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(54) Title: SULFONAMIDE, SULFAMATE AND SULFAMIDE DERIVATIVES OF ANTI-CANCER AGENTS

(57) Abstract: The present invention is directed to compounds having formula (I): A-L-R¹, wherein A is an anticancer agent comprising at least one group selected from the group comprising OH, NH and NH₂ and L is a direct bond or L is a linker and R¹ is a sulfonamide, sulfamate or sulfamide group. L is substituted on O of OH or on N of NH or NH₂ of A or wherein L replaces OH of A, or O-L replaces a C(=O)-OH group of A and wherein in the case L is a direct bond R¹ is substituted on O of OH or on N of NH or NH₂ of A or wherein R¹ replaces OH of A, or O-R¹ replaces a C(=O)-OH group of A. The invention is also directed to a treatment of cancer with the compounds.



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Title: Sulfonamide, sulfamate and sulfamide derivatives of anti-cancer agents

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The invention

The present invention is directed to sulfonamide sulfamide and/or sulfamate derivatives of anticancer agents or agents having an antiproliferative activity. The anticancer agents are functionalized with Sulfonamide,
10 sulfamate and/or sulfamide to obtain a dual drug activity and an additional tumour targeting.

Although many anticancer drugs have been used, many of them still lack specificity for the tumor. In addition, due to inadequate perfusion, tumours develop hypoxia and extracellular acidosis. This acidic environment is
15 responsible for multidrug resistance and most anticancer drugs do not work well on cells that are present in extracellular acidic environment. In addition, many anticancer agents do not work at all or work less on stem cells. Furthermore, some anticancer agents need to be activated by intracellular low pH. Moreover, some anticancer agents have a fast
20 pharmacokinetic with a short half life.

The compounds of the present invention address at least one of the issues described above. Compounds of the present invention are more tumour specific. The compounds of the present invention decrease the pH of cancer cells especially if they are in an acidic environment, making the cells
25 more sensitive to the anticancer agent.

The compounds of the present invention are also suitable in normoxic conditions. The compounds of the present invention are especially suitable for the tumour cells which are in an acidic environment but not hypoxic or recently reoxygenated. The compounds of the present invention
30 may also increase the extracellular pH, Increasing the extracellular pH increases the uptake of the anticancer agent. The compounds of the present invention may also decrease the intracellular pH. Making the intracellular

pH more acidic increases the conversion in active compound (e.g. temozolomide). Furthermore the compounds of the present do not need irradiation to become active. The compounds of the present invention may also be active in stem cells. Stem cells may be more sensitive to the compounds of the present invention. It was also found that the compounds of the present invention have an increased half life in plasma.

Calvert et al: (Eur. J. Cancer, 4 (6), (1968) pages 627-636) discloses derivatives of sulphanilamide that accumulate in neoplastic tissue. It discloses aryl-2-halogenoalkylamines, which are nitrogen musters and have been shown to possess significant tumour growth inhibitory activity. Calvert et al. discloses a sulfonamide (formula III). However when looking at the compounds without the sulfonamide, it can be seen that the anticancer agent does not comprise a OH, NH or NH₂.

Barnard, P. J. et al: (Arch. It. Pat. Clin. Tumori, 8(3-4), 141-51 (1965)) discloses a series of alkylating sulphonamides. The alkylating compounds are of the type (XCH₂CH₂)₂N-phenyl-SO₂NHR. However the anticancer agent without the sulfonamide, does not comprise a OH, NH or NH₂.

Hawkins et al: (J. Theoret. Biol 5 (2), (1963), pages 236-248) discloses (BrCH₂CH₂)₂NC₆H₄SO₂NH₂ which is compound IC 56 of Barnard et al. The anticancer agent without the sulfonamide, (BrCH₂CH₂)₂NC₆H₄ does not comprise OH, NH or NH₂.

Palmer et al: (J Med. Chem, am. Chem. Soc.US, 37 (1) (1994), page 2175-2184) discloses antitumor agents such as 5-[N,N-bis(2-chloroethyl)amino]-2,4-dinitrobenzamide and sulfonamide derivatives. The sulfonamide derivatives are different from the compounds of the present invention.

Bardos et al: (Annal New York acad sci., 163 (2) (1969), pages 1006-1025) discloses alkylating agents of which some are sulfonamides.

However from the sulfonamide compounds, the anticancer agent does not comprise OH, NH or NH₂

Lora-Tamayo et al: (Anales de la Real Sociedad Espanola de Fisica y Quimica, serie B: 62 (12) (1966), pages 1385-1390) describes the
 5 synthesis of bis (2-chloroethyl) amino benzamido-3-ethoxycarbonyl-propansulfonamide. However, the anticancer agent therefrom does not comprise OH, NH or NH₂

WO 2015/025283 is directed towards nimorazol derivatives however, nimorazol itself does not have an OH, NH, or NH₂ group.

10 FR 2 489 825 A1 discloses derivatives of oxazaphosphorines (cyclophosphamides). However, the anticancer agent therefrom does not comprise OH, NH or NH₂

Gueto et al: (Bioorg Med Chem. 16 (5) (2007), pages 2439-2447) discloses Src inhibitors based on benzotriazine derivatives. The compounds
 15 without the sulfonamide however show no anticancer activity.

US 2005/245524 discloses benzotriazine compounds however none of the substituents of the nitrogen of the sulfonamide fit the definition of R² or R³ of the present invention.

WO 2012/087115 discloses sulfonamides. The compounds without
 20 the sulfonamide are not anticancer agents.

Summary of the invention

In a first aspect the present invention is directed to compound according to formula (I)

25 A-L-R¹ (I)

A is an anticancer agent comprising at least one OH group or one NH group L is a direct bond or L is a linker selected from the group consisting of C₁₋₆alkyl, C(=O)N(R⁶), C₁₋₆alkyl-C(=O)N(R⁶)C₁₋₆alkyl, C₁₋₆alkyl-C(=O)N(R⁶), C(=O)N(R⁶)-C₁₋₆alkyl, N(R⁶)C(=O)N(R⁶), C₁₋₆alkylN(R⁶)C(=O)N(R⁶)C₁₋₆alkyl, C₁₋₆alkylN(R⁶)C(=O)N(R⁶),
 30

- $N(R^6)C(=O)N(R^6)C_{1-6}alkyl$, $N(R^6)C(=S)N(R^6)$, $C_{1-6}alkylN(R^6)C(=S)N(R^6)C_{1-6}alkyl$, $C_{1-6}alkylN(R^6)C(=S)N(R^6)$, $N(R^6)C(=S)N(R^6)C_{1-6}alkyl$, $-O-C(=O)N(R^6)$, $C_{1-6}alkyl-O-C(=O)N(R^6)C_{1-6}alkyl$, $C_{1-6}alkyl-O-C(=O)N(R^6)$, $-O-C(=O)N(R^6)C_{1-6}alkyl$, $N(R^6)C(=O)$, $C_{1-6}alkylN(R^6)C(=O)C_{1-6}alkyl$, $C_{1-6}alkylN(R^6)C(=O)$,
 5 $N(R^6)C(=O)C_{1-6}alkyl$, $N(R^6)C(=S)$, $C_{1-6}alkylN(R^6)C(=S)C_{1-6}alkyl$, $C_{1-6}alkylN(R^6)C(=S)$, $N(R^6)C(=S)C_{1-6}alkyl$, $C(=O)N(R^6)C_{1-6}alkylN(R^6)C(=S)N(R^6)$, $C_{1-6}alkylC(=O)N(R^6)C_{1-6}alkylN(R^6)C(=S)N(R^6)C_{1-6}alkyl$, $C_{1-6}alkylC(=O)N(R^6)C_{1-6}alkylN(R^6)C(=S)N(R^6)$, $C(=O)N(R^6)C_{1-6}alkylN(R^6)C(=S)N(R^6)C_{1-6}alkyl$, $C(=O)N(R^6)C_{1-6}alkylN(R^6)C(=O)N(R^6)$, $C_{1-6}alkylC(=O)N(R^6)C_{1-6}alkylN(R^6)C(=O)N(R^6)C_{1-6}alkyl$, $C_{1-6}alkylC(=O)N(R^6)C_{1-6}alkyl-OC(=O)$, $C_{1-6}alkylC(=O)N(R^6)C_{1-6}alkyl-OC(=O)C_{1-6}alkyl$, $C_{1-6}alkylC(=O)N(R^6)C_{1-6}alkyl-OC(=O)$, $C(=O)N(R^6)C_{1-6}alkyl-OC(=O)C_{1-6}alkyl$, $O-C(=O)$, $C_{1-6}alkyl-O-C(=O)C_{1-6}alkyl$, $C_{1-6}alkyl-O-C(=O)$, $O-C(=O)C_{1-6}alkyl$, -
 10 $C(=O)$, $C_{1-6}alkyl-C(=O)C_{1-6}alkyl$, $C_{1-6}alkyl-C(=O)$, $C(=O)C_{1-6}alkyl$, $C(=S)N(R^6)$, $C_{1-6}alkyl-C(=S)N(R^6)C_{1-6}alkyl$, $C_{1-6}alkyl-C(=S)N(R^6)$, $C(=S)N(R^6)-C_{1-6}alkyl$, $N(R^6)$, $C_{1-6}alkyl-N(R^6)C_{1-6}alkyl$, $C_{1-6}alkyl-N(R^6)$, $N(R^6)C_{1-6}alkyl$, $O-C(=O)C_{1-6}alkylC(=O)N(R^6)$, $C_{1-6}alkyl-O-C(=O)C_{1-6}alkylC(=O)N(R^6)C_{1-6}alkyl$, $C_{1-6}alkyl-O-C(=O)C_{1-6}alkylC(=O)N(R^6)$, $O-C(=O)C_{1-6}alkylC(=O)N(R^6)C_{1-6}alkyl$, $O-C(=O)C_{1-6}alkylN(R^6)C(=O)$, $C_{1-6}alkyl-O-C(=O)C_{1-6}alkylN(R^6)C(=O)C_{1-6}alkyl$, $C_{1-6}alkyl-O-C(=O)C_{1-6}alkylN(R^6)C(=O)$, $O-C(=O)C_{1-6}alkylN(R^6)C(=O)C_{1-6}alkyl$, $(O-CH_2CH_2)_n$, $C_{1-6}alkyl(O-CH_2CH_2)_nC_{1-6}alkyl$, $C_{1-6}alkyl(O-CH_2CH_2)_n$, $(O-CH_2CH_2)_nC_{1-6}alkyl$, $(CH_2CH_2-O)_n$, $C_{1-6}alkyl(CH_2CH_2-O)_nC_{1-6}alkyl$, $C_{1-6}alkyl(CH_2CH_2-O)_n$,
 20 $(CH_2CH_2-O)_nC_{1-6}alkyl$;
 25

n is 1-12;

- optionally the L is further substituted with a substituent selected from the group comprising halo, hydroxy, amino, nitro, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{1-6}alkyloxy$, $di(C_{1-6}alkyl)amino$, hydroxyamino,
 30 hydroxycarbonyl, carbonyl, carbonyl $C_{1-6}alkyl$, carbonyl $C_{1-6}alkyloxy$, $C_{1-6}alkyl$

alkylcarbonyl, NR^4R^5 , heterocyclic, C_{3-7} cycloalkyl, , hydroxy C_{1-6} alkyl, amino C_{1-6} alkyl, cyano, SiFR^8R^9 , or $\text{OP}(=\text{O})(\text{OR}^{10})_2$;

R^1 is $\text{SO}_2\text{NR}^2\text{R}^3$, $\text{OSO}_2\text{NR}^2\text{R}^3$, $\text{NR}^7\text{SO}_2\text{NR}^2\text{R}^3$, NR^7SO_2 -phenyl, aryl substituted with $\text{SO}_2\text{NR}^2\text{R}^3$, aryl substituted with $\text{OSO}_2\text{NR}^2\text{R}^3$, aryl substituted with $\text{NR}^7\text{SO}_2\text{NR}^2\text{R}^3$;

R^2 , R^3 is each independently hydrogen, halo, hydroxy, or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with with a substituent selected from the group comprising halo, hydroxy, amino, nitro, carbonyl, cyano, or a leaving group;

R^4 , R^5 , R^6 , R^7 is each independently hydrogen, halo, hydroxy, or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with with a substituent selected from the group comprising halo, hydroxy, amino, nitro, C_{1-6} alkyloxy, di(C_{1-6} alkyl)amino, hydroxyamino, hydroxycarbonyl, carbonyl, carbonyl C_{1-6} alkyl, carbonyl C_{1-6} alkyloxy, C_{1-6} alkylcarbonyl, heterocyclic, C_{3-7} cycloalkyl, hydroxy C_{1-6} alkyl or amino C_{1-6} alkyl , cyano, $\text{OP}(=\text{O})(\text{OR}^{10})_2$, SiFR^8R^9 , or a leaving group;

R^8 and R^9 is each independently a C_{1-12} alkyl, or C_{2-12} alkenyl;

R^{10} is hydrogen, C_{1-20} alkyl, or C_{2-20} alkenyl, aryl, amino C_{1-12} alkyl, carbonyl C_{1-12} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, or NR^4R^5 ;

wherein L is substituted on O of OH or on N of NH or NH_2 of A or wherein L replaces OH of A, or O-L replaces a $\text{C}(=\text{O})\text{-OH}$ group of A, and wherein in the case L is a direct bond R^1 is substituted on O of OH or on N of NH or NH_2 of A, or wherein R^1 replaces OH of A, or O- R^1 replaces a $\text{C}(=\text{O})\text{-OH}$ group of A, .

Detailed description

Definitions

For the purpose of the present invention, anticancer agent is a compound that has antiproliferative activity. Anticancer agent include

chemotherapeutic agents, and agents used for targeted therapy or molecularly targeted therapy.

Alkylating agents are the oldest group of chemotherapeutics in use today. Originally derived from mustard gas used in World War I, there are now many types of alkylating agents in use. They are so named because of their ability to alkylate many molecules, including proteins, RNA and DNA. This ability to bind covalently to DNA via their alkyl group is the primary cause for their anti-cancer effects. DNA is made of two strands and the molecules may either bind twice to one strand of DNA (intrastrand crosslink) or may bind once to both strands (interstrand crosslink). If the cell tries to replicate crosslinked DNA during cell division, or tries to repair it, the DNA strands can break. This leads to a form of programmed cell death called apoptosis. Alkylating agents will work at any point in the cell cycle and thus are known as cell cycle-independent drugs. For this reason the effect on the cell is dose dependent; the fraction of cells that die is directly proportional to the dose of drug.

The subtypes of alkylating agents are the nitrogen mustards, nitrosoureas, tetrazines, aziridines, and derivatives, and non-classical alkylating agents. Nitrogen mustards include cyclophosphamide, melphalan, chlorambucil, and ifosfamide. Nitrosoureas include N-Nitroso-N-methylurea (MNU), carmustine (BCNU), lomustine (CCNU) and semustine (MeCCNU), fotemustine and streptozotocin. SN 30444 (2-[bis(2-bromoethyl)amino]-N-(2-hydroxyethyl)-5-nitrobenzamide) and Chlorine-derivative of SN 30444 (2-[bis(2-chloroethyl)amino]-N-(2-hydroxyethyl)-5-nitrobenzamide) are prodrugs of alkylating agents. They are converted by nitroreductase (NTR) enzymes in DNA alkylating agents. Tetrazines include dacarbazine, mitozolomide and temozolomide. Aziridines include thiotepa, mytomycin and diaziquone (AZQ). Cisplatin and derivatives include cisplatin, carboplatin and oxaliplatin. They impair cell function by forming covalent bonds with the amino, carboxyl, sulfhydryl, and phosphate groups

in biologically important molecules. Non-classical alkylating agents include procarbazine and hexamethylmelamine.

Since cancer cells, in general, proliferate faster and with less error-correcting than healthy cells, cancer cells are more sensitive to DNA damage — such as being alkylated. Alkylating agents are used to treat several cancers. However, they are also toxic to normal cells (cytotoxic), leading to damage, in particular in cells that divide frequently, as those in the gastrointestinal tract, bone marrow, testicles and ovaries, which can cause loss of fertility. Most of the alkylating agents are also carcinogenic. Dialkylating agents can react with two different 7-N-guanine residues, and, if these are in different strands of DNA, the result is cross-linkage of the DNA strands, which prevents uncoiling of the DNA double helix. If the two guanine residues are in the same strand, the result is called limpet attachment of the drug molecule to the DNA.

Monoalkylating agents can react only with one 7-N of guanine.

Limpet attachment and monoalkylation do not prevent the separation of the two DNA strands of the double helix but do prevent vital DNA-processing enzymes from accessing the DNA. The final result is inhibition of cell growth or stimulation of apoptosis, cell suicide.

Anti-metabolites are a group of molecules that impede DNA and RNA synthesis. Many of them have a similar structure to the building blocks of DNA and RNA. The building blocks are nucleotides; a molecule comprising a nucleobase, a sugar and a phosphate group. The nucleobases are divided into purines (guanine and adenine) and pyrimidines (cytosine, thymine and uracil). Anti-metabolites resemble either nucleobases or nucleosides (a nucleotide without the phosphate group), but have altered chemical groups. These drugs exert their effect by either blocking the enzymes required for DNA synthesis or becoming incorporated into DNA or RNA. By inhibiting the enzymes involved in DNA synthesis, they prevent mitosis because the DNA cannot duplicate itself. Also, after

misincorporation of the molecules into DNA, DNA damage can occur and programmed cell death (apoptosis) is induced. Unlike alkylating agents, anti-metabolites are cell cycle dependent. This means that they only work during a specific part of the cell cycle, in this case S-phase (the DNA
5 synthesis phase). For this reason, at a certain dose, the effect plateaus and proportionally no more cell death occurs with increased doses.

Subtypes of the anti-metabolites are the anti-folates, fluoropyrimidines, deoxynucleoside analogues and thiopurines.

The anti-folates include methotrexate and pemetrexed.

10 Methotrexate inhibits dihydrofolate reductase (DHFR), an enzyme that regenerates tetrahydrofolate from dihydrofolate. When the enzyme is inhibited by methotrexate, the cellular levels of folate coenzymes diminish. These are required for thymidylate and purine production, which are both essential for DNA synthesis and cell division. Pemetrexed is another anti-
15 metabolite that affects purine and pyrimidine production, and therefore also inhibits DNA synthesis. It primarily inhibits the enzyme thymidylate synthase, but also has effects on DHFR, aminoimidazole carboxamide ribonucleotide formyltransferase and glycineamide ribonucleotide formyltransferase. The fluoropyrimidines include fluorouracil and
20 capecitabine. Fluorouracil is a nucleobase analogue that is metabolised in cells to form at least two active products; 5-fluorouridine monophosphate (FUMP) and 5-fluoro-2'-deoxyuridine 5'-phosphate (fdUMP). FUMP becomes incorporated into RNA and fdUMP inhibits the enzyme thymidylate synthase; both of which lead to cell death. Capecitabine is a prodrug of 5-
25 fluorouracil that is broken down in cells to produce the active drug. The deoxynucleoside analogues include cytarabine, gemcitabine, decitabine, Vidaza, fludarabine, nelarabine, cladribine, clofarabine and pentostatin. The thiopurines include thioguanine and mercaptopurine.

Anti-microtubule agents

Anti-microtubule agents are plant-derived chemicals that block cell division by preventing microtubule function. Microtubules are an important cellular structure composed of two proteins; α -tubulin and β -tubulin. They are hollow rod shaped structures that are required for cell division, among other cellular functions. Microtubules are dynamic structures, which means that they are permanently in a state of assembly and disassembly. Vinca alkaloids and taxanes are the two main groups of anti-microtubule agents, and although both of these groups of drugs cause microtubule disfunction, their mechanisms of action are completely opposite. The vinca alkaloids prevent the formation of the microtubules, whereas the taxanes prevent the microtubule disassembly. By doing so, they prevent the cancer cells from completing mitosis. Following this, cell cycle arrest occurs, which induces programmed cell death (apoptosis). Also, these drugs can affect blood vessel growth; an essential process that tumours utilise in order to grow and metastasise.

Vinca alkaloids are derived from the Madagascar periwinkle, *Catharanthus roseus* (formerly known as *Vinca rosea*). They bind to specific sites on tubulin, inhibiting the assembly of tubulin into microtubules. The original vinca alkaloids are completely natural chemicals that include vincristine and vinblastine. Following the success of these drugs, semi-synthetic vinca alkaloids were produced: vinorelbine, vindesine, and vinflunine. These drugs are cell cycle-specific. They bind to the tubulin molecules in S-phase and prevent proper microtubule formation required for M-phase.

Taxanes are natural and semi-synthetic drugs. The first drug of their class, paclitaxel, was originally extracted from the Pacific Yew tree, *Taxus brevifolia*. Now this drug and another in this class, docetaxel, are produced semi-synthetically from a chemical found in the bark of another Yew tree; *Taxus baccata*. These drugs promote microtubule stability, preventing their disassembly. Paclitaxel prevents the cell cycle at the

boundary of G2-M, whereas docetaxel exerts its effect during S-phase. Taxanes present difficulties in formulation as medicines because they are poorly soluble in water.

Podophyllotoxin is an anti-neoplastic lignan obtained primarily
5 from the American Mayapple (*Podophyllum peltatum*) and Himalayan Mayapple (*Podophyllum hexandrum* or *Podophyllum emodi*). It has anti-microtubule activity, and its mechanism is similar to that of vinca alkaloids in that they bind to tubulin, inhibiting microtubule formation. Podophyllotoxin is used to produce two other drugs with different
10 mechanisms of action: etoposide and teniposide.

Topoisomerase I and II Inhibitors

Topoisomerase inhibitors are drugs that affect the activity of two enzymes: topoisomerase I and topoisomerase II. When the DNA double-strand helix is unwound, during DNA replication or transcription, for
15 example, the adjacent unopened DNA winds tighter (supercoils), like opening the middle of a twisted rope. The stress caused by this effect is in part aided by the topoisomerase enzymes. They produce single- or double-strand breaks into DNA, reducing the tension in the DNA strand. This allows the normal unwinding of DNA to occur during replication or
20 transcription. Inhibition of topoisomerase I or II interferes with both of these processes.

Two topoisomerase I inhibitors, irinotecan and topotecan, are semi-synthetically derived from camptothecin, which is obtained from the Chinese ornamental tree *Camptotheca acuminata*. Drugs that target
25 topoisomerase II can be divided into two groups. The topoisomerase II poisons cause increased levels enzymes bound to DNA. This prevents DNA replication and transcription, causes DNA strand breaks, and leads to programmed cell death (apoptosis). These agents include etoposide, doxorubicin, mitoxantrone and teniposide. The second group, catalytic
30 inhibitors, are drugs that block the activity of topoisomerase II, and

therefore prevent DNA synthesis and translation because the DNA cannot unwind properly. This group includes novobiocin, merbarone, and

Cytotoxic antibiotics

The cytotoxic antibiotics are a varied group of drugs that have
5 various mechanisms of action. The group includes the anthracyclines and other drugs including actinomycin, bleomycin, plicamycin, and mitomycin. Doxorubicin and daunorubicin were the first two anthracyclines, and were obtained from the bacterium *Streptomyces peucetius*. Derivatives of these compounds include epirubicin and idarubicin. Other clinically used drugs in
10 the anthracycline group are pirarubicin, aclarubicin, and mitoxantrone. The mechanisms of anthracyclines include DNA intercalation (molecules insert between the two strands of DNA), generation of highly reactive free radicals that damage intercellular molecules and topoisomerase inhibition.

Actinomycin is a complex molecule that intercalates DNA and prevents
15 RNA synthesis. Bleomycin, a glycopeptide isolated from *Streptomyces verticillus*, also intercalates DNA, but produces free radicals that damage DNA. This occurs when bleomycin binds to a metal ion, becomes chemically reduced and reacts with oxygen. Mitomycin is a cytotoxic antibiotic with the ability to alkylate DNA.

20 Targeted agents or agents for targeted cancer therapies are drugs or other substances that block the growth and spread of cancer by interfering with specific molecules ("molecular targets") that are involved in the growth, progression, and spread of cancer. Targeted cancer therapies are sometimes called "molecularly targeted drugs," "molecularly targeted
25 therapies," "precision medicines," or similar names. Targeted therapies differ from standard chemotherapy in that targeted therapies act on specific molecular targets that are associated with cancer, whereas most standard chemotherapies act on all rapidly dividing normal and cancerous cells. In addition, targeted therapies are deliberately chosen or designed to interact
30 with their target, whereas many standard chemotherapies were identified

because they kill cells. Furthermore, targeted therapies are often cytostatic (that is, they block tumour cell proliferation), whereas standard chemotherapy agents are cytotoxic (that is, they kill tumour cells). Several targeted therapies are directed against HER-2, including trastuzumab (Herceptin®), which is approved to treat certain breast and stomach cancers that overexpress HER-2. The cell growth signaling protein BRAF is present in an altered form (known as BRAF V600E) in many melanomas. Vemurafenib (Zelboraf®) targets this mutant form of the BRAF protein and is approved to treat patients with inoperable or metastatic melanoma that contains this altered BRAF protein. Targeted therapy includes small molecules and monoclonal antibodies. For the purpose of the present invention, the targeted agent include small molecules and not monoclonal antibodies. Targeted agents may include tyrosine kinase inhibitors, ALK inhibitors, PARP inhibitors, Phosphoinositide 3-kinase inhibitors, VEGF receptor inhibitors, MEK inhibitors, CDK inhibitors, Hsp90 inhibitors, folate receptor targeting agents, serine/threonine kinase inhibitors, FGFR tyrosine kinase inhibitors, mTOR inhibitor, Bcl2 inhibitor, EZH2 inhibitor, Notch inhibitors, ATM inhibitors, MELK inhibitors, EGF receptor inhibitors.

20

Aspects and embodiments of the invention

In a first aspect the present invention is directed to compound having formula A-L-R¹. For the purpose of the present invention, A is an anticancer agent comprising at least one group selected from the group comprising OH, NH and NH₂. It is to be understood that anticancer agent A comprises a OH, NH or NH₂ when in the original state and not being connected to L-R¹ or R¹. The linking of L-R¹ or R¹ is on the position of the OH, NH, NH₂ of A. Such linking depends on the nature of A, whether it is an OH, or NH/NH₂ and depends further on L and R¹. For example, A is connected to either L-R¹ or R¹ via the O or N of OH, NH or NH₂ and

effectively replaces (one of) the hydrogen on OH, NH, or NH₂. It is also possible that L-R¹ or R¹ replaces the OH. Often the L-R¹ or R¹ then comprises a NH group and this NH group replaces the OH group of active agent A. Examples are compounds 10, 11, 12, 56, 58, Furthermore, a O-L-R¹ group or O-R¹ group may replace a C(=O)OH group on A. The O of the O-L-R¹ or O-R¹ replaces the C(=O)OH group of active agent A. Examples are compounds 13, 14, 15, 59

A comprises a O, NH, or N group that is linked to either L-R¹ or R¹ in case L is a direct bond. The L may be substituted on O of OH or on N of NH or NH₂ of A and wherein in the case L is a direct bond R¹ may be substituted on O of OH or on N of NH or NH₂ of A. This means that anticancer agent A may be connected to either L-R¹ or R¹ via a N atom from a NH or NH₂ group or via a O atom from an OH comprised in the original anticancer agent A. In case wherein the OH group of A is replaced, either L-R¹ or R¹ is connected to A on the position of the OH via an NH group of either either L or R¹. In case where an C(=O)OH group is replaced by O-L-R¹ group or O-R¹ group the O-L-R¹ group or O-R¹ group connected to A in the position of the C(=O)OH group via the O of the O-L-R¹ group or O-R¹ group.

It is to be understood that the OH, NH or NH₂ of A is present in the original anticancer agent, meaning before being linked to L-R¹ or R¹. When A is connected to either L or R¹ at least one of the hydrogens is no longer present and A comprises a O, NH, or N group that is linked to either L-R¹ or R¹ in case L is a direct bond. The linking of A to L-R¹ or R¹ may also occur by replacing the OH group of A by a NH₂ group or by NH group from e.g. L or R¹. See for examples compounds 10, 20-27. In case A comprises a carboxylic acid group C(=O)-OH group, this may also be replaced by C-O-C(=O)-NH-group, see for example compound 13, 14, 15. In the present invention, the carboxylic acid group C(=O)-OH of A may be used to link L or R¹. The newly formed bond may be an amide ((C=O)-NH-) or ester ((C=O)-

O). A skilled person is well aware of how to link L or R¹ to A via a OH, NH, or NH₂.

In a preferred embodiment of the present invention and/or
embodiments thereof L is substituted on N of NH or NH₂ of A and wherein
5 in the case L is a direct bond R¹ is substituted on N of NH or NH₂ of A. This
means that when substituted with L-R¹ or R¹ A comprises a N or NH group
linked to L-R¹ or R¹.

In a preferred embodiment of the present invention and/or
embodiments L is substituted on the O of OH in of A or L replaces OH of A,
10 or O-L replaces a C(=O)-OH group of A. In the case L is a direct bond R¹ is
substituted on O of OH of A, or R¹ replaces OH of A, or O-R¹ replaces a
C(=O)-OH group of A,.

In a preferred embodiment of the present invention and/or
embodiments L is substituted on the O of OH of A or L replaces OH of A, or
15 wherein in the case L is a direct bond R¹ is substituted on O of OH of A, or
R¹ replaces OH of A,

In a preferred embodiment of the present invention and/or
embodiments L is substituted on the O of OH of A or L replaces OH of A, or
wherein in the case L is a direct bond R¹ is substituted on O of OH of A.

20 In a preferred embodiment of the present invention and/or
embodiments L replaces OH of A, or wherein in the case L is a direct bond
R¹ replaces OH of A.

In a preferred embodiment of the present invention and/or
embodiments O-L replaces a C(=O)-OH group of A, or wherein in the case L
25 is a direct bond O-R¹ replaces a C(=O)-OH group of A.

In a preferred embodiment of the present invention and/or
embodiments A is a nucleoside or nucleoside derivative.

In a preferred embodiment of the present invention and/or
embodiments L is substituted on the O of OH in sugar group of A or L
30 replaces OH of the sugar group of A, or wherein in the case L is a direct

bond R¹ is substituted on O of OH of sugar group of A, or R¹ replaces OH of the sugar group of A, In a preferred embodiment of the invention and/or embodiments thereof A comprises a NH₂ group. This means that the original anticancer agent A comprises a NH₂. When connected to either L-R¹ or to R¹ the compound of the present invention comprises an anticancer agent A comprising a NH linked to L-R¹ or to R¹ in the case L is a direct bond. In a preferred embodiment of the invention and/or embodiments thereof the NH group of the original compound A is not part of a ringstructure. It is to be understood that NH being part of a ringstructure means that the N of NH participates in the ring, such as in pyrimidine or imidazole.

In a preferred embodiment of the present invention and/or embodiments thereof, A is an anticancer agent selected from the group comprising Alkylating agents, Anti-metabolites, Anti-microtubule agents, Topoisomerase inhibitors, Cytotoxic antibiotics, targeted agents, DNA repair inhibitors, and antiviral drugs having antiproliferative effect.

For the purpose of the present invention and/or embodiments thereof alkylating agents may be nitrogen mustards, nitrobenzamide mustards, nitrosoureas, tetrazines, aziridines, and derivatives thereof. Nitrogen mustards include cyclophosphamide, melphalan, chlorambucil, ifosfamide, and prodrugs like SN 30444 (2-[bis(2-bromoethyl)amino]-N-(2-hydroxyethyl)-5-nitrobenzamide) Chlorine-derivative of SN 30444 (2-[bis(2-chloroethyl)amino]-N-(2-hydroxyethyl)-5-nitrobenzamide). Nitrosoureas include N-Nitroso-N-methylurea (MNU), carmustine (BCNU), lomustine (CCNU) and semustine (MeCCNU), fotemustine and streptozotocin. Tetrazines include dacarbazine, mitozolomide and temozolomide. Aziridines include thiotepa, mytomycin and diaziquone (AZQ). Non-classical alkylating agents include procarbazine and hexamethylmelamine.

For the purpose of the present invention, suitable alkylating agents may be selected from the group consisting of Cyclophosphamide, ,

Uramustine or uracil mustard, Melphalan, Chlorambucil, SN 30444 (2-[bis(2-bromoethyl)amino]-N-(2-hydroxyethyl)-5-nitrobenzamide) Chlorine-derivative of SN 30444 (2-[bis(2-chloroethyl)amino]-N-(2-hydroxyethyl)-5-nitrobenzamide), Ifosfamide, Bendamustine, Nitrosoureas, PCNU,
 5 Carmustine, Lomustine, Spiromustine, Streptozocin, Chlorozotocin, Semustine, Ethylnitrosourea, procarbazine tetrazines, dacarbazine, mitozolomide, temozolomide, leucine sarcolysine, aziridinylnbenzoquinone (AZQ: NSC-182986), cyanomorpholino-doxorubin, doxorubicin, Dianhydrogalactitol, Fluorodopan, hepsulfam, hycanthone
 10 methanesulfonate, Ametycin, Piperazinedione, Porfiromycin, improsan.

Anti-metabolites may be divided into subtypes such as the anti-folates, fluoropyrimidines, deoxynucleoside analogues and thiopurines.

The anti-folates include methotrexate and pemetrexed. The fluoropyrimidines include fluorouracil and capecitabine which is a prodrug
 15 of fluorouracil. The deoxynucleoside analogues include cytarabine, gemcitabine, decitabine, Vidaza, fludarabine, nelarabine, cladribine, clofarabine and pentostatin. The thiopurines include thioguanine and mercaptopurine. In a preferred embodiment of the present invention and/or
 20 embodiments thereof, nucleosides are substituted on the OH of the sugar moiety with either L or R¹ in case L is a direct bond.

Suitable anti-metabolites may be methotrexate, methotrexate derivatives, NSC 174121, NSC132483, NSC184692, NSC134033, NSC623017, and pemetrexed, Trimetrexate, fluorouracil and capecitabine(=prodrug of fluorouracil), . Floxuridin, cytarabine, gemcitabine,
 25 decitabine, Vidaza, fludarabine, nelarabine, cladribine, clofarabine and pentostatin. The thiopurines include thioguanine and mercaptopurine, Alanosine, Acivicin, Baker's Antifol soluble, Dichloroallyl lawsone, PALA, 3-HP, 5-HP, alpha-TGdR, beta- TGdR Aphidicolin glycinate, ancitabine hydrochloride, Guanazole, Hydroxyurea, Inosine dialdehyde, Macbecin II,
 30 Imidazole-Pyrazole, Thioguanine, 6-Mercaptopurine.

Anti-microtubule agents may be vinca alkaloids and taxanes, or podophyllotoxin and derivatives thereof. Suitable anti-microtubule and antimitotic agents are Vinca alkaloids and taxanes, vinorelbine, vindesine, and vinflunine, vinblastine, vincristine, vincaminol, vincamajine, vineridine, and vinburnine. Vinpocetine, paclitaxel, docetaxel, taxol analogue NSC608832, Podophyllotoxin, etoposide and teniposide, allocolchicine, Halichondrin B, colchicine, N-Benzoyl-deacetylcolchicine, dolastatin 10, maytansin, 3-demethylthiocolchicine, 3-tritylthio-L-alanine

Topoisomerase inhibitors may be divided into Topoisomerase I and II Inhibitors. Suitable topoisomerase inhibitors are irinotecan and topotecan, etoposide, doxorubicin, mitoxantrone and teniposide, novobiocin, merbarone, and aclarubicin. Suitable topoisomerase I inhibitors may be selected from the group consisting of camptothecin, 9-amino Camptothecin, 10-hydroxycamptothecin, 14-Chloro-20(S)-camptothecin hydrate, 9-Amino-20-(R,S)-camptothecin, camptothecin derivative NSC295500, 7-Chlorocamptothecin, camptothecin derivative NSC606985, Camptothecin derivative NSC374028, Camptothecin derivative NSC374028, 9-methoxycamptothecin, camptothecin derivative NSC295501, camptothecin derivative NSC606172, camptothecin derivative NSC606173, Camptothecin phosphate, Camptothecin lysinate HCl, Camptothecin glutamate, Camptothecin butylglycinate ester hydrochloride, Camptothecin hemisuccinate, Camptothecin ethylglycinate ester hydrochloride, and morpholinoadriamycin.

Suitable Topoisomerase II inhibitors may be selected from the group consisting of Amonafide, Amsacrine, anthrapyrazole, Pyrazoloacridine, bisantrene, Daunorubicin, doxorubicin, menogaril, N,N-Dibenzyl daunorubicin hydrochloride, piroxantrone, zorubicin, VM-26, and VP-16.

Cytotoxic antibiotics include the anthracyclines and other drugs including actinomycin, bleomycin, plicamycin, and mitomycin.

Suitable cytotoxic antibiotics are anthracyclines actinomycin, bleomycin, plicamycin, and mitomycin. Doxorubicin daunorubicin, pirarubicin, aclarubicin, and mitoxantrone, epirubicin, idarubicin, valrubicin, Mithramycin, salinomycin.

5 Targeted agents or agents for targeted cancer therapies are drugs or other substances that block the growth and spread of cancer by interfering with specific molecules ("molecular targets") that are involved in the growth, progression, and spread of cancer. Suitable targets are tyrosine kinase, JAK (Janus kinase), ALK (anaplastic lymphoma kinase), PARP
10 (poly ADP ribose polymerase), Phosphoinositide 3-kinase, VEGF receptor, B-Raf, MEK, CDK, Hsp90, folate receptor, Serine/threonine kinase, FGFR tyrosine kinase, mTOR, Bcl2, Notch, ATM (Ataxia telangiectasia mutated) kinase, MELK (maternal embryonic leucine zipper kinase), EGF receptor and EZH2.

15 Tyrosine kinase inhibitors are suitable targeted agents. Suitable tyrosine kinase inhibitors are imatinib mesylate Gefitinib, Erlotinib hydrochloride, Sorafenib, Sunitinib, Dasatinib, Lapatinib, Nilotinib, Bortezomib, and tamoxifen,

Suitable Janus kinase (JAK) inhibitors are CYT387, Lestaurtinib,
20 Pacritinib, and famitinib . Suitable JAK-2 inhibitor is chloroquine which inhibits autophagy.

Suitable ALK inhibitors are Alectinib, AP26113, nerviano, PF-06463922, CEP-37440, and X-396.

Suitable PARP inhibitor are olaparib iniparib, BMN-673,
25 rucaparib, veliparib, CEP 8983, MK4827, 3-aminobenzamide, and AZD2461.

Suitable Phosphoinositide 3-kinase inhibitor are idelalisib, PX-866, IPI-145, BAY 80-6946, SF1126, GDC 0941, buparlisib, XL147, XL765, palomid 529, IC-87114, TG100-115, PI 103, GNE 477, and CUDC-907.

Suitable VEGF receptor inhibitors are apatinib, lenvatinib,
30 motesanib, and Regorafenib.

Suitable B-Raf inhibitor are vemurafenib, dabrafenib, LGX818, sorafenib, PLX4720, and GDC-0879.

Suitable MEK inhibitors are trametinib, selumetinib, binimetinib, PD-325901, cobimetinib, and CI-1040,.

5 Suitable CDK inhibitors are Palbociclib and LEE011.

Suitable Hsp90 inhibitors are Geldanamycin, radicicol, and tanespimycin.

Suitable Folate receptor targeting agent is vintafolide.

10 Suitable Serine/threonine kinase inhibitor are temsirolimus and everolimus.

Suitable FGFR tyrosine kinase inhibitor is AZD4547.

Suitable mTOR inhibitor is AZD8055

Suitable Bcl2 inhibitors are navitoclax, Obatoclax, and gossypol.

Suitable EZH2 inhibitor is GSK126.

15 Suitable Notch inhibitors are MK0752, gamma-secretase inhibitors, DAPT (N-[N-(3,5-Difluorophenylacetyl-L-alanyl)]-S-phenylglycine t-Butyl ester), Lilly GSI L685,458, compound E ((s,s)-2-(3,5-Difluorophenyl)-acetylamino]-N-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-propionamide), diazepine-type structures, DBZ
20 (dibenzazepine), JLK6 (7-amino-4-chloro-3-methoxyisocoumarin), Compound 18 ([11-endo]-N-(5,6,7,8,9,10-hexahydro- 6,9-methano benzo[9][8]annulen-11-yl)-thiophene-2-sulfonamide), alpha-secretase inhibitors, BMS-708163 (Avagacestat), gamma secretase modulator 3, gamma secretase modulator 2, gamma secretase modulator 1, RO4929097,
25 Semagacestat (LY450139), MK0752, LY411575, LY2811376, Flurizan, MRK560, L-685,458, Begacestat, TC-E-5006, PF3084014, LY3039478, LY900009, E2012, compound W, BMS 299897, FLI-06..

30 Suitable ATM (Ataxia telangiectasia mutated) kinase inhibitors are CP 466722, KU-60019, VE-821, VE-822, Torin 2, Mirin (CAS 299953-00-7).

Suitable MELK (maternal embryonic leucine zipper kinase) inhibitor is OTSSP167 (CAS#1431697-89-0).

Suitable EGF receptor inhibitor is PR610E, or its hypoxia activated prodrug Hypoxia, formally known as PR610, afatinib, gefitinib.

5 In a preferred embodiment of the present invention and/or embodiments thereof A is not a compound selected from the group consisting of Tyrosine kinase inhibitors, JAK inhibitors, VEGF receptor inhibitors, B-Raf inhibitors, MEK inhibitors, PARP inhibitors, Phosphoinositide 3-kinase inhibitors, Hsp90 inhibitors, folate receptor
10 targeting agents, serine/threonine kinase inhibitors, FGFR tyrosine kinase inhibitors, ALK inhibitorss, Bcl2 inhibitors, and EZH2 inhibitors.

In a preferred embodiment of the present invention and/or embodiments thereof A is not a compound selected from the group consisting Tyrosine kinase inhibitors, JAK inhibitors, VEGF receptor
15 inhibitors, B-Raf inhibitors, Hsp90 inhibitors, folate receptor targeting agents, serine/threonine kinase inhibitors, FGFR tyrosine kinase inhibitors, and Bcl2 inhibitors.

In a preferred embodiment of the present invention and/or embodiments thereof A is selected from the group consisting ALK inhibitors,
20 PARP inhibitors, Phosphoinositide 3-kinase inhibitors, CDK inhibitors, mTOR inhibitors, MELK, inhibitors, ATM inhibitor, EZH2 inhibitors, EGFR inhibitors.

In a preferred embodiment of the present invention and/or embodiments thereof A is selected from the group consisting CDK
25 inhibitors, and mTOR inhibitors, MELK inhibitors, ATM inhibitors, EGFR inhibitors. .

In a preferred embodiment of the present invention and/or embodiments thereof A is selected from the group consisting CDK inhibitors, and mTOR inhibitors, EGFR inhibitors..

In a preferred embodiment of the present invention and/or embodiments thereof A is selected from the group consisting MELK inhibitors, ATM inhibitors.

In a preferred embodiment of the present invention and/or
5 embodiments thereof A is CDK inhibitors.

In a preferred embodiment of the present invention and/or embodiments thereof A is mTOR inhibitor.

In a preferred embodiment of the present invention and/or embodiments thereof A is a MELK inhibitor.

10 In a preferred embodiment of the present invention and/or embodiments thereof A is an ATM inhibitor.

In a preferred embodiment of the present invention and/or embodiments thereof A is an EGFR inhibitor.

In a preferred embodiment of the present invention and/or
15 embodiments thereof, the LHRH receptor (gonadotropin-releasing hormone receptor) inhibitors such as AEZS-108 are not suitable.

In a preferred embodiment of the present invention and/or embodiments thereof A is a targeted agent.

In a preferred embodiment of the present invention and/or
20 embodiments thereof A is selected from the group consisting of nerviano, tirapazemin, tirapazamin derivative, 7,8-dihydro-6H-indeno[5,6-e][1,2,4]triazine 1-oxide, chlorambucil, bromine-derivative of chlorambucil, VE-821, VE-822, SN 30444 (2-[bis(2-bromoethyl)amino]-N-(2-hydroxyethyl)-5-nitrobenzamide) Chlorine-derivative of SN 30444 (2-[bis(2-
25 chloroethyl)amino]-N-(2-hydroxyethyl)-5-nitrobenzamide), cidofovir, cyclophosphamide, bromine-derivative of cyclophosphamide, MK0752, PR610, PR610E, chloroquine, PF03084014, temozolomide, CP466722, Torin 2, OTSSP167 (CAS#1431697-89-0), dasatinib, CEP-37440, PF-06463922, iniparib, 3 aminobenzamide, BAY 80-6946, Buparlisib, PI-103, Palomid 527,
30 IC-87114, GNE 477, CUDC-907, Selumetinib, binimetinib, AZD8055,

palbociclib, LEE011, Lestaurtinib, veliparib, MK4827, GCD-0879, , and GSK126.

In a preferred embodiment of the present invention and/or
embodiments thereof A is selected from the group consisting of nerviano,
5 dasatinib, CEP-37440, PF-06463922, iniparib, 3 aminobenzamide, BAY 80-
6946, Buparlisib, PI-103, Palomid 527, IC-87114, GNE 477, CUDC-907,
Selumetinib, binimetinib, AZD8055, palbociclib, LEE011, Lestaurtinib,
veliparib, MK4827, GCD-0879, MK0752, and GSK126.

In a more preferred embodiment of the present invention and/or
10 embodiments thereof A is selected from the group consisting of nerviano,
dasatinib, CEP-37440, PF-06463922, iniparib, 3 aminobenzamide, BAY 80-
6946, Buparlisib, PI-103, Palomid 527, IC-87114, GNE 477, CUDC-907,
Selumetinib, binimetinib, AZD8055, palbociclib, LEE011.

In a more preferred embodiment of the present invention and/or
15 embodiments thereof A is selected from the group consisting of nerviano,
dasatinib, CEP-37440, PF-06463922, iniparib, 3 aminobenzamide, BAY 80-
6946, Buparlisib, PI-103, Palomid 527, IC-87114, GNE 477, CUDC-907,
Selumetinib, binimetinib, AZD8055, palbociclib, LEE011, tirapazemin,
tirapazamin derivative, 7,8-dihydro-6H-indeno[5,6-e][1,2,4]triazine 1-oxide,
20 chlorambucil, bromine-derivative of chlorambucil, VE-821, VE-822, SN
30444, Chlorine-derivative of SN 30444, cidofovir, cyclophosphamide,
bromine-derivative of cyclophosphamide, MK0752, Notch inhibitor,
temozolomide, CP466722, Torin 2, OTSSP167 (CAS#1431697-89-0) PR610,
PR610E, chloroquine, PF03084014.

25 In a more preferred embodiment of the present invention and/or
embodiments thereof A is selected from the group consisting of tirapazemin,
tirapazamin derivative, 7,8-dihydro-6H-indeno[5,6-e][1,2,4]triazine 1-oxide,
chlorambucil, bromine-derivative of chlorambucil, VE-821, VE-822, SN
30444, Chlorine-derivative of SN 30444, cidofovir, cyclophosphamide,
30 bromine-derivative of cyclophosphamide, MK0752, Notch inhibitor,

temozolomide, CP466722, Torin 2, OTSSP167 (CAS#1431697-89-0), PR610, PR610E, chloroquine, PF03084014.

In a preferred embodiment of the present invention and/or
embodiments thereof A is not a compound selected from the group
5 consisting imatinib mesylate Gefitinib, Erlotinib hydrochloride, Sorafenib,
Sunitinib, Lapatinib, Nilotinib, Bortezomib, tamoxifen, Pacritinib, and
famitinib, CYT387, Alectinib, AP26113, X-396, ABT-737, Obatoclax, and
gossypol, BMN-637, olaparib, rucaparib, CEP 8983, idelalisib, PX-866, IPI-
145, GDC-0941, SF1126, XL 147, XL 765, TG100-115, AZD2461, apatinib,
10 lenvatinib, motesanib, and Regorafenib. vemurafenib, dabrafenib, LGX818,
sorafenib, PLX4720, PD-325901, cobimetinib, CI-1040, trametinib,
Geldanamycin, radicicol, tanespimycin.famitinib, salinomycin, vintafolide,
temsirolimus, everolimus. AZD4547, navitoclax.

In a preferred embodiment of the present invention and/or
15 embodiments thereof, A is not ABT-737.

In a preferred embodiment of the present invention and/or
embodiments thereof, A is selected from the group comprising Alkylating
agents, anti-metabolites, topoisomerase I inhibitors, and targeted agents. In
a preferred embodiment of the present invention and/or embodiments
20 thereof, A is selected from the group comprising alkylating agents and
targeting agents.

In a preferred embodiment of the invention and/or embodiments
thereof A is an anticancer agent that does not comprise a nitro-imidazol
group. In a preferred embodiment of the invention and/or embodiments
25 thereof A is not a nitrosourea, taxane, vinca alkaloid, anthracycline,
podophyllotoxin, or podophyllotoxin derivatives. In a preferred embodiment
of the invention and/or embodiments thereof A is a Tetrazine or a
nitrogenmustard. In a preferred embodiment of the invention and/or
embodiments thereof A is not hepsulfam

In a preferred embodiment of the invention and/or embodiments thereof A is selected from the group consisting of Tirapazamin, tirapazamin derivative, 7,8-dihydro-6H-indeno[5,6-e][1,2,4]triazine 1-oxide, chlorambucil, bromine derivative of chlorambucil, MK0752, VE-821, VE-822, cyclophosphamide, bromine derivative of cyclophosphamide, mephalan, bromine derivative of mehphalan, torin 2, OTSSP167 ((CAS#1431697-89-0), PR610, PR610E, chloroquine, PF03084014, bendamustine, procarbazine, dacarbazine, mitozolomide, temozolomide, SN 30444, chlorine derivative of SN 30444, ariziridinybenzoquinone (NSC182986), dianhydrogalactitol, hycanthone methanesulfonate, ethylnitrosourea, acivicin, hydroxyurea, nitrosourea, imidazole-pyazole, 3-tritylthio-L-alanine, mitoxantrone, camptothecin, 9-amino camptothecin, 10-hydroxycamptothecin, 14-chloro-20(S)-camptothecin hydrate, 9-amino-20-(R,S)-camptothecin, 7-chlorocamptothecin, NSC606985, NSC374028, 9-methoxycamptothecin, NSC295501, NSC606172, NSC606173, camptothecin lysinate HCl, camptothecin glutamate, camptothecin hemisuccinate, amonafide, cidofovir, aphidicolin glycinate, 3-demethylthiocolchine, irinotecan, toptecan, camptothecin butylglycinate ester hydrochloride, camptothecin ethylglycinate ester hydrochloride, amsacrine, uramustine, methotrexate, pemetrexed, NSC174121, NSC132483, NSC184692, NSC 134033, NSC6230172, 5-fluorouracil, capecitabine, gemcitabine, arabinosylcytosine, decitabine, azacitidine, nelarabine, cladribine, clofarabine, pentostatin, thioguanine, mercaptopurine, 3-hydroxy-2-formylpyridine thiosemicarbazone, 5-hydroxypicolinaldehyde thiosemicarbazone, alpha-TGdR, beta-TGdR, cyclocitidine, thioguanine, 6-mercaptopurine, piroxantrone, nerviano, dasatinib, CEP-37440, PF-06463922, iniparib, 3 aminobenzamide, BAY 80-6946, Buparlisib, PI-103, Palomid 527, IC-87114, GNE 477, CUDC-907, Selumetinib, binimetinib, AZD8055, palbociclib, LEE011, Lestaurtinib, veliparib, MK4827, GCD-0879, MK0752, and GSK126.

In a preferred embodiment of the invention and/or embodiments thereof A is selected from the group consisting Tirapazamin, tirapazamin derivative, 7,8-dihydro-6H-indeno[5,6-e][1,2,4]triazine 1-oxide, chlorambucil, VE-821, VE-822, cyclophosphamide, bromine derivative of cyclophosphamide, mephalan, bromine derivative of chlorambucil, MK0752, SN 30444, chlorine derivative of SN 30444, torin 2, OTSSP167 ((CAS#1431697-89-0), PR610, PR610E, chloroquine, PF03084014, bendamustine, procarbazine, dacarbazine, mitozolomide, temozolomide, ariziridinylbenzoquinone (NSC182986), dianhydrogalactitol, hycanthone methanesulfonate, ethylnitrosourea, acivicin, hydroxyurea, nitrosourea, imidazole-pyazole, 3-tritylthio-L-alanine, mitoxantrone, camptothecin, 9-amino camptothecin, 10-hydroxycamptothecin, 14-chloro-20(S)-camptothecin hydrate, 9-amino-20-(R,S)-camptothecin, 7-chlorocamptothecin, NSC606985, NSC374028, 9-methoxycamptothecin, NSC295501, NSC606172, NSC606173, camptothecin lysinate HCl, camptothecin glutamate, camptothecin hemisuccinate, amonafide, cidofovir, aphidicolin glycinate, 3-demethylthiocolchine, irinotecan, toptecan, camptothecin butylglycinate ester hydrochloride, camptothecin ethylglycinate ester hydrochloride, amsacrine, nerviano, dasatinib, CEP-37440, PF-06463922, iniparib, 3 aminobenzamide, BAY 80-6946, Buparlisib, PI-103, Palomid 527, IC-87114, GNE 477, CUDC-907, Selumetinib, binimetinib, AZD8055, palbociclib, and LEE011.

In a preferred embodiment of the invention and/or embodiments thereof A is selected from the group consisting Tirapazamin, tirapazamin derivative, 7,8-dihydro-6H-indeno[5,6-e][1,2,4]triazine 1-oxide, chlorambucil, VE-821, VE-822, cyclophosphamide, bromine derivative of cyclophosphamide, bromine derivative of mephalan, mephalan, bromine derivative of chlorambucil, MK0752, OTSSP167 ((CAS#1431697-89-0), PR610, PR610E, chloroquine, PF03084014, bendamustine, procarbazine, mitozolomide, temozolomide, SN 30444, chlorine derivative of SN 30444,

torin 2, ariziridinylbenzoquinone (NSC182986), dianhydrogalactitol, hycanthone methanesulfonate, ethylnitrosourea, acivicin, hydroxyurea, nitrosourea, imidazole-pyazole, 3-tritylthio-L-alanine, mitoxantrone, camptothecin, 9-amino camptothecin, 10-hydroxycamptothecin, 14-chloro-
5 20(S)-camptothecin hydrate, 9-amino-20-(R,S)-camptothecin, 7-chlorocamptothecin, NSC606985, NSC374028, 9-methoxycamptothecin, NSC295501, NSC606172, NSC606173, camptothecin lysinate HCl, camptothecin glutamate, camptothecin hemisuccinate, amonafide, cidofovir, aphidicolin glycinate, 3-demethylthiocolchine, irinotecan, topotecan,
10 camptothecin butylglycinate ester hydrochloride, camptothecin ethylglycinate ester hydrochloride, amsacrine, nerviano, dasatinib, CEP-37440, PF-06463922, iniparib, 3 aminobenzamide, BAY 80-6946, Buparlisib, PI-103, Palomid 527, IC-87114, GNE 477, CUDC-907, Selumetinib, binimetinib, AZD8055, palbociclib, and LEE011.

15 In a preferred embodiment of the invention and/or embodiments thereof A is selected from the group consisting Tirapazamin, tirapazamin derivative, 7,8-dihydro-6H-indeno[5,6-e][1,2,4]triazine 1-oxide chlorambucil, VE-821, VE-822, cyclophosphamide, bromine derivative of
cyclophosphamide mephalan, bromine derivative of mephalan, bromine
20 derivative of chlorambucil, MK0752, OTSSP167 ((CAS#1431697-89-0), PR610, PR610E, chloroquine, PF03084014, bendamustine, procarbazine, mitozolomide, temozolomide, SN 30444, chlorine derivative of SN 30444, torin 2, ariziridinylbenzoquinone (NSC182986), hycanthone methanesulfonate, ethylnitrosourea, acivicin, hydroxyurea, nitrosourea,
25 imidazole-pyazole, 3-tritylthio-L-alanine, mitoxantrone, camptothecin, 9-amino camptothecin, 10-hydroxycamptothecin, 14-chloro-20(S)-camptothecin hydrate, 9-amino-20-(R,S)-camptothecin, 7-chlorocamptothecin, NSC606985, NSC374028, 9-methoxycamptothecin, NSC295501, NSC606172, NSC606173, camptothecin lysinate HCl,
30 camptothecin glutamate, camptothecin hemisuccinate, amonafide, cidofovir,

aphidicolin glycinate, 3-demethylthiocolchine, irinotecan, toptecan, camptothecinbutylglycinate ester hydrochloride, camptothecinethylglycinate esterhydrochloride, amsacrine, nerviano, dasatinib, CEP-37440, PF-06463922, iniparib, 3 aminobenzamide, BAY 80-6946, Buparlisib, PI-103,
 5 Palomid 527, IC-87114, GNE 477, CUDC-907, Selumetinib, binimetinib, AZD8055, palbociclib, and LEE011.

In a preferred embodiment of the invention and/or embodiments thereof A is selected from the group consisting Tirapazamin, tirapazamin derivative, 7,8-dihydro-6H-indeno[5,6-e][1,2,4]triazine 1-oxide,
 10 chlorambucil, VE-821, VE-822, cyclophosphamide, bromine derivative of cyclophosphamide mephalan, bromine derivative of mephalan, bromine derivative of chlorambucil, MK0752, OTSSP167 (CAS#1431697-89-0), PR610, PR610E, chloroquine, PF03084014, temozolomide, SN 30444, chlorine derivative of SN 30444, torin 2, cidofovir.

15 In a preferred embodiment of the invention and/or embodiments thereof A is not a compound selected from the group consisting of Improsan, ifosfamide, spiromustine, N-(2-Chloroethyl)-N'-(2,6-dioxo-3-piperidinyl)-N-nitrosourea (PCNU), peperazinedione (NSC-135758), semustine, carmustine, lomustine, streptozocin, chlorozotocin, leucine sarcolysine,
 20 cyanomorpholino-doxorubicin, doxorubicin, fluorodopan, ametycin, profiromycin, trimetrexate, fludarabine, alanosine, pyrazofurin, triazinate, dichloroallyl lawsone, ftorafur fluorofur, dihydro-5-azacytidine, PALA, guanazole, inosine dialdehyde, macbecin II, vinblastine, vincristine, vindisine, vinorelbine, vincaminol, vincamajine, vineridine, vinflunine,
 25 docetaxel, paclitaxel, podophyllotoxin, etoposide, teniposide, allocolchicine, halichondrin B, colchine, N-Benzoyl-deacetylcolchicine, dolastatin 10, maytansin, NSC608832, novobiocin, aclarubicin, merbarone, NSC295500, camptothecin phosphate, morpholinoadriamycin, anthrapyrazole, pyrazoloacridine, bisantrene, daunorubicin, deoxorubicin, menogaril, N,N-
 30 Dibenzyl daunorubicin hydrochloride, zorobicin, VM-26, VP-16, epirubicin,

idarubicin, valrubicin, actinomycin, bleomycin, plicamycin, mitomycin C, pirarubicin, Mithramycin, imatinib mesylate Gefitinib, Erlotinib hydrochloride, Sorafenib, Sunitinib, Lapatinib, Nilotinib, Bortezomib, tamoxifen, Pacritinib, and famitinib, CYT387, Alectinib, AP26113, X-396, 5 ABT-737, Obatoclax, and gossypol, BMN-637, olaparib, rucaparib, CEP 8983, idelalisib, PX-866, IPI-145, GDC-0941, SF1126, XL 147, XL 765, TG100-115, AZD2461, apatinib, lenvatinib, motesanib, and Regorafenib. vemurafenib, dabrafenib, LGX818, sorafenib, PLX4720, PD-325901, cobimetinib, CI-1040, trametinib, Geldanamycin, radicicol, 10 tanespimycin.famitinib, salinomycin, vintafolide, temsirolimus, everolimus. AZD4547, and navitoclax,

In a preferred embodiment of the invention and/or embodiments thereof A has 6 or less ring structures, preferably 5 or less, preferably 4 or less, preferably 3 or less, preferably 2 or less, preferably 1 ring structure.. In 15 a preferred embodiment of the invention and/or embodiments thereof A has a maximum of 6 ring structures, preferably a maximum of 5 ring structures, preferably a maximum of 4 ring structures, preferably a maximum of 3 ring structures, preferably a maximum of 2 ring structures. A ring or ring structure is a cyclic structure comprising 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 20 16, 18, 20, 22, 24, 26, 28, 30, 34, 36, 38, 40 or more atoms. A ring or ring structure may be aromatic, saturated, partially unsaturated, or unsaturated. The ring may be a carbon ring, wherein the atoms of the ring are all carbon atoms. The ring may also be a hetero cycle wherein at least one of the atoms in the ring is a hetero atom such as O, N, P, or S, and the 25 remainder being carbon atoms. Preferred hetero cycles are hetero cycles with O or N. The rings may be fused as in anthracene, naphthalene and quinoline. For single rings, i.e. not fused, the ring preferably comprise 4, 5, 6, 7, or 8 atoms, more preferably, 5 or 6 atoms. For fused rings, the individual rings that are fused comprise each preferably 3, 4, 5, 6, 7, or 8 30 atoms, more preferably, 4, 5, or 6 atoms, more preferably 5 or 6 atoms. In a

preferred embodiment of the present invention and/or embodiments thereof the total number of atoms that are present in a ring is less than 40, more preferably less than 36, more preferably less than 30, more preferably less than 26, more preferably less than 22, more preferably less than 18, more preferably less than 16, more preferably less than 14, more preferably less than 12.

In a preferred embodiment of the invention and/or embodiments thereof A does not comprise a sulfonamide, sulfamide, or a sulfamate group. It is to be understood that the original anticancer agent A preferably does not comprise a sulfonamide, sulfamide, or a sulfamate group. A sulphonamide is a SO_2NR_2 group, a sulfamate is a $\text{O-SO}_2\text{NR}_2$ group and a sulfamide is a NRSO_2NR_2 group, wherein R is a substituent such as hydrogen, halogen, alkyl.

In a preferred embodiment of the invention and/or embodiments thereof A has a molecular weight of less than 1500 D, preferably less than 1200 D, preferably less than 1000 D, more preferably less than 800 D, more preferably less than 700 D, more preferably less than 600 D, more preferably less than 550 D, more preferably less than 500 D, more preferably less than 450 D, more preferably less than 400 D. In a preferred embodiment of the invention and/or embodiments thereof A has a molecular weight from 150 D to 1200 D, more preferably from 180 D to 1000 D, more preferably from 200 D to 800 D, more preferably from 250 D to 700 D, more preferably from 300 D to 600 D, more preferably from 350 D to 500 D, more preferably from 400 D to 450 D, more preferably from 180 D to 1000 D, more preferably from 180 D to 750 D, more preferably from 180 D to 550 D, more preferably from 180 D to 500 D, more preferably from 180 D to 450 D. In a preferred embodiment of the invention and/or embodiments thereof the compound has a molecular weight of less than 1600 D, preferably less than 1400 D, preferably less than 1200 D, more preferably less than 1000 D, more preferably less than 800 D, more preferably less than 700 D, more

preferably less than 600 D, more preferably less than 550 D, more preferably less than 500 D, more preferably less than 450 D. In a preferred embodiment of the invention and/or embodiments thereof the compound has a molecular weight from 150 D to 1500 D, more preferably from 180 D to 1200 D, more preferably from 200 D to 1000 D, more preferably from 250 D to 800 D, more preferably from 300 D to 700 D, more preferably from 350 D to 600 D, more preferably from 400 D to 500 D, more preferably from 180 D to 1000 D, more preferably from 180 D to 750 D, more preferably from 180 D to 550 D, more preferably from 180 D to 500 D, more preferably from 180 D to 450 D.

In a preferred embodiment of the invention and/or embodiments thereof A has no more than 7 hydrogen bond donors, preferably no more than 6 hydrogen bond donors, preferably no more than 5 hydrogen bond donors, preferably no more than 4 hydrogen bond donors, preferably no more than 3 hydrogen bond donors, preferably no more than 2 hydrogen bond donors. A hydrogen bond donor is a OH or NH group. The number of hydrogen bond donors is expressed as the sum of OH and NH bonds. In a preferred embodiment of the invention and/or embodiments thereof the compound has no more than 7 hydrogen bond donors, preferably no more than 6 hydrogen bond donors, preferably no more than 5 hydrogen bond donors, preferably no more than 4 hydrogen bond donors, preferably no more than 3 hydrogen bond donors, preferably no more than 2 hydrogen bond donors.

In a preferred embodiment of the invention and/or embodiments thereof A has no more than 15 hydrogen bond acceptors, preferably no more than 14 hydrogen bond acceptors, preferably no more than 12 hydrogen bond acceptors, preferably no more than 10 hydrogen bond acceptors, preferably no more than 9 hydrogen bond acceptors, preferably no more than 8 hydrogen bond acceptors, preferably no more than 7 hydrogen bond acceptors, preferably no more than 6 hydrogen bond acceptors, preferably no

more than 5 hydrogen bond acceptors, preferably no more than 4 hydrogen bond acceptors. Hydrogen bond acceptors is expressed as the sum of O and N atoms. In a preferred embodiment of the invention and/or embodiments thereof the compound has no more than 15 hydrogen bond acceptors,
5 preferably no more than 14 hydrogen bond acceptors, preferably no more than 12 hydrogen bond acceptors, preferably no more than 10 hydrogen bond acceptors, preferably no more than 9 hydrogen bond acceptors, preferably no more than 8 hydrogen bond acceptors, preferably no more than 7 hydrogen bond acceptors, preferably no more than 6 hydrogen bond
10 acceptors, preferably no more than 5 hydrogen bond acceptors, preferably no more than 4 hydrogen bond acceptors.

In a preferred embodiment of the invention and/or embodiments thereof A has a octanol-water partition coefficient LogP of no greater than 7, preferably a LogP of no greater than 6, preferably a LogP of no greater than
15 5.5, preferably a LogP of no greater than 5, preferably a LogP of no greater than 4.5, preferably a LogP of no greater than 4, preferably a LogP of no greater than 3.5, preferably a LogP of no greater than 3, preferably a LogP of no greater than 2.5, preferably a LogP of no greater than 2, preferably a LogP of no greater than 1.5, preferably a LogP of no greater than 1,
20 preferably a LogP of no greater than 0.5. In a preferred embodiment of the invention and/or embodiments thereof A has a octanol-water partition coefficient LogP of less than 7, preferably a LogP of less than 6, preferably a LogP of less than 5.5, preferably a LogP of less than 5, preferably a LogP of less than 4.5, preferably a LogP of less than 4, preferably a LogP of less than
25 3.5, preferably a LogP of less than 3, preferably a LogP of less than 2.5, preferably a LogP of less than 2, preferably a LogP of less than 1.5, preferably a LogP of less than 1, preferably a LogP of less than 0.5. A partition-coefficient (logP) or distribution-coefficient (logD) is the ratio of concentrations of a compound in a mixture of two immiscible phases at
30 equilibrium. These coefficients are a measure of the difference in solubility

of the compound in these two phases. In a preferred embodiment of the invention and/or embodiments thereof A has a octanol-water partition coefficient LogP from -0.9 to $+7.0$, preferably a LogP from -0.4 to $+6.5$, preferably a LogP from -0.1 to $+6.1$, preferably a LogP from $+0.1$ to $+5.9$,
5 preferably a LogP from $+0.4$ to $+5.6$, preferably a LogP from -0.9 to $+5.1$, preferably a LogP from $+1.2$ to $+4.8$, preferably a LogP from $+1.4$ to $+4.2$, preferably a LogP from $+1.8$ to $+3.8$, preferably a LogP from $+2.2$ to $+3.5$, preferably a LogP from $+2.8$ to $+3.2$.

In a preferred embodiment of the invention and/or embodiments thereof the compound has a octanol-water partition coefficient LogP of no
10 greater than 7, preferably a LogP of no greater than 6, preferably a LogP of no greater than 5.5, preferably a LogP of no greater than 5, preferably a LogP of no greater than 4.5, preferably a LogP of no greater than 4, preferably a LogP of no greater than 3.5, preferably a LogP of no greater
15 than 3, preferably a LogP of no greater than 2.5, preferably a LogP of no greater than 2, preferably a LogP of no greater than 1.5, preferably a LogP of no greater than 1, preferably a LogP of no greater than 0.5. In a preferred embodiment of the invention and/or embodiments thereof the compound has a octanol-water partition coefficient LogP of less than 7, preferably a LogP
20 of less than 6, preferably a LogP of less than 5.5, preferably a LogP of less than 5, preferably a LogP of less than 4.5, preferably a LogP of less than 4, preferably a LogP of less than 3.5, preferably a LogP of less than 3, preferably a LogP of less than 2.5, preferably a LogP of less than 2, preferably a LogP of less than 1.5, preferably a LogP of less than 1,
25 preferably a LogP of less than 0.5. In a preferred embodiment of the invention and/or embodiments thereof the compound has a octanol-water partition coefficient LogP from -0.9 to $+7.0$, preferably a LogP from -0.4 to $+6.5$, preferably a LogP from -0.1 to $+6.1$, preferably a LogP from $+0.1$ to $+5.9$, preferably a LogP from $+0.4$ to $+5.6$, preferably a LogP from -0.9 to
30 $+5.1$, preferably a LogP from $+1.2$ to $+4.8$, preferably a LogP from $+1.4$ to

+4.2, preferably a LogP from +1.8 to +3.8, preferably a LogP from +2.2 to +3.5, preferably a LogP from +2.8 to +3.2.

In a preferred embodiment of the invention and/or embodiments thereof A has a Molar refractivity from 20 to 150, preferably a Molar
5 refractivity from 30 to 140, preferably a Molar refractivity from 40 to 130, preferably a Molar refractivity from 50 to 120, preferably a Molar refractivity from 60 to 100, preferably a Molar refractivity from 70 to 90, preferably a Molar refractivity from 75 to 85. In a preferred embodiment of the invention and/or embodiments thereof the compound has a Molar
10 refractivity from 20 to 150, preferably a Molar refractivity from 30 to 140, preferably a Molar refractivity from 40 to 130, preferably a Molar refractivity from 50 to 120, preferably a Molar refractivity from 60 to 100, preferably a Molar refractivity from 70 to 90, preferably a Molar refractivity from 75 to 85.

15 In a preferred embodiment of the invention and/or embodiments thereof A comprises 20 to 70 atoms preferably 25 to 65 atoms, preferably 30 to 60 atoms, preferably 32 to 55 atoms, preferably 35 to 52 atoms, preferably 38 to 50 atoms, preferably 40 to 48 atoms, preferably 42 to 46 atoms, preferably 44 to 45 atoms. The number of atoms includes H-bond donors
20 e.g.; OH's and NH's and H-bond acceptors e.g.; N's and O's. In a preferred embodiment of the invention and/or embodiments thereof the compound comprises 20 to 70 atoms preferably 25 to 65 atoms, preferably 30 to 60 atoms, preferably 32 to 55 atoms, preferably 35 to 52 atoms, preferably 38 to 50 atoms, preferably 40 to 48 atoms, preferably 42 to 46 atoms, preferably
25 44 to 45 atoms.

In a preferred embodiment of the invention and/or embodiments thereof A has a polar surface area no greater than $140 \text{ \AA}^2$, preferably no greater than $120 \text{ \AA}^2$, preferably no greater than $100 \text{ \AA}^2$, preferably no greater than $90 \text{ \AA}^2$, preferably no greater than $80 \text{ \AA}^2$, preferably no greater
30 than $75 \text{ \AA}^2$, preferably no greater than $60 \text{ \AA}^2$, preferably no greater than 50

Å². The polar surface area (PSA) of a molecule is defined as the surface sum over all polar atoms, primarily oxygen and nitrogen, also including their attached hydrogens. In a preferred embodiment of the invention and/or embodiments thereof the compound has a polar surface area no greater than 140 Å², preferably no greater than 120 Å², preferably no greater than 100 Å², preferably no greater than 90 Å², preferably no greater than 80 Å², preferably no greater than 75 Å², preferably no greater than 60 Å², preferably no greater than 50 Å².

In a preferred embodiment of the invention and/or embodiments thereof A comprises not more than 15 rotatable bonds, preferably not more than 12 rotatable bonds, preferably not more than 10 rotatable bonds, preferably not more than 9 rotatable bonds, preferably not more than 8 rotatable bonds, preferably not more than 7 rotatable bonds, preferably not more than 6 rotatable bonds, preferably not more than 5 rotatable bonds, preferably not more than 4 rotatable bonds, preferably not more than 3 rotatable bonds, preferably not more than 2 rotatable bonds. Rotatable bond is defined as any single non-ring bond, bounded to non-terminal heavy (i.e., non-hydrogen) atom. Amide C-N bonds are not considered because of their high rotational energy barrier (F. Veber et al., J.Med.Chem. 2002, 45, 2615-2623). In a preferred embodiment of the invention and/or embodiments thereof the compound comprises not more than 15 rotatable bonds, preferably not more than 12 rotatable bonds, preferably not more than 10 rotatable bonds, preferably not more than 9 rotatable bonds, preferably not more than 8 rotatable bonds, preferably not more than 7 rotatable bonds, preferably not more than 6 rotatable bonds, preferably not more than 5 rotatable bonds, preferably not more than 4 rotatable bonds, preferably not more than 3 rotatable bonds, preferably not more than 2 rotatable bonds.

In a preferred embodiment of the invention and/or embodiments thereof A has an cell proliferation inhibiting activity of less than 10 mM, less than 5 mM, less than 1 mM, less than 100 μM, less than 10 μM, less

than 1 μm , less than 100 nM, less than 10 nM, less than 1 nM, less than 100 pM, less than 10 pM, less than 1 pM. The proliferation inhibition activity means the lowest concentration wherein 50% of the maximal inhibition of cell proliferation is reached, or wherein 50% inhibition of the biological activity of cancer cells is reached. The 50% of the maximal inhibition of cell proliferation is sometimes referred to as GI50. The 50% inhibition of the biological activity of cancer cells is sometimes referred to as IC50. Thus in a preferred embodiment of the invention and/or embodiments thereof A has an GI50 of less than 10 mM, less than 5 mM, less than 1 mM, less than 100 μM , less than 10 μM , less than 1 μm , less than 100 nM, less than 10 nM, less than 1 nM, less than 100 pM, less than 10 pM, less than 1 pM.

Thus in a preferred embodiment of the invention and/or embodiments thereof A has an IC50 of less than 10 mM, less than 5 mM, less than 1 mM, less than 100 μM , less than 10 μM , less than 1 μm , less than 100 nM, less than 10 nM, less than 1 nM, less than 100 pM, less than 10 pM, less than 1 pM.

In a preferred embodiment of the invention and/or embodiments thereof A fulfils at least two of the rules defined below .

1. A has a molecular weight of less than 1500 D, preferably less than 1200 D, preferably less than 1000 D, more preferably less than 800 D, more preferably less than 700 D, more preferably less than 600 D, more preferably less than 550 D, more preferably less than 500 D, more preferably less than 450 D, more preferably less than 400 D.

2. A has no more than 7 hydrogen bond donors, preferably no more than 6 hydrogen bond donors, preferably no more than 5 hydrogen bond donors, preferably no more than 4 hydrogen bond donors, preferably no more than 3 hydrogen bond donors, preferably no more than 2 hydrogen bond donors.

3. A has no more than 15 hydrogen bond acceptors, preferably no more than 14 hydrogen bond acceptors, preferably no more than 12

hydrogen bond acceptors, preferably no more than 10 hydrogen bond acceptors, preferably no more than 9 hydrogen bond acceptors, preferably no more than 8 hydrogen bond acceptors, preferably no more than 7 hydrogen bond acceptors, preferably no more than 6 hydrogen bond acceptors,
5 preferably no more than 5 hydrogen bond acceptors, preferably no more than 4 hydrogen bond acceptors.

4. A has a octanol-water partition coefficient LogP of no greater than 7, preferably a LogP of no greater than 6, preferably a LogP of no greater than 5.5, preferably a LogP of no greater than 5, preferably a LogP
10 of no greater than 4.5, preferably a LogP of no greater than 4, preferably a LogP of no greater than 3.5, preferably a LogP of no greater than 3, preferably a LogP of no greater than 2.5, preferably a LogP of no greater than 2, preferably a LogP of no greater than 1.5, preferably a LogP of no greater than 1, preferably a LogP of no greater than 0.5.

15 5. A has a Molar refractivity from 20 to 150, preferably a Molar refractivity from 30 to 140, preferably a Molar refractivity from 40 to 130, preferably a Molar refractivity from 50 to 120, preferably a Molar refractivity from 60 to 100, preferably a Molar refractivity from 70 to 90, preferably a Molar refractivity from 75 to 85.

20 6. A comprises 20 to 70 atoms preferably 25 to 65 atoms, preferably 30 to 60 atoms, preferably 32 to 55 atoms, preferably 35 to 52 atoms, preferably 38 to 50 atoms, preferably 40 to 48 atoms, preferably 42 to 46 atoms, preferably 44 to 45 atoms.

7. A has a polar surface area no greater than $140 \text{ \AA}^2$, preferably no
25 greater than $120 \text{ \AA}^2$, preferably no greater than $100 \text{ \AA}^2$, preferably no greater than $90 \text{ \AA}^2$, preferably no greater than $80 \text{ \AA}^2$, preferably no greater than $75 \text{ \AA}^2$, preferably no greater than $60 \text{ \AA}^2$, preferably no greater than $50 \text{ \AA}^2$.

8. A comprises not more than 15 rotatable bonds, preferably not
30 more than 12 rotatable bonds, preferably not more than 10 rotatable bonds,

preferably not more than 9 rotatable bonds, preferably not more than 8 rotatable bonds, preferably not more than 7 rotatable bonds, preferably not more than 6 rotatable bonds, preferably not more than 5 rotatable bonds, preferably not more than 4 rotatable bonds, preferably not more than 3
5 rotatable bonds, preferably not more than 2 rotatable bonds.

9. A has an IC₅₀ of less than 10 mM, less than 5 mM, less than 1 mM, less than 100 μ M, less than 10 μ M, less than 1 μ m, less than 100 nM, less than 10 nM, less than 1 nM, less than 100 pM, less than 10 pM, less than 1 pM.

10 In a preferred embodiment of the invention and/or embodiments thereof A comprises not more than 10 rotatable bonds and has a polar surface area no greater than 140 $\text{\AA}^2$.

In a preferred embodiment of the invention and/or embodiments thereof A comprises not more than 10 rotatable bonds and has a polar
15 surface area no greater than 90 $\text{\AA}^2$.

In a preferred embodiment of the invention and/or embodiments thereof the compound has a carbonic anhydrase inhibitory activity of of less than 10 mM, less than 5 mM, less than 1 mM, less than 100 μ M, less than 10 μ M, less than 1 μ m, less than 100 nM, less than 10 nM, less than 1 nM,
20 less than 100 pM, less than 10 pM, less than 1 pM.

In a preferred embodiment of the invention and/or embodiments thereof the compound has a carbonic anhydrase inhibitory IX activity of of less than 10 mM, less than 5 mM, less than 1 mM, less than 100 μ M, less than 10 μ M, less than 1 μ m, less than 100 nM, less than 10 nM, less than 1
25 nM, less than 100 pM, less than 10 pM, less than 1 pM.

In a preferred embodiment of the invention and/or embodiments thereof the compound has a IC₅₀ for carbonic anhydrase of of less than 10 mM, less than 5 mM, less than 1 mM, less than 100 μ M, less than 10 μ M, less than 1 μ m, less than 100 nM, less than 10 nM, less than 1 nM, less than
30 100 pM, less than 10 pM, less than 1 pM.

In a preferred embodiment of the invention and/or embodiments thereof the compound has a IC₅₀ for carbonic anhydrase IX of less than 10 mM, less than 5 mM, less than 1 mM, less than 100 μ M, less than 10 μ M, less than 1 μ m, less than 100 nM, less than 10 nM, less than 1 nM, less than 100 pM, less than 10 pM, less than 1 pM.

In a preferred embodiment of the invention and/or embodiments thereof the compound fulfils at least two of the rules defined below .

1. The compound has a molecular weight of less than 1500 D, preferably less than 1200 D, preferably less than 1000 D, more preferably less than 800 D, more preferably less than 700 D, more preferably less than 600 D, more preferably less than 550 D, more preferably less than 500 D, more preferably less than 450 D, more preferably less than 400 D.

2. The compound has no more than 7 hydrogen bond donors, preferably no more than 6 hydrogen bond donors, preferably no more than 5 hydrogen bond donors, preferably no more than 4 hydrogen bond donors, preferably no more than 3 hydrogen bond donors, preferably no more than 2 hydrogen bond donors.

3. The compound has no more than 15 hydrogen bond acceptors, preferably no more than 14 hydrogen bond acceptors, preferably no more than 12 hydrogen bond acceptors, preferably no more than 10 hydrogen bond acceptors, preferably no more than 9 hydrogen bond acceptors, preferably no more than 8 hydrogen bond acceptors, preferably no more than 7 hydrogen bond acceptors, preferably no more than 6 hydrogen bond acceptors, preferably no more than 5 hydrogen bond acceptors, preferably no more than 4 hydrogen bond acceptors.

4. The compound has a octanol-water partition coefficient LogP of no greater than 7, preferably a LogP of no greater than 6, preferably a LogP of no greater than 5.5, preferably a LogP of no greater than 5, preferably a LogP of no greater than 4.5, preferably a LogP of no greater than 4, preferably a LogP of no greater than 3.5, preferably a LogP of no greater

than 3, preferably a LogP of no greater than 2.5, preferably a LogP of no greater than 2, preferably a LogP of no greater than 1.5, preferably a LogP of no greater than 1, preferably a LogP of no greater than 0.5.

5 5. The compound has a Molar refractivity from 20 to 150, preferably a Molar refractivity from 30 to 140, preferably a Molar refractivity from 40 to 130, preferably a Molar refractivity from 50 to 120, preferably a Molar refractivity from 60 to 100, preferably a Molar refractivity from 70 to 90, preferably a Molar refractivity from 75 to 85.

10 6. The compound comprises 20 to 70 atoms preferably 25 to 65 atoms, preferably 30 to 60 atoms, preferably 32 to 55 atoms, preferably 35 to 52 atoms, preferably 38 to 50 atoms, preferably 40 to 48 atoms, preferably 42 to 46 atoms, preferably 44 to 45 atoms.

15 7. The compound has a polar surface area no greater than $140 \text{ \AA}^2$, preferably no greater than $120 \text{ \AA}^2$, preferably no greater than $100 \text{ \AA}^2$, preferably no greater than $90 \text{ \AA}^2$, preferably no greater than $80 \text{ \AA}^2$, preferably no greater than $75 \text{ \AA}^2$, preferably no greater than $60 \text{ \AA}^2$, preferably no greater than $50 \text{ \AA}^2$.

20 8. The compound comprises not more than 15 rotatable bonds, preferably not more than 12 rotatable bonds, preferably not more than 10 rotatable bonds, preferably not more than 9 rotatable bonds, preferably not more than 8 rotatable bonds, preferably not more than 7 rotatable bonds, preferably not more than 6 rotatable bonds, preferably not more than 5 rotatable bonds, preferably not more than 4 rotatable bonds, preferably not more than 3 rotatable bonds, preferably not more than 2 rotatable bonds.

25 9. The compound has an IC₅₀ for proliferation of less than 10 mM, less than 5 mM, less than 1 mM, less than 100 μM , less than 10 μM , less than 1 μM , less than 100 nM, less than 10 nM, less than 1 nM, less than 100 pM, less than 10 pM, less than 1 pM.

30 10. The compound has IC₅₀ for carbonic anhydrase IX of less than 10 mM, less than 5 mM, less than 1 mM, less than 100 μM , less than

10 μM , less than 1 μM , less than 100 nM, less than 10 nM, less than 1 nM,
less than 100 pM, less than 10 pM, less than 1 pM.

In a preferred embodiment of the invention and/or embodiments
thereof the compound comprises not more than 10 rotatable bonds and has a
5 polar surface area no greater than 140 $\text{\AA}^2$.

In a preferred embodiment of the invention and/or embodiments
thereof the compound comprises not more than 10 rotatable bonds and has a
polar surface area no greater than 90 $\text{\AA}^2$.

In a preferred embodiment of the invention and/or embodiments
10 thereof the compound comprises a chelating agent comprising a metal ion
suitable for imaging, fluorescent moiety, or a ^{18}F containing moiety.

Suitable chelating agents are chelating agents that can complex
metal ions. Suitable chelating agents may be selected from DOTA, DTPA,
Deferoxamine, DOTA-TATE, DOTATOC, DTPA-BMA, EOB-DTPA, HP-
15 DO3A, BOPTA.

In a preferred embodiment of the invention and/or embodiments
thereof the compound comprises a chelating agent comprising a metal ion
suitable for imaging. Metal ions suitable for imaging may be metal ions that
are used in PET scans, MRI and so on. Suitable metal ion for imaging may
20 be selected from the group consisting of Cobalt-57, Copper-64, Copper-67,
Gallium-67, Gallium-68, Germanium-68, Indium-111, Iodine-123, Iodine-
124, Krypton-81m, Rubidium-81, Rubidium, Strontium-82, Thallium-201,
Iron, Iron oxide, Gadolinium-64, Zirconium-89.

In a preferred embodiment of the invention and/or embodiments
25 thereof the compound comprises fluorescent moiety. A fluorescent moiety is
a fluorescent chemical compound that can re-emit light upon light
excitation. Fluorescent moiety typically contain several combined aromatic
groups, or plane or cyclic molecules with several π bonds. Fluorescent
moieties may be used as a tracer in fluids, as a dye for staining of certain
30 structures, as a substrate of enzymes, or as a probe or indicator.

Suitable fluorescent moieties may be selected from the group comprising fluorescent protein such as GFP (green), YFP (yellow) and RFP (red) or Non-protein organic fluorescent moiety such as Xanthene derivatives e.g. fluorescein, rhodamine, Oregon green, eosin, and Texas red; Cyanine derivatives e.g. cyanine, indocarbocyanine, oxacarbocyanine, thiocarbocyanine, and merocyanine; Naphthalene derivatives (dansyl and prodan derivatives); Coumarin derivatives, , oxadiazole derivatives e.g. pyridyloxazole, nitrobenzoxadiazole and benzoxadiazole; Anthracene derivatives e.g. anthraquinones, including DRAQ5, DRAQ7 and CyTRAK Orange; Pyrene derivatives e.g. cascade blue; Oxazine derivatives e.g. Nile red, Nile blue, cresyl violet, oxazine 170; Acridine derivatives e.g. proflavin, acridine orange, acridine yellow; Arylmethine derivatives e.g. auramine, crystal violet, malachite green; Tetrapyrrole derivatives e.g. porphyrin, phthalocyanine, bilirubin.

In a preferred embodiment of the invention and/or embodiments thereof the compound comprises a ^{18}F containing moiety. ^{18}F containing moieties may be used for imaging and therapy. Suitable ^{18}F containing moieties may be selected from the group consisting of ^{18}F fluorothymidine, ^{18}F -miso (fluoromisonidazole), ^{18}F -choline, and ^{18}F fluorodeoxyglucose, florbetapir-fluorine-18, fallypride (^{18}F), ^{18}F -EF5.

Compounds of the present invention are more tumour specific. The compounds of the present invention decrease the pH of cancer cells especially if they are in an acidic environment, making the cells more sensitive to the anticancer agent.

In a preferred embodiment of the invention and/or embodiments thereof the compounds of the present invention are active in normoxic conditions.

In a preferred embodiment of the invention and/or embodiments thereof the compounds of the present invention are active in tumour cells which are in an acidic environment.

In a preferred embodiment of the invention and/or embodiments thereof the compounds of the present invention increase the extracellular pH.

In a preferred embodiment of the invention and/or embodiments thereof the compounds of the present invention decrease the intracellular pH.

In a preferred embodiment of the invention and/or embodiments thereof the compounds of the present do not need irradiation to become active.

In a preferred embodiment of the invention and/or embodiments thereof the compounds of the present invention are active in stem cells.

In a preferred embodiment of the invention and/or embodiments thereof the compounds of the present invention have a increased half life in plasma.

In a preferred embodiment of the invention and/or embodiments thereof the compounds of the present invention inhibit carbonic anhydrase, preferably carbonic anhydrase IX.

In a preferred embodiment of the invention and/or embodiments thereof the compounds of the present invention inhibit selectively carbonic anhydrase IX.

The compound of the invention and/or embodiments thereof comprise a linker L. Linker L is a direct bond or L is a linker selected from the group consisting of C₁₋₆alkyl, C(=O)N(R⁶), C₁₋₆alkyl-C(=O)N(R⁶)C₁₋₆alkyl, C₁₋₆alkyl-C(=O)N(R⁶), C(=O)N(R⁶)-C₁₋₆alkyl, N(R⁶)C(=O)N(R⁶), C₁₋₆alkylN(R⁶)C(=O)N(R⁶)C₁₋₆alkyl, C₁₋₆alkylN(R⁶)C(=O)N(R⁶), N(R⁶)C(=O)N(R⁶)C₁₋₆alkyl, N(R⁶)C(=S)N(R⁶), C₁₋₆alkylN(R⁶)C(=S)N(R⁶)C₁₋₆alkyl, C₁₋₆alkylN(R⁶)C(=S)N(R⁶), N(R⁶)C(=S)N(R⁶)C₁₋₆alkyl, -O-C(=O)N(R⁶), C₁₋₆alkyl-O-C(=O)N(R⁶)C₁₋₆alkyl, C₁₋₆alkyl-O-C(=O)N(R⁶), -O-C(=O)N(R⁶)C₁₋₆alkyl, N(R⁶)C(=O), C₁₋₆alkylN(R⁶)C(=O)C₁₋₆alkyl, C₁₋₆alkylN(R⁶)C(=O), N(R⁶)C(=O)C₁₋₆alkyl, N(R⁶)C(=S), C₁₋₆alkylN(R⁶)C(=S)C₁₋₆alkyl, C₁₋

- ${}_{6}\text{alkylN(R}^6\text{)C(=S)}$, $\text{N(R}^6\text{)C(=S)C}_{1-6}\text{alkyl}$, $\text{C(=O)N(R}^6\text{)C}_{1-6}\text{alkylN(R}^6\text{)C(=S)N(R}^6\text{)}$, $\text{C}_{1-6}\text{alkylC(=O)N(R}^6\text{)C}_{1-6}\text{alkylN(R}^6\text{)C(=S)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C(=O)N(R}^6\text{)C}_{1-6}\text{alkylC(=O)N(R}^6\text{)C}_{1-6}\text{alkylN(R}^6\text{)C(=S)N(R}^6\text{)}$, $\text{C(=O)N(R}^6\text{)C}_{1-6}\text{alkylN(R}^6\text{)C(=S)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C(=O)N(R}^6\text{)C}_{1-6}\text{alkylN(R}^6\text{)C(=O)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkylC(=O)N(R}^6\text{)C}_{1-6}\text{alkylN(R}^6\text{)C(=O)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C(=O)N(R}^6\text{)C}_{1-6}\text{alkylN(R}^6\text{)C(=O)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C(=O)N(R}^6\text{)C}_{1-6}\text{alkyl-OC(=O)}$, $\text{C}_{1-6}\text{alkylC(=O)N(R}^6\text{)C}_{1-6}\text{alkyl-OC(=O)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkylC(=O)N(R}^6\text{)C}_{1-6}\text{alkyl-OC(=O)}$, $\text{C(=O)N(R}^6\text{)C}_{1-6}\text{alkyl-OC(=O)C}_{1-6}\text{alkyl}$, O-C(=O) , $\text{C}_{1-6}\text{alkyl-O-C(=O)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl-O-C(=O)}$, $\text{O-C(=O)C}_{1-6}\text{alkyl}$, C(=O) , $\text{C}_{1-6}\text{alkyl-C(=O)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl-C(=O)}$, $\text{C(=O)C}_{1-6}\text{alkyl}$, $\text{C(=S)N(R}^6\text{)}$, $\text{C}_{1-6}\text{alkyl-C(=S)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl-C(=S)N(R}^6\text{)}$, $\text{C(=S)N(R}^6\text{)-C}_{1-6}\text{alkyl}$, $\text{N(R}^6\text{)}$, $\text{C}_{1-6}\text{alkyl-N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl-N(R}^6\text{)}$, $\text{N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{O-C(=O)C}_{1-6}\text{alkylC(=O)N(R}^6\text{)}$, $\text{C}_{1-6}\text{alkyl-O-C(=O)C}_{1-6}\text{alkylC(=O)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl-O-C(=O)C}_{1-6}\text{alkylC(=O)N(R}^6\text{)}$, $\text{O-C(=O)C}_{1-6}\text{alkylC(=O)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{O-C(=O)C}_{1-6}\text{alkylN(R}^6\text{)C(=O)}$, $\text{C}_{1-6}\text{alkyl-O-C(=O)C}_{1-6}\text{alkylN(R}^6\text{)C(=O)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl-O-C(=O)C}_{1-6}\text{alkylN(R}^6\text{)C(=O)C}_{1-6}\text{alkyl}$, $\text{O-C(=O)C}_{1-6}\text{alkylN(R}^6\text{)C(=O)C}_{1-6}\text{alkyl}$, $\text{(O-CH}_2\text{CH}_2\text{)}_n$, $\text{C}_{1-6}\text{alkyl(O-CH}_2\text{CH}_2\text{)}_n\text{C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl(O-CH}_2\text{CH}_2\text{)}_n$, $\text{(O-CH}_2\text{CH}_2\text{)}_n\text{C}_{1-6}\text{alkyl}$, $\text{(CH}_2\text{CH}_2\text{-O)}_n$, $\text{C}_{1-6}\text{alkyl(CH}_2\text{CH}_2\text{-O)}_n\text{C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl(CH}_2\text{CH}_2\text{-O)}_n$, $\text{(CH}_2\text{CH}_2\text{-O)}_n\text{C}_{1-6}\text{alkyl}$;

n is 1-12;

- optionally the L is further substituted with a substituent selected from the group comprising halo, hydroxy, amino, nitro, $\text{C}_{1-6}\text{alkyl}$, C_2 - alkenyl , $\text{C}_{2-6}\text{alkynyl}$, $\text{C}_{1-6}\text{alkyloxy}$, $\text{di(C}_{1-6}\text{alkyl)amino}$, hydroxyamino, hydroxycarbonyl, carbonyl, carbonyl $\text{C}_{1-6}\text{alkyl}$, carbonyl $\text{C}_{1-6}\text{alkyloxy}$, $\text{C}_{1-6}\text{alkylcarbonyl}$, NR^4R^5 , heterocyclic, $\text{C}_{3-7}\text{cycloalkyl}$, , hydroxy $\text{C}_{1-6}\text{alkyl}$, amino $\text{C}_{1-6}\text{alkyl}$, cyano, SiFR^8R^9 , or $\text{OP(=O)(OR}^{10}\text{)}_2$;

- In a preferred embodiment of the present invention and/or embodiments thereof L is a direct bond, $\text{C}_{1-6}\text{alkyl}$, $\text{C(=O)N(R}^6\text{)}$, $\text{C}_{1-6}\text{alkyl-C(=O)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl-C(=O)N(R}^6\text{)}$, $\text{N(R}^6\text{)C(=O)N(R}^6\text{)}$, $\text{C}_{1-6}\text{alkyl}$;

${}_{6\text{alkyl}}\text{N(R}^6\text{)C(=O)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkylN(R}^6\text{)C(=O)N(R}^6\text{)}$,
 $\text{N(R}^6\text{)C(=O)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkylN(R}^6\text{)C(=S)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkylN(R}^6\text{)C(=S)N(R}^6\text{)}$, $\text{N(R}^6\text{)C(=S)N(R}^6\text{)C}_{1-6}\text{alkyl}$, O-C(=O) , $\text{C}_{1-6}\text{alkyl-O-C(=O)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl-O-C(=O)}$, $\text{O-C(=O)C}_{1-6}\text{alkyl}$, $-\text{O-C(=O)N(R}^6\text{)}$, $\text{C}_{1-6}\text{alkyl-O-C(=O)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl-O-C(=O)N(R}^6\text{)}$, $-\text{O-C(=O)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $(\text{O-CH}_2\text{CH}_2)_n$, $\text{C}_{1-6}\text{alkyl(O-CH}_2\text{CH}_2)_n\text{C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl(O-CH}_2\text{CH}_2)_n$, $(\text{O-CH}_2\text{CH}_2)_n\text{C}_{1-6}\text{alkyl}$, $\text{C(=O)N(R}^6\text{)C}_{1-6}\text{alkylN(R}^6\text{)C(=O)N(R}^6\text{)}$, $\text{C}_{1-6}\text{alkylC(=O)N(R}^6\text{)C}_{1-6}\text{alkylN(R}^6\text{)C(=O)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkylC(=O)N(R}^6\text{)C}_{1-6}\text{alkylN(R}^6\text{)C(=O)N(R}^6\text{)}$, $\text{C(=O)N(R}^6\text{)C}_{1-6}\text{alkylN(R}^6\text{)C(=O)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $(\text{O-CH}_2\text{CH}_2)_n$, $(\text{CH}_2\text{CH}_2\text{-O})_n$, $\text{C}_{1-6}\text{alkyl(CH}_2\text{CH}_2\text{-O})_n\text{C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl(CH}_2\text{CH}_2\text{-O})_n$, or $(\text{CH}_2\text{CH}_2\text{-O})_n\text{C}_{1-6}\text{alkyl}$;

In a preferred embodiment of the present invention and/or
 embodiments thereof L is a direct bond, $\text{C}_{1-6}\text{alkyl}$, $\text{C(=O)N(R}^6\text{)}$, $\text{C}_{1-6}\text{alkyl-C(=O)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl-C(=O)N(R}^6\text{)}$, $\text{N(R}^6\text{)C(=O)N(R}^6\text{)}$, $\text{C}_{1-6}\text{alkylN(R}^6\text{)C(=O)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkylN(R}^6\text{)C(=O)N(R}^6\text{)}$,
 $\text{N(R}^6\text{)C(=O)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkylN(R}^6\text{)C(=S)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkylN(R}^6\text{)C(=S)N(R}^6\text{)}$, O-C(=O) , $\text{C}_{1-6}\text{alkyl-O-C(=O)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl-O-C(=O)}$, $(\text{O-CH}_2\text{CH}_2)_n$, $\text{C}_{1-6}\text{alkyl(O-CH}_2\text{CH}_2)_n\text{C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl(O-CH}_2\text{CH}_2)_n$, $(\text{O-CH}_2\text{CH}_2)_n\text{C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkylC(=O)N(R}^6\text{)C}_{1-6}\text{alkylN(R}^6\text{)C(=O)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkylC(=O)N(R}^6\text{)C}_{1-6}\text{alkylN(R}^6\text{)C(=O)N(R}^6\text{)}$, $(\text{CH}_2\text{CH}_2\text{-O})_n$, $\text{C}_{1-6}\text{alkyl(CH}_2\text{CH}_2\text{-O})_n\text{C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl(CH}_2\text{CH}_2\text{-O})_n$, $(\text{O-CH}_2\text{CH}_2)_n$, or $(\text{CH}_2\text{CH}_2\text{-O})_n\text{C}_{1-6}\text{alkyl}$;

In a preferred embodiment of the present invention and/or
 embodiments thereof L is a direct bond, $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl-C(=O)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl-C(=O)N(R}^6\text{)}$, $\text{C}_{1-6}\text{alkylN(R}^6\text{)C(=O)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkylN(R}^6\text{)C(=O)N(R}^6\text{)}$, $\text{C}_{1-6}\text{alkylN(R}^6\text{)C(=S)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkylN(R}^6\text{)C(=S)N(R}^6\text{)}$, $\text{C}_{1-6}\text{alkyl-O-C(=O)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl-O-C(=O)}$, $(\text{O-CH}_2\text{CH}_2)_n$, $(\text{CH}_2\text{CH}_2\text{-O})_n$, or $\text{C}_{1-6}\text{alkyl(CH}_2\text{CH}_2\text{-O})_n$;

In a preferred embodiment of the present invention and/or
 embodiments thereof L is a cleavable linker.

In a preferred embodiment of the present invention and/or
embodiments thereof L is selected from the group consisting of a direct
bond, C(=O)N(R⁶), C₁₋₆alkyl-C(=O)N(R⁶)C₁₋₆alkyl, C₁₋₆alkyl-C(=O)N(R⁶),
N(R⁶)C(=O)N(R⁶), C₁₋₆alkylN(R⁶)C(=O)N(R⁶)C₁₋₆alkyl, C₁₋₆alkylN(R⁶)C(=O)N(R⁶), N(R⁶)C(=O)N(R⁶)C₁₋₆alkyl, C₁₋₆alkylN(R⁶)C(=S)N(R⁶)C₁₋₆alkyl, C₁₋₆alkylN(R⁶)C(=S)N(R⁶), O-C(=O), C₁₋₆alkyl-O-C(=O)C₁₋₆alkyl, C₁₋₆alkyl-O-C(=O), C(=O), C₁₋₆alkyl-C(=O)C₁₋₆alkyl,
C₁₋₆alkyl-C(=O), C(=O)C₁₋₆alkyl, C(=S)N(R⁶), C₁₋₆alkyl-C(=S)N(R⁶), C₁₋₆alkyl-C(=S)N(R⁶), C(=S)N(R⁶)-C₁₋₆alkyl, N(R⁶), C₁₋₆alkyl-N(R⁶), C₁₋₆alkyl-N(R⁶),
C₁₋₆alkyl-N(R⁶), N(R⁶)C₁₋₆alkyl, (O-CH₂CH₂)_n, C₁₋₆alkyl(O-CH₂CH₂)_n, C₁₋₆alkyl(O-CH₂CH₂)_n, (O-CH₂CH₂)_nC₁₋₆alkyl, C₁₋₆alkylC(=O)N(R⁶)C₁₋₆alkylN(R⁶)C(=O)N(R⁶)C₁₋₆alkyl, C₁₋₆alkylC(=O)N(R⁶)C₁₋₆alkylN(R⁶)C(=O)N(R⁶), (O-CH₂CH₂)_n, (CH₂CH₂-O)_n, C₁₋₆alkyl(CH₂CH₂-O)_nC₁₋₆alkyl, C₁₋₆alkyl(CH₂CH₂-O)_n, and (CH₂CH₂-O)_nC₁₋₆alkyl.

In a preferred embodiment of the present invention and/or
embodiments thereof L is selected from the group consisting of a direct
bond, C₁₋₆alkyl-C(=O)N(R⁶)C₁₋₆alkyl, C₁₋₆alkyl-C(=O)N(R⁶), C₁₋₆alkylN(R⁶)C(=O)N(R⁶)C₁₋₆alkyl, C₁₋₆alkylN(R⁶)C(=O)N(R⁶), C₁₋₆alkylN(R⁶)C(=S)N(R⁶)C₁₋₆alkyl, C₁₋₆alkylN(R⁶)C(=S)N(R⁶), C₁₋₆alkyl-O-C(=O)C₁₋₆alkyl, C₁₋₆alkyl-O-C(=O), C(=O), C₁₋₆alkyl-C(=O), C(=O)C₁₋₆alkyl, C(=S)N(R⁶), C₁₋₆alkyl-C(=S)N(R⁶), C(=S)N(R⁶)-C₁₋₆alkyl, N(R⁶), C₁₋₆alkyl-N(R⁶), N(R⁶)C₁₋₆alkyl, (O-CH₂CH₂)_n, (CH₂CH₂-O)_n, and C₁₋₆alkyl(CH₂CH₂-O)_n.

In a preferred embodiment of the present invention and/or
embodiments thereof L is selected from the group consisting of a direct
bond, C₁₋₆alkyl-C(=O)N(R⁶)C₁₋₆alkyl, C₁₋₆alkyl-C(=O)N(R⁶), C₁₋₆alkylN(R⁶)C(=O)N(R⁶)C₁₋₆alkyl, C₁₋₆alkylN(R⁶)C(=O)N(R⁶), C₁₋₆alkylN(R⁶)C(=S)N(R⁶)C₁₋₆alkyl, C₁₋₆alkylN(R⁶)C(=S)N(R⁶), C₁₋₆alkyl-O-C(=O)C₁₋₆alkyl, C₁₋₆alkyl-O-C(=O), C(=O), C₁₋₆alkyl-C(=O), C(=S)N(R⁶), C₁₋₆alkyl-C(=S)N(R⁶), C(=S)N(R⁶)-C₁₋₆alkyl, N(R⁶), C₁₋₆alkyl-N(R⁶), N(R⁶)C₁₋₆alkyl, (O-CH₂CH₂)_n, (CH₂CH₂-O)_n, and C₁₋₆alkyl(CH₂CH₂-O)_n.

${}_{6\text{alkyl}}\text{-C(=S)N(R}^6\text{)}$, $\text{N(R}^6\text{)}$, $\text{C}_{1-6}\text{alkyl-N(R}^6\text{)}$, $(\text{O-CH}_2\text{CH}_2)_n$, $(\text{CH}_2\text{CH}_2\text{-O})_n$, and $\text{C}_{1-6}\text{alkyl}(\text{CH}_2\text{CH}_2\text{-O})_n$.

In a preferred embodiment of the present invention and/or
embodiments thereof L is selected from the group consisting of a direct
5 bond, $\text{C}_{1-6}\text{alkyl-C(=O)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl-C(=O)N(R}^6\text{)}$, $\text{C}_{1-6}\text{alkylN(R}^6\text{)C(=O)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkylN(R}^6\text{)C(=O)N(R}^6\text{)}$, $\text{C}_{1-6}\text{alkylN(R}^6\text{)C(=S)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkylN(R}^6\text{)C(=S)N(R}^6\text{)}$, $\text{C}_{1-6}\text{alkyl-O-C(=O)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl-O-C(=O)}$, C(=O) , $\text{C}_{1-6}\text{alkyl-C(=O)}$, $\text{C(=S)N(R}^6\text{)}$, $\text{C}_{1-6}\text{alkyl-C(=S)N(R}^6\text{)}$, $\text{N(R}^6\text{)}$, $\text{C}_{1-6}\text{alkyl-N(R}^6\text{)}$, $(\text{O-CH}_2\text{CH}_2)_n$, $(\text{CH}_2\text{CH}_2\text{-O})_n$, and
10 $\text{C}_{1-6}\text{alkyl}(\text{CH}_2\text{CH}_2\text{-O})_n$.

In a preferred embodiment of the present invention and/or
embodiments thereof L is a direct bond, $\text{C}_{1-6}\text{alkyl}$, $\text{C(=O)N(R}^6\text{)}$, $\text{C}_{1-6}\text{alkyl-C(=O)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl-C(=O)N(R}^6\text{)}$, $\text{N(R}^6\text{)C(=O)N(R}^6\text{)}$, $\text{C}_{1-6}\text{alkylN(R}^6\text{)C(=O)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkylN(R}^6\text{)C(=O)N(R}^6\text{)}$,
15 $\text{N(R}^6\text{)C(=O)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkylN(R}^6\text{)C(=S)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkylN(R}^6\text{)C(=S)N(R}^6\text{)}$, $\text{N(R}^6\text{)C(=S)N(R}^6\text{)C}_{1-6}\text{alkyl}$, O-C(=O) , $\text{C}_{1-6}\text{alkyl-O-C(=O)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl-O-C(=O)}$, $\text{O-C(=O)C}_{1-6}\text{alkyl}$, $\text{-O-C(=O)N(R}^6\text{)}$, C(=O) , $\text{C}_{1-6}\text{alkyl-C(=O)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl-C(=O)}$, $\text{C(=O)C}_{1-6}\text{alkyl}$, $\text{C(=S)N(R}^6\text{)}$, $\text{C}_{1-6}\text{alkyl-C(=S)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl-C(=S)N(R}^6\text{)}$, $\text{C(=S)N(R}^6\text{)-C}_{1-6}\text{alkyl}$,
20 $\text{N(R}^6\text{)}$, $\text{C}_{1-6}\text{alkyl-N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl-N(R}^6\text{)}$, $\text{N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl-O-C(=O)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl-O-C(=O)N(R}^6\text{)}$, $\text{-O-C(=O)N(R}^6\text{)C}_{1-6}\text{alkyl}$, $(\text{O-CH}_2\text{CH}_2)_n$, $\text{C}_{1-6}\text{alkyl}(\text{O-CH}_2\text{CH}_2)_n\text{C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl}(\text{O-CH}_2\text{CH}_2)_n$, $(\text{O-CH}_2\text{CH}_2)_n\text{C}_{1-6}\text{alkyl}$, $(\text{O-CH}_2\text{CH}_2)_n$, $(\text{CH}_2\text{CH}_2\text{-O})_n$, $\text{C}_{1-6}\text{alkyl}(\text{CH}_2\text{CH}_2\text{-O})_n\text{C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl}(\text{CH}_2\text{CH}_2\text{-O})_n$, or $(\text{CH}_2\text{CH}_2\text{-O})_n\text{C}_{1-6}\text{alkyl}$.

In a preferred embodiment of the present invention and/or
embodiments thereof L is a direct bond, $\text{C}_{1-6}\text{alkyl}$, $\text{C(=O)N(R}^6\text{)}$, $\text{C}_{1-6}\text{alkyl-C(=O)N(R}^6\text{)}$, $\text{N(R}^6\text{)C(=O)N(R}^6\text{)}$, $\text{C}_{1-6}\text{alkylN(R}^6\text{)C(=O)N(R}^6\text{)}$, $\text{C}_{1-6}\text{alkylN(R}^6\text{)C(=S)N(R}^6\text{)}$, $\text{N(R}^6\text{)C(=S)N(R}^6\text{)}$, -O-C(=O) , $\text{-O-C(=O)N(R}^6\text{)}$, $\text{C}_{1-6}\text{alkyl-O-C(=O)N(R}^6\text{)}$, C(=O) , $\text{C(=O)C}_{1-6}\text{alkyl}$, $\text{C(=S)N(R}^6\text{)}$, $\text{C(=S)N(R}^6\text{)-C}_{1-6}\text{alkyl}$,
30 $\text{C}_{1-6}\text{alkyl}$, $\text{N(R}^6\text{)}$, $\text{C}_{1-6}\text{alkyl-N(R}^6\text{)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl-N(R}^6\text{)}$, $\text{N(R}^6\text{)C}_{1-6}\text{alkyl}$, $(\text{O-CH}_2\text{CH}_2)_n$, $(\text{CH}_2\text{CH}_2\text{-O})_n$, $\text{C}_{1-6}\text{alkyl}(\text{O-CH}_2\text{CH}_2)_n\text{C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl}(\text{O-CH}_2\text{CH}_2)_n$, $(\text{O-CH}_2\text{CH}_2)_n\text{C}_{1-6}\text{alkyl}$, $(\text{O-CH}_2\text{CH}_2)_n$, $(\text{CH}_2\text{CH}_2\text{-O})_n$, $\text{C}_{1-6}\text{alkyl}(\text{CH}_2\text{CH}_2\text{-O})_n\text{C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl}(\text{CH}_2\text{CH}_2\text{-O})_n$, or $(\text{CH}_2\text{CH}_2\text{-O})_n\text{C}_{1-6}\text{alkyl}$.

$\text{CH}_2\text{CH}_2)_n$, $\text{C}_{1-6}\text{alkyl}(\text{O}-\text{CH}_2\text{CH}_2)_n$, $(\text{O}-\text{CH}_2\text{CH}_2)_n$, $(\text{CH}_2\text{CH}_2-\text{O})_n$, or $\text{C}_{1-6}\text{alkyl}(\text{CH}_2\text{CH}_2-\text{O})_n$.

In a preferred embodiment of the present invention and/or
embodiments thereof L is a direct bond, $\text{C}_{1-6}\text{alkyl}$, $\text{C}(=\text{O})\text{N}(\text{R}^6)$,
5 $\text{N}(\text{R}^6)\text{C}(=\text{O})\text{N}(\text{R}^6)$, $\text{N}(\text{R}^6)\text{C}(=\text{S})\text{N}(\text{R}^6)$, $-\text{O}-\text{C}(=\text{O})$, $-\text{O}-\text{C}(=\text{O})\text{N}(\text{R}^6)$, $\text{C}(=\text{O})$,
 $\text{C}(=\text{S})\text{N}(\text{R}^6)$, $\text{N}(\text{R}^6)$, $(\text{O}-\text{CH}_2\text{CH}_2)_n$, or $(\text{CH}_2\text{CH}_2-\text{O})_n$.

In a preferred embodiment of the present invention and/or
embodiments thereof L is a direct bond, $\text{C}_{1-6}\text{alkyl}$, $\text{C}(=\text{O})\text{N}(\text{R}^6)$,
 $\text{N}(\text{R}^6)\text{C}(=\text{O})\text{N}(\text{R}^6)$, $\text{N}(\text{R}^6)\text{C}(=\text{S})\text{N}(\text{R}^6)$, $-\text{O}-\text{C}(=\text{O})$, $\text{C}(=\text{O})$, $\text{N}(\text{R}^6)$, or $-\text{O}-$
10 $\text{C}(=\text{O})\text{N}(\text{R}^6)$.

In a preferred embodiment of the present invention and/or
embodiments thereof L is a direct bond, $\text{C}_{1-6}\text{alkyl}$, $(\text{O}-\text{CH}_2\text{CH}_2)_n$, or
 $(\text{CH}_2\text{CH}_2-\text{O})_n$.

In a preferred embodiment of the present invention and/or
15 embodiments thereof n is 1-10.

In a preferred embodiment of the present invention and/or
embodiments thereof n is 1-8.

In a preferred embodiment of the present invention and/or
embodiments thereof n is 1-6.

20 In a preferred embodiment of the present invention and/or
embodiments thereof n is 1-4.

In a preferred embodiment of the present invention and/or
embodiments thereof n is 1-2.

25 In a preferred embodiment of the present invention and/or
embodiments thereof L is a direct bond.

In aspects and/or embodiments of the present invention, the
compounds comprise a R^1 group. The R^1 is $\text{SO}_2\text{NR}^2\text{R}^3$, $\text{OSO}_2\text{NR}^2\text{R}^3$,
 $\text{NR}^7\text{SO}_2\text{NR}^2\text{R}^3$, NR^4SO_2 -phenyl, aryl substituted with $\text{SO}_2\text{NR}^2\text{R}^3$, aryl
substituted with $\text{OSO}_2\text{NR}^2\text{R}^3$, or aryl substituted with $\text{NR}^7\text{SO}_2\text{NR}^2\text{R}^3$;

It is to be understood that the R^1 group is connected to L or A via the S atom of the SO_2 group in case R^1 is $SO_2NR^2R^3$. R^1 group is connected to L or A via the O in case R^1 is $O-SO_2NR^2R^3$. R^1 group is connected to L or A via the N of NR^4 in case R^1 is NR^4SO_2 -phenyl. R^1 group is connected to L or A via the N of NR^7 in case R^1 is $NR^7SO_2NR^2R^3$. R^1 group is connected to L or A via the aryl group in case R^1 aryl substituted with $SO_2NR^2R^3$, aryl substituted with $OSO_2NR^2R^3$, or aryl substituted with $NR^7SO_2NR^2R^3$. R^1 is not connected to L or A via N of the NR^2R^3 group. R^1 is not connected to L or A via the S atom of SO_2 in cases R^1 is not $SO_2NR^2R^3$. R^1 is not connected to L or A via the O atom of the SO_2 group. Only when there is a $O-SO_2$ group may R^1 be connected via an O atom, but this is the O atom of $O-SO_2$. It should be noted that these connection are the only ones that make sense when looking at the groups as defined for R^1 .

In a preferred embodiment of the present invention and/or embodiments thereof R^1 is R^1 is $SO_2NR^2R^3$, $OSO_2NR^2R^3$, $NR^7SO_2NR^2R^3$, aryl substituted with $SO_2NR^2R^3$, aryl substituted with $OSO_2NR^2R^3$, or aryl substituted with $NR^7SO_2NR^2R^3$.

In a preferred embodiment of the present invention and/or embodiments thereof R^1 is R^1 is SO_2NH_2 , OSO_2NH_2 , $NR^7SO_2NH_2$, aryl substituted with SO_2NH_2 , aryl substituted with OSO_2NH_2 , or aryl substituted with $NR^7SO_2NH_2$.

For the purpose of the present invention, aryl is an aromatic cyclic compound comprising 5-12 atoms, and may mono-cyclic, bi- or tricyclic. Aryl may contain heteroatoms and may be referred to as heteroaryl. The term aryl thus comprises aromatic cyclic compounds comprising only C-atoms and also aromatic cyclic compounds comprising heteroatoms next to C atoms. Aryl may be selected from the group consisting of phenyl, thiadiazolyl, naphthalenyl, pyridinyl, indolyl, quinolinyl, imidazolyl, furanyl, thienyl, oxadiazolyl, tetrazolyl, benzofuranyl or tetrahydrofuranyl; each aryl can optionally be substituted with one, two or three substituents each

independently selected from halo, hydroxy, hydroxyC₁₋₆alkyl, C₁₋₆alkyl, amino, polyhaloC₁₋₆alkyl and C₁₋₆alkyloxy; and each phenyl or naphthalenyl can optionally be substituted with a bivalent radical selected from methylenedioxy and ethylenedioxy; each pyridinyl, indolyl, quinoliny, imidazolyl, furanyl, thienyl, oxadiazolyl, tetrazolyl, benzofuranyl, or tetrahydrofuranyl can optionally be substituted with one, two or three substituents each independently selected from halo, hydroxy, C₁₋₆alkyl, amino, polyhaloC₁₋₆alkyl, aryl, arylC₁₋₆alkyl or C₁₋₆alkyloxy; and each pyridinyl, indolyl, quinoliny, imidazolyl, furanyl, thienyl, benzofuranyl, or tetrahydrofuranyl can optionally be substituted with a bivalent radical selected from methylenedioxy or ethylenedioxy.

In a preferred embodiment of the present invention and/or embodiments thereof, aryl is phenyl, thiadiazolyl, or naphthenyl, more preferably phenyl or thiadiazolyl, more preferably phenyl.

In a preferred embodiment of the present invention and/or embodiments thereof, the aryl is substituted with a substituent selected from the group comprising hydrogen, halo, hydroxy, amino, nitro, carboxyamine, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkyloxy, di(C₁₋₆alkyl)amino, hydroxyamino, hydroxycarbonyl, carbonyl, carbonylC₁₋₆alkyl, carbonylC₁₋₆alkyloxy, C₁₋₆alkylcarbonyl, NR⁴R⁵, heterocyclic, C₃₋₇cycloalkyl, hydroxyC₁₋₆alkyl, aminoC₁₋₆alkyl, cyano, or OP(=O)(OR¹⁰)₂.

In a preferred embodiment of the present invention and/or embodiments thereof, the aryl is substituted with a substituent selected from the group comprising hydrogen, halo, hydroxy, amino, nitro, carboxyamine, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkyloxy, di(C₁₋₆alkyl)amino, hydroxyamino, hydroxycarbonyl, carbonyl, NR⁴R⁵, hydroxyC₁₋₆alkyl, aminoC₁₋₆alkyl, cyano, or OP(=O)(OR¹⁰)₂.

In a preferred embodiment of the present invention and/or embodiments thereof, the aryl is substituted with a substituent selected from the group comprising hydrogen, halo, hydroxy, amino, nitro,

carboxyamine, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkyloxy, NR⁴R⁵, or cyano.

In a preferred embodiment of the present invention and/or
embodiments thereof, the aryl is substituted with a substituent selected
5 from the group comprising hydrogen, halo, hydroxy, amino, nitro, or cyano.

In a preferred embodiment of the present invention and/or
embodiments thereof, the aryl is substituted with a substituent selected
from the group comprising hydrogen, halo, or cyano.

In a preferred embodiment of the present invention and/or
10 embodiments thereof, the aryl is not further substituted.

In a preferred embodiment of the present invention and/or
embodiments thereof, the C₁₋₆alkyl is optionally substituted with with a
substituent selected from the group comprising halo, hydroxy, amino, nitro,
C₁₋₆alkyloxy, di(C₁₋₆alkyl)amino, hydroxyamino, hydroxycarbonyl, carbonyl,
15 carbonylC₁₋₆alkyl, carbonylC₁₋₆alkyloxy, C₁₋₆alkylcarbonyl, , heterocyclic, C₃₋₇cycloalkyl, , hydroxyC₁₋₆alkyl or aminoC₁₋₆alkyl , cyano, OP(=O)(OR¹⁰), or a
leaving group. It is to be understood that C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆
alkyloxy, hydroxyC₁₋₆alkyl, and aminoC₁₋₆alkyl may be likewise substituted
with a substituent selected from the group comprising halo, hydroxy, amino,
20 nitro, C₁₋₆alkyloxy, di(C₁₋₆alkyl)amino, hydroxyamino, hydroxycarbonyl,
carbonyl, carbonylC₁₋₆alkyl, carbonylC₁₋₆alkyloxy, C₁₋₆alkylcarbonyl, ,
heterocyclic, C₃₋₇cycloalkyl, , hydroxyC₁₋₆alkyl or aminoC₁₋₆alkyl , cyano,
OP(=O)(OR¹⁰), or a leaving group.

In a preferred embodiment of the present invention and/or
25 embodiments thereof, the C₁₋₆alkyl is optionally substituted with with a
substituent selected from the group comprising halo, hydroxy, amino, nitro,
hydroxyamino, hydroxycarbonyl, carbonyl, cyano, OP(=O)(OR¹⁰), or a
leaving group.

In a preferred embodiment of the present invention and/or
30 embodiments thereof, the C₁₋₆alkyl is optionally substituted with with a

substituent selected from the group comprising halo, hydroxy, amino, nitro, hydroxyamino, hydroxycarbonyl, carbonyl, or cyano.

In a preferred embodiment of the present invention and/or
embodiments thereof, the R^2 , R^3 is each independently hydrogen, halo,
5 hydroxy, or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with
with a substituent selected from the group comprising halo, hydroxy, amino,
nitro, carbonyl, cyano, or a leaving group;

In a preferred embodiment of the present invention and/or
embodiments thereof, the R^4 , R^5 , R^6 , R^7 is each independently hydrogen,
10 halo, hydroxy, or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted
with with a substituent selected from the group comprising halo, hydroxy,
amino, nitro, C_{1-6} alkyloxy, di(C_{1-6} alkyl)amino, hydroxyamino,
hydroxycarbonyl, carbonyl, carbonyl C_{1-6} alkyl, carbonyl C_{1-6} alkyloxy, C_{1-6}
alkylcarbonyl, heterocyclic, C_{3-7} cycloalkyl, hydroxy C_{1-6} alkyl or amino C_{1-6}
15 alkyl, cyano, $OP(=O)(OR^{10})_2$, $SiFR^8R^9$, or a leaving group;

In a preferred embodiment of the present invention and/or
embodiments thereof, the R^8 and R^9 is each independently a C_{1-12} alkyl, or C_{2-12} alkenyl;

In a preferred embodiment of the present invention and/or
20 embodiments thereof, the R^{10} is hydrogen, C_{1-20} alkyl, or C_{2-20} alkenyl, aryl,
amino C_{1-12} alkyl, carbonyl C_{1-12} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl,
or NR^4R^5 ;

In a more preferred embodiment of the present invention and/or
embodiments thereof, R^8 and R^9 is each independently a C_{1-12} alkyl, or C_{2-12} alkenyl,
25 being straight or branched, more preferably C_{1-6} alkyl, or C_{2-6} alkenyl, more preferably methyl, ethyl, propyl, or butyl, more preferably,
propyl, or butyl, more preferably isopropyl or tertiary butyl. In a preferred
embodiment of the present invention and/or embodiments thereof, R^8 and R^9
are the same.

In a preferred embodiment of the present invention and/or embodiments thereof, the compounds are functionalized with SiFR⁸R⁹, wherein R⁸ and R⁹ is each independently a C₁₋₆alkyl, tertiary butyl, isopropyl, preferably tertiary butyl, isopropyl, methyl, ethyl.

5 Compounds with SiFR⁸²R⁹ may be used for PET imaging by exchanging the normal ¹⁹F by the radioactive ¹⁸F. In a more preferred embodiment of the present invention and/or embodiments thereof, the compound comprises a SiFR⁸R⁹ group, and F is ¹⁸F.

For the purpose of the present invention, a leaving group is a
10 molecular fragment that departs with a pair of electrons in heterolytic bond cleavage. Leaving groups can be anions or neutral molecules. Common anionic leaving groups are halides such as Cl⁻, Br⁻, and I⁻, and sulfonate esters, such as *para*-toluenesulfonate ("tosylate", TsO⁻) or diazonium, oxonium. Common neutral molecule leaving groups are water (H₂O), and
15 ammonia.

In a preferred embodiment of the present invention and/or embodiments thereof, a leaving group is halogen, tosylate, mesylate, fluorosulfonates, triflates, brosylate, nonaflates, C₁₋₁₂alkylN₂, C₁₋₁₂alkylOC₁₋₁₂alkyl, C₁₋₁₂alkylOSO₂F, C₁₋₁₂alkylOSO₂perfluoratedC₁₋₆alkyl, nitrate,
20 phosphate, C₁₋₆alkylSC₁₋₆alkyl, tetraC₁₋₆alkylammonium, halogenC₁₋₆alkyl, C₁₋₆alkylOaryl, C₁₋₆alkylhydroxy, carbonylC₁₋₆alkyloxyC₁₋₆alkyl. In a more preferred embodiment of the present invention and/or embodiments thereof, a leaving group is halogen, tosylate, mesylate, fluorosulfonates, triflates, nonaflates, C₁₋₁₂alkylN₂, C₁₋₁₂alkylOSO₂F, C₁₋₁₂alkylOSO₂perfluoratedC₁₋₆alkyl, halogenC₁₋₆alkyl. In a more preferred embodiment of the present invention and/or embodiments thereof, a leaving group is iodide, bromide, chloride, tosylate, or mesylate.
25

In a preferred embodiment of the present invention and/or embodiments thereof, R^2 , R^3 is each independently hydrogen, hydroxy, or C_{1-6} alkyl, more preferably C_{1-3} alkyl, more preferably C_{1-2} alkyl, more preferably C_1 alkyl.

5 In a more preferred embodiment of the present invention and/or embodiments thereof, R^2 , R^3 is each independently hydrogen, C_{1-6} alkyl, more preferably C_{1-3} alkyl, more preferably C_{1-2} alkyl, more preferably C_1 alkyl.

In a more preferred embodiment of the present invention and/or embodiments thereof, R^2 , R^3 is hydrogen.

10 In a more preferred embodiment of the present invention and/or embodiments thereof, R^4 , R^5 is each independently hydrogen, hydroxy, or C_{1-6} alkyl, more preferably C_{1-3} alkyl, more preferably C_{1-2} alkyl, more preferably C_1 alkyl.

In a more preferred embodiment of the present invention and/or
15 embodiments thereof, R^4 , R^5 is each independently hydrogen, C_{1-6} alkyl, more preferably C_{1-3} alkyl, more preferably C_{1-2} alkyl, more preferably C_1 alkyl.

In a more preferred embodiment of the present invention and/or embodiments thereof, R^4 , R^5 is hydrogen.

In a more preferred embodiment of the present invention and/or
20 embodiments thereof, R^6 is hydrogen, hydroxy, or C_{1-6} alkyl, more preferably C_{1-3} alkyl, more preferably C_{1-2} alkyl, more preferably C_1 alkyl.

In a more preferred embodiment of the present invention and/or embodiments thereof, R^6 is hydrogen, C_{1-6} alkyl, more preferably C_{1-3} alkyl, more preferably C_{1-2} alkyl, more preferably C_1 alkyl.

25 In a more preferred embodiment of the present invention and/or embodiments thereof, R^6 is hydrogen.

In a preferred embodiment of the present invention and/or embodiments thereof, R^7 is hydrogen, hydroxy, or C_{1-6} alkyl, more preferably C_{1-3} alkyl, more preferably C_{1-2} alkyl, more preferably C_1 alkyl.

In a more preferred embodiment of the present invention and/or embodiments thereof, R⁷ is hydrogen, C₁₋₆alkyl, more preferably C₁₋₃alkyl, more preferably C₁₋₂alkyl, more preferably C₁alkyl.

In a more preferred embodiment of the present invention and/or
5 embodiments thereof, R⁷ is hydrogen.

In a preferred embodiment of the present invention and/or
embodiments thereof, R¹⁰ is hydrogen, C₁₋₂₀alkyl, or C₂₋₂₀alkenyl, aryl,
aminoC₁₋₁₂alkyl, carbonylC₁₋₁₂alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl,
or NR⁴R⁵. In a more preferred embodiment of the present invention and/or
10 embodiments thereof, R¹⁰ is hydrogen, C₁₋₁₆alkyl, C₂₋₁₆alkenyl, aryl,
aminoC₁₋₁₂alkyl, carbonylC₁₋₁₂alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl,
or NR⁴R⁵. In a more preferred embodiment of the present invention and/or
embodiments thereof, R¹⁰ is hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, aryl, aminoC₁₋₆
alkyl, carbonylC₁₋₁₂alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, or NR⁴R⁵.
15 In a more preferred embodiment of the present invention and/or
embodiments thereof, R¹⁰ is hydrogen, C₁₋₂₀alkyl, C₂₋₂₀alkenyl, aryl,
aminoC₁₋₁₂alkyl, carbonylC₁₋₁₂alkyl, hydroxyC₁₋₆alkyl, or NR⁴R⁵. In a more
preferred embodiment of the present invention and/or embodiments thereof,
R¹⁰ is hydrogen, C₁₋₂₀alkyl, C₂₋₂₀alkenyl, aryl, aminoC₁₋₁₂alkyl, or NR⁴R⁵. In
20 a more preferred embodiment of the present invention and/or embodiments
thereof, R¹⁰ is hydrogen, C₁₋₂₀alkyl, or C₂₋₂₀alkenyl, or aryl, or NR⁴R⁵. In a
more preferred embodiment of the present invention and/or embodiments
thereof, R¹⁰ is hydrogen, C₁₋₁₆alkyl, C₂₋₁₆alkenyl, or aryl, or NR⁴R⁵. In a more
preferred embodiment of the present invention and/or embodiments thereof,
25 R¹⁰ is hydrogen, C₁₋₁₂alkyl, C₂₋₁₂alkenyl, or aryl, or NR⁴R⁵. In a more
preferred embodiment of the present invention and/or embodiments thereof,
R¹⁰ is hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, or aryl, or NR⁴R⁵. In a more preferred
embodiment of the present invention and/or embodiments thereof, R¹⁰ is
hydrogen, C₁₋₂₀alkyl, or C₂₋₂₀alkenyl, or NR⁴R⁵. In a more preferred

embodiment of the present invention and/or embodiments thereof, R¹⁰ is hydrogen, C₁₋₂₀alkyl, or NR⁴R⁵.

In another aspect of the present invention and/or embodiments thereof the compounds may be used as a medicine, especially in the
5 treatment of cancer.

In a preferred embodiment of the present invention and/or embodiments thereof the cancer is selected from the group of breast carcinoma, brain carcinoma, kidney carcinoma, colorectal carcinoma, lung carcinoma, head and neck carcinoma, esophageal carcinoma, hepatocellular carcinoma, cholangiocarcinoma, renal cel carcinomal, testis carcinoma,
10 cervix carcinoma, endometrium carcinoma, ovarian carcinoma, Squamous cell carcinoma, Basal cell carcinoma, Glioma, Ependymoma, mesothelioma, papillary thyroid carcinoma, thyroid carcinoma, follicular thyroid carcinoma, follicular lymphoma, non-Hodgkin's lymphoma, adenocarcinoma, stomach carcinoma, duodenum carcinoma, biliary carcinoma, pancreas
15 carcinoma, and bladder carcinoma, preferably the the cancer is colorectum cancer.

In a aspect of the present invention is directed to treatment of cancer comprising administering a compound of aspects and/embodiments of
20 the present invention.

In a preferred embodiment of the present invention and/or embodiments thereof the treatment of cancer may be in combination with other cancer therapies, such as radiotherapy and chemotherapy.

In a preferred embodiment of the present invention and/or
25 embodiments thereof the treatment comprises administering to a patient in need of a treatment an effective dose of a compound of aspects and/embodiments of the present invention.

Suitable the effective dose of compounds of the present invention is the effective dose of the original anticancer agent A.

The effective dose will depend on the anticancer agent and the tumour to be treated. A skilled person is well aware of methods to determine the effective dose of a compound.

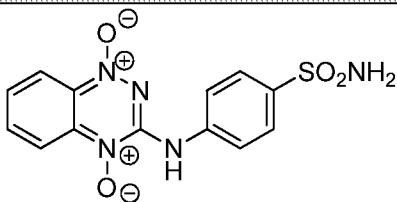
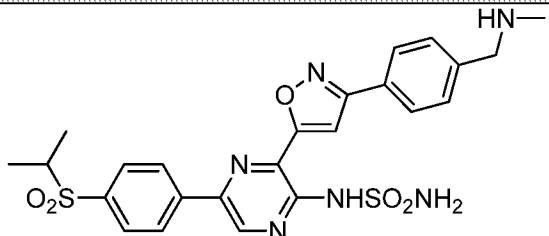
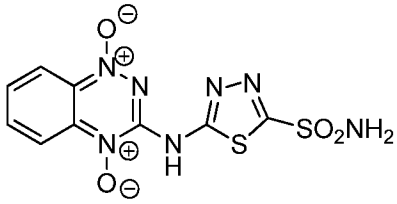
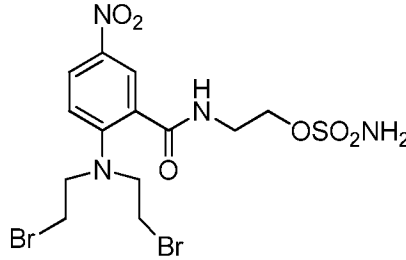
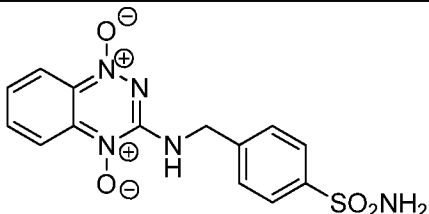
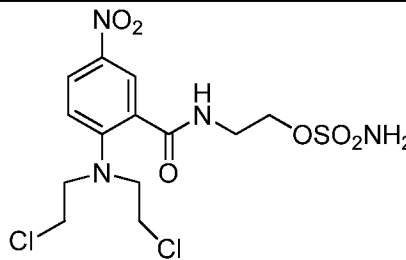
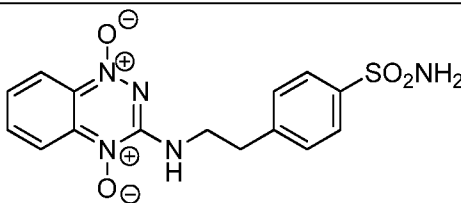
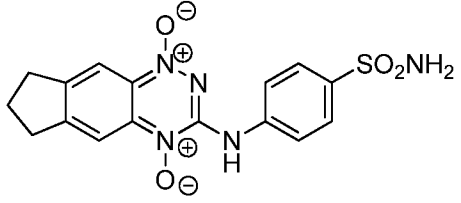
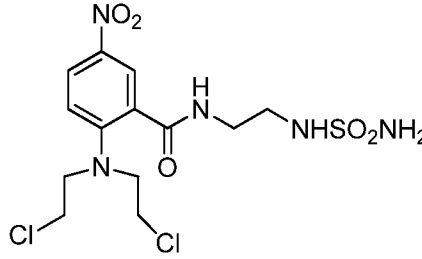
An effective dose (ED) is the dose or amount of compound that
5 produces a therapeutic response or desired effect in some fraction of the subjects taking it. A therapeutic response may be a decreased growth of the tumour, a reduction of the tumour size, reduction of metastasis, removal of metastasis, or removal of the primary tumour.

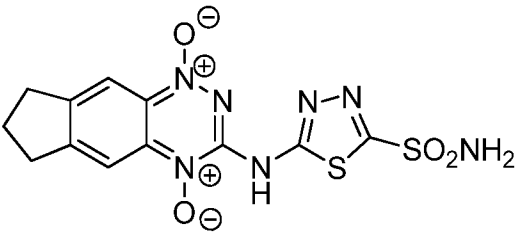
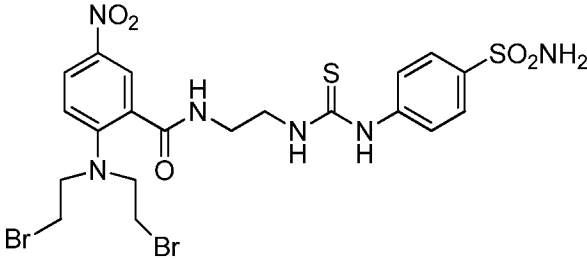
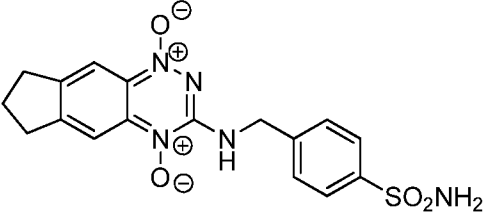
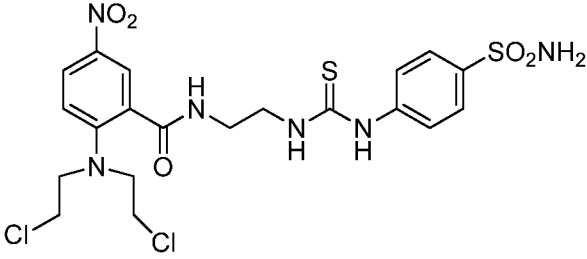
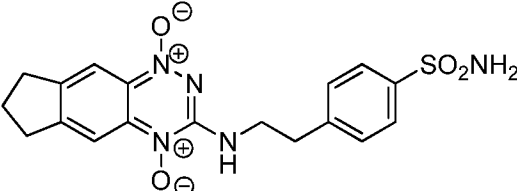
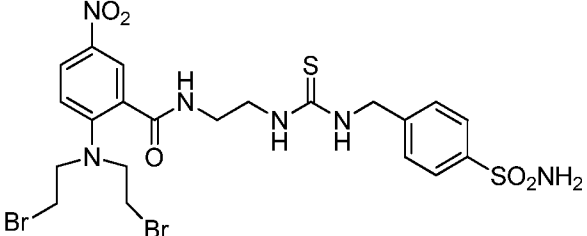
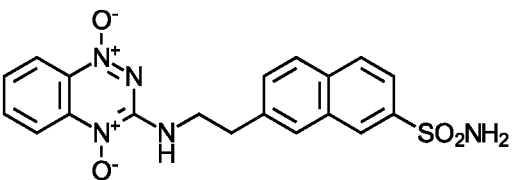
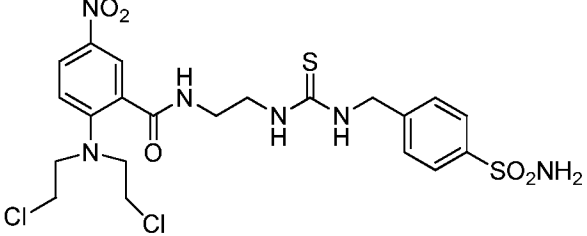
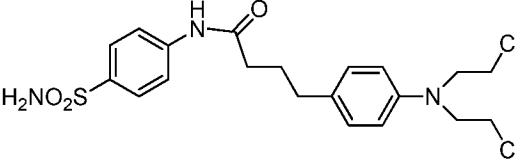
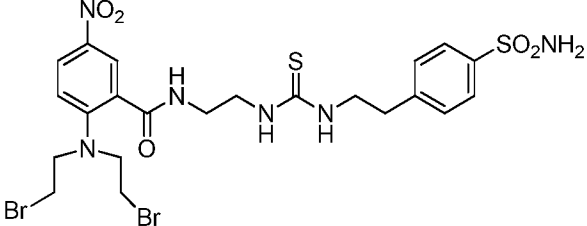
The present invention also features methods of using or preparing
10 or formulating such pharmaceutical compositions. The pharmaceutical compositions can be prepared using conventional pharmaceutical excipients and compounding techniques known to those skilled in the art of preparing dosage forms. It is anticipated that the compounds of the invention can be administered by oral, parenteral, rectal, topical, or ocular routes,
15 intravenous or by inhalation or by nasal spray. Preparations may also be designed to give slow release of the active ingredient. The preparation may be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, powders for reconstitution, liquid preparations, or suppositories. Preferably, compounds may be administered by intravenous infusion or
20 topical administration, but more preferably by oral administration.

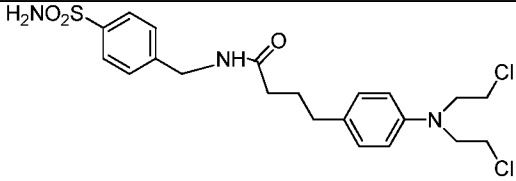
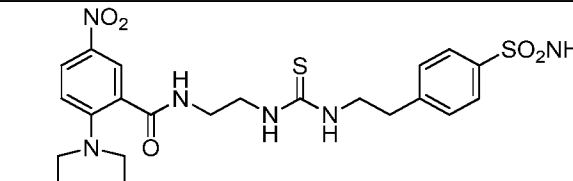
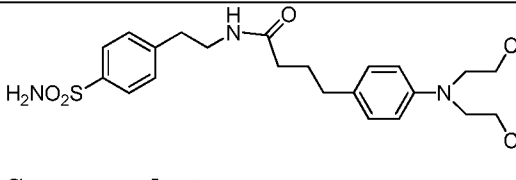
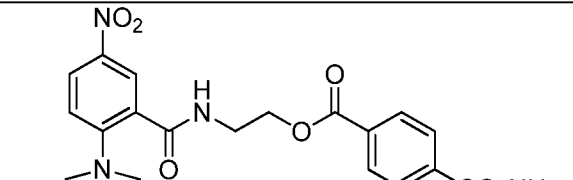
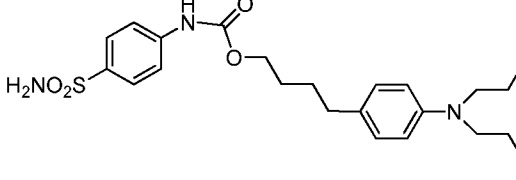
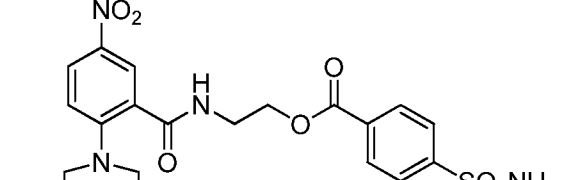
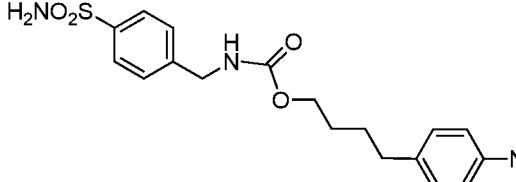
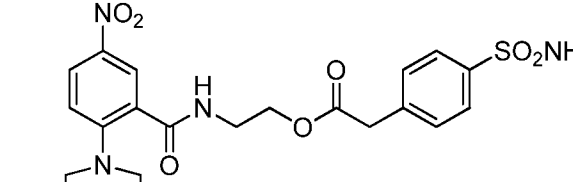
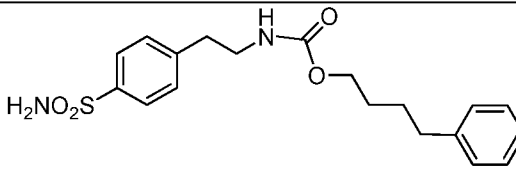
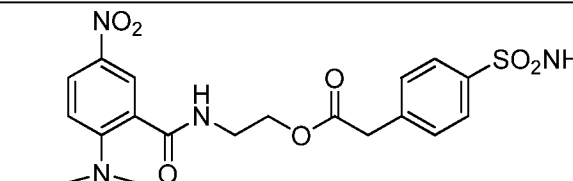
For oral administration, the compounds of the invention may be provided in the form of tablets or capsules, or as a solution, emulsion, or suspension. Tablets for oral use may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert diluents,
25 disintegrating agents, binding agents, lubricating agents, sweetening agents, flavoring agents, coloring agents and preservatives. Suitable inert fillers include sodium and calcium carbonate, sodium and calcium phosphate, lactose, starch, sugar, glucose, methyl cellulose, magnesium stearate, mannitol, sorbitol, and the like; typical liquid oral excipients
30 include ethanol, glycerol, water and the like. Starch, polyvinyl-pyrrolidone,

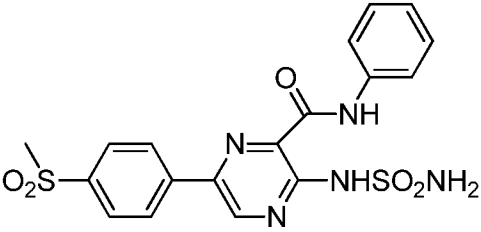
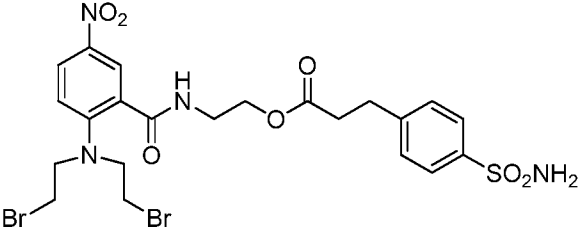
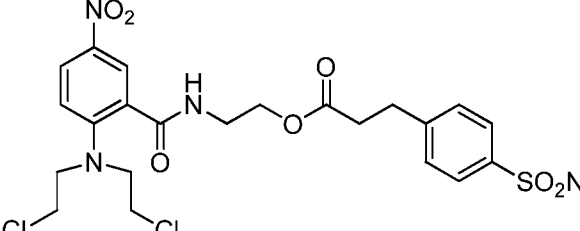
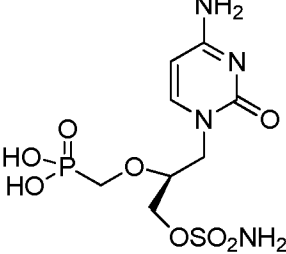
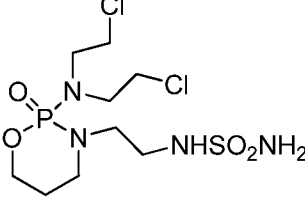
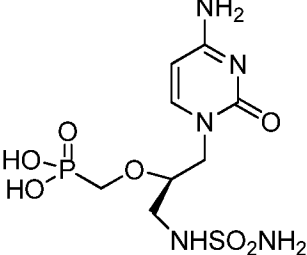
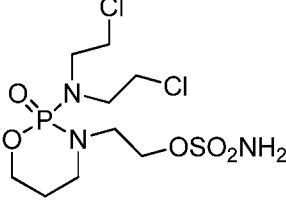
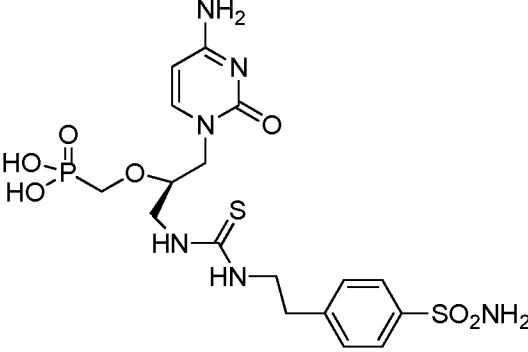
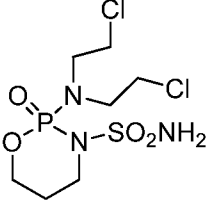
sodium starch glycolate, microcrystalline cellulose, and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin. The lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate to delay absorption in the gastrointestinal tract, or may be coated with an enteric coating. Capsules for oral use include hard gelatin capsules in which the active ingredient is mixed with a solid, semi-solid, or liquid diluent, and soft gelatin capsules wherein the active ingredient is mixed with water, an oil such as peanut oil or olive oil, liquid paraffin, a mixture of mono and diglycerides of short chain fatty acids, polyethylene glycol 400, or propylene glycol. Liquids for oral administration may be suspensions, solutions, emulsions or syrups or may be presented as a dry product for reconstitution with water or other suitable vehicles before use. Compositions of such liquid may contain pharmaceutically-acceptable excipients such as suspending agents (for example, sorbitol, methyl cellulose, sodium alginate, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel and the like); non-aqueous vehicles, which include oils (for example, almond oil or fractionated coconut oil), propylene glycol, ethyl alcohol or water; preservatives (for example, methyl or propyl p- hydroxybenzoate or sorbic acid); wetting agents such as lecithin; and, if needed, flavoring or coloring agents. The compounds of this invention may also be administered by non-oral routes.

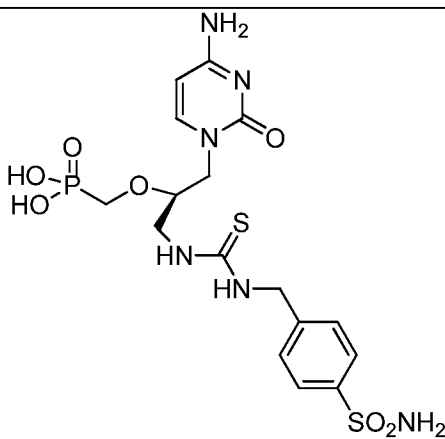
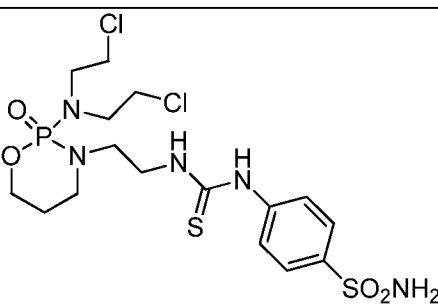
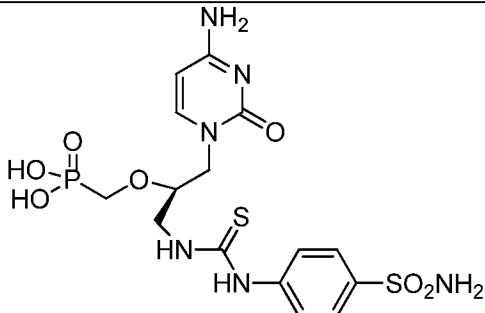
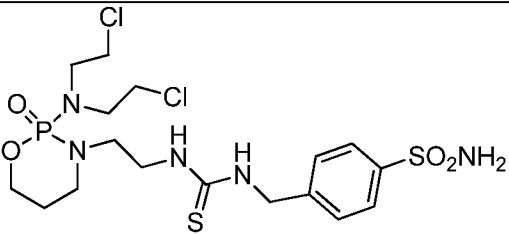
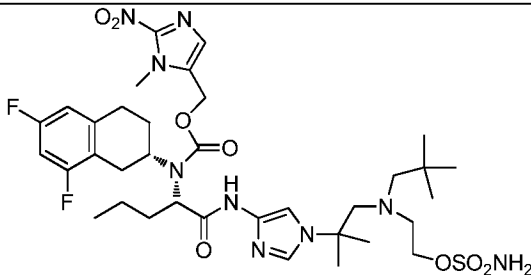
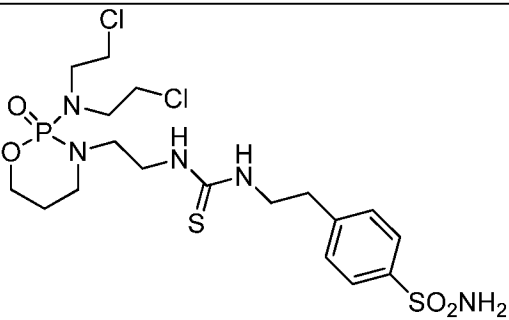
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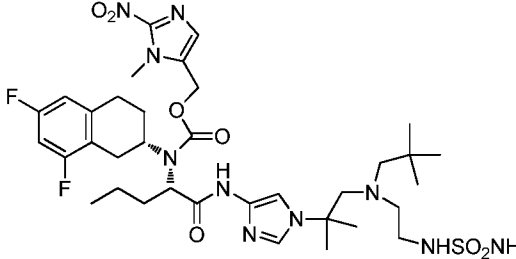
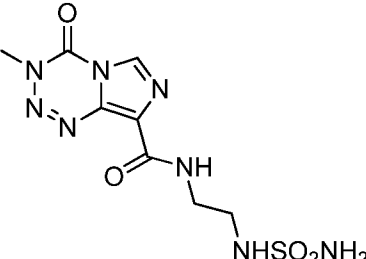
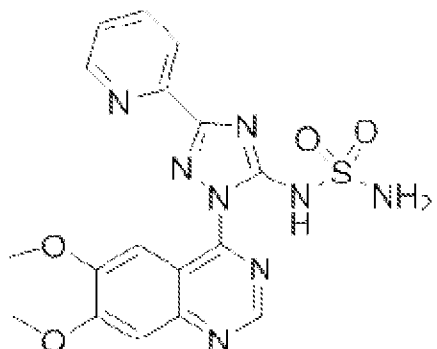
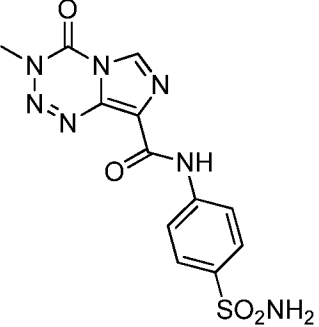
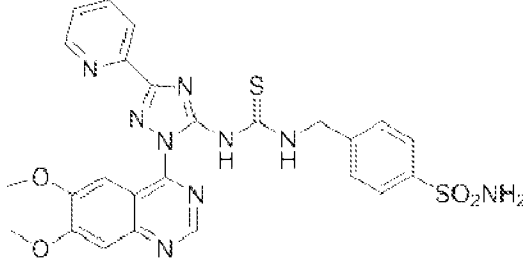
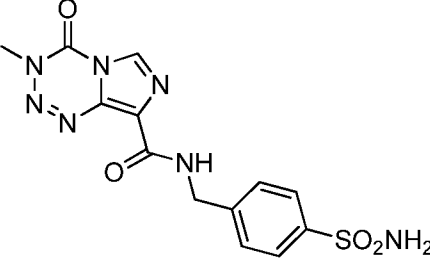
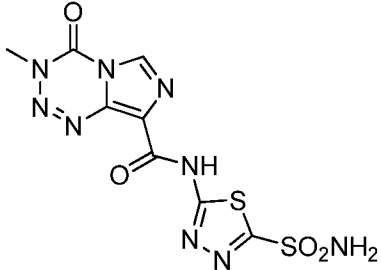
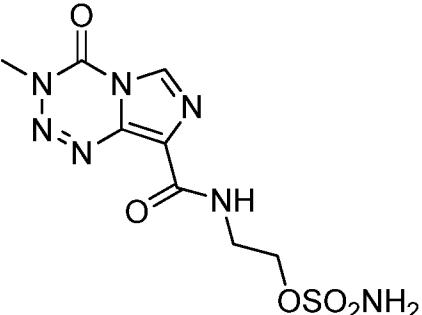
Compound	
 Compound 1	 Compound 17
 Compound 2	 Compound 18
 Compound 3	 Compound 19
 Compound 4	Compound 20
 Compound 5	

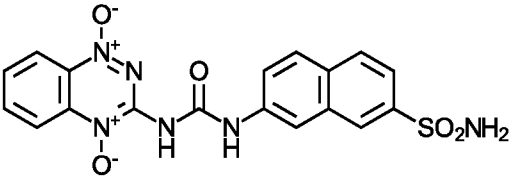
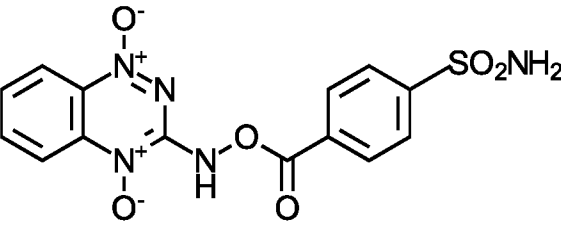
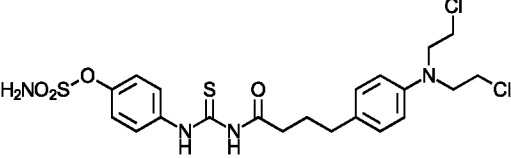
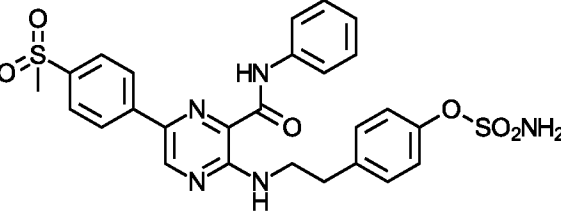
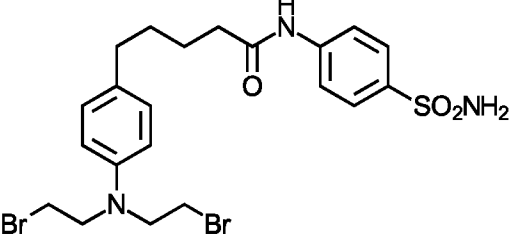
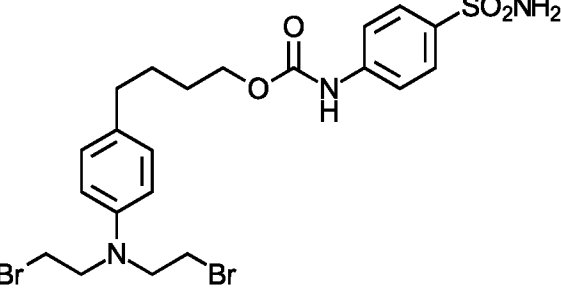
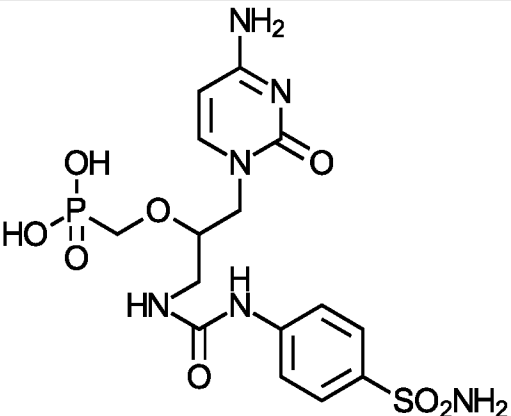
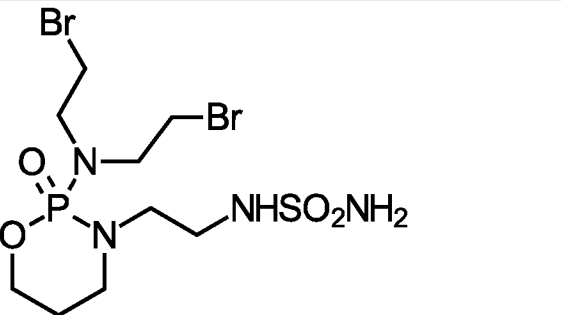
 Compound 6	Compound 21  Compound 22
 Compound 7	 Compound 23
 Compound 8	 Compound 24
 Compound 9	 Compound 25
	

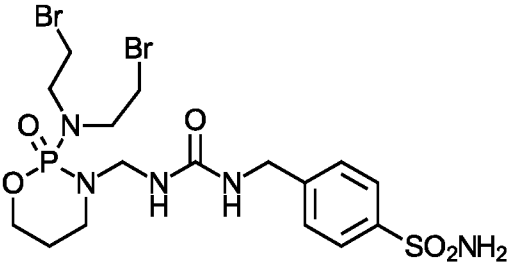
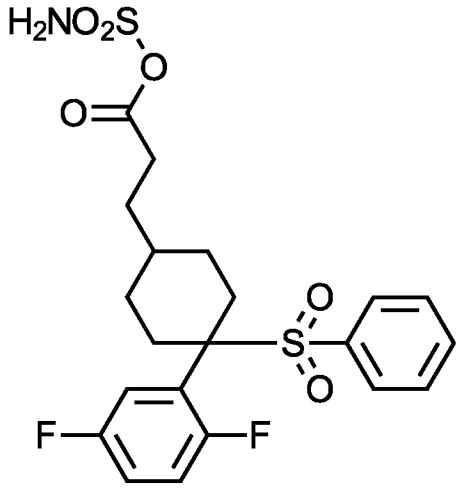
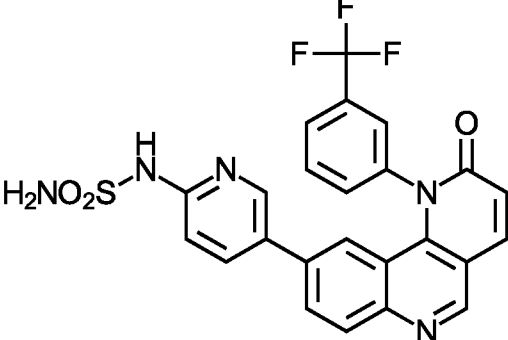
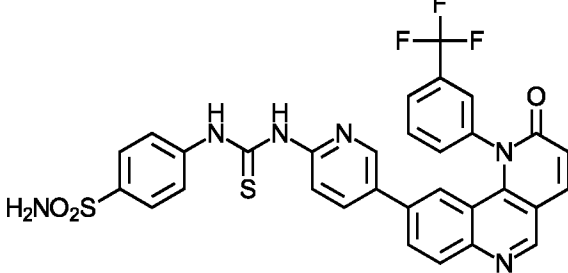
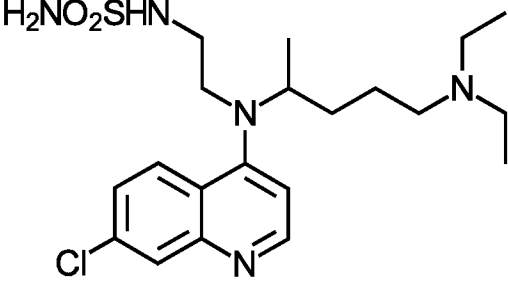
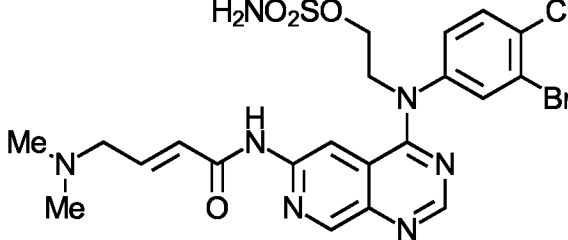
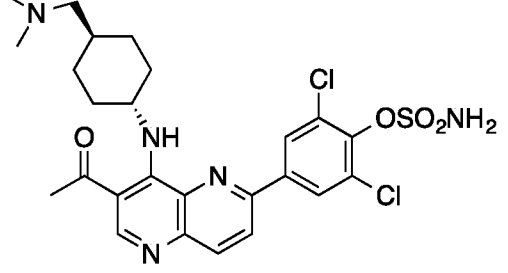
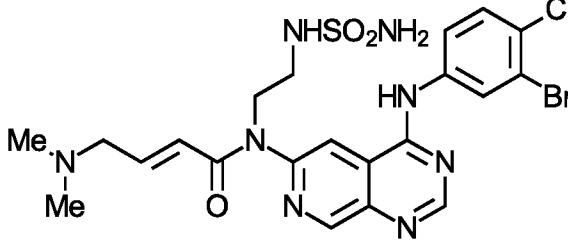
Compound 10  Compound 11	Compound 26  Compound 27
 Compound 12	 Compound 28
 Compound 13	 Compound 29
 Compound 14	 Compound 30
 Compound 15	 Compound 31

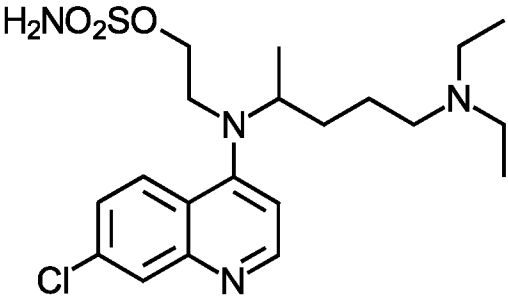
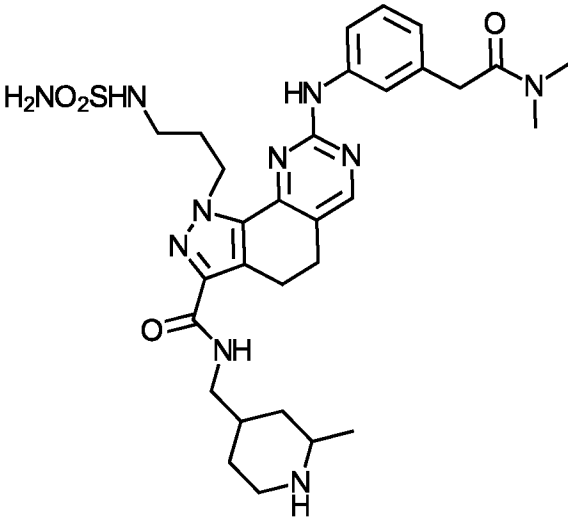
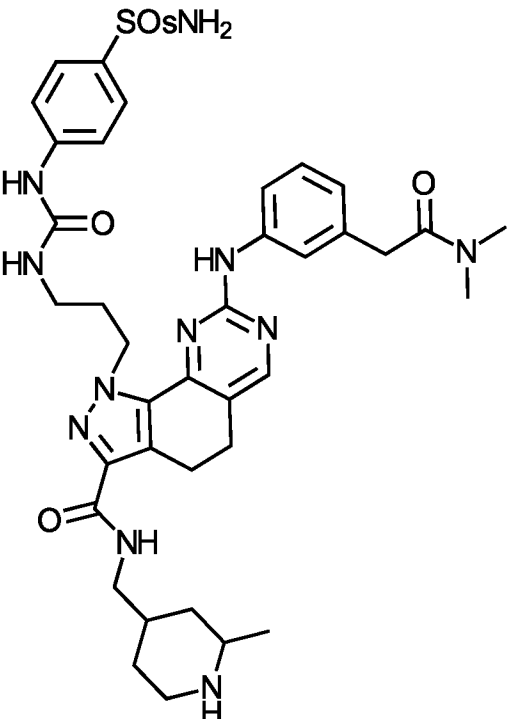
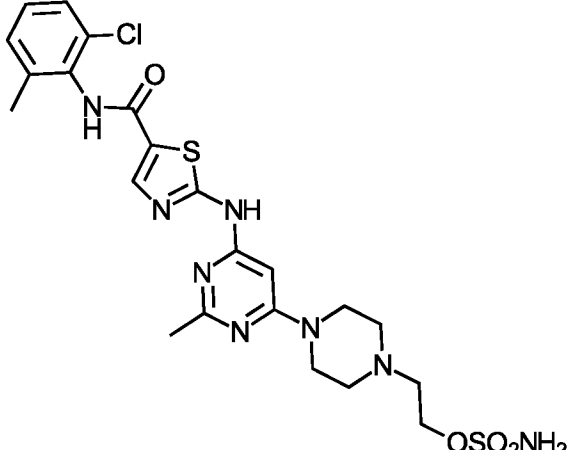
 Compound 16	 Compound 32
	 Compound 33
 Compound 34	 Compound 39
 Compound 35	 Compound 40
 Compound 41	 Compound 41

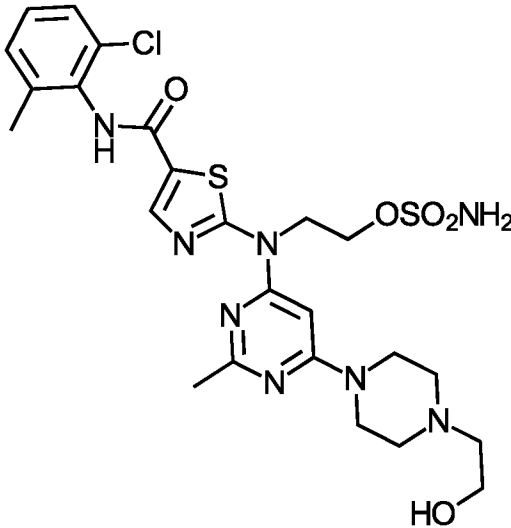
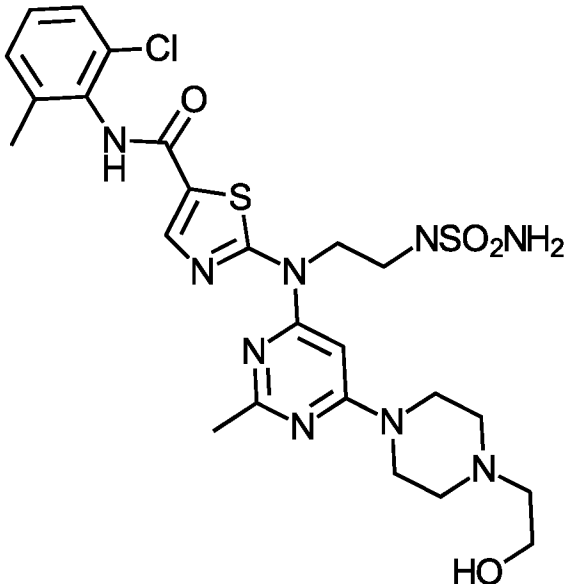
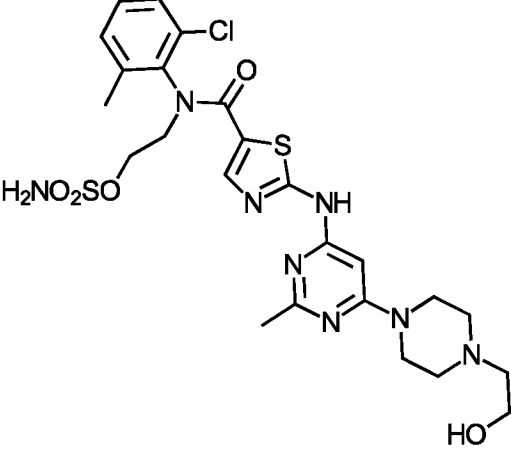
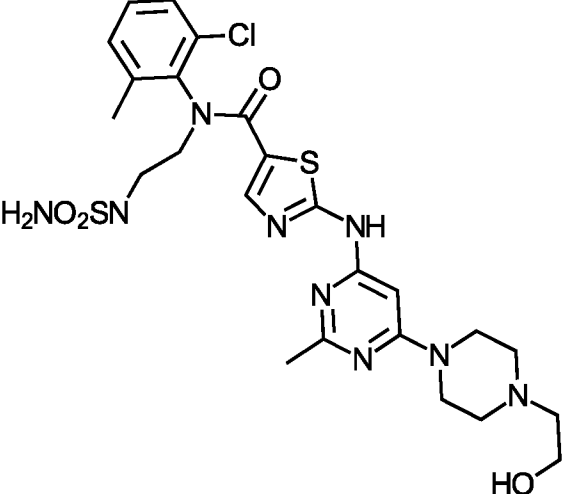
Compound 36 	 Compound 42
Compound 37 	 Compound 43
Compound 38  Compound 45	 Compound 44

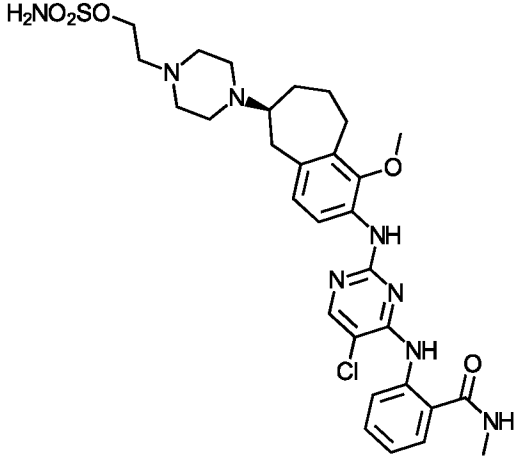
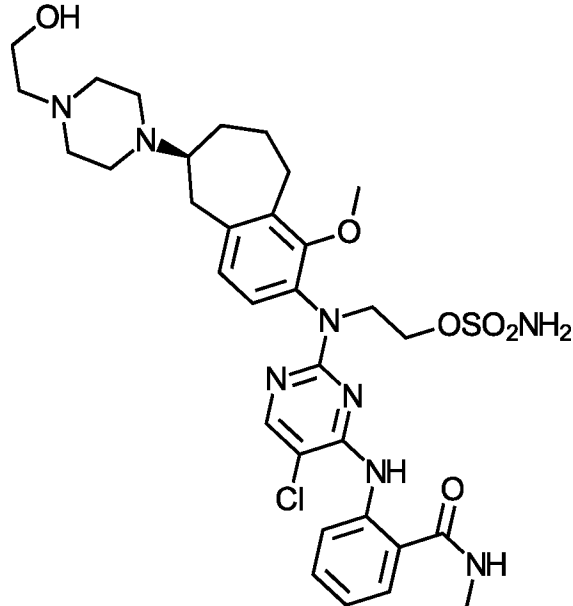
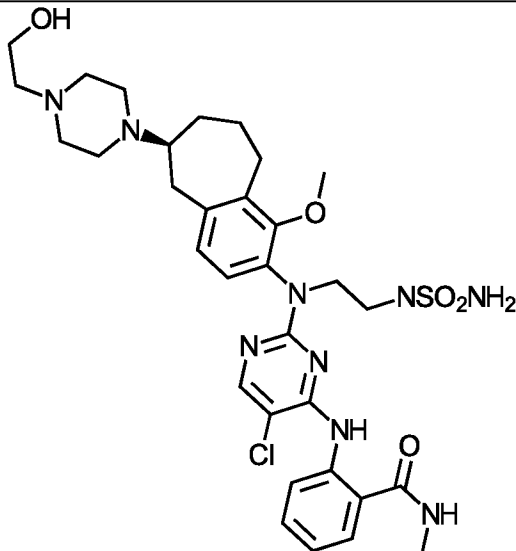
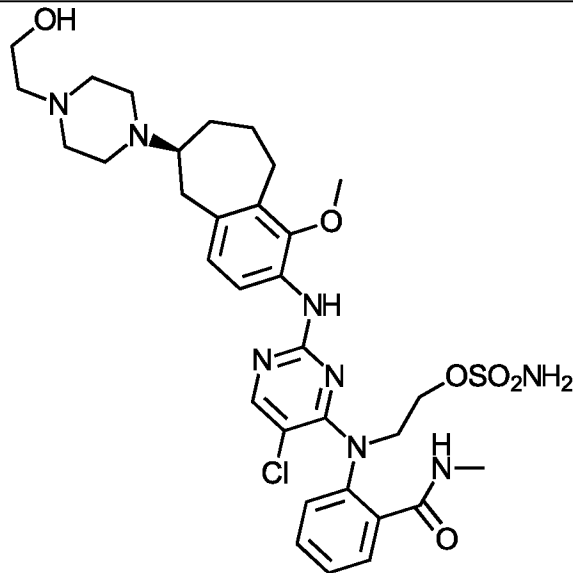
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 Compound 53	 Compound 48
 Compound 54	 Compound 49
 Compound 50	 Compound 51

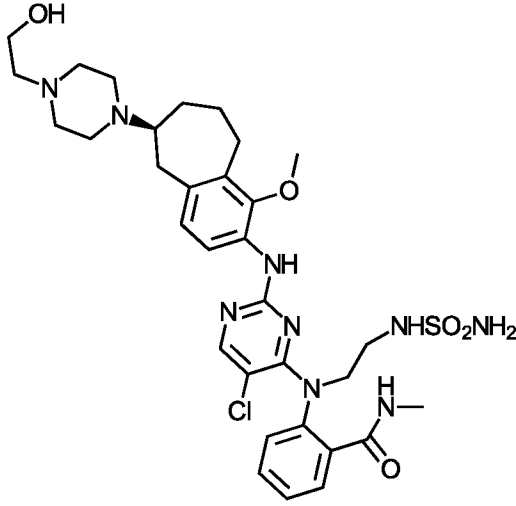
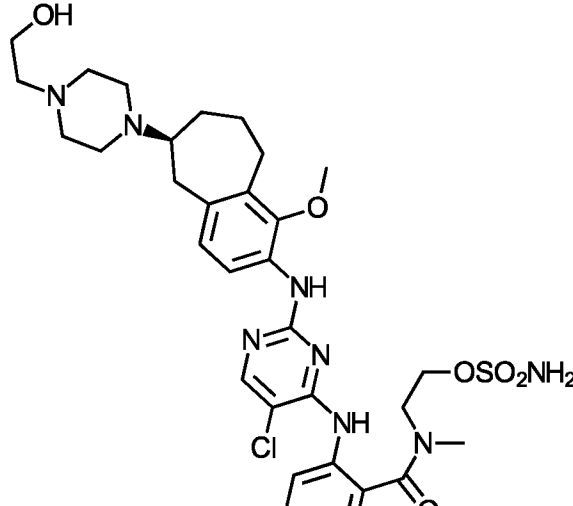
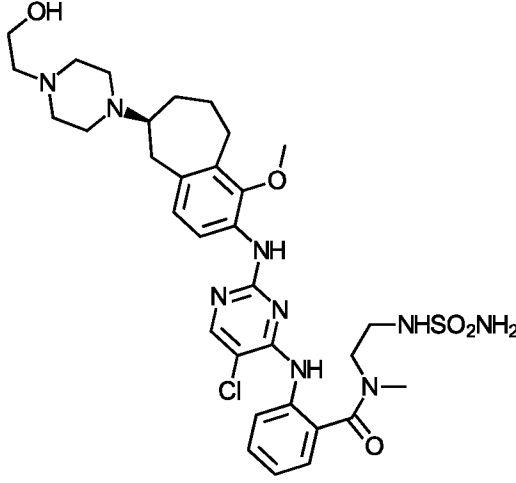
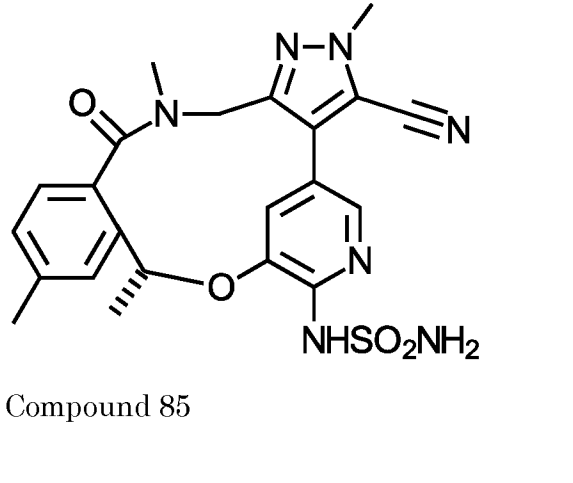
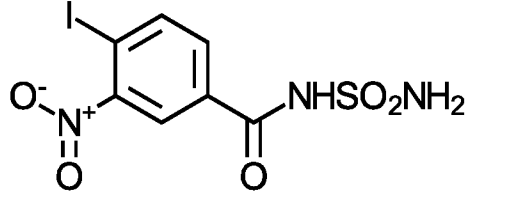
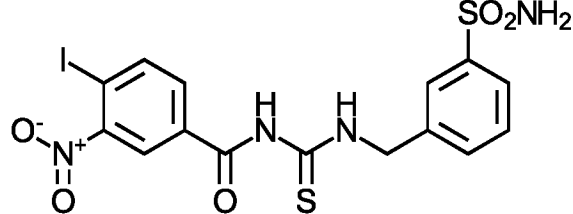
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 Compound 56	 Compound 57
 Compound 58	 Compound 59
 Compound 60	 Compound 61

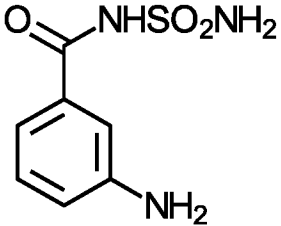
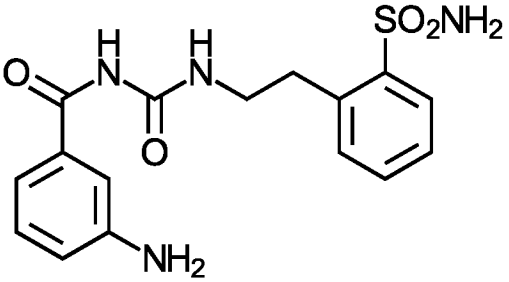
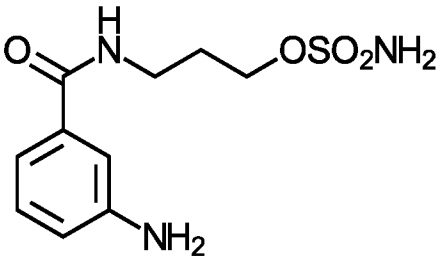
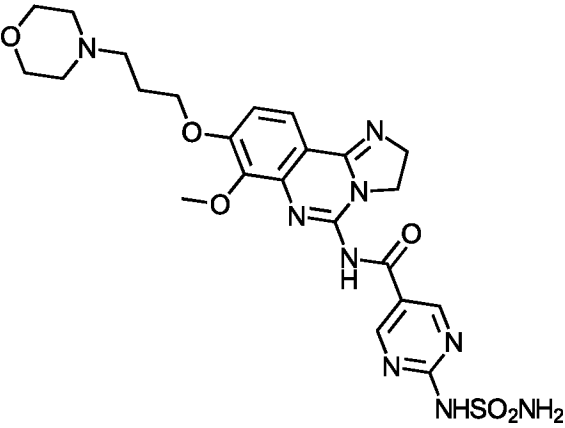
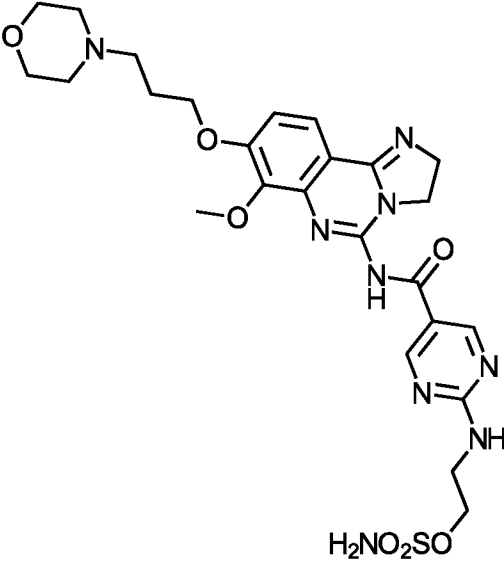
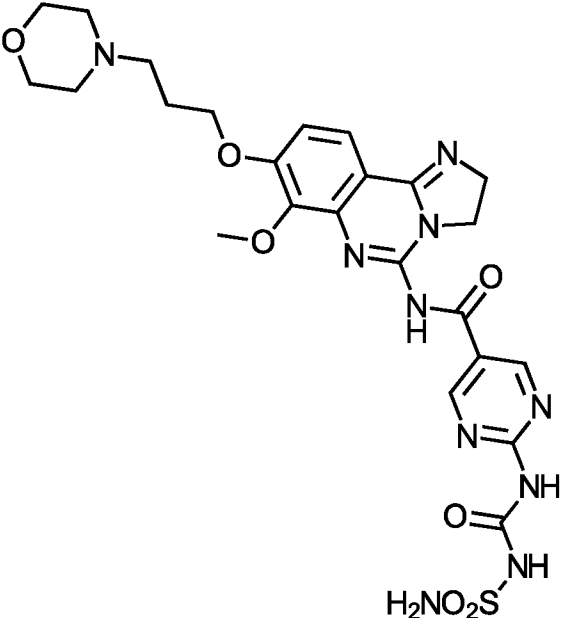
 Compound 62	 Compound 63
 Compound 64	 Compound 65
 Compound 69	 Compound 68
 Compound 66	 Compound 67

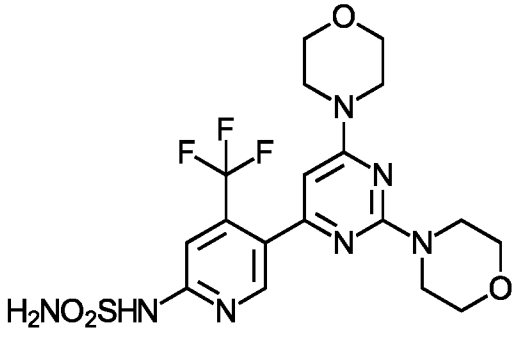
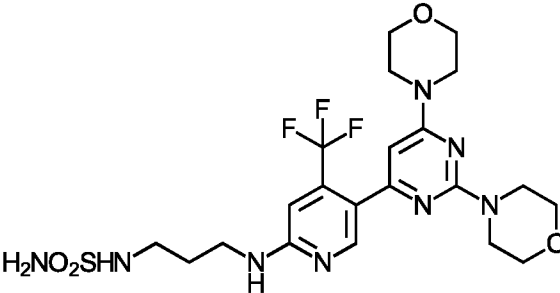
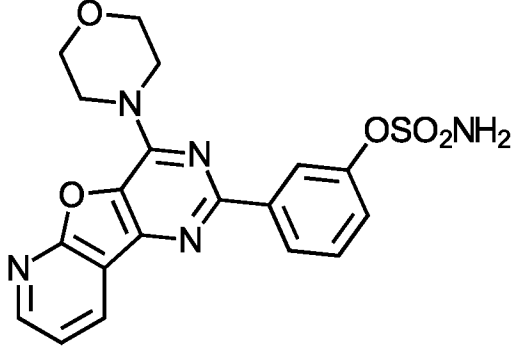
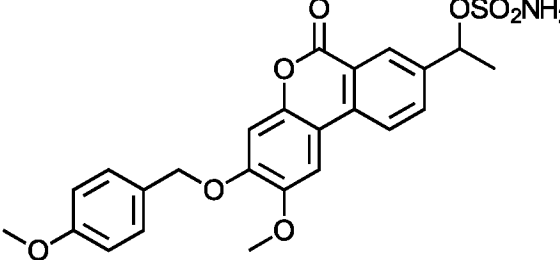
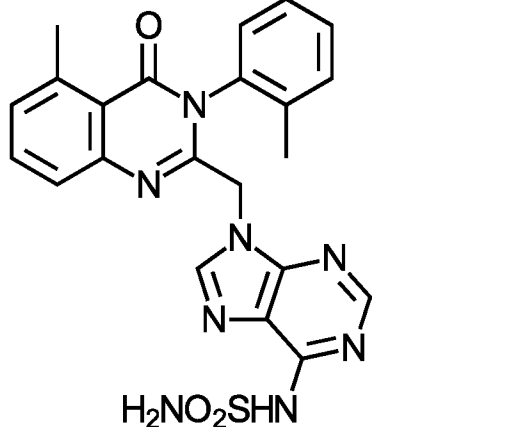
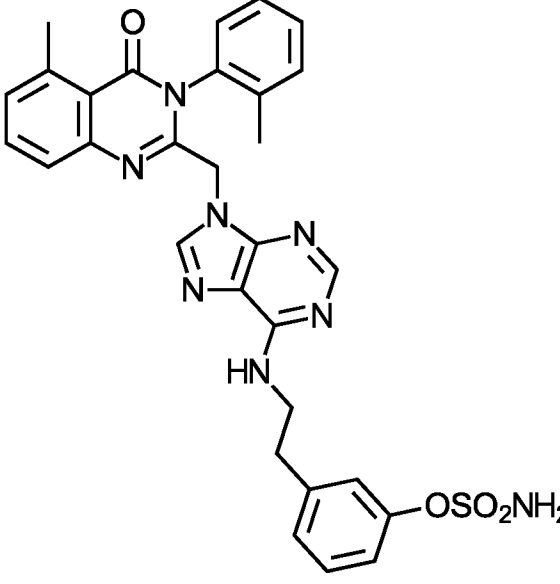
 Compound 70	 Compound 71
 Compound 72	 Compound 73

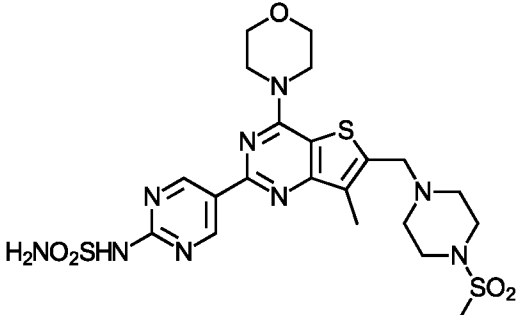
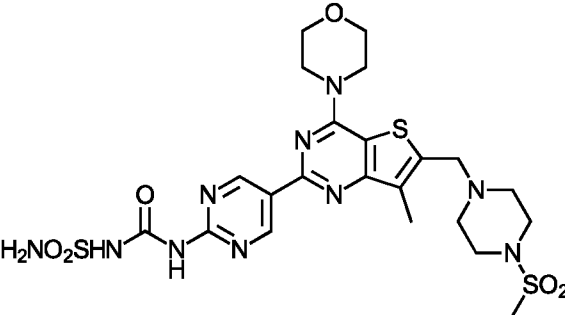
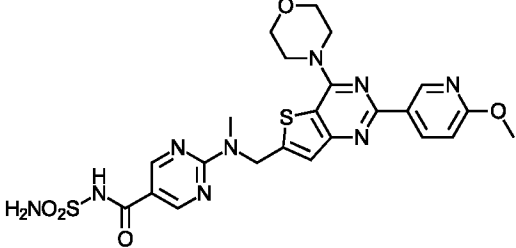
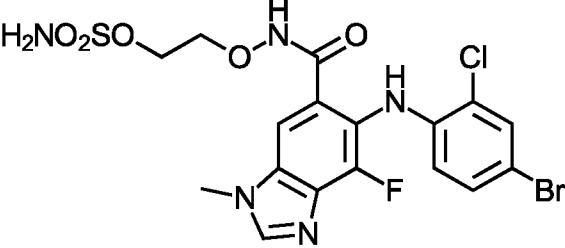
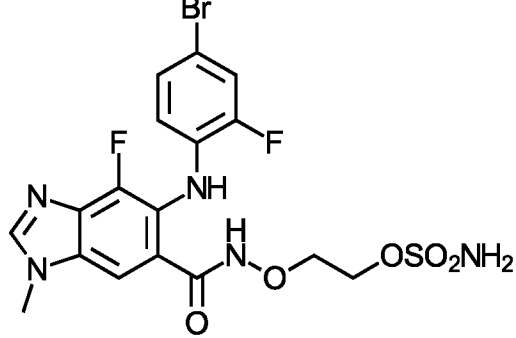
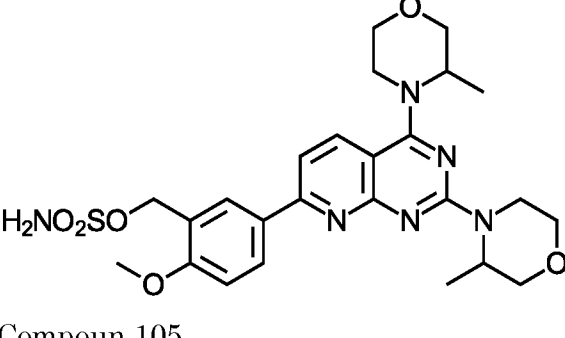
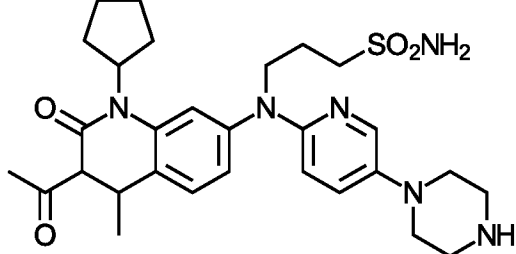
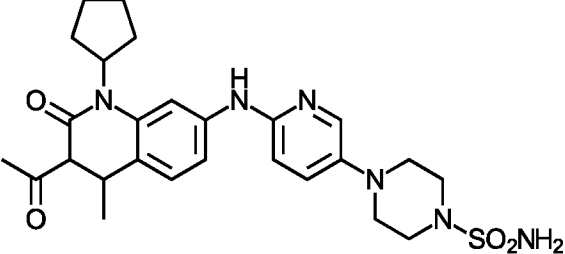
 Compound 74	 Compound 75
 Compound 76	 Compound 77

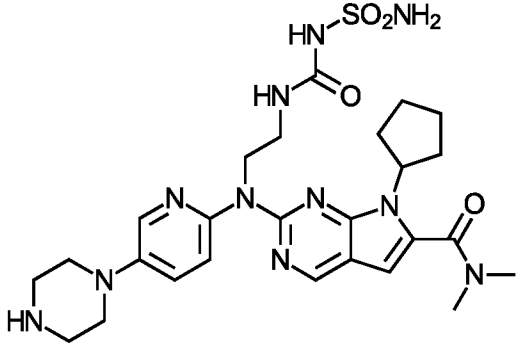
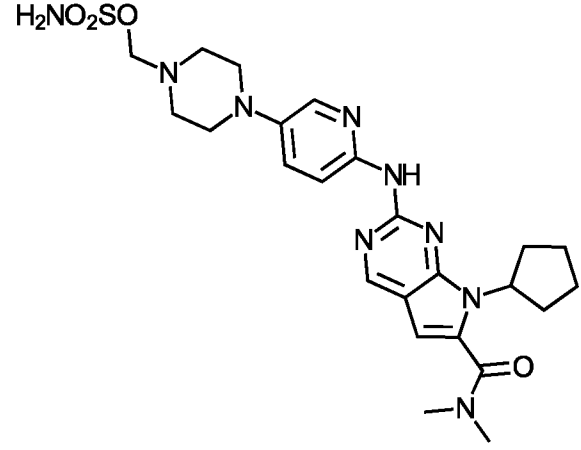
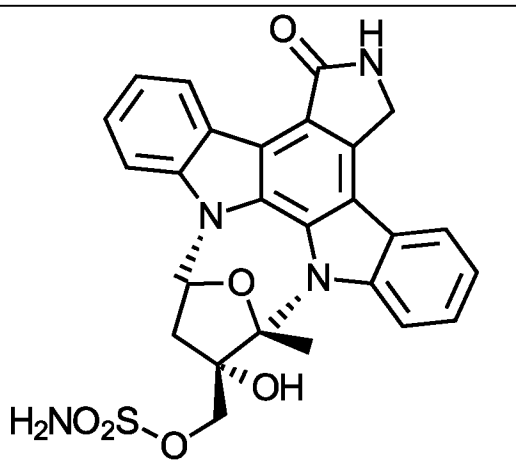
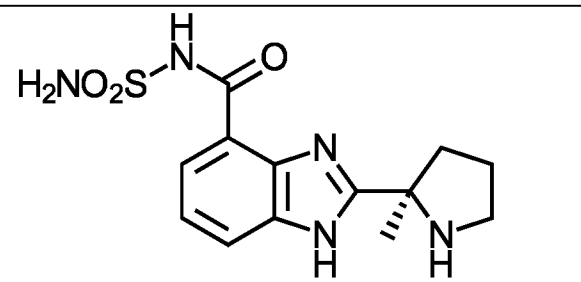
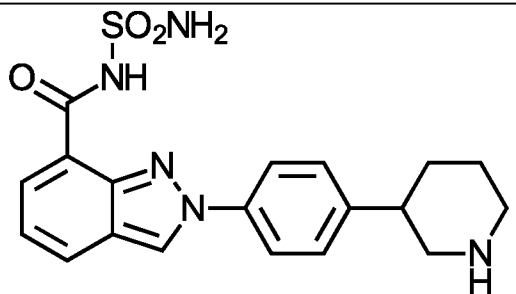
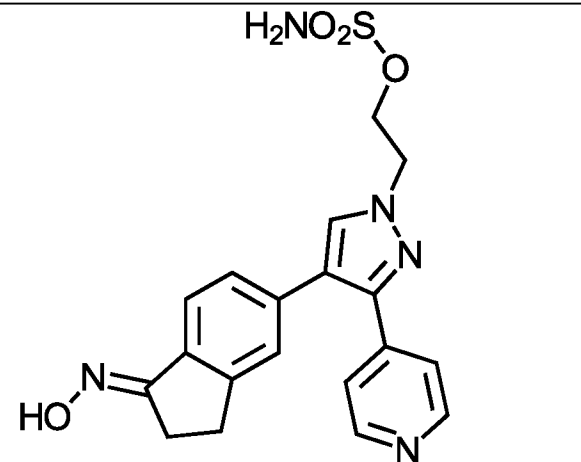
 Chemical structure of Compound 78: A piperazine ring with a 2-hydroxyethyl group and a 7-methoxy-8-(2-chloro-4-((methylamino)carbonyl)phenyl)-1H-imidazo[5,1-b]indol-3-yl group is attached to a 2-methoxy-3-(2-chloro-4-((methylamino)carbonyl)phenyl)-1H-imidazo[5,1-b]indol-5-yl group via a cyclooctyl bridge.	 Chemical structure of Compound 79: A piperazine ring with a 2-hydroxyethyl group and a 7-methoxy-8-(2-chloro-4-((methylamino)carbonyl)phenyl)-1H-imidazo[5,1-b]indol-3-yl group is attached to a 2-methoxy-3-(2-chloro-4-((methylamino)carbonyl)phenyl)-1H-imidazo[5,1-b]indol-5-yl group via a cyclooctyl bridge. The piperazine ring is also substituted with a 2-(hydroxymethyl)ethylanesulfonamide group.
Compound 78	Compound 79
 Chemical structure of Compound 80: A piperazine ring with a 2-hydroxyethyl group and a 7-methoxy-8-(2-chloro-4-((methylamino)carbonyl)phenyl)-1H-imidazo[5,1-b]indol-3-yl group is attached to a 2-methoxy-3-(2-chloro-4-((methylamino)carbonyl)phenyl)-1H-imidazo[5,1-b]indol-5-yl group via a cyclooctyl bridge. The piperazine ring is also substituted with a 2-(hydroxymethyl)ethylanesulfonamide group.	 Chemical structure of Compound 81: A piperazine ring with a 2-hydroxyethyl group and a 7-methoxy-8-(2-chloro-4-((methylamino)carbonyl)phenyl)-1H-imidazo[5,1-b]indol-3-yl group is attached to a 2-methoxy-3-(2-chloro-4-((methylamino)carbonyl)phenyl)-1H-imidazo[5,1-b]indol-5-yl group via a cyclooctyl bridge. The piperazine ring is also substituted with a 2-(hydroxymethyl)ethylanesulfonamide group.
Compound 80	Compound 81

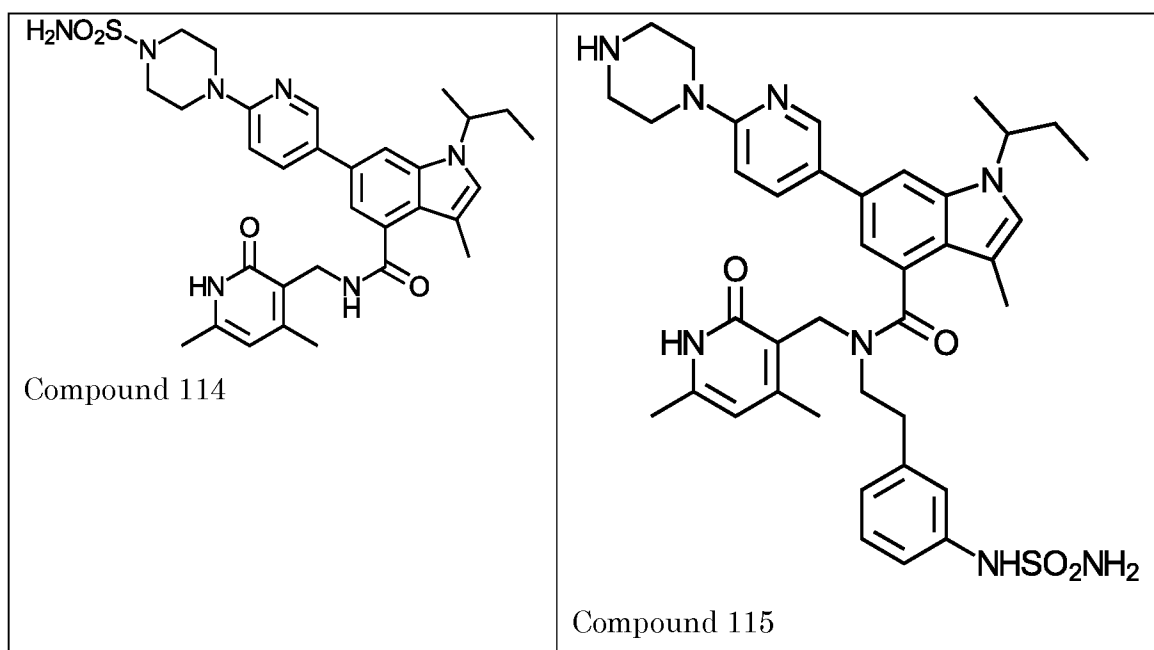
 Compound 82	 Compound 83
 Compound 84	 Compound 85
 Compound 86	 Compound 87

 Compound 88	 Compound 89
 Compound 90	 Compound 91
 Compound 92	 Compound 93

 Compound 94	 Compound 95
 Compound 96	 Compound 97
 Compound 98	 Compound 99

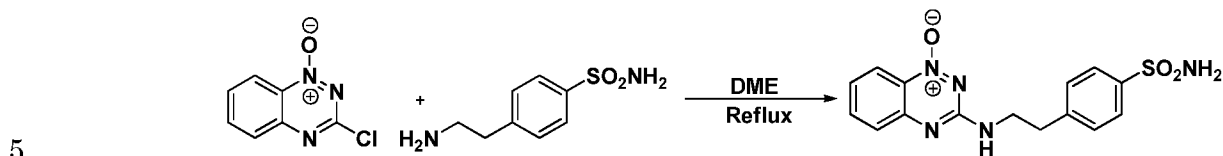
 Compound 100	 Compound 101
 Compound 102	 Compound 103
 Compound 104	 Compound 105
 Compound 106	 Compound 107

 Compound 108	 Compound 109
 Compound 110	 Compound 111
 Compound 112	 Compound 113



Experimental:

Synthesis of Compound 4



Ref:

J Med Chem. 2012 July 12; 55(13): 6047–6060

Procedure:

10 4-(2-aminoethyl) benzene sulfonamide (3eq) was added to stirred solution of 3-chlorobenzo[e][1,2,4]triazine 1-oxide (1eq) in 30 ml of DME allowed to stir at reflux temperature for overnight.

Work-Up:

15 Reaction mixture cooled to room temperature and solvent was evaporated then residue was washed with NH_4OH and extracted with EtOAc. Organic layer was dried over sodium sulfate and evaporated to get crude.

Purification:

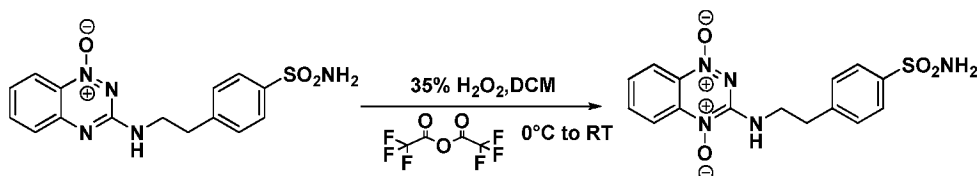
20 Crude was purified through column by using 99:1 to 98:2 DCM:MeOH. Data: Mass: MS ($\text{ESI}^+/\text{ESI}^-$) m/z 346.10 $[\text{M}+\text{H}]^+$.

^1H NMR (400 MHz, DMSO) δ 8.15 (s, 1H), 8.13 (s, 1H), 8.03 (s, 1H), 7.82 – 7.71 (m, 3H), 7.60 (d, $J = 8.0$, 1H), 7.47 (d, $J = 8.0$, 2H), 7.38 – 7.30 (m, 1H), 7.28 (s, 2H), 3.60 (d, $J = 6.2$, 2H), 3.01 (dd, $J = 6.2$ 2H).

25 ^{13}C NMR (101 MHz, DMSO) δ 158.80, 143.70, 142.07, 135.76, 129.25, 125.92, 124.66, 119.93, 41.92, 34.09.

TLC Eluent: 9:1 DCM:MeOH, Rf: 0.35, % of Yield: 94%.

5

**Ref:**

J.Med.Chem, 2008, 51, 6853-6865

Procedure:

Hydrogen peroxide (10 eq) was added drop wise to a stirred
 10 solution of trifluoroacetic anhydride (10eq) in DCM at 0°C. The mixture was
 stirred at 0°C for 5 min warmed to room temperature stirred for 10 min and
 cooled to 5°C. The mixture was added to stirred solution of 3-(4-
 sulfamoylphenethylamino)benzo[e][1,2,4]triazine 1-oxide(1eq) in DCM at
 0°C and mixture stirred at room temperature for overnight.

15

Work-Up:

The reaction mixture was carefully diluted with water and
 basifies with aqueous NH₄OH and extracted with CHCl₃. Organic layer
 dried over sodium sulfate and evaporated to get crude.

Purification:

20 Crude was applied to column chromatography to afford pure
 product by using 1:99 to 2:98 MeOH:DCM

Data:

Mass: MS (ESI⁺/ESI⁻) *m/z* 362.09 [M+H]⁺.

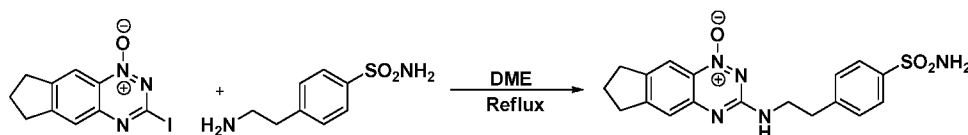
25 ¹H NMR (400 MHz, DMSO) δ 8.31 (t, *J* = 6.1, 1H), 8.22 (d, *J* = 8.1,
 1H), 8.13 (d, *J* = 8.1, 1H), 7.97 – 7.89 (m, 1H), 7.75 (d, *J* = 8.3, 2H), 7.61 –
 7.53 (m, 1H), 7.47 (d, *J* = 8.3, 2H), 7.29 (s, 2H), 3.67 (dd, *J* = 7.2, 6.1, 2H),
 3.03 (t, *J* = 7.2, 2H).

^{13}C NMR (101 MHz, DMSO) δ 149.67, 143.19, 142.16, 138.19, 135.48, 130.07, 129.26, 127.04, 125.71, 121.13, 116.89, 41.76, 34.18.

TLC Eluent: 9:1 DCM:MeOH, Rf: 0.48, % of Yield: 96%.

5

Synthesis of compound 8



Ref:

10 J.Med.Chem, 2008, 51, 6853-6865

Procedure:

4-(2-aminoethyl) benzene sulfonamide (3eq) was added to stirred solution of 3-iodo-7,8-dihydro-6H-indeno[5,6-e][1,2,4]triazine 1-oxide (1eq) in 30 ml of DME allowed to stir at reflux temperature for 2 overnight.

15

Work-Up:

Reaction mixture cooled to room temperature and solvent was evaporated then residue was washed with NH_4OH and extracted with EtOAc. Organic layer was dried over sodium sulfate and evaporated to get crude.

20

Purification:

Crude was purified through column by using 99:1 to 98:2 DCM:MeOH

Data:

Mass: MS (ESI⁺/ESI⁻) m/z 386.13 $[\text{M}+\text{H}]^+$.

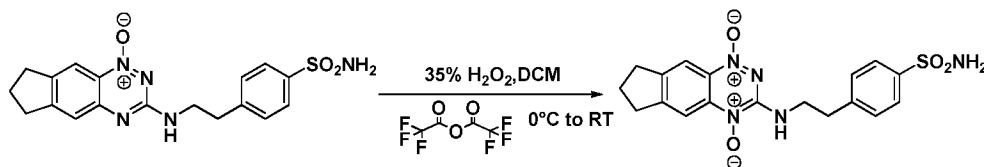
25

^1H NMR (400 MHz, DMSO) δ 7.95 (s, 1H), 7.82 (s, 1H), 7.74 (t, J = 10.0, 2H), 7.49 – 7.39 (m, 3H), 7.28 (s, 2H), 3.57 (dd, J = 13.0, 6.8, 2H), 3.02 – 2.90 (m, 6H), 2.11 – 1.99 (m, 2H).

^{13}C NMR (101 MHz, DMSO) δ 157.56, 153.64, 142.79, 141.97,
130.10 – 127.99, 125.35, 112.78, 41.77, 32.35, 31.60, 25.25

TLC Eluent: 9:1 DCM:MeOH, Rf: 0.44, %of Yield: 85%

5



Ref: J.Med.Chem, 2008, 51, 6853-6865

Procedure:

Hydrogen peroxide (10 eq) was added drop wise to a stirred solution of trifluoroacetic anhydride (10eq) in DCM at 0°C. The mixture was stirred at 0°C for 5 min warmed to room temperature stirred for 10 min and cooled to 5°C. The mixture was added to stirred solution of 3-(4-sulfamoylphenethylamino)-7,8-dihydro-6H-indeno[5,6-e][1,2,4]triazine 1-oxide (1eq) in DCM at 0°C and mixture stirred at room temperature for 3 overnight.

15

Work-Up:

The reaction mixture was carefully diluted with water and basified with aqueous NH_4OH and extracted with CHCl_3 . Organic layer dried over sodium sulfate and evaporated to get crude.

Purification:

20

Crude was applied to column chromatography to afford pure product by using 1:99 to 2:98 MeOH:DCM

Data:

Mass: MS (ESI⁺/ESI⁻) m/z 402.12 $[\text{M}+\text{H}]^+$.

^1H NMR (400 MHz, DMSO) δ 8.19 (s, 1H), 7.98 (d, $J = 24.2$, 2H), 7.75 (d, $J = 7.8$, 2H), 7.46 (d, $J = 7.7$, 2H), 7.29 (s, 2H), 3.65 (d, $J = 6.2$, 2H), 3.12 – 2.92 (m, 6H), 2.17 – 1.99 (m, 2H).

25

^{13}C NMR (101 MHz, DMSO) δ 154.56, 149.25, 145.07, 143.22, 142.15, 129.23, 125.71, 41.76, 32.74, 31.80, 25.24.

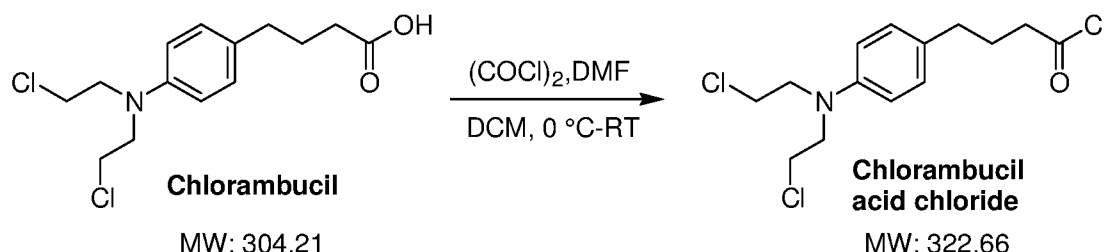
TLC Eluent: 9:1 DCM:MeOH, Rf: 0.4, % of Yield: 46%

Synthesis of compound

Synthesis of Compound 9-12

5

Preparation of chlorambucil acid chloride:



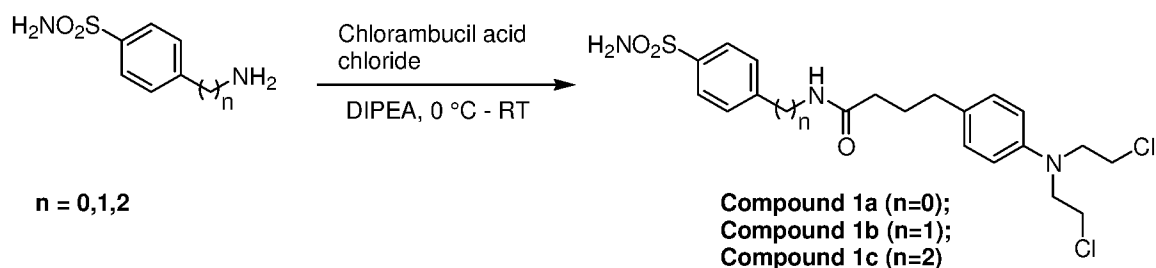
Experimental Procedure:

10

To a stirred solution of chlorambucil (5.0 g, 1.0 equ.) in dichloromethane (DCM) (25.0 mL, 5.0 vol.) and catalytic amount of *N,N*-dimethylformamide, was added oxalyl chloride (4.16 g, 2.0 equ.) slowly over a period of 1.0 h at 5-10 °C. The reaction mixture was stirred at ambient temperature for 2-3 h and consumption of the starting material was monitored by TLC (Sampling for TLC: Aliquot was quenched in methanol and spotted for TLC, 30% ethyl acetate in hexane). After completion of the reaction, excess oxalyl chloride and DCM were removed under reduced pressure to obtain chlorambucil acid chloride (5.3 g) as pale green solid which was used as such in the next step.

20

General scheme for the synthesis of amides (compounds 9-12):



1a=10+9

1b=11

1c=12

Note: For the synthesis of compound 1b (n=1; 11), hydrochloride
5 salt of 4-aminomethylbenzenesulfonamide was used in place of free amine.

Procedure for the synthesis of compound 9/10:

To a stirred solution of sulphanilamide (3.2 g, 1.1 equ.) in
anhydrous THF (35 mL, 7 vol.) was added *N,N*-diisopropylethylamine (10.62
10 g, 5.0 eq.) and cooled it to 0 °C. To this cold solution was added a solution of
chlorambucil acid chloride (prepared from 5.0 g of chlorambucil) in THF (15
mL, 3 vol.) slowly over a period of 30 min at 5-10 °C. The reaction mixture
was stirred at ambient temperature for 2-3 h. The reaction was monitored
by TLC (50% ethyl acetate in hexane). After reaction completion, the
15 reaction mixture was added into water and extracted with ethyl acetate (50
mL x 2). The combined organic layer was washed successively with 2 *N* HCl
solution (25 mL), 10% sodium bicarbonate solution (25 mL) and water (25
mL). The organic layer was dried over anhydrous sodium sulphate and
filtered. Evaporation of the solvent under reduced pressure gave the pale
20 yellow solid as crude product. The solid thus obtained was stirred in diethyl
ether (25 mL, 5 vol.) and filtered to give the compound **9/10** as off-white
solid (6.5 g, 87 %).

Procedure for the synthesis of compound 11:

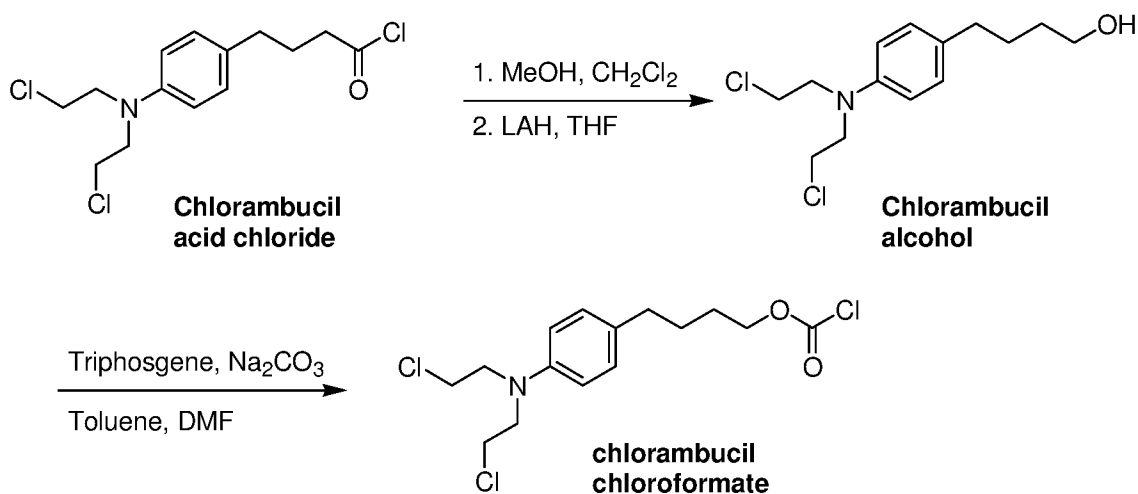
25 To a stirred suspension of 4-aminomethylbenzenesulfonamide
hydrochloride (5.6 g, 25 mmol) in acetonitrile (50 mL) was added *N,N*-
diisopropylethylamine (16 mL, 92 mmol) and cooled it to 0 °C. To this
suspension was added slowly a solution of chlorambucil acid chloride (7.42 g,
23 mmol) in acetonitrile (35 mL) over a period of 30 min and stirred
30 overnight at ambient temperature. Consumption of the starting material

was monitored by TLC (50% ethyl acetate in hexanes). After completion, reaction mixture poured into 1 *N* HCl (100 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic layer was washed with saturated NaHCO₃ solution (200 mL) and dried over anhydrous Na₂SO₄.

- 5 Evaporation of the solvent under reduced pressure gave pale yellow solid as crude product. The crude product was stirred with diisopropyl ether (100 mL) and filtered to obtain compound **11** as off-white solid (6.8 g, 66%).

Procedure for the synthesis of compound 12:

- 10 To a stirred suspension of 4-aminoethylbenzenesulfonamide (5.0 g, 25 mmol) in acetonitrile (50 mL) was added *N,N*-diisopropylethylamine (16 mL, 92 mmol) and cooled it to 0 °C. To this suspension was added slowly a solution of chlorambucil acid chloride (7.42 g, 23 mmol) in acetonitrile (35 mL) over a period of 30 min and stirred overnight at ambient temperature.
- 15 Consumption of the starting material was monitored by TLC (50% ethyl acetate in hexanes). After completion, reaction mixture poured into 1 *N* HCl (100 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic layer was washed with saturated NaHCO₃ solution (200 mL) and dried over anhydrous Na₂SO₄. Evaporation of the solvent gave pale yellow
- 20 solid as crude product. The crude product was stirred with diisopropyl ether (100 mL) and filtered to obtain compound **12** as off-white solid (9.0 g, 75%).

Synthesis of compounds 13-15**Preparation of chlorambucil alcohol:**

5

Experimental Procedure:**Procedure for the synthesis of chlorambucil methyl ester.**

Chlorambucil acid chloride (prepared from 25 g of chlorambucil) was dissolved in dichloromethane (125 mL) and to this was slowly added methanol (75 mL, 3 vol.) at 15-20 °C over a period of 1 h. The reaction mixture was stirred at ambient temperature for 2 h. The reaction mixture was concentrated and then the residue was dissolved in ethyl acetate (125 mL, 5 vol.) and washed successively with 5 % sodium bicarbonate solution and water. Evaporation of the solvent under reduced pressure gave the chlorambucil methyl ester (25 g, 95%) as light brown oil which was used as such in the next step.

Procedure for the synthesis of chlorambucil alcohol.

To the suspension of lithium aluminium hydride (5.96 g, 2 eq.) in anhydrous THF (100 mL, 4 vol.), was added chlorambucil methyl ester (25 g, 1.0 eq.) in THF (50 mL, 2 vol.) at 0-5 °C over a period of 1 h. After complete addition, the reaction mixture was allowed to stir at ambient temperature

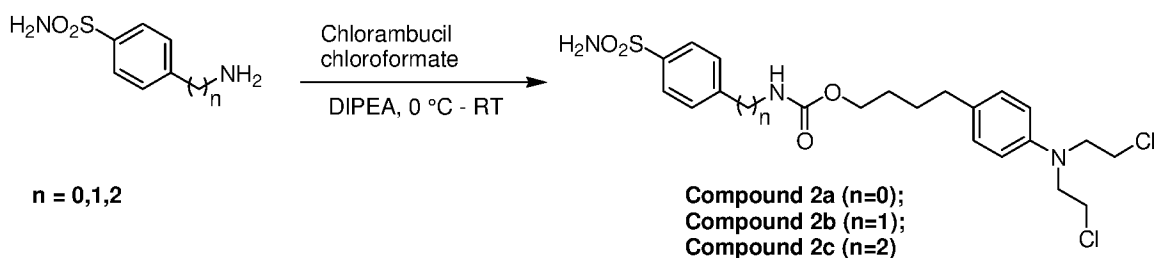
for 2-3 h. Consumption of the starting material was monitored by TLC (20 % ethyl acetate in hexanes). After completion, the reaction mixture was cooled to 0-5 °C and quenched slowly with ethyl acetate (250 mL, 10 vol.) followed by water (100 mL, 4 vol.). The reaction mixture was filtered through celite and the celite bed was washed with ethyl acetate (50 mL, 2 vol.). The organic layer was washed with water (100 mL, 4 vol.) and dried over anhydrous sodium sulphate. Evaporation of the solvent under reduced pressure gave the crude alcohol (22.5 g, 99%) as pale yellow oil. The crude was used as such in the next step.

Procedure for the synthesis of chlorambucil chloroformate

To a solution of triphosgene (11.2 g, 0.55 eq.) in toluene (300 mL, 15 vol.) was added DMF (1.4 g), sodium carbonate (8 g, 1.1 eq.) at ambient temperature. The reaction mixture cooled to 0-5 °C and maintained for 30 minutes at the same temperature. To this stirred reaction mixture was added a solution of chlorambucil alcohol (20 g, 1.0 eq.) in toluene (100 mL, 5 vol.) at 0-5 °C over a period of 30 min. The reaction mixture was stirred at ambient temperature for 4-5 h. Consumption of the starting material was monitored by TLC (40% ethyl acetate in hexane). After completion, reaction mixture was filtered and the solid was washed with toluene (100 mL, 5 vol.). Evaporation of the solvent under reduced pressure gave the chlorambucil chloroformate (16 g, 64%) as yellow viscous liquid which was used as such for the synthesis of carbamates (compounds 13-15).

General scheme for the synthesis of carbamates

(compounds 13-15):



2a=13

2b=14

2c=15

Note: For the synthesis of compound 2b (n=1), hydrochloride salt
5 of 4-aminomethylbenzenesulfonamide was used in place of free amine.

Procedure for the synthesis of compound 13:

To a solution of sulphanilamide (7.3 g, 1.0 eq.) in 1,4-dioxane (225 mL, 15 vol.) and *N,N*-diisopropylethylamine (13.72 g, 2.5 eq.), was added solution of chlorambucil chloroformate (15 g, 1.0 eq.) in 1,4-dioxane (75 mL,
10 5 vol.) over a period of 1 h and stirred overnight at ambient temperature. Consumption of the starting material was monitored by TLC (40% ethyl acetate in hexanes). After completion, reaction mixture was concentrated and then the residue obtained was dissolved in ethyl acetate (150 mL, 10 vol.). The organic layer was washed successively with 2 *N* HCl solution (100
15 mL x 2), water and dried over anhydrous Na₂SO₄. Evaporation of the solvent under reduced pressure gave the pale yellow solid as crude product. The crude product thus obtained was purified by column chromatography using silica gel (40% ethyl acetate in hexanes) to obtain compound 13 (10.5 g, 51 %) as off-white solid.

20 **Procedure for the synthesis of compound 14:**

To a suspension of 4-aminomethylbenzenesulfonamide hydrochloride (8.3 g, 37.4 mmol) in acetonitrile (83 mL) was added *N,N*-diisopropylethylamine (29.6 mL, 170 mmol) and cooled it to 0 °C. To this suspension was added slowly a solution of chlorambucil chloroformate (12.0
25 g, 34 mmol) in acetonitrile (60 mL) over a period of 45 min and stirred overnight at ambient temperature. Reaction mixture poured into 1 *N* HCl (150 mL) and extracted with ethyl acetate (150 mL x 3). The combined organic layer was washed with saturated NaHCO₃ solution (300 mL) and dried over anhydrous Na₂SO₄. Evaporation of the solvent gave dark yellow
30 viscous oil as crude product which was stirred for 15 h in diisopropyl ether

(150 mL) at ambient temperature when the product precipitates out. The precipitate thus obtained was filtered, washed with diisopropyl ether and dried in hot air oven at 45 °C for 2-3 hours to obtain compound 14 (12.5 g, 73%) as off-white solid.

5 **Procedure for the synthesis of compound 15:**

To a suspension of 4-aminoethylbenzenesulfonamide (7.5 g, 37.4 mmol) in acetonitrile (75 mL) was added *N,N*-diisopropylethylamine (29.6 mL, 170 mmol) and cooled it to 0 °C. To this suspension was added slowly a solution of chlorambucil chloroformate (12.0 g, 34 mmol) in acetonitrile (60
10 mL) over a period of 45 min and stirred overnight at ambient temperature. Reaction mixture poured into 1 *N* HCl (150 mL) and extracted with ethyl acetate (150 mL x 3). The combined organic layer was washed with saturated NaHCO₃ solution (300 mL) and dried over anhydrous Na₂SO₄. Evaporation of the solvent gave dark yellow viscous oil as crude product
15 which was stirred for 15 h in diisopropyl ether (150 mL) at ambient temperature when the product precipitates out. The precipitate thus obtained was filtered, washed with diisopropyl ether and dried in hot air oven at 45 °C for 2-3 hours to obtain compound 15 (13.4 g, 70%) as pale yellow solid.

20

Assays

Carbonic Anhydrase (CA) Inhibition Assays.

Compounds were assayed as inhibitors of tumour-associated hCA IX using the CO₂ hydrase assay (Table 2).

25 An Applied Photophysics stopped-flow instrument was used for assaying the CA-catalyzed CO₂ hydration activity (Khalifah, R. G. The carbon dioxide hydration activity of carbonic anhydrase. I. Stop-flow kinetic studies on the native human isoenzymes B and C. J. Biol. Chem. 1971, 246, 2561–2573). Phenol red (at a concentration of 0.2 mM) was used as an
30 indicator, working at the absorbance maximum of 557 nm, with 20 mM

Hepes (pH 7.5) as buffer and 20 mM Na₂SO₄ (for maintaining constant the ionic strength), following the initial rates of the CA-catalyzed CO₂ hydration reaction for a period of 10–100 s. The CO₂ concentrations ranged from 1.7 to 17 mM for the determination of the kinetic parameters and inhibition constants. For each inhibitor, at least six traces of the initial 5–10% of the reaction were used for determining the initial velocity. The uncatalyzed rates were determined in the same manner and subtracted from the total observed rates. Stock solutions of inhibitor (0.1 mM) were prepared in distilled–deionized water, and dilutions up to 0.01 nM were done thereafter with distilled–deionized water. Inhibitor and enzyme solutions were preincubated together for 15 min at room temperature prior to assay to allow for the formation of the E–I complex. The inhibition constants were obtained by nonlinear least-squares methods using PRISM 3 and represent the mean from at least three different determinations. CA isoforms were recombinant (Bioorg Med Chem Lett. 2007 Feb 15;17(4):987-92. Epub 2006 Nov 17. Inhibition of membrane-associated carbonic anhydrase isozymes IX, XII and XIV with a library of glycoconjugate benzenesulfonamides. Wilkinson BL1, Bornaghi LF, Houston TA, Innocenti A, Vullo D, Supuran CT, Poulsen SA. + Khalifah, R. G. The carbon dioxide hydration activity of carbonic anhydrase. I. Stop-flow kinetic studies on the native human isoenzymes B and C. J. Biol. Chem. 1971, 246) .

Exponentially growing colorectal (HT- 29, ATCC HTB-38) and cervical (HeLa, ATCC CCL-2) carcinoma cells were cultured in Dulbecco's Modified Eagle's Medium supplemented with 10% fetal bovine serum. Low oxygen conditions were acquired in a hypoxic workstation (Ruskin INVIVO2 1000). The atmosphere in the chamber consisted of 0.2% O₂ (hypoxia), 5% CO₂, and residual N₂. In parallel, normoxic (20% O₂) dishes were incubated in air with 5% CO₂. pH of the culture medium was immediately measured at the end of each experiment as previously described ((Dubois, L.; Douma, K.; Supuran, C. T.; Chiu, R. K.; van

Zandvoort, M. A.; Pastorekova', S.; Scozzafava, A.; Wouters, B. G.; Lambin, P. Imaging the hypoxia surrogate marker CA IX requires expression and catalytic activity for binding fluorescent sulfonamide inhibitors. *Radiother. Oncol.* 2007, 83, 367–373).

5 Compounds Preparation. Compounds were dissolved in culture medium containing 1% DMSO at the indicated final concentrations just before addition to the cells.

Delta pH assay

10 To investigate the efficacy of compounds, their effects on hypoxia-induced extracellular acidification was evaluated by measuring changes in pH before and after exposure to the compounds (Dubois, L.; Douma, K.; Supuran, C. T.; Chiu, R. K.; van Zandvoort, M. A.; Pastorekova', S.; Scozzafava, A.; Wouters, B. G.; Lambin, P. Imaging the hypoxia surrogate
15 marker CA IX requires expression and catalytic activity for binding fluorescent sulfonamide inhibitors. *Radiother. Oncol.* 2007, 83, 367–373). For this purpose, HT29 colorectal carcinoma cells were grown under ambient air or lowered oxygen concentrations and exposed to compounds in 1 mM concentrations. Data are expressed as the difference between medium
20 pH values ($\Delta\text{pHe} = \text{pH after incubation} - \text{pH before incubation}$). It can be seen that acidification is reduced.

Toxicity assay

25 As toxicity assay, the MTT assay is used. The MTT assay is a colorimetric assay for assessing cell viability. NAD(P)H-dependent cellular oxidoreductase enzymes reflects the number of viable cells present. These enzymes are capable of reducing the tetrazolium dye MTT 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide to its insoluble formazan, which has a purple color.

Radio S (DMF) Assay:

The Radio S assays is a clonogenic assay of radiation with and without drug under hypoxic conditions: the clonogenic assay enables an assessment of the differences in reproductive viability (capacity of cells to produce progeny; i.e. a single cell to form a colony of 50 or more cells) between control untreated cells and cells that have undergone exposure to ionizing radiation under hypoxia with and without drug. , The assay has become the most widely accepted technique in radiation biology and has been widely used for evaluating the radiation sensitivity of different cell lines. Further, the clonogenic assay is commonly used for monitoring the efficacy of radiation modifying compounds and for determining the effects of cytotoxic agents and other anti-cancer therapeutics on colony forming ability, in different cell lines. A typical clonogenic survival experiment using adherent cells lines involves three distinct components, 1) treatment of the cell monolayer in tissue culture flasks, 2) preparation of single cell suspensions and plating an appropriate number of cells in petri dishes and 3) fixing and staining colonies following a relevant incubation period, which could range from 1-3 weeks, depending on the cell line.

20

Table 2: Results

Compound	Ki CAIX (nM)	Delta pH (1mM)	Tox. 2 or 24 hours hypoxia 0,2%CAIX + cells	RadioS. (DMF)
1	14 nM	0,3	SF 27% (2 hrs, 300 μ M)	
2	19 nM	0,45	SF 32% (2 hrs, 300 μ M)	
	11 nM	0,5	SF 30%	

3			(2 hrs, 300 μ M)	
4	13,5 nM	0,4	SF 30% (2 hrs, 300 μ M)	
5	17 nM	0,35	SF 21% (2 hrs, 300 μ M)	
6	22nM	0,4	SF 19% (2 hrs, 300 μ M)	
7	9 nM	0,5	SF 17% (2 hrs, 300 μ M)	
8	8 nM	0,3	SF 14% (2 hrs, 300 μ M)	
10	23 nM	0,3	SF 14% (2 hrs, 300 μ M)	
11	19 nM	0,4	SF 17% (2 hrs, 300 μ M)	
12	12 nM	0,56	SF 22% (2 hrs, 300 μ M)	
13	9 nM	0,46	SF 17% (2 hrs, 300 μ M)	
14	14 nM	0,51	SF 15% (2 hrs, 300 μ M)	
15	9 nM	0,42	SF 9% (2 hrs, 300 μ M)	
16	9 nM	0,3	SF 44% (2 hrs, 300 μ M)	1,9
19	27nM	0,4	SF 24% (2 hrs, 300 μ M)	
21	21 nM	0,3	SF 25 % (2 hrs, 300 μ M)	

23	9 nM	0,35	SF 21 % (2 hrs, 300 μ M)	
25	15 nM	0,3	SF 19 % (2 hrs, 300 μ M)	
39	14 nM	0,3	SF 17% (2 hrs, 300 μ M)	
45	14 nM	0,3	SF 29% (24 hrs, 300 μ M) in NOTCH + cells	
47	Ki: 16nM	0,3	SF 172 (2 hrs, 100 μ M)	
53	22 nM	0,3	SF 39% (2 hrs, 300 μ M)	1,8 in vitro

Claims

1. Compound according to formula (I)

5 A-L-R¹ (I)

A is an anticancer agent comprising at least one group selected from the group comprising OH, NH and NH₂

L is a direct bond or L is a linker selected from the group consisting of C₁₋₆alkyl, C(=O)N(R⁶), C₁₋₆alkyl-C(=O)N(R⁶)C₁₋₆alkyl, C₁₋₆alkyl-C(=O)N(R⁶), C(=O)N(R⁶)-C₁₋₆alkyl, N(R⁶)C(=O)N(R⁶), C₁₋₆alkylN(R⁶)C(=O)N(R⁶)C₁₋₆alkyl, C₁₋₆alkylN(R⁶)C(=O)N(R⁶), N(R⁶)C(=O)N(R⁶)C₁₋₆alkyl, N(R⁶)C(=S)N(R⁶), C₁₋₆alkylN(R⁶)C(=S)N(R⁶)C₁₋₆alkyl, C₁₋₆alkylN(R⁶)C(=S)N(R⁶), N(R⁶)C(=S)N(R⁶)C₁₋₆alkyl, -O-C(=O)N(R⁶), C₁₋₆alkyl-O-C(=O)N(R⁶)C₁₋₆alkyl, C₁₋₆alkyl-O-C(=O)N(R⁶), -O-C(=O)N(R⁶)C₁₋₆alkyl, N(R⁶)C(=O), C₁₋₆alkylN(R⁶)C(=O)C₁₋₆alkyl, C₁₋₆alkylN(R⁶)C(=O), N(R⁶)C(=O)C₁₋₆alkyl, N(R⁶)C(=S), C₁₋₆alkylN(R⁶)C(=S)C₁₋₆alkyl, C₁₋₆alkylN(R⁶)C(=S), N(R⁶)C(=S)C₁₋₆alkyl, C(=O)N(R⁶)C₁₋₆alkylN(R⁶)C(=S)N(R⁶), C₁₋₆alkylC(=O)N(R⁶)C₁₋₆alkylN(R⁶)C(=S)N(R⁶)C₁₋₆alkyl, C₁₋₆alkylC(=O)N(R⁶)C₁₋₆alkylN(R⁶)C(=S)N(R⁶), C(=O)N(R⁶)C₁₋₆alkyl, C₁₋₆alkylC(=O)N(R⁶)C₁₋₆alkylN(R⁶)C(=O)N(R⁶)C₁₋₆alkyl, C₁₋₆alkylC(=O)N(R⁶)C₁₋₆alkylN(R⁶)C(=O)N(R⁶)C₁₋₆alkyl, C(=O)N(R⁶)C₁₋₆alkyl-OC(=O), C₁₋₆alkylC(=O)N(R⁶)C₁₋₆alkyl-OC(=O)C₁₋₆alkyl, C₁₋₆alkylC(=O)N(R⁶)C₁₋₆alkyl-OC(=O), C(=O)N(R⁶)C₁₋₆alkyl-OC(=O)C₁₋₆alkyl, O-C(=O), C₁₋₆alkyl-O-C(=O)C₁₋₆alkyl, C₁₋₆alkyl-O-C(=O), O-C(=O)C₁₋₆alkyl, C(=O), C₁₋₆alkyl-C(=O)C₁₋₆alkyl, C₁₋₆alkyl-C(=O), C(=O)C₁₋₆alkyl, C(=S)N(R⁶), C₁₋₆alkyl-C(=S)N(R⁶)C₁₋₆alkyl, C₁₋₆alkyl-C(=S)N(R⁶), C(=S)N(R⁶)-C₁₋₆alkyl, N(R⁶), C₁₋₆alkyl-N(R⁶)C₁₋₆alkyl, C₁₋₆alkyl-N(R⁶), N(R⁶)C₁₋₆alkyl, O-C(=O)C₁₋₆alkylC(=O)N(R⁶), C₁₋₆alkyl-O-C(=O)C₁₋₆alkylC(=O)N(R⁶)C₁₋₆alkyl, C₁₋₆alkyl-O-C(=O)C₁₋₆alkylC(=O)N(R⁶), O-

$C(=O)C_{1-6}alkylC(=O)N(R^6)C_{1-6}alkyl$, $O-C(=O)C_{1-6}alkylN(R^6)C(=O)$, $C_{1-6}alkyl-O-C(=O)C_{1-6}alkylN(R^6)C(=O)C_{1-6}alkyl$, $C_{1-6}alkyl-O-C(=O)C_{1-6}alkylN(R^6)C(=O)$, $O-C(=O)C_{1-6}alkylN(R^6)C(=O)C_{1-6}alkyl$, $(O-CH_2CH_2)_n$, $C_{1-6}alkyl(O-CH_2CH_2)_nC_{1-6}alkyl$, $C_{1-6}alkyl(O-CH_2CH_2)_n$, $(O-CH_2CH_2)_nC_{1-6}alkyl$,
 5 $(CH_2CH_2-O)_n$, $C_{1-6}alkyl(CH_2CH_2-O)_nC_{1-6}alkyl$, $C_{1-6}alkyl(CH_2CH_2.O)_n$,
 $(CH_2CH_2.O)_nC_{1-6}alkyl$;

n is 1-12;

optionally the L is further substituted with a substituent selected from the group comprising halo, hydroxy, amino, nitro, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{1-6}alkyloxy$, $di(C_{1-6}alkyl)amino$, hydroxyamino, hydroxycarbonyl, carbonyl, carbonyl $C_{1-6}alkyl$, carbonyl $C_{1-6}alkyloxy$, $C_{1-6}alkylcarbonyl$, NR^4R^5 , heterocyclic, $C_{3-7}cycloalkyl$, , hydroxy $C_{1-6}alkyl$, amino $C_{1-6}alkyl$, cyano, $SiFR^8R^9$, or $OP(=O)(OR^{10})_2$;

R^1 is $SO_2NR^2R^3$, $OSO_2NR^2R^3$, $NR^7SO_2NR^2R^3$, NR^4SO_2 -phenyl, aryl substituted with $SO_2NR^2R^3$, aryl substituted with $OSO_2NR^2R^3$, or aryl substituted with $NR^7SO_2NR^2R^3$;

R^2 , R^3 is each independently hydrogen, halo, hydroxy, or $C_{1-6}alkyl$, wherein the $C_{1-6}alkyl$ is optionally substituted with with a substituent selected from the group comprising halo, hydroxy, amino, nitro, carbonyl, cyano, or a leaving group;

R^4 , R^5 , R^6 , R^7 is each independently hydrogen, halo, hydroxy, or $C_{1-6}alkyl$, wherein the $C_{1-6}alkyl$ is optionally substituted with with a substituent selected from the group comprising halo, hydroxy, amino, nitro, $C_{1-6}alkyloxy$, $di(C_{1-6}alkyl)amino$, hydroxyamino, hydroxycarbonyl, carbonyl, carbonyl $C_{1-6}alkyl$, carbonyl $C_{1-6}alkyloxy$, $C_{1-6}alkylcarbonyl$, heterocyclic, $C_{3-7}cycloalkyl$, hydroxy $C_{1-6}alkyl$ or amino $C_{1-6}alkyl$, cyano, $OP(=O)(OR^{10})_2$, $SiFR^8R^9$, or a leaving group;

R^8 and R^9 is each independently a $C_{1-12}alkyl$, or $C_{2-12}alkenyl$;

R^{10} is hydrogen, $C_{1-20}alkyl$, or $C_{2-20}alkenyl$, aryl, amino $C_{1-12}alkyl$, carbonyl $C_{1-12}alkyl$, hydroxy $C_{1-6}alkyl$, $C_{1-6}alkyloxyC_{1-6}alkyl$, or NR^4R^5 ;

wherein L is substituted on O of OH or on N of NH or NH₂ of A or wherein L replaces OH of A, or O-L replaces a C(=O)-OH group of A and wherein in the case L is a direct bond R¹ is substituted on O of OH or on N of NH or NH₂ of A, or R¹ replaces OH of A, or O-R¹ replaces a C(=O)-OH group of A.

2. Compound according to claim 1 wherein A is an anticancer agent selected from the group comprising Alkylating agents, Anti-metabolites, Anti-microtubule agents, Topoisomerase inhibitors, Cytotoxic antibiotics, targeted agents, preferably selected from the group comprising Alkylating agents, anti-metabolites, topoisomerase I inhibitors, targeted agents, more preferably selected from the group comprising alkylating agents and targeting agents.

3. Compound according to claim 1 or 2 wherein A is selected from the group consisting of Tirapazamin, chlorambucil, MK0752, SN 30444 Chlorine-derivative of SN 30444, cyclophosphamide, bromine-derivative of cyclophosphamide, MK0752, Notch inhibitor, temozolomide, CP466722, Torin 2, OTSSP167, VE-821, VE-822, PR610, PR610E, chloroquine, PF03084014, mephalan, chlorambucil, bendamustine, procarbazine, dacarbazine, mitozolomide, ariziridinybenzoquinone (NSC182986), dianhydrogalactitol, hycanthone methanesulfonate, ethylnitrosourea, acivicin, hydroxyurea, nitrosourea, imidazole-pyazole, 3-tritylthio-L-alanine, mitoxantrone, camptothecin, 9-amino camptothecin, 10-hydroxycamptothecin, 14-chloro-20(S)-camptothecin hydrate, 9-amino-20-(R,S)-camptothecin, 7-chlorocamptothecin, NSC606985, NSC374028, 9-methoxycamptothecin, NSC295501, NSC606172, NSC606173, camptothecin lysinate HCl, camptothecin glutamate, camptothecinhemisuccinate, amonafide, cidofovir, aphidicolin glycinate, 3-demethylthiocolchine, irinotecan, toptecan, camptothecinbutylglycinate ester hydrochloride, camptothecinethylglycinate esterhydrochloride, amsacrine, uramustine, methotrexate, pemetrexed, NSC174121,

NSC132483, NSC184692, NSC 134033, NSC6230172, 5-fluorouracil, capecitabine, gemcitabine, arabinosylcytosine, decitabine, azacitidine, nelarabine, cladribine, clofarabine, pentostatin, thioguanine, mercaptopurine, 3-hydroxy-2-formylpyridine thiosemicarbazone, 5-
5 hydroxypicolinaldehyde thiosemicarbazone, alpha-TGdR, beta-TGdR, cyclocitidine, thioguanine, 6-mercaptopurine, piroxantrone, nerviano, dasatinib, CEP-37440, PF-06463922, iniparib, 3 aminobenzamide, BAY 80-6946, Buparlisib, PI-103, Palomid 527, IC-87114, GNE 477, CUDC-907, Selumetinib, binimetinib, AZD8055, palbociclib, LEE011, Lestaurtinib,
10 veliparib, MK4827, GCD-0879, MK0752, and GSK126.

4. Compound according to anyone of claim 1-3 wherein A is selected from the group consisting Tirapazamin, chlorambucil, MK0752, VE-821, VE-822, , SN 30444, Chlorine-derivative of SN 30444, cyclophosphamide, bromine-derivative of cyclophosphamide, MK0752, Notch
15 inhibitor, temozolomide, CP466722, Torin 2, OTSSP167, PR610, PR610E, chloroquine, PF03084014, mephalan, chlorambucil, bendamustine, procarbazine, dacarbazine, mitozolomide, ariziridinybenzoquinone (NSC182986), dianhydrogalactitol, hycanthone methanesulfonate, ethylnitrosourea, acivicin, hydroxyurea, nitrosourea, imidazole-pyazole, 3-
20 tritylthio-L-alanine, mitoxantrone, camptothecin, 9-amino camptothecin, 10-hydroxycamptothecin, 14-chloro-20(S)-camptothecin hydrate, 9-amino-20-(R,S)-camptothecin, 7-chlorocamptothecin, NSC606985, NSC374028, 9-methoxycamptothecin, NSC295501, NSC606172, NSC606173, camptothecin lysinate HCl, camptothecin glutamate,
25 camptothecinhemisuccinate, amonafide, aphidicolin glycinate, 3-demethylthiocolchine, irinotecan, toptecan, camptothecinbutylglycinate ester hydrochloride, camptothecinethylglycinate esterhydrochloride, amsacrine, nerviano, dasatinib, CEP-37440, PF-06463922, iniparib, 3 aminobenzamide, BAY 80-6946, Buparlisib, PI-103, Palomid 527, IC-87114,
30 GNE 477, CUDC-907, Selumetinib, binimetinib, AZD8055, palbociclib, and LEE011.

5. Compound according to anyone of claim 1-4 wherein A is not a compound selected from the group consisting of Improsan, ifosfamide, spiromustine, N-(2-Chloroethyl)-N'-(2,6-dioxo-3-piperidinyl)-N-nitroso-urea (PCNU), peperazinedione (NSC-135758), semustine, carmustine, lomustine, streptozocin, chlorozotocin, leucine sarcolysine, cyanomorpholino-doxorubicin, doxorubicin, fluorodopan, ametycin, profiromycin, trimetrexate, fludarabine, alanosine, pyrazofurin, triazinate, dichloroallyl lawsone, ftorafur fluorofur, dihydro-5-azacytidine, PALA, guanazole, inosine dialdehyde, macbecin II, vinblastine, vincristine, vindisine, vinorelbine, vincaminol, vincamajine, vineridine, vinflunine, docetaxel, paclitaxel, podophyllotoxin, etoposide, teniposide, allocolchicine, halichondrin B, colchine, N-Benzoyl-deacetylcolchicine, dolastatin 10, maytansin, NSC608832, novobiocin, aclarubicin, merbarone, NSC295500, camptothecin phosphate, morpholinoadriamycin, anthrapyrazole, pyrazoloacridine, bisantrene, daunorubicin, deoxorubicin, menogaril, N,N-Dibenzyl-daunorubicin hydrochloride, zorobicin, VM-26, VP-16, epirubicin, idarubicin, valrubicin, actinomycin, bleomycin, plicamycin, mitomycin C, pirarubicin, Mithramycin, imatinib mesylate Gefitinib, Erlotinib hydrochloride, Sorafenib, Sunitinib, Lapatinib, Nilotinib, Bortezomib, tamoxifen, Pacritinib, and famitinib, CYT387, Alectinib, AP26113, X-396, ABT-737, Obatoclax, and gossypol, BMN-637, olaparib, rucaparib, CEP 8983, idelalisib, PX-866, IPI-145, GDC-0941, SF1126, XL 147, XL 765, TG100-115, AZD2461, apatinib, lenvatinib, motesanib, and Regorafenib. vemurafenib, dabrafenib, LGX818, sorafenib, PLX4720, PD-325901, cobimetinib, CI-1040, trametinib, Geldanamycin, radicicol, tanespimycin.famitinib, salinomycin, vintafolide, temsirolimus, everolimus. AZD4547, and navitoclax

6. Compound according to anyone of claim 1-5 wherein A is not selected from the group consisting of nitrosoourea, taxane, vinca alkaloid, anthracycline, podophyllotoxin, and podophyllotoxin derivatives.

5 7. Compound according to anyone of claim 1-6 wherein A is not hepsulfam

8. Compound according to anyone of claim 1-6 wherein A is an anticancer agent that does not comprise a nitro-imidazol group.

10

9. Compound according to anyone of the previous claims wherein A comprises a NH_2 group, preferably the NH group is not part of a ringstructure.

15

10. Compound according to anyone of the previous claims wherein A has 6 or less ring structures, preferably 5 or less, preferably 4 or less, preferably 3 or less.

20

11. Compound according to claim 9 wherein L is substituted on N of NH_2 of A and wherein in the case L is a direct bond R^1 is substituted on N of NH_2 of A .

25

12. Compound according to anyone of the previous claims wherein L is substituted on the O of OH of A or wherein L replaces OH of A, or O-L replaces a $\text{C}(=\text{O})\text{-OH}$ group of A or wherein in the case L is a direct bond R^1 is substituted on O of OH of of A or R^1 replaces OH of A, or O- R^1 replaces a $\text{C}(=\text{O})\text{-OH}$ group of A.

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13. Compound according to anyone of the previous claims wherein A does not comprise a sulfonamide, sulfamide, or a sulfamate group.

14. Compound according to anyone of the previous claims wherein R² and R³ are each hydrogen.

15. Compound according to anyone of the previous claims
5 wherein L is a direct bond.

16. Compound according to anyone of the previous claims wherein A has a IC₅₀ for proliferation of less than 10 mM, less than 5 mM, less than 1 mM, less than 100 μM, less than 10 μM, less than 1 μm, less
10 than 100 nM, less than 10 nM, less than 1 nM, less than 100 pM, less than 10 pM, less than 1 pM.

17. Compound according to anyone of the previous claims wherein A has a molecular weight of less than 1500 D, preferably less than
15 1200 D, preferably less than 1000 D, more preferably less than 800 D, more preferably less than 700 D, more preferably less than 600 D, more preferably less than 550 D, more preferably less than 500 D, more preferably less than 450 D, more preferably less than 400 D. [Molecular weight from 180 to 500]

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18. Compound according to anyone of the previous claims wherein A has no more than 7 hydrogen bond donors, preferably no more than 6 hydrogen bond donors, preferably no more than 5 hydrogen bond donors, preferably no more than 4 hydrogen bond donors, preferably no
25 more than 3 hydrogen bond donors, preferably no more than 2 hydrogen bond donors. [O-H, NH bonds] max 5 H-bond donors (expressed as the sum of OHs and NHs),

19. Compound according to anyone of the previous claims
30 wherein A has no more than 15 hydrogen bond acceptors, preferably no more than 14 hydrogen bond acceptors, preferably no more than 12

hydrogen bond acceptors, preferably no more than 10 hydrogen bond acceptors, preferably no more than 9 hydrogen bond acceptors, preferably no more than 8 hydrogen bond acceptors, preferably no more than 7 hydrogen bond acceptors, preferably no more than 6 hydrogen bond acceptors, preferably no more than 5 hydrogen bond acceptors, preferably no more than 4 hydrogen bond acceptors. - max 10 H-bond acceptors (expressed as the sum of Os and Ns

20. Compound according to anyone of the previous claims wherein A has a octanol-water partition coefficient $\text{Log } P$ of no greater than 7, preferably a $\text{Log } P$ of no greater than 6, preferably a $\text{Log } P$ of no greater than 5.5, preferably a $\text{Log } P$ of no greater than 5, preferably a $\text{Log } P$ of no greater than 4.5, preferably a $\text{Log } P$ of no greater than 4, preferably a $\text{Log } P$ of no greater than 3.5, preferably a $\text{Log } P$ of no greater than 3, preferably a $\text{Log } P$ of no greater than 2.5, preferably a $\text{Log } P$ of no greater than 2, preferably a $\text{Log } P$ of no greater than 1.5, preferably a $\text{Log } P$ of no greater than 1, preferably a $\text{Log } P$ of no greater than 0.5,. [Partition coefficient $\log P$ in -0.4 to $+5.6$ range]

21. Compound according to anyone of the previous claims wherein A has a Molar refractivity from 40 to 130.

22. Compound according to anyone of the previous claims wherein A comprises 20 to 70 atoms preferably 25 to 65 atoms, preferably 30 to 60 atoms, preferably 32 to 55 atoms, preferably 35 to 52 atoms, preferably 38 to 50 atoms, preferably 40 to 48 atoms, preferably 42 to 46 atoms, preferably 44 to 45 atoms.

23. Compound according to anyone of the previous claims wherein A has a polar surface area no greater than $140 \text{ \AA}^2$, preferably no greater than $120 \text{ \AA}^2$, preferably no greater than $100 \text{ \AA}^2$, preferably no

greater than $90 \text{ \AA}^2$, preferably no greater than $80 \text{ \AA}^2$, preferably no greater than $75 \text{ \AA}^2$, preferably no greater than $60 \text{ \AA}^2$, preferably no greater than $50 \text{ \AA}^2$.

5 24. Compound according to anyone of the previous claims wherein A comprises not more than 15 rotatable bonds, preferably not more than 12 rotatable bonds, preferably not more than 10 rotatable bonds, preferably not more than 9 rotatable bonds, preferably not more than 8 rotatable bonds, preferably not more than 7 rotatable bonds, preferably not more than 6 rotatable bonds, preferably not more than 5 rotatable bonds, preferably not more than 4 rotatable bonds, preferably not more than 3 rotatable bonds, preferably not more than 2 rotatable bonds.

15 25. Compound according to anyone of the previous claims wherein A fulfils at least two of the rules defined in claims 16 to 23.

26. Compound according to anyone of the previous claims wherein A comprises not more than 10 rotatable bonds and has a polar surface area no greater than $140 \text{ \AA}^2$

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27. Compound according to anyone of the previous claims wherein the compound comprises a chelating agent comprising a metal ion suitable for imaging, fluorescent moiety, or a ^{18}F containing moiety.

25 28. Compound according to anyone of the previous claims wherein L is selected from the group consisting of a direct bond, $\text{C}_{1-6}\text{alkyl}$ - $\text{C}(=\text{O})\text{N}(\text{R}^6)\text{C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl}-\text{C}(=\text{O})\text{N}(\text{R}^6)$, $\text{C}_{1-6}\text{alkylN}(\text{R}^6)\text{C}(=\text{O})\text{N}(\text{R}^6)\text{C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkylN}(\text{R}^6)\text{C}(=\text{O})\text{N}(\text{R}^6)$, $\text{C}_{1-6}\text{alkylN}(\text{R}^6)\text{C}(=\text{S})\text{N}(\text{R}^6)\text{C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkylN}(\text{R}^6)\text{C}(=\text{S})\text{N}(\text{R}^6)$, $\text{C}_{1-6}\text{alkyl}-\text{O}-\text{C}(=\text{O})\text{C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyl}-\text{O}-\text{C}(=\text{O})$, $\text{C}(=\text{O})$, $\text{C}_{1-6}\text{alkyl}-\text{C}(=\text{O})$, $\text{C}(=\text{O})\text{C}_{1-6}\text{alkyl}$, $\text{C}(=\text{S})\text{N}(\text{R}^6)$, $\text{C}_{1-6}\text{alkyl}-\text{C}(=\text{S})\text{N}(\text{R}^6)$, $\text{C}(=\text{S})\text{N}(\text{R}^6)-\text{C}_{1-6}\text{alkyl}$, $\text{N}(\text{R}^6)$, $\text{C}_{1-6}\text{alkyl}-\text{N}(\text{R}^6)$, $\text{N}(\text{R}^6)\text{C}_{1-6}\text{alkyl}$, $(\text{O}-\text{CH}_2\text{CH}_2)_n$,

30

(CH₂CH₂-O)_n, and C₁₋₆alkyl(CH₂CH₂-O)_n, preferably L is selected from the group consisting of a direct bond, C₁₋₆alkyl, C(=O)N(R⁶), N(R⁶)C(=O)N(R⁶), N(R⁶)C(=S)N(R⁶), -O-C(=O), -O-C(=O)N(R⁶), (O-CH₂CH₂)_n, or (CH₂CH₂-O)_n, preferably L is a direct bond, C₁₋₆alkyl, C(=O)N(R⁶), N(R⁶)C(=O)N(R⁶),
 5 N(R⁶)C(=S)N(R⁶), -O-C(=O), or -O-C(=O)N(R⁶).

29. Compound according to anyone of the previous claims wherein R¹ is SO₂NR²R³, OSO₂NR²R³, NR⁷SO₂NR²R³, aryl substituted with SO₂NR²R³, aryl substituted with OSO₂NR²R³, or aryl substituted with
 10 NR⁷SO₂NR²R³, preferably wherein R¹ is SO₂NH₂, OSO₂NH₂, NR⁷SO₂NH₂, aryl substituted with SO₂NH₂, aryl substituted with OSO₂NH₂, or aryl substituted with NR⁷SO₂NH₂, preferably aryl is phenyl thiadiazolyl, or naphthenyl, more preferably phenyl.

15 30. Compound according to anyone of the previous claims wherein the C₁₋₆alkyl is substituted with with a substituent selected from the group comprising halo, hydroxy, amino, nitro, C₁₋₆alkyloxy, di(C₁₋₆alkyl)amino, hydroxyamino, hydroxycarbonyl, carbonyl, carbonylC₁₋₆alkyl, carbonylC₁₋₆alkyloxy, C₁₋₆alkylcarbonyl, , heterocyclic, C₃₋₇cycloalkyl, , hydroxyC₁₋₆alkyl
 20 or aminoC₁₋₆alkyl , cyano, OP(=O)(OR¹⁰), or a leaving group.

31. Compound according to anyone of the previous claims wherein R², R³ is each independently hydrogen, halo, hydroxy, or C₁₋₆alkyl.

32. Compound according to anyone of the previous claims wherein
 25 R⁴, R⁵, R⁶, R⁷ is each independently hydrogen, halo, hydroxy, or C₁₋₆alkyl, wherein the C₁₋₆alkyl is optionally substituted with with a substituent selected from the group comprising halo, hydroxy, amino, nitro, C₁₋₆alkyloxy, di(C₁₋₆alkyl)amino, hydroxyamino, hydroxycarbonyl, carbonyl, carbonylC₁₋₆alkyl, carbonylC₁₋₆alkyloxy, C₁₋₆alkylcarbonyl, heterocyclic, C₃₋₇cycloalkyl,
 30 hydroxyC₁₋₆alkyl or aminoC₁₋₆alkyl , cyano, OP(=O)(OR¹⁰)₂, SiFR⁸R⁹, or a leaving group;

33. Compound according to anyone of the previous claims wherein R⁸ and R⁹ is each independently a C₁₋₁₂alkyl, or C₂₋₁₂alkenyl.

5 34. Compound according to anyone of the previous claims wherein R¹⁰ is hydrogen, C₁₋₂₀alkyl, or C₂₋₂₀alkenyl, aryl, aminoC₁₋₁₂alkyl, carbonylC₁₋₁₂alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, or NR⁴R⁵.

10 35. Compound according to anyone of the previous claims wherein R⁴, R⁵ is each independently hydrogen, hydroxy, or C₁₋₆alkyl, more preferably C₁₋₃alkyl, more preferably C₁₋₂alkyl, more preferably C₁alkyl.

15 36. Compound according to anyone of the previous claims wherein R⁶ is hydrogen, hydroxy, or C₁₋₆alkyl, more preferably C₁₋₃alkyl, more preferably C₁₋₂alkyl, more preferably C₁alkyl.

20 37. Compound according to anyone of the previous claims wherein R⁷ is hydrogen, hydroxy, or C₁₋₆alkyl, more preferably C₁₋₃alkyl, more preferably C₁₋₂alkyl, more preferably C₁alkyl.

25 38. Compound according to anyone of the previous claims wherein R¹⁰ is hydrogen, C₁₋₂₀alkyl, or C₂₋₂₀alkenyl, aryl, aminoC₁₋₁₂alkyl, carbonylC₁₋₁₂alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, or NR⁴R⁵.

30 39. Compound according to anyone of the previous claims for use as a medicine.

 40. Compound according to anyone of the claims 1-38 for use according to claim 39, for use in the treatment of cancer.

41. Compound according to anyone of claims 1-38 for use
according to claim 40 wherein the cancer is selected from the group of breast
carcinoma, brain carcinoma, kidney carcinoma, colorectal carcinoma, lung
carcinoma, head and neck carcinoma, esophageal carcinoma, hepatocellular
5 carcinoma, cholangiocarcinoma, renal cel carcinomal, testis carcinoma,
cervix carcinoma, endometrium carcinoma, ovarian carcinoma, Squamous
cell carcinoma, Basal cell carcinoma, Glioma, Ependymoma, mesothelioma,
papillary thyroid carcinoma, thyroid carcinoma, follicular thyroid
carcinoma, follicular lymphoma, non-Hodgkin's lymphoma, adenocarcinoma,
10 stomach carcinoma, duodenum carcinoma, biliary carcinoma, pancreas
carcinoma, , and bladder carcinoma.

42. Compound according to anyone of claims 1-38 for use
according to any one of claims 39 to 41 wherein the cancer is colorectum
15 cancer.

43. Treatment of cancer comprising administering a
compound according to anyone of claims 1-38.