Claims

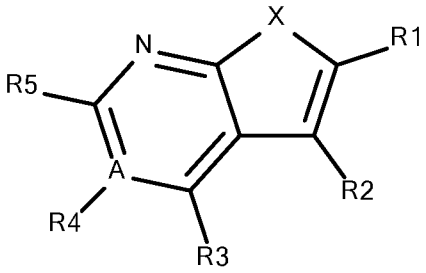
1. An allosteric inhibitor of Chromodomain-helicase-DNA-binding protein 1-like (ALC1), wherein the inhibitor specifically binds to an allosteric binding pocket formed by an amino acid stretch spanning amino acid residues 101 to 219 of SEQ ID NO: 1.

2. The allosteric inhibitor of ALC1 of 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 F 193, L200, and E212 of SEQ ID NO: 1.

3. The allosteric inhibitor of ALC1 of claim 1 or 2, wherein the inhibitor 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 and/or the sidechains of L101, Y153, C156, L157, A160, L163, E175, R178, L179, L186, H187, L190, F193, T202, N208, E212, and/or L213, more preferably with the backbone of D174. H177, and R178, and the sidechain of Y153, E175. R178, H187, T202, N208 and E212, preferably the inhibitor non-covalently binds to:

   (i) the aromatic ring of the sidechain of Y153 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 Y153 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.

4. The inhibitor of ALC1 of claim 3, wherein the allosteric inhibitor has the structure of formula (I):



wherein

(i) R_5 comprises an aromatic ring that pi-stacks with the aromatic ring of Y153; and/or

(ii) N is a hydrogen bond accepting group for the terminal OH of Y153; and/or

(iii) R_1 comprises a group that is a hydrogen bond donating group to the backbone carbonyl oxygen of H177; and/or

(iv) R_3 comprises a carbohalogen or hydrogen bond donating group that binds to the carbonyl oxygen of the backbone of D174; and/or

(v) R_1 and R_2 together form an aromatic or heteroaromatic monocyle comprising a hydrogen bond donating or accepting group especially at or adjacent to the R_1 position which can act as a hydrogen bond doating or accepting group to the side chain of E175 and/or R178; and/or

(vi) R_1 and R_2 together form a substituted carbo- or heteromonocycle comprising a hydrogen bond donating or accepting group, preferably at or adjacent to the R_1 position which is a hydrogen bond donating or accepting group to the side chain of R178; and/or

(vii) R_3 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) R_1 and R_2 together form an aromatic or heteroaromatic monocyle comprising a hydrogen bond donating or accepting group especially at or adjacent to the R_2 position which can act as a hydrogen bond donating or accepting group to the side chain of T202 and/or N208; and/or

(ix) R_4 is H or -C_{1-3}-alkyl, preferably H; and/or

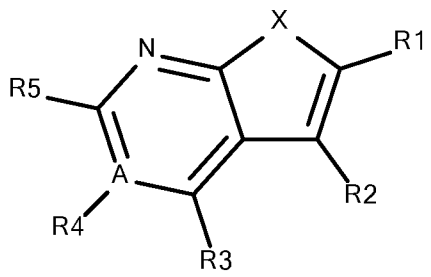
(x) R_5 is -$(CH_2)_m$-L, or -$(CH_2)_m$-(CH=CH)-L, wherein m is 0, 1 or 2, preferably 0 or 1, and L is a 5, 6 or 7 membered carbo- or heterocycle, or adamantyl, optionally substituted, preferably with 1, 2, 3 or 4 substituents independently selected from the group consisting of -OH, -NO_2, -CN, -CO-OR_6, -Br, -Cl, -F, -I, -R_9, -O-R_9, and =O, or two adjacent substituents form a 5, 6 or 7 membered carbo- or heterocycle; and/or

(xi) R_4 and R_5 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, -NO_2, -CN, -Br, -Cl, -F, -I, -O-R_9, -R_9, =CH-R_A, preferably R_4 and R_5 together form a C_{5-7}-cycloalkyl; and/or

(xii) X is N or S; and/or

(xiii) A is C or N.

5. The allosteric inhibitor of ALC1 of any of claims 1 to 4, wherein the allosteric inhibitor has the structure of formula (I):



(I)

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

X is N or S;

A is C or N;

R_1 is –CO-OR_6, -CO-R_7, or -CO-NR_6R_A, preferably R_1 is –CO-OR_6;

R_2 is -R_7, -NHR_8, -O-R_7, -C-O-R_7, Br, -C_{3-8}-cycloalkyl (preferably cyclopropyl), or –C_{4-8}-cycloalkenyl (preferably cyclohexenyl);

or

R_1 and R_2 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, -NO_2, -CN, -Br, -Cl, -F, -I, -O-C_{1-3}-alkyl, =O, [-O-CH_2-CH_2]-NH-CH(OH)-O-tBu, ;

R_3 is H, =O, -OH, -O-R_7, -R_7, or –$(CH_2)_m$-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, -NO_2, -CN, -Br, -Cl, -F, -I, -O-C_{1-3}-alkyl, -hydroxyC_{1-3}-alkyl and =O;

R_4 is H or -C_{1-3}-alkyl, preferably H;

R_5 is -$(CH_2)_m$-L, or -$(CH_2)_m$-(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, C_{1-4}-alkyl, or -$N(CH_3)_2$, optionally substituted, preferably with 1, 2, 3 or 4 substituents independently selected from the group consisting of -OH, -NO_2, -CN, -CO-OR_6, -Br, -Cl, -F, -I, -R_9, -O-R_9, =O, and [-O-CH_2-CH_2]$_q$-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

R_4 and R_5 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, -NO_2, -CN, -Br, -Cl, -F, -I, -O-R_9, -R_9, =CH-R_A, and –CH_2-R_A, preferably R_4 and R_5 together form a C_{5-7}-cycloalkyl;

R_6 is H, -C_{1-6}-alkyl, -C_{2-6}-alkenyl, -C_{2-6}-alkynyl, optionally substituted, preferably R_6 is H;

R_7 is -C_{1-3}-alkyl, -C_{2-3}-alkenyl, -C_{2-3}-alkynyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -Br, -Cl, -F, -I, -CH_3, -OCH_3, or -SCH_3;

R_8 is H or C_{1-6}-alkyl, preferably H,

R_9 is -C_{1-6}-alkyl, -C_{2-6}-alkenyl, -C_{2-6}-alkynyl, -C_{1-6}-alkyl-aryl, or C_{1-6}-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, -NO_2, -CN, -$CONH_2$, -CONH-C_{1-3}-alkyl (preferably –CONH-CH_3), -NH-CO-C_{1-3}-alkyl (preferably -NH-CO-CH_3), -C_{1-6}-alkyl (preferably -CH_3, ethyl, propyl, t-butyl, or pentyl), -C_{1-3}-haloalkyl (preferably-CF_3, or -CHF_2), -O-CHF_2, -O-CF_3, carbocycle (preferably cyclopropyl, cyclohexyl or phenyl), -O-carbocycle (preferably phenoxy), heterocycle (preferably pyrazolyl), -CO-heterocycle (preferably –CO-(1-pyrrolidinyl)),-SO_2-CH_3, -SO_2-N(CH_3)$_2$, -O-C_{1-4}-alkyl (preferably -OCH_3), -O-C_{1-3}-alkyl-O-C_{1-3}-alkyl (preferably –O-CH_2-O-CH_3), -SCH_3, or when R_9 is -C_{1-6}-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, -NO_2, -CN, -Br, -Cl, -F, -I, -R_9, -O-R_7, -O-(CH_2)$_o$-R_9, -SO_2NH_2, and =O, wherein o is 0 or 1.

6. A bifunctional compound comprising the allosteric inhibitor of ALC1 of claims 1 to 5 and a compound which recruits E3 ubiquitin ligase to ALC1 (E3 recruiter), wherein the allosteric inhibitor of ALC1 and the E3 recruiter are covalently linked, optionally through a linker.

7. A pharmaceutical composition comprising the allosteric inhibitor of ALC1 of claims 1 to 5 or the bifunctional compound of claim 6 and a pharmaceutically acceptable excipient.

8. An ALC1 inhibitor (ALC1i) for use in a method for treating or ameliorating a proliferative disease in a patient, wherein the method comprises the administration of said ALC1i and optionally the administration of a Poly(ADP-ribose)-Polymerase inhibitor (PARPi).

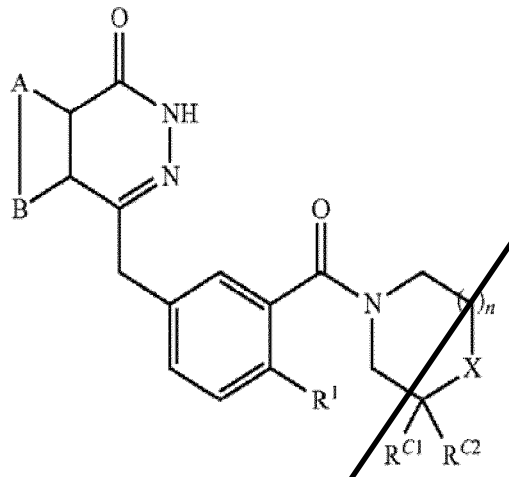
9. A PARPi for use in treating or ameliorating a proliferative disease in a patient, wherein the method comprises the administration of said PARPi and the administration of ALC1i.

10. The ALC1i for use of claim 8 or the PARPi for use of claim 9, wherein the PARPi lowers PARP activity and/or inhibits PARP1, PARP2 and/or PARP3, preferably PARP2 on chromatin, wherein preferably 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 (II)



(II)

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

A and B together represent an optionally substituted, fused aromatic ring;

X is NR^X or CR^XR^Y;

if $X=NR^X$ then n is 1 or 2 and if $X=CR^XR^Y$ 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;

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;

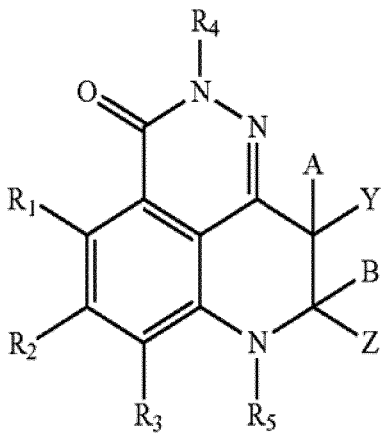
R^{C1} and R^{C2} are independently selected from the group consisting of hydrogen and C_{1-4} alkyl

or when X is CR^XR^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

R^1 is selected from H and halo;

and

(b) formula (III)



(III)

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

Y and Z are each independently selected from the group consisting of:

1. an aryl group optionally substituted with 1, 2, or 3 R_6 ;
2. a heteroaryl group optionally substituted with 1, 2, or 3 R_6;
3. a substituent independently selected from the group consisting of hydrogen, alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, hydroxyalkylene, oxo, heterocycloalkyl, heterocycloalkylalkyl, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, (R_AR_B)alkylene, (NR_AR_B)carbonyl, (NR_AR_B)carbonylalkylene, (NR_AR_B)sulfonyl, and (R_AR_B)sulfonylalkylene;

wherein each 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, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{2-6}-alkynyl, aryl, arylalkyl, C_{3-8}-cycloalkylalkyl, haloalkoxy, haloalkyl, hydroxyalkylene, oxo, heteroaryl, heteroarylalkoxy, heteroaryloxy, heteroarylthio, heteroarylalkylthio, heterocycloalkoxy, C_{2-8}-heterocycloalkylthio, heterocyclooxy, heterocyclothio, NR_AR_B, (R_AR_B)C_{1-6}-alkylene, (NR_AR_B)carbonyl, (R_AR_B)carbonylalkylene, (NR_AR_B)sulfonyl, and (NR_AR_B)sulfonylalkylene;

R_1, R_2, and R_3 are each independently selected from the group consisting of hydrogen, halogen, alkenyl, alkoxy, alkoxycarbonyl, alkyl, cycloalkyl, alkynyl, cyano, haloalkoxy, haloalkyl, hydroxyl, hydroxyalkylene, nitro, NR_AR_B, NR_AR_B alkylene, and (R_AR_B)carbonyl;

A and B are each independently selected from hydrogen, Br, Cl, F, I, OH, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, alkoxy, alkoxyalkyl wherein C_{1-6}-alkyl, C_{3-8}-cycloalkyl, alkoxy, alkoxyalkyl are optionally substituted with at least one substituent selected from OH, NO_2, CN, Br, Cl, F, I, C_{1-6}-alkyl, and C_{3-8}-cycloalkyl, wherein B is not OH;

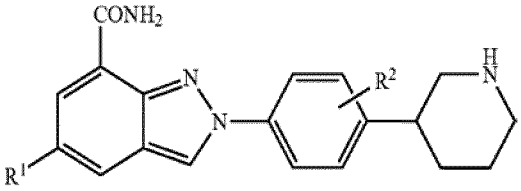
R_A, and R_B are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, and alkylcarbonyl; or RA and RB taken together with the atom to which they are attached form a 3-10 membered heterocycle ring optionally having one to three heteroatoms or hetero functionalities selected from the group consisting of -O-, -NH, -N(C_{1-6}-alkyl)-, -NCO(C_{1-6}-alkyl)-, -N(aryl)-, -N(aryl-C_{1-6}-alkyl-), -N(substituted-aryl-C_{1-6}-alkyl-)-, -N(heteroaryl)-, -N(heteroaryl-C_1-C_6 -alkyl-)-, -N(substituted-heteroaryl-C_{1-6} 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;

R_4 and R_5 are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkoxyalkyl, haloalkyl, hydroxyalkylene, and (NR_AR_B)alkylene;

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

(iii) that inhibits PARP1 and PARP2 is selected from the group consisting of a compound of

(a) formula (IV)



(IV)

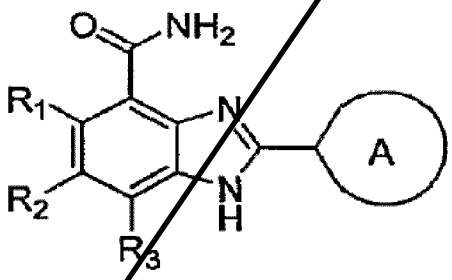
and isomers, salts, solvates, chemically protected forms, and prodrugs thereof wherein:

R_1 is hydrogen or fluorine; and

R_2 is hydrogen or fluorine;

and

(b) formula (V)



(V)

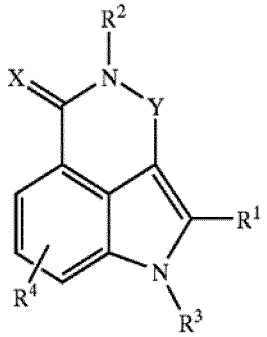
and isomers, salts, solvates, chemically protected forms, and prodrugs thereof wherein:

R_1, R_2, and R_3 are independently selected from the group consisting of hydrogen, alkenyl, alkoxy, alkoxycarbonyl, alkyl, alkynyl, cyano, haloalkoxy, haloalkyl, halogen, hydroxy, hydroxyalkyl, nitro, NR_AR_B, and (NR_AR_B)carbonyl;

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, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, cyano, haloalkoxy, haloalkyl, halogen, heterocycle, heterocyclealkyl, heteroaryl, heteroarylalkyl, hydroxy, hydroxyalkyl, nitro, NR_CR_D, (NR_CR_D)alkyl, (NR_CR_D)carbonyl, (NR_CR_D)carbonylalkyl, 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, and alkycarbonyl

(iii) that inhibits PARP1, PARP2 and PARP3 is acompound of formula (VI)



(V)

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

R_1 is: H; halogen; cyano; an optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group (e.g., unsubstituted or substituted with one or more substituents selected from halogen, hydroxy, nitro, and amino, alkoxy, 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)-R_{10}, where R_{10} is: H; an optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group (e.g., unsubstituted or substituted with one or more substituents selected from halogen, hydroxy, nitro, amino, and alkyl and aryl groups unsubstituted or substituted with one or more substituents selected from halo, hydroxy, nitro, and amino); or OR_{100} or $NR_{100}R_{110}$, where R_{100} and R_{110} are each independently H or an optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group (e.g., unsubstituted or substituted with one or more substituents selected from alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl groups unsubstituted or substituted with one or more substituents selected from halogen, hydroxy, nitro, amino, and alkyl and aryl groups unsubstituted or substituted with one or more substituents selected from halogen, hydroxy, nitro, and optionally substituted amino groups);

R_2 is H or alkyl;

R_3 is H or alkyl;

R_4 is H, halogen or alkyl;

X is O or S;

Y is $(CR_5R_6)(CR_7R_8)_n$ or N-C(R_5), where:

n is 0 or 1;

R_5 and R_6 are each independently H or an optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group (e.g., unsubstituted or substituted with one or more substituents selected from halogen, hydroxy, nitro, amino, and lower alkyl, lower alkoxy, or aryl groups unsubstituted or substituted

with one or more substituents selected from halogen, hydroxy, nitro, and amino); and

R_7 and R_8 are each independently H or an optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group (e.g., unsubstituted or substituted with one or more substituents selected from halogen, hydroxy, nitro, amino, and lower alkyl, lower alkoxy, and aryl groups unsubstituted or substituted with one or more substituents selected from halogen, hydroxy, nitro, and amino);

where when R_1, R_4, R_5, R_6, and R_7 are each H, R_8 is not unsubstituted phenyl.

11. The ALC1i for use of claim 8 or 10 or the PARPi for use of claim 9 or 10, wherein the PARPi is selected from the group consisting of Olaparib, Talazoparib, Niraparib, Rucaparib, and Veliparib, in particular of Veliparib, Olaparib, and Talazoparib.

12. The ALC1i for use of claim 8, 10 or 11 or the PARPi for use of claim 9 to 11, wherein the ALC1i is a direct inhibitor of the ATPase activity of ALC1, or is an allosteric inhibitor of ALC1, wherein preferably the ALC1i is the inhibitor of ALC1 of any of claims 1 to 5 or a bifunctional compound of claim 6.

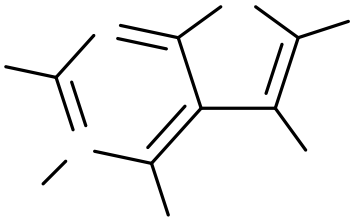
13. The ALC1i for use of claim 8 or 10 to 12 or the PARPi for use of claim 9 to 12, wherein the proliferative disease is selected from a BRCA-1 and/or BRCA-2-deficient tumor, and a tumor in which expression of PARP-1, PARP-2, PARP-3 and/or ALC1 is increased in comparison to non-tumor cells, and/or wherein the proliferative disease is selected from hepatocellular carcinoma, breast cancer, ovarian cancer, prostate cancer, colorectal cancer.

14. The ALC1i for use of claim 8 or 10 to 13 or the PARPi for use of claim 9 to 13, wherein the PARPi and ALC1i are administered concomitantly or separately.

15. A kit of parts comprising separately packaged a PARPi and an ALC1i or a composition comprising a PARPi and an ALC1i, preferably with instructions for use to treat or ameliorate a proliferative disease.

CLAIMS

1. An allosteric inhibitor of Chromodomain-helicase-DNA-binding protein 1-like (ALC1), in which the allosteric inhibitor has the structure of formula (I):



(I)

and isomers, salts, solvates, chemically protected forms, and prodrugs thereof, in which:

X is N or S;

A is C or N;

R_1 is –CO-OR_6, -CO-R_7, or -CO-NR_6R_A;

R_2 is -R_7, -NHR_8, -O-R_7, -C-O-R_7, Br, -C_{3-8}-cycloalkyl, or –C_{4-8}-cycloalkenyl;

or

R_1 and R_2 together form a 5, 6 or 7 membered carbo- or heterocycle, optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO_2, -CN, -Br, -Cl, -F, -I, -O-C_{1-3}-alkyl, =O, [-O-CH_2-CH_2]-NH-CH(OH)-O-tBu, ;

R_3 is H, =O, -OH, -O-R_7, -R_7, or –$(CH_2)_m$-L, in which m is 0, 1 or 2, and L is a 5, 6 or 7 membered carbo- or heterocycle, optionally substituted;

R_4 is H or -C_{1-3}-alkyl;

R_5 is -$(CH_2)_m$-L, or -$(CH_2)_m$-(CH=CH)-L, in which m is 0, 1 or 2, preferably 0 or 1, and L is a 5, 6 or 7 membered carbo- or heterocycle, adamantyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, or -$N(CH_3)_2$, optionally substituted;

or

R_4 and R_5 together form a 5, 6, or 7 membered carbocycle, optionally substituted;

R_6 is H, -C_{1-6}-alkyl, -C_{2-6}-alkenyl, -C_{2-6}-alkynyl, optionally substituted;

R_7 is -C_{1-3}-alkyl, -C_{2-3}-alkenyl, -C_{2-3}-alkynyl, optionally substituted;

R_8 is H or C_{1-6}-alkyl,

R_9 is -C_{1-6}-alkyl, -C_{2-6}-alkenyl, -C_{2-6}-alkynyl, -C_{1-6}-alkyl-aryl, or C_{1-6}-alkyl-heteroaryl, optionally substituted with 1, 2 or 3 substituents selected from the group consisting of -Br, -Cl, -F, -I, -NO_2, -CN, -$CONH_2$, -CONH-C_{1-3}-alkyl, -NH-CO-C_{1-3}-alkyl, -C_{1-6}-alkyl, -C_{1-3}-haloalkyl, -O-CHF_2, -O-CF_3, carbocycle, -O-carbocycle, heterocycle, -CO-heterocycle, -O-C_{1-3}-alkyl-O-C_{1-3}-alkyl, -SCH_3, or when R_9 is -C_{1-6}-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.

2. An allosteric inhibitor of ALC1 according to Claim 1, in which

R_1 is –CO-OR_6;

R_3 is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO_2, -CN, -Br, -Cl, -F, -I, -O-C_{1-3}-alkyl, -hydroxyC_{1-3}-alkyl and =O;

R_5 is optionally substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of -OH, -NO_2, -CN, -CO-OR_6, -Br, -Cl, -F, -I, -R_9, -O-R_9, =O, and [-O-CH_2-CH_2]$_q$-NH-biotin with q being 1, 2, 3, or 4, or two adjacent substituents form a 5, 6 or 7 membered carbo- or heterocycle;

R_4 and R_5 together form a 5, 6, or 7 membered carbocycle, optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of -OH, -NO_2, -CN, -Br, -Cl, -F, -I, -O-R_9, -R_9, =CH-R_A, and –CH_2-R_A, preferably R_4 and R_5 together form a C_{5-7}-cycloalkyl;

R_7 is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of -Br, -Cl, -F, -I, -CH_3, -OCH_3, or -SCH_3; and/or

R_A is optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of -OH, -NO_2, -CN, -Br, -Cl, -F, -I, -R_9, -O-R_7, -O-$(CH_2)_o$-R_9, -SO_2NH_2, and =O, in which o is 0 or 1.

3. A bifunctional compound comprising an allosteric inhibitor of ALC1 according to Claims 1 or 2 and a compound which recruits E3 ubiquitin ligase to ALC1 (E3 recruiter), in which the allosteric inhibitor of ALC1 and the E3 recruiter are covalently linked, optionally through a linker.

4. A pharmaceutical composition comprising an allosteric inhibitor of ALC1 according to Claims 1 or 2 or a bifunctional compound according to Claim 3 and a pharmaceutically acceptable excipient.

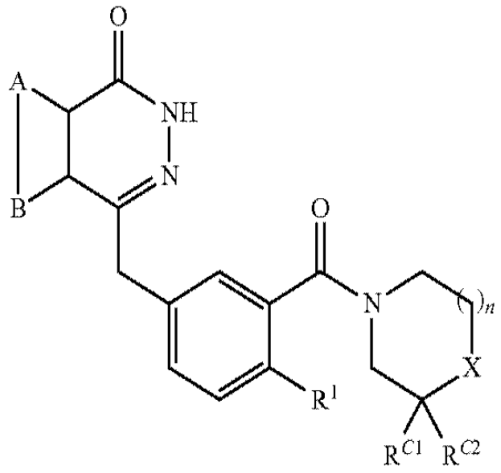
5. Use of an ALC1 inhibitor (ALC1i) according to Claim 1 or 2 in the preparation of a medicament for treating or ameliorating a proliferative disease in a patient, in which the composition optionally comprises a Poly(ADP-ribose)-Polymerase inhibitor (PARPi).

6. Use according to Claim 5, in which the PARPi lowers PARP activity and/or inhibits PARP1, PARP2 and/or PARP3, preferably PARP2 on chromatin, in which preferably 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 (II)



(II)

and isomers, salts, solvates, chemically protected forms, and prodrugs thereof in which:

A and B together represent an optionally substituted, fused aromatic ring;

X is NR^X or CR^XR^Y;

if X=NR^X then n is 1 or 2 and if X=CR^XR^Y then n is l;

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

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

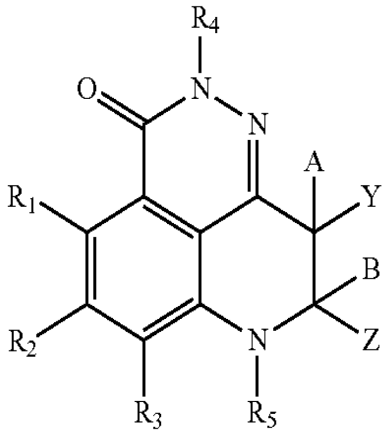
or R^X and R^Y may together form a spiro-C_{3-7} cycloalkyl or heterocyclyl group;

R^{C1} and R^{C2} are independently selected from the group consisting of hydrogen and C_{l-4} alkyl or when X is CR^XR^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

R^1 is selected from H and halo;

and

(b) formula (III)



(III)

and isomers, salts, solvates, chemically protected forms, and prodrugs thereof in which:

Y and Z are each independently selected from the group consisting of:

1. an aryl group optionally substituted with 1, 2, or 3 R_6 ;

2. a heteroaryl group optionally substituted with 1, 2, or 3 R_6;

3. a substituent independently selected from the group consisting of hydrogen, alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, hydroxyalkylene, oxo, heterocycloalkyl, heterocycloalkylalkyl, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl

alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, (R_AR_B)alkylene, (NR_AR_B)carbonyl, (NR_AR_B)carbonylalkylene, (NR_AR_B)sulfonyl, and (R_AR_B)sulfonylalkylene;

in which each 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, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{2-6}-alkynyl, aryl, arylalkyl, C_{3-8}-cycloalkylalkyl, haloalkoxy, haloalkyl, hydroxyalkylene, oxo, heteroaryl, heteroarylalkoxy, heteroaryloxy, heteroarylthio, heteroarylalkylthio, heterocycloalkoxy, C_{2-8}-heterocycloalkylthio, heterocyclooxy, heterocyclothio, NR_AR_B, (R_AR_B)C_{1-6}-alkylene, (NR_AR_B)carbonyl, (R_AR_B)carbonylalkylene, (NR_AR_B)sulfonyl, and (NR_AR_B)sulfonylalkylene;

R_1, R_2, and R_3 are each independently selected from the group consisting of hydrogen, halogen, alkenyl, alkoxy, alkoxycarbonyl, alkyl, cycloalkyl, alkynyl, cyano, haloalkoxy, haloalkyl, hydroxyl, hydroxyalkylene, nitro, NR_AR_B, NR_AR_B alkylene, and (R_AR_B)carbonyl;

A and B are each independently selected from hydrogen, Br, Cl, F, I, OH, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, alkoxy, alkoxyalkyl in which C_{1-6}-alkyl, C_{3-8}-cycloalkyl, alkoxy, alkoxyalkyl are optionally substituted with at least one substituent selected from OH, NO_2, CN, Br, Cl, F, I, C_{1-6}-alkyl, and C_{3-8}-cycloalkyl, in which B is not OH;

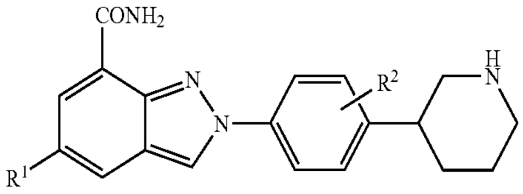
R_A, and R_B are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, and alkylcarbonyl; or RA and RB taken together with the atom to which they are attached form a 3-10 membered heterocycle ring optionally having one to three heteroatoms or hetero functionalities selected from the group consisting of -O-, -NH, -N(C_{1-6} -alkyl)-, -NCO(C_{1-6}-alkyl)-, -N(aryl)-, -N(aryl-C_{1-6}-alkyl-), -N(substituted-aryl-C_{1-6}-alkyl-)-, -N(heteroaryl)-, -N(heteroaryl-C_1-C_6 -alkyl-)-, -N(substituted-heteroaryl-C_{1-6} alkyl-)-, and -S- or S(O)q-, in which q is 1 or 2 and the 3-10 membered heterocycle ring is optionally substituted with one or more substituents;

R_4 and R_5 are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkoxyalkyl, haloalkyl, hydroxyalkylene, and (NR_AR_B)alkylene;

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

(iii) that inhibits PARP1 and PARP2 is selected from the group consisting of a compound of

(a) formula (IV)



(IV)

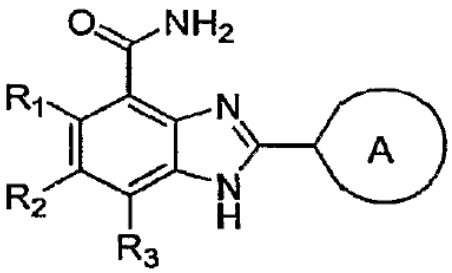
and isomers, salts, solvates, chemically protected forms, and prodrugs thereof in which:

R_1 is hydrogen or fluorine; and

R_2 is hydrogen or fluorine;

and

(b) formula (V)



(V)

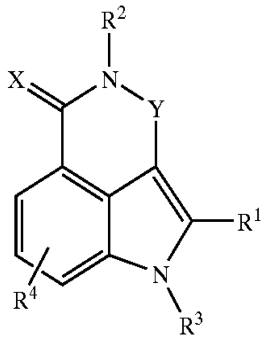
and isomers, salts, solvates, chemically protected forms, and prodrugs thereof in which:

R_1, R_2, and R_3 are independently selected from the group consisting of hydrogen, alkenyl, alkoxy, alkoxycarbonyl, alkyl, alkynyl, cyano, haloalkoxy, haloalkyl, halogen, hydroxy, hydroxyalkyl, nitro, NR_AR_B, and (NR_AR_B)carbonyl;

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, in which the nonaromatic ring is optionally substituted with 1, 2, or 3 substituents selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, cyano, haloalkoxy, haloalkyl, halogen, heterocycle, heterocyclealkyl, heteroaryl, heteroarylalkyl, hydroxy, hydroxyalkyl, nitro, NR_CR_D, (NR_CR_D)alkyl, (NR_CR_D)carbonyl, (NR_CR_D)carbonylalkyl, 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, and alkycarbonyl

(iii) that inhibits PARP1, PARP2 and PARP3 is a compound of formula (VI)



(V)

and isomers, salts, solvates, chemically protected forms, and prodrugs thereof in which:

R_1 is: H; halogen; cyano; an optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group (e.g., unsubstituted or substituted with one or more substituents selected from halogen, hydroxy, nitro, and amino, alkoxy, 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)-R_{10}, where R_{10} is: H; an optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group (e.g., unsubstituted or substituted with one or more substituents selected from halogen, hydroxy, nitro, amino, and alkyl and aryl groups unsubstituted or substituted with one or more substituents selected from halo, hydroxy, nitro, and amino); or OR_{100} or $NR_{100}R_{110}$, where R_{100} and R_{110} are each independently H or an optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group (e.g., unsubstituted or substituted with one or more substituents selected from alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl groups unsubstituted or substituted with one or more substituents selected from halogen, hydroxy, nitro, amino, and alkyl and aryl groups unsubstituted or substituted with one or more substituents selected from halogen, hydroxy, nitro, and optionally substituted amino groups);

R_2 is H or alkyl;

R_3 is H or alkyl;

R_4 is H, halogen or alkyl;

X is O or S;

Y is $(CR_5R_6)(CR_7R_8)_n$ or N-C(R_5), where:

N is 0 or 1;

R_5 and R_6 are each independently H or an optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group (e.g., unsubstituted or substituted with one or more substituents selected from halogen, hydroxy, nitro, amino, and lower alkyl, lower alkoxy, or aryl groups unsubstituted or substituted with one or more substituents selected from halogen, hydroxy, nitro, and amino); and

R_7 and R_8 are each independently H or an optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group (e.g., unsubstituted or substituted with one or more substituents selected from halogen, hydroxy, nitro, amino, and lower alkyl, lower alkoxy, and aryl groups unsubstituted or substituted with one or more substituents selected from halogen, hydroxy, nitro, and amino);

where when R_1, R_4, R_5, R_6, and R_7 are each H, R_8 is not unsubstituted phenyl.

7. Use according to Claim 5 or 6, in which the PARPi is selected from the group consisting of Olaparib, Talazoparib, Niraparib, Rucaparib, and Veliparib, in particular of Veliparib, Olaparib, and Talazoparib.

8. Use according to Claim 5, 6 or 7, in which the proliferative disease is selected from a BRCA-1 and/or BRCA-2-deficient tumor, and a tumor in which expression of PARP-1, PARP-2, PARP-3 and/or ALC1 is increased in comparison to non-tumor cells, and/or in which the proliferative disease is selected from hepatocellular carcinoma, breast cancer, ovarian cancer, prostate cancer, colorectal cancer.

9. Use according to any of Claims 5 to 8, in which the PARPi and ALC1i are administered concomitantly or separately.

10. A kit of parts comprising separately packaged a PARPi and an ALC1i or a composition comprising a PARPi and an ALC1i, preferably with instructions for use to treat or ameliorate a proliferative disease.

11. An allosteric inhibitor of ALC1 according to Claim 1, in which R_1 and R_2 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, -NO_2, -CN, -Br, -Cl, -F, -I, -O-C_{1-3}-alkyl, and =O, preferably -OH and =O and R_3 is H, =O, -OH, -R_7, or –$(CH_2)_m$-L, in which 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, -NO_2, -CN, -Br, -Cl, -F, -I, -O-C_{1-3}-alkyl, and -hydroxyC_{1-3}-alkyl.

12. An allosteric inhibitor of ALC1 according to Claim 1, in which A is C, R_1 and R_2 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, -NO_2, -CN, -Br, -Cl, -F, -I, -O-C_{1-3}-alkyl, and =O, preferably -OH and =O and R_3 is H, =O, -OH, -R_7, or –$(CH_2)_m$-L, in which 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, -NO_2, -CN, -Br, -Cl, -F, -I, -O-C_{1-3}-alkyl, and -hydroxyC_{1-3}-alkyl.

13. An allosteric inhibitor of ALC1 according to Claim 1, in which R_1 and R_2 together form an uracil or 3-deazauracil and R_3 is H, =O, -OH, -R_7, or –$(CH_2)_m$-L, in which 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, -NO_2, -CN, -Br, -Cl, -F, -I, -O-C_{1-3}-alkyl, and -hydroxyC_{1-3}-alkyl.

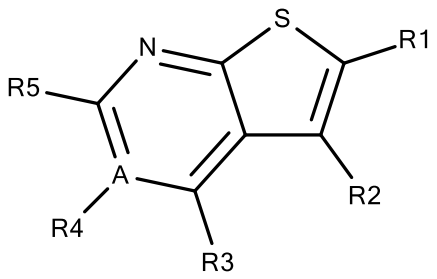
14. An allosteric inhibitor of ALC1 according to Claim 1, in which R_3 is -C_{1-3}-alkyl, i.e. C_1-, C_2-, C_3-alkyl, or –$(CH_2)_m$-L, in which m is 0 and L is phenyl or a 5 membered heteroaryl, preferably phenyl, optionally substituted, preferably with 1, 2, or 3 substituents independently selected from the group consisting of -NO_2, -CN, -Br, -Cl, -F, -I, -O-C_{1-3}-alkyl, and -hydroxyC_{1-3}-alkyl.

15. An allosteric inhibitor of ALC1 according to Claim 1, in which R_1 and R_2 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, -NO_2, -CN, -Br, -Cl, -F, -I, -O-C_{1-3}-alkyl, and =O, preferably -OH and =O and R_3 is -C_{1-3}-alkyl, i.e. C_1-, C_2-, C_3-alkyl, or –$(CH_2)_m$-L, in which 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 -NO_2, -CN, -Br, -Cl, -F, -I, -O-C_{1-3}-alkyl, and -hydroxyC_{1-3}-alkyl and R_3 is -C_{1-3}-alkyl, i.e. C_1-, C_2-, C_3-alkyl, or –$(CH_2)_m$-L, in which 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 -NO_2, -CN, -Br, -Cl, -F, -I, -O-C_{1-3}-alkyl, and -hydroxyC_{1-3}-alkyl.

16. An allosteric inhibitor of ALC1 according to Claim 1, in which R_3 is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF_2H, or CF_3.

17. An allosteric inhibitor of ALC1 according to Claim 1, in which the allosteric inhibitor has the structure of formula (Ia):



(Ia)

and isomers, salts, solvates, chemically protected forms, and prodrugs thereof, in which:

A is C or N;

R_1 is –COOH

R_2 is -CH_3 or -NH_2

or

R_1 and R_2 together form a uracil or 3-deazauracil;

R_3 is H, =O, -OH, thiophenyl, phenyl, 3,4,5 hydroxymethyl phenyl, CF_2H, or CF_3;

R_4 is H

R_5 is -L, or -CH_2-(CH=CH)-L, in which 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, -NO_2, -Br, -Cl, -F, CH_3, -O-R_9, and =O, or two adjacent substituents form a 5 or 6 membered heterocycle;

or

R_4 and R_5 together form a 5 or 6 membered non-substituted or mono substituted heterocycloalkyl, preferably with =CH-R_A substituted at the R_4 position;

R_9 is -C_{1-4}-alkyl, i.e. C_1-, C_2-, C_3-, or C_4-alkyl, -C_{2-4}-alkenyl, i.e. C_2-, C_3-, or C_4-alkenyl, or -C_{1-6}-alkyl-aryl, i.e. C_1-, C_2-, C_3-, C_4-, C_5- or C_6-alkyl-aryl, optionally substituted with 1 or 2 substituents selected from the group consisting of -Cl, -CH_3, -OCH_3, or -SCH_3;

R_A is a substituted carbocycle with 1 or 2 substituents independently selected from the group consisting of -Br, -Cl, -F, -O-$(CH_2)_o$-R_9, or -SCH_3, in which o is 0 or 1.

18. An allosteric inhibitor of ALC1 according to Claim 1, in which the allosteric inhibitor has one of the following structures:

