CLAIMS:

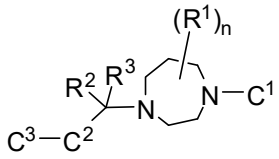
1. Use of a CXCR7 inhibitor in the preparation of a medicament for treating cancer in an individual, wherein

the individual has aberrant expression of FRS2β;

the cancer is selected from the group consisting of breast cancer, uterine cancer, ovarian cancer, cervical cancer, stomach cancer, pancreatic cancer, rectal cancer, kidney cancer, renal cancer, bladder cancer, prostate cancer, and adrenal cancer; and

the CCR7 inhibitor has the structure of Formula I or Formula II.

~~2. The use of claim 1, wherein the CXCR7 inhibitor has the structure of Formula I~~



(I)

or pharmaceutically acceptable salts, hydrates, N-oxides, isotopically enriched or enantiomerically enriched versions thereof, wherein

the subscript n is an integer of from 0 to 2;

each R^1, when present, is independently selected from the group consisting of C_{1-4} alkyl, $-CO_2R^a$, $-X-CO_2R^a$, $-CONR^aR^b$ and $-X-CONR^aR^b$;

R^2 and R^3 are each members independently selected from the group consisting of H, $-R^a$, $-XR^a$, $-XNR^aR^b$, $-XNHCONR^aR^b$, $-XNHCOR^a$, $-X-O-CONR^aR^b$, $-XNHSO_2R^a$, $-CO_2R^a$, $-X-CO_2R^a$, $-CONR^aR^b$ and $-X-CONR^aR^b$; or taken together are oxo;

C^1 is selected from the group consisting of monocyclic or fused-bicyclic aryl and heteroaryl, wherein the heteroaryl group has from 1-3 heteroatoms as ring members selected from N, O and S; and wherein said aryl and heteroaryl groups are optionally substituted with from 1 to 3 R^4 substituents;

C^2 is monocyclic four-, five-, six- or seven-membered ring selected from the group consisting of benzene, heteroaromatic, cycloalkane, and heterocycloalkane, wherein the heteroaromatic and heterocycloalkane rings have from 1-3 heteroatoms as ring members selected from N, O and S; and wherein each of said monocyclic C^2 rings are optionally substituted with from 1 to 3 R^5 substituents;

C^3 is selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{3-8} cycloalkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl, heteroaryl-C_{1-4} alkyl, and four- to six-membered heterocycloalkyl, wherein the heterocycloalkyl group or portion has from 1-3 heteroatoms selected from N, O and S, and wherein the heteroaryl group has from 1-3 heteroatoms as ring members selected from N, O and S, and each C^3 is optionally substituted with from 1-3 R^6 substituents;

each R^4 is independently selected from the group consisting of halogen, -CN, -NO_2, -R^c, -CO_2R^a, -NR^aR^b, -OR^a, -X-CO_2R^a, -$CONR^aR^b$ and -X-$CONR^aR^b$;

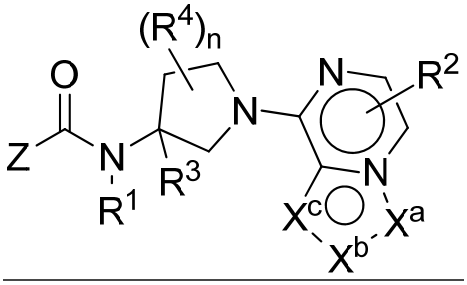
wherein within each of R^1, R^2, R^3 and R^4, each R^a and R^b is independently selected from hydrogen, C_{1-8} alkyl, C_{3-7} cycloalkyl, C_{1-8} haloalkyl, and four- to six-membered heterocycloalkyl, or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a four-, five- or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O or S; within R^4 each R^c is independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, aryl and heteroaryl, and wherein the aliphatic and cyclic portions of R^a, R^b and R^c are optionally further substituted with from one to three halogen, hydroxy, methyl, alkoxy, amino, alkylamino, dialkylamino, carboxamide, carboxy alkyl ester, carboxylic acid, heteroaryl, and four- to six-membered heterocycloalkyl groups; and wherein the heterocycloalkyl portions of R^2, R^3 and R^4 are optionally substituted with oxo; and optionally when two R^4 substituents are on adjacent atoms, are combined to form a fused five or six-membered ring having carbon and oxygen atoms as ring members;

each R^5 is independently selected from the group consisting of halogen, -CN, -NO_2, -R^f, -CO_2R^d, -COR^d, -NR^dR^e, -OR^d, -X-CO_2R^d, -$CONR^dR^e$ and -X-$CONR^dR^e$; wherein each R^d and R^e is independently selected from hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylalkyl, and four- to six-membered

heterocycloalkyl or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O or S; each R^f is independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, and C_{3-6} cycloalkyl, and wherein the aliphatic and cyclic portions of R^d, R^e and R^f are optionally further substituted with from one to three halogen, hydroxy, methyl, alkoxy, amino, alkylamino, dialkylamino, carboxamide, carboxy alkyl ester, carboxylic acid, heteroaryl, four- to six-membered heterocycloalkyl groups;

each R^6 is independently selected from the group consisting of halogen, -CN, -NO_2, -R^i, -CO_2R^g, -COR^g, -NR^gR^h, -OR^g, -X-CO_2R^g, -X-COR^g, -$CONR^g$ R^h and -X-$CONR^gR^h$, wherein each R^g and R^h is independently selected from hydrogen, C_{1-8} alkyl and C_{1-8} haloalkyl; each R^i is independently selected from the group consisting of C_{1-8} alkyl and C_{1-8} haloalkyl; and

each X is a linking group having the formula -$(CH_2)_mO(CH_2)_p$-, wherein the subscripts m and p are integer of from 0 to 5, and m + p is from 0 to 6, wherein the methylene groups are optionally substituted with one or two methyl groups; or



(II)

or a pharmaceutically acceptable salt, hydrate, N-oxide, isotopically enriched or enantiomerically enriched version or a rotamer thereof, wherein

each of ring vertices X^a, X^b and X^c is independently selected from the group consisting of N, NH, N(R^2), O, CH and C(R^2);

the subscript n is 0, 1 or 2;

Z is selected from the group consisting of

(i) monocyclic or fused-bicyclic aryl and heteroaryl, wherein the heteroaryl group has from 1-4 heteroatoms as ring members selected from N, O and S; and wherein said aryl and heteroaryl groups are optionally substituted with from 1 to 5 R^5 substituents;

(ii) monocyclic four-, five-, six- or seven-membered ring selected from the group consisting of cycloalkane, and heterocycloalkane, wherein the heterocycloalkane rings have from 1-3 heteroatoms as ring members selected from N, O and S; and wherein each of said monocyclic Z rings are optionally substituted with from 1 to 3 R^5 substituents;

R^1 is a member selected from the group consisting of H and C_{1-8} alkyl, wherein the alkyl portion is optionally substituted with halogen, $-NR^aR^b$, $-OR^a$, $-CO_2R^a$, and $-CONR^aR^b$;

each R^2 is independently selected from the group consisting of H, halogen, CN, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} hydroxyalkyl, $-OR^a$, $-CO_2R^a$, $-X-CO_2R^a$, $-NR^aR^b$, $-CONR^aR^b$ and $-X-CONR^aR^b$;

R^3 is a member selected from the group consisting of H, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} hydroxyalkyl, $-CO_2R^a$, $-X-CO_2R^a$, $-CONR^aR^b$ and $-X-CONR^aR^b$;

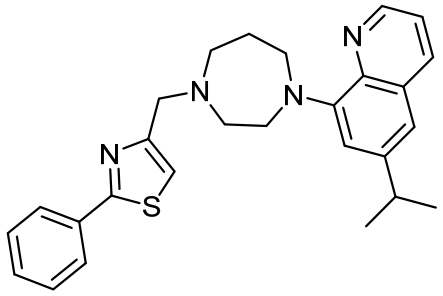
each R^4 , when present, is a member independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} hydroxyalkyl, $-OR^a$, $-CO_2R^a$, $-X-CO_2R^a$, $-NR^aR^b$, $-CONR^aR^b$ and $-X-CONR^aR^b$;

each R^5 is a member independently selected from the group consisting of halogen, CN, -X-CN, C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{3-5} spirocycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} haloalkyl, C_{1-8} hydroxyalkyl, $-OR^a$, $-CO_2R^a$, $-X-CO_2R^a$, $-NR^aR^b$, $-CONR^aR^b$, $-X-CONR^aR^b$, aryl, 5- or 6-membered heteroaryl, and 3-, 4-, 5- or 6-membered heterocyclic wherein the heteroatoms present as ring vertices of the heteroaryl and heterocyclic rings are selected from N, O and S, and wherein the aryl, heteroaryl and hetereocyclic portions of R^5 are optionally further substituted with 1-3 R^a;

each R^a and R^b is independently selected from the group consisting of hydrogen, hydroxyl, halogen, cyano, C_{1-8} alkyl, C_{1-8} alkoxy,C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylalkyl, amino, C_{1-8} alkylamino, di C_{1-8} alkylamino, carboxamide, carboxy C_{1-4} alkyl ester, carboxylic acid, and $-SO_2-$ C_{1-8} alkyl;

each X is a C_{1-4} alkylene linking group or a linking group having the formula $-(CH_2)_mO(CH_2)_p-$, wherein the subscripts m and p are integer of from 0 to 5, and m + p is from 0 to 6, wherein any of the methylene portions of X are optionally substituted with one or two methyl groups.

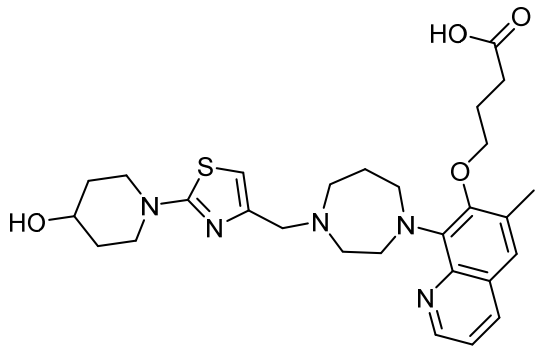
~~3~~2. The use of claim ~~2~~ 1, wherein the CXCR7 inhibitor has the structure of Compound 1



(Compound 1)

or a pharmaceutically acceptable salt thereof.

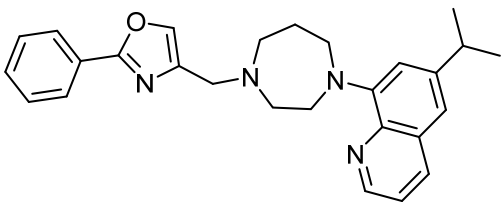
~~4~~ 3. The use of claim ~~2~~ 1, wherein the CXCR7 inhibitor has the structure of Compound 2



(Compound 2)

or a pharmaceutically acceptable salt thereof.

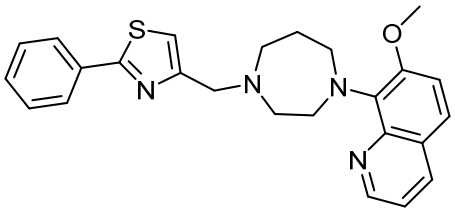
~~5~~4. The use of claim ~~2~~ 1, wherein the CXCR7 inhibitor has the structure of Compound 3



(Compound 3)

or a pharmaceutically acceptable salt thereof.

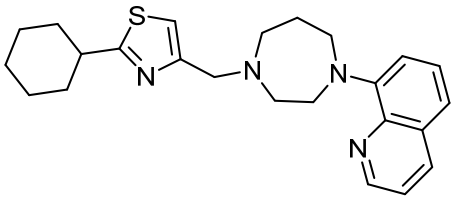
~~6~~5. The use of claim ~~2~~ 1, wherein the CXCR7 inhibitor has the structure of Compound 4



(Compound 4)

or a pharmaceutically acceptable salt thereof.

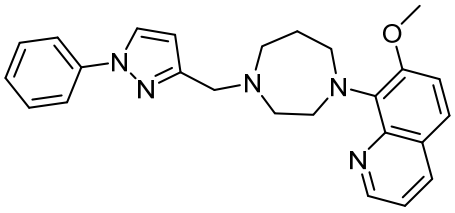
~~7~~6. The use of claim ~~2~~ 1, wherein the CXCR7 inhibitor has the structure of Compound 5



(Compound 5)

or a pharmaceutically acceptable salt thereof.

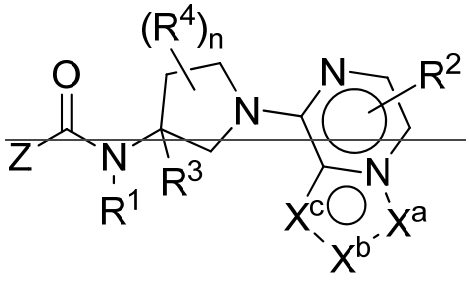
~~8~~ 7. The use of claim ~~2~~ 1, wherein the CXCR7 inhibitor has the structure of Compound 6



(Compound 6)

or a pharmaceutically acceptable salt thereof.

~~9. The use of claim 1, wherein the CXCR7 inhibitor has the structure of Formula II~~



~~(II)~~

or a pharmaceutically acceptable salt, hydrate, N-oxide, isotopically enriched or enantiomerically enriched version or a rotamer thereof, wherein

each of ring vertices X^a, X^b and X^e is independently selected from the group consisting of N, NH, N(R^2), O, CH and C(R^2);

the subscript n is 0, 1 or 2;

Z is selected from the group consisting of

(i) monocyclic or fused-bicyclic aryl and heteroaryl, wherein the heteroaryl group has from 1-4 heteroatoms as ring members selected from N, O and S; and wherein said aryl and heteroaryl groups are optionally substituted with from 1 to 5 R^5 substituents;

(ii) monocyclic four-, five-, six- or seven-membered ring selected from the group consisting of cycloalkane, and heterocycloalkane, wherein the heterocycloalkane rings have from 1-3 heteroatoms as ring members selected from N, O and S; and wherein each of said monocyclic Z rings are optionally substituted with from 1 to 3 R^5 substituents;

R^1 is a member selected from the group consisting of H and C_{1-8} alkyl, wherein the alkyl portion is optionally substituted with halogen, $-NR^aR^b$, $-OR^a$, $-CO_2R^a$, and $-CONR^aR^b$;

each R^2 is independently selected from the group consisting of H, halogen, CN, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} hydroxyalkyl, $-OR^a$, $-CO_2R^a$, $-X-CO_2R^a$, $-NR^aR^b$, $-CONR^aR^b$ and $-X-CONR^aR^b$;

R^3 is a member selected from the group consisting of H, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} hydroxyalkyl, $-CO_2R^a$, $-X-CO_2R^a$, $-CONR^aR^b$ and $-X-CONR^aR^b$;

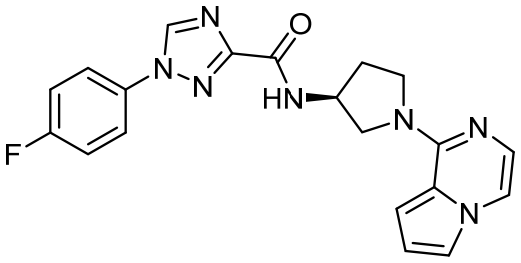
each R^4, when present, is a member independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} hydroxyalkyl, $-OR^a$, $-CO_2R^a$, $-X-CO_2R^a$, $-NR^aR^b$, $-CONR^aR^b$ and $-X-CONR^aR^b$;

each R^5 is a member independently selected from the group consisting of halogen, CN, -X-CN, C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{3-5} spirocycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} haloalkyl, C_{1-8} hydroxyalkyl, $-OR^a$, $-CO_2R^a$, $-X-CO_2R^a$, $-NR^aR^b$, $-CONR^aR^b$, $-X-CONR^aR^b$, aryl, 5- or 6-membered heteroaryl, and 3-, 4-, 5- or 6-membered heterocyclic wherein the heteroatoms present as ring vertices of the heteroaryl and heterocyclic rings are selected from N, O and S, and wherein the aryl, heteroaryl and hetereocyclic portions of R^5 are optionally further substituted with 1-3 R^a;

~~each R^a and R^b is independently selected from the group consisting of hydrogen, hydroxyl, halogen, cyano, C_{1-8} alkyl, C_{1-8} alkoxy,C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylalkyl, amino, C_{1-8} alkylamino, di C_{1-8} alkylamino, carboxamide, carboxy C_{1-4} alkyl ester, carboxylic acid, and $-SO_2-C_{1-8}$ alkyl;~~

~~each X is a C_{1-4} alkylene linking group or a linking group having the formula $-(CH_2)_m-O-(CH_2)_p-$, wherein the subscripts m and p are integer of from 0 to 5, and m + p is from 0 to 6, wherein any of the methylene portions of X are optionally substituted with one or two methyl groups.~~

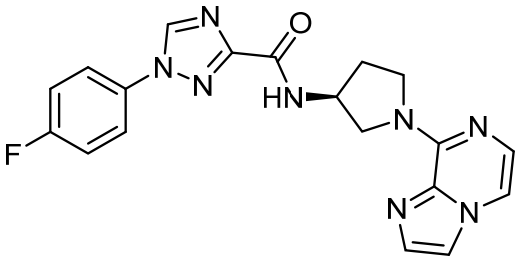
~~10~~8. The use of claim ~~9~~ 1, wherein the CXCR7 inhibitor has the structure of Compound 7



(Compound 7)

or a pharmaceutically acceptable salt thereof.

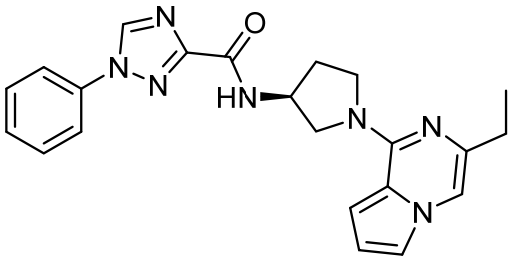
~~11~~9. The use of claim ~~9~~ 1, wherein the CXCR7 inhibitor has the structure of Compound 8



(Compound 8)

or a pharmaceutically acceptable salt thereof.

~~12~~10. The use of claim ~~9~~ 1, wherein the CXCR7 inhibitor has the structure of Compound 9



(Compound 9)

or a pharmaceutically acceptable salt thereof.

~~13. The use of any one of claims 1 to 12, wherein the cancer is selected from the group consisting of breast cancer, uterine cancer, ovarian cancer, cervical cancer, stomach cancer, pancreatic cancer, rectal cancer, kidney cancer, renal cancer, bladder cancer, prostate cancer, and adrenal cancer.~~

~~14~~11. The use of any one of claims 1 to ~~12~~ 10, wherein the cancer is breast cancer.

~~15~~12. The use of any one of claims 1 to ~~14~~ 11, wherein the individual expresses FRS2β in one or more luminal progenitor cells.

~~16~~13. The use of any one of claims 1 to ~~11~~ 9 or ~~14~~ 11, wherein the individual expresses FRS2β in one or more mammary luminal progenitor cells.

~~17~~14. The use of any one of claims 1 to ~~16~~ 13, further comprising an additional therapeutic agent to be administered to the individual.

~~18~~15. The use of any one of claims 1 to ~~16~~ 13, further comprising a therapeutically effective amounts of an anti-IGF1 antibody and a CXCR4 inhibitor to be administered to the individual.

~~19~~16. The use of any one of claims 1 to ~~16~~ 13, further comprising a therapeutically effective amount of an anti-IGF1 antibody to be administered to the individual.

~~20~~17. The use of any one of claims 1 to ~~16~~ 13, further comprising a therapeutically effective amount of a CXCR4 inhibitor to be administered to the individual.

~~21~~18. The use of any one of claims 1 to ~~20~~ 17, wherein prior to administration of a CXCR7 inhibitor or an additional therapeutic agent the individual was diagnosed with having aberrant expression of FRS2β.

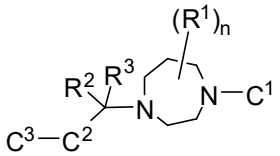
~~22~~19. Use of a CXCR7 inhibitor in the preparation of a medicament for preventing precancerous cells aberrantly expressing FRS2β from developing into cancer in an individual, wherein

the individual has precancerous cells aberrantly expressing FRS2β,

the cancer is selected from the group consisting of breast cancer, uterine cancer, ovarian cancer, cervical cancer, stomach cancer, pancreatic cancer, rectal cancer, kidney cancer, renal cancer, bladder cancer, prostate cancer, and adrenal cancer; and

the CXCR7 inhibitor has the structure of Formula I or Formula II.

~~23. The use of claim 22, wherein the CXCR7 inhibitor has the structure of Formula I~~



(I)

or pharmaceutically acceptable salts, hydrates, N-oxides, isotopically enriched or enantiomerically enriched versions thereof, wherein

the subscript n is an integer of from 0 to 2;

each R^1, when present, is independently selected from the group consisting of C_{1-4} alkyl, $-CO_2R^a$, $-X-CO_2R^a$, $-CONR^aR^b$ and $-X-CONR^aR^b$;

R^2 and R^3 are each members independently selected from the group consisting of H, $-R^a$, $-XR^a$, $-XNR^aR^b$, $-XNHCONR^aR^b$, $-XNHCOR^a$, $-X-O-CONR^aR^b$, $-XNHSO_2R^a$, $-CO_2R^a$, $-X-CO_2R^a$, $-CONR^aR^b$ and $-X-CONR^aR^b$; or taken together are oxo;

C^1 is selected from the group consisting of monocyclic or fused-bicyclic aryl and heteroaryl, wherein the heteroaryl group has from 1-3 heteroatoms as ring members selected from N, O and S; and wherein said aryl and heteroaryl groups are optionally substituted with from 1 to 3 R^4 substituents;

C^2 is monocyclic four-, five-, six- or seven-membered ring selected from the group consisting of benzene, heteroaromatic, cycloalkane, and heterocycloalkane, wherein the heteroaromatic and heterocycloalkane rings have from 1-3 heteroatoms as ring members selected from N, O and S; and wherein each of said monocyclic C^2 rings are optionally substituted with from 1 to 3 R^5 substituents;

C^3 is selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{3-8} cycloalkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl, heteroaryl-C_{1-4} alkyl, and four- to six-membered heterocycloalkyl, wherein the heterocycloalkyl group or portion has from 1-3 heteroatoms selected from N, O and S, and wherein the heteroaryl group has from 1-3 heteroatoms as ring members selected from N, O and S, and each C^3 is optionally substituted with from 1-3 R^6 substituents;

each R^4 is independently selected from the group consisting of halogen, -CN, -NO_2, -R^c, -CO_2R^a, -NR^aR^b, -OR^a, -X-CO_2R^a, -$CONR^aR^b$ and -X-$CONR^aR^b$;

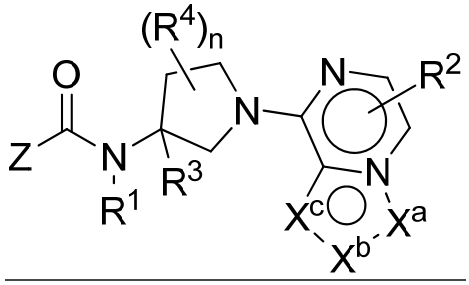
wherein within each of R^1, R^2, R^3 and R^4, each R^a and R^b is independently selected from hydrogen, C_{1-8} alkyl, C_{3-7} cycloalkyl, C_{1-8} haloalkyl, and four- to six-membered heterocycloalkyl, or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a four-, five- or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O or S; within R^4 each R^c is independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, aryl and heteroaryl, and wherein the aliphatic and cyclic portions of R^a, R^b and R^c are optionally further substituted with from one to three halogen, hydroxy, methyl, alkoxy, amino, alkylamino, dialkylamino, carboxamide, carboxy alkyl ester, carboxylic acid, heteroaryl, and four- to six-membered heterocycloalkyl groups; and wherein the heterocycloalkyl portions of R^2, R^3 and R^4 are optionally substituted with oxo; and optionally when two R^4 substituents are on adjacent atoms, are combined to form a fused five or six-membered ring having carbon and oxygen atoms as ring members;

each R^5 is independently selected from the group consisting of halogen, -CN, -NO_2, -R^f, -CO_2R^d, -COR^d, -NR^dR^e, -OR^d, -X-CO_2R^d, -$CONR^dR^e$ and -X-$CONR^dR^e$; wherein each R^d and R^e is independently selected from hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylalkyl, and four- to six-membered

heterocycloalkyl or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O or S; each R^f is independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, and C_{3-6} cycloalkyl, and wherein the aliphatic and cyclic portions of R^d, R^e and R^f are optionally further substituted with from one to three halogen, hydroxy, methyl, alkoxy, amino, alkylamino, dialkylamino, carboxamide, carboxy alkyl ester, carboxylic acid, heteroaryl, four- to six-membered heterocycloalkyl groups;

each R^6 is independently selected from the group consisting of halogen, -CN, -NO_2, -R^i, -CO_2R^g, -COR^g, -NR^gR^h, -OR^g, -X-CO_2R^g, -X-COR^g, -$CONR^g$ R^h and -X-$CONR^gR^h$, wherein each R^g and R^h is independently selected from hydrogen, C_{1-8} alkyl and C_{1-8} haloalkyl; each R^i is independently selected from the group consisting of C_{1-8} alkyl and C_{1-8} haloalkyl; and

each X is a linking group having the formula -$(CH_2)_mO(CH_2)_p$-, wherein the subscripts m and p are integer of from 0 to 5, and m + p is from 0 to 6, wherein the methylene groups are optionally substituted with one or two methyl groups; or



(II)

or a pharmaceutically acceptable salt, hydrate, N-oxide, isotopically enriched or enantiomerically enriched version or a rotamer thereof, wherein

each of ring vertices X^a, X^b and X^c is independently selected from the group consisting of N, NH, N(R^2), O, CH and C(R^2);

the subscript n is 0, 1 or 2;

Z is selected from the group consisting of

(i) monocyclic or fused-bicyclic aryl and heteroaryl, wherein the heteroaryl group has from 1-4 heteroatoms as ring members selected from N, O and S; and wherein said aryl and heteroaryl groups are optionally substituted with from 1 to 5 R^5 substituents;

(ii) monocyclic four-, five-, six- or seven-membered ring selected from the group consisting of cycloalkane, and heterocycloalkane, wherein the heterocycloalkane rings have from 1-3 heteroatoms as ring members selected from N, O and S; and wherein each of said monocyclic Z rings are optionally substituted with from 1 to 3 R^5 substituents;

R^1 is a member selected from the group consisting of H and C_{1-8} alkyl, wherein the alkyl portion is optionally substituted with halogen, $-NR^aR^b$, $-OR^a$, $-CO_2R^a$, and $-CONR^aR^b$;

each R^2 is independently selected from the group consisting of H, halogen, CN, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} hydroxyalkyl, $-OR^a$, $-CO_2R^a$, $-X-CO_2R^a$, $-NR^aR^b$, $-CONR^aR^b$ and $-X-CONR^aR^b$;

R^3 is a member selected from the group consisting of H, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} hydroxyalkyl, $-CO_2R^a$, $-X-CO_2R^a$, $-CONR^aR^b$ and $-X-CONR^aR^b$;

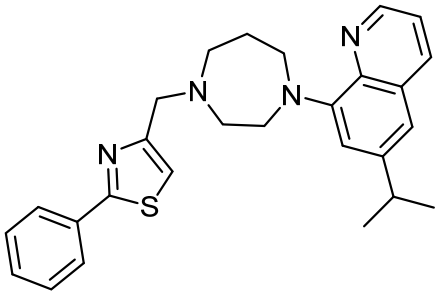
each R^4 , when present, is a member independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} hydroxyalkyl, $-OR^a$, $-CO_2R^a$, $-X-CO_2R^a$, $-NR^aR^b$, $-CONR^aR^b$ and $-X-CONR^aR^b$;

each R^5 is a member independently selected from the group consisting of halogen, CN, -X-CN, C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{3-5} spirocycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} haloalkyl, C_{1-8} hydroxyalkyl, $-OR^a$, $-CO_2R^a$, $-X-CO_2R^a$, $-NR^aR^b$, $-CONR^aR^b$, $-X-CONR^aR^b$, aryl, 5- or 6-membered heteroaryl, and 3-, 4-, 5- or 6-membered heterocyclic wherein the heteroatoms present as ring vertices of the heteroaryl and heterocyclic rings are selected from N, O and S, and wherein the aryl, heteroaryl and hetereocyclic portions of R^5 are optionally further substituted with 1-3 R^a;

each R^a and R^b is independently selected from the group consisting of hydrogen, hydroxyl, halogen, cyano, C_{1-8} alkyl, C_{1-8} alkoxy,C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylalkyl, amino, C_{1-8} alkylamino, di C_{1-8} alkylamino, carboxamide, carboxy C_{1-4} alkyl ester, carboxylic acid, and $-SO_2-$ C_{1-8} alkyl;

each X is a C_{1-4} alkylene linking group or a linking group having the formula $-(CH_2)_mO(CH_2)_p-$, wherein the subscripts m and p are integer of from 0 to 5, and m + p is from 0 to 6, wherein any of the methylene portions of X are optionally substituted with one or two methyl groups.

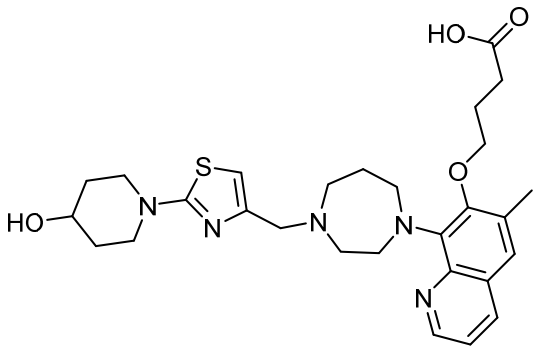
2420. The use of claim 23 19, wherein the CXCR7 inhibitor has the structure of Compound 1



(Compound 1)

or a pharmaceutically acceptable salt thereof.

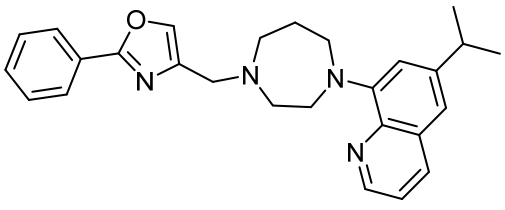
2521. The use of claim 23 19, wherein the CXCR7 inhibitor has the structure of Compound 2



(Compound 2)

or a pharmaceutically acceptable salt thereof.

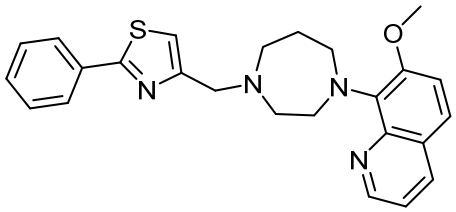
2622. The use of claim 23 19, wherein the CXCR7 inhibitor has the structure of Compound 3



(Compound 3)

or a pharmaceutically acceptable salt thereof.

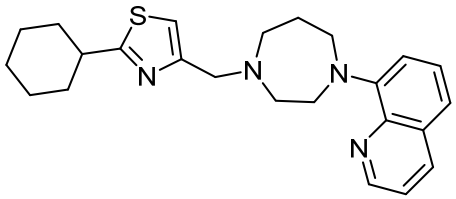
2723. The use of claim 23 19, wherein the CXCR7 inhibitor has the structure of Compound 4



(Compound 4)

or a pharmaceutically acceptable salt thereof.

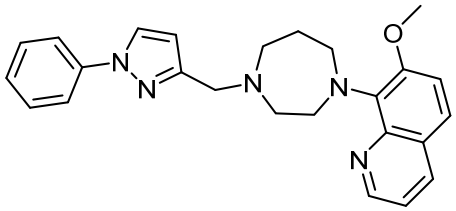
~~28~~ 24. The use of claim ~~23~~ 19, wherein the CXCR7 inhibitor has the structure of Compound 5



(Compound 5)

or a pharmaceutically acceptable salt thereof.

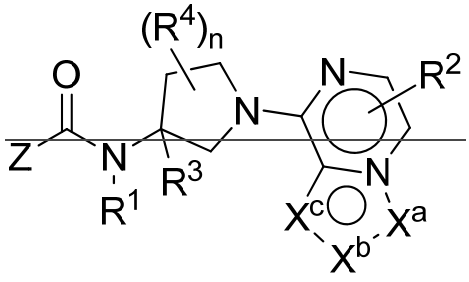
~~29~~ 25. The use of claim ~~23~~ 19, wherein the CXCR7 inhibitor has the structure of Compound 6



(Compound 6)

or a pharmaceutically acceptable salt thereof.

~~30. The use of claim 22, wherein the CXCR7 inhibitor has the structure of Formula II~~



~~(II)~~

or a pharmaceutically acceptable salt, hydrate, N-oxide, isotopically enriched or enantiomerically enriched version or a rotamer thereof, wherein

each of ring vertices X^a, X^b and X^e is independently selected from the group consisting of N, NH, $N(R^2)$, O, CH and $C(R^2)$;

the subscript n is 0, 1 or 2;

Z is selected from the group consisting of

(i) monocyclic or fused-bicyclic aryl and heteroaryl, wherein the heteroaryl group has from 1-4 heteroatoms as ring members selected from N, O and S; and wherein said aryl and heteroaryl groups are optionally substituted with from 1 to 5 R^5 substituents;

(ii) monocyclic four-, five-, six- or seven-membered ring selected from the group consisting of cycloalkane, and heterocycloalkane, wherein the heterocycloalkane rings have from 1-3 heteroatoms as ring members selected from N, O and S; and wherein each of said monocyclic Z rings are optionally substituted with from 1 to 3 R^5 substituents;

R^1 is a member selected from the group consisting of H and C_{1-8} alkyl, wherein the alkyl portion is optionally substituted with halogen, $-NR^aR^b$, $-OR^a$, $-CO_2R^a$, and $-CONR^aR^b$;

each R^2 is independently selected from the group consisting of H, halogen, CN, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} hydroxyalkyl, $-OR^a$, $-CO_2R^a$, $-X-CO_2R^a$, $-NR^aR^b$, $-CONR^aR^b$ and $-X-CONR^aR^b$;

R^3 is a member selected from the group consisting of H, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} hydroxyalkyl, $-CO_2R^a$, $-X-CO_2R^a$, $-CONR^aR^b$ and $-X-CONR^aR^b$;

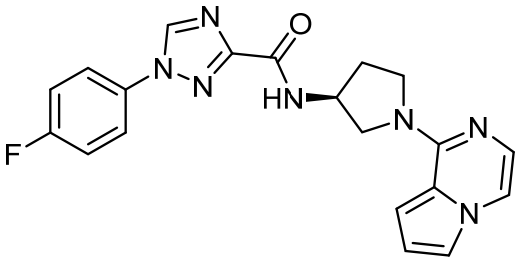
each R^4, when present, is a member independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} hydroxyalkyl, $-OR^a$, $-CO_2R^a$, $-X-CO_2R^a$, $-NR^aR^b$, $-CONR^aR^b$ and $-X-CONR^aR^b$;

each R^5 is a member independently selected from the group consisting of halogen, CN, -X-CN, C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{3-5} spirocycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} haloalkyl, C_{1-8} hydroxyalkyl, $-OR^a$, $-CO_2R^a$, $-X-CO_2R^a$, $-NR^aR^b$, $-CONR^aR^b$, $-X-CONR^aR^b$, aryl, 5- or 6-membered heteroaryl, and 3-, 4-, 5- or 6-membered heterocyclic wherein the heteroatoms present as ring vertices of the heteroaryl and heterocyclic rings are selected from N, O and S, and wherein the aryl, heteroaryl and hetereocyclic portions of R^5 are optionally further substituted with 1-3 R^a;

~~each R^a and R^b is independently selected from the group consisting of hydrogen, hydroxyl, halogen, cyano, C_{1-8} alkyl, C_{1-8} alkoxy,C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylalkyl, amino, C_{1-8} alkylamino, di C_{1-8} alkylamino, carboxamide, carboxy C_{1-4} alkyl ester, carboxylic acid, and $-SO_2-C_{1-8}$ alkyl;~~

~~each X is a C_{1-4} alkylene linking group or a linking group having the formula $-(CH_2)_m-O-(CH_2)_p-$, wherein the subscripts m and p are integer of from 0 to 5, and m + p is from 0 to 6, wherein any of the methylene portions of X are optionally substituted with one or two methyl groups.~~

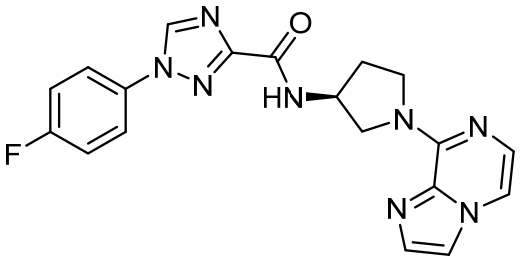
~~31~~26. The use of claim ~~30~~19 wherein the CXCR7 inhibitor has the structure of Compound 7



(Compound 7)

or a pharmaceutically acceptable salt thereof.

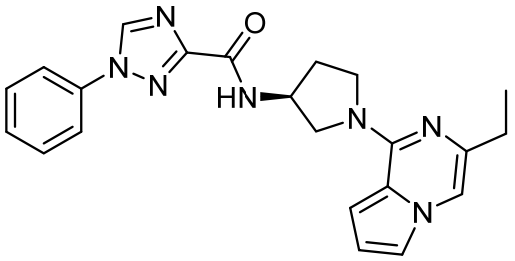
~~32~~27. The use of claim ~~30~~ 19, wherein the CXCR7 inhibitor has the structure of Compound 8



(Compound 8)

or a pharmaceutically acceptable salt thereof.

~~33~~28. The use of claim ~~30~~ 19, wherein the CXCR7 inhibitor has the structure of Compound 9



(Compound 9)

or a pharmaceutically acceptable salt thereof.

~~34. The use of any one of claims 22 to 33, wherein the cancer is selected from the group consisting of breast cancer, uterine cancer, ovarian cancer, cervical cancer, stomach cancer, pancreatic cancer, rectal cancer, kidney cancer, renal cancer, bladder cancer, prostate cancer, and adrenal cancer.~~

~~35~~29. The use of any one of claims ~~22~~19 to ~~33~~ 28, wherein the cancer is breast cancer.

~~36~~30. The use of any one of claims ~~22~~19 to ~~35~~ 29, wherein said precancerous cells aberrantly expressing FRS2β are precancerous luminal progenitor cells expressing FRS2β.

~~37~~31. The use of claim ~~22~~19 to ~~33~~28 or ~~35~~ 29, wherein said precancerous cells aberrantly expressing FRS2β are precancerous mammary luminal progenitor cells expressing FRS2β.

~~38~~32. The use of any one of claims ~~22~~19 to ~~37~~ 31, further comprising an additional therapeutic agent to be administered to the individual.

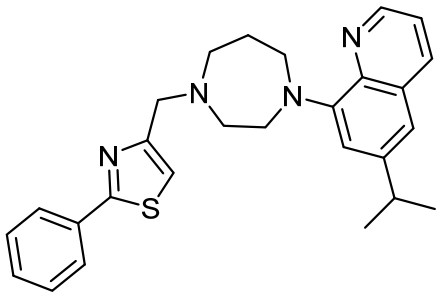
~~39~~33. The use of any one of claims ~~22~~19 to ~~37~~ 31, further comprising a therapeutically effective amounts of an anti-IGF1 antibody and a CXCR4 inhibitor to be administered to the individual.

~~40~~34. The use of any one of claims ~~22~~19 to ~~37~~ 31, further comprising a therapeutically effective amount of an anti-IGF1 antibody to be administered to the individual.

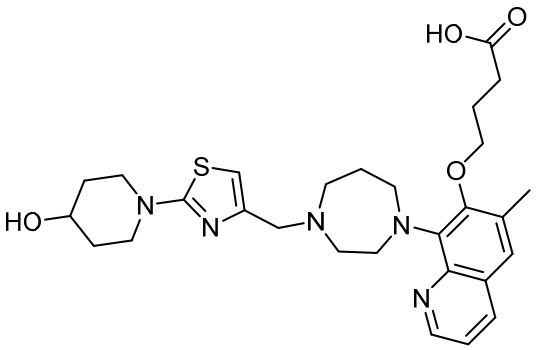
~~41~~35. The use of any one of claims ~~22~~19 to ~~37~~ 31, further comprising a therapeutically effective amount of a CXCR4 inhibitor to be administered to the individual.

~~42~~36. The use of any one of claims ~~22~~19 to ~~41~~ 35, wherein prior to administration of a CXCR7 inhibitor or an additional therapeutic agent the individual was diagnosed with having aberrant expression of FRS2β.

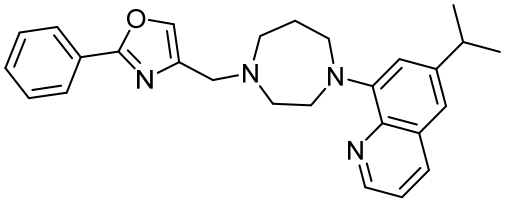
~~43~~37. Use of a compound selected from the group consisting of



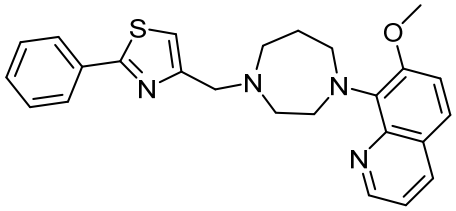
(Compound 1),



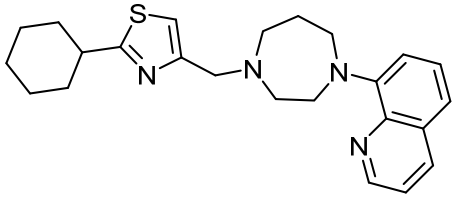
(Compound 2),



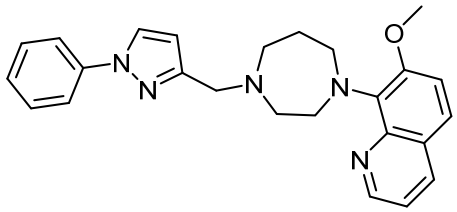
(Compound 3),



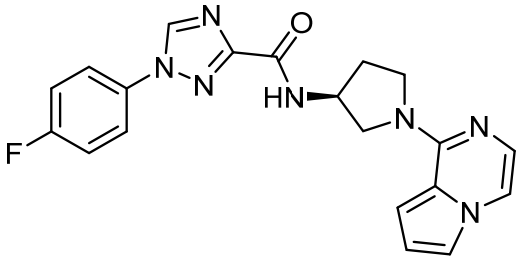
(Compound 4),



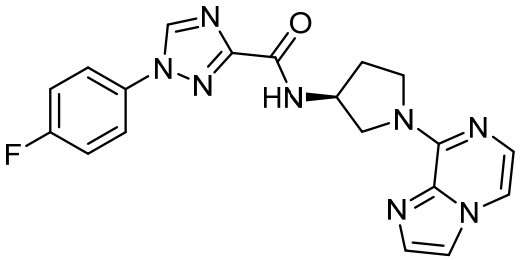
(Compound 5),



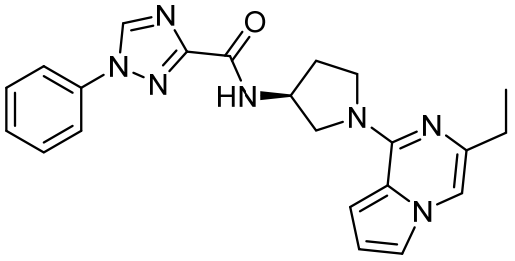
(Compound 6),



(Compound 7),



(Compound 8), and



(Compound 9)

or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for treating breast cancer in an individual.

~~44 The use of claim 43~~, wherein prior to administration the individual has been diagnosed as having aberrant expression of FRS2β

~~45~~38 The use of claim ~~42~~37 ~~or claim 44~~, further comprising an additional therapeutic agent to be administered to the individual.