B. In case of synergism lowest CI50 along with corresponding compound concentrations is presented.

Cell Line	$IC_{50, mono}$ [M] compound A	$IC_{50, mono}$ [M] compound B	Combination (viability) A [M]	plus B [M]	CI_{50}
RT112	2.3E-08	2.5E-07	4.3E-09	3.9E-08	0.39
SW780	9.7E-08	1.8E-06	1.5E-08	1.4E-07	0.23
JMSU1	4.3E-07	1.1E-07	3.0E-08	2.0E-08	0.25
J82	5.0E-07	2.2E-05	1.4E-07	1.3E-06	0.34

Figure 1. Synergistic combination of PI3K inhibitor compound A (Copanlisib) with FGFR inhibitor compound B in RT112 cells. The combination of PI3K inhibitor compound A (copanlisib) and FGFR inhibitor compound B was tested and compared to the single agent activity in RT112 cells using the CellTiter-Glo® Luminescent Cell Viability Assay. RT112 cells harbor a FGFR3-TACC3 fusion and FGFR3 mutations but no activating PIK3CA mutations are known. The combination treatment shows synergistic effects on proliferation and viability for all concentration combinations used.

Figure 2. Synergistic combination of PI3K inhibitor compound A (Copanlisib) with FGFR inhibitor compound B in SW780 cells. The combination of PI3K inhibitor compound A

(copanlisib) and FGFR inhibitor compound B was tested and compared to the single agent activity in SW780 cells using the CellTiter-Glo® Luminescent Cell Viability Assay. RT112 cells harbor a FGFR3-BAIAP2L1 fusion and a FGFR3 mutation but no activating PIK3CA mutations are known. The combination treatment shows synergistic effects on proliferation and viability for all concentration combinations used.

Figure 3. Synergistic combination of PI3K inhibitor compound A (Copanlisib) with FGFR inhibitor compound B in JMSU1 cells. The combination of PI3K inhibitor compound A (copanlisib) and FGFR inhibitor compound B was tested and compared to the single agent activity in JMSU1 cells using the CellTiter-Glo® Luminescent Cell Viability Assay. JMSU1 cells overexpress FGFR1 but no activating PIK3CA mutations are known. The combination treatment shows synergistic effects on proliferation and viability for all concentration combinations used.

Figure 4. Synergistic combination of PI3K inhibitor compound A (Copanlisib) with FGFR inhibitor compound B in J82 cells. The combination of PI3K inhibitor compound A (copanlisib) and FGFR inhibitor compound B was tested and compared to the single agent activity in J82 cells using the CellTiter-Glo® Luminescent Cell Viability Assay. J82 cells overexpress FGFR1 and harbor a FGFR3 mutation as well as a slightly activating PIK3CA mutation and loss-of-PTEN. The combination treatment shows synergistic effects on proliferation and viability for all concentration combinations used.

Figures 5, 6 and 7. Beneficial combination of PI3K inhibitor compound A (copanlisib) and FGFR inhibitor compound B (rogaratinib) in RT112 bladder cancer xenograft model, implanted subcutaneously in SCID mice. The combination of PI3K inhibitor compound A and FGFR inhibitor compound B was tested and compared to the single agent activity in the urothelial bladder cancer model RT112 for which in vitro synergism was observed (see Figure 1). Treatment was initiated at a tumor size of 66 mm^3. RT112-tumor bearing mice were treated intravenously with 10 mg/kg (filled squares) of compound A (copanlisib) and with 2 different doses of compound B (rogaratinib, 24 mg/kg (closed

triangles) / 38 mg/kg (closed diamonds)) and in combination of compound A and compound B at the respective doses. The dosing schedule for compound A is depicted in Figure 5 with arrows. Figure 5 displays tumor growth as mean tumor volume over time and Figure 6 shows the tumor weight for the rogaratinib monotherapy and combination groups at the end of the experiment on day 31. Figure 7 shows the relative body weight. A maximal body weight loss of 2.8% and 4.6% was observed compared to starting body weight in both monotherapy and combination therapy with both 24 and 38 mg/kg of compound B, respectively. Individual treatment holidays were given based on body weight loss in some animals whenever loss was >10% of maximal body weight. A generalized dose reduction in compound B for the combination was introduced on treatment days 4 to 6 and 11 to 32, and for the monotherapy of compound B on days 11 to 32 due to body weight loss in the combination group. A two day treatment holiday for compound A was introduced due to body weight loss in the combination therapy with 38 mg/kg of compound B and 10 mg/kg of compound A.

At day 20, the timepoint for termination of the vehicle group, treatment of PI3K inhibitor compound A (copanlisib, 10mg/kg) was inactive with a T/C of 68% (Table 6). FGFR inhibitor compound B at 24mg/kg and 38mg/kg was active with T/C of 39 and 34%, respectively. Combination of compound A with either 24 mg/kg or 38 mg/kg compound B yielded a tumor growth inhibition with 39 and 25% T/C, respectively. Treatment was pursued for compound A at 24 and 38 mg/kg and the combination groups. Thirty one days after start of treatment the groups were stopped. The addition of compound A (10 mg/kg) to either 24 or 38 mg/kg of compound B led to a statistically significant decrease in tumor volume as compared to the respective monotherapy groups of compound B ($p<0.01$ for both comparisons). This result was confirmed on the tumor weights measured on the same day.

In conclusion, at termination of the respective treatment groups, rogaratinib showed single agent activity and the combination of copanlisib with rogaratinib led to significant treatment benefit for the two rogaratinib doses tested compared to the respective monotherapy.

Table 6: Efficacy of PI3K inhibitor compound A (copanlisib) and FGFR inhibitor compound B in RT112 xenograft tumor model

Treatment group	%T/C[a] volume day 20	Max. Body weight loss[b] (%)
Vehikel p.o. 2QD	100	0,0
COMPOUND B 24 mg/kg p.o. 2QD->QD	39	-2,8
COMPOUND B 38 mg/kg p.o. 2QD->QD	34	-4,6
COMPOUND A 10mg/kg i.v. 2on 5off	68	-0,3
COMPOUND B 24 mg/kg p.o. 2QD->QD, COMPOUND A 10 mg/kg i.v. 2on 5 off	39	-2,1
COMPOUND B 38 mg/kg p.o. 2QD->QD, COMPOUND A 10 mg/kg i.v. 2on 5off	25	-6,3

a) T/C= Treatment/ Control ratio, Calculated from mean tumor volume or final tumor weights at the time of termination of the vehicle t group (day 20).

b) Body Weight Loss: the maximum mean body weight loss expressed as a percent of the starting weight of the animal. Weight loss greater than 20% is considered toxic.

Example 2. Synergistic combination of PI3K inhibitor compound A (copanlisib) and FGFR inhibitor compound B (rogaratinib) in hepatocellular carcinoma models.

There is increasing evidence for the role of FGF signaling in hepatocellular carcinoma. In line with this increased FGFR expression is observed in a fraction of clinical and preclinical HCC samples (Table 1). The antiproliferative activity and effect on viability of compound A (Copanlisib) and FGFR inhibitor compound B was evaluated in combination and compared to the single agent activity in human HCC cell lines using the CellTiter-Glo® Luminescent Cell Viability Assay as described in the Materials and Methods section. Surprisingly, combining compound A (Copanlisib) and FGFR inhibitor compound B for treating HCC cells results in synergistic inhibition of proliferation and reduced viability compared to single agent treatment in cell lines with and without aberrations in the PI3K pathway as demonstrated in Figures 8-11. Data are summarized in Tables 7 and 8.

Table 7. Calculated combination indices at IC_{50} (CI_{50}) from proliferation analysis of hepatocellular carcinoma cell lines treated with combinations of compound A (Copanlisib) and FGFR inhibitor compound B. In case of synergism lowest CI50 along with corresponding compound concentrations is presented.

Cell Line	$IC_{50, mono}$ [M] compound A	$IC_{50, mono}$ [M] compound B	Combination (proliferation) A [M] plus B [M]		CI_{50}
Hep3B	1.5E-07	5.3E-08	6.1E-08	1.5E-08	0.68
HUH7	2.1E-07	1.4E-07	8.9E-08	2.2E-08	0.57
SNU387	1.7E-08	7.1E-07	4.8E-09	4.3E-08	0.34
SNU449	8.9E-08	1.9E-05	4.5E-08	4.0E-07	0.50

Table 8. Calculated combination indices at IC_{50} (CI_{50}) from viability analysis of hepatocellular carcinoma cell lines treated with combinations of compound A (Copanlisib) and FGFR inhibitor compound B. In case of synergism lowest CI50 along with corresponding compound concentrations is presented.

Cell Line	$IC_{50, mono}$ [M] compound A	$IC_{50, mono}$ [M] compound B	Combination (viability) A [M] plus B [M]		CI_{50}
Hep3B	4.1E-07	1.3E-07	8.6E-08	3.7E-08	0.49
Huh7	4.9E-07	2.6E-07	8.3E-08	8.3E-08	0.49
SNU387	1.9E-07	7.2E-06	4.1E-08	9.6E-08	0.22
SNU449	1.8E-07	2.4E-05	7.8E-08	7.0E-07	0.45

Figure 8. Synergistic combination of PI3K inhibitor compound A (Copanlisib) with FGFR inhibitor compound B in Hep3B cells. The combination of PI3K inhibitor compound A (copanlisib) and FGFR inhibitor compound B was tested and compared to the single agent activity in Hep3B cells using the CellTiter-Glo® Luminescent Cell Viability Assay. Hep3B cells overexpress FGFR subtypes 1, 2 and 3 but no activating PIK3CA mutations are known. The combination treatment shows synergistic effects on proliferation and viability for all concentration combinations used.

Figure 9. Synergistic combination of PI3K inhibitor compound A (Copanlisib) with FGFR inhibitor compound B in HUH7 cells. The combination of PI3K inhibitor compound A (copanlisib) and FGFR inhibitor compound B was tested and compared to the single agent activity in HUH7 cells using the CellTiter-Glo® Luminescent Cell Viability Assay. HUH7 cells overexpress FGFR subtypes 3 and 4 but no activating PIK3CA mutations are known. The combination treatment shows synergistic effects on proliferation and viability for all concentration combinations used.

Figure 10. Synergistic combination of PI3K inhibitor compound A (Copanlisib) with FGFR inhibitor compound B in SNU387 cells. The combination of PI3K inhibitor compound A (copanlisib) and FGFR inhibitor compound B was tested and compared to the single agent activity in SNU387 cells using the CellTiter-Glo® Luminescent Cell Viability Assay. SNU387 cells overexpress FGFR1 but no activating PIK3CA mutations are known. The combination treatment shows synergistic effects on proliferation and viability for all concentration combinations used.

Figure 11. Synergistic combination of PI3K inhibitor compound A (Copanlisib) with FGFR inhibitor compound B in SNU449 cells. The combination of PI3K inhibitor compound A (copanlisib) and FGFR inhibitor compound B was tested and compared to the single agent activity in SNU449 cells using the CellTiter-Glo® Luminescent Cell Viability Assay. SNU449 cells overexpress FGFR1 and FGFR4 and harbor a PTEN mutation. The combination treatment shows synergistic effects on proliferation and viability for all concentration combinations used.

Example 3. Beneficial combination of PI3K inhibitor compound A (copanlisib) and FGFR inhibitor compound B (rogaratinib) observed in a mouse clinical trial setup using head and neck cancer models.

Head and neck squamous cell carcinoma (HNSCC) displays multiple ways of activation of FGFR signalling with FGFR1 mutations or amplification in about 35% of cases and shows

a correlation of FGFR mRNA levels to tumor progression. FGFR inhibition resulted therefore in strong anti-tumor efficacy in HNSCC xenograft models with high FGFR1-3 mRNA expression levels (6, 7). These tumorigenic FGFR1 aberrations lead to activation of FGFR1 and downstream signaling pathways including the PI3K/AKT pathway. The PI3K gene *PIK3CA* is frequently mutated in HNSCC and constitutes an attractive targetable oncogene in this indication (8).

The benefit of treating HNSCC models with compound A or compound B or a combination of both was tested in a set of 20 patient-derived HNSCC xenograft models on mice. All models have been selected to overexpress at least one FGFR subtype (FGFR1-4) and data for sensitivity towards standard-of care treatment with cetuximab as well as the mutational status for *PIK3CA* have been correlated. The respective data for two selected models are shown in Table 9. These two models showed sensitivity to compound B (rogaratinib) in monotherapy (HN9897, figure 12, table 10). The treatment effects could be further improved by combination of compound A and compound B in both models. Especially in the model HN10632, which is resistant to both monotherapies, there was a significant improvement on the tumor growth rate (Figure 13, table 11).

In summary, the combination of a PI3K inhibitor (compound A) and a FGFR inhibitor (compound B) showed benefit in inhibition of tumor growth in HNSCC PDX models irrespective of their sensitivity to cetuximab or mutational status for *PIK3CA*.

Table 9: FGFR expression in patient derived HNSCC models correlated to cetuximab sensitivity and *PIK3CA* mutational status

Model	**Gene expression (affymetrix data)**				**Cetuximab Resist.**	**PI3K mut**
	FGFR1	**FGFR2**	**FGFR3**	**FGFR4**		
HN10632	2,325	8.815	10.422	2.343	x	no
HN9897	2,325	7.348	10.143	2.343		no

Table 10: treatment effects in HNSCC PDX-model HN9897

Treatment	**Doubling time (days)**	**Rel Growth rate**	**P value**
Vehicle	12.22	1	-

Compound A (10 mg/kg, 2on5off; i.v.)	11.54	1.059	n.s.
Compound B (38 mg/kg, BID, p.o.)	72.57	0.168	n.s.
Compound A (10 mg/kg, 2on5off; i.v.) + Compound B (38 mg/kg, BID, p.o.)	-40.14	-0.304	<0.0001 to vehicle <0.0001 to compound A n.s. to compound B

Table 11: treatment effects in HNSCC PDX-model HN10632

Treatment	**Doubling time (days)**	**Rel Growth rate**	**P value**
Vehicle	11.46	1	-
Compound A (10 mg/kg, 2on5off; i.v.)	13.26	1.009	n.s.
Compound B (38 mg/kg, BID, p.o.)	11.36	0.864	n.s.
Compound A (10 mg/kg, 2on5off; i.v.) + Compound B (38 mg/kg, BID, p.o.)	-22.18	-0.517	0.0132 to vehicle 0.0017 to compound A 0.0433 to compound B

Figure 12. In vivo combination of PI3K inhibitor compound A (Copanlisib) with FGFR inhibitor compound B in a patient-derived HNSCC xenograft model. The combination of PI3K inhibitor compound A (copanlisib) and FGFR inhibitor compound B was tested and compared to the single agent activity in HN9897 model xenografted into the left flank of female NMRI nu/nu mice, with one mouse per group. Mice were treated with either control vehicle, compound A (copanlisib) at 10 mg/kg i.v. 2days-on/5days-off, compound B (rogaratinib) at 38 mg/kg BID or combination of both compound A and compound B. Tumor growth rate was calculated and used for comparing treatment efficacy. HN9897 showed no effect of compound A on tumor growth whereas compound B showed inhibition of growth. The combination of the two compounds showed a tendency for increased anti-tumor efficacy.

Figure 13. In vivo combination of PI3K inhibitor compound A (Copanlisib) with FGFR inhibitor compound B in a patient-derived HNSCC xenograft model. The combination of PI3K inhibitor compound A (copanlisib) and FGFR inhibitor compound B was tested and compared to the single agent activity in HN10632 model xenografted into the left flank of female NMRI nu/nu mice, with one mouse per group. Mice were treated with either control vehicle, compound A (copanlisib) at 10 mg/kg i.v. 2days-on/5days-off, compound B (rogaratinib) at 38 mg/kg BID or combination of both compound A and compound B. Tumor growth rate was calculated and used for comparing treatment efficacy. HN10632 showed no effect of compound A or compound B on tumor growth whereas the combination significantly improved inhibition of tumor growth compared to vehicle and monotherapies.

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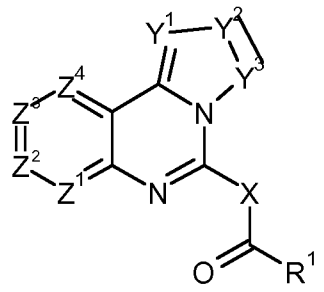
CLAIMS

1. A combination of :

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



(A1)

wherein

X represents CR^5R^6 or NH;

Y^1 represents CR^3 or N;

Chemical bond between Y^2------Y^3 represents a single bond or double bond,

with the proviso that when theY^2------Y^3 represents a double bond,

Y^2 and Y^3 independently represent CR^4 or N, and

when Y^2------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;

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,

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, 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 R^{11}

wherein

R^{11} represents

halogen, nitro, hydroxy, cyano, carboxy, amino, N-(C_{1-6}alkyl)amino, N-(hydroxyC_{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-(carboxyC_{1-6}alkyl)-N-(C_{1-6}alkyl)amino, N-(C_{1-6}alkoxycabonyl)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,

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},

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,

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}

wherein

R^{101} represents

halogen, carboxy, amino, N-(C_{1-6} alkyl)amino, N,N-di(C_{1-6}alkyl)amino, aminocarbonyl, N-(C_{1-6}alkyl)aminocarbonyl, N,N-di(C_{1-6}alkyl)aminocarbonyl, pyridyl,

C_{1-6} alkyl optionally substituted by cyano or mono- di- or tri- halogen,

or

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

R^2 represents hydroxy, halogen, nitro, cyano, amino, N-(C_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, N-(hydroxyC_{1-6}alkyl)amino, N-(hydroxyC_{1-6}alkyl)-N-(C_{1-6}alkyl)amino, C_{1-6} acyloxy, aminoC_{1-6} acyloxy, C_{2-6}alkenyl, aryl,

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

hydroxy, C_{1-6} alkyl, 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, N-(C_{1-6}alkyl)carbonylamino, phenyl, phenyl C_{1-6} alkyl, carboxy, C_{1-6}alkoxycarbonyl, aminocarbonyl, N-(C_{1-6}alkyl)aminocarbonyl, or N,N-di(C_{1-6}alkyl)amino,

-C(O)- R^{20}

wherein

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,

C_{1-6} alkyl optionally substituted by R^{21}

or

C_{1-6} alkoxy optionally substituted by R^{21}

wherein

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- (hydroxyC_{1-6} alkyl) amino, N-(halophenylC_{1-6} alkyl) amino, amino C_{2-6} alkylenyl, C_{1-6} alkoxy, hydroxyC_{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 and N optionally substituted by hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, hydroxyC_{1-6} alkoxy, oxo, amino, aminoC_{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,

wherein

R^{201} represents hydroxy, amino, N-(C_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, N- (halophenylC_{1-6} alkyl) amino, C_{1-6}alkyl, aminoC_{1-6} alkyl, aminoC_{2-6} alkylenyl, C_{1-6} 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, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, hydroxyC_{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 or benzyl;

R^3 represents hydrogen, halogen, aminocarbonyl, or C_{1-6} alkyl optionally substituted by aryl C_{1-6} alkoxy or mono-, di- or tri- halogen;

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

R^5 represents hydrogen or C_{1-6} alkyl; and

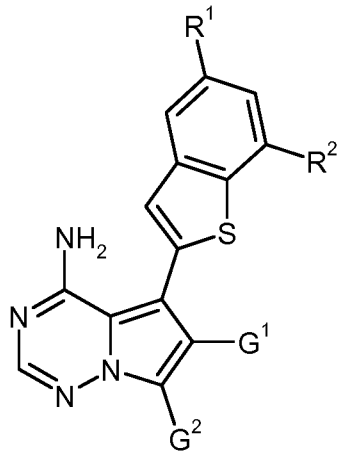
R^6 represents halogen, hydrogen or C_{1-6} alkyl ;

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 ;

and

component B : one or more substituted 5-(1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-4-amine compounds of general formula (B) :



(B),

wherein

R^1 is hydrogen, chloro, methyl or methoxy,

R^2 is hydrogen or methoxy,

with the proviso that at least one of R^1 and R^2 is other than hydrogen,

G^1 represents chloro, $(C_1\text{-}C_4)$-alkyl, $(C_1\text{-}C_4)$-alkoxycarbonyl, 5-membered aza-heteroaryl, or the group $-CH_2\text{-}OR^3$, $-CH_2\text{-}NR^4R^5$ or $-C(=O)\text{-}NR^4R^6$, wherein

R^3 is hydrogen, $(C_1\text{-}C_4)$-alkyl, $(C_3\text{-}C_6)$-cycloalkyl or phenyl,

(*i*) said $(C_1\text{-}C_4)$-alkyl is optionally substituted with hydroxy, $(C_1\text{-}C_4)$-alkoxy, hydroxycarbonyl, $(C_1\text{-}C_4)$-alkoxycarbonyl, amino, aminocarbonyl, mono-$(C_1\text{-}C_4)$-alkylaminocarbonyl, di-

(C_1-C_4)-alkylaminocarbonyl, (C_3-C_6)-cycloalkyl or up to three fluoro atoms,

and

(*ii*) said (C_3-C_6)-cycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy and amino,

and

(*iii*) said phenyl is optionally substituted with one or two substituents independently selected from the group consisting of fluoro, chloro, bromo, cyano, trifluoromethyl, trifluoromethoxy, (C_1-C_4)-alkyl and (C_1-C_4)-alkoxy,

R^4 is hydrogen or (C_1-C_4)-alkyl,

R^5 is hydrogen, (C_1-C_4)-alkyl, (C_1-C_4)-alkylcarbonyl, (C_3-C_6)-cycloalkyl or 4- to 6-membered heterocycloalkyl, wherein

(*i*) said (C_1-C_4)-alkyl is optionally substituted with hydroxy, (C_1-C_4)-alkoxy, hydroxycarbonyl, (C_1-C_4)-alkoxycarbonyl, aminocarbonyl, mono-(C_1-C_4)-alkylaminocarbonyl, di-(C_1-C_4)-alkylaminocarbonyl or (C_3-C_6)-cycloalkyl,

and

(*ii*) said (C_3-C_6)-cycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy and amino,

and

(*iii*) said 4- to 6-membered heterocycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy, oxo and amino,

R^6 is hydrogen, (C_1-C_4)-alkyl, (C_3-C_6)-cycloalkyl or 4- to 6-membered heterocycloalkyl, wherein

(*i*) said (C_1-C_4)-alkyl is optionally substituted with hydroxy, (C_1-C_4)-alkoxy, hydroxycarbonyl, (C_1-C_4)-alkoxycarbonyl, amino, aminocarbonyl, mono-(C_1-C_4)-alkylaminocarbonyl, di-(C_1-C_4)-alkylaminocarbonyl or (C_3-C_6)-cycloalkyl,

and

(*ii*) said (C_3-C_6)-cycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy and amino,

and

(*iii*) said 4- to 6-membered heterocycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy, oxo and amino,

or

R^4 and R^5, or R^4 and R^6, respectively, are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic,

saturated 4- to 7-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from N(R^7) and O, and which may be substituted on ring carbon atoms with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, oxo, hydroxy, amino and aminocarbonyl, and wherein

R^7 is hydrogen, (C_1-C_4)-alkyl, formyl or (C_1-C_4)-alkylcarbonyl,

and

G^2 represents chloro, cyano, (C_1-C_4)-alkyl, or the group -$CR^{8A}R^{8B}$-OH, -CH_2-NR^9R^{10}, -C(=O)-$NR^{11}R^{12}$ or -CH_2-OR^{15}, wherein

R^{8A} and R^{8B} are independently selected from the group consisting of hydrogen, (C_1-C_4)-alkyl, cyclopropyl and cyclobutyl,

R^9 is hydrogen or (C_1-C_4)-alkyl,

R^{10} is hydrogen, (C_1-C_4)-alkyl, (C_1-C_4)-alkylcarbonyl, (C_3-C_6)-cycloalkyl or 4- to 6-membered heterocycloalkyl, wherein

(*i*) said (C_1-C_4)-alkyl is optionally substituted with hydroxy, amino, aminocarbonyl, mono-(C_1-C_4)-alkylaminocarbonyl or di-(C_1-C_4)-alkylaminocarbonyl,

and

(*ii*) said (C_3-C_6)-cycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy and amino,

and

(*iii*) said 4- to 6-membered heterocycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy, oxo and amino,

R^{11} is hydrogen or (C_1-C_4)-alkyl,

R^{12} is hydrogen, (C_1-C_4)-alkyl, (C_3-C_6)-cycloalkyl or 4- to 6-membered heterocycloalkyl, wherein

(*i*) said (C_1-C_4)-alkyl is optionally substituted with hydroxy, amino, aminocarbonyl, mono-(C_1-C_4)-alkylaminocarbonyl or di-(C_1-C_4)-alkylaminocarbonyl,

and

(*ii*) said (C_3-C_6)-cycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy and amino,

and

(*iii*) said 4- to 6-membered heterocycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy, oxo and amino,

or

R^9 and R^{10}, or R^{11} and R^{12}, respectively, are joined and, taken together with the nitrogen atom to which they are attached, form a

monocyclic, saturated 4- to 7-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from $N(R^{13})$, O, S and $S(O)_2$, and which may be substituted on ring carbon atoms with up to three substituents independently selected from the group consisting of fluoro, $(C_1$-$C_4)$-alkyl, oxo, hydroxy, amino and aminocarbonyl, and wherein

R^{13} is hydrogen, $(C_1$-$C_4)$-alkyl, $(C_3$-$C_6)$-cycloalkyl, formyl or $(C_1$-$C_4)$-alkylcarbonyl,

and

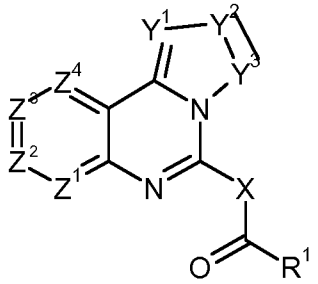
R^{15} is $(C_1$-$C_4)$-alkyl,

with the proviso that G^1 is not chloro when G^2 is chloro or cyano ;

for use in treating bladder cancer, head & neck cancer, particularly head & neck squamous cell carcinoma, or liver cancer.

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)

in which :

X represents CR^5R^6 or NH;

Y^1 represents CR^3 or N;

the chemical bond between Y^2-----Y^3 represents a single bond or double bond,

with the proviso that when theY^2-----Y^3 represents a double bond, Y^2 and Y^3 independently represent CR^4 or N, and

when Y^2-----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;

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,

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,

wherein

R^{11} represents halogen, nitro, hydroxy, cyano, carboxy, amino, N-(C_{1-6}alkyl)amino, N-(hydroxyC_{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-(carboxyC_{1-6}alkyl)-N-(C_{1-6}alkyl)amino, N-(C_{1-6}alkoxycabonyl)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,

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},

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,

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}

wherein

R^{101} represents halogen, carboxy, amino, N-(C_{1-6} alkyl)amino, N,N-di(C_{1-6}alkyl)amino, aminocarbonyl, N-(C_{1-6}alkyl)aminocarbonyl, N,N-di(C_{1-6}alkyl)aminocarbonyl, pyridyl,

C_{1-6} alkyl optionally substituted by cyano or mono- di- or tri-halogen,

and

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

R^2 represents hydroxy, halogen, nitro, cyano, amino, N-(C_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, N-(hydroxyC_{1-6}alkyl)amino, N-(hydroxyC_{1-6}alkyl)-N-(C_{1-6}alkyl)amino, C_{1-6} acyloxy, aminoC_{1-6} acyloxy, C_{2-6}alkenyl, 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, C_{1-6} alkyl, 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, N-(C_{1-6}alkyl)carbonylamino, phenyl, phenyl C_{1-6} alkyl, carboxy, C_{1-6}alkoxycarbonyl, aminocarbonyl, N-(C_{1-6}alkyl)aminocarbonyl, or N,N-di(C_{1-6}alkyl)amino, -C(O)- R^{20}

wherein

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,

C_{1-6} alkyl optionally substituted by R^{21},

or

C_{1-6} alkoxy optionally substituted by R^{21},

wherein

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-(hydroxyC_{1-6} alkyl) amino, N- (halophenylC_{1-6} alkyl) amino, amino C_{2-6} alkylenyl, C_{1-6} alkoxy, hydroxyC_{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 and N , and optionally substituted by hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, hydroxyC_{1-6} alkoxy, oxo, amino, aminoC_{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,

wherein

R^{201} represents hydroxy, amino, N-(C_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, N- (halophenylC_{1-6} alkyl) amino, C_{1-6}alkyl, aminoC_{1-6} alkyl, aminoC_{2-6} alkylenyl, C_{1-6} 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, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, hydroxyC_{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 or benzyl;

R^3 represents hydrogen, halogen, aminocarbonyl, or C_{1-6} alkyl optionally substituted by aryl C_{1-6} alkoxy or mono-, di- or tri- halogen;

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

R^5 represents hydrogen or C_{1-6} alkyl; and

R^6 represents halogen, hydrogen or C_{1-6} 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.

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 ;
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.

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 :
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-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

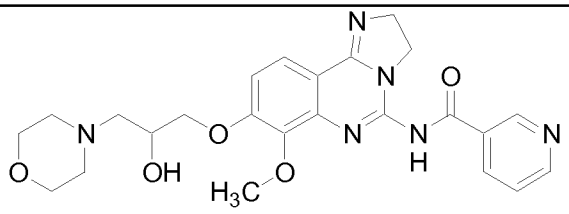
Example 11 : N-(8-{3-[2-(hydroxymethyl)morpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide

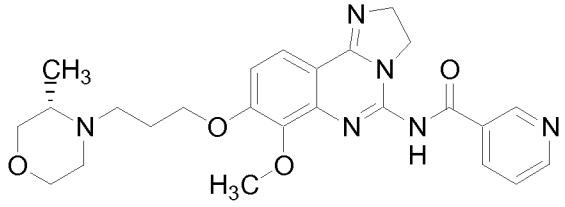
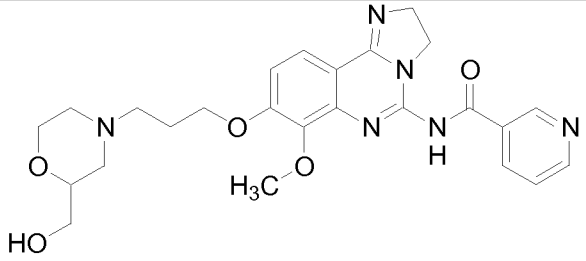
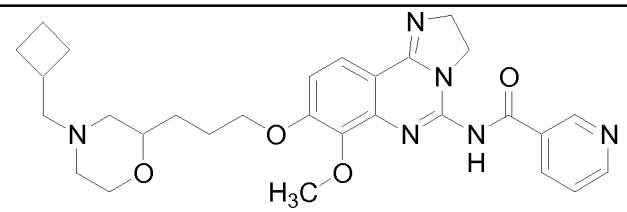
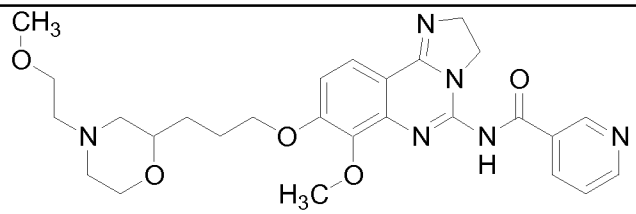
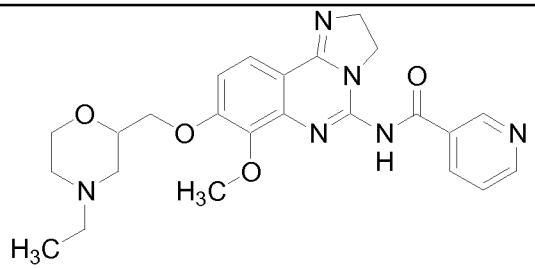
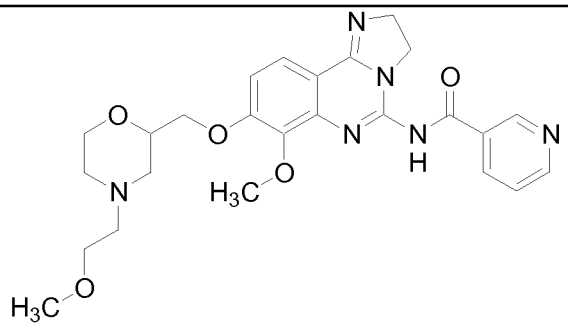
Example 12 : N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide 1-oxide

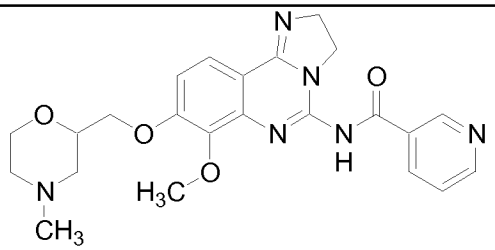
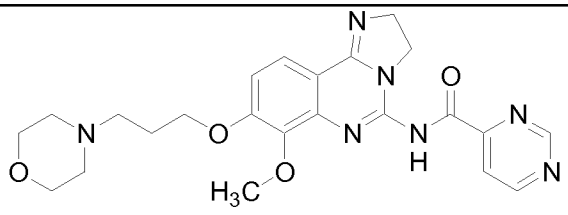
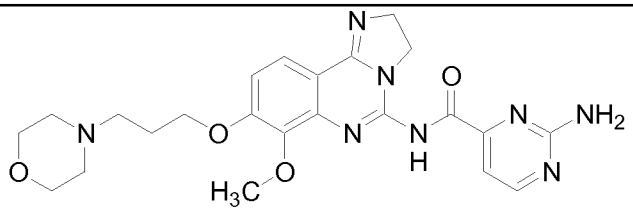
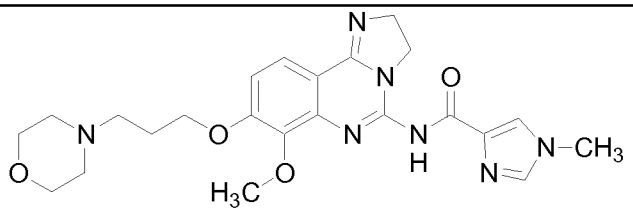
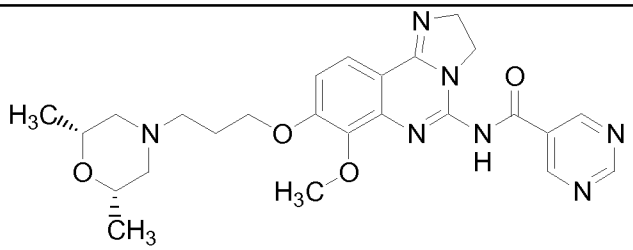
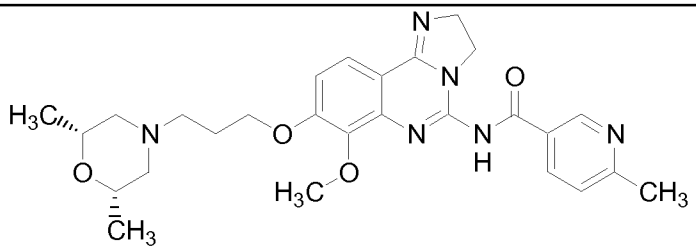
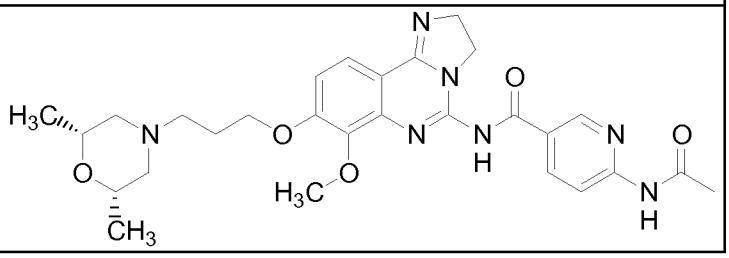
Example 13 : 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide.

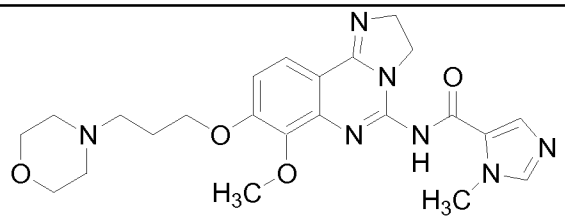
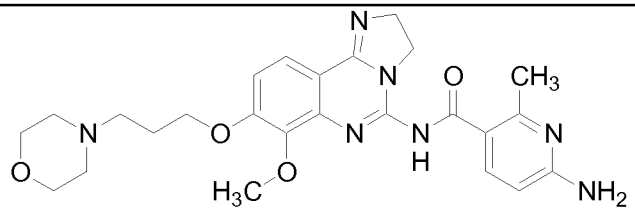
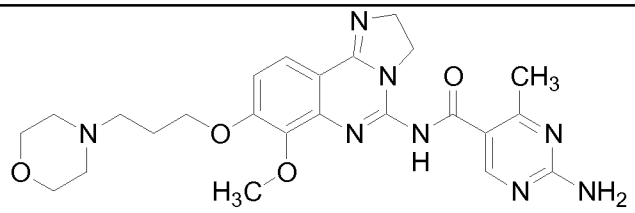
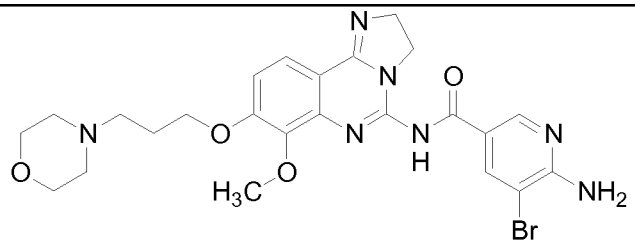
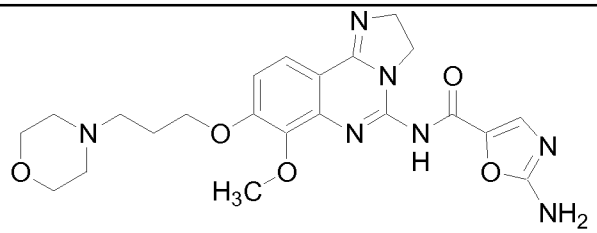
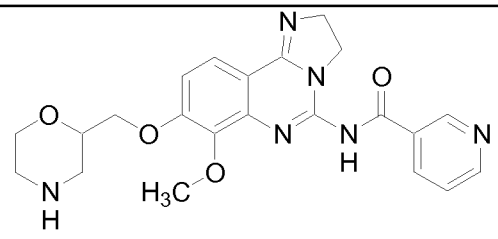
Example 14 : N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-(2-pyrrolidin-1-ylethyl)nicotinamide.

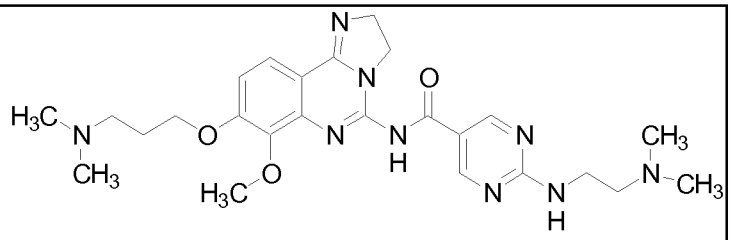
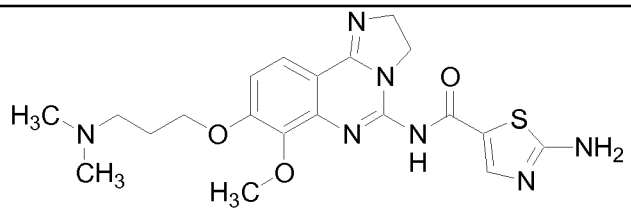
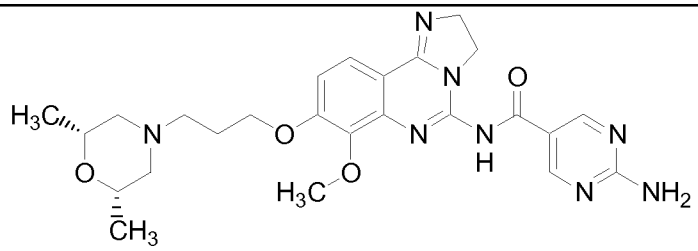
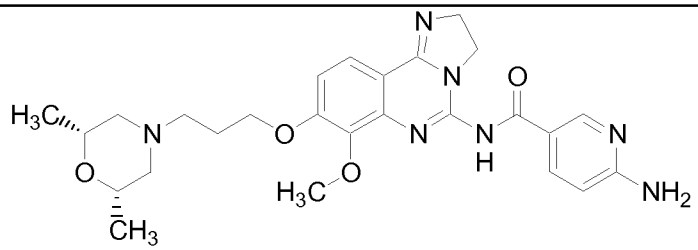
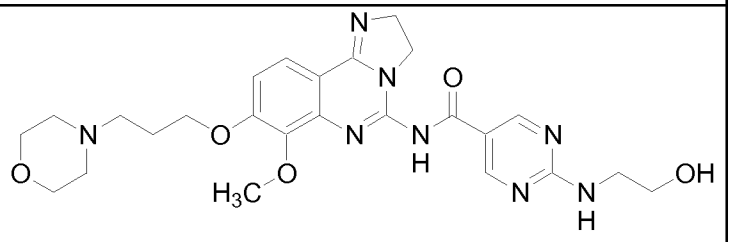
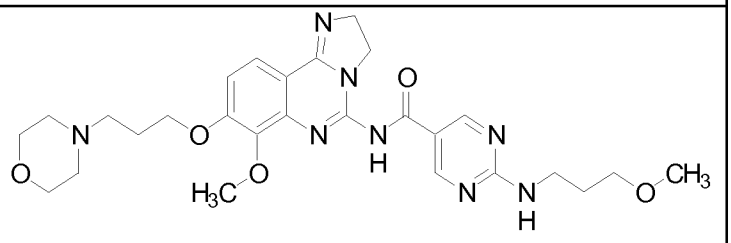
Example 15 : 6-(cyclopentylamino)-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide

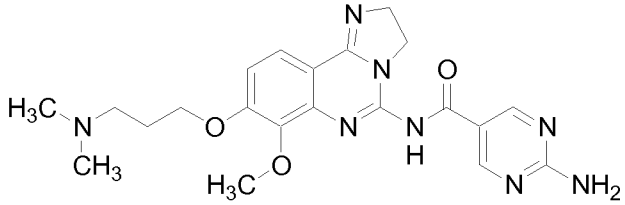
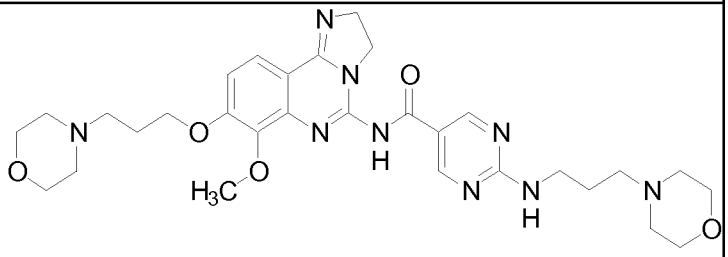
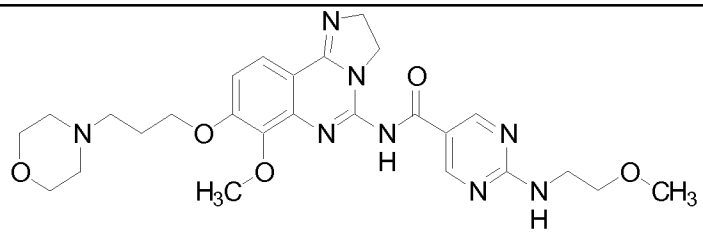
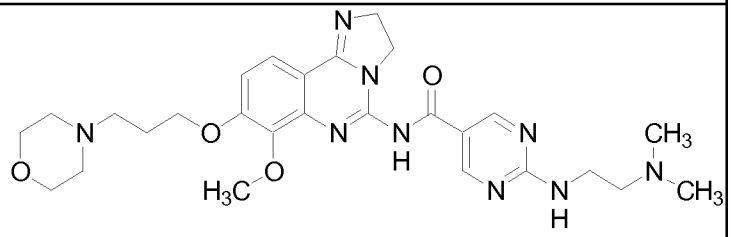
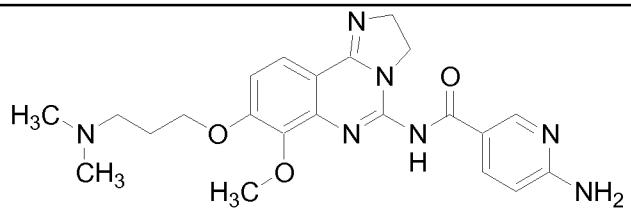
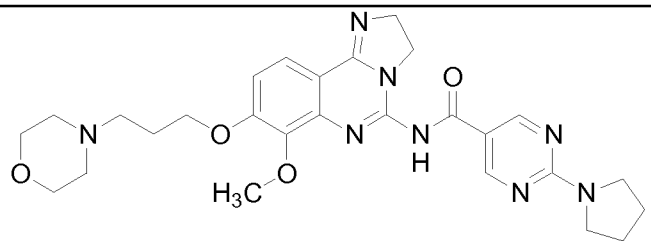
Example	Structure
16	

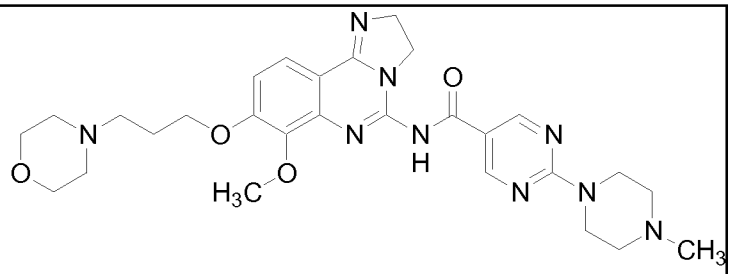
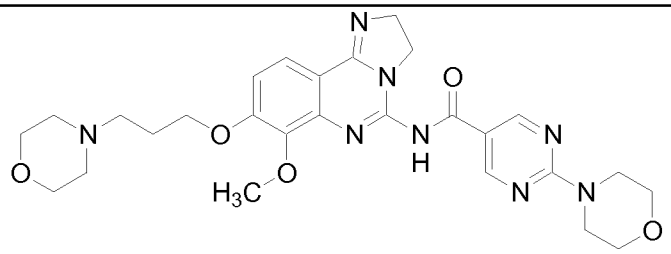
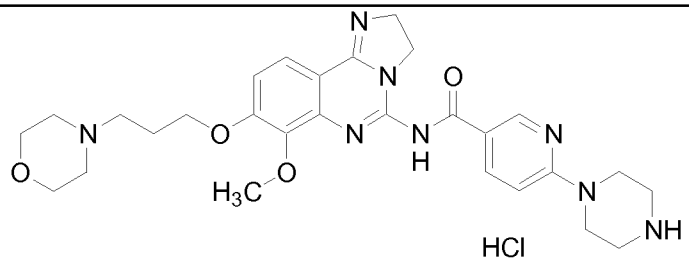
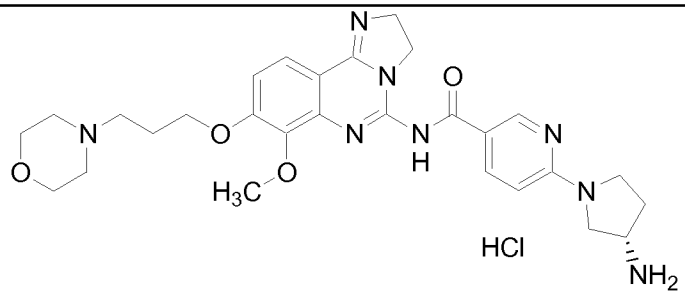
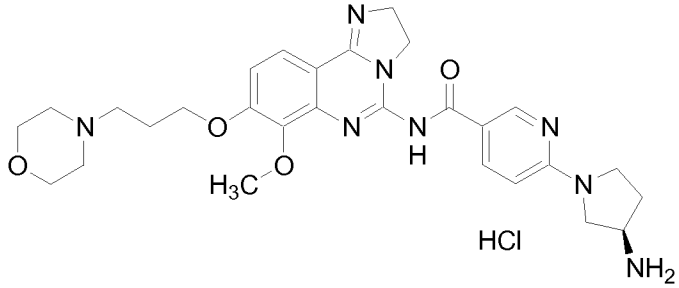
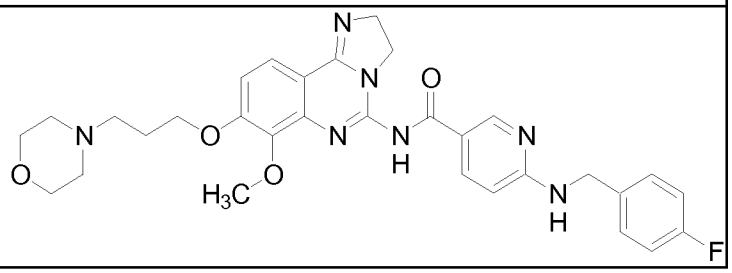
17	
18	
19	
20	
21	
22	

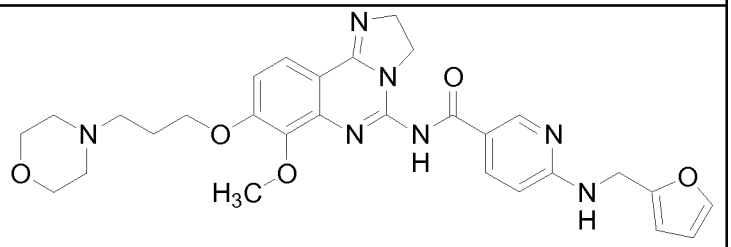
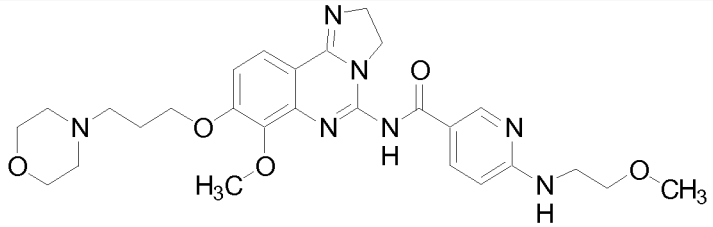
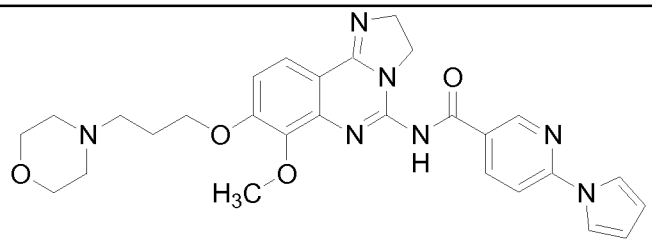
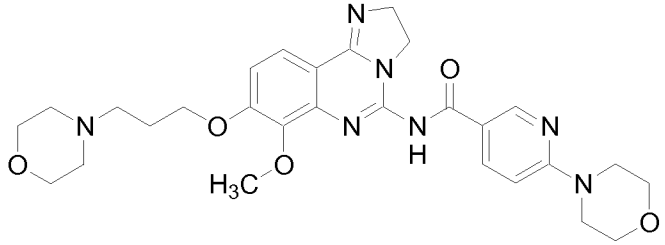
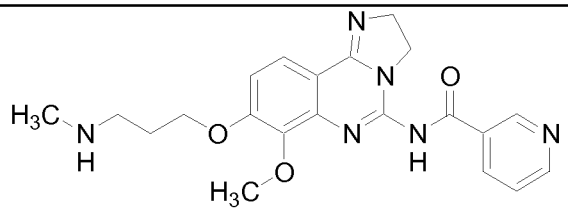
23	
24	
25	
26	
27	
28	
29	

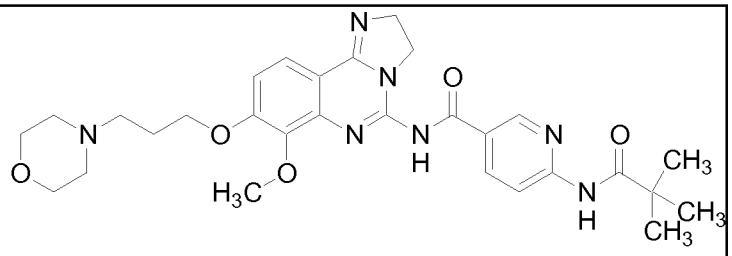
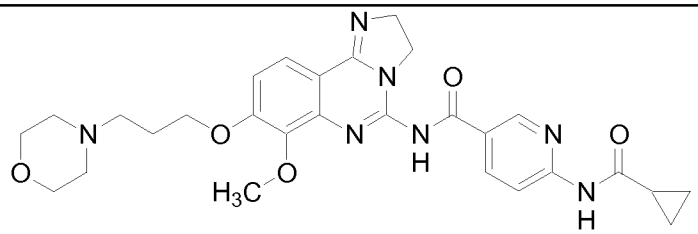
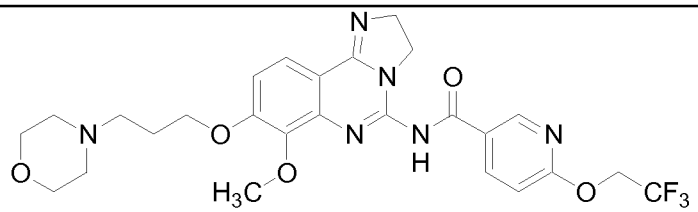
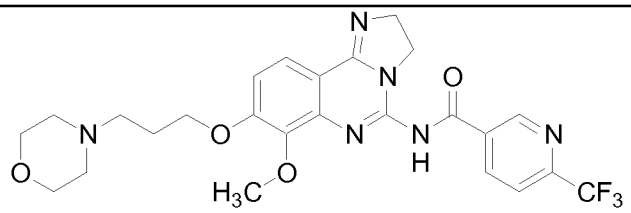
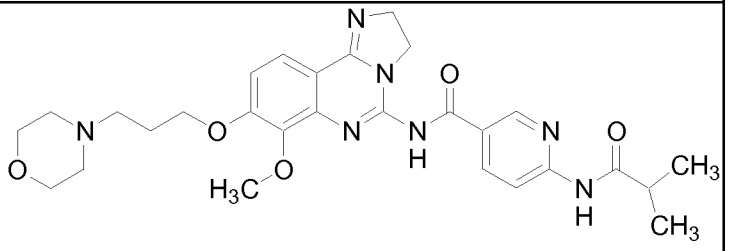
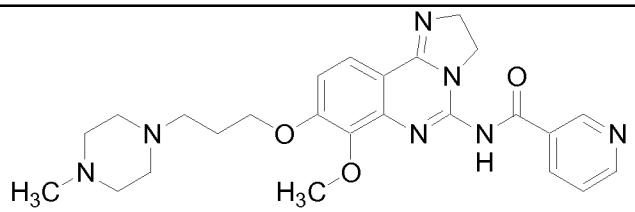
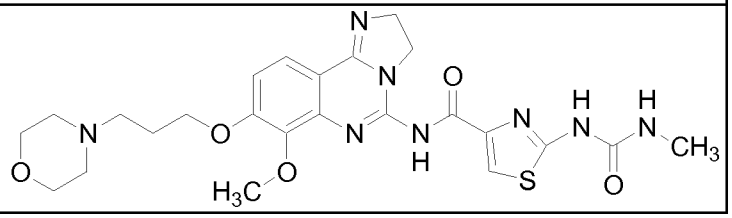
30	
31	
32	
33	
34	
35	

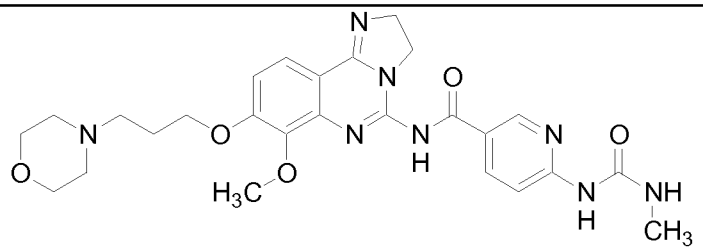
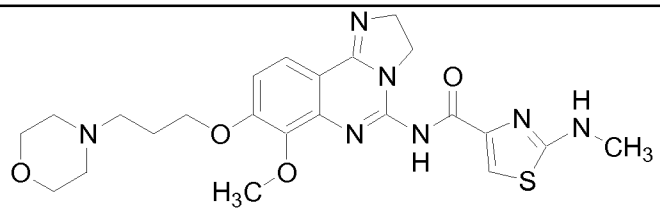
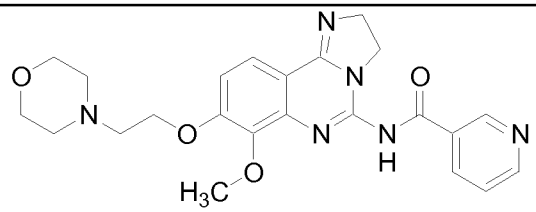
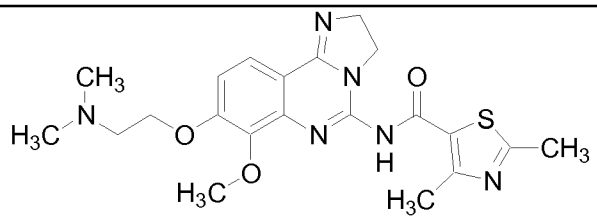
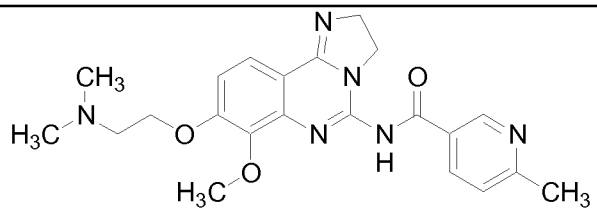
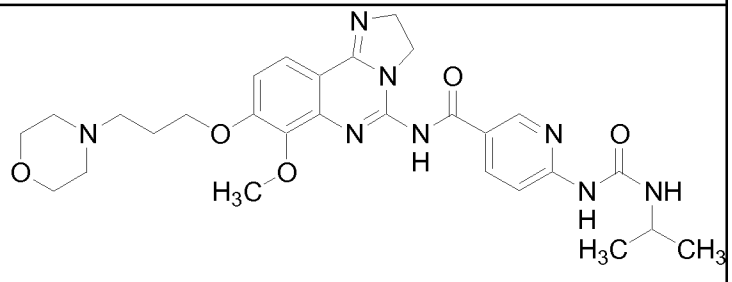
36	
37	
38	
39	
40	
41	

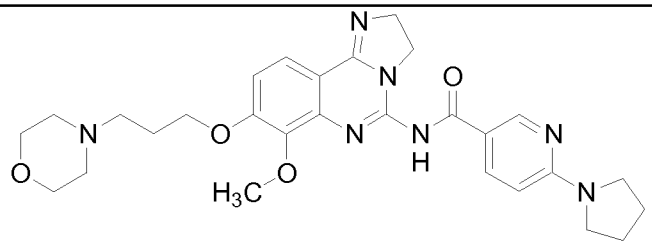
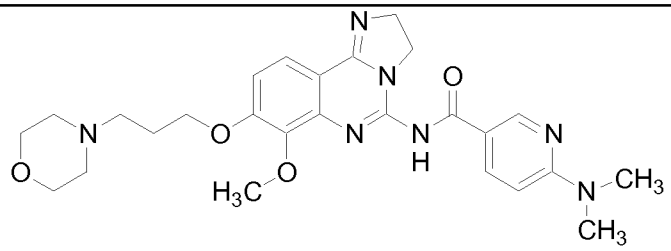
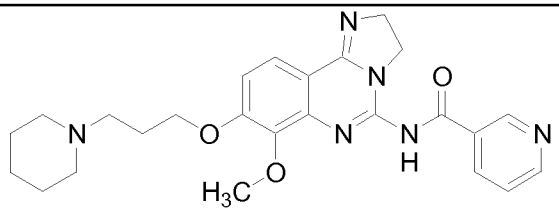
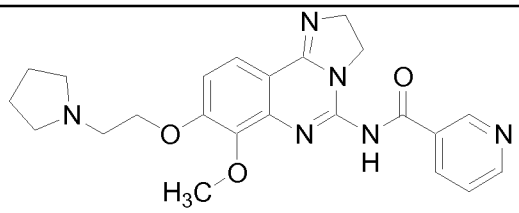
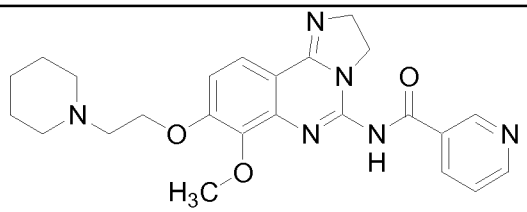
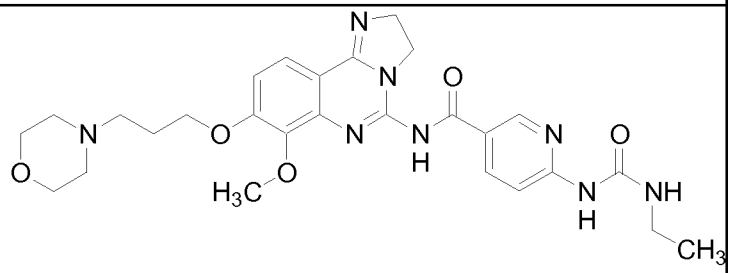
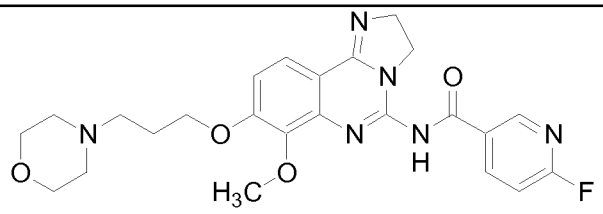
42	
43	
44	
45	
46	
47	

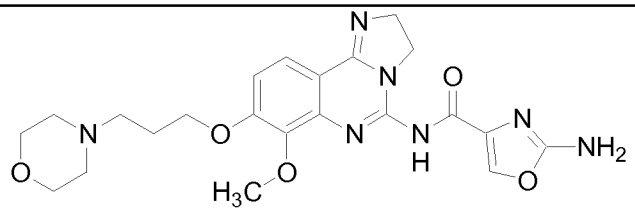
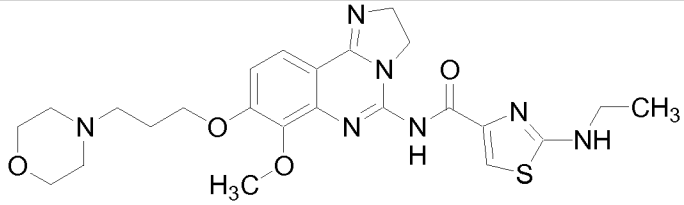
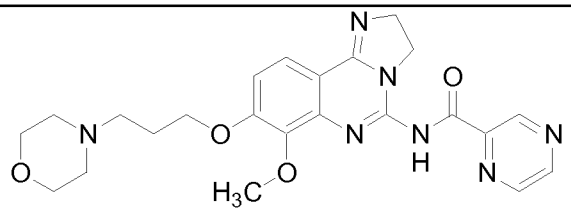
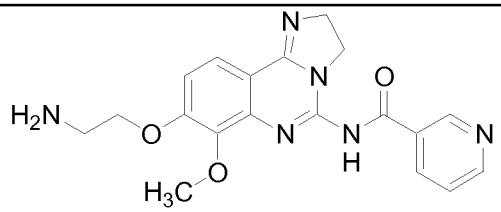
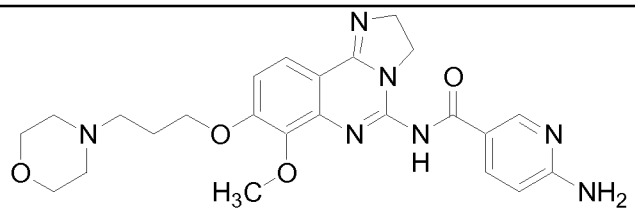
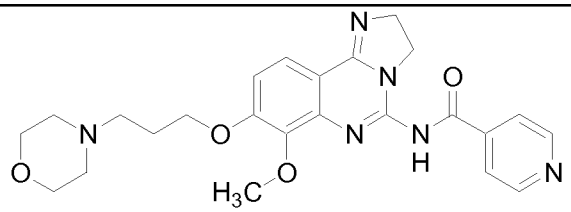
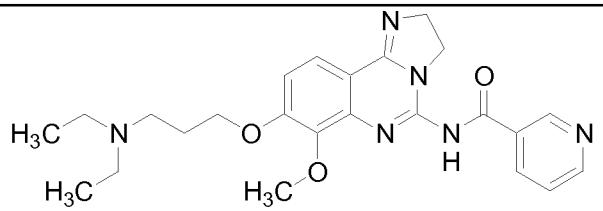
48	
49	
50	
51	
52	
53	

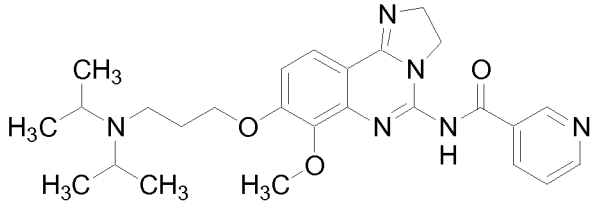
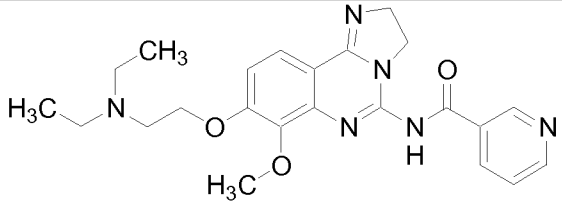
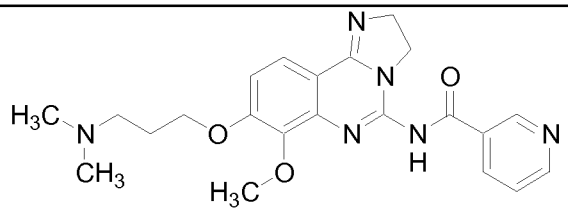
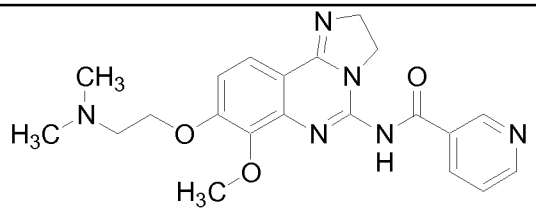
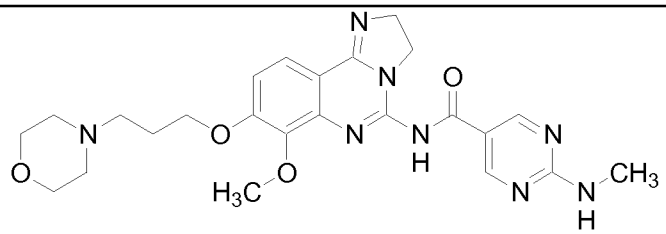
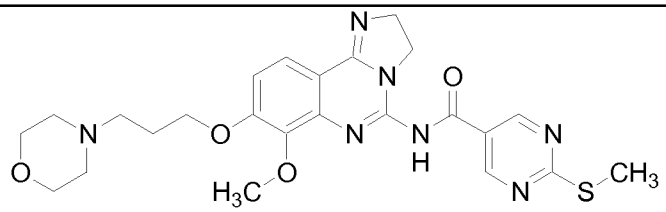
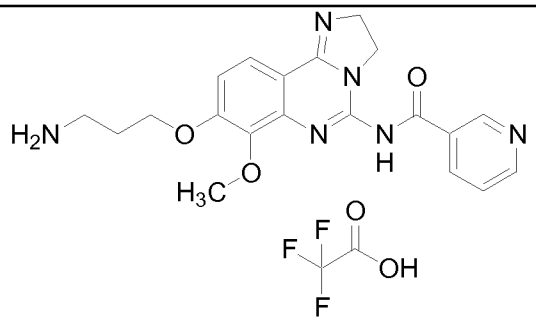
54	
55	
56	
57	
58	

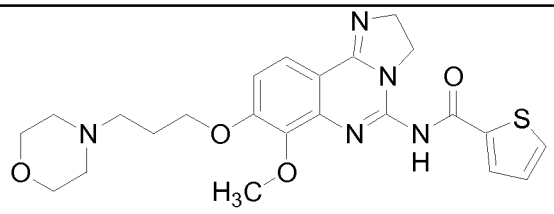
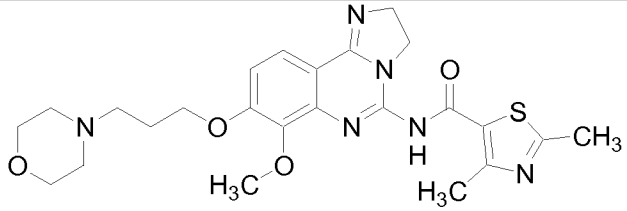
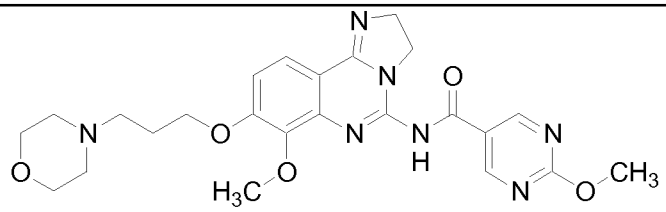
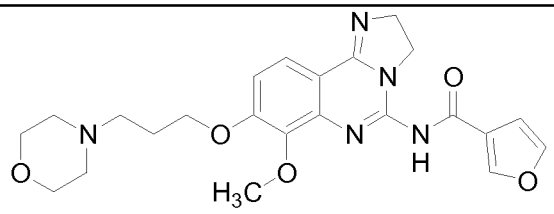
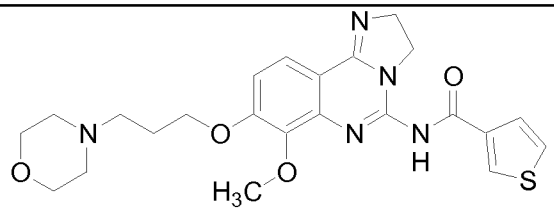
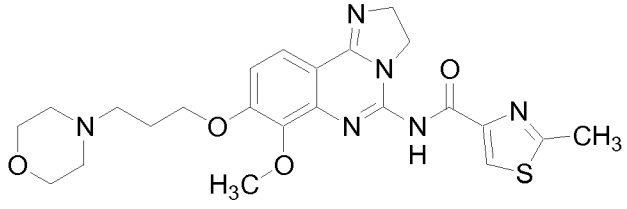
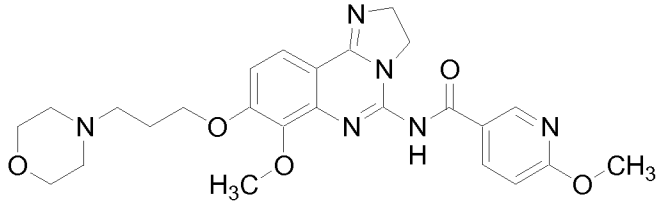
59	
60	
61	
62	
63	
64	
65	

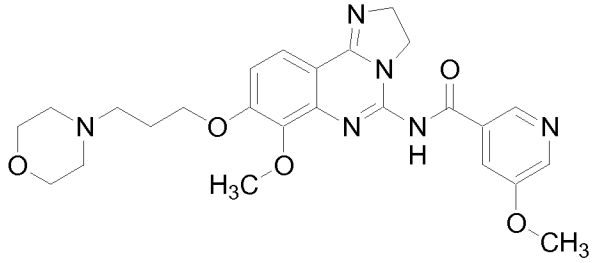
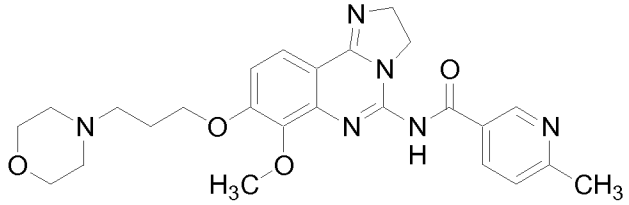
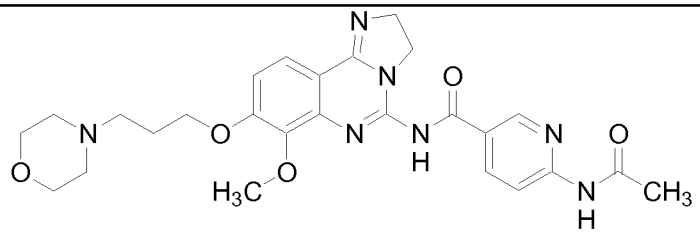
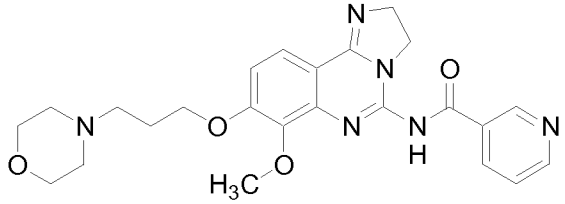
66	
67	
68	
69	
70	
71	

72	
73	
74	
75	
76	
77	
78	

79	
80	
81	
82	
83	
84	
85	

86	
87	
88	
89	
90	
91	
92	

93	
94	
95	
96	
97	
98	
99	

100	
101	
102	
103	

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.

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

said component B is one or more substituted 5-(1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-4-amine compounds of general formula (B) according to claim 1, which is selected from the list consisting of :

Example 1

4-{[4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-2-one

Example 2

4-{[4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-2-one dihydrochloride

Example 3

(*3R*)-3-({[4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}amino)pyrrolidin-2-one dihydrochloride

Example 4

(*3R*)-3-({[4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}amino)pyrrolidin-2-one

Example 5

4-{[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-2-one

Example 6

4-{[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo-[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-2-one dihydrochloride

Example 7

(*3R*)-3-({[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}amino)pyrrolidin-2-one dihydrochloride

Example 8

(*3R*)-3-({[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}amino)pyrrolidin-2-one

Example 9

N^2-{[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}glycinamide dihydrochloride

Example 10

6-(Ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine

Example 11

1-(4-{[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-1-yl)ethanone dihydrochloride

Example 12

[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methanol bis(formiate)

Example 13

4-{[4-Amino-6-(hydroxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-2-one

Example 14

7-{[(*3S*)-3-Amino-3-methylpyrrolidin-1-yl]methyl}-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride

Example 15

7-{[(*3S*)-3-Amino-3-methylpyrrolidin-1-yl]methyl}-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine

Example 16

1-(4-{[4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-1-yl)ethanone dihydrochloride

Example 17

6-(Methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine formiate

Example 18

6-(Ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine

Example 19

6-(Ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine dihydrochloride

Example 20

1-(4-{[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo-[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-1-yl)ethanone

Example 21

4-({4-Amino-6-[(2-hydroxyethoxy)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl}methyl)piperazin-2-one formiate

Example 22

2-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methoxy}ethanol dihydrochloride

Example 23

6-(Butoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine formiate

Example 24

5-(7-Methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)-6-(propoxy-methyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine bis(formiate)

Example 25

6-[(Cyclopropylmethoxy)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine bis(formiate)

Example 26

6-[(Cyclobutyloxy)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine

Example 27

6-(Isopropoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-yl-methyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine formiate

Example 28

6-[(2-Methoxyethoxy)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine formiate

Example 29

5-(7-Methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)-6-[(2,2,2-trifluoroethoxy)methyl]pyrrolo[2,1-f][1,2,4]triazin-4-amine formiate

Example 30

6-[(2-Aminoethoxy)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride

Example 31

Methyl {[4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-yl-methyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methoxy}acetate

Example 32

{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methoxy}acetic acid

Example 33

2-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methoxy}acetamide

Example 34

2-({7-[(4-Acetylpiperazin-1-yl)methyl]-4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl}methoxy)acetamide

Example 35

5-(7-Methoxy-5-methyl-1-benzothiophen-2-yl)-6-(phenoxymethyl)-7-(piperazin-1-yl-methyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine bis(formiate)

Example 36

5-(7-Methoxy-5-methyl-1-benzothiophen-2-yl)-6-[(methylamino)methyl]-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride

Example 37

6-[(Dimethylamino)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride

Example 38

6-[(Ethylamino)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride

Example 39

2-({[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}amino)ethanol trihydrochloride

Example 40

rac-1-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}piperidin-3-ol trihydrochloride

Example 41

1-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}piperidin-4-ol trihydrochloride

Example 42

rac-1-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}pyrrolidin-3-ol trihydrochloride

Example 43

6-[(Diethylamino)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride

Example 44

6-[(Cyclobutylamino)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride

Example 45

5-(7-Methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)-6-(pyrrolidin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride

Example 46

6-[(Cyclopropylamino)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride

Example 47

6-{[(Cyclopropylmethyl)amino]methyl}-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride

Example 48

N-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}glycine trihydrochloride

Example 49

4-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}piperazin-2-one trihydrochloride

Example 50

[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methanol

Example 51

(*3S*)-3-({[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}amino)pyrrolidin-2-one

Example 52

4-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}piperazin-2-one

Example 53

rac-1-({[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}amino)propan-2-ol

Example 54

1-({[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(morpholin-4-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}amino)-2-methylpropan-2-ol

Example 55

1-(4-{[4-Amino-6-(hydroxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-1-yl)ethanone

Example 56

(*3R*)-3-[({7-[(4-Acetylpiperazin-1-yl)methyl]-4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl}methyl)amino]pyrrolidin-2-one

Example 57

1-(4-{[4-Amino-6-{[(2-hydroxy-2-methylpropyl)amino]methyl}-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-1-yl)ethanone

Example 58

4-({4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-6-[(3-oxopiperazin-1-yl)-methyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}methyl)piperazine-1-carbaldehyde formiate

Example 59

4-({7-[(4-Acetylpiperazin-1-yl)methyl]-4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl}methyl)piperazin-2-one

Example 60

Methyl 4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylcarbonyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate bis(formiate)

Example 61

5-(7-Methoxy-5-methyl-1-benzothiophen-2-yl)-6-(1,3-oxazol-5-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride

Example 62

6-(Aminomethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride

Example 63

N-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}acetamide bis(trifluoroacetate)

Example 64

N-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}acetamide dihydrochloride

Example 65

N-({4-Amino-7-[(4-formylpiperazin-1-yl)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl}methyl)acetamide formiate

Example 66

N-({7-[(4-Acetylpiperazin-1-yl)methyl]-4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl}methyl)acetamide

Example 67

N-({4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-[(3-oxopiperazin-1-yl)methyl]pyrrolo[2,1-f][1,2,4]triazin-6-yl}methyl)acetamide

Example 68

4-Amino-6-(hydroxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazine-7-carbonitrile

Example 69

4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazine-7-carbonitrile

Example 70

4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazine-7-carbonitrile

Example 71

4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-6-[(3-oxopiperazin-1-yl)methyl]pyrrolo[2,1-f][1,2,4]triazine-7-carbonitrile

Example 72

N,N'-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazine-6,7-diyl]bis(methylene)}diacetamide

Example 73

2-[4-Amino-6-(hydroxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]propan-2-ol

Example 74

4-{[4-Amino-7-(2-hydroxypropan-2-yl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}piperazin-2-one

Example 75

[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-methylpyrrolo[2,1-f][1,2,4]triazin-6-yl]methanol

Example 76

4-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-methylpyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}piperazin-2-one

Example 77

1-({[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-methylpyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}amino)-2-methylpropan-2-ol formiate

Example 78

1-({[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-methylpyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}amino)-2-methylpropan-2-ol

Example 79

[4-Amino-7-chloro-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methanol

Example 80

4-{[4-Amino-7-chloro-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}piperazin-2-one

Example 81

1-({[4-Amino-7-chloro-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}amino)-2-methylpropan-2-ol formiate

Example 82

1-({[4-Amino-7-chloro-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}amino)-2-methylpropan-2-ol

Example 83

7-Chloro-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-4-amine

Example 84

5-(7-Methoxy-5-methyl-1-benzothiophen-2-yl)-6-methyl-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine formiate

Example 85

6-Chloro-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride

Example 86

[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methanol

Example 87

1-{[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}imidazolidin-2-one

Example 88

4-{[4-Amino-5-(7-methoxy-1-benzothiophen-2-yl)-6-(methoxymethyl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-2-one

Example 89

4-{[4-Amino-6-(methoxymethyl)-5-(5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-2-one

Example 90

1-[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]ethanol

Example 91

[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl](cyclopropyl)methanol

Example 92

(*3S*)-3-({[4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}amino)pyrrolidin-2-one

Example 93

(*3S*)-3-({[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}amino)pyrrolidin-2-one

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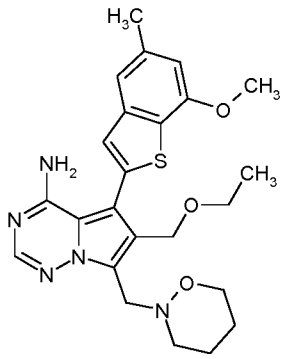
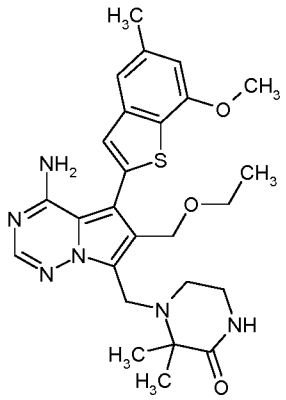
94	
95	

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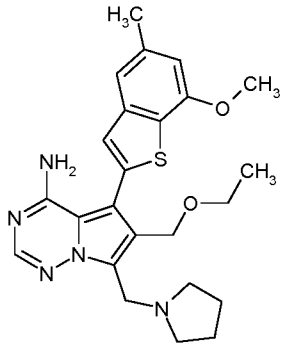
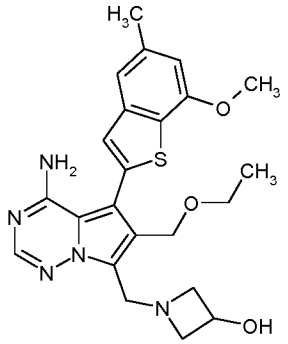
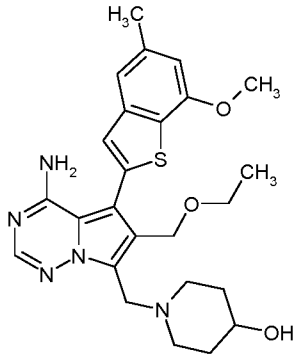
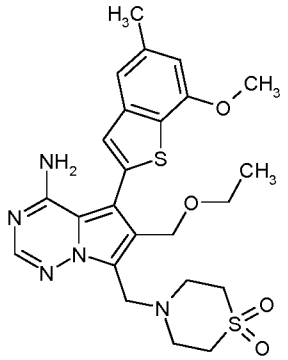
96	
97	
98	
99	

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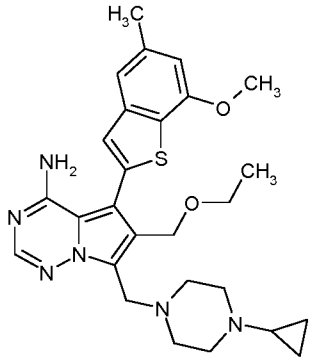
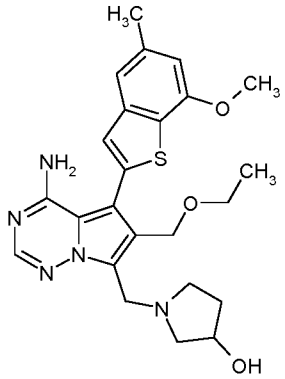
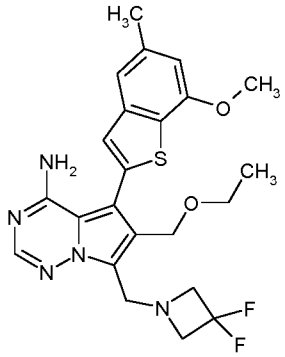
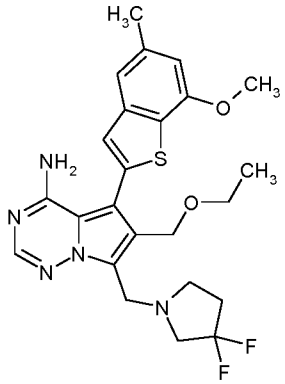
100	
101	
102	
103	

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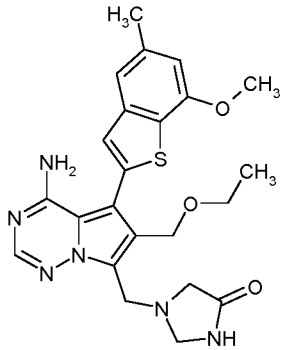
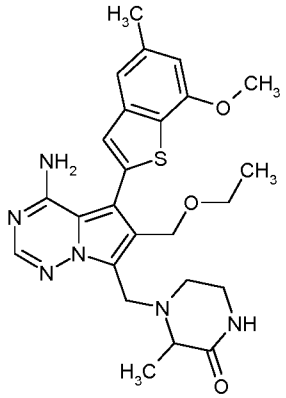
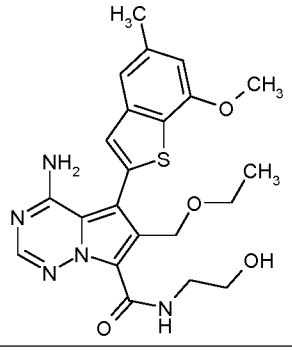
104	
105	

Example 106

4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-*N*-[(*3R*)-2-oxopyrrolidin-3-yl]pyrrolo[2,1-f][1,2,4]triazine-7-carboxamide

Example 107

4-{[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]carbonyl}piperazin-2-one

Example No.	Structure
108	

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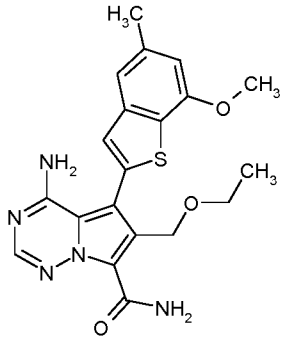
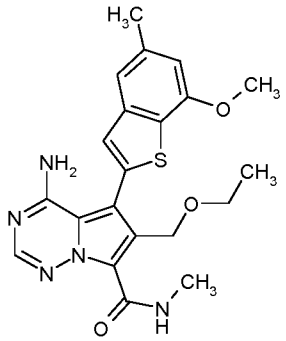
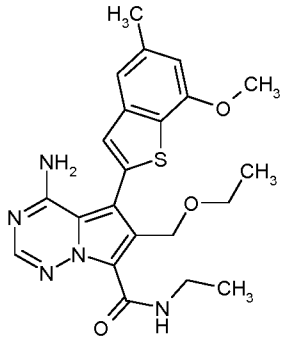
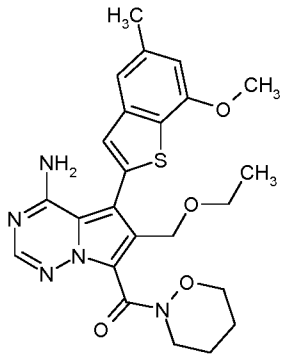
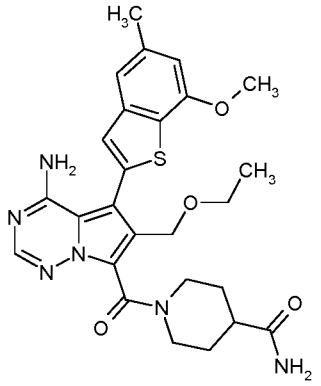
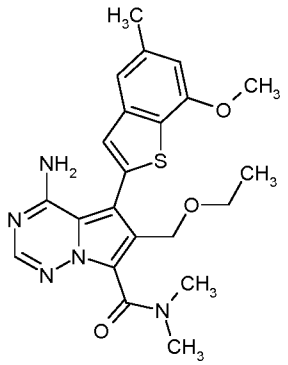
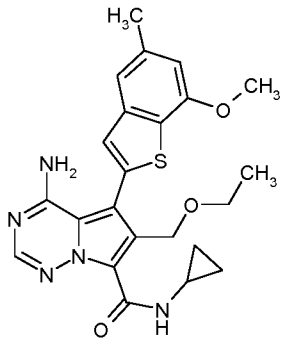
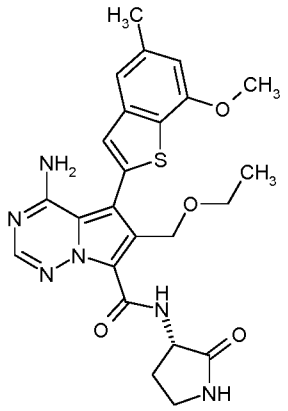
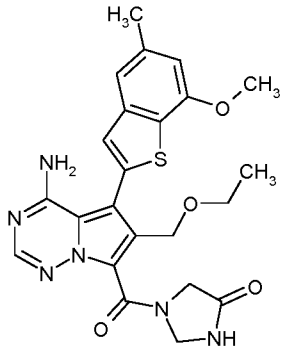
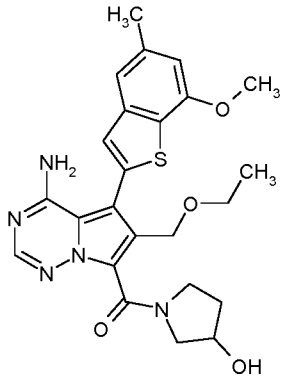
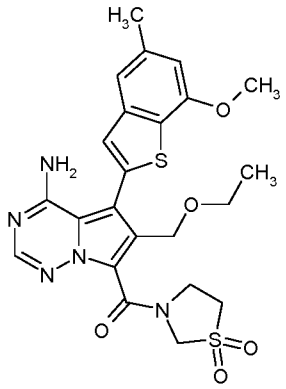
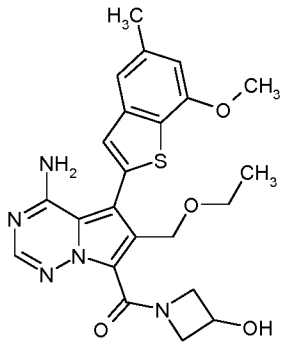
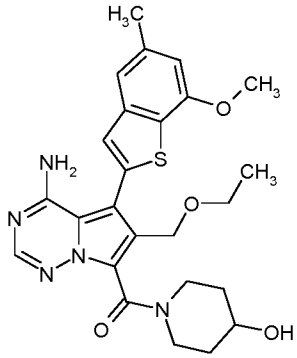
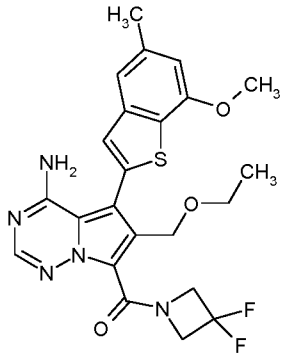
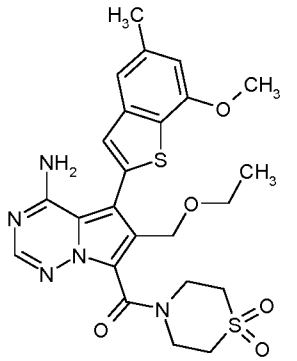
109	
110	
111	
112	

Example No.	Structure
113	
114	
115	
116	

Example No.	Structure
117	
118	
119	
120	

Example No.	Structure
121	
122	
123	

Example 124

4-{[4-Amino-5-(5,7-dimethoxy-1-benzothiophen-2-yl)-6-(methoxymethyl)pyrrolo[2,1-f]-[1,2,4]triazin-7-yl]methyl}piperazin-2-one

Example 125

4-{[4-Amino-7-(hydroxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}piperazin-2-one

Example 126

4-{[4-Amino-7-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}piperazin-2-one

Example 127

4-{[4-Amino-7-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}piperazin-2-one

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.

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

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

7. The combination according to any one of claims 1 to 6, wherein said component B is 4-{[4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-2-one.

8. The combination according to any one of claims 1 to 7, wherein said component A is 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide and said component B is 4-{[4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-2-one.

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

4-{[4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-2-one.

10. Use of a combination according to any one of claims 1 to 9 for the preparation of a medicament for the treatment or prophylaxis of bladder cancer, head & neck cancer, particularly head & neck squamous cell carcinoma, or liver cancer.

11. Use according to claim 10, wherein said cancer is bladder cancer.

12. Use according to claim 10, wherein said cancer is head & neck cancer, particularly head & neck squamous cell carcinoma.

13. Use according to claim 10, wherein said cancer is liver cancer.

14. A method of treatment or prophylaxis of bladder cancer, head & neck cancer, particularly head & neck squamous cell carcinoma, or liver cancer, in a subject, comprising administering to said subject a therapeutically effective amount of a combination accoring to any one of claims 1 to 9.

15. 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, hydrate or stereoisomer thereof, according to any one of claims 1 to 9 ;

component B : one or more substituted 5-(1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-4-amine compounds of general formula (B), or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, according to any one of claims 1 to 9 ;

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,

for use in treating bladder cancer, head & neck cancer, particularly head & neck squamous cell carcinoma, or liver cancer.

16. The kit according to claim 15, wherein said component A is 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide and said component B is 4-{[4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-2-one.

17. The kit according to claim 15, wherein said component A is 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide dihydrochloride and said component B is 4-{[4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-2-one.

Fig. 1/13

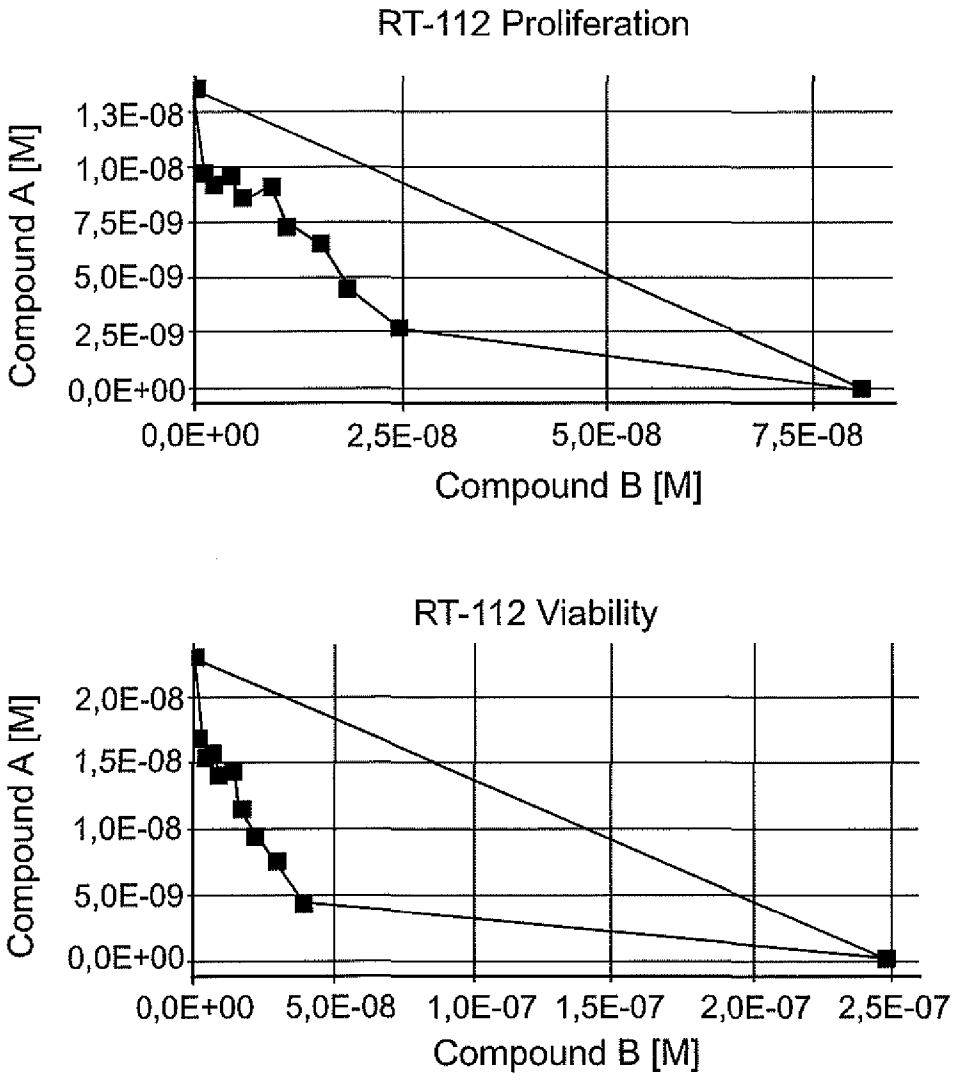

RT-112 Proliferation
Compound A [M]
1,3E-08
1,0E-08
7,5E-09
5,0E-09
2,5E-09
0,0E+00
0,0E+00
2,5E-08
5,0E-08
7,5E-08
Compound B [M]
RT-112 Viability
Compound A [M]
2,0E-08
1,5E-08
1,0E-08
5,0E-09
0,0E+00
0,0E+00
5,0E-08
1,0E-07
1,5E-07
2,0E-07
2,5E-07
Compound B [M]

Fig. 2/13

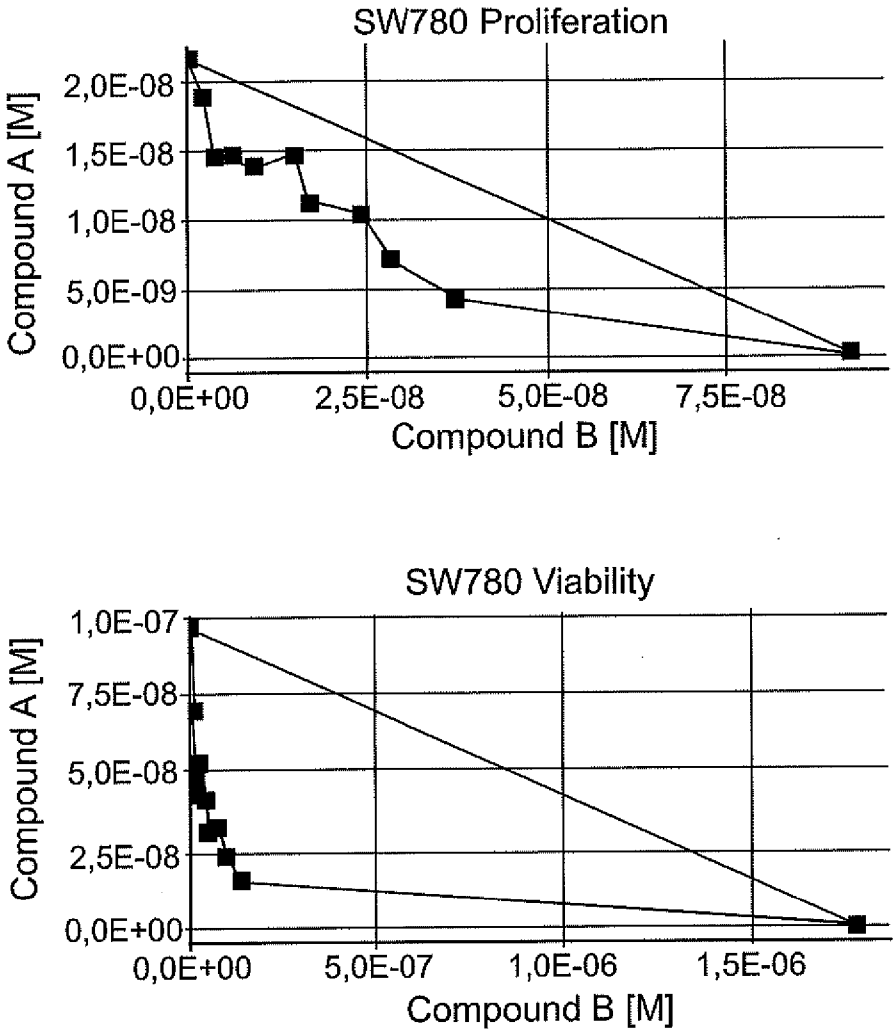
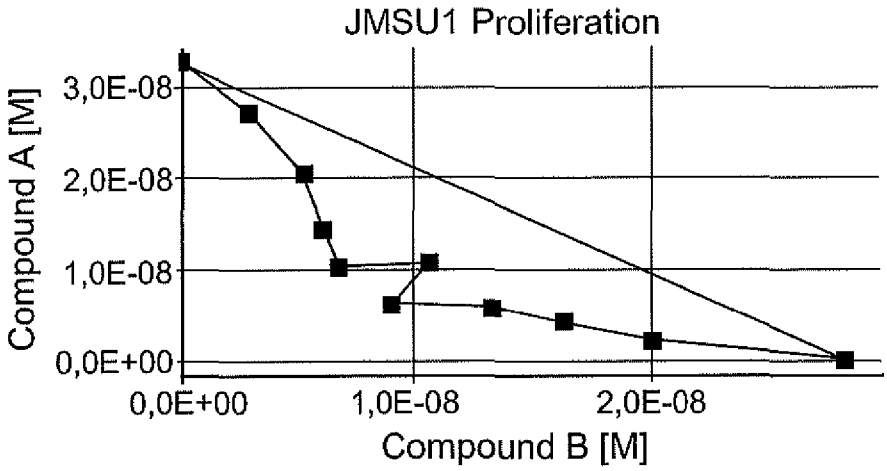

SW780 Proliferation
Compound A [M]
2,0E-08
1,5E-08
1,0E-08
5,0E-09
0,0E+00
0,0E+00
2,5E-08
5,0E-08
7,5E-08
Compound B [M]
SW780 Viability
Compound A [M]
1,0E-07
7,5E-08
5,0E-08
2,5E-08
0,0E+00
0,0E+00
5,0E-07
1,0E-06
1,5E-06
Compound B [M]

Fig. 3/13


JMSU1 Proliferation
Compound A [M]
3,0E-08
2,0E-08
1,0E-08
0,0E+00
0,0E+00
1,0E-08
2,0E-08
Compound B [M]

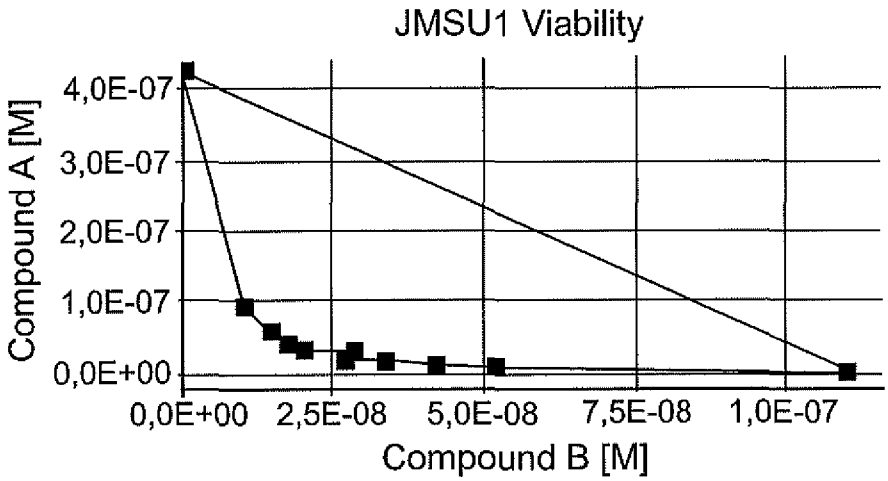

JMSU1 Viability
Compound A [M]
4,0E-07
3,0E-07
2,0E-07
1,0E-07
0,0E+00
0,0E+00
2,5E-08
5,0E-08
7,5E-08
1,0E-07
Compound B [M]

Fig. 4/13

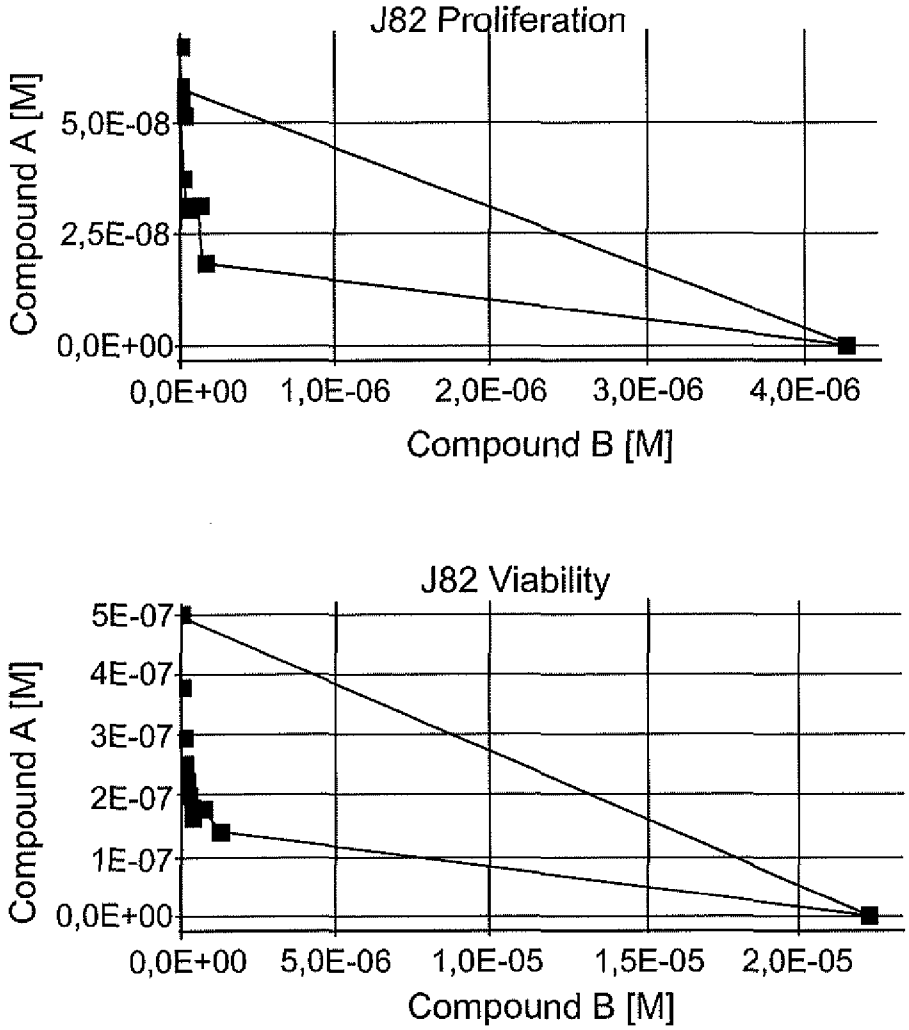

J82 Proliferation
Compound A [M]
5,0E-08
2,5E-08
0,0E+00
0,0E+00
1,0E-06
2,0E-06
3,0E-06
4,0E-06
Compound B [M]
J82 Viability
Compound A [M]
5E-07
4E-07
3E-07
2E-07
1E-07
0,0E+00
0,0E+00
5,0E-06
1,0E-05
1,5E-05
2,0E-05
Compound B [M]

Fig. 5/13

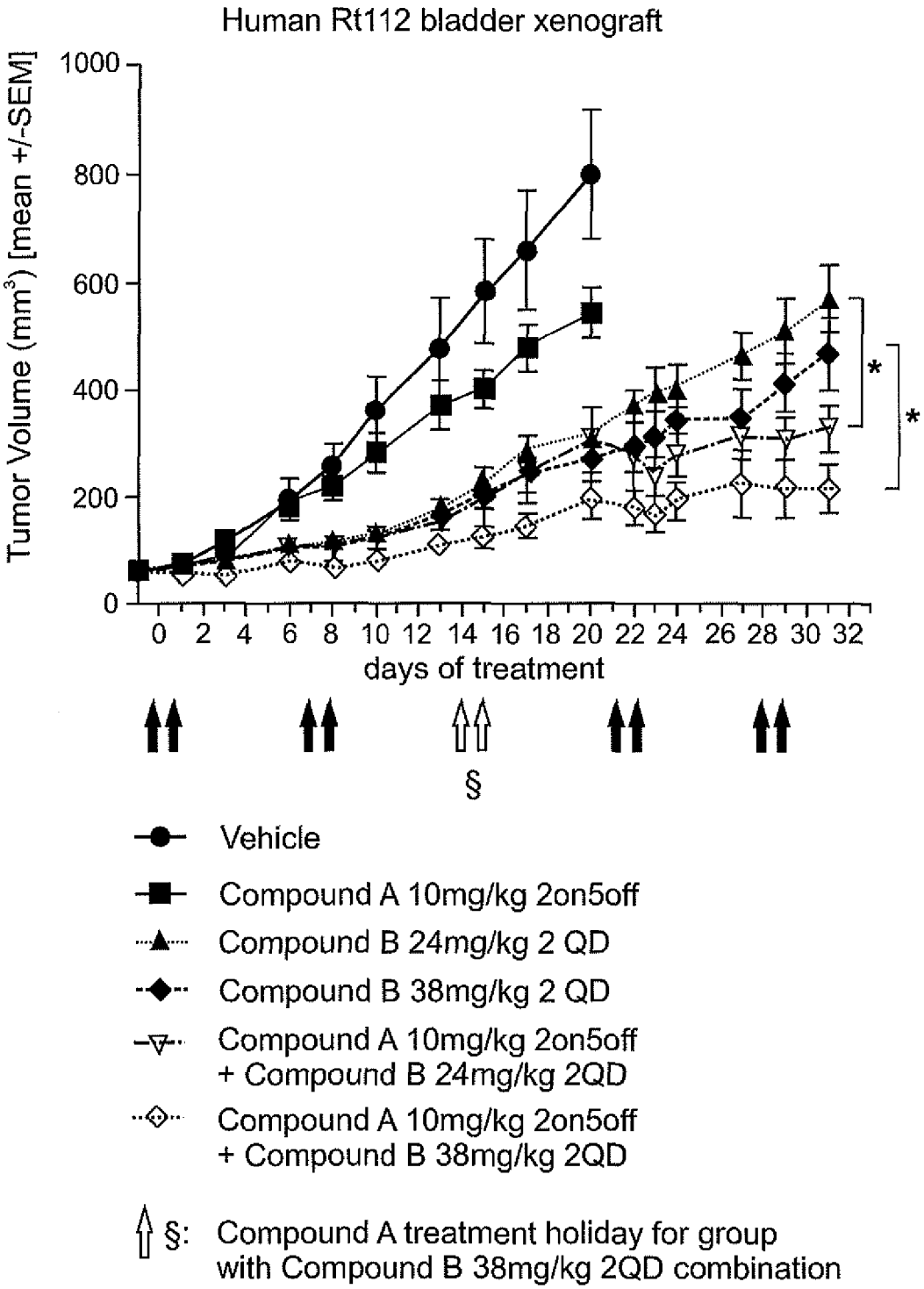

Human Rt112 bladder xenograft
Tumor Volume (mm3) [mean +/-SEM]
1000
800
600
400
200
0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32
days of treatment
*
*
§
Vehicle
Compound A 10mg/kg 2on5off
Compound B 24mg/kg 2 QD
Compound B 38mg/kg 2 QD
Compound A 10mg/kg 2on5off
+ Compound B 24mg/kg 2QD
Compound A 10mg/kg 2on5off
+ Compound B 38mg/kg 2QD
§: Compound A treatment holiday for group
with Compound B 38mg/kg 2QD combination

Fig. 6/13

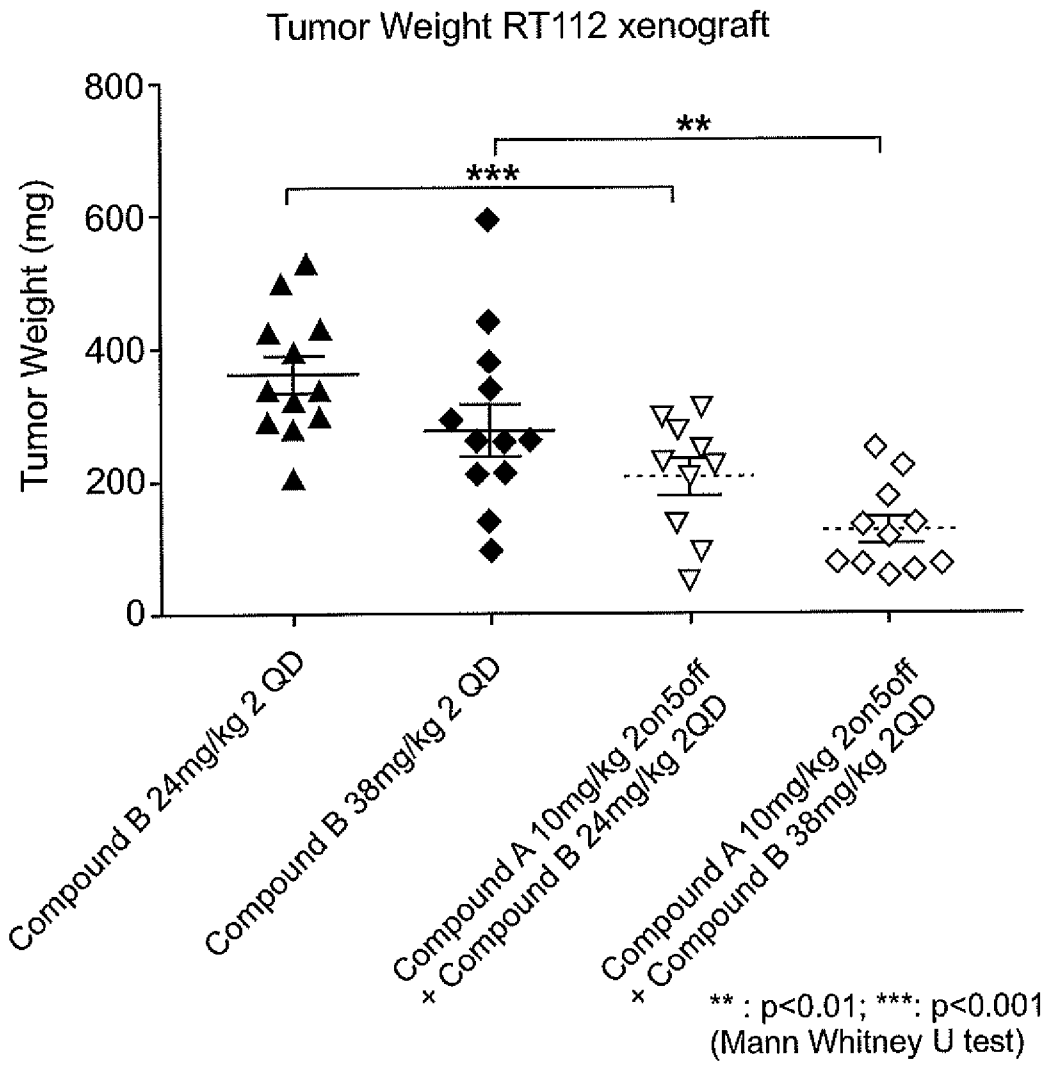

Tumor Weight RT112 xenograft
Tumor Weight (mg)
800
600
400
200
0
**
***
Compound B 24mg/kg 2 QD
Compound B 38mg/kg 2 QD
Compound A 10mg/kg 2on5off + Compound B 24mg/kg 2QD
Compound A 10mg/kg 2on5off + Compound B 38mg/kg 2QD
** : p<0.01; ***: p<0.001
(Mann Whitney U test)

Fig. 7/13

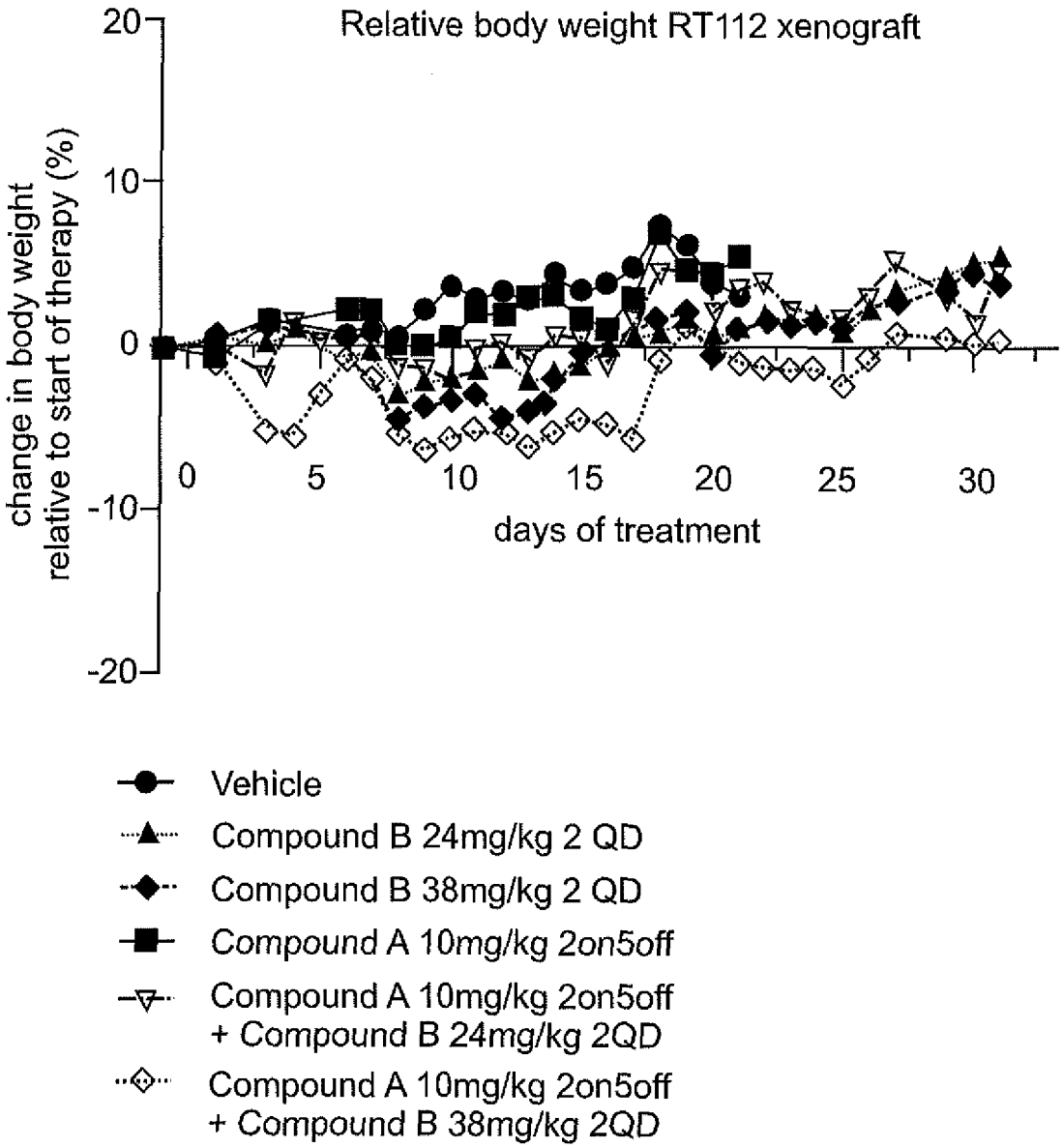
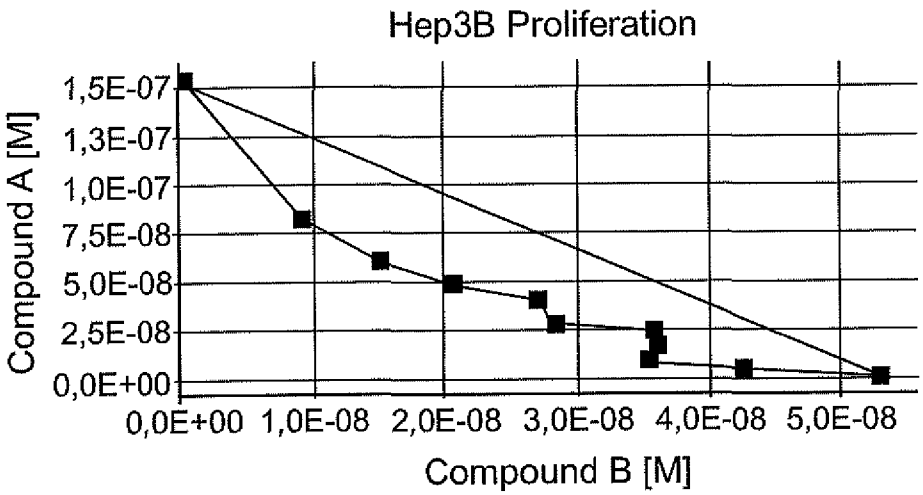

Relative body weight RT112 xenograft
change in body weight relative to start of therapy (%)
20
10
0
-10
-20
0
5
10
15
20
25
30
days of treatment
Vehicle
Compound B 24mg/kg 2 QD
Compound B 38mg/kg 2 QD
Compound A 10mg/kg 2on5off
Compound A 10mg/kg 2on5off + Compound B 24mg/kg 2QD
Compound A 10mg/kg 2on5off + Compound B 38mg/kg 2QD

Fig. 8/13


Hep3B Proliferation
Compound A [M]
1,5E-07
1,3E-07
1,0E-07
7,5E-08
5,0E-08
2,5E-08
0,0E+00
0,0E+00 1,0E-08 2,0E-08 3,0E-08 4,0E-08 5,0E-08
Compound B [M]

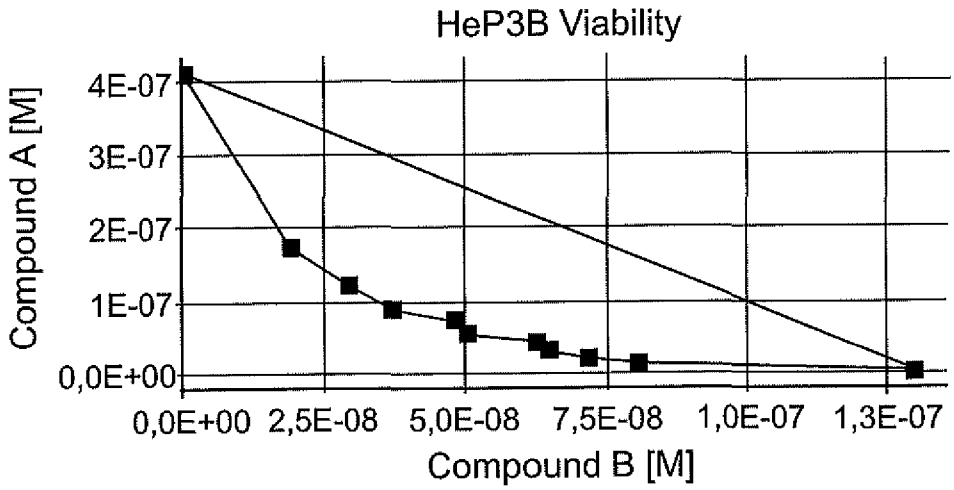
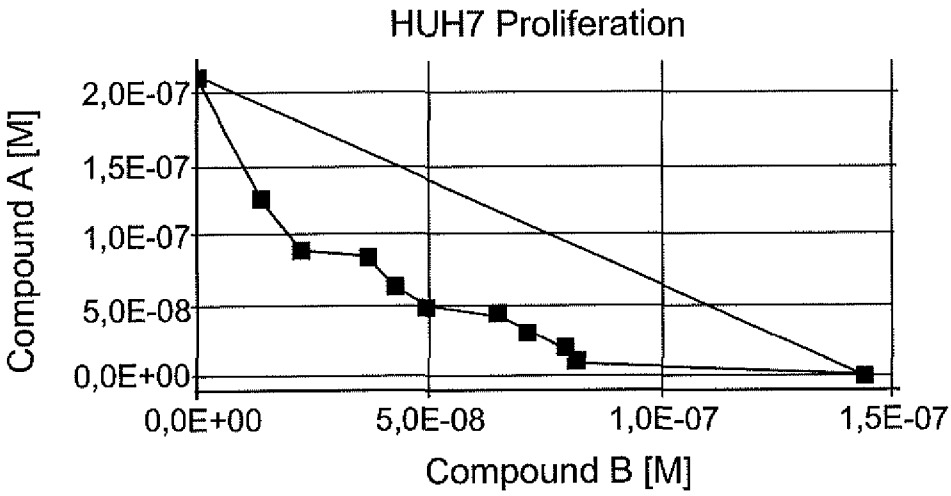

HeP3B Viability
Compound A [M]
4E-07
3E-07
2E-07
1E-07
0,0E+00
0,0E+00 2,5E-08 5,0E-08 7,5E-08 1,0E-07 1,3E-07
Compound B [M]

Fig. 9/13


HUH7 Proliferation
Compound A [M]
2,0E-07
1,5E-07
1,0E-07
5,0E-08
0,0E+00
0,0E+00
5,0E-08
1,0E-07
1,5E-07
Compound B [M]

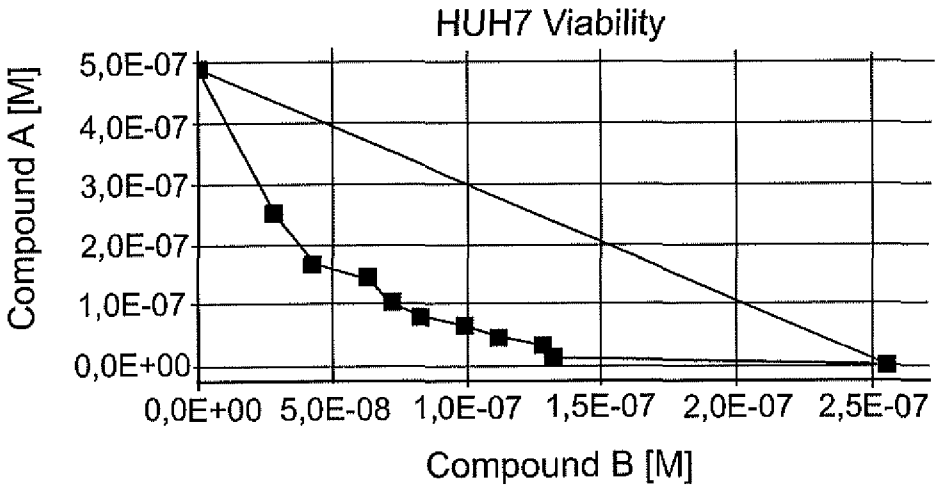

HUH7 Viability
Compound A [M]
5,0E-07
4,0E-07
3,0E-07
2,0E-07
1,0E-07
0,0E+00
0,0E+00
5,0E-08
1,0E-07
1,5E-07
2,0E-07
2,5E-07
Compound B [M]

Fig. 10/13

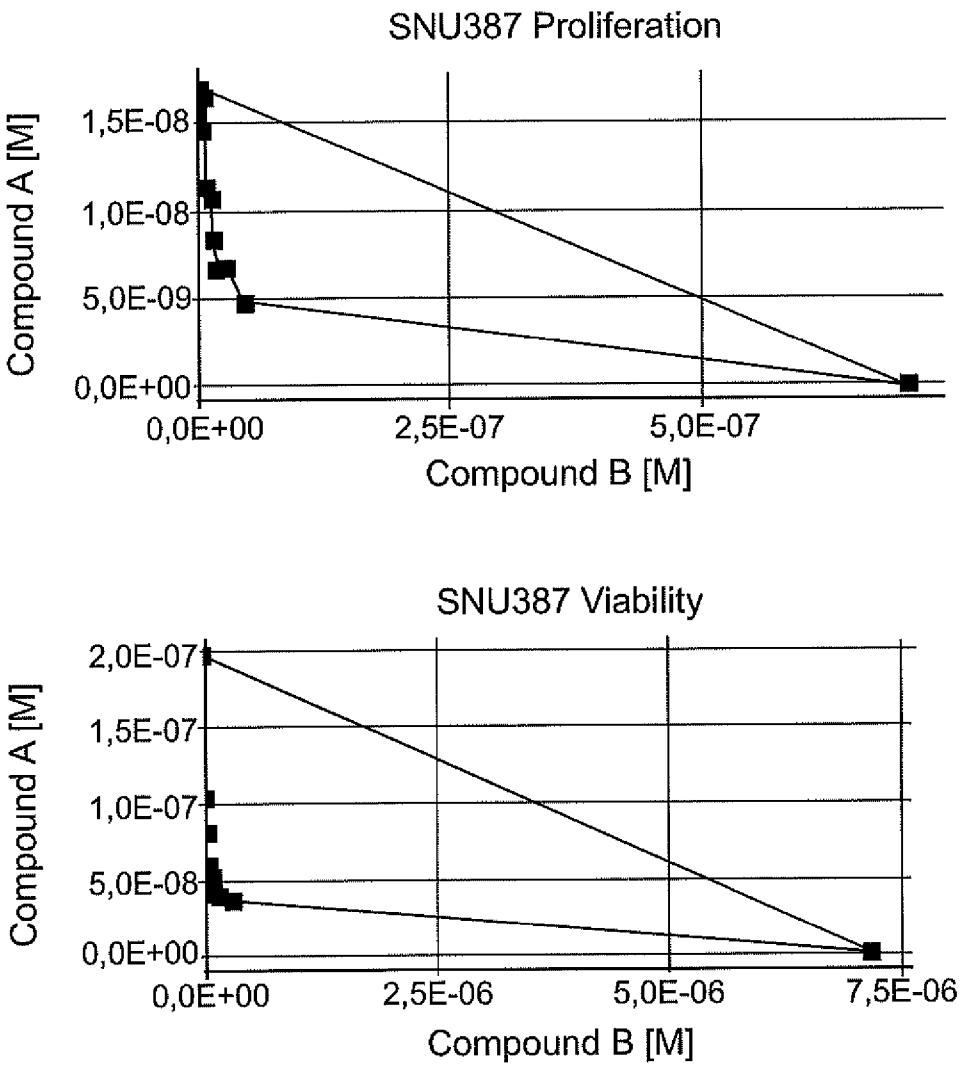
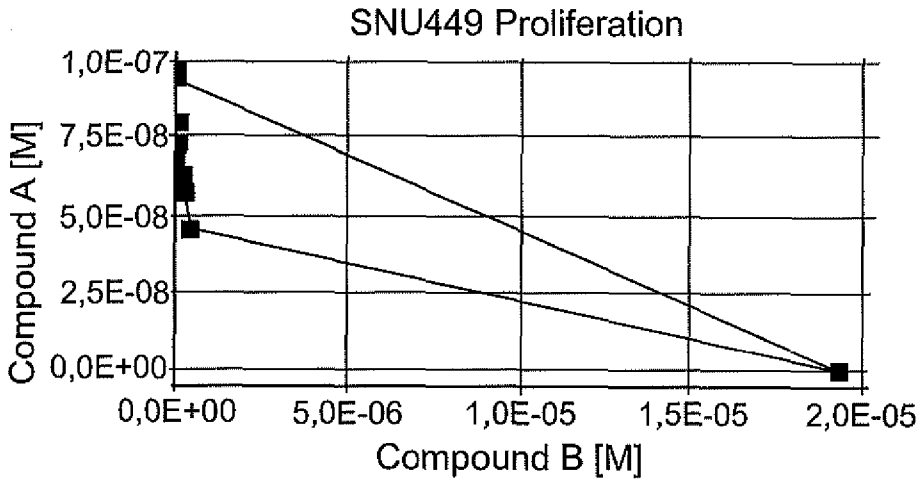

SNU387 Proliferation
Compound A [M]
1,5E-08
1,0E-08
5,0E-09
0,0E+00
0,0E+00
2,5E-07
5,0E-07
Compound B [M]
SNU387 Viability
Compound A [M]
2,0E-07
1,5E-07
1,0E-07
5,0E-08
0,0E+00
0,0E+00
2,5E-06
5,0E-06
7,5E-06
Compound B [M]

Fig. 11/13


SNU449 Proliferation
Compound A [M]
1,0E-07
7,5E-08
5,0E-08
2,5E-08
0,0E+00
0,0E+00
5,0E-06
1,0E-05
1,5E-05
2,0E-05
Compound B [M]

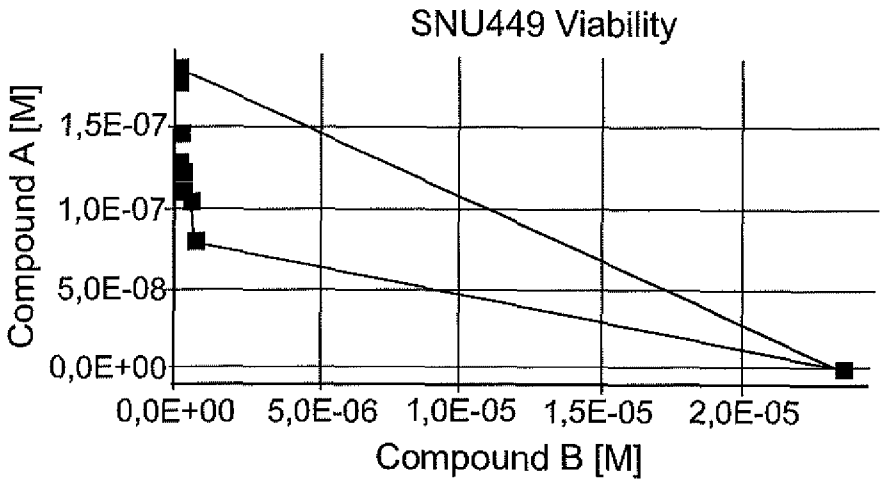

SNU449 Viability
Compound A [M]
1,5E-07
1,0E-07
5,0E-08
0,0E+00
0,0E+00
5,0E-06
1,0E-05
1,5E-05
2,0E-05
Compound B [M]

Fig. 12/13

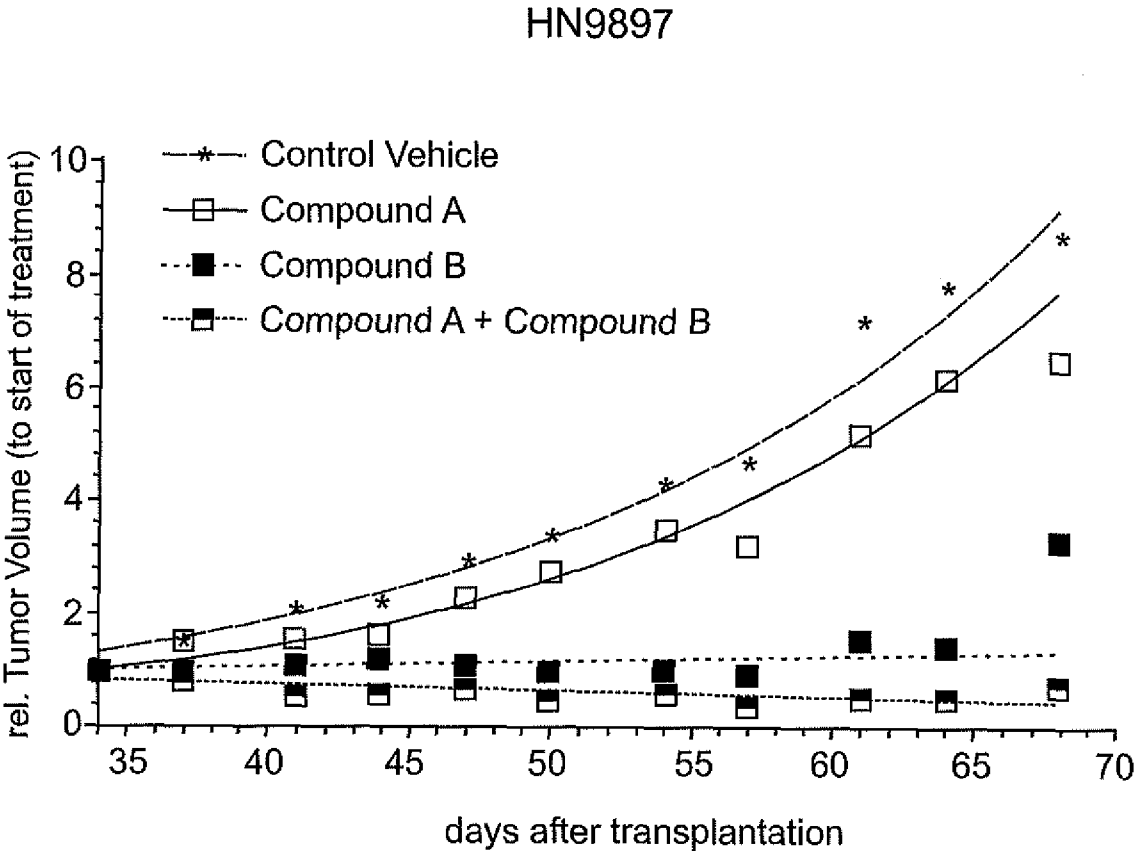
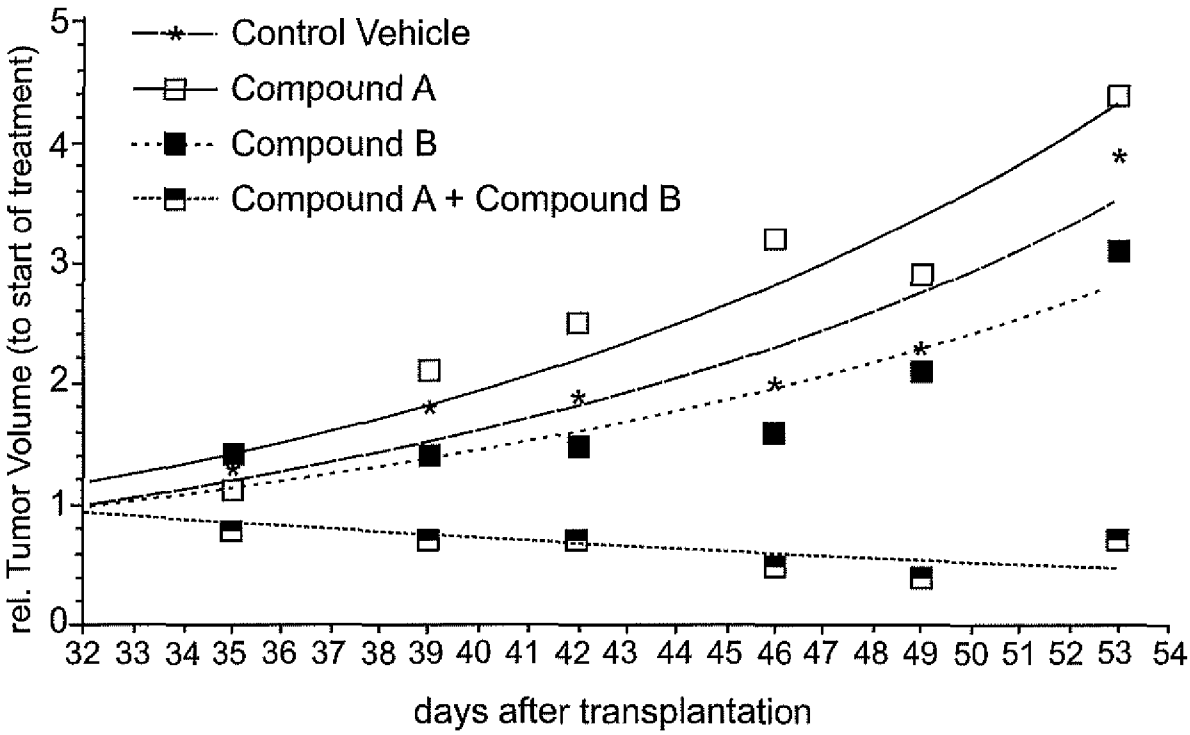

HN9897
Control Vehicle
Compound A
Compound B
Compound A + Compound B
rel. Tumor Volume (to start of treatment)
0
2
4
6
8
10
35
40
45
50
55
60
65
70
days after transplantation

Fig. 13/13

HN10632



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2018/081171

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K45/06 A61K31/519 A61K31/53 A61K31/535 A61K31/5377 A61P35/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data, COMPENDEX, EMBASE, INSPEC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/142312 A1 (BAYER HEALTHCARE AG) 15 September 2016 (2016-09-15) page 75; claims 1,9,10 -----	1-17

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 February 2019	20/02/2019

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2018/081171

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2016142312 A1	15-09-2016	AU 2016231259 A1	21-09-2017
		BR 112017019188 A2	24-04-2018
		CA 2978830 A1	15-09-2016
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		SG 11201707240S A	30-10-2017
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