

**ALC1 INHIBITORS FOR USE IN TREATING CANCER BY POTENTIATING THE EFFECTS OF SEVERAL
CLASSES OF APPROVED CANCER DRUGS**

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The present invention relates to the use of small molecule compounds that allosterically inhibit ALC1 (CHD1L), in particular the use of two classes of allosteric inhibitors of ALC1 (CHD1L), of Formula (I) and Formula (II), that show a potentiating, preferably synergistic effect in the treatment of proliferative disease when combined with several classes of cancer drugs, namely inhibitors of Topoisomerase I, Topoisomerase II, ATM, ATR, Wee1, BRD, and MEK, or when combined with mitomycin C, paclitaxel, with ionizing radiation, or with an antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor. Furthermore, the present invention relates to said inhibitors of ALC1 of Formula (II) that show a synergistic effect in the treatment of pancreatic cancer or fallopian tube cancer when combined with a PARP inhibitor (Poly(ADP-ribose)-Polymerase inhibitor (PARPi)). By being synergistic with said inhibitors classes, ALC1 inhibitors potentiate the cancer cell killing properties of these inhibitors, enabling therapeutic approaches where ALC1 is amplified as an oncogene and/or where the cancer is a homologous recombination deficient (HRD) cancer. Additionally, these ALC1 inhibitors make it possible to overcome said inhibitor resistance mechanisms and enable an alternative approach to the treatment of germline or acquired BRCA1/BRCA2 deficiency, including tumors defined by “BRCAness” or other changes in DNA repair networks. Importantly, the toxicity mechanisms of said drugs with ALC1 inhibitors are non-overlapping, hence no synergistic toxicity is expected.

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Background of the Invention

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Generally, cancers are classified into two categories: blood cancer and solid cancer. Solid cancers occur in almost every part of the body, resulting in pancreatic cancer, breast cancer, oral cancer, liver cancer, uterine cancer, esophageal cancer, and skin cancer among others. Although some methods of treatment include targeted drugs such as Gleevec or Herceptin, the majority of cancers are still treated by chemotherapy or radiation therapy. Since chemotherapies are not targeted therapies, the biggest problems of conventional chemotherapeutic agents are the side effects caused by cytotoxicity on one hand and the development of drug resistance on the other. The latter is the main factor that eventually causes the treatment to fail despite an initial successful response to the chemotherapeutic agents. Therefore, in order to overcome the limitations of such chemotherapeutic agents, it is necessary to develop new targeted therapeutic agents that specifically interfere with cancer cell proliferation.

While in oncology, combinations of known cancer drugs have been shown successful in several cases, it remains the exception that, and it cannot be foreseen whether synergistic effects are achieved by two different drugs in the treatment of proliferative diseases. Therefore, there is a high medical need to develop novel combination therapies in which chemotherapeutic agents with established effectiveness in

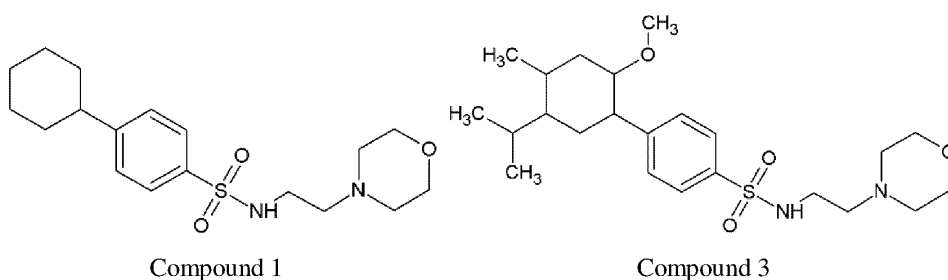
the treatment of cancer are combined with novel anticancer drugs that potentiate the effect of the established treatment regimens.

Without wishing to be bound by any theory the present inventors considered the rationale that ALC1 inhibitors as a known class of cancer drugs could be combined with several classes of known cancer drugs, e.g. inhibitors of Topoisomerase I, Topoisomerase II, ATM, ATR, Wee1, BRD, or MEK, or combined with specific established cancer drugs, namely mitomycin C or paclitaxel, or could be combined with ionizing radiation, or could be combined with an antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor. However, combinations of some representatives of said classes of known cancer drugs with known ALC1 inhibitors did not show synergism.

The present invention is based on the surprising finding that specific ALC1 inhibitors, namely those wherein the inhibitor specifically binds to an allosteric binding pocket formed by an amino acid stretch spanning amino acid residues 101 to 219 of SEQ ID NO: 1, in particular those of Formula (I) and of Formula (II), possess synergistic, anti-proliferative activity when being combined with several classes of known cancer drugs, namely inhibitors of Topoisomerase I, Topoisomerase II, ATM, ATR, Wee1, BRD, MEK, or when being combined with specific established cancer drugs, namely mitomycin C or paclitaxel, or when being combined with ionizing radiation, or when being combined with an antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor. Thus, these combinations are expected to be particularly suitable in the treatment of proliferative disease.

The rationale that, at least for specific combinations, ALC1 inhibitors in combination with other cancer drugs may lead to more than the expected additive efficacy is as follows. Activation of the DNA damage pathway leads to the recruitment of many proteins to damaged chromatin, notably also specific chromatin remodeling enzymes, including the macrodomain-containing nucleosome remodeler ALC1 (CHD1L) (Ahel et al., 2009; Gottschalk et al., 2009; Lehmann et al., 2017; Singh et al., 2017). Macrodomains generally bind ADP-ribose, oligo-ADP-ribose and poly-ADP-ribose (PAR) (Karras et al., 2005), thus proteins containing macrodomains respond and recruit to PARP activation sites on the genome, including during DNA damage and with relevance for cancer. Importantly, PAR or oligo-ADP-ribose binding to the macrodomains of ALC1 robustly turns on chromatin remodeling activity (Ahel et al., 2009; Gottschalk et al., 2009; Lehmann et al., 2017; Singh et al., 2017), revealing ALC1 as an allosterically-regulated chromatin remodeling enzyme, the first of its kind, and one of the very few enzymes whose catalytic activity is directly regulated by PAR. Additionally, ALC1 is a validated oncogene and is often genetically amplified together with PARP1 in BRCA1/2-deficient ovarian and breast cancer samples.

Few ALC1i are described in the art e.g. by Abbott et al. in 2020 (Abbott et al., 2020). This document discloses inhibitors of CHD1L and their *in vitro* antitumor activity. Two of the most active ALC1i described, namely "Compound 1" and "Compound 3", have the following chemical structures:



WO 2022/117782 A1 discloses specific ALC1 inhibitors. In a BRCA negative breast cancer cell line, an at least additive effect is shown when combined with a PARP inhibitor.

- 5 The present inventors tested known ALC1 inhibitors, namely Compounds 1 and 3 as shown above, in combination with the known commercially available ATR inhibitor, namely elimusertib and with the known and commercially available PARP inhibitor olaparib. Contrary to the above rationale, only about additive effects were achieved *in vitro* against cancer cell lines. However, extensive further studies then revealed that specific ALC1 inhibitors, wherein the inhibitors specifically bind to an allosteric binding
- 10 pocket formed by an amino acid stretch spanning amino acid residues 101 to 219 of SEQ ID NO: 1, in particular inhibitors with structures according to Formula (I) and Formula (II), and which inhibit the ATPase function and/or nucleosome remodeling function of ALC1, show synergistic effects in combination with and potentiate the effects of
- a) a number of compounds from several classes of cancer drugs, namely
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- inhibitors of Topoisomerase I (e.g. topotecan)
 - inhibitors of Topoisomerase II (e.g. teniposide)
 - inhibitors of ATM (e.g. AZ-32, AZD-1056, or AZD-1390)
 - inhibitors of ATR (e.g. ceralasertib, elimusertib)
 - inhibitors of WEE1 (e.g. adavosertib)
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- inhibitors of BRD (e.g. BAY-299 or ABBV-744),
 - inhibitors of MEK (e.g. trametinib)
- b) specific established cancer drugs, namely mitomycin C or paclitaxel,
- c) ionizing radiation, and
- d) an antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor (e.g.
- 25 trastuzumab deruxtecan, datopotamab deruxtecan, or sacituzumab govitecan).

Furthermore, it has been found that specific ALC1 inhibitors, with structures according to Formula (II), that inhibit the ATPase function and/or nucleosome remodeling function of ALC1, potentiate the effects of PARP inhibitors (e.g. AZD-5305, niraparib, olaparib, pamiparib, rucaparib, talazoparib, and veliparib) against pancreatic cancer or fallopian tube cancer cell lines. Thus, this combination of specific ALC1

30 inhibitors and PARP inhibitors has been found to be particularly suitable for use in treating pancreatic cancer or fallopian tube cancer.

Thus, the present inventors consider that ALC1 inhibition by the specific ALC1 inhibitors inhibits efficient DNA repair by rendering chromatin less accessible to DNA repair enzymes. This leads to enhanced

cancer cell killing and/or reduce off-target effects of the chemotherapeutic agent or the cancer drugs even if used at lower doses and thus lessen cellular toxicity in non-cancer cells. ALC1 inhibitors used according to the invention, in particular of Formula (I) and Formula (II), may thus also mediate sensitization to compounds a), b), and d) as listed above.

5 The present inventors further expect that manipulation of ALC1 activity via the present ALC1 inhibitors used according to the invention could induce strong anti-proliferative effects and in addition be sufficient to bypass an acquired resistance to compounds a), b), and d) listed above, as well as to PARP1 and PARP2 inhibition. Thus, combined use of the ALC1 inhibitors of the invention, in particular of Formula (I) and Formula (II), respectively, and compounds a), b), and d), PARP1 and/or PARP2 inhibitor treatment
10 can be used for therapies in oncology, including in a relapse condition and when there is progression in advanced clinical progression stages.

 Given the above described relevance of the specific ALC1 inhibitors used according to the invention, in particular of Formula (I) and Formula (II), for cancers, in particular those that are amenable to treatment with adavosertib, AZ-32, AZD-1056, AZD-1390, BAY-299, ABBV-744, trametinib,
15 ceralasertib, elimusertib, paclitaxel, Mitomycin C, teniposide, topotecan, AZD-5305, niraparib, olaparib, rucaparib, veliparib, pamiparib and/or talazoparib, as well as trastuzumab deruxtecan, datopotamab deruxtecan, or sacituzumab govitecan, the present invention provides a novel combination regimen to treat or ameliorate proliferative disease and preferably tumor diseases, in particular characterized by loss of sensitivity to the above-mentioned chemotherapy.

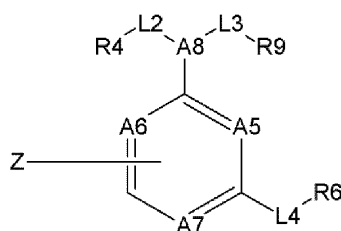
20 Furthermore, the present inventors determined that by using a combination of ALC1 inhibitors used according to the invention, in particular characterized by Formula (I) and Formula (II), and adavosertib, AZ-32, AZD-1056, AZD-1390, BAY-299, ABBV-744, trametinib, ceralasertib, elimusertib, paclitaxel, Mitomycin C, teniposide, topotecan, AZD-5305, niraparib, olaparib, rucaparib, veliparib, pamiparib, or talazoparib, as well as trastuzumab deruxtecan, the effect of adavosertib, AZ-32, AZD-1056, AZD-1390,
25 BAY-299, ABBV-744, trametinib, ceralasertib, elimusertib, paclitaxel, Mitomycin C, teniposide, topotecan, AZD-5305, niraparib, olaparib, rucaparib, veliparib, pamiparib, and talazoparib, as well as trastuzumab deruxtecan, datopotamab deruxtecan, or sacituzumab govitecan, can all surprisingly be enhanced.

 Thus, the use of ALC1 inhibitors used according to the invention, in particular characterized by
30 Formula (I) and Formula (II), in combination with adavosertib, AZ-32, AZD-1056, AZD-1390, BAY-299, ABBV-744, trametinib, ceralasertib, elimusertib, paclitaxel, Mitomycin C, teniposide, topotecan, AZD-5305, niraparib, olaparib, rucaparib, veliparib, pamiparib, or talazoparib, as well as trastuzumab deruxtecan, datopotamab deruxtecan, or sacituzumab govitecan provides *inter alia* (i) an efficient therapy of cancers that are amenable to adavosertib, AZ-32, AZD-1056, AZD-1390, BAY-299, ABBV-744, trametinib,
35 ceralasertib, elimusertib, paclitaxel, Mitomycin C, teniposide, topotecan, AZD-5305, niraparib, olaparib, rucaparib, veliparib, pamiparib, and/or talazoparib, as well as trastuzumab deruxtecan, datopotamab deruxtecan, or sacituzumab govitecan containing chemotherapeutic regimens, (ii) mediate adavosertib, AZ-32, AZD-1056, AZD-1390, BAY-299, ABBV-744, trametinib, ceralasertib, elimusertib, paclitaxel,

Mitomycin C, teniposide, topotecan, AZD-5305, niraparib, olaparib, rucaparib, veliparib, pamiparib, and/or talazoparib, as well as trastuzumab deruxtecan, datopotamab deruxtecan, or sacituzumab govitecan, sensitization, (iii) bypass adavosertib, AZ-32, AZD-1056, AZD-1390, BAY-299, ABBV-744, trametinib, ceralasertib, elimusertib, paclitaxel, Mitomycin C, teniposide, topotecan, AZD-5305, niraparib, olaparib, rucaparib, veliparib, pamiparib, and/or talazoparib, as well as trastuzumab deruxtecan, datopotamab deruxtecan, or sacituzumab govitecan, resistance, (iv) and/or allow the reduction of the amount of adavosertib, AZ-32, AZD-1056, AZD-1390, BAY-299, ABBV-744, trametinib, ceralasertib, elimusertib, paclitaxel, Mitomycin C, teniposide, topotecan, AZD-5305, niraparib, olaparib, rucaparib, veliparib, pamiparib, and/or talazoparib, as well as trastuzumab deruxtecan, datopotamab deruxtecan, or sacituzumab govitecan, that is administered, collectively leading to improved anti-cancer effects and less unwanted side effects.

Summary of the Invention

In a first aspect, the present invention is directed at an allosteric inhibitor of Chromodomain-helicase-DNA-binding protein 1-like (ALC1), wherein the inhibitor specifically binds to an allosteric binding pocket formed by an amino acid stretch spanning amino acid residues 101 to 219 of SEQ ID NO: 1, preferably an inhibitor of ALC1 (ALC1i) according to Formula (I)



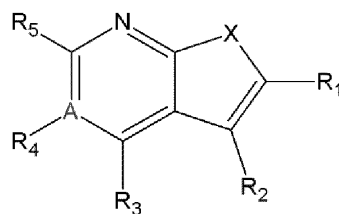
Formula (I)

or pharmaceutically acceptable salts, isomers, solvates, chemically protected forms, and prodrugs thereof, wherein

- A5 and A8 are each independently selected from N or CH;
 - A6 is selected from N or CH, or when A6 takes part in the annulated carbo- or heterocycle Z, then A6 is C;
 - A7 is selected from N or CH, or when A7 takes part in the annulated carbo- or heterocycle Z, then A7 is C;
 - L2 is selected from the group consisting of -CH₂-R₄, -CF₂-R₄, -CH₂-CH₂-R₄, -CH₂-CH₂-CH₂-R₄, -O-R₄, -NH-R₄, -N=R₄;
 - L3 is selected from the group consisting of CH₂-R₅, -CF₂-R₅, -CH₂-CH₂-R₅, -CH₂-CF₂-R₅, -CH₂-CH₂-CH₂-R₅, -O-R₅, -NH-R₅, -N=R₅;
- or
- L2 and L3 together with the A8 to which they are connected form a 5- or 6-membered heterocycle substituted by R₄ and/or R₅;

- L4 is CH₂, -CF₂-, CH₂-CH₂, CH₂-CH₂-CH₂, O, N, and NH, or is absent;
- Z is a 5-, 6- or 7-membered carbo- or heterocycle, optionally substituted with one, two, or three, (preferably one) substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;
- 5 and can be annulated to the central core or connected via a covalent bond
- R4 is 5-, 6- or 7-membered carbo- or heterocycle, optionally substituted with one, two, or three, (preferably one) substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -CF₃, Me, Et, -OMe, and -SMe, or R4 is hydrogen, methyl, or COOH;
- R5 is a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered carbo- or heterocycle, optionally substituted with one, two, or three (preferably one) substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe;
- 10 R6 is a 5-, 6- or 7-membered carbo- or heterocycle, optionally substituted with one, two, or three (preferably one) substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe;
- 15 or R6 is H;
- or
- when A7 takes part in the annulated carbo- or heterocycle Z then A5 and A6 are independently selected from -N or -CH and A8 is selected from -N, -CH, -CH₂-N, -CH₂-CH, or -NH-CH;

- 20 or an inhibitor of ALC1 according to Formula (II):



Formula (II)

- or pharmaceutically acceptable salts, isomers, solvates, chemically protected forms, and prodrugs thereof, wherein:
- 25 X is N or S;
- A is C or N;
- R₁ is -CO-OR₆, -CO-R₇, or -CO-NR₆R_A, preferably R₁ is -CO-OR₆;
- R₂ is -R₇, -NHR₈, -O-R₇, -C-O-R₇, Br, -C₃₋₈-cycloalkyl (preferably cyclopropyl), or -C₄₋₈-cycloalkenyl (preferably cyclohexenyl);
- 30 or
- R₁ and R₂ together form a 5, 6 or 7 membered carbo- or heterocycle, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, =O, [-O-CH₂-CH₂]-NH-CH(OH)-O-tBu, ;

- R₃ is H, =O, -OH, -O-R₇, -R₇, or -(CH₂)_m-L, wherein m is 0, 1 or 2, and L is a 5, 6 or 7 membered carbo- or heterocycle, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, -hydroxyC₁₋₃-alkyl and =O;
- 5 R₄ is H or -C₁₋₃-alkyl, preferably H;
- R₅ is -(CH₂)_m-L, or -(CH₂)_m-(CH=CH)-L, wherein m is 0, 1 or 2, preferably 0 or 1, and L is a 5, 6 or 7 membered carbo- or heterocycle, adamantyl, C₁₋₄-alkyl, or -N(CH₃)₂, optionally substituted, preferably with 1, 2, 3 or 4 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -CO-OR₆, -Br, -Cl, -F, -I, -R₉, -O-R₉, =O, and [-O-CH₂-CH₂]_q-NH-biotin with
- 10 q being 1, 2, 3, or 4, or two adjacent substituents form a 5, 6 or 7 membered carbo- or heterocycle;
- or
- R₄ and R₅ together form a 5, 6, or 7 membered carbocycle, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-R₉, -R₉, =CH-R_A, and -CH₂-R_A, preferably R₄ and R₅ together form a C₅₋₇-cycloalkyl;
- 15 R₆ is H, -C₁₋₆-alkyl, -C₂₋₆-alkenyl, -C₂₋₆-alkynyl, optionally substituted, preferably R₆ is H;
- R₇ is -C₁₋₃-alkyl, -C₂₋₃-alkenyl, -C₂₋₃-alkynyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -Br, -Cl, -F, -I, -CH₃, -OCH₃, or -SCH₃;
- R₈ is H or C₁₋₆-alkyl, preferably H,
- R₉ is -C₁₋₆-alkyl, -C₂₋₆-alkenyl, -C₂₋₆-alkynyl, -C₁₋₆-alkyl-aryl, or C₁₋₆-alkyl-heteroaryl (preferably
- 20 isooxazole, thiazole, tetrazole, 1,2,4-thiadiazole, 1,2,3-thiadiazole, 1,2,5-thiadiazole, pyridine, 1,2,4-oxadiazole, pyrazine, or pyrazole), optionally substituted with 1, 2 or 3 substituents selected from the group consisting of -Br, -Cl, -F, -I, -NO₂, -CN, -CONH₂, -CONH-C₁₋₃-alkyl (preferably -CONH-CH₃), -NH-CO-C₁₋₃-alkyl (preferably -NH-CO-CH₃), -C₁₋₆-alkyl (preferably -CH₃, ethyl, propyl, t-butyl, or pentyl), -C₁₋₃-haloalkyl (preferably -CF₃, or -CHF₂), -O-CHF₂, -O-CF₃, carbocycle
- 25 (preferably cyclopropyl, cyclohexyl or phenyl), -O-carbocycle (preferably phenoxy), heterocycle (preferably pyrazolyl), -CO-heterocycle (preferably -CO-(1-pyrrolidinyl)), -SO₂-CH₃, -SO₂-N(CH₃)₂, -O-C₁₋₄-alkyl (preferably -OCH₃), -O-C₁₋₃-alkyl-O-C₁₋₃-alkyl (preferably -O-CH₂-O-CH₃), -SCH₃, or when R₉ is -C₁₋₆-alkyl-aryl, then two adjacent substituents on the aryl moiety can form a 5, 6 or 7 membered carbo- or heterocycle, which is optionally substituted;
- 30 R_A is H, carbo- or heterocycle, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -R₉, -O-R₇, -O-(CH₂)_o-R₉, -SO₂NH₂, and =O, wherein o is 0 or 1
- for use in treating or ameliorating a proliferative disease, preferably cancer, in a patient in combination with
- 35 a) an inhibitor of Topoisomerase I, Topoisomerase II, ATM, ATR, Wee1, BRD, and/or MEK,
- b) mitomycin C, or paclitaxel,
- c) ionizing radiation, or

- d) an antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor (e.g. trastuzumab deruxtecan, datopotamab deruxtecan, or sacituzumab govitecan);

and/or for use in enhancing efficacy of

- 5 a) an inhibitor of Topoisomerase I, Topoisomerase II, ATM, ATR, Wee1, BRD, and/or MEK
b) mitomycin C, or paclitaxel,
c) ionizing radiation, or
d) an antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor (e.g. trastuzumab deruxtecan, datopotamab deruxtecan, or sacituzumab govitecan)

in treating or ameliorating a proliferative disease, preferably cancer, in a patient,

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In a second aspect, the inhibitor of ALC1 (ALC1i) according to formula (II) is for use in treating or ameliorating pancreatic cancer or fallopian tube cancer in a patient in combination with an inhibitor of PARP, or for use in enhancing efficacy of an inhibitor of PARP in treating or ameliorating pancreatic cancer or fallopian tube cancer in a patient.

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In a third aspect, the present invention is directed at a pharmaceutical composition comprising an ALC1i as defined herein and

- 20 a) an inhibitor of Topoisomerase I, Topoisomerase II, ATM, ATR, Wee1, BRD and/or MEK,
b) mitomycin C, paclitaxel, or
c) an antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor (e.g. trastuzumab deruxtecan, datopotamab deruxtecan, or sacituzumab govitecan).

In a fourth aspect, the present invention is directed to a kit of parts, comprising an ALC1i as described herein with instructions to combine it with

- 25 a) an inhibitor of Topoisomerase I, Topoisomerase II, ATM, ATR, Wee1, BRD, and/or MEK,
b) mitomycin C, or paclitaxel,
c) ionizing radiation; or
d) an antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor (e.g. trastuzumab deruxtecan, datopotamab deruxtecan, or sacituzumab govitecan); or

30 comprising

- a) an inhibitor of Topoisomerase I, Topoisomerase II, ATM, ATR, Wee1, BRD, and/or MEK,
b) mitomycin C, or paclitaxel, or
c) an antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor (e.g. trastuzumab deruxtecan, datopotamab deruxtecan, or sacituzumab govitecan);

35 with instructions to combine it with an ALC1i as defined herein, or
comprising separately packaged an ALC1i as defined herein and

- a) an inhibitor of Topoisomerase I, Topoisomerase II, ATM, ATR, Wee1, BRD, and/or MEK,

- b) mitomycin C, or paclitaxel, or
- c) an antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor (e.g. trastuzumab deruxtecan, datopotamab deruxtecan, or sacituzumab govitecan),

optionally with instructions for use in treating or ameliorating a proliferative disease, preferably cancer.

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Description of the Figures

In the following, the content of the Figures comprised in this specification is described. In this context it is also referred to the detailed description of the invention above and/or below.

Figure 1: Structures and molecule names of selected ALC1 inhibitors. These selected ALC1 inhibitors (or isomers, pharmaceutically acceptable salts, solvates, chemically protected forms, and prodrugs thereof) are preferably used in accordance with the present invention.

Figure 2: Synergy Scores and MSA of cancer cells treated with a combination of ALC1i vs. other drugs.

Results of the 2-D titrations of different combinations of an ALC1i (compound A) with another drug (compound B) in different cancer cell lines are summarized in this table. Drug combinations with an MSA (most synergistic area) score below 9 indicate interactions that are likely not synergistic and are labeled with a “-”. An MSA score between 9-10 is labeled with “+” and indicates that the interaction of compound A and B is likely to be synergistic. MSA scores above 10 are marked “++” are synergistic. MSA scores greater than 20 are labeled as “+++” and considered highly synergistic.

Figure 3: Example for 96-hour SRB assay: pancreatic cancer cell line treated with ALC1i or ATMi.

PSN1 cells were seeded into 96-well plates and treated with titrations of ALC1i-101 or an ATMi (ATM inhibitor AZD-1390). The cells were cultured at 37°C, CO₂ 5% for 4 days, fixed with 10%TCA and stained with sulforhodamine staining to analyze cell survival. The data was normalized to DMSO controls indicating 100 % survival. Inhibitor vs. response curves were fitted with the Synergy Finder using the curve fitting parameter “LL4”. The curves show an average fit of 3 technical replicates.

Figure 4: Example for 2-D titration: co-treatment cell proliferation assay of pancreatic cancer cells.

Cancer cells were seeded into 96-well plates and treated with a 2-D titration of an ALC1i vs. the indicated drug. The cells were cultured at 37°C, CO₂ 5% for 4 days, fixed with 10%TCA and stained with sulforhodamine staining to analyze cell survival. The synergy score is calculated using the Synergy Finder. Treatment with ALC1i-101 in combination with ATMi show highly synergistic area scores of above 10 respectively. MSA scores over 10 are an indication of strong synergy.

Figure 5: cell cycle analysis of ALC1i treated cancer cells.

SUM-149-PT cells were seeded into 6-well plates and treated with ALC1i or DMSO for 48h. Cells were fixed in 75% EtOH and stained with DAPI. FACS analysis shows cells in different cell cycle stages. Treatment with DMSO shows cells in G1, S and G2 phase. Cells treated with ALC1i show enrichment/block in G2 phase.

Figure 6: γH2AX protein levels increase under ALC1i treatment.

PSN1 cells were treated with a titration of ALC1i or DMSO for 24h. A Western Blot was run with antibodies against phosphorylated H2AX (γ H2AX) and α -tubulin. Image of protein bands is shown above, graph below shows γ H2AX protein levels normalized to α -tubulin loading control and normalized to DMSO treated sample.

5 **Figure 7: EC50 values (μ M) of 96 hour SRB assay and 11 days colony formation assay of HR proficient (HRP) and HR deficient (HRD) cells treated with ALCi.**

Different cancer cell lines with a variation of mutations in the homologous recombination repair pathways (HR) were seeded into 96-well plates and treated with titrations of different ALCi. The cells were cultured at 37°C, CO₂ 5% for 4 days (96h) or 11 days (colony formation), fixed with 10%TCA and stained
10 with sulforhodamine staining to analyze cell survival. The data was normalized to DMSO controls indicating 100 % survival. Inhibitor vs. response curves with variable slope (four parameters) were fitted using GraphPad Prism.

Figure 8: List of HR genes.

List of genes involved in DNA Damage Response (DDR) (Human DNA Repair Genes, n.d.) cited in
15 Wood RD, Mitchell M, & Lindahl T Mutation Research, 2005, in Science, 2001, in the reference book DNA Repair and Mutagenesis, 2nd edition, 2006, and in Nature Reviews Cancer, 2011 (modified by R. Wood and M. Lowery on Wednesday 10th June 2020).

Figure 9: List of genes related to the homologous recombination repair pathway (HR).

Summary of genes from Toh & Ngeow, 2021; Kim et al., 2021; Yamamoto & Hirasawa, 2021 and
20 the HRD-signature genes from Peng et al., 2014.

Figure 10: Synergistic effect of ALC1i-101 and trametinib in a MiaPaCa2 CDX experiment.

Detailed Description of the Invention

Before the present invention is described in detail below, it is to be understood that this invention is
25 not limited to the particular methodology, protocols and reagents described herein as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to limit the scope of the present invention which will be limited only by the appended claims. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art.

30 Several documents are cited throughout the text of this specification. Each of the documents cited herein (including all patents, patent applications, scientific publications, manufacturer's specifications, instructions etc.), whether supra or infra, is hereby incorporated by reference in its entirety. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention. Some of the documents cited herein are characterized as being "incorporated by reference".
35 In the event of a conflict between the definitions or teachings of such incorporated references and definitions or teachings recited in the present specification, the text of the present specification takes precedence.

In the following, the elements of the present invention will be described. These elements are listed with specific embodiments, however, it should be understood that they may be combined in any manner and in any number to create additional embodiments. The variously described examples and preferred embodiments should not be construed to limit the present invention to only the explicitly described
5 embodiments. This description should be understood to support and encompass embodiments which combine the explicitly described embodiments with any number of the disclosed and/or preferred elements. Furthermore, any permutations and combinations of all described elements in this application should be considered disclosed by the description of the present application unless the context indicates otherwise.

Definitions

10 To practice the present invention, unless otherwise indicated, conventional methods of chemistry, biochemistry, and recombinant DNA techniques are employed which are explained in the literature in the field (cf., e.g., Molecular Cloning: A Laboratory Manual, 2nd Edition, J. Sambrook et al. eds., Cold Spring Harbor Laboratory Press, Cold Spring Harbor 1989).

In the following, some definitions of terms frequently used in this specification are provided. These
15 terms will, in each instance of its use, in the remainder of the specification have the respectively defined meaning and preferred meanings.

As used in this specification and the appended claims, the singular forms “a”, “an”, and “the” include plural referents, unless the content clearly dictates otherwise.

The term “Chromodomain-helicase-DNA-binding protein 1-like” abbreviated CHD1L refers to a
20 protein that is also termed ALC1. The amino acid sequence of human ALC1 is as specified in SEQ ID NO: 1 as known in the art, e.g. as specified in WO2022/117782 A1. The 897 amino acid residues long protein consists of an N-terminal Snf2-like DNA dependent ATPase domain spanning amino acid residues 40 to 513, which contains the conserved helicase motifs critical for catalysis (Flaus et al., 2006). This domain is composed of two RecA like lobes ranging from amino acid residues 48 to 261 and 351 to 513, respectively.
25 The allosteric binding pocket is spatially separated from that part of ALC1 involved in binding ATP. The ATPase domain is followed by a linker region ranging from amino acid residues 514 to 703, which contains a putative coiled-coil region (amino acid residues 638 to 675), and a C-terminal macrodomain (amino acid residues 704 to 897). The macrodomain has been shown to directly interact with the ATPase domain, thereby inhibiting its catalytic function (Lehmann et al., 2017; Singh et al., 2017). This interaction is
30 released upon poly(ADP-ribose) binding to the macrodomain, leading to an activation of the chromatin remodelling enzyme.

Preferably, the terms used herein are defined as described in "A multilingual glossary of biotechnological terms: (IUPAC Recommendations)", Leuenberger, H.G.W, Nagel, B. and Kölbl, H. eds. (1995), Helvetica Chimica Acta, CH-4010 Basel, Switzerland).

35 The term "alkyl" as used in the context of the present invention refers to a saturated straight or branched hydrocarbon chain. Preferably, the chain comprises from 1 to 10 carbon atoms, i.e. 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, e.g. methyl, ethyl propyl (n-propyl or iso-propyl), butyl (n-butyl, iso-butyl, sec-butyl, or tert-butyl), pentyl, hexyl, heptyl, octyl, nonyl, or decyl. Alkyl groups are optionally substituted.

The term "heteroalkyl" as used in the context of the present invention refers to a saturated straight or branched hydrocarbon chain. Preferably, the chain comprises from 1 to 9 carbon atoms, i.e. 1, 2, 3, 4, 5, 6, 7, 8, or 9, e.g. methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl, which is interrupted one or more times, e.g. 1, 2, 3, 4, or 5, with the same or different
5 heteroatoms. Preferably, the heteroatoms are selected from O, S, and N, e.g. $-(CH_2)_n-X-(CH_2)_mCH_3$, with $n = 0, 1, 2, 3, 4, 5, 6, 7, 8, \text{ or } 9$, $m = 0, 1, 2, 3, 4, 5, 6, 7, 8, \text{ or } 9$ and $X = S, O \text{ or } NR'$ with $R' = H \text{ or hydrocarbon (e.g. } C_1 \text{ to } C_6 \text{ alkyl)}$. In particular "heteroalkyl" refers to $O-CH_3$, $-OC_2H_5$, $-CH_2-O-CH_3$, $-CH_2-O-C_2H_5$, $-CH_2-O-C_3H_7$, $-CH_2-O-C_4H_9$, $-CH_2-O-C_5H_{11}$, $C_2H_4-O-CH_3$, $-C_2H_4-O-C_2H_5$, $-C_2H_4-O-C_3H_7$, $-C_2H_4-O-C_4H_9$ etc. Heteroalkyl groups are optionally substituted.

10 The term "haloalkyl" refers to a saturated straight or branched hydrocarbon chain in which one or more hydrogen atoms are replaced by halogen atoms, e.g. by fluorine, chlorine, bromine or iodine. Preferably, the chain comprises from 1 to 10 carbon atoms, i.e. 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10. In particular, "haloalkyl" refers to $-CH_2F$, $-CHF_2$, $-CF_3$, $-C_2H_4F$, $-C_2H_3F_2$, $C_2H_2F_3$, $-C_2HF_4$, $-C_2F_5$, $-C_3H_6F$, $-C_3H_5F_2$, $-C_3H_4F_3$, $-C_3H_3F_4$, $-C_3H_2F_5$, $-C_3HF_6$, $-C_3F_7$, CH_2Cl , $-CHCl_2$, $-CCl_3$, $-C_2H_4Cl$, $-C_2H_3Cl_2$, $C_2H_2Cl_3$, $-C_2HCl_4$, C_2Cl_5 , $-C_3H_6Cl$, $-C_3H_5Cl_2$, $C_3H_4Cl_3$, $-C_3H_3Cl_4$, $-C_3H_2Cl_5$, $-C_3HCl_6$, and $-C_3Cl_7$. Haloalkyl
15 groups are optionally substituted.

The term "5, 6, or 7 membered carbocycle" is used in the context of the present invention to refer to "cycloalkyl", "cycloalkenyl" or "aryl" with 5, 6, or 7 carbon atoms forming a ring.

The term "cycloalkyl" includes cyclopentyl, cyclohexyl, and cycloheptyl. Cycloalkyl groups are
20 optionally substituted.

The term "cycloalkenyl" includes cyclopentenyl, cyclohexenyl, and cycloheptenyl. Cycloalkenyl groups are optionally substituted.

The term "aryl" refers to a polyunsaturated, typically aromatic, hydrocarbon group which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently. Preferably,
25 the aryl group comprises 6 to 10 carbon atoms, i.e. a C_{6-10} aryl group. In a preferred embodiment, an aryl group is a phenyl group, which is most preferred, or a naphthyl group. Aryl is optionally substituted.

The term "5, 6, or 7 membered heterocycle" is used in the context of the present invention to refer to monocyclic "5, 6, or 7 membered heterocycloalkyl" or monocyclic "5, 6, or 7 membered heteroaryl" with 5, 6, or 7 atoms forming a ring.

30 The term "5, 6, or 7 membered heterocycloalkyl" refers to a saturated monocycle, wherein at least one of the carbon atoms are replaced by 1, or 2 (for the five membered ring) or 1, 2, or 3 (for the six membered ring) or 1, 2, 3, or 4 (for the seven membered ring) of the same or different heteroatoms, preferably selected from O, N and S. Preferred examples of heterocycloalkyl include 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, 35 tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, or 2-piperazinyl. Heterocycloalkyl groups are optionally substituted.

The term "heteroaryl" as used in the context of the present invention refers to a 5, 6 or 7-membered aromatic monocyclic ring wherein at least one of the carbon atoms are replaced by 1, 2, or 3 (for the five

membered ring) or 1, 2, 3, or 4 (for the six membered ring) of the same or different heteroatoms, preferably selected from O, N and S. Examples of preferred heteroaryls are furanyl, thienyl, oxazolyl, isoxazolyl, 1,2,5-oxadiazolyl, 1,2,3-oxadiazolyl, pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, thiazolyl, isothiazolyl, 1,2,3-thiadiazolyl, 1,2,5-thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl. Heteroaryl groups are optionally substituted.

The term "aralkyl" corresponds to an arylalkyl residue, i.e. an alkyl that is substituted with an aryl group as defined above.

If two or more radicals can be selected independently from each other, then the term "independently" means that the radicals may be the same or may be different.

The term "optionally substituted" in each instance if not further specified refers to halogen (in particular F, Cl, Br, or I), -NO₂, -CN, -OR^{'''}, -NR[']R^{''}, -COOR^{'''}, -CONR[']R^{''}, -NR[']COR^{''}, -NR^{'''}COR^{'''}, -NR[']CONR[']R^{''}, -NR[']SO₂E, -COR^{'''}, -SO₂NR[']R^{''}, -OOCR^{'''}, -CR^{'''}R^{'''}OH, -R^{'''}OH, and -E;

R['] and R^{''} are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, and heteroaryl or together form a heteroaryl, or heterocycloalkyl;

R^{'''} and R^{'''} are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkoxy, aryl, aralkyl, heteroaryl, and -NR[']R^{''};

E is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, alkoxyalkyl, heterocycloalkyl, an alicyclic system, aryl and heteroaryl; optionally substituted.

"Pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia (United States Pharmacopeia-33/National Formulary-28 Reissue, published by the United States Pharmacopeia Convention, Inc., Rockville Md., publication date: April 2010) or other generally recognized pharmacopeia for use in animals, and more particularly in humans.

The term "pharmaceutically acceptable salt" refers to a salt of a compound of the present invention. Suitable pharmaceutically acceptable salts of the compound of the present invention include acid addition salts which may, for example, be formed by mixing a solution of a compound described herein or a derivative thereof with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compound of the invention carries an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts (e.g., sodium or potassium salts); alkaline earth metal salts (e.g., calcium or magnesium salts); and salts formed with suitable organic ligands (e.g., ammonium, quaternary ammonium and amine cations formed using counteranions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl sulfonate and aryl sulfonate). Illustrative examples of pharmaceutically acceptable salts include but are not limited to: acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, calcium edetate, camphorate, camphorsulfonate, camsylate, carbonate, chloride, citrate,

clavulanate, cyclopentanepropionate, digluconate, dihydrochloride, dodecylsulfate, edetate, edisylate, estolate, esylate, ethanesulfonate, formate, fumarate, gluceptate, glucoheptonate, gluconate, glutamate, glycerophosphate, glycolylarsanilate, hemisulfate, heptanoate, hexanoate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroiodide, 2-hydroxyethanesulfonate, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, lauryl sulfate, malate, maleate, malonate, mandelate, mesylate, methanesulfonate, methylsulfate, mucate, 2-naphthalenesulfonate, napsylate, nicotinate, nitrate, N-methylglucamine ammonium salt, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, pectinate, persulfate, 3-phenylpropionate, phosphate/diphosphate, picrate, pivalate, polygalacturonate, propionate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, undecanoate, valerate, and the like (see, for example, Berge, S. M., et al, "Pharmaceutical Salts", Journal of Pharmaceutical Science, 1977, 66, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

In addition to salt forms, the present invention provides compounds which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide a compound of Formula (I) or Formula (II), and especially a compound shown in Fig. 1. A prodrug is an active or inactive compound that is modified chemically through *in vivo* physiological action, such as hydrolysis, metabolism and the like, into a compound of this invention following administration of the prodrug to a patient. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme. The suitability and techniques involved in making and using prodrugs are well known by those skilled in the art. For a general discussion of prodrugs involving esters, see Svensson L.A. and Tunek A. (1988) Drug Metabolism Reviews 19(2): 165-194 and Bundgaard H. "Design of Prodrugs", Elsevier Science Ltd. (1985). Examples of a masked carboxylate anion include a variety of esters, such as alkyl (for example, methyl, ethyl), cycloalkyl (for example, cyclohexyl), aralkyl (for example, benzyl, p-methoxybenzyl), and alkylcarbonyloxyalkyl (for example, pivaloyloxymethyl). Amines have been masked as arylcarbonyloxymethyl substituted derivatives which are cleaved by esterases *in vivo* releasing the free drug and formaldehyde (Bundgaard H. et al. (1989) J. Med. Chem. 32(12): 2503-2507). Also, drugs containing an acidic NH group, such as imidazole, imide, indole and the like, have been masked with N-acyloxymethyl groups (Bundgaard H. "Design of Prodrugs", Elsevier Science Ltd. (1985)). Hydroxy groups have been masked as esters and ethers. EP 0 039 051 A2 discloses Mannich-base hydroxamic acid prodrugs, their preparation and use.

The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are
5 intended to be encompassed within the scope of the present invention.

As used herein, “para position” when referring to the substituent of an aryl means that the substituent occupies the position opposite to the position at which the aryl is linked to the backbone of the compound.

As used herein, a “patient” means any mammal or bird that may benefit from a treatment with the compounds described herein. Preferably, a “patient” is selected from the group consisting of laboratory
10 animals, domestic animals, or primates including chimpanzees and human beings. It is particularly preferred that the “patient” is a human being.

As used herein, “treat”, “treating” or “treatment”, or ameliorating, respectively, of a disease or disorder means accomplishing one or more of the following: (a) reducing the severity of the disorder; (b)
15 limiting or preventing development of symptoms characteristic of the disorder(s) being treated; (c) inhibiting worsening of symptoms characteristic of the disorder(s) being treated; (d) limiting or preventing recurrence of the disorder(s) in patients that have previously had the disorder(s); and (e) limiting or preventing recurrence of symptoms in patients that were previously symptomatic for the disorder(s).

As used herein, “prevent”, “preventing”, “prevention”, or “prophylaxis” of a disease or disorder
20 means preventing that a disorder occurs in a subject for a certain amount of time. For example, if a compound described herein is administered to a subject with the aim of preventing a disease or disorder, said disease or disorder is prevented from occurring at least on the day of administration and preferably also on one or more days (e.g. on 1 to 30 days; or on 2 to 28 days; or on 3 to 21 days; or on 4 to 14 days; or on 5 to 10 days) following the day of administration.

A “pharmaceutical composition” according to the invention may be present in the form of a composition, wherein the different active ingredients and diluents and/or carriers are admixed with each other, or may take the form of a combined preparation, where the active ingredients are present in partially
25 or totally distinct form. An example for such a combination or combined preparation is a kit-of-parts.

An “effective amount” is an amount of a therapeutic agent sufficient to achieve the intended
30 purpose. The effective amount of a given therapeutic agent will vary with factors such as the nature of the agent, the route of administration, the size and species of the animal to receive the therapeutic agent, and the purpose of the administration. The effective amount in each individual case may be determined empirically by a skilled artisan according to established methods in the art.

The term “carrier”, as used herein, refers to a diluent, adjuvant, excipient, or vehicle with which
35 the therapeutic agent is administered. Such pharmaceutical carriers can be sterile liquids, such as saline solutions in water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. A saline solution is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and

glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatine, malt, rice flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsions, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. The compounds of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with free amino groups such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with free carboxyl groups such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin. Such compositions will contain a therapeutically effective amount of the compound, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

SEQ ID NO 1:

MERAGATSRGGQAPGFLLRLHTEGRAEAARVQEQLRQWGLTGIHLRSYQLEGVNWLAQR
 FHCQNGCILGDEMGLGKTCQTIALFIYLAGRLNDEGPFLILCPLSVLSNWKEEMQRFAPG
 LSCVTYAGDKKEERACLQQDLKQESRFHVLLTTYEICLKDASFLKSFPWSVLVDEAHLRK
 NQSSLLHKTLSFVSFVSLLLTGTPIQNSLQELYSLLSFVEPDLFSKEEVGDFIQRYQDI
 EKESESASELHKLLQPFLRRVKAEVATELPKKTEVVYHGMALQKKYYKAILMKDLDA
 FENETAKKVKLQNILSQLRKCDHPYLFDGVEPEPFEVGDHLTEASGKLHLLDKLLAFLY
 SGGHRVLLFSQMTQMLDILQDYMDYRGYSYERVDGSVRGEERHLAIKNFGQQPIFVFLLS
 TRAGGVGMNLTAADTVIFVDSDFNPQNDLQAAARAHRIGQNKSVKVIRLIGRDTVEEIVY
 RKAASKLQLTNMIEGGHFTLGAQKPAADADLQSEILKFGLDKLLASEGSTMDEIDLES
 ILGETKDGQWVSDALPAAEGSRDQEEGKNHMYLFEGKDYSEPSKEDRKSFEQLVNLQK
 TLLEKASQEGRSLRNKGSVLIPGLVEGSTKRKRVLSPPELEDQRKKRQEAATAKRRRLIEE
 KKRQKEEAHKKKMAWWESNNYQSFCPLPSESEPEDLENGEESSAELDYQDPDATSLKYV
 SGDVTHPQAGAEDALIVHCVDDSGHWGRGGLFTALEKRSAEPRKIYELAGKMKDLSLGGV
 LLFPVDDKESRNKGQDLLALIVAQHRDRSNVLSGIKMAALEEGLKKIFLAAKKKKASVHL
 PRIGHATKGFNWYGTERLIRKHLAARGIPTIYIYFPRSKSAVLHSQSSSSSRQLVP

Embodiments of the Invention

The present inventors have identified and characterized ALC1 inhibitors that appear to be involved in allosteric regulation of the nucleosome sliding activity of ALC1. These compounds specifically bind to an allosteric pocket and are capable of inhibiting activity of ALC1. Compounds that bind to the ATPase site of ALC1 and block the ATPase activity have to compete with ATP for binding to the ATPase site.

These compounds had been tested for their ability to kill different tumor cell lines one of which was BRCA deficient.

The present inventors have identified that said allosteric inhibitors of ALC1 (CHD1L), in particular those of Formula (I) and Formula (II), show a potentiating, preferably synergistic effect in the treatment of proliferative disease when combined with several classes of cancer drugs, namely inhibitors of Topoisomerase I, Topoisomerase II, ATM, ATR, Wee1, BRD, and MEK, with mitomycin C, paclitaxel, with ionizing radiation, or with an antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor.

Furthermore, it has been found that said inhibitors of ALC1 of Formula (II) show a synergistic effect in the treatment of pancreatic cancer or fallopian tube cancer when combined with a PARP inhibitor.

The present inventors considered the rationale that ALC1 inhibitors as a known class of cancer drugs could be combined with several other classes of known cancer drugs, e.g. inhibitors of Topoisomerase I, Topoisomerase II, ATM, ATR, Wee1, BRD, or MEK, with mitomycin C, or paclitaxel, with ionizing radiation, or with an antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor. However, tests with known ALC1i showed not over-additive efficacies against cancer cell lines. The present invention is based on the surprising finding that said specific allosteric ALC1 inhibitors, preferably those of Formula (I) and of Formula (II), possess synergistic anti-proliferative activity when combined with inhibitors of Topoisomerase I, Topoisomerase II, ATM, ATR, Wee1, BRD, and MEK, with mitomycin C, or paclitaxel, with ionizing radiation, or with an antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor. Thus, these combinations are expected to be suitable in the treatment of proliferative diseases.

The ALC1 inhibitors, preferably those characterized by Formula (I) and Formula (II), the latter being known from the art (WO 2022/117782 A1), which are used in accordance with the present invention, appear to be involved in allosteric regulation of the nucleosome sliding activity of ALC1. These compounds specifically bind to an allosteric pocket and are capable of inhibiting activity of ALC1. Compounds that bind to the ATPase site of ALC1 and block the ATPase activity have to compete with ATP for binding to the ATPase site. Since the cellular ATP concentration is in the range of 1 to 10 mM depending on the cellular compartment, very high binding affinities in the low nanomolar range are required to successfully prevent ATP from binding to the ATPase site of ALC1. The allosteric inhibitors of ALC1 used according to the invention, in particular those that are characterized by Formula (I) and Formula (II), do not have this limitation since they do not have to prevent ATP from binding but inhibit ALC1's activity through a different mechanism. The present inventors have identified ALC1 inhibitors that are capable of specifically binding to an allosteric pocket of ALC1. The question remained and has been not answered by the art yet, whether these specific ALC1 inhibitors would provide synergistic efficacy with other classes of cancer drugs.

In a **first aspect**, the present invention is directed at an allosteric inhibitor of Chromodomain-helicase-DNA-binding protein 1-like (ALC1), wherein the inhibitor specifically binds to an allosteric binding pocket formed by an amino acid stretch spanning amino acid residues 101 to 219 of SEQ ID NO:

1 for use in treating or ameliorating a proliferative disease in a patient in combination with and/or for use in enhancing the efficacy in treating a proliferative disease of

- a) an inhibitor of Topoisomerase I, Topoisomerase II, ATM, ATR, Wee1, BRD, and/or MEK, or
- b) mitomycin C, paclitaxel,
- 5 c) ionizing radiation, or
- d) an antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor (e.g. trastuzumab deruxtecan, datopotamab deruxtecan, or sacituzumab govitecan).

The term “specifically binds” as used in this context indicates a K_D of the compound to full length human ALC1 with an amino acid sequence according to SEQ ID NO: 1 of 200 μM or lower, preferably of 100 μM , more preferably of 50 μM , more preferably of 10 μM or lower, more preferably of 5 μM or lower, even more preferably of 1 μM and even more preferably of 500 nM or lower. The skilled person is well aware of how to measure dissociation constants of small molecules with regard to proteins, which includes surface plasmon resonance. Preferably the K_D of a compound of the invention is measured by immobilizing full length human ALC1 on the surface of a chip and the compound is subsequently applied to the immobilized protein. Preferably such measurement is carried out at 37°C.

In a preferred embodiment of the present invention, the allosteric inhibitor of ALC1 used according to the invention exhibits an IC_{50} value in a FRET based nucleosome remodeling assay of 500 μM or less, preferably 250 μM or less, more preferably 100 μM or less, more preferably 50 μM or less, more preferably 10 μM or less, more preferably 5 μM or less, or even more preferably 1 μM or less. The K_D and the IC_{50} as described herein are determined as disclosed in WO 2022/117782 A1.

Not every amino acid within the amino acid stretch spanning amino acid residues 101 to 219 of SEQ ID NO: 1 is forming the surface of the allosteric pocket of ALC1 available for binding to the compounds used according to the invention. This is due to the fact that some amino acids are buried in the pocket and are poorly accessible and others are not even part of the pocket but are located within or on the outside surface of ALC1. Thus, in a preferred embodiment the allosteric binding pocket to which the inhibitors of ALC1 used according to the present invention specifically bind comprises or consists of amino acids L101, Y153, C156, L157, A160, L163, K164, V173, D174, E175, A176, H177, R178, L179, S183, L186, H187, T189, L190, F193, L200, L201, T202, N208, S209, E212, L213, L216, and F219 of SEQ ID NO: 1, more preferably the binding pocket comprises or consists of Y153, C156, L157, A160, L163, V173, E175, R178, L186, H187, L190 F 193, L200, and E212 of SEQ ID NO: 1. The skilled person can model the allosteric binding pocket of ALC1 based on the homology to other chromatin remodelling enzymes. Such models are also depicted in WO2022/117782 A1 with and without compounds used in the invention in the pocket. WO2022/117782 A1 depicts how the skilled person can visualize the suitability of a given compound to fit into the allosteric binding pocket, and thus provides further guidance on the selection of compounds that fulfill the steric, hydrophobicity, and hydrophilicity as well as charge requirements in the pocket. A minimal set of structural coordinates of the amino acids of ALC1 involved in binding to the compounds of the invention is provided in Fig. 20 of WO2022/117782 A1. That is, with the detailed teaching given in

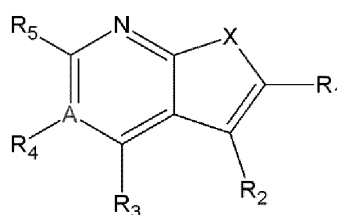
WO2022/117782 A1, it can be determined whether the inhibitor specifically binds to the allosteric binding pocket formed by an amino acid stretch spanning amino acid residues 101 to 219 of SEQ ID NO: 1.

Based on their orientation within the pocket the different amino acids that are accessible at the surface of the pocket can form different non-covalent bonds, in particular hydrogen bonds, ionic interactions, van der Waals interactions and hydrophobic interactions. Accordingly, in a preferred embodiment the inhibitor used according to the invention forms non-covalent bond(s) with one or more amino acids of the allosteric binding pocket, preferably with one or more of the backbone of amino acids L157, A160, K164, V173, D174, H177, R178, L179, L186, N208, and/or E212 of ALC1 and/or the sidechains of L101, Y153, C156, L157, A160, L163, E175, R178, L179, L186, H187, L190, F193, T202, N208, E212, or L213 of ALC1, more preferably with the backbone of D174, H177, and R178 of ALC1, and the sidechain of Y153, E175, R178, H187, T202, N208 and/or E212 of ALC1.

In a preferred embodiment the inhibitor of ALC1 used according to the invention non-covalently binds to:

- (i) the aromatic ring of the sidechain of amino acid Y153 of ALC1 ring face-to-face or edge-to-face pi-pi interaction with aromatic carbo- or heterocyclic substituents or forming cation-pi, polar-pi, or halogen-pi interactions with polar, charged, or carbo-halogen substituents;
- (ii) the terminal oxygen of the sidechain of amino acid Y153 of ALC1 with a hydrogen bond donating group;
- (iii) the carbonyl oxygen of the backbone of H177 with carbo halogens or hydrogen bond donating groups;
- (iv) the carbonyl oxygen of the backbone of D174 with carbo halogens or hydrogen bond donating groups;
- (v) the sidechain of E175 with a hydrogen bond donating or accepting group;
- (vi) the sidechain of R178 with a hydrogen bond donating or accepting group;
- (vii) the backbone carbonyl oxygen of R178 with carbo halogens or hydrogen bond donating groups;
- (viii) the sidechain of H187 ring face-to-face or edge-to-face pi-pi interaction with aromatic carbo- or heterocyclic substituents or forming cation-pi, polar-pi, or halogen-pi interactions with polar, charged, or carbo-halogen substituents or with a hydrogen bond donating or accepting group
- (ix) the sidechain of T202 with a hydrogen bond donating or accepting group;
- (x) the sidechain of N208 with a hydrogen bond donating or accepting group; and
- (xi) the sidechain of E212 with a hydrogen bond donating or accepting group.

In an preferred embodiment, the inhibitor of ALC1 (ALC1i) used according to the invention is an inhibitor of ALC1 (ALC1i) according to Formula (II)



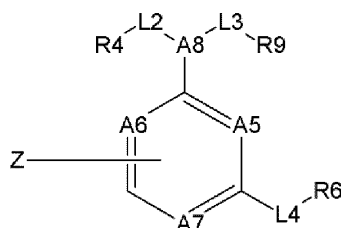
Formula (II)

wherein

- (i) R₅ comprises an aromatic ring that pi-stacks with the aromatic ring of Y153; and/or
- 5 (ii) N is a hydrogen bond accepting group for the terminal OH of Y153; and/or
- (iii) R₁ comprises a group that is a hydrogen bond donating group to the backbone carbonyl oxygen of H177; and/or
- (iv) R₃ comprises a carbohalogen or hydrogen bond donating group that binds to the carbonyl oxygen of the backbone of D174; and/or
- 10 (v) R₁ and R₂ together form an aromatic or heteroaromatic monocycle comprising a hydrogen bond donating or accepting group especially at or adjacent to the R₁ position which can act as a hydrogen bond donating or accepting group to the side chain of E175 and/or R178; and/or
- (vi) R₁ and R₂ together form a substituted carbo- or heteromonocycle comprising a hydrogen bond donating or accepting group, preferably at or adjacent to the R₁ position which is a
- 15 (vii) R₃ comprises an aromatic ring that pi-stacks with the aromatic ring H187 or is an electron poor substituent, especially at, forming polar-pi or cation-pi interactions with the aromatic ring of H187; and/or
- (viii) R₁ and R₂ together form an aromatic or heteroaromatic monocycle comprising a hydrogen
- 20 bond donating or accepting group especially at or adjacent to the R₂ position which can act as a hydrogen bond donating or accepting group to the side chain of T202 and/or N208; and/or
- (ix) R₄ is H or -C₁₋₃-alkyl, preferably H; and/or
- (x) R₅ is -(CH₂)_m-L, or -(CH₂)_m-(CH=CH)-L, wherein m is 0, 1 or 2, preferably 0 or 1, and L
- 25 is a 5, 6 or 7 membered carbo- or heterocycle, or adamantyl, optionally substituted, preferably with 1, 2, 3 or 4 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -CO-OR₆, -Br, -Cl, -F, -I, -R₉, -O-R₉, and =O, or two adjacent substituents form a 5, 6 or 7 membered carbo- or heterocycle; and/or
- (xi) R₄ and R₅ together form a 5, 6, or 7 membered carbocycle, optionally substituted, preferably
- 30 with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-R₉, -R₉, =CH-R_A, preferably R₄ and R₅ together form a C₅₋₇-cycloalkyl; and/or
- (xii) X is N or S; and/or
- (xiii) A is C or N;

or pharmaceutically acceptable salts, isomers, solvates, chemically protected forms, and prodrugs thereof.

In a preferred embodiment, the inhibitor of ALC1 (ALC1i) used according to the invention is an inhibitor of ALC1 (ALC1i) according to **Formula (I)**



Formula (I)

wherein

A5 and A8 are each independently selected from N or CH;

A6 is selected from N or CH, or when A6 takes part in the annulated carbo- or heterocycle Z, in particular a 5, 6, or 7 membered carbo- or heterocycle, then A6 is C;

A7 is selected from N or CH, or when A7 takes part in the annulated carbo- or heterocycle Z, in particular a 5, 6, or 7 membered carbo- or heterocycle, then A7 is C;

L2 is selected from the group consisting of -CH₂-R₄, -CF₂-R₄, -CH₂-CH₂-R₄, -CH₂-CH₂-CH₂-R₄, -O-R₄, -NH-R₄, -N=R₄;

L3 is selected from the group consisting of CH₂-R₉, -CF₂-R₉, -CH₂-CH₂-R₉, -CH₂-CF₂-R₉, -CH₂-CH₂-CH₂-R₉, -O-R₉, -NH-R₉, -N=R₉;

or

L2 and L3 together with the A8 to which they are connected form a 5- or 6-membered heterocycle substituted by R₄ and/or R₉;

L4 is CH₂, -CF₂-, CH₂-CH₂-, CH₂-CH₂-CH₂-, O, N, and NH, or is absent;

Z is a 5-, 6- or 7-membered carbo- or heterocycle, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;

and can be annulated to the central core or connected via a covalent bond

R₄ is 5-, 6- or 7-membered carbo- or heterocycle, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -CF₃, Me, Et, -OMe, and -SMe, or R₄ is hydrogen, methyl, or COOH;

R₉ is a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered carbo- or heterocycle, optionally substituted with one, two, or three (preferably one) substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe;

R₆ is a 5-, 6- or 7-membered carbo- or heterocycle, optionally substituted with one, two, or three (preferably one) substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe;

or R6 is H;

or

when A7 takes part in the annulated carbo- or heterocycle Z then A5 and A6 are independently selected from -N or -CH and A8 is selected from -N, -CH, -CH₂-N, -CH₂-CH, or -NH-CH;

- 5 or pharmaceutically acceptable salt, isomers, solvate, chemically protected form, or prodrugs thereof for use in treating or ameliorating a proliferative disease in a patient in combination with an inhibitor of Topoisomerase I, Topoisomerase II, ATM, ATR, Wee1, BRD and/or MEK, with mitomycin C, paclitaxel, an antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor, such as trastuzumab deruxtecan, or with ionizing radiation.

10

Preferred embodiments of the inhibitor of ALC1 (ALC1i) according to formula (I)

The ALC1i according to Formula (I) preferably shows inhibition >50% at concentrations at or below 250 μM, preferably has an IC₅₀ of < 250 μM, and more preferably of < 25 μM. The IC₅₀ is preferably measured in a FRET based nucleosome remodeling assay as described in WO 2022/117782 A1.

- 15 The ALC1i according to Formula (I) preferably has an EC₅₀ of < 250 μM, preferably of < 50 μM; and more preferably of < 10 μM. The EC₅₀ is preferably measured in cell proliferation assay with an SRB based readout as described in WO 2022/117782 A1.

If not specifically indicated otherwise, the residues with normal, i.e. not subscript, integers, relate to compounds of formula (I), those residues with subscript integers relate to compounds of formula (II).

- 20 In an embodiment, it is preferred that in the inhibitor of ALC1 (ALC1i) according to formula (I): A5 and A6 are N; and

A7 takes part in the annulated carbo- or heterocycle Z, in particular a 5, 6, or 7 membered carbo- or heterocycle Z, preferably carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂.

- 25 In an embodiment it is preferred that in the inhibitor of ALC1 (ALC1i) according to formula (I): A5 and A6 are N;

A7 takes part in the annulated carbo- or heterocycle, preferably carbocycle Z, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂; and

- 30 A8 is -CH₂-N, -CH₂-CH, or -NH-CH, preferably -NH-CH.

In an embodiment it is preferred that in the inhibitor of ALC1 (ALC1i) according to formula (I): A5 is N and A8 is -N or -CH.

- In an embodiment it is preferred that in the inhibitor of ALC1 (ALC1i) according to formula (I): A5 is N and A8 is -N or -CH; and

A6 takes part in the annulated carbo- or heterocycle, preferably carbocycle Z.

In a particularly preferred embodiment A5, A7 and A8 are N.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 takes part in the annulated carbo- or heterocycle Z, in particular a 5, 6, or 7 membered carbo- or heterocycle Z, preferably carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, which optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂.

10 In an embodiment it is preferred that in the inhibitor of ALC1 (ALC1i) according to formula (I):

L2 is selected from the group consisting of -CH₂-R₄, -CH₂-CH₂- R₄, -CH₂-CH₂-CH₂-R₄.

In an embodiment it is preferred that:

L2 is selected from the group consisting of -CH₂-R₄, -CF₂- R₄, -CH₂-CH₂-R₄, -CH₂-CH₂-CH₂-R₄, -NH-R₄; and

15 R₄ is 6-membered aryl or 5-, 6- or 7-membered heteroaryl, preferably 5- or 6 -membered heteroaryl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -CF₃, Me, Et, -OMe, and -SMe, or R₄ is hydrogen, methyl, or COOH.

In an embodiment it is preferred that:

L3 is selected from the group consisting of -CH₂-R₉, -CH₂-CH₂- R₉, and -CH₂-CF₂-R₉.

20 In an embodiment it is preferred that:

L3 is selected from the group consisting of -CH₂-R₉, -CH₂-CH₂- R₉, -CH₂-CF₂-R₉; and

R₉ is a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered carbo- or heterocycle, optionally substituted with one, two, or three (preferably one) substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe.

25 In an embodiment it is preferred that in the inhibitor of ALC1 (ALC1i) according to formula (I):

L2 and L3 together with the A8 to which they are connected form a 5- or 6-membered heterocycle substituted by R₄ and R₉.

In an embodiment it is preferred that:

L2 and L3 together with the A8 to which they are connected form a 5- or 6-membered heterocycle substituted by R₄ and R₉;

30 R₄ is hydrogen, methyl, or COOH; and

R₉ is a 4-, 5-, 6-, 7-membered carbo- or heterocycle, preferably phenyl or 5- or 6-membered heteroaryl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe.

35 In an embodiment it is preferred that in the inhibitor of ALC1 (ALC1i) according to formula (I):

L4 is absent.

In a particularly preferred embodiment A5, A7 and A8 are N; and

L4 is absent.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbo- or heterocycle Z, in particular a 5, 6, or 7 membered carbo- or heterocycle Z, preferably carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, which optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂; and

5 L4 is absent.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂; and

10 L4 is absent.

In a particularly preferred embodiment A5, A7 and A8 are N; and

L4 is absent

R6 is a 6 membered aryl or 5-, 6- or 7-membered heteroaryl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

15

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbo- or heterocycle Z, in particular a 5, 6, or 7 membered carbo- or heterocycle Z, preferably carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, which optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂; and

20 L4 is absent

R6 is a 6 membered aryl or 5-, 6- or 7-membered heteroaryl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

25

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂; and

30 L4 is absent

R6 is a 6 membered aryl or 5-, 6- or 7-membered heteroaryl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N; and

35 L4 is absent

R6 is phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbo- or heterocycle Z, in particular a 5, 6, or 7 membered carbo- or heterocycle Z, preferably carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, which optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;

L4 is absent; and

R6 is phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;

L4 is absent; and

R6 is a phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, which is optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;

L4 is absent; and

R6 is phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, which is optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;

L4 is absent; and

R6 is a phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In an embodiment it is preferred that:

R4 is hydrogen, methyl, COOH or tetrazolyl.

In an embodiment it is preferred that:

L2 is -CH₂-R4, -CH₂-CH₂-R4, -CH₂-CH₂-CH₂-R4; and

R4 is hydrogen, methyl, COOH or tetrazolyl.

In an embodiment it is preferred that:

R9 is any 4-, 5-, 6- 7-, 8-, 9-, or 10-membered carbo- or heterocycle, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -CF₃, Me, Et, -OMe, and -SMe.

In an embodiment it is preferred that:

- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe.

In an embodiment it is preferred that:

- L3 is selected from the group consisting of -CH₂-R₉, -CH₂-CH₂-R₉, -CH₂-CF₂-R₉; and
 R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe.

In an embodiment it is preferred that:

- R6 is a 6 membered aryl or 5-, 6- or 7-membered heteroaryl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe
 or R6 is H.

In an embodiment it is preferred that:

- L4 is absent; and
 R6 is a 5-, or 6-membered carbo- or heterocycle, preferably 6-membered carbo- or heterocycle, optionally substituted with one, two, or three (preferably one) substituents selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In above embodiment it is preferred that:

- Z is a 6 membered aryl, or a 5-, 6-membered heteroaryl, preferably phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂.

In an embodiment, it is preferred that:

- A5 is N;

one of A6 and A7 is CH and the other one is N; or one of A6 and A7 is C and takes part in the annulated carbo- or heterocycle Z and the other one is N;

A8 is N or CH;

L2, L3, L4 are independently from each other selected from the group consisting of CH₂, -CF₂-, CH₂-

5 CH₂, CH₂-CH₂-CH₂, O, N, and NH, or are absent, or L2 and L3 together with the A8 to which they are connected form a 5- or 6-membered heterocycle substituted by R4 and R9;

Z is any 5-, 6- or 7-membered carbo- or heterocycle and can be annulated to the central core or connected via a covalent bond and optionally substituted with one, two, or three (preferably one) substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;

R4 is any 5-, 6- or 7-membered carbo- or heterocycle, optionally substituted with one, two, or three (preferably one) substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -CF₃, Me, Et, -OMe, and -SMe, or R4 is hydrogen, methyl, or COOH;

15 R9 is a 4-, 5-, 6- 7-, 8-, 9-, or 10-membered carbo- or heterocycle, optionally substituted with one, two, or three (preferably one) substituents selected from the group consisting of -Br, -Cl, -F, -I, -CF₃, Me, Et, -OMe, and -SMe;

R6 is a 5-, 6- or 7-membered carbo- or heterocycle, optionally substituted with one, two, or three (preferably one) substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe, or R6 is H

or

when A7 takes part in the annulated carbo- or heterocycle Z then A5 and A6 are N and A8 is selected from -N, -CH, -CH₂-N, -CH₂-CH, or -NH-CH, preferably -CH₂-N, -CH₂-CH, or -NH-CH;

25 wherein R4, R9, and R6.

In an embodiment it is preferred that:

A5 is N;

one of A6 and A7 is C and takes part in the annulated carbo- or heterocycle Z and the other one is N;

A8 is N;

30 L2 is CH₂-CH₂ and L3 is CH₂-CH₂ or CH₂-CF₂; or L2 and L3 together with the A8 to which they are connected form a 5- or 6-membered heterocycle (preferably piperidine or a pyrrolidine) substituted by R4 and R9;

L4 is absent;

35 Z is a 6-membered carbo- or heterocycle annulated to the central core, wherein Z is optionally substituted with one, two, or three (preferably one) substituents selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and NO₂;

R4 is COOH or CH₂N₄;

- R9 is a 4-, 5-, 6-, 7-, or 10-membered carbo- or heterocycle, optionally substituted with one, two, or three, preferably one) substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
- R6 is a 5- or 6-membered carbo- or heterocycle, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe,
 5 or R6 is H.
- In an embodiment it is preferred that in the inhibitor of ALC1 (ALC1i) according to formula (I):
 each one of A5, A7 and A8 is N;
- 10 A6 is C and takes part in the annulated carbo- or heterocycle Z, preferably 5-, 6- or 7-membered carbo- or heterocycle, optionally substituted with one, two, or three (preferably one) substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe;
- L2 is CH₂-CH₂-R4;
- L3 is CH₂-CH₂-R4 or -CH₂-CF₂-R9;
- 15 or L2 and L3 together with the A8 to which they are connected form a piperidine ring or a pyrrolidine ring, substituted by R4 and R9;
- L4 is absent;
- Z is phenyl or cyclohexyl annulated to the central core, wherein Z is optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -OH,
 20 Me, -CF₃, -OMe, and -NO₂;
- R4 is COOH or tetrazolyl;
- R9 is phenyl, cyclobutyl, cyclopentyl or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -CF₃, Me, -CH₂-CF₃, and -OMe;
- 25 R6 is a 6-membered carbo- or heterocycle, preferably phenyl or cyclohexyl; more preferably phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of Br, -Cl, -F, Me, -CF₃, -OMe, and -NO₂.
- In a particularly preferred embodiment A5, A7 and A8 are N;
- L2 is -CH₂-R4, -CH₂-CH₂- R4, -CH₂-CH₂-CH₂-R4;
- 30 R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH; and
- L4 is absent.
- In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbo- or heterocycle Z, in particular a 5, 6, or 7 membered carbo- or heterocycle Z, preferably carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, which optionally substituted with one, two,
 35 or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;
- L2 is -CH₂-R4, -CH₂-CH₂- R4, -CH₂-CH₂-CH₂-R4;
- R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH; and

L4 is absent.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br,

5 -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂; and

L4 is absent.

In a particularly preferred embodiment A5, A7 and A8 are N;

L2 is -CH₂-R₄, -CH₂-CH₂- R₄, -CH₂-CH₂-CH₂-R₄;

R₄ is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;

10 L4 is absent; and

R₆ is a phenyl or 5-, 6- or 7-membered heteroaryl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

15 In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbo- or heterocycle Z, in particular a 5, 6, or 7 membered carbo- or heterocycle Z, preferably carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, which optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;

L2 is -CH₂-R₄, -CH₂-CH₂- R₄, -CH₂-CH₂-CH₂-R₄;

20 R₄ is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;

L4 is absent; and

R₆ is a 6 membered aryl or 5-, 6- or 7-membered heteroaryl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

25 In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;

L2 is -CH₂-R₄, -CH₂-CH₂- R₄, -CH₂-CH₂-CH₂-R₄;

30 R₄ is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;

L4 is absent; and

R₆ is a 6 membered aryl or 5-, 6- or 7-membered heteroaryl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

35 In a particularly preferred embodiment A5, A7 and A8 are N;

L2 is -CH₂-R₄, -CH₂-CH₂- R₄, -CH₂-CH₂-CH₂-R₄;

R₄ is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;

L4 is absent; and

R6 is phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbo- or heterocycle Z, in particular a 5, 6, or 7 membered carbo- or heterocycle Z, preferably carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, which optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;

L2 is -CH₂-R₄, -CH₂-CH₂- R₄, -CH₂-CH₂-CH₂-R₄;

R₄ is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;

10 L₄ is absent; and

R6 is phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;

L2 is -CH₂-R₄, -CH₂-CH₂- R₄, -CH₂-CH₂-CH₂-R₄;

R₄ is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;

L₄ is absent; and

20 R6 is a phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, which is optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;

L2 is -CH₂-R₄, -CH₂-CH₂- R₄, -CH₂-CH₂-CH₂-R₄;

R₄ is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;

L₄ is absent; and

30 R6 is phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl. which is optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;

35 L2 is -CH₂-R₄, -CH₂-CH₂- R₄, -CH₂-CH₂-CH₂-R₄;

R₄ is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;

L₄ is absent; and

R6 is a phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N;

L4 is absent; and

- 5 R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, 10 spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe.

- In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the 15 annulated carbo- or heterocycle Z, in particular a 5, 6, or 7 membered carbo- or heterocycle Z, preferably carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, which optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;

L4 is absent; and

- 20 R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, 25 spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe.

- In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the 30 annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;

L4 is absent; and

- 35 R9 is C₅ to C₇-cycloalkyl, i.e. C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl,

spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe.

5 In a particularly preferred embodiment A5, A7 and A8 are N;

L4 is absent;

R9 is C₅ to C₇-cycloalkyl, i.e. C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6
 10 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s)
 15 selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
 R6 is a 6 membered aryl or 5-, 6- or 7-membered heteroaryl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the
 20 annulated carbo- or heterocycle Z, in particular a 5, 6, or 7 membered carbo- or heterocycle Z, preferably carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, which optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;

L4 is absent;

25 R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl,
 30 spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
 R6 is a 6 membered aryl or 5-, 6- or 7-membered heteroaryl, optionally substituted with one, two, or
 35 three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, optionally

substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;

L4 is absent;

- 5 R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
- 10 R6 is a 6 membered aryl or 5-, 6- or 7-membered heteroaryl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.
- 15

In a particularly preferred embodiment A5, A7 and A8 are N;

L4 is absent;

- 20 R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
- 25 R6 is phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

- 30 In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbo- or heterocycle Z, in particular a 5, 6, or 7 membered carbo- or heterocycle Z, preferably carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, which optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;

L4 is absent;

- 35 R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe;

more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and

R6 is phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;

L4 is absent;

R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and

R6 is a phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, which is optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;

L4 is absent;

R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and

R6 is phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, which is optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;

L4 is absent;

R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and

R6 is a phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N; and

L3 is selected from the group consisting of -CH₂-R9, -CH₂-CH₂-R9, and -CH₂-CF₂-R9

L4 is absent; and

R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbo- or heterocycle Z, in particular a 5, 6, or 7 membered carbo- or heterocycle Z, preferably carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, which optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;

L3 is selected from the group consisting of -CH₂-R9, -CH₂-CH₂-R9, and -CH₂-CF₂-R9;

L4 is absent; and

- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe.
- 10 In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂; and
- L3 is selected from the group consisting of -CH₂-R₉, -CH₂-CH₂- R₉, and -CH₂-CF₂-R₉;
- 15 L4 is absent; and
- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, i.e. C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe.
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- 25 In a particularly preferred embodiment A5, A7 and A8 are N;
- L3 is selected from the group consisting of -CH₂-R₉, -CH₂-CH₂- R₉, and -CH₂-CF₂-R₉;
- L4 is absent;
- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, i.e. C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
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- 35

- R6 is a 6 membered aryl or 5-, 6- or 7-membered heteroaryl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.
- In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbo- or heterocycle Z, in particular a 5, 6, or 7 membered carbo- or heterocycle Z, preferably carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, which optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;
- L3 is selected from the group consisting of -CH₂-R9, -CH₂-CH₂- R9, and -CH₂-CF₂-R9;
- L4 is absent; and
- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
- R6 is a 6 membered aryl or 5-, 6- or 7-membered heteroaryl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.
- In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;
- L3 is selected from the group consisting of -CH₂-R9, -CH₂-CH₂- R9, and -CH₂-CF₂-R9;
- L4 is absent; and
- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe
- R6 is a 6 membered aryl or 5-, 6- or 7-membered heteroaryl, optionally substituted with one, two, or three,

preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N;

- L3 is selected from the group consisting of -CH₂-R₉, -CH₂-CH₂- R₉, and -CH₂-CF₂-R₉;
- 5 L4 is absent;
- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe;
- 10 more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
- 15 R6 is phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

- In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbo- or heterocycle Z, in particular a 5, 6, or 7 membered carbo- or heterocycle Z, preferably carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, which optionally substituted with one, two,
- 20 or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂; and

- L3 is selected from the group consisting of -CH₂-R₉, -CH₂-CH₂- R₉, and -CH₂-CF₂-R₉;
- L4 is absent;
- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe;
- 25 more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
- 30 R6 is phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

- 35 In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂; and

- L3 is selected from the group consisting of -CH₂-R₉, -CH₂-CH₂- R₉, and -CH₂-CF₂-R₉;
 L4 is absent;
 R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
 R6 is a phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, which is optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂; and

- L3 is selected from the group consisting of -CH₂-R₉, -CH₂-CH₂- R₉, and -CH₂-CF₂-R₉;
 L4 is absent; and
 R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe
 R6 is phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, which is optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂; and

- L3 is selected from the group consisting of -CH₂-R₉, -CH₂-CH₂- R₉, and -CH₂-CF₂-R₉;
 L4 is absent;
 R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or

- 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
- 5 R6 is a phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.
- 10 In a particularly preferred embodiment A5, A7 and A8 are N; and
- L2 is selected from the group consisting of -CH₂-R4, -CH₂-CH₂- R4, and -CH₂-CH₂-CH₂-R4;
- L3 is selected from the group consisting of -CH₂-R9, -CH₂-CH₂- R9, and -CH₂-CF₂-R9;
- L4 is absent; and
- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-
- 15 , C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe.
- 20 In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbo- or heterocycle Z, in particular a 5, 6, or 7 membered carbo- or heterocycle Z, preferably carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, which optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;
- 25 L2 is selected from the group consisting of -CH₂-R4, -CH₂-CH₂- R4, and -CH₂-CH₂-CH₂-R4;
- L3 is selected from the group consisting of -CH₂-R9, -CH₂-CH₂- R9, and -CH₂-CF₂-R9;
- 30 L4 is absent; and
- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe;
- 35 more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe,

more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe.

- In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂; and
- L2 is selected from the group consisting of -CH₂-R₄, -CH₂-CH₂- R₄, and -CH₂-CH₂-CH₂-R₄;
- L3 is selected from the group consisting of -CH₂-R₉, -CH₂-CH₂- R₉, and -CH₂-CF₂-R₉;
- L4 is absent; and
- 10 R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, 15 spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N;

- 20 L2 is selected from the group consisting of -CH₂-R₄, -CH₂-CH₂- R₄, and -CH₂-CH₂-CH₂-R₄;
- L3 is selected from the group consisting of -CH₂-R₉, -CH₂-CH₂- R₉, and -CH₂-CF₂-R₉;
- L4 is absent;
- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 25 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
- 30 R6 is a 6 membered aryl or 5-, 6- or 7-membered heteroaryl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

- 35 In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbo- or heterocycle Z, in particular a 5, 6, or 7 membered carbo- or heterocycle Z, preferably carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, which optionally substituted with one, two,

or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;

L2 is selected from the group consisting of -CH₂-R₄, -CH₂-CH₂- R₄, and -CH₂-CH₂-CH₂-R₄;

L3 is selected from the group consisting of -CH₂-R₉, -CH₂-CH₂- R₉, and -CH₂-CF₂-R₉;

5 L4 is absent; and

R₉ is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and

10 R₆ is a 6 membered aryl or 5-, 6- or 7-membered heteroaryl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂; and

L2 is selected from the group consisting of -CH₂-R₄, -CH₂-CH₂- R₄, and -CH₂-CH₂-CH₂-R₄;

L3 is selected from the group consisting of -CH₂-R₉, -CH₂-CH₂- R₉, and -CH₂-CF₂-R₉;

L4 is absent; and

25 R₉ is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; R₆ is a 6 membered aryl or 5-, 6- or 7-membered heteroaryl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N;

L2 is selected from the group consisting of -CH₂-R₄, -CH₂-CH₂- R₄, and -CH₂-CH₂-CH₂-R₄;

- L3 is selected from the group consisting of -CH₂-R₉, -CH₂-CH₂- R₉, and -CH₂-CF₂-R₉;
 L4 is absent;
 R₉ is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
 R₆ is phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.
- In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbo- or heterocycle Z, in particular a 5, 6, or 7 membered carbo- or heterocycle Z, preferably carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, which optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂; and
- L2 is selected from the group consisting of -CH₂-R₄, -CH₂-CH₂- R₄, and -CH₂-CH₂-CH₂-R₄;
 L3 is selected from the group consisting of -CH₂-R₉, -CH₂-CH₂- R₉, and -CH₂-CF₂-R₉;
 L4 is absent;
 R₉ is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
 R₆ is phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.
- In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂; and
- L2 is selected from the group consisting of -CH₂-R₄, -CH₂-CH₂- R₄, and -CH₂-CH₂-CH₂-R₄;
 L3 is selected from the group consisting of -CH₂-R₉, -CH₂-CH₂- R₉, and -CH₂-CF₂-R₉;

- L4 is absent;
- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, i.e. C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
- R6 is a phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, which is optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂; and

- L2 is selected from the group consisting of -CH₂-R₄, -CH₂-CH₂- R₄, and -CH₂-CH₂-CH₂-R₄;
- L3 is selected from the group consisting of -CH₂-R₉, -CH₂-CH₂- R₉, and -CH₂-CF₂-R₉;
- L4 is absent; and
- R9 is C₅ to C₇-cycloalkyl C₄ to C₇-cycloalkyl, i.e. C₄-, i.e. C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe
- R6 is phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl. which is optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂; and

- L2 is selected from the group consisting of -CH₂-R₄, -CH₂-CH₂- R₄, and -CH₂-CH₂-CH₂-R₄;
- L3 is selected from the group consisting of -CH₂-R₉, -CH₂-CH₂- R₉, and -CH₂-CF₂-R₉;
- L4 is absent;

- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, i.e. C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
- 10 R6 is a phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.
In a particularly preferred embodiment A5, A7 and A8 are N; and
- L3 is selected from the group consisting of -CH₂-R9, -CH₂-CH₂- R9, and -CH₂-CF₂-R9
- L4 is absent; and
- 15 R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;
- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, i.e. C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe.
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- 25 In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbo- or heterocycle Z, in particular a 5, 6, or 7 membered carbo- or heterocycle Z, preferably carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, which optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;
- 30 L3 is selected from the group consisting of -CH₂-R9, -CH₂-CH₂- R9, and -CH₂-CF₂-R9;
- L4 is absent; and
- R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;
- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one
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substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe.

- In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂; and
- L3 is selected from the group consisting of -CH₂-R9, -CH₂-CH₂- R9, and -CH₂-CF₂-R9;
- L4 is absent; and
- R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;
- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe.
- In a particularly preferred embodiment A5, A7 and A8 are N;
- L3 is selected from the group consisting of -CH₂-R9, -CH₂-CH₂- R9, and -CH₂-CF₂-R9;
- L4 is absent;
- R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;
- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
- R6 is a 6 membered aryl or 5-, 6- or 7-membered heteroaryl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbo- or heterocycle Z, in particular a 5, 6, or 7 membered carbo- or heterocycle Z, preferably carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, which optionally substituted with one, two,

or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;

L3 is selected from the group consisting of -CH₂-R₉, -CH₂-CH₂- R₉, and -CH₂-CF₂-R₉;

L4 is absent; and

5 R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;

R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and

10 R6 is a 6 membered aryl or 5-, 6- or 7-membered heteroaryl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂; and

L3 is selected from the group consisting of -CH₂-R₉, -CH₂-CH₂- R₉, and -CH₂-CF₂-R₉;

L4 is absent; and

R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;

25 R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; R6 is a 6 membered aryl or 5-, 6- or 7-membered heteroaryl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N;

L3 is selected from the group consisting of -CH₂-R₉, -CH₂-CH₂- R₉, and -CH₂-CF₂-R₉;

- L4 is absent;
- R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;
- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
- R6 is phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbo- or heterocycle Z, in particular a 5, 6, or 7 membered carbo- or heterocycle Z, preferably carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, which optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂; and

- L3 is selected from the group consisting of -CH₂-R9, -CH₂-CH₂- R9, and -CH₂-CF₂-R9;
- L4 is absent;
- R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;
- R9 C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
- R6 is phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂; and

- L3 is selected from the group consisting of -CH₂-R9, -CH₂-CH₂- R9, and -CH₂-CF₂-R9;
- L4 is absent;

- R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;
- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
- R6 is a phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, which is optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂; and

- L3 is selected from the group consisting of -CH₂-R9, -CH₂-CH₂- R9, and -CH₂-CF₂-R9;
- L4 is absent; and
- R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;
- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe
- R6 is phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl. which is optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂; and

- L3 is selected from the group consisting of -CH₂-R9, -CH₂-CH₂- R9, and -CH₂-CF₂-R9;
- L4 is absent;
- R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;

- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, i.e. C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
- 10 R6 is a phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.
In a particularly preferred embodiment A5, A7 and A8 are N; and
- L2 is selected from the group consisting of -CH₂-R₄, -CH₂-CH₂- R₄, and -CH₂-CH₂-CH₂-R₄;
- L3 is selected from the group consisting of -CH₂-R₉, -CH₂-CH₂- R₉, and -CH₂-CF₂-R₉;
- 15 L4 is absent; and
- R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;
- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, i.e. C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe.
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- 25 In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbo- or heterocycle Z, in particular a 5, 6, or 7 membered carbo- or heterocycle Z, preferably carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, which optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;
- 30
- L2 is selected from the group consisting of -CH₂-R₄, -CH₂-CH₂- R₄, and -CH₂-CH₂-CH₂-R₄;
- L3 is selected from the group consisting of -CH₂-R₉, -CH₂-CH₂- R₉, and -CH₂-CF₂-R₉;
- L4 is absent; and
- R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;
- 35 R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, i.e. C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe;

more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂; and

L2 is selected from the group consisting of -CH₂-R4, -CH₂-CH₂- R4, and -CH₂-CH₂-CH₂-R4;
 L3 is selected from the group consisting of -CH₂-R9, -CH₂-CH₂- R9, and -CH₂-CF₂-R9;
 L4 is absent; and
 R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;
 R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N;

L2 is selected from the group consisting of -CH₂-R4, -CH₂-CH₂- R4, and -CH₂-CH₂-CH₂-R4;
 L3 is selected from the group consisting of -CH₂-R9, -CH₂-CH₂- R9, and -CH₂-CF₂-R9;
 L4 is absent;
 R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;
 R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and

- R6 is a 6 membered aryl or 5-, 6- or 7-membered heteroaryl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.
- In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbo- or heterocycle Z, in particular a 5, 6, or 7 membered carbo- or heterocycle Z, preferably carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, which optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;
- L2 is selected from the group consisting of -CH₂-R4, -CH₂-CH₂- R4, and -CH₂-CH₂-CH₂-R4;
- L3 is selected from the group consisting of -CH₂-R9, -CH₂-CH₂- R9, and -CH₂-CF₂-R9;
- L4 is absent; and
- R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;
- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
- R6 is a 6 membered aryl or 5-, 6- or 7-membered heteroaryl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.
- In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂; and
- L2 is selected from the group consisting of -CH₂-R4, -CH₂-CH₂- R4, and -CH₂-CH₂-CH₂-R4;
- L3 is selected from the group consisting of -CH₂-R9, -CH₂-CH₂- R9, and -CH₂-CF₂-R9;
- L4 is absent; and
- R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;
- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one

substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe. R₆ is a 6 membered aryl or 5-, 6- or 7-membered heteroaryl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N;
L2 is selected from the group consisting of -CH₂-R₄, -CH₂-CH₂- R₄, and -CH₂-CH₂-CH₂-R₄;
L3 is selected from the group consisting of -CH₂-R₉, -CH₂-CH₂- R₉, and -CH₂-CF₂-R₉;
L4 is absent;
R₄ is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;
R₉ is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
R₆ is phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbo- or heterocycle Z, in particular a 5, 6, or 7 membered carbo- or heterocycle Z, preferably carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, which optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;

L2 is selected from the group consisting of -CH₂-R₄, -CH₂-CH₂- R₄, and -CH₂-CH₂-CH₂-R₄;
L3 is selected from the group consisting of -CH₂-R₉, -CH₂-CH₂- R₉, and -CH₂-CF₂-R₉;
L4 is absent;
R₄ is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;
R₉ is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe,

- more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
- R6 is phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.
- 5 In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂; and
- L2 is selected from the group consisting of -CH₂-R4, -CH₂-CH₂- R4, and -CH₂-CH₂-CH₂-R4;
- 10 L3 is selected from the group consisting of -CH₂-R9, -CH₂-CH₂- R9, and -CH₂-CF₂-R9;
- L4 is absent;
- R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;
- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or
- 15 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe,
- 20 more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
- R6 is a phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.
- In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the
- 25 annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, which is optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂; and
- L2 is selected from the group consisting of -CH₂-R4, -CH₂-CH₂- R4, and -CH₂-CH₂-CH₂-R4;
- L3 is selected from the group consisting of -CH₂-R9, -CH₂-CH₂- R9, and -CH₂-CF₂-R9;
- 30 L4 is absent; and
- R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;
- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or
- 35 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe,

- more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe
- R6 is phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.
- 5 In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, which is optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂; and
- L2 is selected from the group consisting of -CH₂-R4, -CH₂-CH₂- R4, and -CH₂-CH₂-CH₂-R4;
- 10 L3 is selected from the group consisting of -CH₂-R9, -CH₂-CH₂- R9, and -CH₂-CF₂-R9;
- L4 is absent;
- R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;
- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or
- 15 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe,
- 20 more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
- R6 is a phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe.
- In a particularly preferred embodiment of the above embodiments:
- 25 R6 is phenyl ortho substituted with a substituent selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe, preferably -Br, -Cl, -F, -I, more preferably Br.
- In a particularly preferred embodiment of the above embodiments:
- L4 is absent; and
- R6 is phenyl ortho substituted with a substituent selected from the group consisting of -Br, -Cl, -F, -I, -
- 30 OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe, preferably -Br, -Cl, -F, -I, more preferably Br.
- In a particularly preferred embodiment A5, A7 and A8 are N;
- L2 is selected from the group consisting of -CH₂-R4, -CH₂-CH₂- R4, and -CH₂-CH₂-CH₂-R4;
- L3 is selected from the group consisting of -CH₂-R9, -CH₂-CH₂- R9, and -CH₂-CF₂-R9;
- L4 is absent;
- 35 R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;
- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one

- substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
- 5 more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
- R6 is phenyl ortho substituted with a substituent selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe, preferably -Br, -Cl, -F, -I, more preferably Br.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbo- or heterocycle Z, in particular a 5, 6, or 7 membered carbo- or heterocycle Z, preferably carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, which optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;

- L2 is selected from the group consisting of -CH₂-R4, -CH₂-CH₂- R4, and -CH₂-CH₂-CH₂-R4;
- 15 L3 is selected from the group consisting of -CH₂-R9, -CH₂-CH₂- R9, and -CH₂-CF₂-R9;
- L4 is absent;
- R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;
- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or
- 20 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
- 25 more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
- R6 is phenyl ortho substituted with a substituent selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe, preferably -Br, -Cl, -F, -I, more preferably Br.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;

- L2 is selected from the group consisting of -CH₂-R4, -CH₂-CH₂- R4, and -CH₂-CH₂-CH₂-R4;
- L3 is selected from the group consisting of -CH₂-R9, -CH₂-CH₂- R9, and -CH₂-CF₂-R9;
- 35 L4 is absent;
- R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;
- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or

- 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
- 5 R6 is phenyl ortho substituted with a substituent selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe, preferably -Br, -Cl, -F, -I, more preferably Br
- 10 In a particularly preferred embodiment A5, A7 and A8 are N;
- L2 is selected from the group consisting of -CH₂-R4, -CH₂-CH₂- R4, and -CH₂-CH₂-CH₂-R4;
- L3 is selected from the group consisting of -CH₂-R9, -CH₂-CH₂- R9, and -CH₂-CF₂-R9;
- L4 is absent;
- R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;
- 15 R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
- 20 R6 is phenyl ortho substituted with a substituent selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe, preferably -Br, -Cl, -F, -I, more preferably Br.
- 25 In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbo- or heterocycle Z, in particular a 5, 6, or 7 membered carbo- or heterocycle Z, preferably carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, which optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;
- 30 L2 is selected from the group consisting of -CH₂-R4, -CH₂-CH₂- R4, and -CH₂-CH₂-CH₂-R4;
- L3 is selected from the group consisting of -CH₂-R9, -CH₂-CH₂- R9, and -CH₂-CF₂-R9;
- L4 is absent;
- R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;
- 35 R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe;

- more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
- 5 R6 is phenyl ortho substituted with a substituent selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe, preferably -Br, -Cl, -F, -I, more preferably Br.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;

- L2 is selected from the group consisting of -CH₂-R4, -CH₂-CH₂- R4, and -CH₂-CH₂-CH₂-R4;
- L3 is selected from the group consisting of -CH₂-R9, -CH₂-CH₂- R9, and -CH₂-CF₂-R9;
- L4 is absent;
- 15 R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;
- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe;
- 20 more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
- 25 R6 is phenyl ortho substituted with a substituent selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe, preferably -Br, -Cl, -F, -I, more preferably Br.

- In a particularly preferred embodiment A5, A7 and A8 are N;
- L2 is selected from the group consisting of -CH₂-R4, -CH₂-CH₂- R4, and -CH₂-CH₂-CH₂-R4;
- L3 is selected from the group consisting of -CH₂-R9, -CH₂-CH₂- R9, and -CH₂-CF₂-R9;
- 30 L4 is absent;
- R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;
- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe;
- 35 more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe,

- more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
- R6 is phenyl ortho substituted with a substituent selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe, preferably -Br, -Cl, -F, -I, more preferably Br.
- 5 In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbo- or heterocycle Z, in particular a 5, 6, or 7 membered carbo- or heterocycle Z, preferably carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, which optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;
- 10 L2 is selected from the group consisting of -CH₂-R4, -CH₂-CH₂- R4, and -CH₂-CH₂-CH₂-R4;
L3 is selected from the group consisting of -CH₂-R9, -CH₂-CH₂- R9, and -CH₂-CF₂-R9;
L4 is absent;
R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;
- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-
15 , C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one
20 substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
- R6 is phenyl ortho substituted with a substituent selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe, preferably -Br, -Cl, -F, -I, more preferably Br.
- 25 In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;
- L2 is selected from the group consisting of -CH₂-R4, -CH₂-CH₂- R4, and -CH₂-CH₂-CH₂-R4;
- 30 L3 is selected from the group consisting of -CH₂-R9, -CH₂-CH₂- R9, and -CH₂-CF₂-R9;
L4 is absent;
R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;
- R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-
35 , C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one

substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and

- 5 R6 is phenyl ortho substituted with a substituent selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe, preferably -Br, -Cl, -F, -I, more preferably Br.

In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl, which is optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;

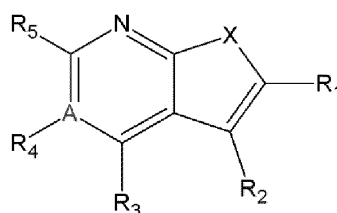
- 10 L2 is selected from the group consisting of -CH₂-R4, -CH₂-CH₂- R4, and -CH₂-CH₂-CH₂-R4;
L3 is selected from the group consisting of -CH₂-R9, -CH₂-CH₂- R9, and -CH₂-CF₂-R9;
L4 is absent;
R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;
R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-
15 , C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one
20 substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
R6 is phenyl ortho substituted with a substituent selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe, preferably -Br, -Cl, -F, -I, more preferably Br.
25 In a particularly preferred embodiment A5, A7 and A8 are N and A6 is C and takes part in the annulated carbocycle Z, in particular a 5, 6, or 7 membered carbocycle Z, preferably phenyl. which is optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂;
L2 is selected from the group consisting of -CH₂-R4, -CH₂-CH₂- R4, and -CH₂-CH₂-CH₂-R4;
30 L3 is selected from the group consisting of -CH₂-R9, -CH₂-CH₂- R9, and -CH₂-CF₂-R9;
L4 is absent;
R4 is hydrogen, methyl, COOH or tetrazolyl, preferably COOH;
R9 is C₄ to C₇-cycloalkyl, i.e. C₄-, C₅-, C₆- or C₇-cycloalkyl, C₆ to C₁₀-bicycloalkyl, i.e. C₆-, C₇-, C₈-
35 , C₉- or C₁₀-bicycloalkyl, C₆ to C₁₀-spiroalkyl, i.e. C₆-, C₇-, C₈-, C₉- or C₁₀-spiroalkyl, phenyl, 5 or 6 membered heteroaryl, adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; more preferably cyclopentyl, cyclohexyl, phenyl, bromo-phenyl, bicyclo[2.2.1]heptyl, spiro[3,3]heptyl, or adamantyl, optionally substituted with one, two, or three, preferably one

substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe, more preferably unsubstituted phenyl or adamantyl substituted with one, or two substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and

- R6 is phenyl ortho substituted with a substituent selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe, preferably -Br, -Cl, -F, -I, more preferably Br.

In a particularly preferred embodiment the inhibitors of ALC1 (ALC1i) according to formula (I) of the first and further aspects of the invention have the specific structures as indicated in Fig. 1.

In the **first aspect**, in a preferred embodiment, the inhibitor of ALC1 (ALC1i) used according to the invention is an inhibitor of ALC1 (ALC1i) according to **Formula (II)**:



Formula (II)

and isomers, salts, solvates, chemically protected forms, and prodrugs thereof, wherein:

X is N or S;

A is C or N;

- R₁ is -CO-OR₆, -CO-R₇, or -CO-NR₆R_A, preferably R₁ is -CO-OR₆;

R₂ is -R₇, -NHR₈, -O-R₇, -C-O-R₇, Br, -C₃₋₈-cycloalkyl (preferably cyclopropyl), or -C₄₋₈-cycloalkenyl (preferably cyclohexenyl);

or

- R₁ and R₂ together form a 5, 6 or 7 membered carbo- or heterocycle, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, =O, [-O-CH₂-CH₂]-NH-CH(OH)-O-tBu, ;

- R₃ is H, =O, -OH, -O-R₇, -R₇, or -(CH₂)_m-L, wherein m is 0, 1 or 2, and L is a 5, 6 or 7 membered carbo- or heterocycle, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, -hydroxyC₁₋₃-alkyl and =O;

R₄ is H or -C₁₋₃-alkyl, preferably H;

- R₅ is -(CH₂)_m-L, or -(CH₂)_m-(CH=CH)-L, wherein m is 0, 1 or 2, preferably 0 or 1, and L is a 5, 6 or 7 membered carbo- or heterocycle, adamantyl, C₁₋₄-alkyl, or -N(CH₃)₂, optionally substituted, preferably with 1, 2, 3 or 4 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -CO-OR₆, -Br, -Cl, -F, -I, -R₉, -O-R₉, =O, and [-O-CH₂-CH₂]_q-NH-biotin with q being 1, 2, 3, or 4, or two adjacent substituents form a 5, 6 or 7 membered carbo- or heterocycle;

or

- R₄ and R₅ together form a 5, 6, or 7 membered carbocycle, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-R₉, -R₉, =CH-R_A, and -CH₂-R_A, preferably R₄ and R₅ together form a C₅₋₇-cycloalkyl;
- R₆ is H, -C₁₋₆-alkyl, -C₂₋₆-alkenyl, -C₂₋₆-alkynyl, optionally substituted, preferably R₆ is H;
- 5 R₇ is -C₁₋₃-alkyl, -C₂₋₃-alkenyl, -C₂₋₃-alkynyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -Br, -Cl, -F, -I, -CH₃, -OCH₃, or -SCH₃;
- R₈ is H or C₁₋₆-alkyl, preferably H,
- R₉ is -C₁₋₆-alkyl, -C₂₋₆-alkenyl, -C₂₋₆-alkynyl, -C₁₋₆-alkyl-aryl, or C₁₋₆-alkyl-heteroaryl (preferably isooxazole, thiazole, tetrazole, 1,2,4-thiadiazole, 1,2,3-thiadiazole, 1,2,5-thiadiazole, pyridine, 1,2,4-
- 10 oxadiazole, pyrazine, or pyrazole), optionally substituted with 1, 2 or 3 substituents selected from the group consisting of -Br, -Cl, -F, -I, -NO₂, -CN, -CONH₂, -CONH-C₁₋₃-alkyl (preferably -CONH-CH₃), -NH-CO-C₁₋₃-alkyl (preferably -NH-CO-CH₃), -C₁₋₆-alkyl (preferably -CH₃, ethyl, propyl, t-butyl, or pentyl), -C₁₋₃-haloalkyl (preferably -CF₃, or -CHF₂), -O-CHF₂, -O-CF₃, carbocycle (preferably cyclopropyl, cyclohexyl or phenyl), -O-carbocycle (preferably phenoxy), heterocycle
- 15 (preferably pyrazolyl), -CO-heterocycle (preferably -CO-(1-pyrrolidinyl)), -SO₂-CH₃, -SO₂-N(CH₃)₂, -O-C₁₋₄-alkyl (preferably -OCH₃), -O-C₁₋₃-alkyl-O-C₁₋₃-alkyl (preferably -O-CH₂-O-CH₃), -SCH₃, or when R₉ is -C₁₋₆-alkyl-aryl, then two adjacent substituents on the aryl moiety can form a 5, 6 or 7 membered carbo- or heterocycle, which is optionally substituted;
- R_A is H, carbo- or heterocycle, optionally substituted, preferably with 1, 2 or 3 substituents independently
- 20 selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -R₉, -O-R₇, -O-(CH₂)_o-R₉, -SO₂NH₂, and =O, wherein o is 0 or 1.

Preferred embodiments of the inhibitor of ALC1 (ALC1i) according to formula (II)

- 25 The ALC1i according to Formula (II) preferably shows inhibition >50% at concentrations at or below 250 μM, preferably has an IC₅₀ of < 250 μM, and more preferably of < 25 μM. The IC₅₀ is preferably measured in a FRET based nucleosome remodeling assay as described in WO 2022/117782 A1.

- The ALC1i according to Formula (II) preferably has an EC₅₀ of < 250 μM, preferably of < 50 μM; and more preferably of < 10 μM. The EC₅₀ is preferably measured in a cell proliferation assay with an SRB
- 30 based readout as described in WO 2022/117782 A1.

When in Formula (II), X is N, this includes the option of X being N-H, and /or when A is N, R₄ may be absent.

In an embodiment, it is preferred that in the inhibitor of ALC1 (ALC1i) according to Formula (II):

- X is N or S;
- 35 A is C or N;
- R₁ is -CO-OR₆, -CO-R₇, or -CO-NR₆R_A, preferably R₁ is -CO-OR₆;
- R₂ is -R₇, -NHR₈, -O-R₇, -C-O-R₇, Br, -C₃₋₈-cycloalkyl (preferably cyclopropyl), or -C₄₋₈-cycloalkenyl (preferably cyclohexenyl);

- or
- R₁ and R₂ together form a 5, 6 or 7 membered carbo- or heterocycle, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, =O, [-O-CH₂-CH₂]-NH-CH(OH)-O-tBu, ;
- 5 R₃ is H, =O, -OH, -O-R₇, -R₇, or -(CH₂)_m-L, wherein m is 0, 1 or 2, and L is a 5, 6 or 7 membered carbo- or heterocycle, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, -hydroxyC₁₋₃-alkyl and =O;
- R₄ is H or -C₁₋₃-alkyl, preferably H;
- 10 R₅ is -(CH₂)_m-L, or -(CH₂)_m-(CH=CH)-L, wherein m is 0, 1 or 2, preferably 0 or 1, and L is a 5, 6 or 7 membered carbo- or heterocycle, adamantyl, C₁₋₄-alkyl, or -N(CH₃)₂, optionally substituted, preferably with 1, 2, 3 or 4 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -CO-OR₆, -Br, -Cl, -F, -I, -R₉, -O-R₉, =O, and [-O-CH₂-CH₂]_q-NH-biotin with q being 1, 2, 3, or 4, or two adjacent substituents form a 5, 6 or 7 membered carbo- or heterocycle;
- 15 or
- R₄ and R₅ together form a 5, 6, or 7 membered carbocycle, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-R₉, -R₉, =CH-R_A, and -CH₂-R_A, preferably R₄ and R₅ together form a C₅₋₇-cycloalkyl;
- R₆ is H, -C₁₋₆-alkyl, -C₂₋₆-alkenyl, -C₂₋₆-alkynyl, optionally substituted, preferably R₆ is H;
- 20 R₇ is -C₁₋₃-alkyl, -C₂₋₃-alkenyl, -C₂₋₃-alkynyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -Br, -Cl, -F, -I, -CH₃, -OCH₃, or -SCH₃;
- R₈ is H or C₁₋₆-alkyl, preferably H,
- R₉ is -C₁₋₆-alkyl, -C₂₋₆-alkenyl, -C₂₋₆-alkynyl, -C₁₋₆-alkyl-aryl, or C₁₋₆-alkyl-heteroaryl (preferably isooxazole, thiazole, tetrazole, 1,2,4-thiadiazole, 1,2,3-thiadiazole, 1,2,5-thiadiazole, pyridine, 1,2,4-oxadiazole, pyrazine, or pyrazole), optionally substituted with 1, 2 or 3 substituents selected from the group consisting of -Br, -Cl, -F, -I, -NO₂, -CN, -CONH₂, -CONH-C₁₋₃-alkyl (preferably -CONH-CH₃), -NH-CO-C₁₋₃-alkyl (preferably -NH-CO-CH₃), -C₁₋₆-alkyl (preferably -CH₃, ethyl, propyl, t-butyl, or pentyl), -C₁₋₃-haloalkyl (preferably -CF₃, or -CHF₂), -O-CHF₂, -O-CF₃, carbocycle (preferably cyclopropyl, cyclohexyl or phenyl), -O-carbocycle (preferably phenoxy), heterocycle (preferably pyrazolyl), -CO-heterocycle (preferably -CO-(1-pyrrolidinyl)), -SO₂-CH₃, -SO₂-N(CH₃)₂, -O-C₁₋₄-alkyl (preferably -OCH₃), -O-C₁₋₃-alkyl-O-C₁₋₃-alkyl (preferably -O-CH₂-O-CH₃), -SCH₃, or when R₉ is -C₁₋₆-alkyl-aryl, then two adjacent substituents on the aryl moiety can form a 5, 6 or 7 membered carbo- or heterocycle, which is optionally substituted;
- 25 30
- R_A is H, carbo- or heterocycle, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -R₉, -O-R₇, -O-(CH₂)_o-R₉, -SO₂NH₂, and =O, wherein o is 0 or 1.
- 35

According to the invention, it is preferred that in the inhibitor of ALC1 (ALC1i) according to formula (II):

X is N or S;

A is C or N;

5 R₁ is -CO-OR₆, -CO-R₇, or -CO-NR₆R_A, preferably R₁ is -CO-OR₆;

R₂ is -R₇, -NHR₈, -O-R₇, -C-O-R₇;

or

R₁ and R₂ together form a 5, 6 or 7 membered carbo- or heterocycle, optionally substituted, preferably with

1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and =O;

R₃ is H, =O, -OH, -O-R₇, -R₇, or -(CH₂)_m-L, wherein m is 0, 1 or 2, and L is a 5, 6 or 7 membered carbo- or heterocycle, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, -hydroxyC₁₋₃-alkyl and =O;

15 R₄ is H or -C₁₋₃-alkyl, preferably H;

R₅ is -(CH₂)_m-L, or -(CH₂)_m-(CH=CH)-L, wherein m is 0, 1 or 2, preferably 0 or 1, and L is a 5, 6 or 7 membered carbo- or heterocycle, or adamantyl, optionally substituted, preferably with 1, 2, 3 or 4 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -CO-OR₆, -Br, -Cl, -F, -I, -R₉, -O-R₉, and =O, or two adjacent substituents form a 5, 6 or 7 membered carbo- or heterocycle;

or

R₄ and R₅ together form a 5, 6, or 7 membered carbocycle, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-R₉, -R₉, =CH-R_A, preferably R₄ and R₅ together form a C₅₋₇-cycloalkyl;

25 R₆ is H, -C₁₋₆-alkyl, i.e. C₁-, C₂-, C₃-, C₄-, C₅- or C₆-alkyl, -C₂₋₆-alkenyl, i.e. C₂-, C₃-, C₄-, C₅- or C₆-alkenyl, -C₂₋₆-alkynyl, i.e. C₂-, C₃-, C₄-, C₅- or C₆-alkynyl, optionally substituted, preferably R₆ is H;

R₇ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-alkynyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -Br, -Cl, -F, -I, -CH₃, -OCH₃, or -SCH₃;

30 R₈ is H or C₁₋₆-alkyl, preferably H,

R₉ is -C₁₋₆-alkyl, i.e. C₁-, C₂-, C₃-, C₄-, C₅- or C₆-alkyl, -C₂₋₆-alkenyl, i.e. C₂-, C₃-, C₄-, C₅- or C₆-alkenyl, -C₂₋₆-alkynyl, i.e. C₂-, C₃-, C₄-, C₅- or C₆-alkynyl, or -C₁₋₆-alkyl-aryl, i.e. C₁-, C₂-, C₃-, C₄-, C₅- or C₆-alkyl-aryl, optionally substituted with 1, 2 or 3 substituents selected from the group consisting of -Br, -Cl, -F, -I, -CH₃, -OCH₃, or -SCH₃

35 R_A is H, carbo- or heterocycle, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -R₉, -O-R₇, -O-(CH₂)_o-R₉, -SO₂NH₂, and =O, wherein o is 0 or 1.

In a preferred embodiment of the invention, X is N.

In a preferred embodiment of the invention, A is C.

In a preferred embodiment of the invention R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-, -alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H;

In a preferred embodiment of the invention, R₁ is -CO-OH.

In a preferred embodiment of the invention, X is N and R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H.

10 In a preferred embodiment of the invention, A is C and R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H.

In a preferred embodiment of the invention, X is N, A is C and R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-, -alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H.

15 i.e. C₂-, C₃-optionally substituted, preferably R₆ is H.

In a preferred embodiment of the invention, X is N, A is C and R₁ is -CO-OH or -CO-NH₂.

In a preferred embodiment of the invention, R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H.

In a preferred embodiment of the invention, X is N and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H.

20 preferably H.

In a preferred embodiment of the invention, A is C and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H.

In a preferred embodiment of the invention, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-, -alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H.

25 optionally substituted, preferably R₆ is H and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H.

In a preferred embodiment of the invention, R₁ is -CO-OH and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H.

In a preferred embodiment of the invention, X is N and R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H.

30 optionally substituted, preferably R₆ is H and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H.

In a preferred embodiment of the invention, A is C and R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H.

In a preferred embodiment of the invention, X is N, A is C and R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-, -alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H.

35 preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-, -alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H.

In a preferred embodiment of the invention, X is N, A is C and R₁ is -CO-OH or -CO-NH₂ and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H.

In a preferred embodiment of the invention, R₁ and R₂ together form a 6 membered aryl or heteroaryl moiety, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and =O, preferably -OH and =O.

In a preferred embodiment of the invention, X is N, and R₁ and R₂ together form a 6 membered aryl or heteroaryl moiety, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and =O, preferably -OH and =O.

In a preferred embodiment of the invention, A is C, and R₁ and R₂ together form a 6 membered aryl or heteroaryl moiety, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and =O, preferably -OH and =O.

In a preferred embodiment of the invention, X is N, A is C and R₁ and R₂ together form a 6 membered aryl or heteroaryl moiety, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and =O, preferably -OH and =O.

In a preferred embodiment of the invention, R₁ and R₂ together form an uracil or 3-deazauracil.

In a preferred embodiment of the invention, X is N, R₁ and R₂ together form an uracil or 3-deazauracil.

In a preferred embodiment of the invention, A is C, and R₁ and R₂ together form an uracil or 3-deazauracil.

In a preferred embodiment of the invention, X is N, A is C and R₁ and R₂ together form an uracil or 3-deazauracil.

In a preferred embodiment of the invention, R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, R₁ is -CO-OH and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-alkynyl, optionally substituted, preferably R₆ is H and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, A is C, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, A is C, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-, -alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, A is C, R₁ is -CO-OH or -CO-NH₂ and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, A is C, R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-, -alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl,

preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, R₁ is -CO-OH and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, A is C, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, A is C, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-, -alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, A is C, R₁ is -CO-OH or -CO-NH₂ and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, R₁ and R₂ together form a 6 membered aryl or heteroaryl moiety, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and =O, preferably -OH and =O and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, R₁ and R₂ together form a 6 membered aryl or heteroaryl moiety, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and =O, preferably -OH and =O and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, A is C, R₁ and R₂ together form a 6 membered aryl or heteroaryl moiety, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and =O, preferably -OH and =O and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, A is C, R₁ and R₂ together form a 6 membered aryl or heteroaryl moiety, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and =O, preferably -OH and =O and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, R₁ and R₂ together form an uracil or 3-deazauracil and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, R₁ and R₂ together form an uracil or 3-deazauracil and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, A is C, R₁ and R₂ together form an uracil or 3-deazauracil and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, A is C, R₁ and R₂ together form an uracil or 3-deazauracil and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, R₁ is -CO-OH and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, A is C, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, A is C, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-, -alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, A is C, R₁ is -CO-OH or -CO-NH₂ R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents

independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, A is C, R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-, -alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H, R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, R₁ is -CO-OH, R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, A is C, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, A is C, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-, -alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl,

preferably H and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

5 In a preferred embodiment of the invention, X is N, A is C, R₁ is -CO-OH or -CO-NH₂ and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

10 In a preferred embodiment of the invention, R₁ and R₂ together form a 6 membered aryl or heteroaryl moiety, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and =O, preferably -OH and =O and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently
15 selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, R₁, R₂ together form a 6 membered aryl or
20 heteroaryl moiety, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and =O, preferably -OH and =O and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl and
25 R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, A is C, R₁ and R₂ together form a 6 membered aryl or heteroaryl moiety, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from
30 the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and =O, preferably -OH and =O and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered
35 heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, A is C, R₁ and R₂ together form a 6 membered aryl or heteroaryl moiety, optionally substituted, preferably with 1, 2 or 3 substituents independently

selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and =O, preferably -OH and =O and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, R₁ and R₂ together form an uracil or 3-deazauracil and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, and R₁ and R₂ together form an uracil or 3-deazauracil and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, A is C, R₁ and R₂ together form an uracil or 3-deazauracil and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, A is C, R₁ and R₂ together form an uracil or 3-deazauracil and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5-hydroxymethyl phenyl, CF₂H, or CF₃.

In a preferred embodiment of the invention, R₁ is -CO-OH and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃.

In a preferred embodiment of the invention, X is N, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-
5 optionally substituted, preferably R₆ is H and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃.

In a preferred embodiment of the invention, A is C, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-
10 optionally substituted, preferably R₆ is H and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃.

In a preferred embodiment of the invention, X is N, A is C, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-, -alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5
hydroxymethyl phenyl, CF₂H, or CF₃.

15 In a preferred embodiment of the invention, X is N, A is C, R₁ is -CO-OH or -CO-NH₂ and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃.

In a preferred embodiment of the invention, R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃.

In a preferred embodiment of the invention, X is N, R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃.
20

In a preferred embodiment of the invention, A is C, R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃.

In a preferred embodiment of the invention, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-, -alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-
25 optionally substituted, preferably R₆ is H and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃.

In a preferred embodiment of the invention, R₁ is -CO-OH, R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃.

In a preferred embodiment of the invention, X is N, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-
30 optionally substituted, preferably R₆ is H and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃.

In a preferred embodiment of the invention, A is C, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-
35 optionally substituted, preferably R₆ is H and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃.

In a preferred embodiment of the invention, X is N, A is C, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-, -alkenyl, -C₂₋₃-alkynyl,

i.e. C₂-, C₃-optionally substituted, preferably R₆ is H and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃.

In a preferred embodiment of the invention, X is N, A is C, R₁ is -CO-OH or -CO-NH₂ and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃.

In a preferred embodiment of the invention, R₁ and R₂ together form a 6 membered aryl or heteroaryl moiety, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and =O, preferably -OH and =O and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃.

In a preferred embodiment of the invention, X is N, R₁ and R₂ together form a 6 membered aryl or heteroaryl moiety, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and =O, preferably -OH and =O and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃.

In a preferred embodiment of the invention, A is C, R₁ and R₂ together form a 6 membered aryl or heteroaryl moiety, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and =O, preferably -OH and =O and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃.

In a preferred embodiment of the invention, X is N, A is C, R₁ and R₂ together form a 6 membered aryl or heteroaryl moiety, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and =O, preferably -OH and =O and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃.

In a preferred embodiment of the invention, R₁ and R₂ together form an uracil or 3-deazauracil and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃.

In a preferred embodiment of the invention, X is N, R₁ and R₂ together form an uracil or 3-deazauracil and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃.

In a preferred embodiment of the invention, A is C, R₁ and R₂ together form an uracil or 3-deazauracil and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃.

In a preferred embodiment of the invention, X is N, A is C and R₁ and R₂ together form an uracil or 3-deazauracil and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃.

In a preferred embodiment of the invention, A is N and R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H.

In a preferred embodiment of the invention, X is N, A is N and R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-, -alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H.

In a preferred embodiment of the invention, X is N, A is N and R₁ is -CO-OH or -CO-NH₂.

In a preferred embodiment of the invention, A is N and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H.

In a preferred embodiment of the invention, A is N and R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃- optionally substituted, preferably R₆ is H and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H.

In a preferred embodiment of the invention, X is N, A is N and R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-, -alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H.

In a preferred embodiment of the invention, X is N, A is N and R₁ is -CO-OH or -CO-NH₂ and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H.

In a preferred embodiment of the invention, A is N, and R₁ and R₂ together form a 6 membered aryl or heteroaryl moiety, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and =O, preferably -OH and =O.

In a preferred embodiment of the invention, X is N, A is N and R₁ and R₂ together form a 6 membered aryl or heteroaryl moiety, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and =O, preferably -OH and =O.

In a preferred embodiment of the invention, A is N, and R₁ and R₂ together form an uracil or 3-deazauracil.

In a preferred embodiment of the invention, X is N, A is N and R₁ and R₂ together form an uracil or 3-deazauracil.

In a preferred embodiment of the invention, A is N, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃- optionally substituted, preferably R₆ is H and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, A is N, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-, -alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, A is N, R₁ is -CO-OH or -CO-NH₂ and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, A is N, R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, A is N, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, A is N, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-, -alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, A is N, R₁ is -CO-OH or -CO-NH₂ and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, A is N, R₁ and R₂ together form a 6 membered aryl or heteroaryl moiety, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and =O, preferably -OH and =O and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, A is N, R₁ and R₂ together form a 6 membered aryl or heteroaryl moiety, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and =O, preferably -OH and =O and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, A is N, R₁ and R₂ together form an uracil or 3-deazauracil and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, A is N, R₁ and R₂ together form an uracil or 3-deazauracil and R₃ is H, =O, -OH, -R₇, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5, 6 or 7 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, A is N, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, A is N, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-, -alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, A is N, R₁ is -CO-OH or -CO-NH₂, R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, A is N, R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-, -alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H, R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, R₁ is -CO-OH, R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, A is N, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, A is N, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-, -alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, A is N, R₁ is -CO-OH or -CO-NH₂ and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, A is N, R₁ and R₂ together form a 6 membered aryl or heteroaryl moiety, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and =O, preferably -OH and =O and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, A is N, R₁ and R₂ together form a 6 membered aryl or heteroaryl moiety, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and =O, preferably -OH and =O and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, A is N, R₁ and R₂ together form an uracil or 3-deazauracil and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, X is N, A is N, R₁ and R₂ together form an uracil or 3-deazauracil and R₃ is -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-alkyl, or -(CH₂)_m-L, wherein m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and -hydroxyC₁₋₃-alkyl.

In a preferred embodiment of the invention, A is N, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃.

In a preferred embodiment of the invention, X is N, A is N, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-, -alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃.

In a preferred embodiment of the invention, X is N, A is N, R₁ is -CO-OH or -CO-NH₂ and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃.

In a preferred embodiment of the invention, A is N, R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃.

In a preferred embodiment of the invention, A is N, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-

optionally substituted, preferably R₆ is H and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃.

In a preferred embodiment of the invention, X is N, A is N, R₁ is -CO-OR₆, or -CO-NR₆R_A preferably R₆ is H, -C₁₋₃-alkyl, i.e. C₁-, C₂-, C₃-, -alkyl, -C₂₋₃-alkenyl, i.e. C₂-, C₃-, -alkenyl, -C₂₋₃-alkynyl, i.e. C₂-, C₃-optionally substituted, preferably R₆ is H and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃.

In a preferred embodiment of the invention, X is N, A is N, R₁ is -CO-OH or -CO-NH₂ and R₂ is -NHR₈, wherein R₈ is H or C₁₋₆-alkyl, preferably H and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃.

In a preferred embodiment of the invention, A is N, R₁ and R₂ together form a 6 membered aryl or heteroaryl moiety, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and =O, preferably -OH and =O and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃.

In a preferred embodiment of the invention, X is N, A is N, R₁ and R₂ together form a 6 membered aryl or heteroaryl moiety, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, and =O, preferably -OH and =O and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃.

In a preferred embodiment of the invention, A is N, R₁ and R₂ together form an uracil or 3-deazauracil and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃.

In a preferred embodiment of the invention, X is N, A is N and R₁ and R₂ together form an uracil or 3-deazauracil and R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃.

In a preferred embodiment of the invention, R₅ is -(CH₂)_m-L, , wherein m is 0, or 1 or -(CH₂)-(CH=CH)-L and L is phenyl or a 5, or 6 membered heteroaryl, or adamantyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -CO-OR₆, -Br, -Cl, -F, -I, -R₉, -O-R₉, and =O, or two adjacent substituents form a 5, 6 or 7 membered carbo- or heterocycle.

In a preferred embodiment of the invention, R₄ and R₅ together form a 5 or 6 membered non-substituted or mono substituted heterocycloalkyl, preferably with =CH-R_A substituted at the R₄ position.

In a preferred embodiment of the invention, R_A is a substituted carbocycle with 1 or 2 substituents independently selected from the group consisting of -Br, -Cl, -F, -O-(CH₂)_o-R₉, or -SCH₃, wherein o is 0 or 1.

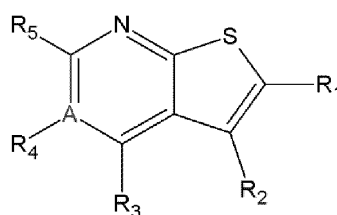
In a preferred embodiment of the invention, R₄ and R₅ together form a 5 or 6 membered non-substituted or mono substituted heterocycloalkyl, preferably with =CH-R_A substituted at the R₄ position, wherein R_A is a substituted carbocycle with 1 or 2 substituents independently selected from the group consisting of -Br, -Cl, -F, -O-(CH₂)_o-R₉, or -SCH₃, wherein o is 0 or 1.

In a preferred embodiment of the invention, R₉ is -C₁₋₄-alkyl, i.e. C₁-, C₂-, C₃-, or C₄-alkyl, -C₂₋₄-alkenyl, i.e. C₂-, C₃-, or C₄-alkenyl, or -C₁₋₆-alkyl-aryl, i.e. C₁-, C₂-, C₃-, C₄-, C₅- or C₆-alkyl-aryl,

optionally substituted with 1 or 2 substituents selected from the group consisting of -Cl, -CH₃, -OCH₃, or -SCH₃.

In a preferred embodiment of the invention, R₅ is -(CH₂)_m-L, , wherein m is 0, or 1 or -(CH₂)-(CH=CH)-L and L is phenyl or a 5, or 6 membered heteroaryl, or adamantyl, optionally substituted,
 5 preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -CO-OR₆, -Br, -Cl, -F, -I, -R₉, -O-R₉, and =O, or two adjacent substituents form a 5, 6 or 7 membered carbo- or heterocycle, wherein R₉ is -C₁₋₄-alkyl, i.e. C₁-, C₂-, C₃-, or C₄-alkyl, -C_{2,4}-alkenyl, i.e. C₂-, C₃-, or C₄-alkenyl, or -C₁₋₆-alkyl-aryl, i.e. C₁-, C₂-, C₃-, C₄-, C₅- or C₆-alkyl-aryl, optionally substituted with 1 or 2 substituents selected from the group consisting of -Cl, -CH₃, -OCH₃, or
 10 -SCH₃.

In a particularly preferred embodiment of the invention, the ALC1i has the structure of Formula (IIa):



Formula (IIa)

and isomers, salts, solvates, chemically protected forms, and prodrugs thereof, wherein:

15 A is C or N;

R₁ is -COOH

R₂ is -CH₃ or -NH₂

or

R₁ and R₂ together form a uracil or 3-deazauracil;

20 R₃ is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF₂H, or CF₃;

R₄ is H

R₅ is -L, or -CH₂-(CH=CH)-L, wherein L is a 6 membered carbo- or heterocycle, or adamantyl, optionally substituted with 1 or 2 substituents independently selected from the group consisting of -OH, -NO₂, -Br, -Cl, -F, CH₃, -O-R₉, and =O, or two adjacent substituents form a 5 or 6 membered
 25 heterocycle;

or

R₄ and R₅ together form a 5 or 6 membered non-substituted or mono substituted heterocycloalkyl, preferably with =CH-R_A substituted at the R₄ position;

R₉ is -C₁₋₄-alkyl, i.e. C₁-, C₂-, C₃-, or C₄-alkyl, -C_{2,4}-alkenyl, i.e. C₂-, C₃-, or C₄-alkenyl, or -C₁₋₆-alkyl-aryl, i.e. C₁-, C₂-, C₃-, C₄-, C₅- or C₆-alkyl-aryl, optionally substituted with 1 or 2 substituents
 30 selected from the group consisting of -Cl, -CH₃, -OCH₃, or -SCH₃;

R_A is a substituted carbocycle with 1 or 2 substituents independently selected from the group consisting of -Br, -Cl, -F, -O-(CH₂)_o-R₉, or -SCH₃, wherein o is 0 or 1.

In a particularly preferred embodiment, the ALC1i of the invention have the specific structures as indicated in Fig. 1.

According to the present invention, the ALC1i are used in combination with an inhibitor of Topoisomerase I, Topoisomerase II, ATM, ATR, Wee1, BRD, and/or MEK, or with mitomycin C, paclitaxel, with ionizing radiation, or with an antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor.

The enzyme topoisomerase I (TOPI) is involved in relaxation of supercoiled DNA. It removes helical constraints that otherwise hinder DNA replication and transcription. Suitable inhibitors of Topoisomerase I are known in the art and are commercially available. Examples for use in accordance with the invention are irinotecan, SN-38, topotecan, camptothecin (NSC-100880) or derivatives thereof, such as hydroxy camptothecine, 7-ethylcamptothecin, or 9-aminocamptothecin, rubitecan, Genz-644282 (CAS No. 529488-28-6), belotecan (CKD-602) hydrochloride, or beta-lapachone. Irinotecan, SN-38, or topotecan are preferred, irinotecan is most preferred (preferably in the form of its active metabolite SN-38).

Topoisomerase II (TOPII) manages DNA tangles and supercoils. It can pass one double helix through another, untangling DNA by cutting both strands of the DNA helix simultaneously. Suitable inhibitors of Topoisomerase II are known in the art and are commercially available. Examples of inhibitors of Topoisomerase II for use in accordance with the invention are teniposide, etoposide, anthracyclines like aclarubicin, epirubicin, idarubicin, doxorubicin, daunorubicin, pirarubicin (NSC-333054), zorubicin, aclarubicin or caminomycin, amonafide, mitoxantrone (NSC-301739), pixantrone maleate, dexrazoxane, ellipticine hydrochloride, phenoxodiol (hagin E), etoposide (VP-16), voreloxin (SNS-595) hydrochloride, and amsacrine. Teniposide and etoposide are preferred.

Ataxia telangiectasia mutant (ATM) is a serine/threonine protein kinase belonging to the phosphatidylinositol 3-kinase-related kinase (PIKK) family of protein kinase. Suitable inhibitors of ATM are known in the art and are commercially available. Examples of inhibitors of ATM for use in accordance with the invention are AZ-32 (CAS No. 2288709-96-4), AZD-0156 (CAS No. 1821428-35-6), AZD-1390 (CAS No. 2089288-03-7), RP-3500 (camonsertib; CAS No. 2417489-10-0), KU-55933 (CAS No. 587871-26-9), KU-60019 (CAS No. 925701-49-1), CP-466722 (CAS No. 1080622-86-1), torin 2 (CAS No. 1223001-51-1), schisandrin B (Sch B) (CAS No. 61281-37-6), AZ20 (CAS No. 1233339-22-4), Berzosertib (VE-822) (CAS No. 1232416-25-9), CGK 733 (CAS No. 905973-89-9), ETP-46464 (CAS No. 1345675-02-6), AZ31 (CAS No. 2088113-98-6), VX-803 (M4344) (CAS No. 1613191-99-3), or M4076 (CAS No. 2495096-26-7). AZ-32, AZD-0156, and AZD-1390 are preferred.

ATR (Ataxia-Telangiectasia Mutated (ATM) and Rad3-related protein kinase) is a serine/threonine protein kinase. Suitable inhibitors of ATR are known in the art and are commercially available. Examples of inhibitors of ATR for use in accordance with the invention are ceralasertib (AZD6738) (CAS No. 1352226-88-0), elimusertib, VX-803 (M4344) (CAS No. 1613191-99-3), AZ20 (CAS No. 1233339-22-4), ETP-46464 (CAS No. 1345675-02-6), Berzosertib (VE-822) (CAS No. 1232416-25-9), Dactolisib (BEZ235) (CAS No. 915019-65-7), VE-821 (CAS No. 1232410-49-9), Schisandrin B (Sch B) (CAS No. 61281-37-6), HAMNO (NSC-111847) (CAS No. 138736-73-9), Torin 2 (CAS No. 1223001-51-1), CGK

733 (CAS No. 905973-89-9), RP-3500 (CAS No. 2417489-10-0), or SKLB-197 (CAS No. 2713577-16-1). Ceralasertib and elimusertib are preferred.

The WEE1 G2 Checkpoint kinase has a crucial role in cell cycle regulation and DNA damage recognition / repair. Suitable inhibitors of WEE1 are known in the art and are commercially available.

5 Examples of inhibitors of WEE1 for use in accordance with the invention are adavosertib (CAS No. 955365-80-7), Zn-C3 (CAS No. 2376146-48-2), PD0166285 (CAS No. 185039-89-8), or Debio 0123 (CAS No. 2243882-74-6). Adavosertib is preferred.

Bromodomains are a family of evolutionarily conserved motifs that bind the acetylated lysines in histone tails and recruit transcriptional machinery promoting target gene transcription. Inhibitors of
10 bromodomains (BET inhibitors) are known in the art and are commercially available. Examples of inhibitors of BRD for use in accordance with the invention are BAY-299 (CAS No. 2080306-23-4), ABBV-774 (CAS No. 2138861-99-9), (+)-JQ1 (CAS No. 1268524-70-4), I-BET762 (CAS No. 1260907-17-2), OTX015 (CAS No. 202590-98-5), I-BET151 (CAS No. 1300031-49-5), CPI-203 (CAS No. 1446144-04-2), PFI-1 (CAS No. 1403764-72-6), MS436 (CAS. No. 1395084-25-9), CPI-0610 (CAS No. 1380087-89-
15 7), see e.g. M. Pérez-Salvia et al. EPIGENETICS, 2017, 12(5), 323–339), or RVX2135 (CAS No. 1253733-17-3), FT-1101 (CAS No. 1776060-36-6), BAY1238097 (CAS. No. 1564268-08-1), INCB054329 (CAS. No. 1628607-64-6), BMS-986158 (CAS. No. 1800340-40-2), ABBV-075 (CAS. No. 1445993-26-9), GS-5829 (CAS. No. 1637771-14-2), and PLX51107 (CAS No. 1627929-55-8). BAY-299 and ABBV-774 are preferred.

20 MEK is an integral part of the MAP kinase signal transduction pathway. MEK acts as a dual-specificity kinase, phosphorylating both serine/threonine and tyrosine residues. It specifically activates the extracellular signal-regulated kinase (ERK) through phosphorylation, which then goes on to regulate various targets in the cell, influencing processes such as growth, proliferation, differentiation, and survival. Examples of inhibitors of MEK for use in accordance with the invention are trametinib (CAS No. 871700-
25 17-3), cobimetinib (CAS No. 934660-93-2), binimetinib (CAS No. 606143-89-9), selumetinib (CAS No. 606143-52-6)

In the **second** aspect, the present invention is directed to the ALC1i according to Formula (II) as described above for use in treating or ameliorating pancreatic cancer or fallopian tube cancer in a patient in combination with an inhibitor of PARP, or for use in enhancing efficacy of an inhibitor of PARP in treating
30 or ameliorating pancreatic cancer or fallopian tube cancer in a patient. The preferred embodiments described herein for the first aspect are also preferred for the second aspect, in particular the definitions of the ALC1i according to Formula (II) and of the PARP inhibitors.

In a preferred embodiment, (i) the ALC1i according to formula (II) potentiates the cancer-cell killing efficacy of the PARPi, (ii) a reduced amount of PARPi is administered, and/or (iii) PARPi resistance is
35 bypassed.

That is, the present invention also relates to the ALC1i according to Formula (II) for use in treating or ameliorating pancreatic cancer, which is preferred, or fallopian tube cancer in a patient in combination with an inhibitor of PARP. Generally, inhibitors of PARP (PARPi) are known in the art and are

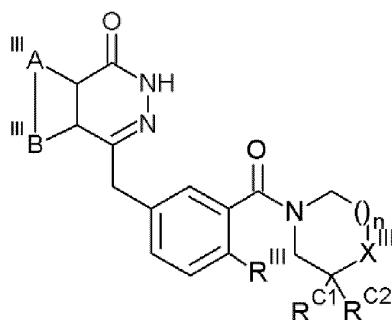
commercially available. For recognition of single-strand and double-strand breaks (SSBs/DSBs), the nuclear Poly-ADP-ribose polymerase (PARP) enzymes are early key factors in the DNA damage response (DDR). Using the metabolite NAD^+ , PARP-1 and -2 add poly-ADP-ribose (PAR) chains to chromatin components and to factors belonging to the DDR, while PARP-3 targets chromatin components via mono-ADP-ribosylation. PARPs get recruited to DNA lesions by recognizing specifically altered, DNA-damage induced structures, which activates their PARylation activity, which in turn regulates their activity and the activity of other DDR and chromatin proteins, facilitating the DDR (Ray Chaudhuri and Nussenzweig, 2017).

This catalytic activity can be inhibited by NAD^+ analogues and has become of particular interest and clinically useful in genetically-defined cancers. Notably, by targeting synthetic lethality in the context of BRCA1 or BRCA2 deficiency, so-called PARP inhibitors (PARPi) are used to treat homologous-recombination (HR)-deficient and other cancers. This is thought to occur by lowering PARP activity and/or by biochemically “trapping” of PARP-1/2/3 on chromatin (Murai et al., 2012, 2014). While “trapping” remains molecularly ill-defined, the term defines an enhanced recruitment, association and/or retention of PARP-1/2/3 enzymes on damaged chromatin, typically induced by treatment of PARP-1 enzyme with PARP inhibitors (PARPi), or a decrease in the release of PARP-1/2/3 enzymes following their initial recruitment, which leads to a prolonged retention. This biochemically manifests itself in an enhanced steady-state association/retention/binding (“trapping”) of the PARP enzymes with damaged genome regions/loci.

Due to the clinical advent of PARPi, PARP-1 has emerged as a powerful target for an increasing list of cancers, including in combination with immuno-oncology therapies, such as the Lynparza/Keytruda trials, to give all but one of many examples. Moreover, first-line PARPi therapies and applications in contexts outside of germline BRCA-1/2 mutations are becoming possible.

In a preferred embodiment, the PARPi:

- (i) that lowers PARP activity is selected from small interfering RNA, and
- (ii) that inhibits PARP1 is selected from the group consisting of a compound of
 - (a) formula (III)



(III)

and isomers, salts, solvates, chemically protected forms, and prodrugs thereof wherein:

^{III}A and ^{III}B together represent an optionally substituted, fused aromatic ring;

X^{III} is NR^X or $CR^X R^Y$;

if $X^{III}=NR^X$ then n is 1 or 2 and if $X^{III}=CR^X R^Y$ then n is 1;

R^X is selected from the group consisting of H, optionally substituted C_{1-20} alkyl, C_{5-20} aryl, C_{3-20} heterocyclyl, amido, thioamido, ester, acyl, and sulfonyl groups;

5 R^Y is selected from H, hydroxy, amino;

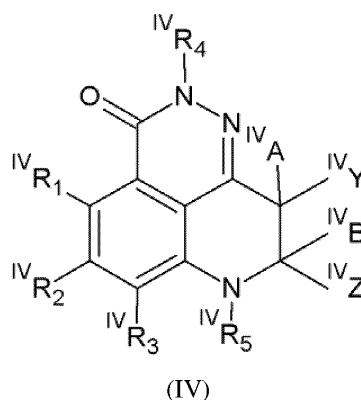
or R^X and R^Y may together form a spiro- C_{3-7} cycloalkyl or heterocyclyl group;

R^{C1} and R^{C2} are independently selected from the group consisting of hydrogen and C_{1-4} alkyl or when X^{III} is $CR^X R^Y$, R^{C1} , R^{C2} , R^X and R^Y , together with the carbon atoms to which they are attached, may form an optionally substituted fused aromatic ring; and

10 R^{III} is selected from H and halo;

and

(b) formula (IV)



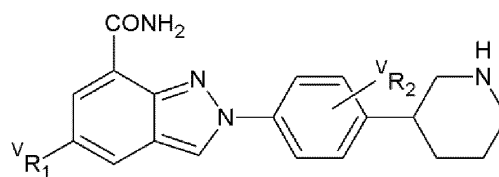
15 and isomers, salts, solvates, chemically protected forms, and prodrugs thereof wherein:

^{IV}Y and ^{IV}Z are each independently selected from the group consisting of:

1. an aryl group optionally substituted with 1, 2, or 3 $^{IV}R_6$;
2. a heteroaryl group optionally substituted with 1, 2, or 3 $^{IV}R_6$;
3. a substituent independently selected from the group consisting of hydrogen, alkenyl (e.g. C_{2-6} -alkenyl), alkoxy (e.g. C_{1-6} -alkoxy), alkoxyalkyl (e.g. C_{1-6} -alkoxy- C_{1-6} -alkyl), alkoxyalkyl (e.g. C_{1-6} -alkoxy-alkyl), alkoxyalkyl (e.g. C_{1-6} -alkoxy-alkyl), alkyl (e.g. C_{1-6} -alkyl), alkynyl (e.g. C_{2-6} -alkynyl), arylalkyl (e.g. aryl- C_{1-6} -alkyl), cycloalkyl (e.g. C_{3-8} -cycloalkyl), cycloalkylalkyl (e.g. C_{3-8} -cycloalkyl- C_{1-6} -alkyl), haloalkyl (e.g. C_{1-6} -haloalkyl), hydroxyalkylene (e.g. hydroxy- C_{1-6} -alkylene), oxo, heterocycloalkyl (e.g. C_{2-8} -heterocycloalkyl), heterocycloalkylalkyl (e.g. C_{2-8} -heterocycloalkyl- C_{1-6} -alkyl), alkylcarbonyl (e.g. C_{1-6} -alkyl-carbonyl), arylcarbonyl, heteroarylcarbonyl, alkylsulfonyl (e.g. C_{1-6} -alkyl-sulfonyl), arylsulfonyl, heteroarylsulfonyl, $(R_A R_B)$ alkylene (e.g. $(R_A R_B)$ - C_{1-6} -alkylene), $(NR_A R_B)$ carbonyl, $(NR_A R_B)$ carbonylalkylene (e.g. $NR_A R_B$ carbonyl- C_{1-6} -alkylene), $(NR_A R_B)$ sulfonyl, and $(R_A R_B)$ sulfonylalkylene (e.g. $(R_A R_B)$ sulfonyl- C_{1-6} -alkylene);

30 wherein each $^{IV}R_6$ is selected from OH, NO_2 , CN, Br, Cl, F, I, C_{1-6} -alkyl, C_{3-8} -cycloalkyl, C_{2-8} -heterocycloalkyl; C_{2-6} -alkenyl, alkoxy (e.g. C_{1-6} -alkoxy), alkoxyalkyl (e.g. C_{1-6} -alkoxy- C_{1-6} -

- alkyl), alkoxycarbonyl (e.g. C₁₋₆-alkoxy-carbonyl), alkoxycarbonylalkyl (e.g. C₁₋₆-alkoxy-carbonyl-C₁₋₆-alkyl), C₂₋₆-alkynyl, aryl, arylalkyl (e.g. aryl-C₁₋₆-alkyl), C₃₋₈-cycloalkylalkyl (e.g. C₃₋₈-cycloalkyl-C₁₋₆-alkyl, haloalkoxy (e.g. C₁₋₆-haloalkoxy), haloalkyl (e.g. C₁₋₆-haloalkyl), hydroxyalkylene (e.g. hydroxy-C₁₋₆-alkylene), oxo, heteroaryl, heteroarylalkoxy (e.g. heteroaryl-C₁₋₆-alkoxy), heteroaryloxy, heteroarylthio, heteroarylalkylthio (e.g. heteroaryl-C₁₋₆-alkylthio), heterocycloalkoxy (e.g. C₂₋₈-heterocycloalkoxy), C₂₋₈-heterocycloalkylthio, heterocyclooxy, heterocyclothio, NR_AR_B, (R_AR_B)C₁₋₆-alkylene, (NR_AR_B)carbonyl, (R_AR_B)carbonylalkylene (e.g. R_AR_B)carbonyl-C₁₋₆-alkylene), (NR_AR_B)sulfonyl, and (NR_AR_B)sulfonylalkylene (e.g. (NR_AR_B)sulfonyl-C₁₋₆-alkylene);
- ^{IV}R₁, ^{IV}R₂, and ^{IV}R₃ are each independently selected from the group consisting of hydrogen, halogen, alkenyl (e.g. C₂₋₆-alkenyl), alkoxy (e.g. C₁₋₆-alkoxy), alkoxycarbonyl (e.g. C₁₋₆-alkoxy-carbonyl), alkyl (e.g. C₁₋₆-alkyl), cycloalkyl (e.g. C₃₋₈-cycloalkyl), alkynyl (e.g. C₂₋₆-alkynyl), cyano, haloalkoxy (e.g. C₁₋₆-haloalkoxy), haloalkyl (e.g. C₁₋₆-haloalkyl), hydroxyl, hydroxyalkylene (e.g. hydroxy-C₁₋₆-alkylene), nitro, NR_AR_B, NR_AR_B alkylene (e.g. NR_AR_B C₁₋₆-alkylene), and (R_AR_B)carbonyl;
- ^{IV}A and ^{IV}B are each independently selected from hydrogen, Br, Cl, F, I, OH, C₁₋₆-alkyl, C₃₋₈-cycloalkyl, alkoxy (e.g. C₁₋₆-alkoxy), alkoxyalkyl (e.g. C₁₋₆-alkoxy-C₁₋₆-alkyl), wherein C₁₋₆-alkyl, C₃₋₈-cycloalkyl, alkoxy, alkoxyalkyl are optionally substituted with at least one substituent selected from OH, NO₂, CN, Br, Cl, F, I, C₁₋₆-alkyl, and C₃₋₈-cycloalkyl, wherein ^{IV}B is not OH;
- R_A, and R_B are independently selected from the group consisting of hydrogen, alkyl (e.g. C₁₋₆-alkyl), cycloalkyl (e.g. C₃₋₈-cycloalkyl), and alkylcarbonyl (e.g. C₁₋₆-alkyl-carbonyl); or R_A and R_B taken together with the atom to which they are attached form a 3-10 membered heterocycle ring optionally having one to three heteroatoms or hetero functionalities selected from the group consisting of -O-, -NH, -N(C₁₋₆-alkyl)-, -NCO(C₁₋₆-alkyl)-, -N(aryl)-, -N(aryl-C₁₋₆-alkyl)-, -N(substituted-aryl-C₁₋₆-alkyl)-, -N(heteroaryl)-, -N(heteroaryl-C₁₋₆-alkyl)-, -N(substituted-heteroaryl-C₁₋₆-alkyl)-, and -S- or S(O)_q-, wherein q is 1 or 2 and the 3-10 membered heterocycle ring is optionally substituted with one or more substituents;
- ^{IV}R₄ and ^{IV}R₅ are each independently selected from the group consisting of hydrogen, alkyl (e.g. C₁₋₆-alkyl), cycloalkyl (e.g. C₃₋₈-cycloalkyl), alkoxyalkyl (e.g. C₁₋₆-alkoxy-C₁₋₆-alkyl), haloalkyl (e.g. C₁₋₆-haloalkyl), hydroxyalkylene (e.g. hydroxy-C₁₋₆-alkylene), and (NR_AR_B)alkylene (e.g. NR_AR_B C₁₋₆-alkylene);
- (iii) that inhibits PARP1 and PARP2 is selected from the group consisting of a compound of
- (a) formula (V)



(V)

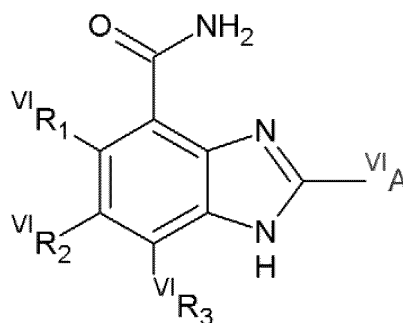
and isomers, salts, solvates, chemically protected forms, and prodrugs thereof wherein:

$^{\text{V}}\text{R}_1$ is hydrogen or fluorine; and

5 $^{\text{V}}\text{R}_2$ is hydrogen or fluorine;

and

(b) formula (VI)



(VI)

and isomers, salts, solvates, chemically protected forms, and prodrugs thereof wherein:

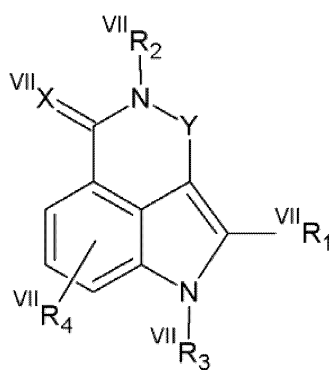
$^{\text{VI}}\text{R}_1$, $^{\text{VI}}\text{R}_2$, and $^{\text{VI}}\text{R}_3$ are independently selected from the group consisting of hydrogen, alkenyl (e.g. C_{1-6} -alkenyl), alkoxy (e.g. C_{1-6} -alkoxy), alkoxycarbonyl (e.g. C_{1-6} -alkoxycarbonyl), alkyl (e.g. C_{1-6} -alkyl), alkynyl (e.g. C_{1-6} -alkynyl), cyano, haloalkoxy (e.g. C_{1-6} -haloalkoxy), haloalkyl (e.g. C_{1-6} -haloalkyl), halogen, hydroxy, hydroxyalkyl (e.g. C_{1-6} -hydroxyalkyl), nitro, $\text{NR}_\text{A}\text{R}_\text{B}$, and $(\text{NR}_\text{A}\text{R}_\text{B})\text{carbonyl}$;

$^{\text{VI}}\text{A}$ is a nonaromatic 4, 5, 6, 7, or 8-membered ring that contains 1 or 2 nitrogen atoms and, optionally, one sulfur or oxygen atom, wherein the nonaromatic ring is optionally substituted with 1, 2, or 3 substituents selected from the group consisting of alkenyl (e.g. C_{1-6} -alkenyl), alkoxy (e.g. C_{1-6} -alkoxy), alkoxyalkyl (e.g. C_{1-6} -alkoxy- C_{1-6} -alkyl), alkoxycarbonyl (e.g. C_{1-6} -alkoxycarbonyl), alkoxycarbonylalkyl (e.g. C_{1-6} -alkoxycarbonyl- C_{1-6} -alkyl), alkyl (e.g. C_{1-6} -alkyl), alkynyl (e.g. C_{1-6} -alkynyl), aryl, arylalkyl (e.g. aryl- C_{1-6} -alkyl), cycloalkyl (e.g. C_{3-8} -cycloalkyl), cycloalkylalkyl (e.g. C_{3-8} -cycloalkyl- C_{1-6} -alkyl), cyano, haloalkoxy (e.g. C_{1-6} -haloalkoxy), haloalkyl (e.g. C_{1-6} -haloalkyl), halogen, heterocycle, heterocyclealkyl (e.g. heterocycle- C_{1-6} -alkyl), heteroaryl, heteroarylalkyl (e.g. heteroaryl- C_{1-6} -alkyl), hydroxy, hydroxyalkyl (e.g. C_{1-6} -hydroxyalkyl), nitro, $\text{NR}_\text{C}\text{R}_\text{D}$, $(\text{NR}_\text{C}\text{R}_\text{D})\text{alkyl}$ (e.g. $(\text{NR}_\text{C}\text{R}_\text{D})\text{-C}_{1-6}\text{-alkyl}$),

(NR_CR_D)carbonyl, (NR_CR_D)carbonylalkyl (e.g. (NR_CR_D)carbonyl-C₁₋₆-alkyl), and (NR_CR_D)sulfonyl; and

R_A, R_B, R_C, and R_D are independently selected from the group consisting of hydrogen, alkyl (e.g. C₁₋₆-alkyl), and alkylcarbonyl (e.g. C₁₋₆-alkylcarbonyl).

- 5 (iv) that inhibits PARP1, PARP2 and PARP3 is a compound of formula (VII)



(VII)

and isomers, salts, solvates, chemically protected forms, and prodrugs thereof wherein:

- 10 ^{VII}R₁ is: H; halogen; cyano; an optionally substituted alkyl (e.g. C₁₋₆-alkyl), alkenyl (e.g. C₂₋₆-alkenyl), alkynyl (e.g. C₂₋₆-alkynyl), cycloalkyl (e.g. C₃₋₈-cycloalkyl), heterocycloalkyl (e.g. C₂₋₈-heterocycloalkyl), aryl, or heteroaryl group (e.g., unsubstituted or substituted with one or more substituents selected from halogen, hydroxy, nitro, and amino, alkoxy (e.g. C₁₋₆-alkoxy), alkyl (e.g. C₁₋₆-alkyl), and aryl groups unsubstituted or substituted with one or more substituents selected from halogen, hydroxy, nitro, carboxy, and optionally substituted amino and ether groups (such as O-aryl)); or -C(O)-R₁₀, where R₁₀ is: H; an optionally substituted alkyl (e.g. C₁₋₆-alkyl), alkenyl (e.g. C₁₋₆-alkenyl), alkynyl (e.g. C₁₋₆-alkynyl), cycloalkyl (e.g. C₃₋₈-cycloalkyl), heterocycloalkyl (e.g. C₂₋₈-heterocycloalkyl), aryl, or heteroaryl group (e.g., unsubstituted or substituted with one or more substituents selected from halogen, hydroxy, nitro, amino, and alkyl (e.g. C₁₋₆-alkyl) and aryl groups unsubstituted or substituted with one or more substituents selected from halo, hydroxy, nitro, and amino); or OR₁₀₀ or NR₁₀₀R₁₁₀, where R₁₀₀ and R₁₁₀ are each independently H or an optionally substituted alkyl (e.g. C₁₋₆-alkyl), alkenyl (e.g. C₂₋₆-alkenyl), alkynyl (e.g. C₂₋₆-alkynyl), cycloalkyl (e.g. C₃₋₈-cycloalkyl), heterocycloalkyl (e.g. C₂₋₈-heterocycloalkyl), aryl, or heteroaryl group (e.g., unsubstituted or substituted with one or more substituents selected from alkyl (e.g. C₁₋₆-alkyl), alkenyl (e.g. C₂₋₆-alkenyl), alkynyl (e.g. C₂₋₆-alkynyl), cycloalkyl (e.g. C₃₋₈-cycloalkyl), heterocycloalkyl (e.g. C₂₋₈-heterocycloalkyl), aryl, and heteroaryl groups unsubstituted or substituted with one or more substituents selected from halogen, hydroxy, nitro, amino, and alkyl (e.g. C₁₋₆-alkyl) and aryl groups unsubstituted or substituted with one or more substituents selected from halogen, hydroxy, nitro, and optionally substituted amino groups);
- 15
- 20
- 25
- 30

$^{VII}R_2$ is H or alkyl (e.g. C₁₋₆-alkyl);

$^{VII}R_3$ is H or alkyl (e.g. C₁₋₆-alkyl);

$^{VII}R_4$ is H, halogen or alkyl (e.g. C₁₋₆-alkyl);

^{VII}X is O or S;

5 Y is $(C^{VII}R_5^{VII}R_6)(C^{VII}R_7^{VII}R_8)_n$ or $N-C(^{VII}R_5)$, where:

n is 0 or 1;

$^{VII}R_5$ and $^{VII}R_6$ are each independently H or an optionally substituted alkyl (e.g. C₁₋₆-alkyl), alkenyl (e.g. C₂₋₆-alkenyl), alkynyl (e.g. C₂₋₆-alkynyl), cycloalkyl (e.g. C₃₋₈-cycloalkyl), heterocycloalkyl (e.g. C₂₋₈-heterocycloalkyl), aryl, or heteroaryl group (e.g., unsubstituted or substituted with one or more substituents selected from halogen, hydroxy, nitro, amino, and lower alkyl (e.g. C₁₋₄-alkyl), lower alkoxy (e.g. C₁₋₄-alkoxy), or aryl groups unsubstituted or substituted with one or more substituents selected from halogen, hydroxy, nitro, and amino); and

10

$^{VII}R_7$ and $^{VII}R_8$ are each independently H or an optionally substituted alkyl (e.g. C₁₋₆-alkyl), alkenyl (e.g. C₂₋₆-alkenyl), alkynyl (e.g. C₂₋₆-alkynyl), cycloalkyl (e.g. C₃₋₈-cycloalkyl), heterocycloalkyl (e.g. C₂₋₈-heterocycloalkyl), aryl, or heteroaryl group (e.g., unsubstituted or substituted with one or more substituents selected from halogen, hydroxy, nitro, amino, and lower alkyl (e.g. C₁₋₄-alkyl), lower alkoxy (e.g. C₁₋₄-alkoxy), and aryl groups unsubstituted or substituted with one or more substituents selected from halogen, hydroxy, nitro, and amino);

15

20

where when $^{VII}R_1$, $^{VII}R_4$, $^{VII}R_5$, $^{VII}R_6$, and $^{VII}R_7$ are each H, $^{VII}R_8$ is not unsubstituted phenyl.

In a preferred embodiment of the invention, the PARPi is selected from the group consisting of AZD-5305, olaparib, talazoparib, niraparib, pamiparib, rucaparib, and veliparib, in particular the group consisting of olaparib, talazoparib, niraparib, pamiparib, rucaparib, and veliparib.

25

In a preferred embodiment of the invention, the ALC1i and the inhibitor of Topoisomerase I, Topoisomerase II, ATM, ATR, Wee1, BRD, MEK, or of PARP, or mitomycin C, paclitaxel, ionizing radiation, or an antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor are administered simultaneously or subsequently.

30

In a **third** aspect the present invention relates to a pharmaceutical composition comprising the ALC1i as specified for the first aspect of the invention and an inhibitor of Topoisomerase I, Topoisomerase II, ATM, ATR, Wee1, BRD, and/or MEK, or mitomycin C, or paclitaxel, or an antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor preferably for use in treating and/or amelioration of a proliferative disease, preferably cancer.

35

In a **fourth** aspect, the present invention is directed to a kit of parts, comprising an ALC1i as described herein with instructions to combine it with an inhibitor of Topoisomerase I, Topoisomerase II, ATM, ATR, Wee1, BRD, and/or MEK, or mitomycin C, or paclitaxel, or ionizing radiation, or an antibody

drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor, or comprising an inhibitor of Topoisomerase I, Topoisomerase II, ATM, ATR, Wee1, BRD, and/or MEK, or mitomycin C, or paclitaxel or an antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor, with instructions to combine it with an ALC1i as defined herein, or comprising separately packaged an ALC1i as defined herein and an inhibitor of Topoisomerase I, Topoisomerase II, ATM, ATR, Wee1, BRD, and/or MEK, or mitomycin C, paclitaxel or, or an antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor, optionally with instructions for use in treating or ameliorating a proliferative disease, preferably cancer.

In one preferred embodiment of all aspects of the invention, the ALC1i used is a compound of formula (I) or a compound of formula (II), more preferably a compound having a structure as shown in Figure 1, or isomers, pharmaceutically acceptable salts, solvates, chemically protected forms, and prodrugs thereof. The preferred pharmaceutically acceptable salt is the sodium salt.

In one preferred embodiment, the ALC1i as defined above, the pharmaceutical composition as defined above, and/or the kit of parts as defined above is for use in treating or ameliorating a proliferative disease, preferably cancer, more preferably the proliferative disease selected from a BRCA-1 and/or BRCA-2-deficient tumor, and/or the proliferative disease is selected from hepatocellular carcinoma, breast cancer, ovarian cancer, fallopian tube cancer, prostate cancer, colorectal cancer, or pancreatic cancer.

BRCA1 and BRCA2 proteins are involved in both promoting homologous recombination (HR)-mediated DNA repair and controlling the stability of stalled replication forks. Many tumor types, including, e.g., breast cancer, ovarian cancer, prostate cancer, pancreatic carcinomas, fallopian tube cancer, peritoneal cancer, acute myeloid leukemia, and uveal melanoma often have underlying defects in BRCA1 or BRCA2 activity. These defects are often due to germline or somatic mutations in the BRCA1 or BRCA2 genes. These tumors, with underlying defects in HR repair, are typically sensitive to PARP inhibitors. However, they can develop PARP inhibitor resistance over the time. To treat such tumors the use of the ALC1i for use according to the invention is particularly suitable if used alone or in combination with PARPi. In a preferred embodiment of the ALC1i for use according to the invention, or the pharmaceutical composition or the kit according to the invention, the proliferative disease is selected from a cancer.

As used herein, the term “cancer”, which preferably is a tumor (also called neoplasm), in particular a solid tumor, refers to cells having the capacity for autonomous growth. Examples of such cells include cells having an abnormal state or condition characterized by rapidly proliferating cell growth. The term is meant to include cancerous growths, e.g., tumors; oncogenic processes, metastatic tissues, and malignantly transformed cells, tissues, or organs, irrespective of histopathologic type or stage of invasiveness. Also included are malignancies of the various organ systems, such as respiratory, cardiovascular, renal, reproductive, hematological, neurological, hepatic, gastrointestinal, and endocrine systems; as well as adenocarcinomas which include malignancies such as most colon cancers, renal-cell carcinoma, prostate cancer and/or testicular tumors, non-small cell carcinoma of the lung, and cancer of the small intestine. Cancer that is “naturally arising” includes any cancer that is not experimentally induced by implantation of cancer cells into a subject, and includes, for example, spontaneously arising cancer, cancer caused by

exposure of a patient to a carcinogen(s), cancer resulting from insertion of a transgenic oncogene or knockout of a tumor suppressor gene, and cancer caused by infections, e.g., viral infections. The term “carcinoma” is art recognized and refers to malignancies of epithelial or endocrine tissues. The term also includes carcinosarcomas, which include malignant tumors composed of carcinomatous and sarcomatous tissues. An “adenocarcinoma” refers to a carcinoma derived from glandular tissue or in which the tumor cells form recognizable glandular structures. The term “sarcoma” is art recognized and refers to malignant tumors of mesenchymal derivation. The term “hematopoietic neoplastic disorders” includes diseases involving hyperplastic/neoplastic cells of hematopoietic origin. A hematopoietic neoplastic disorder can arise from myeloid, lymphoid or erythroid lineages, or precursor cells thereof.

In some embodiments of the aspects of the invention, the cancer is breast cancer, ovarian cancer, prostate cancer, pancreatic carcinomas, gastric cancer, gastroesophageal cancer, non-small cell lung cancer, colorectal cancer, hepatocellular carcinoma, uterine cancer, bone cancer (preferably osteosarcoma), gastric cancer, gastroesophageal cancer, non-small cell lung cancer, bladder cancer, endometrial cancer, brain cancer, in particular astrocytoma cancer or glioma cancer, cervix cancer, kidney cancer (in particular RCC), thyroid cancer, fallopian tube cancer, peritoneal cancer, acute myeloid leukemia, or uveal melanoma. In some embodiments, the cancer is basal-like cancer, basal-like breast cancer, triple negative breast cancer, high grade cancer, or high grade serous ovarian cancer cell. In a particularly preferred embodiment in accordance with the various aspects of the invention, the cancer is breast cancer, prostate cancer, pancreatic carcinomas, fallopian tube cancer, colorectal cancer, hepatocellular carcinoma, or bone cancer (preferably osteosarcoma). In a particularly preferred embodiment, the cancer is selected from the group consisting of ovarian cancer, fallopian tube cancer, primary peritoneal cancer, breast cancer, castration resistant prostate cancer, and pancreatic ductal adenocarcinoma, in particular metastatic ovarian cancer, metastatic fallopian tube cancer, metastatic primary peritoneal cancer, metastatic breast cancer, metastatic castration resistant prostate cancer, and metastatic pancreatic ductal adenocarcinoma.

In some embodiments of the aspects of the invention, the cancer to be treated has at least one mutation in a homologous recombination (HR) gene, i.e. is a HR deficient cancer. A cancer that is HR deficient refers to a cancer that has one or more cells having abnormal levels or activities of at least one HR gene. These abnormal levels or activities interfere with the normal HR gene function and can cause a defect in HR-mediated DNA repair or decrease the stability of replication forks. In a preferred embodiment, the cancer to be treated is BRCA1 deficient and/or BRCA2 deficient. A cancer that is BRCA1 deficient or BRCA2 deficient refers to a cancer that has one or more cells having abnormal BRCA1 levels or activities, or abnormal BRCA2 levels or activities. These abnormal levels or activities interfere with the normal function of BRCA1 or BRCA2 and can cause a defect in HR-mediated DNA repair or decrease the stability of replication forks. Preferably, the proliferative disease is selected from a BRCA-1 and/or BRCA-2-deficient tumor, and/or the proliferative disease is selected from hepatocellular carcinoma, breast cancer, ovarian cancer, fallopian tube cancer, prostate cancer, colorectal cancer, gastric cancer, gastroesophageal cancer, non-small cell lung cancer, or pancreatic cancer.

Particularly preferred examples of cancers treatable according the various aspects of the invention are ovarian cancer, fallopian tube cancer, primary peritoneal cancer, breast cancer, prostate cancer, pancreatic cancer, gastric cancer, colorectal cancer, and pulmonary cancer.

5 Particularly preferred examples of cancers treatable according to the various aspects of the invention are ovarian cancer, fallopian tube cancer, primary peritoneal cancer, breast cancer, prostate cancer, and pancreatic cancer. Preferably, the cancer is metastatic cancer, in particular a stage IV cancer.

Preferably, the cancer to be treated in accordance with the various aspects of the invention has relapsed or progressed, preferably after a first line chemotherapy. Thus, preferably, the combinations according to the present invention are for use as second line or third line therapy, more preferably for second
10 line or third line therapy for the treatment of a HR deficient cancer.

Preferably, the cancer to be treated is at stage III (locally advanced) or IV (metastatic).

Preferably, the cancer to be treated in accordance with the various aspects of the invention has underlying defects in DNA damage repair, like HR repair, i.e. is a HR deficient cancer (HRD cancer), in particular a HR deficient ovarian cancer, HR deficient fallopian tube cancer, HR deficient primary
15 peritoneal cancer, HR deficient breast cancer, HR deficient (castration resistant) prostate cancer, or HR deficient pancreatic cancer, such as pancreatic ductal adenocarcinoma (mPDAC). In a particularly preferred embodiment, these cancers are advanced or metastatic, most preferred metastatic. In one embodiment, the cancer cells have mutations/deletions/insertions in one or more DNA repair genes as listed in Figures 8 and/or 9, in particular ARID1A, ATM, ATRX, BAP1, BLM, BRCA1, BRCA2, BARD1, BRIP1, CHEK1,
20 CHEK2, FANCA/C/D2/E/F/G/L, MRE11A, NBN, PALB2, RAD50, RAD51C, RAD51D, RAD51, RAD51B and/or WRN. Most preferred are BRCA1/2.

In one embodiment, the cancer to be treated or the cancer patients to be treated are selected based on the presence of tumor markers. In the clinical setting cancer/patient selection would include but is not limited to eligible tumor biomarkers, i.e., deleterious mutations including ARID1A, ATM, ATRX, BAP1,
25 BLM, BRCA1, BRCA2, BARD1, BRIP1, CHEK1, CHEK2, FANCA/C/D2/E/F/G/L, MRE11A, NBN, PALB2, RAD50, RAD51C, RAD51D, RAD51, RAD51B and/or WRN, which are preferred, BRCA1/2 being most preferred, and/or other gene variants in the HR pathway as listed in Figures 8 and/or 9.

In one preferred embodiment, the ALC1i is used in combination with several classes of cancer drugs, namely inhibitors of Topoisomerase I, preferably irinotecan, preferably in the form of its active metabolite
30 SN-38, Topoisomerase II, ATM, ATR, Wee1, BRD, and MEK, or combined with mitomycin C paclitaxel, with ionizing radiation, or with an antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor, in treating or ameliorating a proliferative disease in a patient, in particular cancer. Preferably, the cancer is HR deficient cancer, in particular BRCA-1 and/or BRCA-2-deficient. The preferred ALC1i used are ALCi-2, ALCi-160, ALCi-101, or ALCi-123, or pharmaceutically acceptable
35 salt, isomers, solvate, chemically protected form, or prodrugs thereof, particularly preferred ALCi-2 or ALCi-101, or pharmaceutically acceptable salt, isomers, solvate, chemically protected form, or prodrugs thereof, ALCi-101 being most preferred. The most preferable pharmaceutically acceptable salt is the sodium

salt. Most preferred, the sodium salt of ALCi-101 is used. Optionally, the cancer does not include pancreatic cancer, in particular when the ACL1i is used in combination with irinotecan or SN-38.

In a specifically preferred embodiment, the ACL1i is used in combination with several classes of cancer drugs as listed above, preferably an antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor, such as trastuzumab deruxtecan, datopotamab deruxtecan (which is preferred), or sacituzumab govitecan, in treating or ameliorating a proliferative disease in a patient, in particular cancer, such as HR deficient cancer, in particular BRCA-1 and/or BRCA-2-deficient. The preferred cancer is hepatocellular carcinoma, breast cancer, ovarian cancer, fallopian tube cancer, primary peritoneal cancer, prostate cancer, colorectal cancer, or pancreatic cancer. Preferably the cancer is advanced or metastatic, the latter being preferred. The preferred ALC1i used are ALCi-2, ALCi-160, ALCi-101, or ALCi-123, particularly preferred ALCi-2 or ALCi-101, the latter being most preferred.

Preferably, the patient to be treated in accordance with the various aspects of the invention is a cancer patient, preferably having the cancer as defined above, e.g. breast cancer, ovarian cancer, prostate cancer, pancreatic carcinomas, gastric, gastroesophageal, non-small cell lung cancer, colorectal cancer, hepatocellular carcinoma, uterine cancer, bone cancer (preferably osteosarcoma), fallopian tube cancer, peritoneal cancer, acute myeloid leukemia, or uveal melanoma, more preferably ovarian cancer, fallopian tube cancer, primary peritoneal cancer, breast cancer, prostate cancer, and pancreatic cancer, and optionally having mutations/deletions/insertions in one or more of the HR genes as listed in Figures 8 and/or 9, preferably BRCA1/2. In a particular preferred embodiment, the cancer patient has a HR deficient cancer, in particular BRCA-1 and/or BRCA-2-deficient. Optionally, patients having pancreatic cancer are not included, in particular when the ACL1i is used in combination with irinotecan or SN-38.

Preferably, the patient to be treated in accordance with the various aspects of the invention is a cancer patient, preferably having the cancer as defined above, e.g. breast cancer, ovarian cancer, prostate cancer, pancreatic carcinomas, gastric, gastroesophageal, non-small cell lung cancer, colorectal cancer, hepatocellular carcinoma, uterine cancer, bone cancer (preferably osteosarcoma), fallopian tube cancer, peritoneal cancer, acute myeloid leukemia, or uveal melanoma, more preferably ovarian cancer, fallopian tube cancer, primary peritoneal cancer, breast cancer, prostate cancer, or pancreatic cancer, which preferably is a HR deficient cancer, and the patient is receiving or has received at least one previous cancer therapy, preferably the agents used in combination with the ACL1i as defined above, and the patient did not show or did only show partial or unsatisfactory response, typically after several cycles of treatment. In a preferred embodiment, the previous cancer therapy included administration of at least one antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor, such as trastuzumab deruxtecan, datopotamab deruxtecan (which is preferred), or sacituzumab govitecan.

In one preferred embodiment, the ALC1i as defined above, in the pharmaceutical composition as defined above, and/or in the kit of parts as defined above, the ACL1i is combined with any one of adavosertib, AZ-32, AZD-1056, AZD-1390, BAY-299, ABBV-744, trametinib, ceralasertib, elimusertib, paclitaxel, Mitomycin C, teniposide, topotecan, AZD-5305, niraparib, olaparib, rucaparib, veliparib, pamiparib, talazoparib, trastuzumab deruxtecan, datopotamab deruxtecan, and/or sacituzumab govitecan.

In one preferred embodiment, the ALC1i as defined above, in the pharmaceutical composition as defined above, and/or in the kit of parts as defined above, the ACL1i is administered orally, preferably as a tablet or capsule.

Experimental Section

Combination therapy of an ALC1i with other drugs

ALC1 inhibitors

ALC1 is an allosterically regulated chromatin remodeler that relaxes chromatin and plays an important role in response to DNA damage. It is implicated in different repair pathways like nucleotide excision repair or base excision repair and is known to regulate replication fork progression at DNA damage sites (Ooka et al., 2018).

Inhibition of ALC1 via specific small molecules (ALC1i) used according to the invention leads to inefficient DNA repair by rendering chromatin less accessible to DNA repair enzymes potentiating the accumulation of DNA damage. Disruption of the chromatin remodeling forces of ALC1 through ALC1i enables a highly selective therapy of several cancer-types. Treatment of cancer cells with ALC1i leads to increase of γ H2AX protein levels, a marker for DNA damage (see Figure 6). Surprisingly, in our hands, treatment of cancer cells with ALC1i lead to cell cycle arrest in the G2 phase (see Figure 5), resembling the effect of an inhibitor for PARP1/2, olaparib, which also induces DNA damage and leads to an increased G2, M-phase (Zhao et al., 2018, Wu et al., 2018).

Topoisomerase 1 inhibitors

The enzyme topoisomerase 1 (TOP1) is involved in relaxation of supercoiled DNA. It removes helical constraints that otherwise hinder DNA replication and transcription (GILMOUR, 1986).

A transient single strand break in the double helix leads to DNA passage events or controlled rotation about the DNA-break (Wang, 1996).

Together with the 5' phosphate group of the DNA during the topoisomerase reaction, TOP1 forms a covalent link intermediate (TOP1-DNA-cleavage complex, TOP1cc). During this process, toxic DNA lesions can occur by covalently trapped TOP1 on the DNA (Takahashi et al., 2010).

Defects in TOP1 function lead to blockage of cellular proliferation. Under normal conditions, a balance between the utilization of TOP1 catalytic activity in order to maintain DNA topology and the accumulation of toxic DNA damage due to TOP1 trapping is critical (Li & Liu, 2016).

Topoisomerase 1 inhibitors interrupt DNA replication and induce DNA breaks, leading to slowed proliferation and cytotoxicity.

Irinotecan, IUPAC name (S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo1H-pyrido[3',4':6,7]-indolizino[1,2-b]quinolin-9-yl-[1,4'bipiperidine]-1'-carboxylate is a TOP1 inhibitor (TOP1i) analog of the naturally-occurring alkaloid, camptothecin. Also known as CPT-11, irinotecan is currently marketed formulated as an aqueous solution as Camptosar® (irinotecan hydrochloride injection). Irinotecan arrests uncontrolled cell growth by inhibiting the unwinding of DNA and thereby preventing DNA replication. The active metabolite of Irinotecan is SN-38.

Topotecan (IUPAC: (19S)-8-[(dimethylamino)methyl]-19-ethyl-7,19-dihydroxy-17-oxa-3,13-diazapentacyclo[11.8.0.0.2,11.0.4,9.0.15,20]henicosa-1(21),2,4(9),5,7,10,15(20)-heptaene-14,18-dione) is a

TOP1i that leads to stabilization of the TOP1-DNA covalent complex during S-Phase. Mediated single strand breaks cannot be re-ligated and develop to DNA double strand breaks (*NCBI – Topotecan, n.d.-a*).

Datopotamab deruxtecan (Dato-DXd) is an antibody-drug conjugate (ADC) consisting of a humanized anti-TROP2 IgG1 monoclonal antibody attached to a topoisomerase I inhibitor payload via a tetrapeptide-based cleavable linker. According to the present invention, ADCs comprising a topoisomerase I inhibitor are also considered to be covered by the topoisomerase I inhibitors used in combination with the ALC1i in accordance with the invention. Preferably a combination of an ALC1i used according to the present invention and datopotamab deruxtecan is used, in particular for treating (e.g. triple negative) breast cancer or non-small-cell lung cancer.

10 Synergy of topoisomerase 1 inhibitors with ALC1i

Inhibition of TOP1 results in DNA nicks and resealing associated with DNA relaxation during the process of replication. As a result of a collapsed replication fork, DNA strand breaks arise (Holm, 1989).

Inhibition of ALC1 on top of TOP1 may not only promote replication fork disruption but also contribute to additional accumulation of DNA damage which cannot be repaired because of changes in chromatin accessibility or reorganization. It is hypothesized that via this mechanism, ALC1i co-dosed with topotecan or other TOP1i would lead to potentiation, through up to additive inhibition of cancer cell proliferation. As shown hererin for other cancer agents, up to additive combination effects could be obtained for known ALC1i compounds. Contrary thereto, surprisingly synergistic inhibition of cancer cell proliferation was observed by the combinations of the invention.

Thus, according to the present invention ALC1 inhibition via specific ALC1i synergistically impacts the cellular response to the DNA damage induced by TOP1i. Thus, the present inventors determined that by using a combination of a TOP1i and a specific ALC1i, the effects of both inhibitors can be synergistically enhanced. As TOP1i topotecan shows high MSA scores in combination with said specific ALC1i used according to the invention, thus, it can be expected that this will also be the case for other TOP1i. Thus, preferably a combination of an ALC1i used according to the present invention and a TOP1i is used, in particular for treating colorectal cancer.

Topoisomerase 2 inhibitors

Topoisomerase 2 (TOP2) manages DNA tangles and supercoils. It can pass one double helix through another, untangling DNA by cutting both strands of the DNA helix simultaneously (Holm, 1989). This leads to an increase / decrease of the linking number of DNA loops by two units, promoting chromosome disentanglement.

As an intermediate of this process, transient DNA double strand breaks are generated, possibly leading to toxic genome fragmentation (McClendon & Osheroff, 2007).

TOP2 enzymes are involved in numerous DNA processes including recombination, separation of daughter chromosomes and chromatin condensation / de-condensation. TOP2-DNA cleavage complexes are essential for its cellular function. Excessively low levels of these complexes lead to mitotic failure, while excessively high levels lead to conversion of transient strand breaks to permanent double strand breaks,

resulting in the inhibition of essential DNA processes initiating multiple recombination and repair pathways (Fortune & Osherooff, 2000).

TOP2 inhibitors like etoposide, doxorubicin, or teniposide increase the levels of the TOP2-DNA cleavage complex and are used as front-line therapy against several solid tumors.

5 Teniposide (IUPAC: (5S,5aR,8aR,9R)-5-[[[(2R,4aR,6R,7R,8R,8aS)-7,8-dihydroxy-2-thiophen-2-yl-4,4a,6,7,8,8a-hexahydropyrano[3,2-d][1,3]dioxin-6-yl]oxy]-9-(4-hydroxy-3,5-dimethoxyphenyl)-5a,6,8a,9-tetrahydro-5H-[2]benzofuro[6,5-f][1,3]benzodioxol-8-one) is a TOP2i with antineoplasmtic activity. It forms complexes with TOP2 and DNA resulting in DNA strand breaks; DNA-protein crosslinks and inhibition of DNA strand re-ligation. It acts in the late S and early G-phase of the cell cycle (*NCBI –*
10 *Teniposide, n.d-b*).

Synergy of topoisomerase 2 inhibitors with ALC1i

Inhibition of TOP2 with TOP2-poisons leads to DNA double strand breaks activating DNA recombination and repair processes, which require the DNA damage repair protein ALC1. It can thus be hypothesized that an additional inhibition of ALC1 via small molecule inhibitors will lead to accumulation
15 of DNA damage that cannot be repaired, thus, the combination of an ALC1i with teniposide, etoposide or other TOP2i may lead to increased cancer cell killing.

This hypothesis led to a part of the present invention which indicates that ALC1 inhibition via the specific ALC1i used in the present invention synergistically impacts the cellular response to induced by the TOP2i teniposide. Thus, the present inventors determined that by using a combination of an inhibitor of
20 TOP2 and an inhibitor of ALC1 of the invention, the effects of both inhibitors can be synergistically enhanced.

ATM inhibitors

Ataxia telangiectasia mutant (ATM) is a serine/threonine protein kinase belonging to the
25 phosphatidylinositol 3-kinase-related kinase (PIKK) family of protein kinase. ATM, together with its downstream target Chk2, is the major signaling pathway activated by DNA double strand breaks (DSBs). In response to DSBs, activated ATM in cooperation with the MRN complex, CtIP and MRE11, initiates strand resection to generate tracts of single stranded DNA (ssDNA) (You et al., 2009). These ssDNA form the initiating substrate for homologous recombination repair (HRR) and activating platform for the
30 activation of ATR-Chk1 pathway (Mimitou & Symington, 2009), direct effectors of multiple DNA damage and replication checkpoints. Consistent with its crucial role in maintaining genomic integrity, the human and mice with inherited defects in ATM are predisposed to lymphoma and radiosensitive (Shiloh & Kastan, 2001, Xu et al., 1996). The observations that radiation and essentially all genotoxic anticancer agents potently activate the ATM-Chk2 signaling pathway have stimulated much interest in whether ATM could
35 be manipulated pharmacologically to enhance the efficacy of conventional therapies.

AZ-32 (IUPAC: *N*-methyl-4-(6-phenylimidazo[1,2-a]pyrazin-3-yl)benzamide) is an orally bioavailable ATM inhibitor that blocks the DNA damage response. It has good blood-brain barrier penetration, radio-sensitizes glioma cells in vitro and improves survival in orthotopic mouse models.

AZD-0156 (IUPAC: 8-[6-[3-(dimethylamino)propoxy]pyridin-3-yl]-3-methyl-1-(oxan-4-yl)imidazo[4,5-c]quinolin-2-one) is a first in class orally bioavailable ATM inhibitor. It is a permeable, highly soluble compound with excellent preclinical pharmacokinetic properties. The oral administration of AZD-0156 also shows efficacy in the mouse xenograft model when combined with DSB inducing agents.

5 It is currently undergoing further clinical assessment.

AZD-1390 (IUPAC: 7-fluoro-3-methyl-8-[6-(3-piperidin-1-ylpropoxy)pyridin-3-yl]-1-propan-2-ylimidazo[4,5-c]quinolin-2-one) is an orally bioavailable ATM inhibitor. It can efficiently cross the blood-brain barrier. In *in vivo* syngeneic and patient-derived glioma as well as orthotopic lung-brain metastatic models, AZD-1390 sensitized tumors to radiotherapy.

10 Synergy of ATM inhibitors with ALC1i

The synthetic lethal principle has been successfully applied to cancer therapy as exemplified by the PARP inhibitors in patients with BRCA1/BRCA2 mutations. Accumulating evidence supports the idea that defects in many other HRR genes also sensitize tumor cells to PARP inhibitors (McCabe et al., 2006). Particularly, human and mouse cells with ATM deficiency are also sensitized to PARP inhibition (Löser et al., 2010, Williamson et al., 2010). It thus can be hypothesized that an ATM inhibitor could potentiate tumor cells to BRCAness and have synergistic effects with ALC1i by a similar mechanism.

ATMi leads to accumulation of DNA damage, similar to ALC1i. It thus can be hypothesized that the combination of both ATMi with an ALC1i of the invention leads to a massive increase of not repaired DNA and may potentiate cancer cell killing.

20

ATR inhibitors

ATR (Ataxia-Telangiectasia Mutated (ATM) and Rad3-related protein kinase), a serine/threonine protein kinase upregulated in a variety of cancer cell types, plays a key role in DNA repair, cell cycle progression and cell survival. ATR is an important component of the DNA damage response (DDR) (Williamson et al., 2016). It induces homologous recombination (HR)-dependent repair (Kim et al., 2016). ATR is responsible for signaling single stranded DNA (ssDNA), principally due to replication stress (RS), to the S and G2/M checkpoints and DNA repair, one of key G2 checkpoint regulators (Bradbury et al., 2022). Also, ATR is essential regulator of immune checkpoint proteins such as PD-L1 in response to DNA damage. ATR inhibition in tumor cells may either increase the sensitivity of tumor cells to genotoxic agents and/or cell death by apoptosis or cellular senescence (Barnieh et al., 2021).

30

Ceralasertib (AZD6738, CAS No. 1352226-88-0, ChEMBL4285417, AZD-6738, IUPAC name: imino-methyl-[1-[6-[(3*R*)-3-methylmorpholin-4-yl]-2-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)pyrimidin-4-yl]cyclopropyl]-oxo- λ^6 -sulfane) is a morpholino-pyrimidine-based inhibitor of ATR kinase with potential antineoplastic activity. Upon oral administration, ceralasertib selectively inhibits ATR activity by blocking the downstream phosphorylation of the serine/threonine protein kinase CHK1. This prevents ATR-mediated signaling, results in the inhibition of DNA damage checkpoint activation, disruption of DNA damage repair, and the induction of tumor cell apoptosis. In addition, ceralasertib sensitizes tumor cells to chemo- and radiotherapy (NCBI - Ceralasertib, n.d.-c).

35

Elimusertib (CAS No. 1876467-74-1, elimusertib, BAY-1895344, BAY 1895344, BAY1895344 IUPAC: (3*R*)-3-methyl-4-[4-(2-methylpyrazol-3-yl)-8-(1*H*-pyrazol-5-yl)-1,7-naphthyridin-2-yl]morpholine) is an orally available ATR-specific kinase inhibitor, with potential antineoplastic activity. Upon oral administration, elimusertib selectively binds to and inhibits the activity of ATR, which prevents ATR-mediated signaling. This inhibits DNA damage checkpoint activation, disrupts DNA damage repair and induces apoptosis in ATR-overexpressing tumor cells (*NCBI* - Elimusertib, n.d.-d).

Synergy of ATR inhibitors with ALC1i

ATR is specifically activated in response to extensive single stranded DNA structures (ssDNA) (Barnieh et al., 2021b). ALC1 inhibition of ALC1 leads to a dysfunctional single strand DNA break repair, requiring the ATR pathway to be activated in order to initiate this DNA repair. Due to the dependence on ATR activity in the context of an ALC1 inhibitor, it can be hypothesized that ATR inhibitors and the specific ALC1 inhibitors used in the invention would exhibit synergistic anti-proliferative effect. Synergy testing with ALC1 inhibitors used in the invention and ceralasertib and elimusertib confirmed that ALC1 inhibition using the compounds of the invention is synergistic with ATR inhibition.

Wee1 inhibitors

The WEE1 G2 Checkpoint kinase has a crucial role in cell cycle regulation and DNA damage recognition / repair. The main downstream target of WEE1 is the cyclin dependent kinase 1(CDK1) B1 complex. WEE1 is deregulated in cancer cells weakening the cell cycle regulation and allowing the high proliferation rate. Therefore, overexpression of kinases like WEE1 in DDR is fundamental for the maintenance of genetic stability (Ghelli Luserna di Rorà et al., 2020). In case of an inactive p53, the cell cycle is entirely regulated by G2/M checkpoint.

Inhibition of WEE1 leads to impairment of the G2-DNA damage checkpoint. Upon treatment with DNA damaging agents, inhibition of WEE1 prevents phosphorylation of the cyclin-dependent kinase 1 (CDK1, CDC2) and potentially leads to apoptosis. Cells lacking the cell cycle checkpoint G1, like most of the p53 deficient cancer cells, rely on the G2 checkpoint in case of DNA damage. Invalidation of the G2 checkpoint may sensitize p53-deficient tumors to antineoplastic agents and enhance their cytotoxic effect (*NCBI* - Adavosertib, n.d.-e).

Adavosertib (MK-1775, AZD 1775, IUPAC name: 1-[6-(2-hydroxypropan-2-yl)pyridin-2-yl]-6-[4-(4-methylpiperazin-1-yl)anilino]-2-prop-2-enylpyrazolo[3,4-d]pyrimidin-3-one) is a small molecule inhibitor of WEE1. It selectively targets the tyrosine kinase to inactivate the CDC2/cyclin B complex. It has been used for the treatment of neoplasms, ovarian cancer, glioblastoma and other tumors (*NCBI* - Adavosertib n.d.-e).

Synergy of Wee1 inhibitors with ALC1i

The cell cycle arrest phenotype exhibited by cells after treatment with adavosertib results in reduced proliferation. This effect is mirrored by ALC1 inhibition as shown in Figure 5, leading the authors to hypothesize that the number of cells escaping the cell cycle arrest would be dramatically decreased with co treatment of WEE1 inhibitors and ALC1 inhibitors, resulting in synergistic anti-proliferative effects. This

hypothesis was confirmed by co treatment with the specific ALC1 inhibitors used in the invention and the WEE1 inhibitor adavosertib.

BRD inhibitors

5 Bromodomains are a family of evolutionarily conserved motifs that bind the acetylated lysines in histone tails and recruit transcriptional machinery promoting target gene transcription. Bromodomain inhibitors prevent interaction between the bromodomain and the acetyl group, causing the downregulation of certain genes (Pérez-Salvia & Esteller, 2016).

BAY-299 (C25H23N3O4, BAY-299, 2080306-23-4, BAY 299, BAY299, ChEMBL4086276, IUPAC: 6-(3-hydroxypropyl)-2-(1,3,6-trimethyl-2-oxobenzimidazol-5-yl)benzo[de]isoquinoline-1,3-dione) (NCBI BAY-299, n.d.-f) is a dual inhibitor of the bromodomain and PHD finger (BRPF) family member BRPF2 and the TATA box binding protein-associated factors TAF1 and TAF1L (Bouché et al., 2017).

ABBV-744 (C28H30FN3O4, ABBV-744, ABBV744, ABBV 744, 2138861-99-9, IUPAC: N-ethyl-4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(1-hydroxy-1-methylethyl)phenyl]-6,7-dihydro-6-methyl-7-oxo-1H-Pyrrolo[2,3-c]pyridine-2-carboxamide) is an inhibitor of the BDII domain of the BET family (Faivre et al., 2018).

Synergy of BRD inhibitors with ALC1i

The disruption of TAF1 bromodomain function impairs DNA end resection, Replication Protein A (RPA) and Rad51 loading, and HR repair, causing genome instability and hypersensitivity to DNA damage (Peng et al., 2021). The authors thus anticipated that insufficient HR resulting from the action of TAF1 inhibitor BAY-299 synergizes with the inhibition of other DNA repair pathways due to ALC1i effect. Synergy testing with the specific ALC1 inhibitors used in the invention and BAY-299 confirmed that the specific ALC1 inhibitors are synergistic with bromodomain inhibitors.

25 The BET family protein BRD4 not only functions as a master regulator of many genes which play a part in DNA damage response or are involved in checkpoint activation, but also contributes to DNA damage repair in a transcriptionally independent manner. In the latter case, BRD4 facilitates and stabilizes the interaction of 53BP1 that in turn serves as docking sites for the DNA repair complex (PMID: 24954901). The authors thus anticipated that a possible synergistic effect of BETi and DDR inhibitors like ALC1i. Synergy testing with the specific ALC1 inhibitor used in the invention and BET BD2 specific inhibitor confirmed the synergistic effects. It is worth mentioning the low toxicity of BET BD2i compared to pan-BETi.

PARP inhibitors

35 PARP Poly (ADP-ribose) polymerases are a family of 17 proteins involved in several cellular processes, including the stress response, chromatin remodeling, DNA repair and apoptosis. The best described family member is PARP1, which plays role in the detection and repair of single-strand DNA breaks, in alternative DNA repair pathways, including nucleotide excision repair, non-homologous end

joining (both classical and alternative), in homologous recombination and in DNA mismatch repair. PARP inhibitors (PARPi) are a novel class of anti-cancer drugs which compete with NAD⁺ for the PARP catalytically active site. PARPi have shown to be effective in the treatment of HR deficient tumors, especially in tumors with mutations in Breast Cancer Associated 1 and 2 (BRCA1 and BRCA2) genes (Lai et al., 2020).

Synergy of PARP inhibitors with ALC1i

ALC1 is associated with PARPs due to its ability to be directly activated upon poly-(ADP-ribose) synthesis by PARP1 and other PARP family members, its ability to influence the recruitment and release of PARP family members to damaged chromatin, and the robust potentiation of PARPi function seen upon genetic interference with the ALC1 gene (Blessing et al., 2020; Juhász et al., 2020; Hewitt et al., 2021; Verma et al., 2021). The ALC1 deficiency impacts PARP1 trapping, which impairs binding of NHEJ and HR proteins to DNA and suppresses these DNA repair mechanisms (Juhász et al., 2020) and influences PARP2 turnover (Blessing et al., 2020). As demonstrated below (see Figure 2), the specific ALC1 inhibitors used in the invention exhibit synergistic effects with PARP inhibition.

Paclitaxel

Paclitaxel (C₄₇H₅₁NO₁₄, CAS No. 33069-62-4, Synonyms: P88XT4IS4D, Paclitaxel, Taxol, Taxol A, IUPAC: [(1S,2S,3R,4S,7R,9S,10S,12R,15S)-4,12-diacetyloxy-15-[(2R,3S)-3-benzamido-2-hydroxy-3-phenylpropanoyl]oxy-1,9-dihydroxy-10,14,17,17-tetramethyl-11-oxo-6-oxatetracyclo[11.3.1.0^{3,10}.0^{4,7}]heptadec-13-en-2-yl] benzoate) is an antineoplastic agent which acts by inhibiting mitosis. It currently plays a central role in the therapy of ovarian, breast, and lung cancer.

Therapy with paclitaxel has been associated with a low rate of serum enzyme elevations but has not been clearly linked to cases of clinically apparent acute liver injury (NCBI - Paclitaxel, n.d.-h). Paclitaxel binds specifically in a reversible manner to the N-terminal 31 amino acids of the beta-tubulin subunit in the microtubules, promotes the assembly of stable microtubules especially from β -tubulin heterodimers and inhibits their depolymerisation, which results in cell cycle arrest in the G2/M-phase, apoptosis and inhibition of cell replication (Kampan et al., 2015). Promoted ROS generation through enhancing the activity of NADPH oxidase (NOX) associated with plasma membranes (Alexandre et al., 2007).

Synergy of Paclitaxel with ALC1i

Paclitaxel induces the formation of reactive oxygen species, resulting in massive DNA damage. Additionally, paclitaxel suppresses CDK1 expression, resulting in reduced phosphorylation of BRCA1, inducing a BRCAness phenotype and inhibiting the homologous recombination pathway (Yanaihara et al., 2023). Synergy with the specific ALC1 inhibitors used in the invention was confirmed in co-dosing experiments as shown below (see also Figure 2).

Mitomycin C

Mitomycin C (C₁₅H₁₈N₄O₅, mitomycin C, Mitomycin, CAS No. 50-07-7, Ametycine, Mutamycin, IUPAC:[(4*S*,6*S*,7*R*,8*S*)-11-amino-7-methoxy-12-methyl-10,13-dioxo-2,5-diazatetracyclo[7.4.0.0^{2,7}.0^{4,6}]trideca-1(9),11-dien-8-yl]methyl carbamate) is a methylazirinopyrroloindole-dione antineoplastic antibiotic isolated from the bacterium *Streptomyces caespitosus* and other *Streptomyces* bacterial species. Bio-reduced mitomycin C generates oxygen radicals, alkylates DNA, and produces interstrand DNA cross-links, thereby inhibiting DNA synthesis. Preferentially toxic to hypoxic cells, mitomycin C also inhibits RNA and protein synthesis at high concentrations (NCBI - Mitomycin C, n.d.-i).

10 Synergy of Mitomycin C with ALC1i

The numerous types of DNA damage induced by Mitomycin C result in inhibition of cellular proliferation and massive cell death. It may thus be hypothesized that inhibition of ALC1 using the specific ALC1i used in the invention would hamper the repair of this DNA damage, resulting in the potentiation of the anti-proliferative effect of Mitomycin C. Surprisingly, even synergy was confirmed during co-dosing experiments of the specific ALC1 inhibitors used in the invention and Mitomycin C.

Ionizing radiation

Ionizing radiation is an electromagnetic radiation or particle radiation (high energy elementary particles) capable of directly or indirectly producing ions in its passage through matter. The wavelengths of ionizing electromagnetic radiation are equal to or smaller than those of short (far) ultraviolet radiation and include gamma and X-rays (NCBI – ionizing radiation, n.d.-k).

Ionizing radiation induces apoptosis, necrosis, and senescence of cancer cells by causing DNA damage, affects cancer cell organelles, tumor immune response. Cause different types of DNA damage: SSBs, DSBs, DNA crosslink, DNA-Protein crosslinks, indirect DNA damage by reactive oxygen species (ROS)/reactive nitrogen species (RNS) (J. S. Wang et al., 2018).

Synergy of ionizing radiation with ALC1i

The numerous types of DNA damage induced by ionization radiation result in inhibition of cellular proliferation and cell death. The authors hypothesized that inhibition of ALC1 by the ALC1i used in the invention would hamper the repair of this DNA damage, resulting in the potentiation of the anti-proliferative effect of the ionizing radiation. This was confirmed during co-dosing experiments of the specific ALC1 inhibitors used in the invention and ionizing radiation.

Typical dose rates to be used in accordance with the invention are 100–2400 cGy/min for 1 to 5 min.

Antibody drug conjugates (ADC) with tumor specific antibodies conjugated to TOP1 inhibitors**Trastuzumab Deruxtecan (Enhertu)**

Trastuzumab binds to the extracellular domain of the HER2—receptor and prevents homodimerization, HER2-downstream signalling and leads to antibody-dependent cell-mediated cytotoxicity (Nami et al., 2018).

Trastuzumab deruxtecan (sold under the brand name Enhertu) is an antibody drug conjugate (ADC) consisting of the HER2-directed antibody trastuzumab and the cytostatic TOP1i deruxtecan, connected via a tumor-selective cleavable linker. This linker attaches the drug-payload to the antibody and is selectively cleaved by enzymes upregulated in tumor cells. (ENHERTU® (Fam-trastuzumab Deruxtecan-nxki))

Upon drug release, the TOP1i causes DNA damage and cell death (see TOP1i section for detailed mechanism) (ENHERTU® (Fam-trastuzumab Deruxtecan-nxki)). Enhertu is used to treat human epidermal growth factor 2 (HER2) positive breast cancers, non-small cell lung cancer (NSCLC) with a HER2 mutation and gastric or gastroesophageal junction adenocarcinoma that are HER2-positive (ENHERTU® (Fam-trastuzumab Deruxtecan-nxki)).

Sacituzumab govitecan

Sacituzumab govitecan, sold under the brand name Trodelvy by Gilead Sciences, is a Trop-2-directed antibody and topoisomerase inhibitor drug conjugate used for the treatment of metastatic triple-negative breast cancer and metastatic urothelial cancer. Trodelvy binds to Trophoblast cell-surface antigen 2 (TROP2), expressed and associated with poor prognosis in HR+/HER2- breast cancer and triple-negative breast cancers, making TROP2 an attractive tumor-associated antigen for treatments.

Sacituzumab govitecan is a conjugate of the humanized anti-Trop-2 monoclonal antibody linked with topoisomerase 1 inhibitor (TOP1i) SN-38, the active metabolite of irinotecan. Each antibody having on average 7.6 molecules of SN-38 attached. Linkage to an antibody allows the drug to specifically target cells expressing Trop-2. Because free SN-38 is membrane-permeable, it may elicit antitumor effects in adjacent tumor cells (bystander effect) before internalization of the antibody–drug conjugate through hydrolysis of the linker or by intracellular SN-38 release after internalization (Goldenberg et al., 2020).

Sacituzumab govitecan was approved for medical use in the United States in April 2020, and in the European Union in November 2021. The U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) consider it to be a first-in-class medication (European Medicines Agency (EMA), 2021).

Datopotamab deruxtecan

Datopotamab deruxtecan (Dato-DXd) is another Trop2-directed antibody and topoisomerase inhibitor drug conjugate. Datopotamab deruxtecan (Dato-DXd) is a humanized anti-Trop2 immunoglobulin G1 monoclonal antibody covalently linked to deruxtecan, a highly potent topoisomerase I inhibitor (TOP1i), a derivative of exatecan, via a plasma-stable, tumor-selective, tetrapeptide-based cleavable linker,

resulting in reduced systemic exposure and off-target adverse effects. Internalization of Dato-DXd into Trop2-expressing cells leads to death of target tumor cells and bystander killing of neighboring cells in the tumor microenvironment (Okajima et al., 2021).

5 Datopotamab deruxtecan Biologics License Application was accepted in the US for patients with previously treated metastatic HR-positive, HER2-negative breast cancer in April 2024, based on results from the TROPION-Breast01 Phase III trial (Adrian Kemp, 2024).

Synergy of ADCs with ALC1i

10 The above-mentioned ADCs facilitate the transport of the TOP1i into cancer cells and releases the drug at cancer-specific sites. In addition to the cytotoxic effect by binding to its respective surface antigen of the conjugated antibody, the TOP1i disrupts the replication fork and leads to DNA strand breaks.

As mentioned above (TOP1i, description of the drug and synergy with ALC1i), ALC1i on top of the TOP1i may contribute to replication fork stalling and accumulation of additional DNA damage in an even more targeted context. It could thus be hypothesized that ALC1i co-dosed with the targeted release of
15 TOP1i would be suitable in treating HER2-positive and/or Trop1-positive cancer.

As shown in the present invention, ALC1 inhibition via specific ALC1i synergistically impacts the cellular response to the DNA damage induced by Trastuzumab and TOP1i, namely trastuzumab deruxtecan as well as datopotamab deruxtecan and sacituzumab govitecan. Thus, the present inventors determined that by using a combination of an ADC like anti-HER2 antibody with a TOP1i and a specific ALC1i, the effects
20 of both drugs can be synergistically enhanced. As trastuzumab deruxtecan, datopotamab deruxtecan and sacituzumab govitecan show high MSA scores in combination with said specific ALC1i in multiple different cell lines, it can be expected that this will also be the case for other antibody drug conjugates with a tumor specific antibody conjugated to a TOP1 inhibitor. Thus, preferably a combination of an ALC1i used according to the present invention and an antibody drug conjugate with a tumor specific antibody
25 conjugated to a TOP1 inhibitor is used, in particular for treating (e.g. Trop1⁺ or HER2^{low/+}) breast cancer, gastric cancer or non-small cell lung cancer.

MEK inhibitors

Trametinib (C26H23FIN5O4, GSK1120212, CAS No. 871700-17-3, IUPAC: N-(3-{3-Cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-
30 d]pyrimidin-1(2H)-yl}phenyl)acetamide) targets and inhibits the MEK protein, which is part of the MAPK/ERK pathway. This pathway plays a critical role in the growth and development of cancer cells. Trametinib is often used in the treatment of cancers which have a specific mutation in the BRAF gene (BRAF V600E or V600K mutations) or mutations in KRAS.

35 Synergy of MEK inhibitors with ALC1i

MEK inhibitors are known to induce widespread changes to the chromatin landscape of treated cells, including changes to histone acetylation patterns and gene expression levels. MEKi treatment also induces increases in NF-κB activity, indicating increased DNA damage in response to treatment. The

authors hypothesized that inhibition of ALC1 by the ALC1i used in the invention would hamper the repair of this additional DNA damage, resulting in the potentiation of the anti-proliferative effect of MEK inhibitors. This was confirmed during co-dosing experiments of the specific ALC1 inhibitors used in the invention and trametinib *in vivo*.

5

Cell Lines used

cell line	origin of cancer	cancer type
HCC1937	Breast	Ductal Carcinoma, ERneg HER2neg
SUM149PT	Breast	Ductal Carcinoma, ERneg HER2neg
MDA-MB-231	Breast	Adenocarcinoma, ERneg HER2neg
MDA-MB-436	Breast	Adenocarcinoma, ERneg HER2neg
DLD1 BRCA2-/-	Colorectal	Colorectal Adenocarcinoma
DLD1wt	Colorectal	Colorectal Adenocarcinoma
HCT116	Colorectal	Colorectal Adenocarcinoma
SW620	Colorectal	Colorectal Adenocarcinoma
HEPG2	Liver	Hepatocellular Carcinoma
BXPC3	Pancreas	Exocrine Adenocarcinoma
PSN1	Pancreas	Exocrine Adenocarcinoma
PSN1 Talazoparib resistant	Pancreas	Exocrine Adenocarcinoma
22RV1	Prostate	Prostate Adenocarcinoma
DU145	Prostate	Prostate Adenocarcinoma
PC-3	Prostate	Prostate Adenocarcinoma
SKBR3	Breast	Adenocarcinoma, HER2 pos
HCC2429	Lung	Non-Small Cell Lung Cancer
MiaPaCa2	Pancreas	Ductal Adenocarcinoma
T47D	Breast	Ductal Carcinoma ER pos HER2neg

As a BRCA wild-type cell line, MDA-MB-231 cells were used. The cells were established from an aneuploid female human. The cells were extracted from the mammary gland (breast) in the metastatic site as a pleural effusion. (MDA-MB-231 (ATCC® HTB-26™ Homo sapiens epithelial mammary gland) It is available from numerous sources including ATCC® HTB-26™.

As a BRCA negative cell line, SUM149PT cells were used. The cell line is a triple negative breast cancer (TNBC) cell line, derived from primary human invasive ductal carcinoma metastatic nodule from a 40-year-old female. It contains a hemizygous BRCA1 mutation (p.Pro724Leufs*12) and is available from numerous sources including bioIVT.

PSN1 cells were used. The human cell line was derived from pancreatic adenocarcinoma tissue. It harbors an amplification of c-myc and activated c-Ki-ras and a loss of one of the two p53 alleles. The cell line is available from numerous sources including MERCK (94060601).

PSN1 talazoparib resistant cells were generated by treating PSN1 cells with increasing sub-toxic doses of talazoparib for 3 months. These cells show > 10 fold resistance to talazoparib over the parental PSN1 cells.

BxPC3 cells were used. The cells were extracted from the pancreas tissue of a 61-year-old female with adenocarcinoma. The established cell line does not express CFTR (cystic fibrosis transmembrane conductance regulator), but it expresses mucin, the pancreas cancer specific antigen, and CEA (carcinoembryonic antigen). The cells are available from numerous sources including MERCK (93120816).

5 22Rv1 cells were used. The cell line is derived from a xenograft that was serially propagated in mice after castration-induced regression and relapse of the parental CWR22 xenograft that was androgen-dependent. The cells originate from prostate carcinoma and are epithelial. They express PSA (prostate-specific antigen) and have a damaging mutation in BRCA2. The cell line is available at numerous sources including Accegen (ABC-TC0004).

10 DU145 cells were used. The cells were isolated from the brain of a 69-year-old male with prostate cancer, the established cell line has epithelial morphology. It is hypotriploid and has mutations in BRCA1, BRCA2, RAD50, WRN and TP53. The cell line is available at ATCC HTB-81™

 DLD1wt cells were used. The cells were extracted from the large intestine of an adult male patient with colorectal carcinoma and a cell line was established. They are pseudodiploid(2n=46), express p53
15 antigen and have damaging mutations in BRCA2, FANCA, and TP53. The cell line is available at numerous sources including MERCK (90102540).

 DLD1 BRCA2-/- cells were used. This cell line originated from the DLD1-wt and is a BRCA2 knockout cell line. It is available at several sources including Creative Biogene (CSC-RT0028).

 HCT116 cells were used. This cell line originates from colon tissue from an adult male with
20 colorectal carcinoma. It has damaging mutations in BRCA2, FANCA and POLD1. This cell line is available at numerous sources including the DSMZ (ACC 581).

 PC-3 cells were used. The cell line originates from a 62-year-old male patient with a grade IV prostatic adenocarcinoma, specifically from a bone metastasis. The cells are epithelial, near triploid and have a damaging mutation in TP53. They are available at numerous sources including MERCK (90112714).

25 SW620 cells were used. The cells were isolated from the lymph node of a 51-year-old male with Dukes' C colorectal adenocarcinoma and a cell line was established. The cell line is available at numerous sources including ATCC CCL-227™

 T47D cells were used. The cell line was established from a 54-year-old female human with an infiltrating ductal carcinoma of the breast. The cells were extracted from the mammary gland (breast) as a
30 pleural effusion. They are available at numerous sources including ATCC HTB-133™

 HCC1937 cells were used. They were isolated from a 23-year-old female with a primary ductal carcinoma, specifically from a mammary gland. The cell line has a homozygous BRCA1 mutation and is negative for expression of p53 and Her2-neu, the morphology is epithelial. The cells are available at several sources including Amsbio (Cat. No. AMS.EP-CL-0093).

35 MDA-MB-436 cells were used. The cell line is derived from a 43-year-old female with breast adenocarcinoma, it was extracted from the mammary gland in the metastatic site as a pleural effusion. The cells are pleomorphic with multinucleated component cells. They are available at numerous sources including Accegen (Cat. No. ABC-TC0655).

HEPG2 cells were used. The cell line was established from a 15-year-old male patient with a hepatocellular carcinoma. The cells express several major plasma proteins like albumin, fibrinogen, and alpha 2-macroglobulin, the morphology is epithelial-like. The cell line is available at ATCC HB-8065™

SKBR3 (also known as SK-BR-3) is a human breast cancer cell line isolated by the Memorial Sloan-Kettering Cancer Center in 1970 that is used in therapeutic research, especially in context of HER2 targeting. SKBR3 cells were derived from a pleural effusion due to an adenocarcinoma originating in a 43-year-old Caucasian female. The cell line over-expresses the HER2 gene product, which has been implicated in several breast cancer proliferation pathways.

HCC2429 was established from a 34-year old non-smoking woman with metastatic non-small cell lung carcinoma, demonstrating a t(15;19)(q13.2;p13.1) with a BRD4-NUTM1 ex11:ex2 fusion. The cell line is patented by Vanderbilt University Medical Center, Nashville, TN, USA.

MiaPaCa2 cells were also utilized. This cell line was derived from a 65-year-old white male with undifferentiated pancreatic carcinoma. Exhibits neuroendocrine features and described to carry mutations in KRAS, CDKN2A and TP53. This cell line is available at multiple sources, including ATCC (CRL-1420).

Inhibitor vs. Response (cell survival) assay

For validation of the small molecule inhibitors, the pancreatic cell line PSN1 was used. Cells were seeded in 96-well plates (2000 cells/well) and treated with titrations of ALC1 inhibitors in the μM range. As a control for “no-treatment”, DMSO was added to the cells. The cells were cultured at 37°C, CO₂ 5 % for 5 days until they were fixed with 10% TCA for 1h and stained with sulforhodamine dye for 30 minutes. After washing the cells with 1% Acetic Acid, 10 mM Tris (pH 10.5) solution was used to solubilize the stained cells. The absorbance was measured at 492 nm using the SUNRISE TECAN, the data were normalized to 100 % survival (=DMSO control). Inhibitor vs. response curves were fitted with the Synergy Finder using the curve fitting parameter “LL4”. The curves show an average fit of 3 technical replicates.

Synergy with other drugs in cellular assays

For determination of the ZIP synergy score, a 2-D titration of two compounds is added to cells in the 96h-SRB-survival (described above) assay format.

The score is calculated by adding the readout of the survival data from the SRB assay of at least 2 replicate plates to an open-source program called Synergy Finder.

“SynergyFinder (<https://synergyfinder.fimm.fi>) is a stand-alone web-application for interactive analysis and visualization of drug combination screening data. Since its first release in 2017, SynergyFinder has become a widely used web-tool both for the discovery of novel synergistic drug combinations in pre-clinical model systems (e.g. cell lines or primary patient-derived cells), and for better understanding of mechanisms of combination treatment efficacy or resistance” (Ianevski et al. 2020).

In the Zero interaction potency (ZIP) model, the drug interaction relationship is determined by comparison of the change in potency of the dose-dependent curves between individual drugs and their combination (https://synergyfinder.fimm.fi/synergy/synfin_docs/). The model is further described in <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4759128/>.

SynergyFinder uses a cNMF algorithm to detect and replace outlier measurements. The Version used to obtain the data as shown herein are Version 2.0 and 3.0.

The summary synergy score is averaged over all dose combinations from the 2-D titration matrix. The most synergistic area (MSA) shows the most synergistic 3-by-3 dose-window in the dose-response matrix.

For interpretation of the synergy scores calculated in this program, see Table 1:

Table 1:MSA	labeling MSA score	interpretation
MSA less than 9	-	interaction between two drugs is likely not synergistic
MSA between 9 and 10	+	interaction between two drugs is highly likely to be synergistic
MSA between 10 and 20	++	interaction between two drugs is synergistic
MSA >20	+++	interaction between two drugs is highly synergistic

The results for the combinations of the invention of the specific ALC1 inhibitors used according to the invention (compound A) and several examples of other classes of cancer drugs (compound B) on the treatment of different cancer cell lines are summarized in Figure 2. Drug combinations with an MSA (most synergistic area) score below 9 indicate interactions that are likely not synergistic and are labeled with a “-”. An MSA score between 9-10 is labeled with “+” and indicates that the interaction of compound A and B is likely to be synergistic. MSA scores above 10 are marked “++” are synergistic. MSA scores greater than 20 are labeled as “+++” and considered highly synergistic. As comparative Examples, “Compound 1” and “Compound 3” (chemical structure shown above) were tested and were found to provide only additive (MSA score “-”), but no synergistic effect. In contrast, all tested combinations of the specific ALC1 inhibitors used according to the invention show a synergistic anti cancer effect (MSA scores “+”, “++” or even “+++”).

Cell cycle analysis

SUM149PT cells were seeded into 6-well plates and treated with ALC1i or DMSO for 48h. Cells were harvested, washed in PBS before fixation/permeabilization with 75% ice-cold ethanol. After incubation of >30min at 4°C, cells were stained with 1ug/ml DAPI. Flow cytometric analysis was conducted using a FACS Fortessa (BD Bioscience). Flow cytometric analysis of DNA content stained with the DNA intercalator DAPI is indicative for cell cycle (2n = G1 phase; 4n = G2/M phase). Treatment with DMSO shows cells in G1, S and G2 phase. Treatment with ALC1 inhibitors shows enrichment/block of cells in G2 phase.

γH2AX protein level determination with Western Blot

PSN1 cells were seeded into 6-well plates and treated with increasing concentrations of ALC1i-101 or DMSO for 24h. Cells were harvested and lysed using 1xSDS with benzonase. After denaturation,

the samples were loaded onto a gradient gel (Mini-PROTEAN TGX Stain-Free Precast Gels, 4-20%, BioRad 456-8095). Gel electrophoresis was run, and proteins were transferred onto a nitrocellulose membrane using the TransBlot turbo (BioRad). The membrane was blocked for 1h with intercept blocking buffer from LiCor and then stained with the following antibodies:

- 5 1°AB: Anti-γH2AX (Abcam, AB11174), alpha-tubulin (sigma, T9026)
- 2°AB (Licor): IRDye 800CW Goat anti-Rabbit 925-32211, IRDye 680RD Donkey anti-Mouse 925-68072

Images of the membrane were taken using the LiCor. Protein amount was determined via band analysis using (FIJI, image J) and the γH2AX protein bands were normalized to the corresponding α-tubulin bands.

- 10 Finally, the different treatment groups were normalized to the DMSO control to show the percent-change in protein amounts.

Cell derived xenograft (CDX) of MiaPaCa2 cells

To test ALC1i in combination with MEKi *in vivo*, 5 x 10⁵ MiaPaCa2 cells (a pancreatic cancer cell line with KRAS G12C mutation) were injected into the lateral flank of NMRI nude mice in 50% Matrigel
 15 50% PBS. Single treatments and combination treatments were started when average tumor sizes reached 250mm³ for randomization. Treatments were given as an oral suspension on a daily basis. ALC1i-101 was formulated at 250 mg/kg in SyrSpend, MEKi trametinib was formulated at 0.5 mg/kg in 10% Kolliphor and 10% PEG400.

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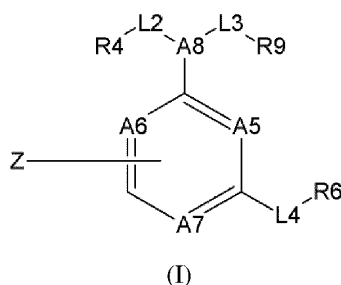
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Claims

1. An allosteric inhibitor of Chromodomain-helicase-DNA-binding protein 1-like (ALC1), wherein the inhibitor specifically binds to an allosteric binding pocket formed by an amino acid stretch spanning amino acid residues 101 to 219 of SEQ ID NO: 1 for use in treating or ameliorating a proliferative disease in a patient in combination with and/or for use in enhancing the efficacy in treating a proliferative disease of
 - a) an inhibitor of Topoisomerase I, Topoisomerase II, ATM, ATR, Wee1, BRD, and/or MEK,
 - b) mitomycin C or paclitaxel,
 - c) ionizing radiation, or
 - d) an antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor.
2. The allosteric inhibitor of ALC1 for use according to claim 1, wherein the allosteric binding pocket comprises or consists of L101, Y153, C156, L157, A160, L163, K164, V173, D174, E175, A176, H177, R178, L179, S183, L186, H187, T189, L190, F193, L200, L201, T202, N208, S209, E212, L213, L216, and F219 of SEQ ID NO: 1, preferably comprises or consists of Y153, C156, L157, A160, L163, V173, E175, R178, L186, H187, L190, F193, L200, and E212 of SEQ ID NO: 1.
3. The inhibitor of ALC1 (ALC1i) for use according to claim 1 or 2, wherein the inhibitor of ALC1 (ALC1i) is according to Formula (I)



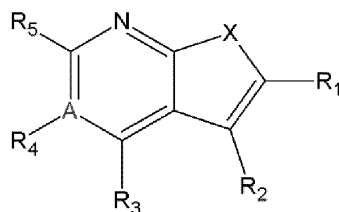
and isomers, salts, solvates, chemically protected forms, and prodrugs thereof, wherein

- (i) A5 and A8 are each independently selected from N or CH;
- (ii) A6 is selected from N or CH, or when A6 takes part in the annulated carbo- or heterocycle Z, then A6 is C;
- (iii) A7 is selected from N or CH, or when A7 takes part in the annulated carbo- or heterocycle Z, then A7 is C;
- (iv) L2 is selected from the group consisting of -CH₂-R₄, -CF₂-R₄, -CH₂-CH₂-R₄, -CH₂-CH₂-CH₂-R₄, -O-R₄, -NH-R₄, -N=R₄;
- (v) L3 is selected from the group consisting of -CH₂-R₉, -CF₂-R₉, -CH₂-CH₂-R₉, -CH₂-CF₂-R₉, -CH₂-CH₂-CH₂-R₉, -O-R₉, -NH-R₉, -N=R₉;

or

- (vi) L2 and L3 together with the A8 to which they are connected form a 5- or 6-membered heterocycle substituted by R4 and/or R9;
- (vii) L4 is CH₂, -CF₂-, CH₂-CH₂, CH₂-CH₂-CH₂, O, N, and NH, or is absent;
- 5 (viii) Z is a 5-, 6- or 7-membered carbo- or heterocycle, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and -NO₂; and can be annulated to the central core or connected via a covalent bond
- (ix) R4 is 5-, 6- or 7-membered carbo- or heterocycle, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -CF₃, Me, Et, -OMe, and -SMe, or R4 is hydrogen, methyl, or COOH;
- 10 (x) R9 is a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered carbo- or heterocycle, optionally substituted with one, two, or three (preferably one) substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe;
- (xi) R6 is a 5-, 6- or 7-membered carbo- or heterocycle, optionally substituted with one, two, or three (preferably one) substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe;
- 15 (xii) or R6 is H;
- or
- 20 (xiii) when A7 takes part in the annulated carbo- or heterocycle Z then A5 and A6 are independently selected from -N or -CH and A8 is selected from -N, -CH, -CH₂-N, -CH₂-CH, or -NH-CH;

or according to Formula (II)



(II)

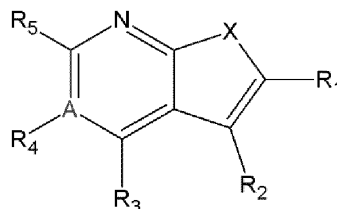
- 25 and isomers, salts, solvates, chemically protected forms, and prodrugs thereof, wherein
- (i) X is N or S;
- (ii) A is C or N;
- (iii) R₁ is -CO-OR₆, -CO-R₇, or -CO-NR₆R_A, preferably R₁ is -CO-OR₆;
- 30 (iv) R₂ is -R₇, -NHR₈, -O-R₇, -C-O-R₇, Br, -C₃₋₈-cycloalkyl (preferably cyclopropyl), or -C₄₋₈-cycloalkenyl (preferably cyclohexenyl);
- or
- (v) R₁ and R₂ together form a 5, 6 or 7 membered carbo- or heterocycle, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting

of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, =O, and [-O-CH₂-CH₂]-NH-CH(OH)-O-tBu;

- (vi) R₃ is H, =O, -OH, -O-R₇, -R₇, or -(CH₂)_m-L, wherein m is 0, 1 or 2, and L is a 5, 6 or 7 membered carbo- or heterocycle, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, -hydroxyC₁₋₃-alkyl and =O;
- (vii) R₄ is H or -C₁₋₃-alkyl, preferably H;
- (viii) R₅ is -(CH₂)_m-L, or -(CH₂)_m-(CH=CH)-L, wherein m is 0, 1 or 2, preferably 0 or 1, and L is a 5, 6 or 7 membered carbo- or heterocycle, adamantyl, C₁₋₄-alkyl, or -N(CH₃)₂, optionally substituted, preferably with 1, 2, 3 or 4 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -CO-OR₆, -Br, -Cl, -F, -I, -R₉, -O-R₉, =O, and [-O-CH₂-CH₂]_q-NH-biotin with q being 1, 2, 3, or 4, or two adjacent substituents form a 5, 6 or 7 membered carbo- or heterocycle;
- or
- (ix) R₄ and R₅ together form a 5, 6, or 7 membered carbocycle, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-R₉, -R₉, =CH-R_A, and -CH₂-R_A, preferably R₄ and R₅ together form a C₅₋₇-cycloalkyl;
- (x) R₆ is H, -C₁₋₆-alkyl, -C₂₋₆-alkenyl, -C₂₋₆-alkynyl, optionally substituted, preferably R₆ is H;
- (xi) R₇ is -C₁₋₃-alkyl, -C₂₋₃-alkenyl, -C₂₋₃-alkynyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -Br, -Cl, -F, -I, -CH₃, -OCH₃, or -SCH₃;
- (xii) R₈ is H or C₁₋₆-alkyl, preferably H,
- (xiii) R₉ is -C₁₋₆-alkyl, -C₂₋₆-alkenyl, -C₂₋₆-alkynyl, -C₁₋₆-alkyl-aryl, or C₁₋₆-alkyl-heteroaryl (preferably isooxazole, thiazole, tetrazole, 1,2,4-thiadiazole, 1,2,3-thiadiazole, 1,2,5-thiadiazole, pyridine, 1,2,4-oxadiazole, pyrazine, or pyrazole), optionally substituted with 1, 2 or 3 substituents selected from the group consisting of -Br, -Cl, -F, -I, -NO₂, -CN, -CONH₂, -CONH-C₁₋₃-alkyl (preferably -CONH-CH₃), -NH-CO-C₁₋₃-alkyl (preferably -NH-CO-CH₃), -C₁₋₆-alkyl (preferably -CH₃, ethyl, propyl, t-butyl, or pentyl), -C₁₋₃-haloalkyl (preferably -CF₃, or -CHF₂), -O-CHF₂, -O-CF₃, carbocycle (preferably cyclopropyl, cyclohexyl or phenyl), -O-carbocycle (preferably phenoxy), heterocycle (preferably pyrazolyl), -CO-heterocycle (preferably -CO-(1-pyrrolidinyl)), -SO₂-CH₃, -SO₂-N(CH₃)₂, -O-C₁₋₄-alkyl (preferably -OCH₃), -O-C₁₋₃-alkyl-O-C₁₋₃-alkyl (preferably -O-CH₂-O-CH₃), -SCH₃, or when R₉ is -C₁₋₆-alkyl-aryl, then two adjacent substituents on the aryl moiety can form a 5, 6 or 7 membered carbo- or heterocycle, which is optionally substituted;
- (xiv) R_A is H, carbo- or heterocycle, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting

of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -R₉, -O-R₇, -O-(CH₂)_o-R₉, -SO₂NH₂, and =O, wherein o is 0 or 1.

4. An inhibitor of ALC1 (ALC1i) according to formula (II)



(II)

and isomers, salts, solvates, chemically protected forms, and prodrugs thereof, wherein

- (i) X is N or S;
- (ii) A is C or N;
- 10 (iii) R₁ is -CO-OR₆, -CO-R₇, or -CO-NR₆R_A, preferably R₁ is -CO-OR₆;
- (iv) R₂ is -R₇, -NHR₈, -O-R₇, -C-O-R₇, Br, -C₃₋₈-cycloalkyl (preferably cyclopropyl), or -C₄₋₈-cycloalkenyl (preferably cyclohexenyl);
or
- (v) R₁ and R₂ together form a 5, 6 or 7 membered carbo- or heterocycle, optionally substituted,
15 preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, =O, and [-O-CH₂-CH₂]-NH-CH(OH)-O-tBu;
- (vi) R₃ is H, =O, -OH, -O-R₇, -R₇, or -(CH₂)_m-L, wherein m is 0, 1 or 2, and L is a 5, 6 or 7 membered carbo- or heterocycle, optionally substituted, preferably with 1, 2, or 3
20 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, -hydroxyC₁₋₃-alkyl and =O;
- (vii) R₄ is H or -C₁₋₃-alkyl, preferably H;
- (viii) R₅ is -(CH₂)_m-L, or -(CH₂)_m-(CH=CH)-L, wherein m is 0, 1 or 2, preferably 0 or 1, and L is a 5, 6 or 7 membered carbo- or heterocycle, adamantyl, C₁₋₄-alkyl, or -N(CH₃)₂, optionally
25 substituted, preferably with 1, 2, 3 or 4 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -CO-OR₆, -Br, -Cl, -F, -I, -R₉, -O-R₉, =O, and [-O-CH₂-CH₂]_q-NH-biotin with q being 1, 2, 3, or 4, or two adjacent substituents form a 5, 6 or 7 membered carbo- or heterocycle;
or
- 30 (ix) R₄ and R₅ together form a 5, 6, or 7 membered carbocycle, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-R₉, -R₉, =CH-R_A, and -CH₂-R_A, preferably R₄ and R₅ together form a C₅₋₇-cycloalkyl;
- (x) R₆ is H, -C₁₋₆-alkyl, -C₂₋₆-alkenyl, -C₂₋₆-alkynyl, optionally substituted, preferably R₆ is H;

- (xi) R₇ is -C₁₋₃-alkyl, -C₂₋₃-alkenyl, -C₂₋₃-alkynyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -Br, -Cl, -F, -I, -CH₃, -OCH₃, or -SCH₃;
- (xii) R₈ is H or C₁₋₆-alkyl, preferably H,
- 5 (xiii) R₉ is -C₁₋₆-alkyl, -C₂₋₆-alkenyl, -C₂₋₆-alkynyl, -C₁₋₆-alkyl-aryl, or C₁₋₆-alkyl-heteroaryl (preferably isooxazole, thiazole, tetrazole, 1,2,4-thiadiazole, 1,2,3-thiadiazole, 1,2,5-thiadiazole, pyridine, 1,2,4-oxadiazole, pyrazine, or pyrazole), optionally substituted with 1, 2 or 3 substituents selected from the group consisting of -Br, -Cl, -F, -I, -NO₂, -CN, -CONH₂, -CONH-C₁₋₃-alkyl (preferably -CONH-CH₃), -NH-CO-C₁₋₃-alkyl (preferably -NH-CO-CH₃), -C₁₋₆-alkyl (preferably -CH₃, ethyl, propyl, t-butyl, or pentyl), -C₁₋₃-haloalkyl (preferably -CF₃, or -CHF₂), -O-CHF₂, -O-CF₃, carbocycle (preferably cyclopropyl, cyclohexyl or phenyl), -O-carbocycle (preferably phenoxy), heterocycle (preferably pyrazolyl), -CO-heterocycle (preferably -CO-(1-pyrrolidinyl)), -SO₂-CH₃, -SO₂-N(CH₃)₂, -O-C₁₋₄-alkyl (preferably -OCH₃), -O-C₁₋₃-alkyl-O-C₁₋₃-alkyl (preferably -O-CH₂-O-CH₃), -SCH₃, or when R₉ is -C₁₋₆-alkyl-aryl, then two adjacent substituents on the aryl moiety can form a 5, 6 or 7 membered carbo- or heterocycle, which is optionally substituted;
- 10 (xiv) R_A is H, carbo- or heterocycle, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -R₉, -O-R₇, -O-(CH₂)₆-R₉, -SO₂NH₂, and =O, wherein
- 15 o is 0 or 1,
- 20 for use in treating or ameliorating pancreatic cancer or fallopian tube cancer in a patient in combination with an inhibitor of PARP, or for use in enhancing efficacy of an inhibitor of PARP in treating or ameliorating pancreatic cancer or fallopian tube cancer in a patient.
- 25 5. The ALC1i for use according to any one of claims 1 to 5, wherein the ALC1i has a structure of Formula (I), wherein
- A5 is N;
- one of A6 and A7 is CH and the other one is N; or one of A6 and A7 is C and takes part in the annulated carbo- or heterocycle Z and the other one is N;
- 30 A8 is N or CH,
- or
- A5 is N;
- one of A6 and A7 is C and takes part in the annulated 5-, 6- or 7-membered carbo- or heterocycle, preferably 5- or 6 membered aryl or heteroaryl Z and the other one is N;
- 35 A8 is N;
- L2 is CH₂-CH₂-R₄ and L3 is CH₂-CH₂-R₉ or CH₂-CF₂-R₉ or L2 and L3 together with the A8 to which they are connected form a 5- or 6-membered heterocycle, preferably piperidinyl or a pyrrolidinyl substituted by R₄ and R₉;

- L4 is absent;
- Z is any 6-membered carbo- or heterocycle, preferably 6-membered aryl or heteroaryl annulated to the central core, wherein Z is optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, -OH, Me, -CF₃, Et, -OMe, -SMe, and NO₂;
- R4 is COOH or tetrazolyl;
- R9 is any 4-, 5-, 6-, or 7-membered carbo- or heterocycle, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -I, Me, -CF₃, Et, -OMe, and -SMe; and
- R6 is any 5- or 6-membered carbo- or heterocycle, optionally substituted with one, two, or three (preferably one) substituents selected from the group consisting of -Br, -Cl, -F, -I, -OH, -NO₂, Me, -CF₃, Et, -OMe, and -SMe, or R6 is H,
- or the ALC1i has a structure of Formula (II), wherein:
- X is N or S;
- A is C or N;
- R₁ is -CO-OR₆, -CO-R₇, or -CO-NR₆R_A, preferably R₁ is -CO-OR₆;
- R₂ is -R₇, -NHR₈, -O-R₇, -C-O-R₇, Br, -C₃₋₈-cycloalkyl (preferably cyclopropyl), or -C₄₋₈-cycloalkenyl (preferably cyclohexenyl);
- or
- R₁ and R₂ together form a 5, 6 or 7 membered carbo- or heterocycle, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, =O, and [-O-CH₂-CH₂]-NH-CH(OH)-O-tBu;
- R₃ is H, =O, -OH, -O-R₇, -R₇, or -(CH₂)_m-L, wherein m is 0, 1 or 2, and L is a 5, 6 or 7 membered carbo- or heterocycle, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-C₁₋₃-alkyl, -hydroxyC₁₋₃-alkyl and =O;
- R₄ is H or -C₁₋₃-alkyl, preferably H;
- R₅ is -(CH₂)_m-L, or -(CH₂)_m-(CH=CH)-L, wherein m is 0, 1 or 2, preferably 0 or 1, and L is a 5, 6 or 7 membered carbo- or heterocycle, adamantyl, C₁₋₄-alkyl, or -N(CH₃)₂, optionally substituted, preferably with 1, 2, 3 or 4 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -CO-OR₆, -Br, -Cl, -F, -I, -R₉, -O-R₉, =O, and [-O-CH₂-CH₂]_q-NH-biotin with q being 1, 2, 3, or 4, or two adjacent substituents form a 5, 6 or 7 membered carbo- or heterocycle;
- or
- R₄ and R₅ together form a 5, 6, or 7 membered carbocycle, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting

of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -O-R₉, -R₉, =CH-R_A, and -CH₂-R_A, preferably R₄ and R₅ together form a C₅₋₇-cycloalkyl;

R₆ is H, -C₁₋₆-alkyl, -C₂₋₆-alkenyl, -C₂₋₆-alkynyl, optionally substituted, preferably R₆ is H;

R₇ is -C₁₋₃-alkyl, -C₂₋₃-alkenyl, -C₂₋₃-alkynyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -Br, -Cl, -F, -I, -CH₃, -OCH₃, or -SCH₃;

R₈ is H or C₁₋₆-alkyl, preferably H,

R₉ is -C₁₋₆-alkyl, -C₂₋₆-alkenyl, -C₂₋₆-alkynyl, -C₁₋₆-alkyl-aryl, or C₁₋₆-alkyl-heteroaryl (preferably isooxazole, thiazole, tetrazole, 1,2,4-thiadiazole, 1,2,3-thiadiazole, 1,2,5-thiadiazole, pyridine, 1,2,4-oxadiazole, pyrazine, or pyrazole), optionally substituted with 1, 2 or 3 substituents selected from the group consisting of -Br, -Cl, -F, -I, -NO₂, -CN, -CONH₂, -CONH-C₁₋₃-alkyl (preferably -CONH-CH₃), -NH-CO-C₁₋₃-alkyl (preferably -NH-CO-CH₃), -C₁₋₆-alkyl (preferably -CH₃, ethyl, propyl, t-butyl, or pentyl), -C₁₋₃-haloalkyl (preferably -CF₃, or -CHF₂), -O-CHF₂, -O-CF₃, carbocycle (preferably cyclopropyl, cyclohexyl or phenyl), -O-carbocycle (preferably phenoxy), heterocycle (preferably pyrazolyl), -CO-heterocycle (preferably -CO-(1-pyrrolidinyl)), -SO₂-CH₃, -SO₂-N(CH₃)₂, -O-C₁₋₄-alkyl (preferably -OCH₃), -O-C₁₋₃-alkyl-O-C₁₋₃-alkyl (preferably -O-CH₂-O-CH₃), -SCH₃, or when R₉ is -C₁₋₆-alkyl-aryl, then two adjacent substituents on the aryl moiety can form a 5, 6 or 7 membered carbo- or heterocycle, which is optionally substituted;

R_A is H, carbo- or heterocycle, optionally substituted, preferably with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO₂, -CN, -Br, -Cl, -F, -I, -R₉, -O-R₇, -O-(CH₂)_o-R₉, -SO₂NH₂, and =O, wherein o is 0 or 1.

6. The ALC1i for use according to any one of claims 1 to 5, wherein the ALC1i has a structure of formula (I), wherein

each one of A₅, A₇ and A₈ is N;

A₆ is C and takes part in the annulated carbo- or heterocycle Z;

L₃ is CH₂-CF₂-R₉ or each one of L₂ and L₃ is CH₂-CH₂; or L₂ and L₃ together with the A₈ to

which they are connected form a piperidine ring or a pyrrolidine ring, substituted by R₄ and R₉;

L₄ is absent;

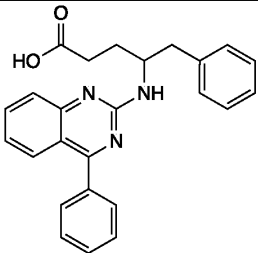
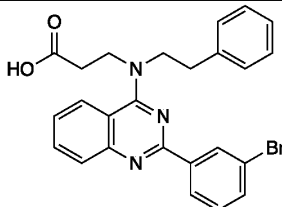
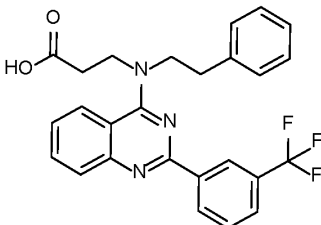
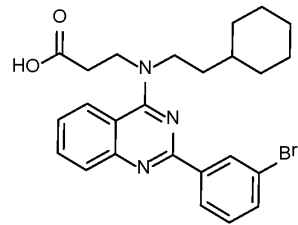
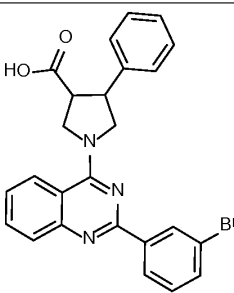
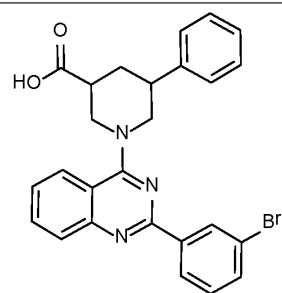
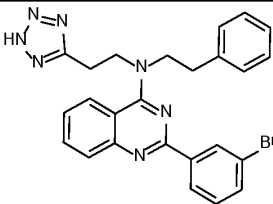
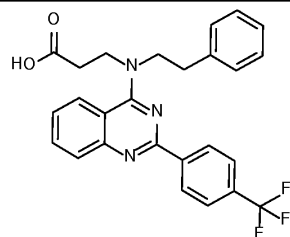
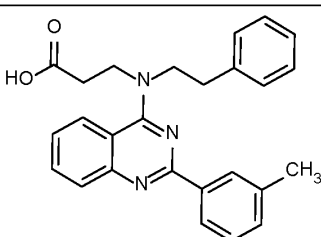
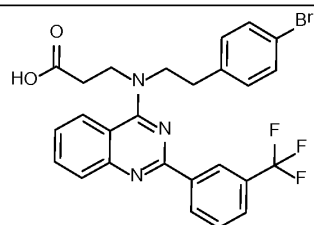
Z is phenyl or cyclohexyl annulated to the central core, wherein Z is optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -F, -OH, Me, -CF₃, -OMe, and -NO₂,

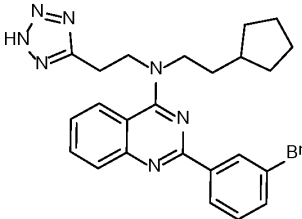
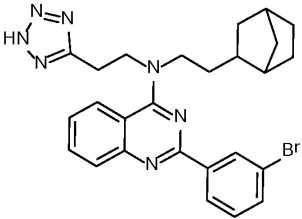
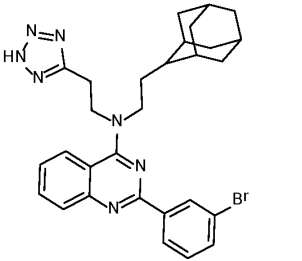
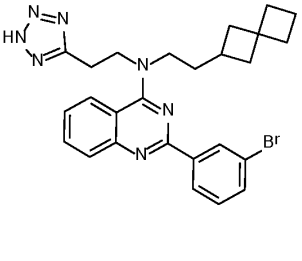
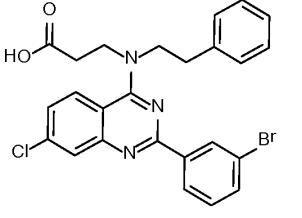
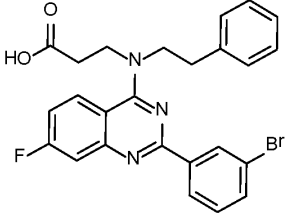
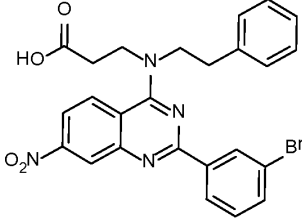
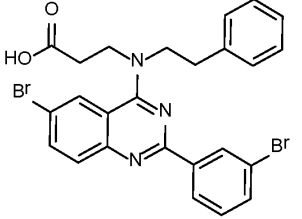
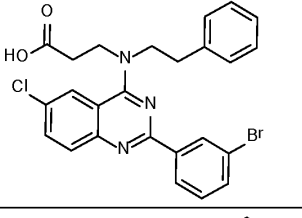
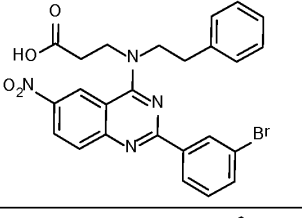
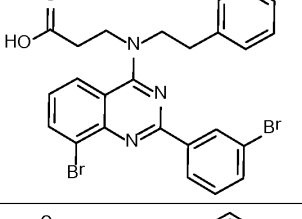
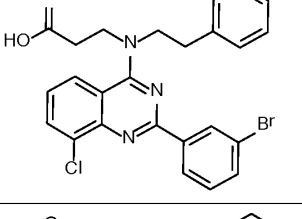
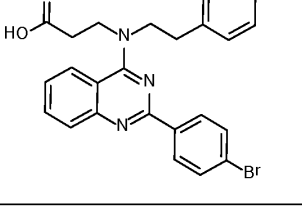
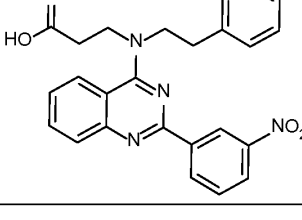
R₄ is COOH or tetrazolyl;

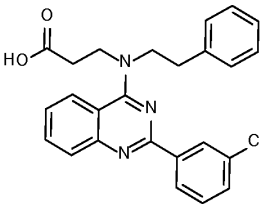
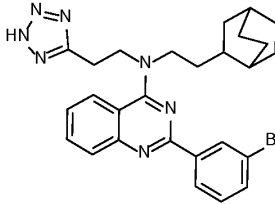
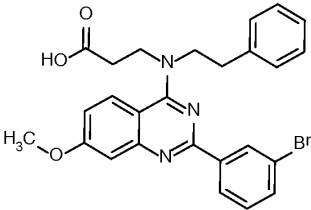
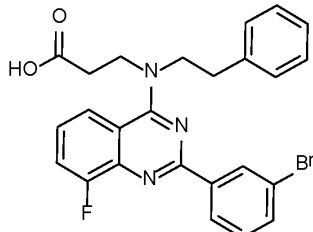
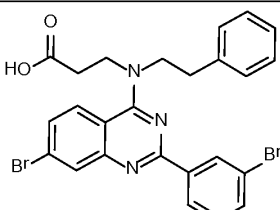
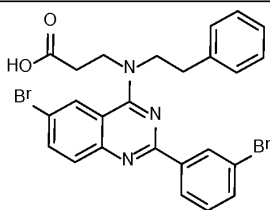
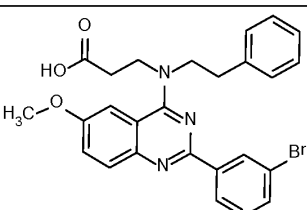
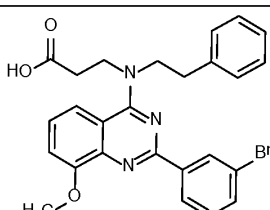
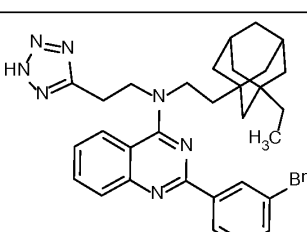
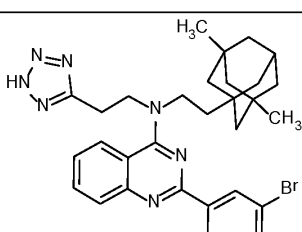
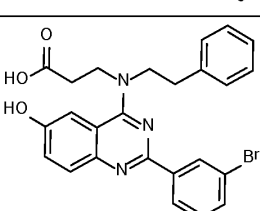
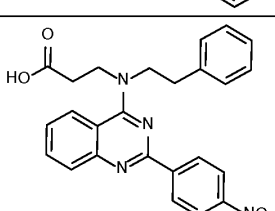
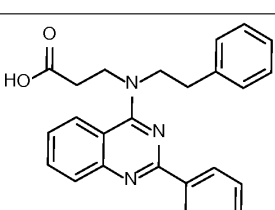
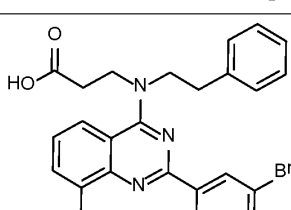
R₉ is phenyl, cyclobutyl, cyclopentyl or adamantyl, optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of -Br, -Cl, -CF₃, Me, -CH₂-CF₃, and -OMe;

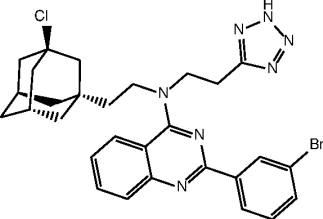
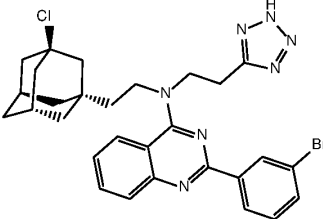
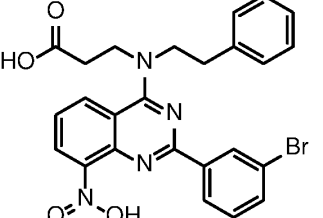
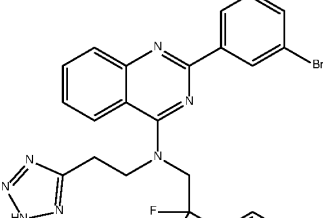
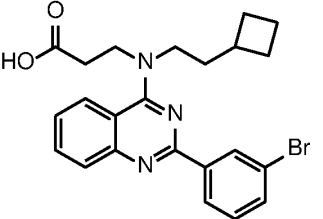
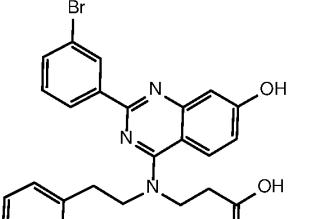
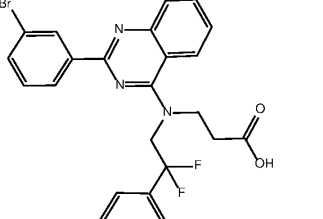
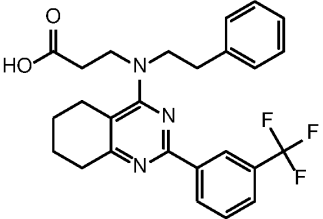
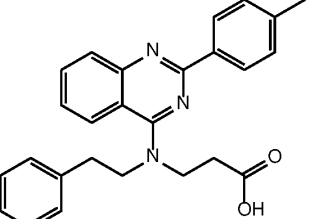
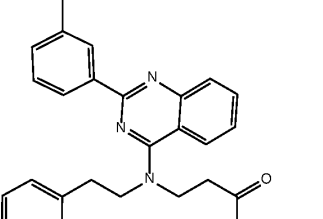
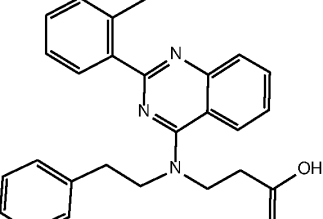
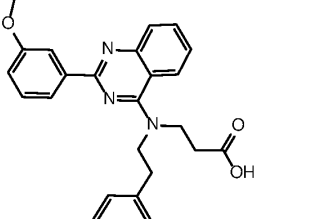
R6 is any 6-membered carbo- or heterocycle (preferably phenyl or cyclohexyl; more preferably phenyl), optionally substituted with one, two, or three, preferably one substituent(s) selected from the group consisting of Br, -Cl, -F, Me, -CF₃, -OMe, and -NO₂.

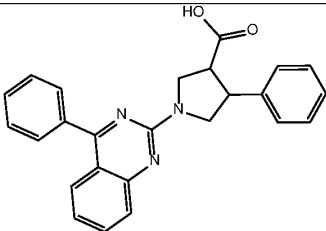
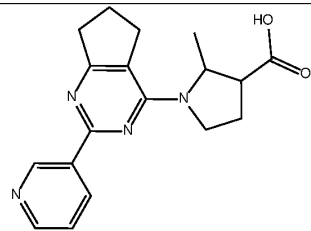
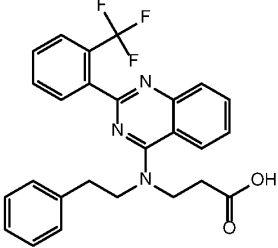
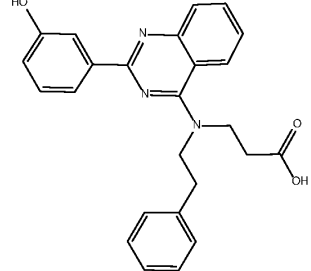
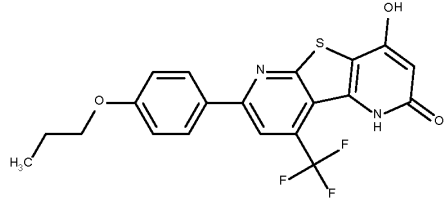
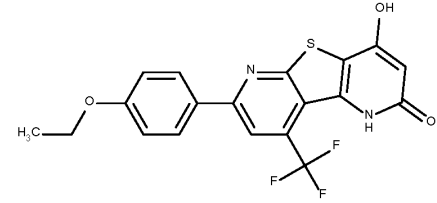
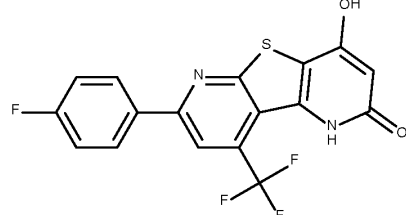
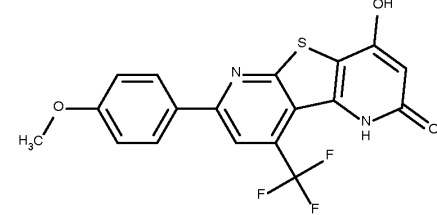
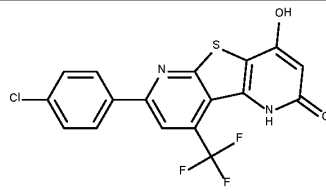
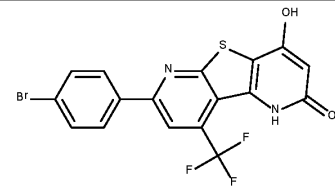
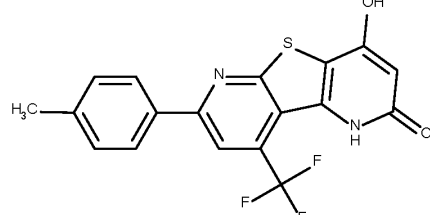
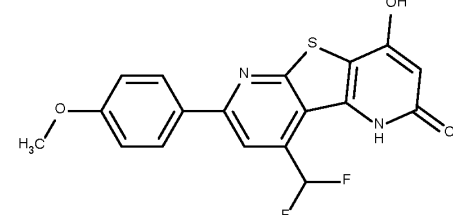
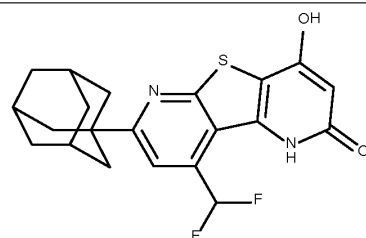
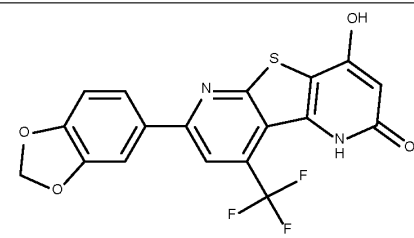
- 5 7. The ALC1i for use according to any of claims 1 to 6, wherein the ALC1i is selected from the group consisting of:

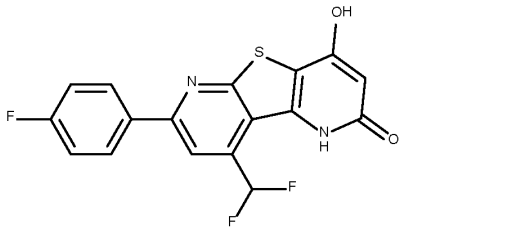
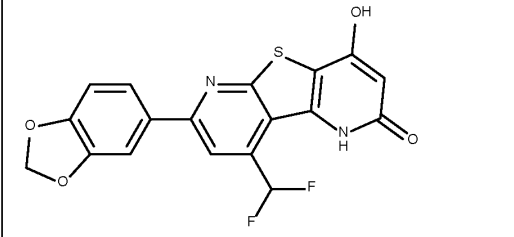
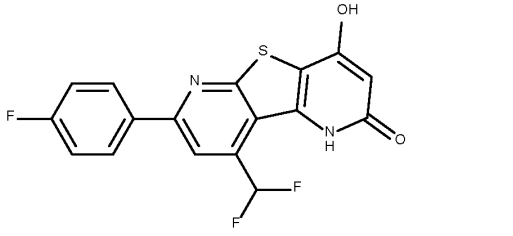
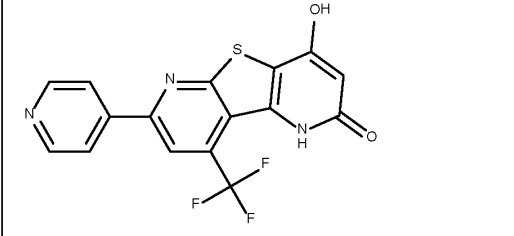
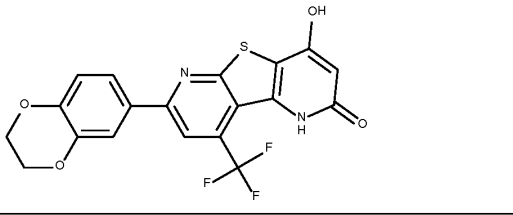
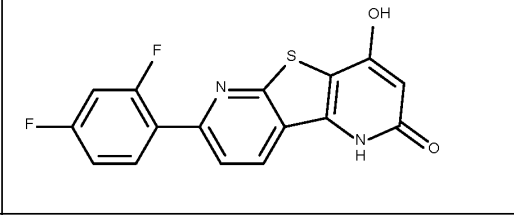
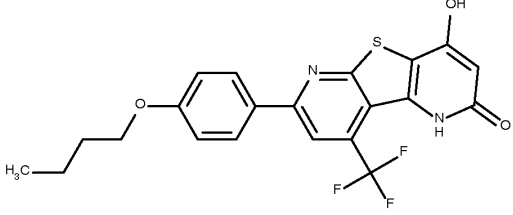
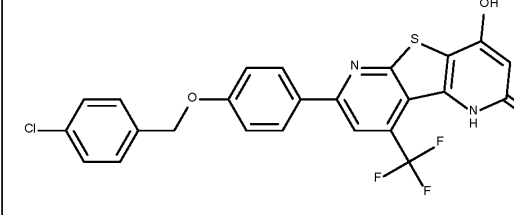
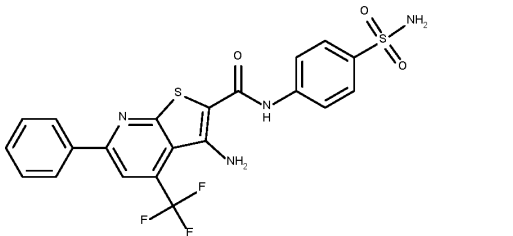
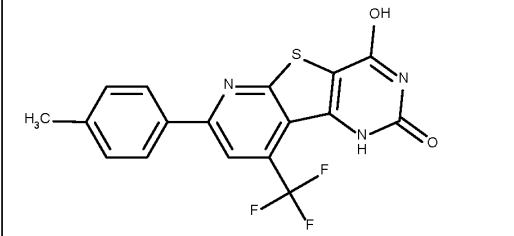
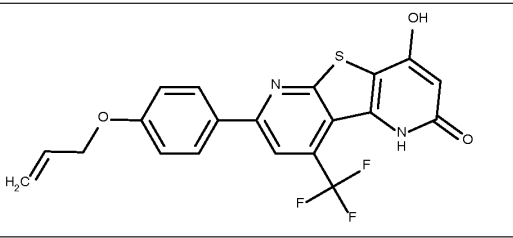
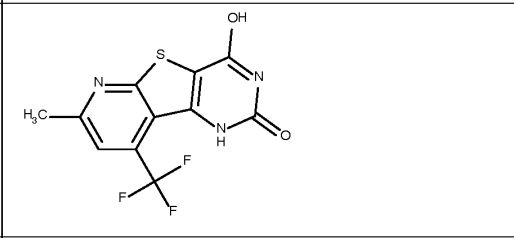
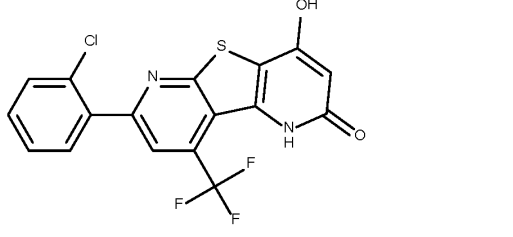
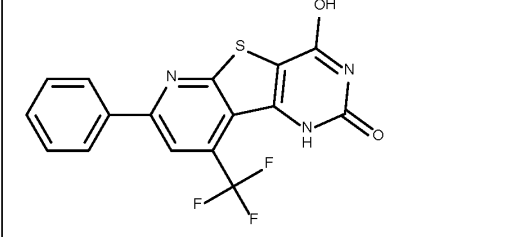
	
	
	
	
	

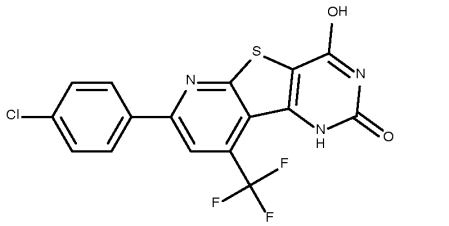
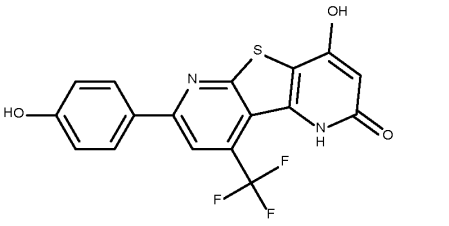
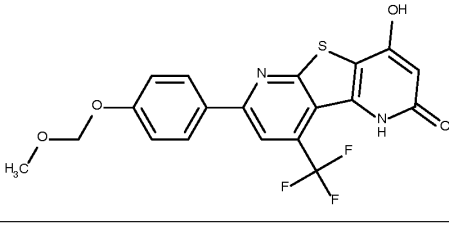
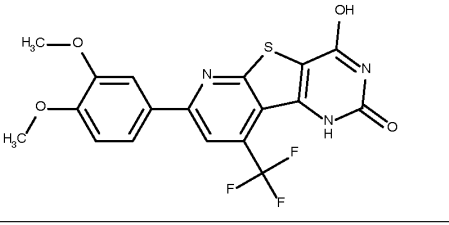
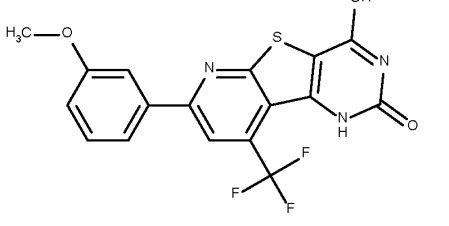
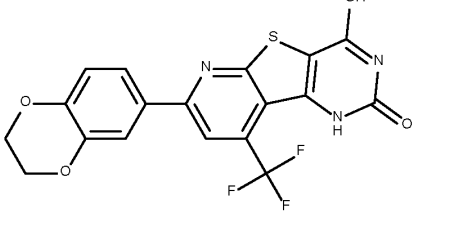
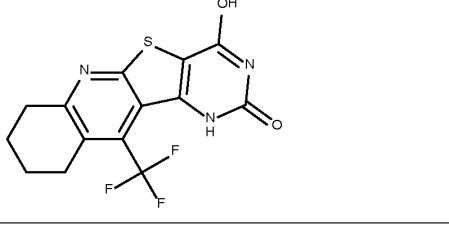
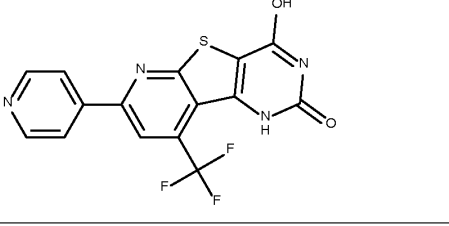
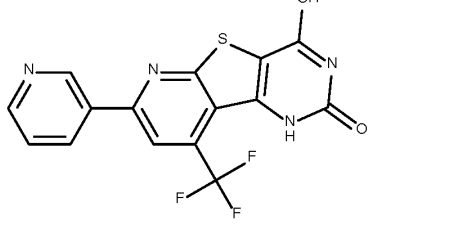
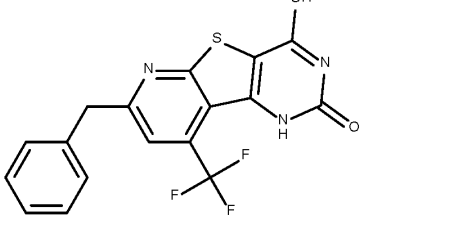
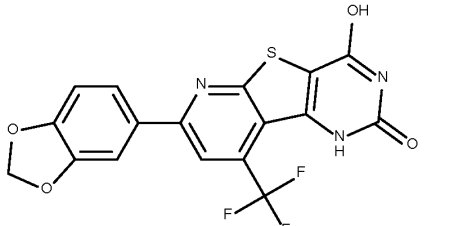
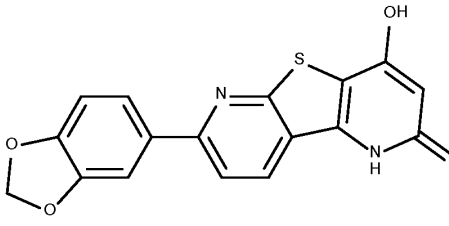
	
	
	
	
	
	
	

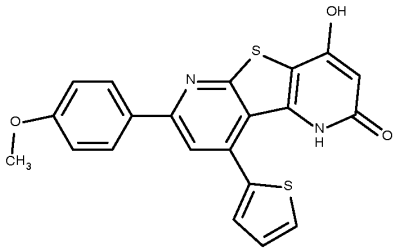
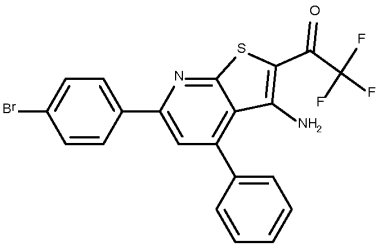
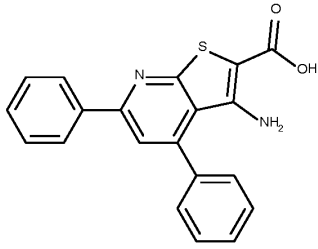
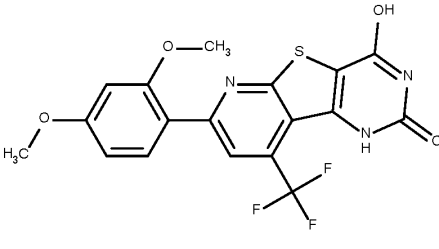
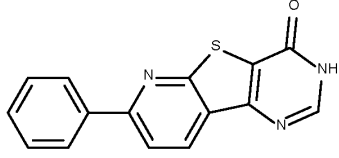
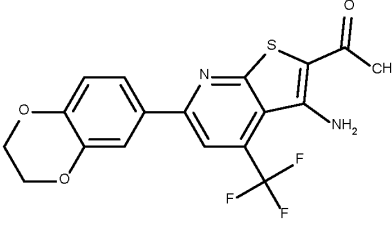
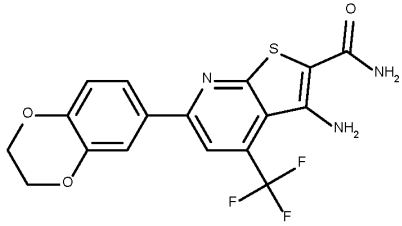
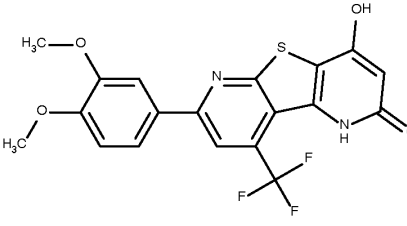
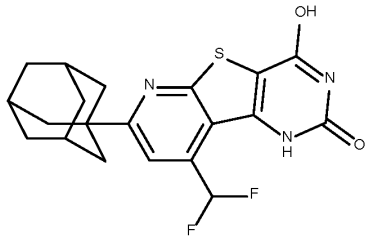
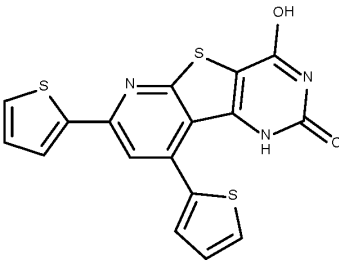
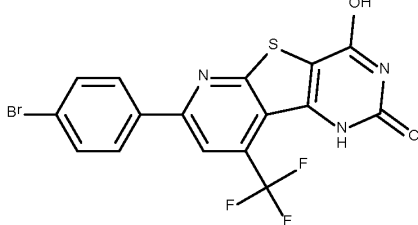
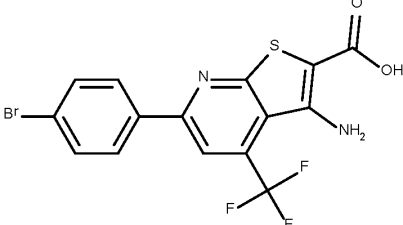
	
	
	
	
	
	
	

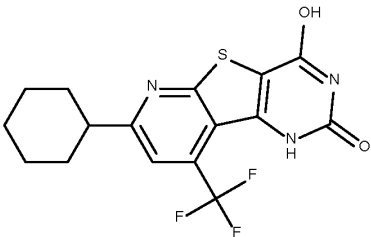
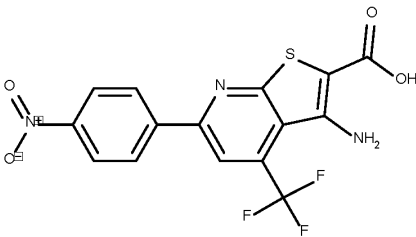
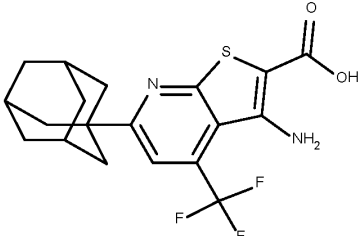
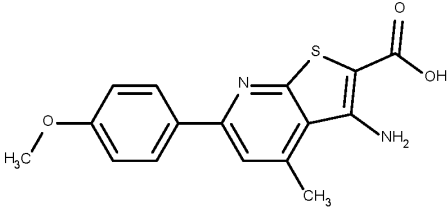
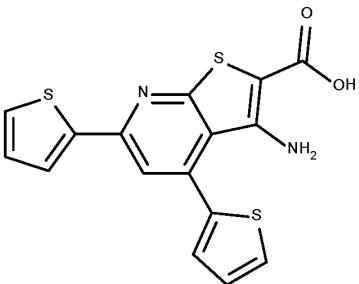
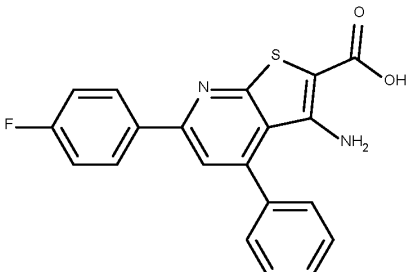
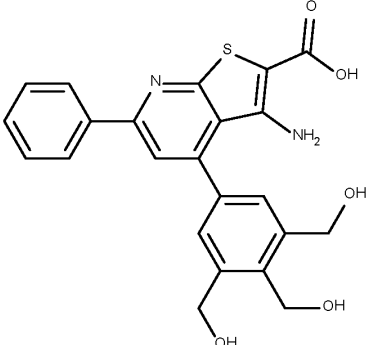
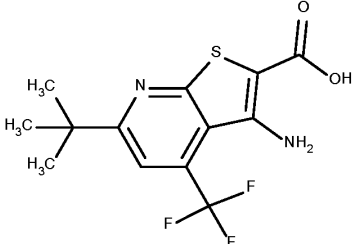
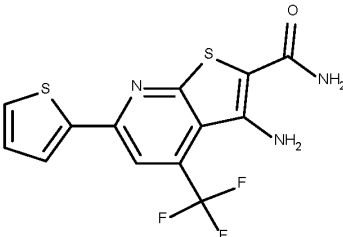
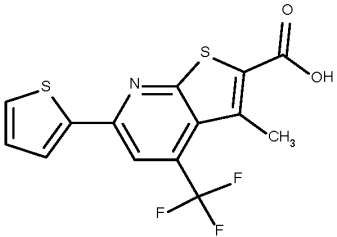
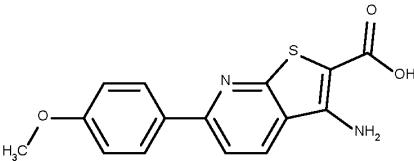
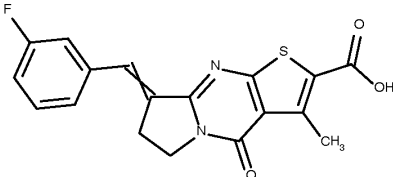
	
	
	
	
	
	

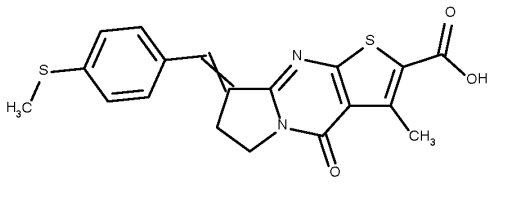
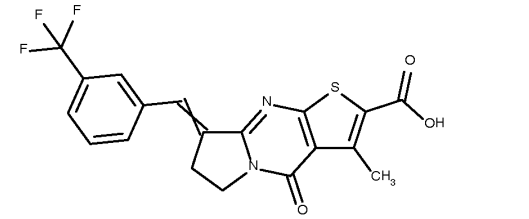
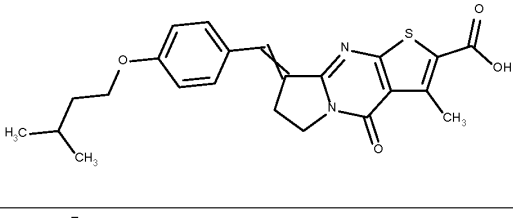
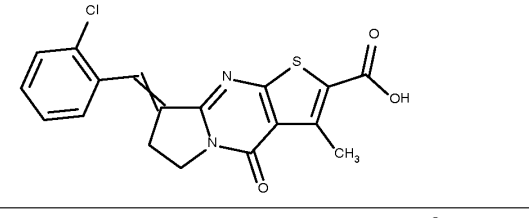
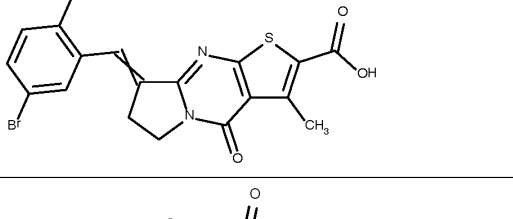
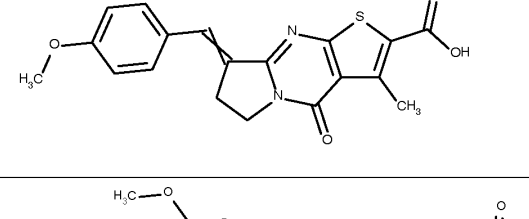
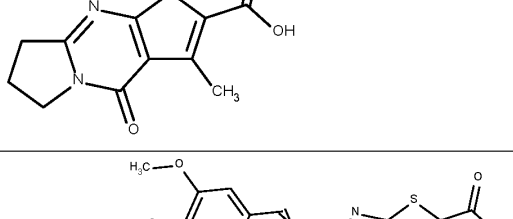
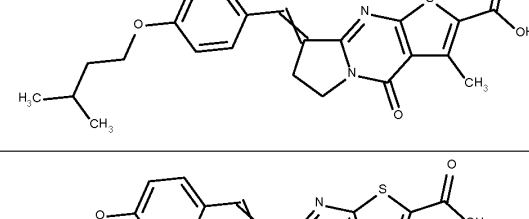
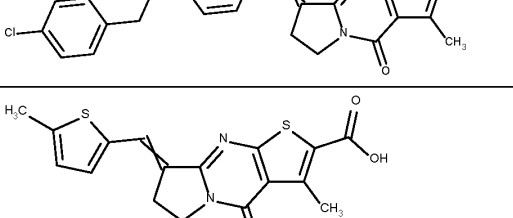
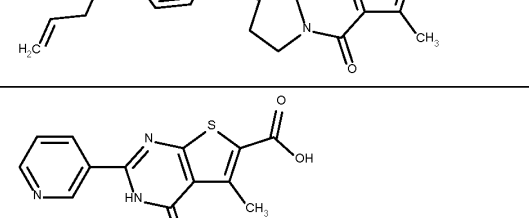
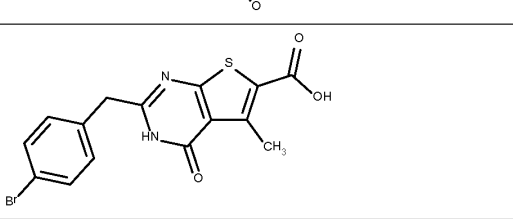
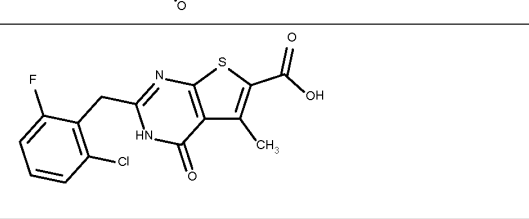
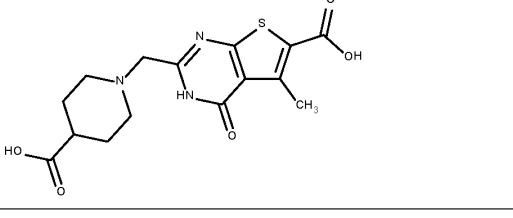
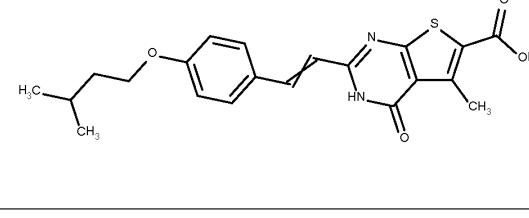
	
	
	
	
	
	
	

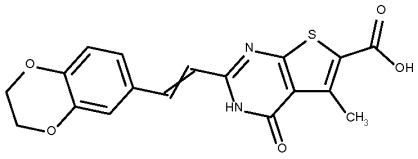
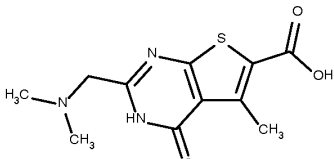
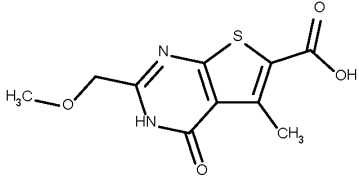
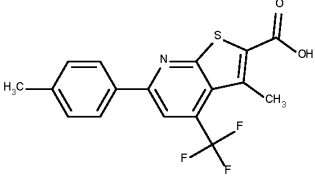
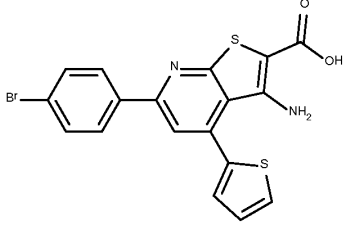
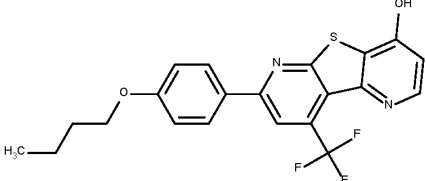
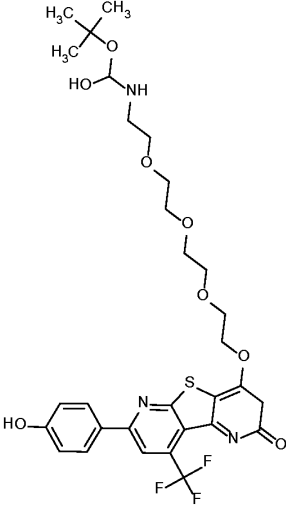
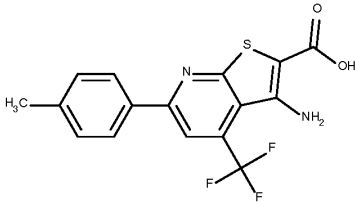
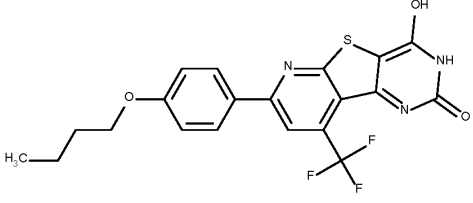
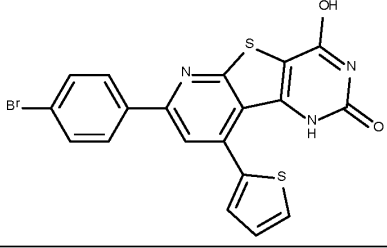
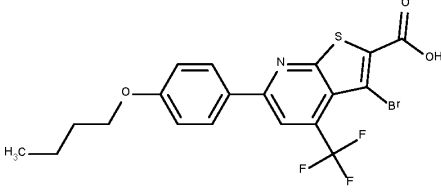
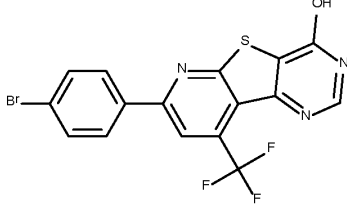
	
	
	
	
	
	
	

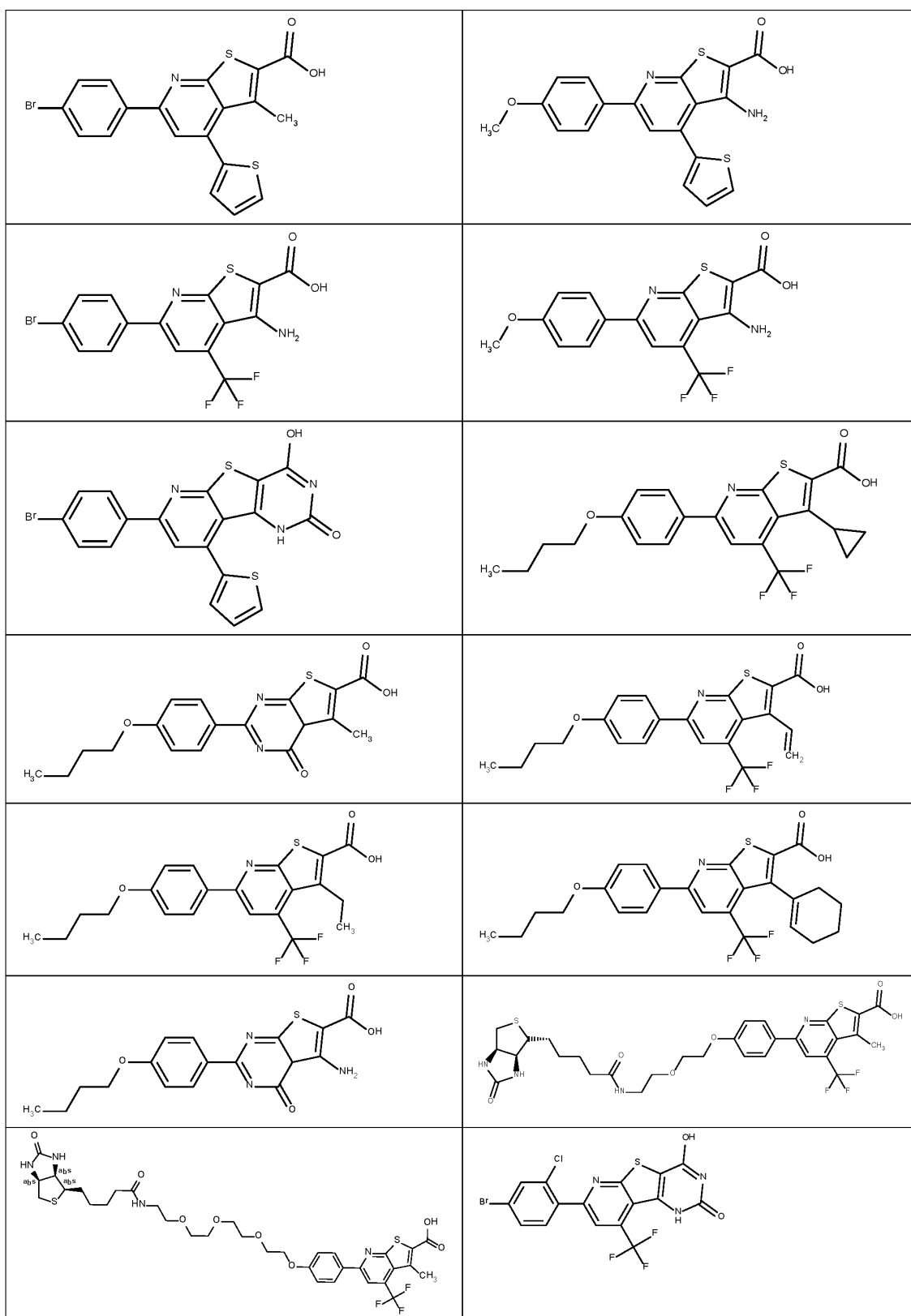
	
	
	
	
	
	

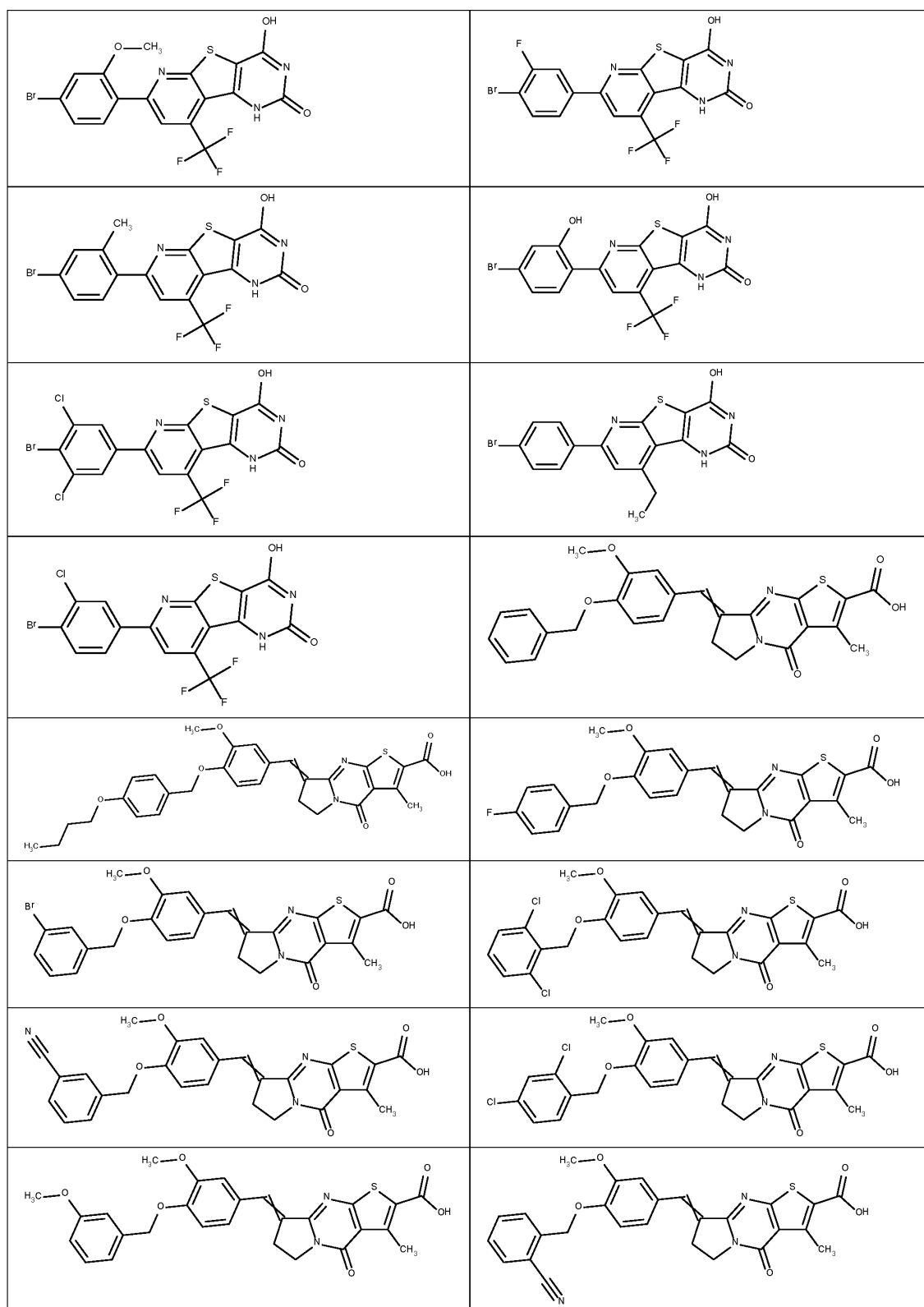
	
	
	
	
	
	

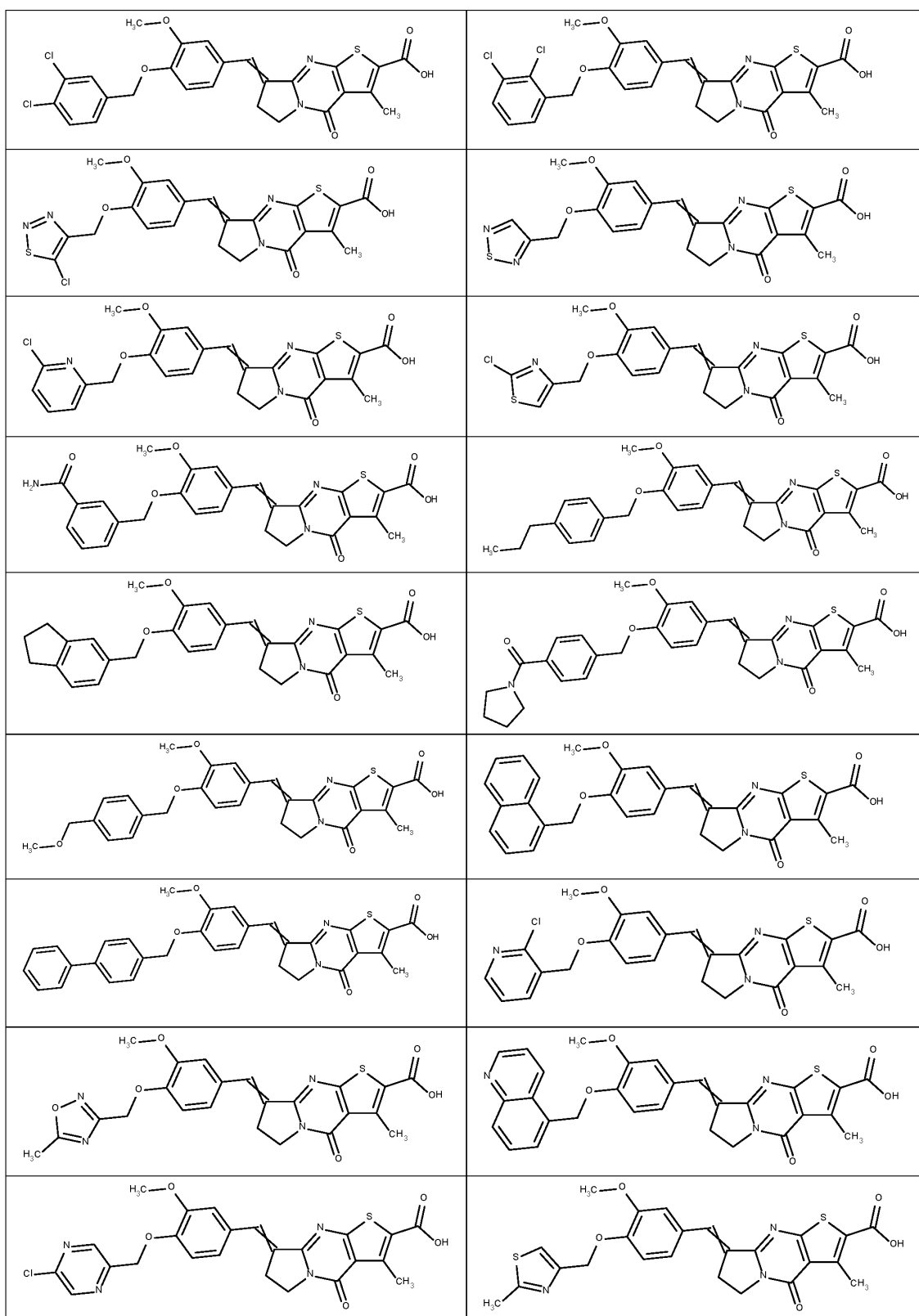
	
	
	
	
	
	

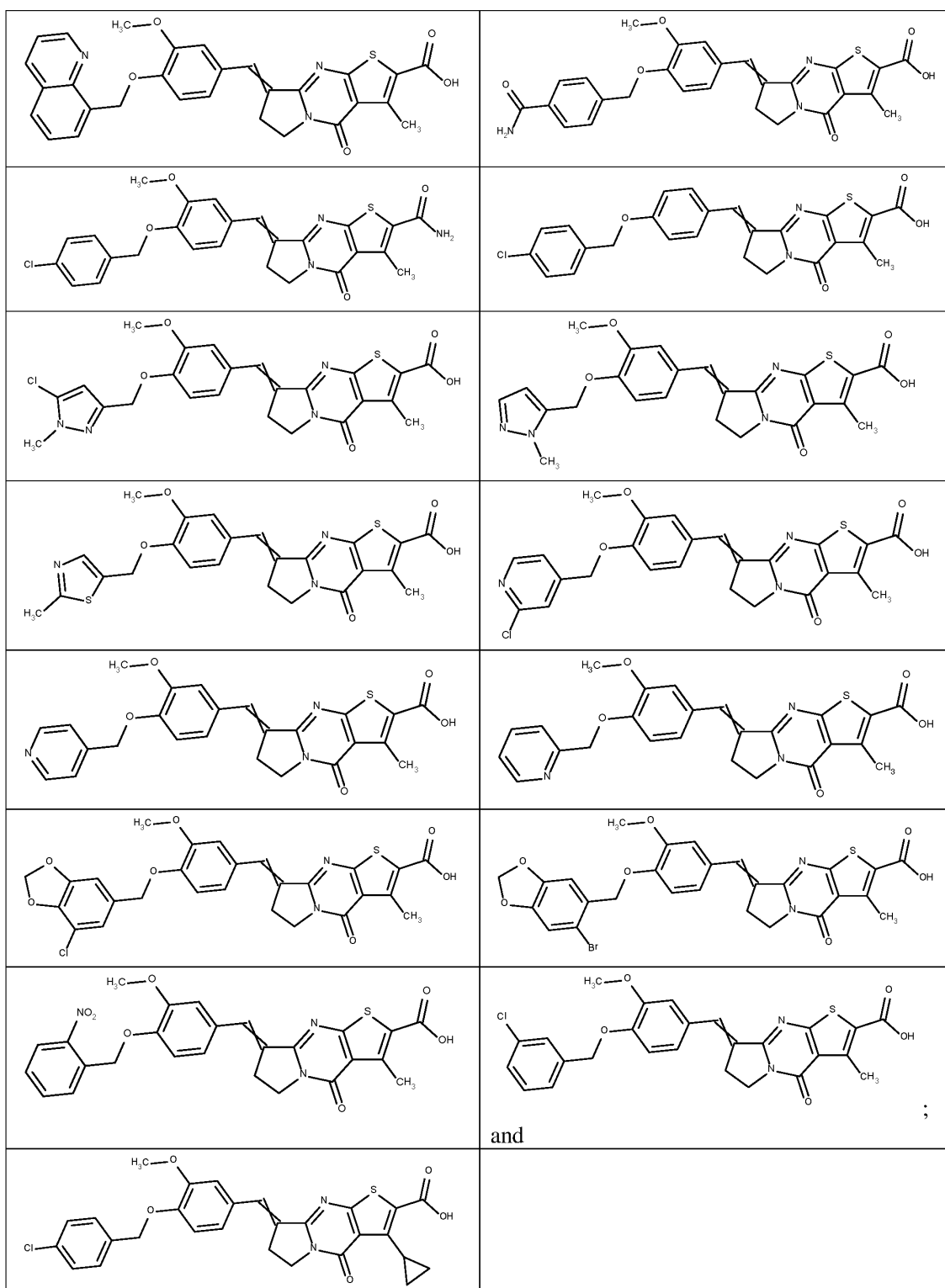
	
	
	
	
	
	
	
	









and isomers, pharmaceutically acceptable salts, solvates, chemically protected forms, and prodrugs thereof.

8. The ALC1i for use according to any of claims 1 to 7, wherein the ALC1i and the inhibitor of Topoisomerase I, Topoisomerase II, ATM, ATR, Wee1, MEK, BRD, or of PARP, or mitomycin C,

paclitaxel, or the antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor, such as trastuzumab deruxtecan, datopotamab deruxtecan, or sacituzumab govitecan, are administered simultaneously or subsequently.

- 5 9. The ALC1i for use according to any of claims 1 to 8, wherein the proliferative disease is selected from a HR deficient cancer, preferably a BRCA-1 and/or BRCA-2-deficient tumor, and/or wherein the proliferative disease is selected from hepatocellular carcinoma, breast cancer, ovarian cancer, fallopian tube cancer, primary peritoneal cancer, prostate cancer, colorectal cancer, or pancreatic cancer.

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10. A pharmaceutical composition comprising an ALC1i as defined in any one of claims 1 to 7 and
- a) an inhibitor of Topoisomerase I, Topoisomerase II, ATM, ATR, Wee1, and/or BRD, MEK,
 - b) mitomycin C or paclitaxel, or
 - c) an antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor.

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11. The pharmaceutical composition of claim 10, which is for use in treating or ameliorating a proliferative disease, preferably the proliferative disease is selected from a HR deficient cancer, preferably a BRCA-1 and/or BRCA-2-deficient tumor, and/or the proliferative disease is selected from hepatocellular carcinoma, breast cancer, ovarian cancer, fallopian tube cancer, primary peritoneal cancer, prostate cancer, colorectal cancer, or pancreatic cancer.

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12. A kit of parts comprising
- (i) an ALC1i as defined in any one of claims 1 to 7 with instructions to combine it with
 - a) an inhibitor of Topoisomerase I, Topoisomerase II, ATM, ATR, Wee1, MEK, and/or BRD,
 - b) mitomycin C or paclitaxel, or
 - c) ionizing radiation; or
 - d) an antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor, or
 - (ii) comprising
 - a) an inhibitor of Topoisomerase I, Topoisomerase II, ATM, ATR, Wee1, MEK, and/or BRD, or
 - b) mitomycin C, paclitaxel, or an antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor,
 - (iii) with instructions to combine it with an ALC1i as defined in any one of claims 1 to 5, or comprising separately packaged an ALC1i as defined in any one of claims 1 to 5 and
 - a) an inhibitor of Topoisomerase I, Topoisomerase II, ATM, ATR, Wee1, MEK, and/or BRD, or

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- b) mitomycin C or paclitaxel, or
- c) an antibody drug conjugate with a tumor specific antibody conjugated to a TOP1 inhibitor,

optionally with instructions for use in treating or ameliorating a proliferative disease.

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- 13. A kit of parts according to claim 12, which is for use in treating or ameliorating a proliferative disease, preferably the proliferative disease is selected from a HR deficient cancer, preferably a BRCA-1 and/or BRCA-2-deficient tumor, and/or the proliferative disease is selected from hepatocellular carcinoma, breast cancer, ovarian cancer, fallopian tube cancer, primary peritoneal cancer, prostate cancer, colorectal cancer, or pancreatic cancer.
10
- 14. The ALC1i for use according to any one of claims 1 to 9, the pharmaceutical compositions according to claim 10 or 11, or the kit according to claim 12 or 13, wherein the ACL1i is combined with any one of adavosertib, AZ-32, AZD-1056, AZD-1390, BAY-299, ABBV-744, trametinib, ceralasertib, 15
elimusertib, paclitaxel, Mitomycin C, teniposide, topotecan, AZD-5305, niraparib, olaparib, rucaparib, veliparib, talazoparib, trastuzumab deruxtecan, datopotamab deruxtecan, and/or sacituzumab govitecan.
- 15. A pharmaceutical composition comprising ALC1i-101 or a salt thereof and trastuzumab deruxtecan 20
for use in treating or ameliorating a proliferative disease, preferably the proliferative disease is selected from a HR deficient cancer, preferably a BRCA-1 and/or BRCA-2-deficient cancer, and/or the proliferative disease is selected from hepatocellular carcinoma, breast cancer, ovarian cancer, fallopian tube cancer, primary peritoneal cancer, prostate cancer, colorectal cancer, or pancreatic cancer.
25
- 16 A pharmaceutical composition comprising ALC1i-101 or a salt thereof and trastuzumab deruxtecan which is for use in treating advanced or metastatic cancer with homologous recombination deficiency (HRD) mutations.
- 30 17. The ALC1i for use according to any one of claims 1 to 9, the pharmaceutical compositions according to claim 10, 11, 15 or 16, or the kit according to claim 12 or 13, wherein the patient to be treated is receiving or received trastuzumab deruxtecan and does or did not show at least a partial response, preferably after several treatment cycles.