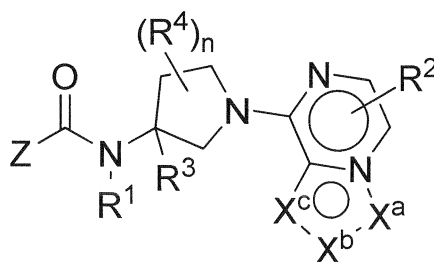


BRIEF SUMMARY

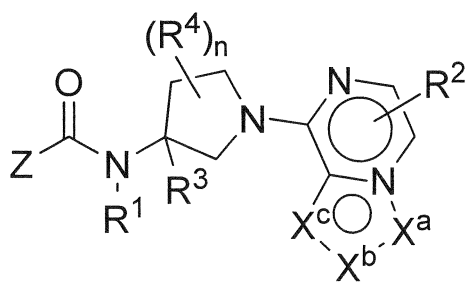
[0016] The present disclosure provides, ~~in one aspect,~~ compounds having formula I,



(I)

5 or pharmaceutically acceptable salts, hydrates or N-oxides thereof. The various groups (e.g., R^1 , R^2 , R^3 , R^4 , Z, X^a , X^b , X^c and the subscript n) are described in the Detailed Description of the Invention.

[0016a] In one aspect of the present disclosure, there is provided a compound having formula I



(I)

10 or a pharmaceutically acceptable salt, hydrate, isotopically enriched or enantiomerically enriched version thereof, wherein

15 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

20 (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 R⁵ substituents;

R¹ is a member selected from the group consisting of H and C₁₋₈ alkyl, wherein the alkyl portion is optionally substituted with halogen, -NR^aR^b, -OR^a, -CO₂R^a, and -CONR^aR^b;

each R² is independently selected from the group consisting of H, halogen, CN, C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₁₋₈ hydroxyalkyl, -OR^a, -CO₂R^a, -X-CO₂R^a, -NR^aR^b, -CONR^aR^b and -X-CONR^aR^b;

R³ is a member selected from the group consisting of H, C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₁₋₈ hydroxyalkyl, -CO₂R^a, -X-CO₂R^a, -CONR^aR^b and -X-CONR^aR^b;

each R⁴, when present, is a member independently selected from the group consisting of C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₁₋₈ hydroxyalkyl, -OR^a, -CO₂R^a, -X-CO₂R^a, -NR^aR^b, -CONR^aR^b and -X-CONR^aR^b;

each R⁵ is a member independently selected from the group consisting of halogen, CN, -X-CN, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkenyl, C₃₋₅ spirocycloalkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₈ haloalkyl, C₁₋₈ hydroxyalkyl, -OR^a, -CO₂R^a, -X-CO₂R^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 heterocyclic portions of R⁵ 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, C₁₋₈ alkyl, C₁₋₈ alkoxy, C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkylalkyl, amino, C₁₋₈ alkylamino, di C₁₋₈ alkylamino, carboxamide, carboxy C₁₋₄ alkyl ester, carboxylic acid, and -SO₂- C₁₋₈ alkyl;

each X is a C₁₋₄ alkylene linking group or a linking group having the formula -(CH₂)_mO(CH₂)_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.

[0017] The compounds provided herein are useful for binding to CXCR7, and treating diseases that are dependent, at least in part, on CXCR7 activity. Accordingly, the present disclosure provides in another aspect, a pharmaceutical composition containing one or more of the above-noted compounds in admixture with a pharmaceutically acceptable excipient.

[0018] The present disclosure also provides methods for treating various diseases, discussed further herein, comprising administering to a subject in need to such treatment a therapeutically effective amount of a compound of the above formula for a period of time sufficient to treat the disease. In another aspect, the present disclosure provides a compound as defined herein for use in treating a disease or disorder in a mammal. In another aspect, the present disclosure provides use of a compound as defined herein in the manufacture of a medicament for the treatment of a disease or disorder selected from the group consisting of cancer, inflammation and ~~neural or progenitor/stem cell~~ hematopoietic disorders.

[0019] The present disclosure also provides methods of diagnosing disease in an individual.

In these methods, the compounds provided herein are administered in labeled form to a subject, followed by diagnostic imaging to determine the presence or absence of CXCR7. The method of diagnosing disease may be carried out by contacting a tissue or blood sample with a labeled compound as

provided herein and determining the presence, absence, or amount of CXCR7 in the sample.

In another aspect, the present disclosure provides a method for imaging a tumor, organ, or tissue, said method comprising detecting a radiolabeled or detectable form of a compound as defined herein in a subject who had been administered the compound to determine where the

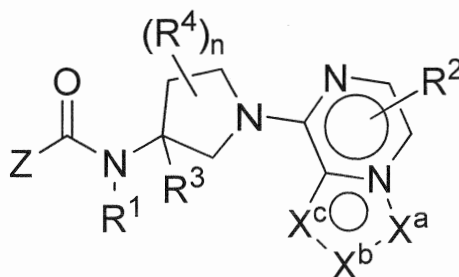
5 compound is concentrated in the subject. In another aspect, the present disclosure provides a method for detecting elevated levels of CXCR7 in a sample, said method comprising (a) contacting a sample suspected of having elevated levels of CXCR7 with a radiolabeled or detectable form of a compound as defined herein; (b) determining a level of compound that is bound to CXCR7 present in the sample to determine the level of CXCR7 present in the
10 sample; and (c) comparing the level determined in step (b) with a control sample to determine if elevated levels of CXCR7 are present in the sample.

[0020] In some embodiments, an amount of a chemotherapeutic agent or radiation is administered to the subject prior to, subsequent to or in combination with the compounds of the present disclosure. In some embodiments, the amount is sub-therapeutic when the
15 chemotherapeutic agent or radiation is administered alone.

[0020a] In another aspect, the present disclosure provides an *in vitro* method of inhibiting the binding of chemokines I-TAC or SDF-1 to a CXCR7 receptor, comprising contacting a compound as defined herein with a cell that expresses the CXCR7 receptor for a time sufficient to inhibit the binding of the chemokines to the CXCR7 receptor.

WHAT IS CLAIMED IS:

1. A compound having formula I



(I)

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(R²), O, CH and C(R²);

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 R⁵ 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 R⁵ substituents;

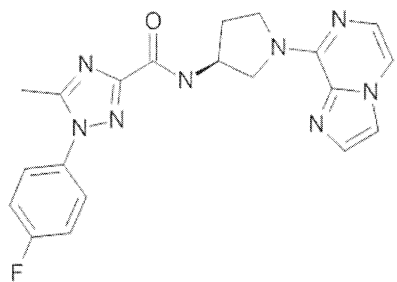
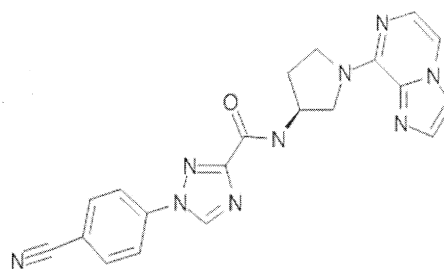
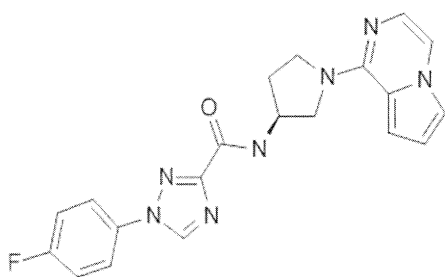
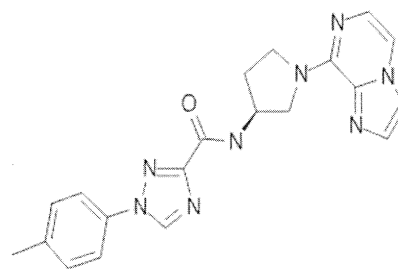
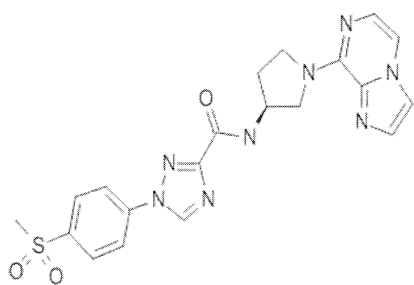
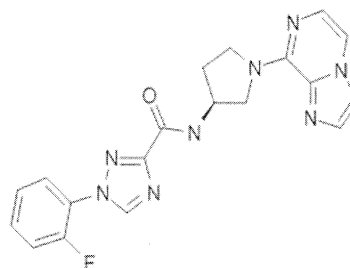
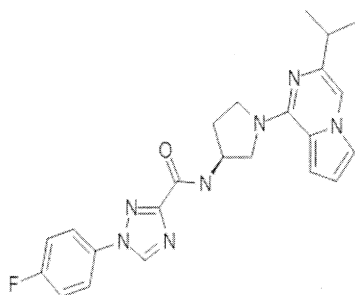
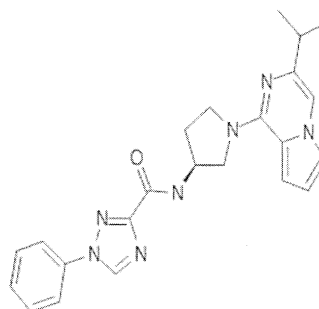
R¹ is a member selected from the group consisting of H and C₁₋₈ alkyl, wherein the alkyl portion is optionally substituted with halogen, -NR^aR^b, -OR^a, -CO₂R^a, and -CONR^aR^b; each R² is independently selected from the group consisting of H, halogen, CN, C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₁₋₈ hydroxyalkyl, -OR^a, -CO₂R^a, -X-CO₂R^a, -NR^aR^b, -CONR^aR^b and -X-CONR^aR^b;

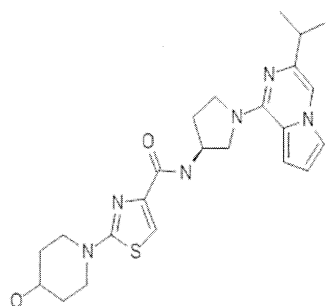
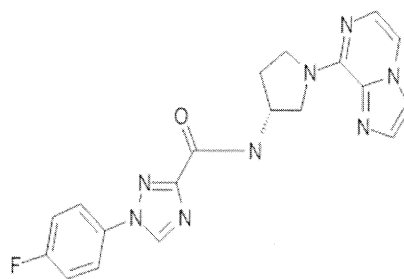
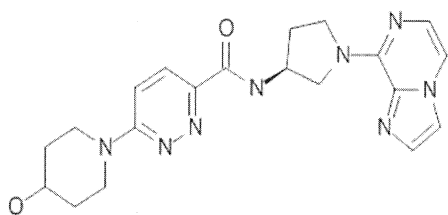
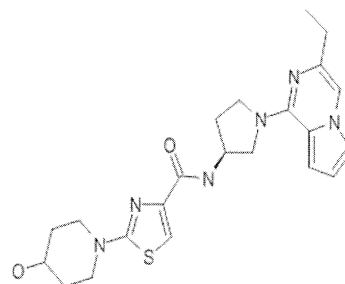
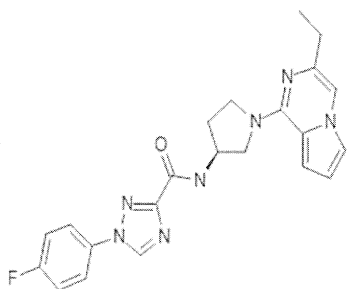
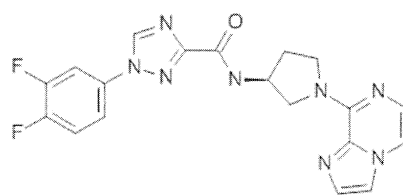
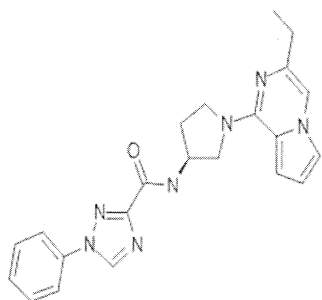
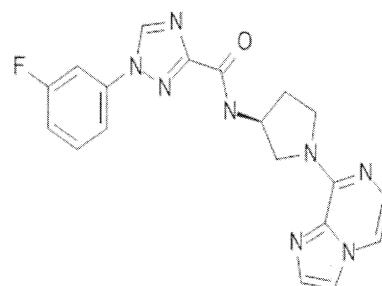
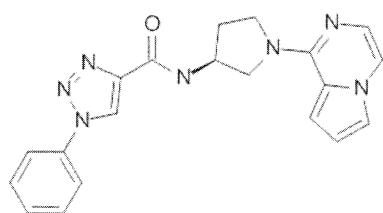
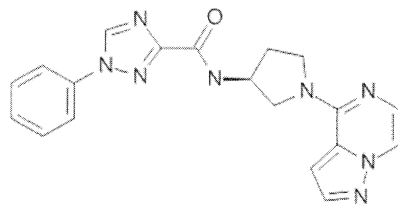
R³ is a member selected from the group consisting of H, C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₁₋₈ hydroxyalkyl, -CO₂R^a, -X-CO₂R^a, -CONR^aR^b and -X-CONR^aR^b;

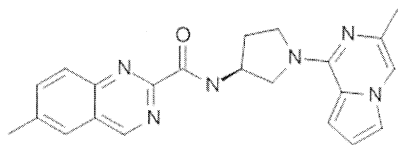
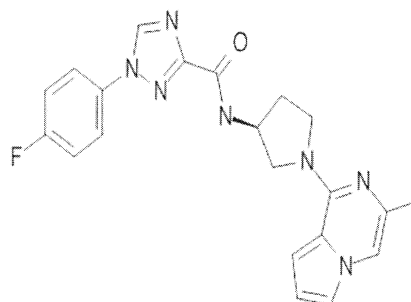
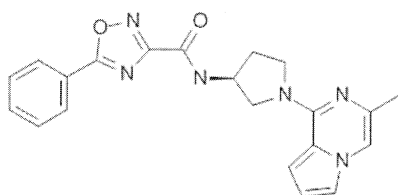
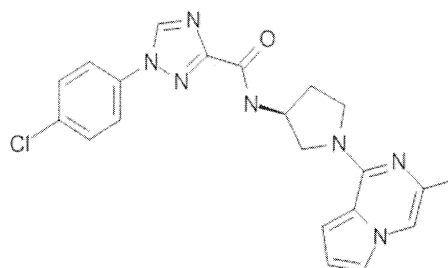
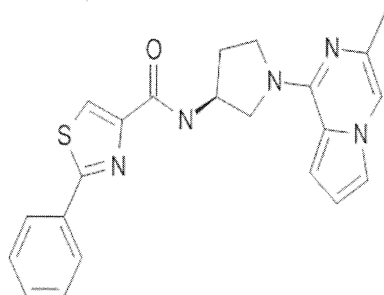
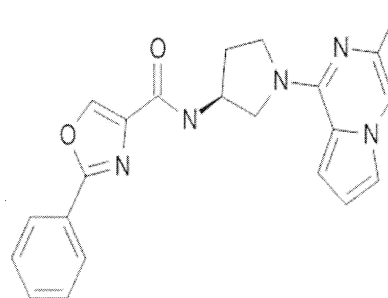
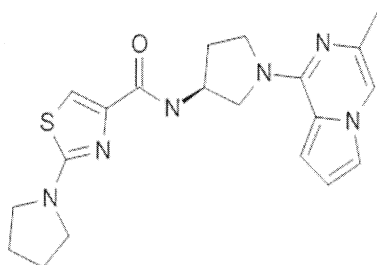
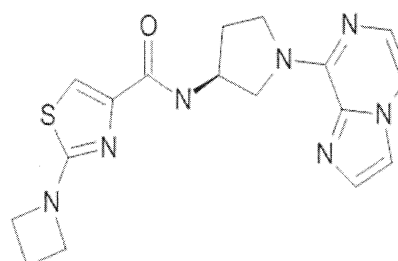
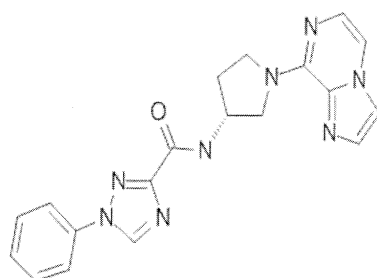
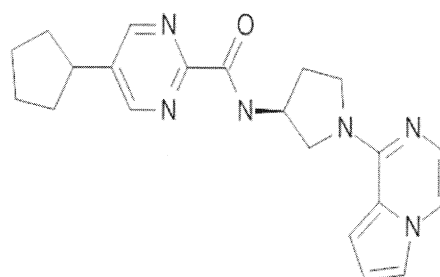
each R⁴, when present, is a member independently selected from the group consisting of C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₁₋₈ hydroxyalkyl, -OR^a, -CO₂R^a, -X-CO₂R^a, -NR^aR^b, -CONR^aR^b and -X-CONR^aR^b;

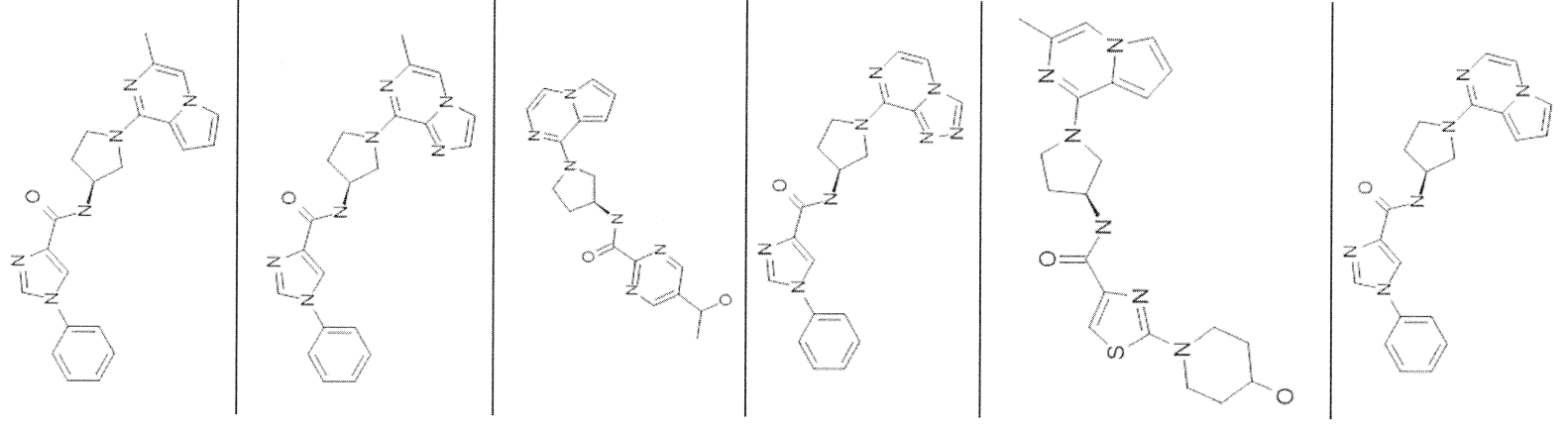
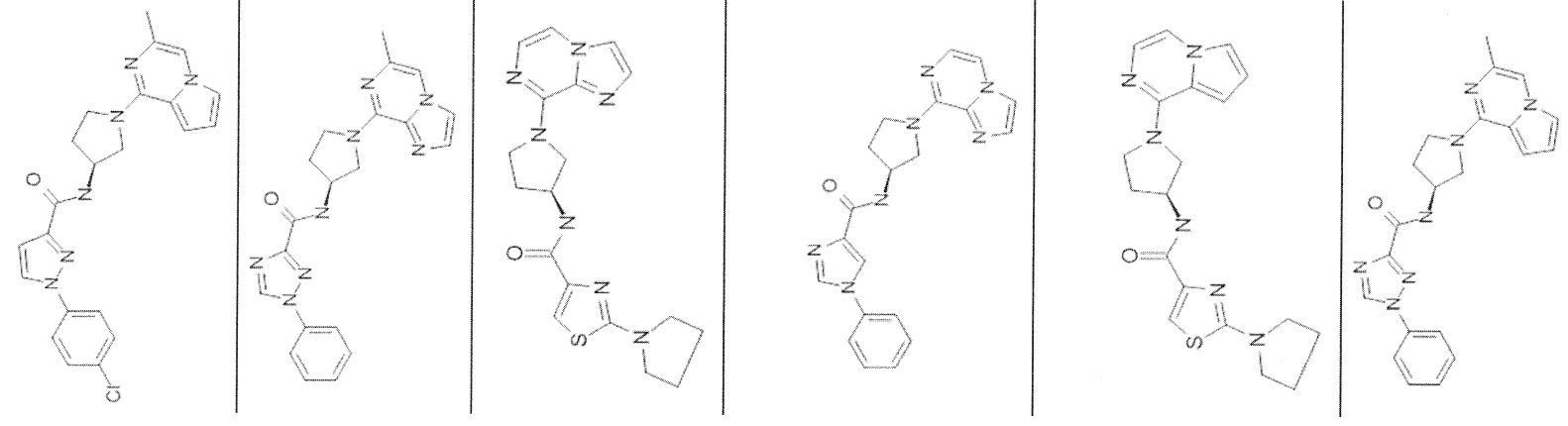
~~17.~~ The compound of claim 1, selected from the compounds of the Examples.

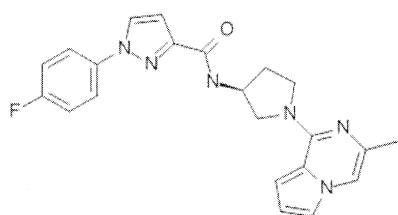
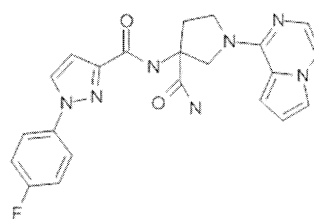
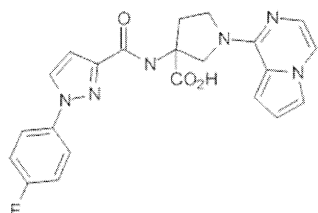
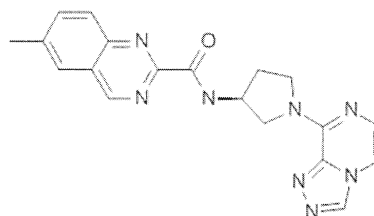
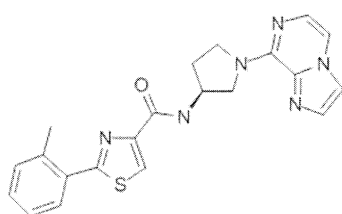
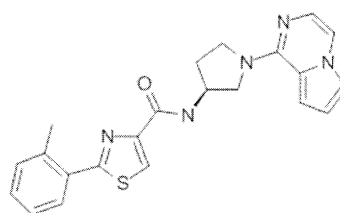
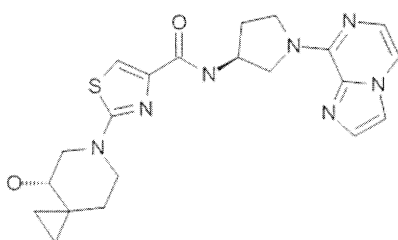
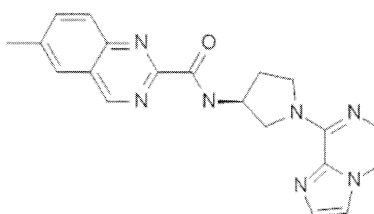
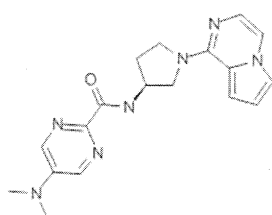
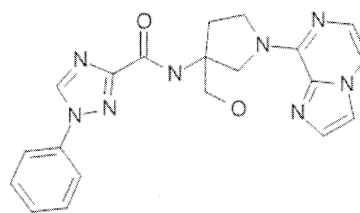
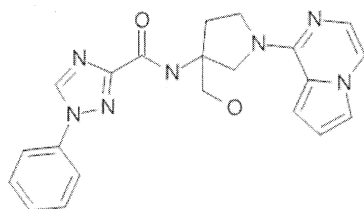
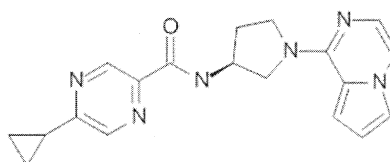
~~1817.~~ The compound of claim 1, selected from those in Table 1, the group consisting of:

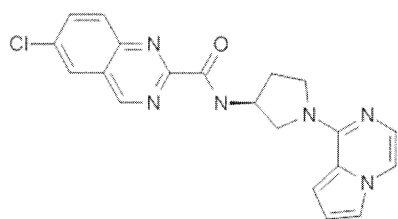
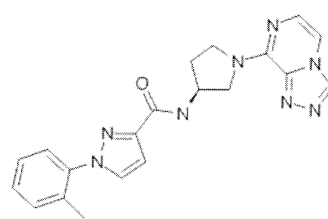
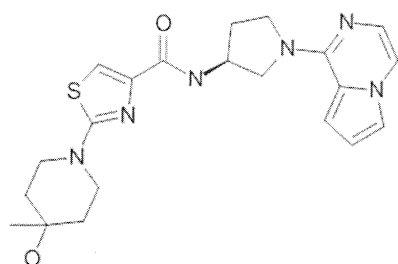
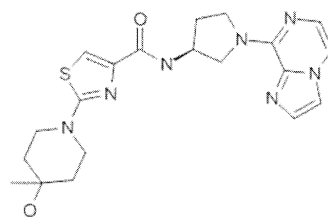
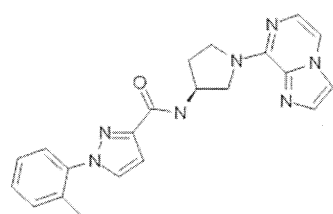
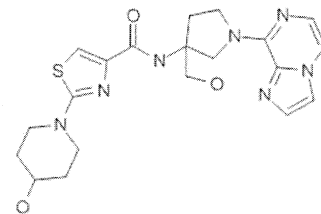
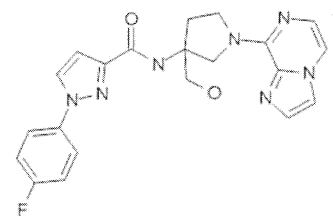
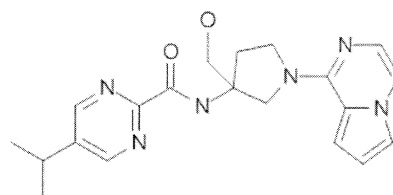
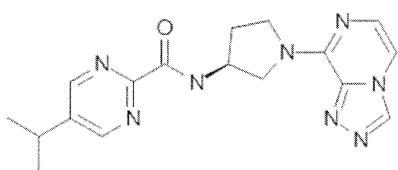
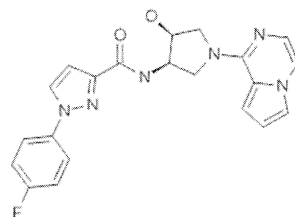
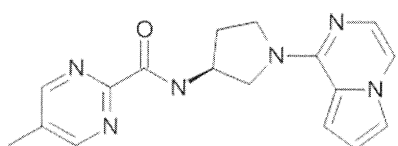
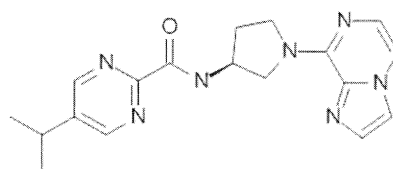


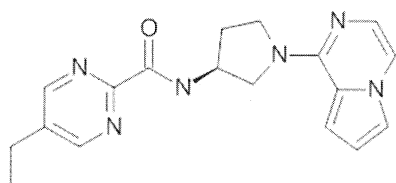
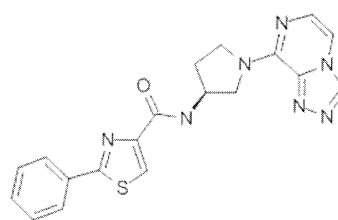
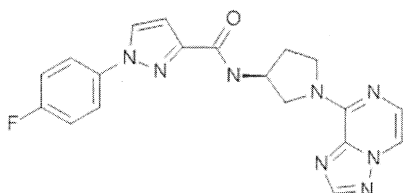
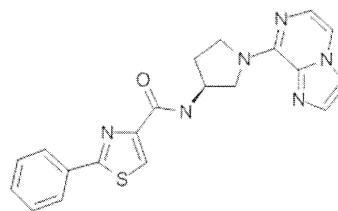
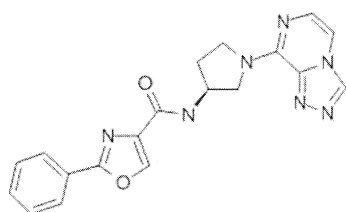
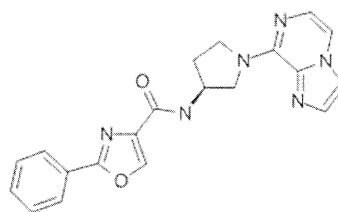
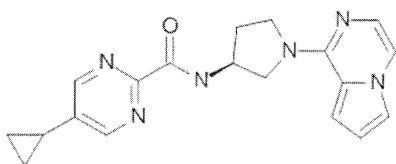
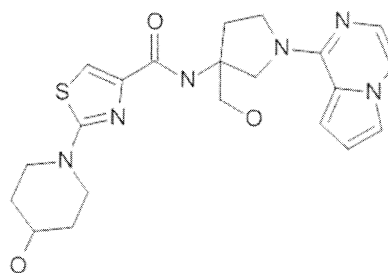
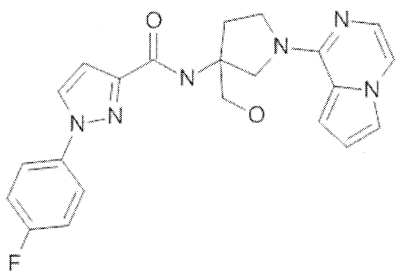
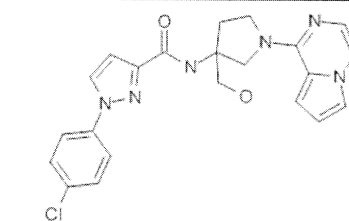
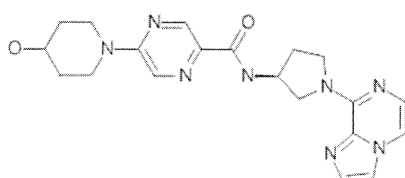
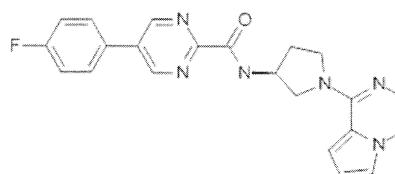


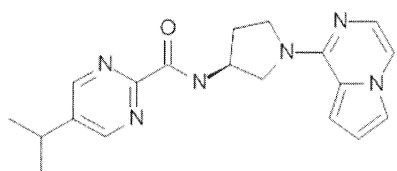
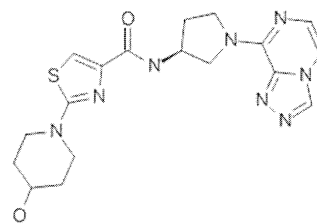
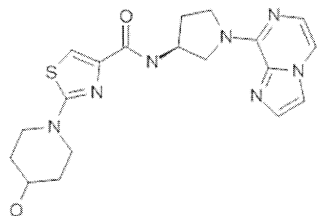
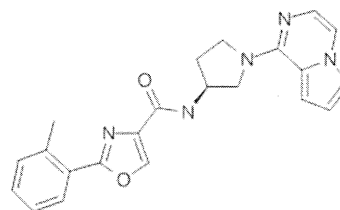
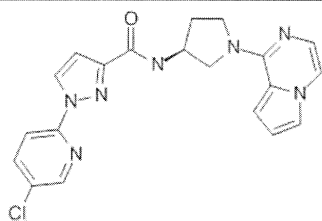
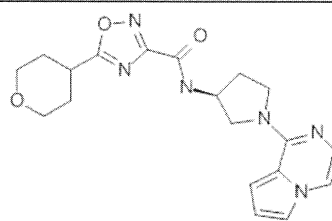
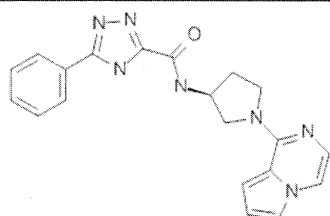
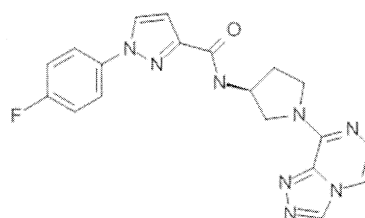
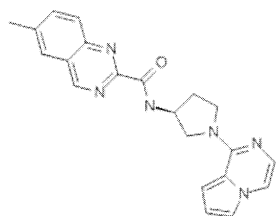
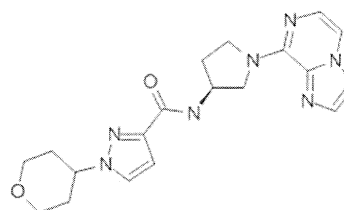
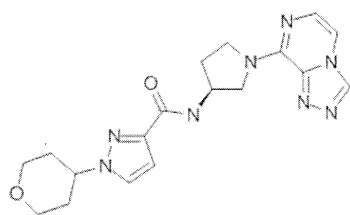
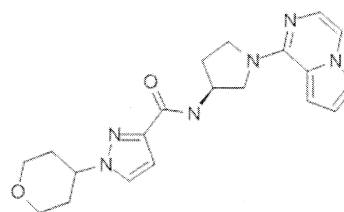
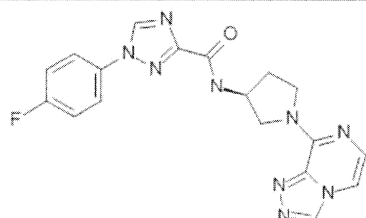
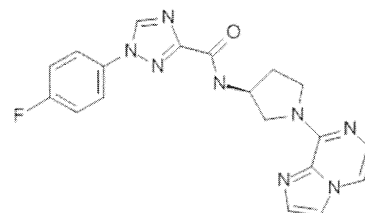


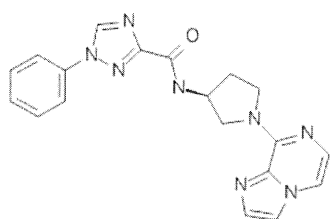
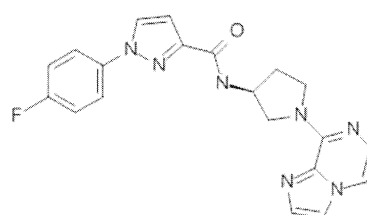
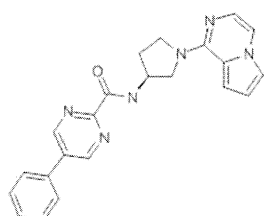
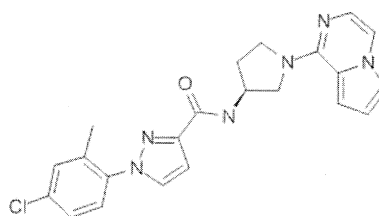
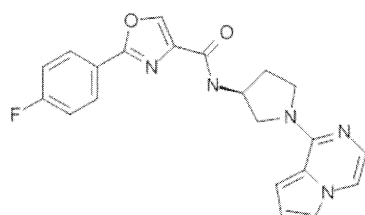
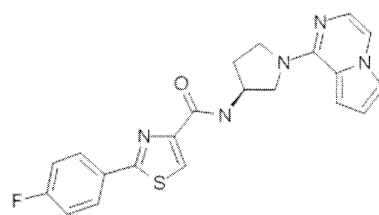
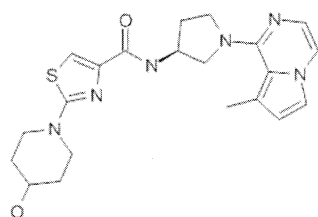
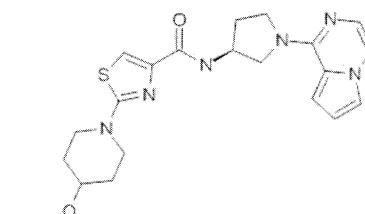
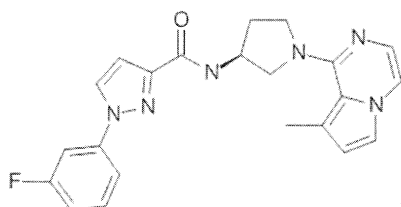
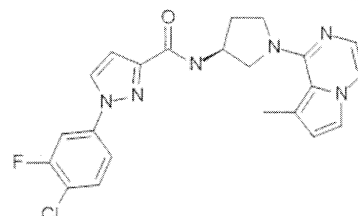
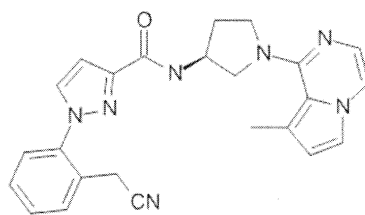
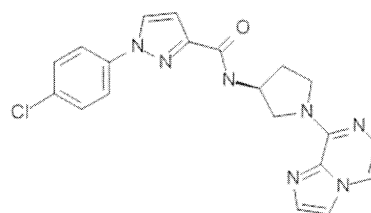
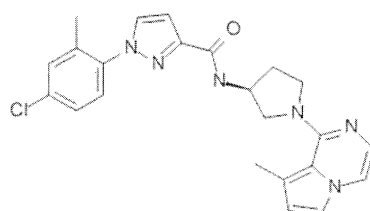
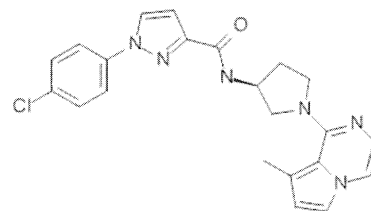


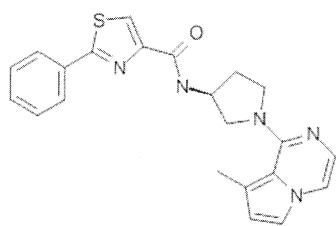
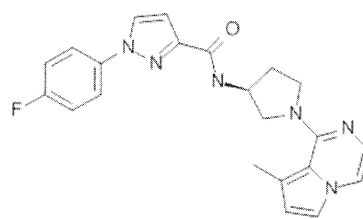
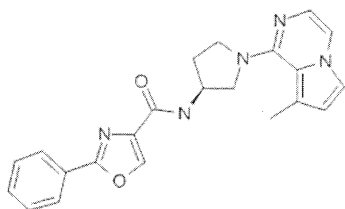
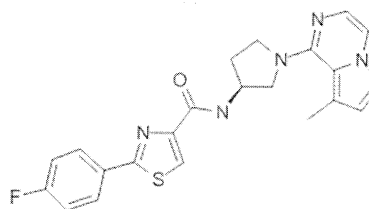
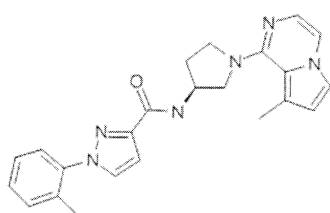
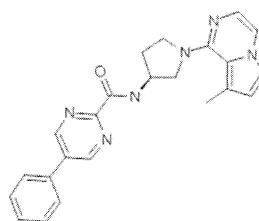
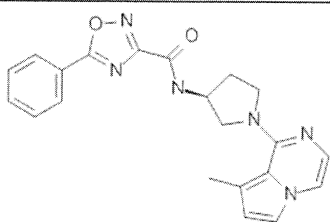
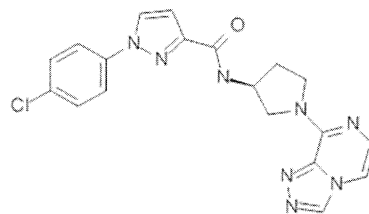
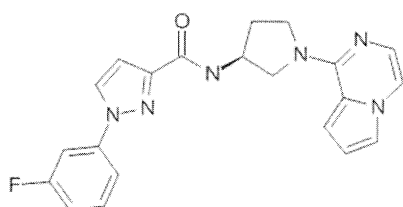
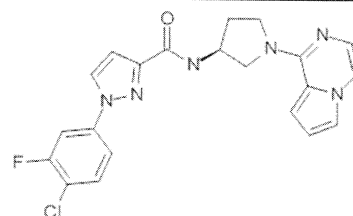
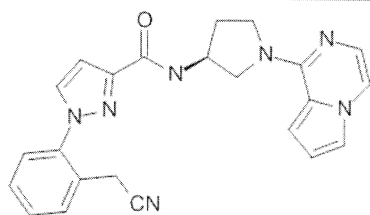
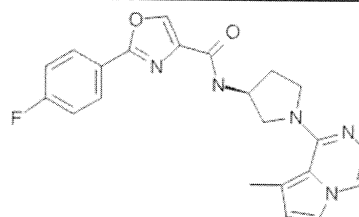
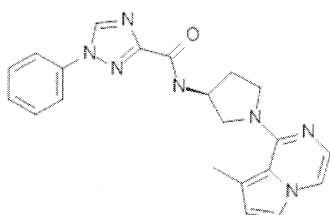
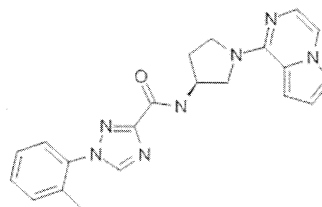


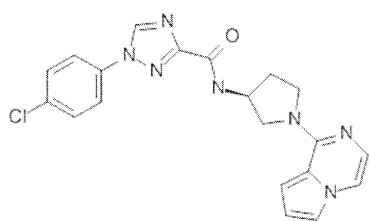
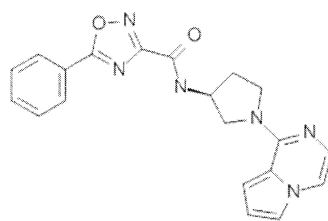
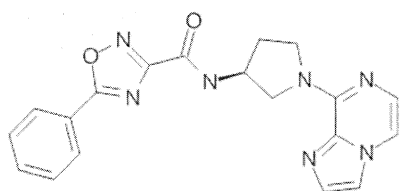
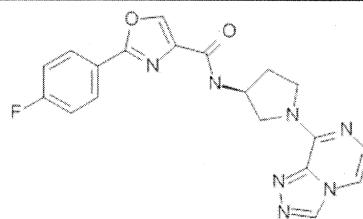
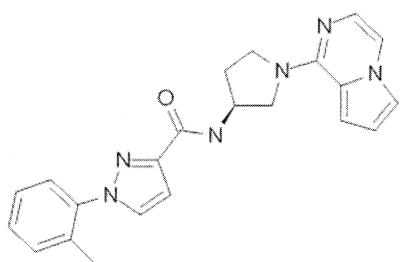
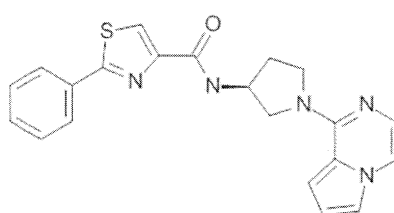
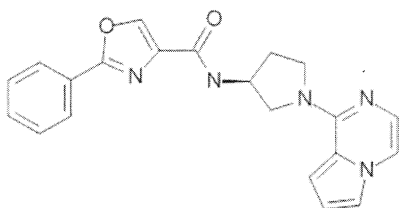
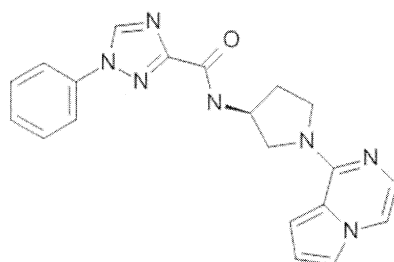
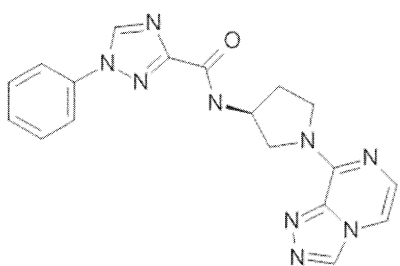
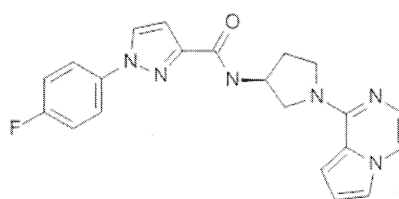
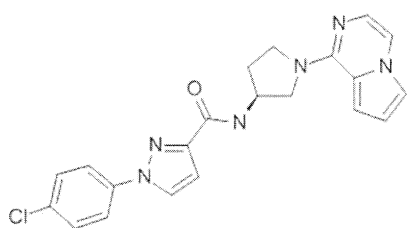












or a pharmaceutically acceptable salt thereof.

1918. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable excipient.

2019. The pharmaceutical composition of claim ~~1918~~, wherein the compound is a compound of ~~Table 1~~claim 17.

2120. A compound of claim 1 for use in treating a disease or disorder in a mammal.

2221. The compound of claim ~~2120~~, wherein the compound is a compound of ~~Table 1~~claim 17.

2322. The compound of claim ~~2120~~, wherein said disease or disorder is selected from the group consisting of cancer, inflammation and ~~neural or progenitor/stem cell~~ hematopoietic disorders.

2423. An *in vitro* method of inhibiting the binding of chemokines I-TAC or SDF-1 to a CXCR7 receptor, comprising contacting a compound of claim 1 with a cell that expresses the CXCR7 receptor for a time sufficient to inhibit the binding of the chemokines to the CXCR7 receptor.

2524. The *in vitro* method of claim ~~2423~~, wherein the compound is a compound of ~~Table 1~~claim 17.

2625. A method for imaging a tumor, organ, or tissue, said method comprising:

detecting a radiolabeled or detectable form of a compound of any of claims 1 to 15 in a subject who had been administered said compound to determine where said compound is concentrated in said subject.

2726. A method in accordance with claim 2625, wherein said compound is radiolabeled.

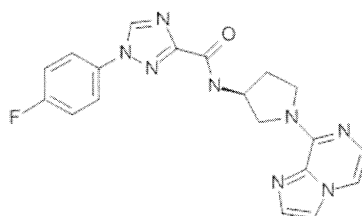
2827. A method for detecting elevated levels of CXCR7 in a sample, said method comprising:

- (a) contacting a sample suspected of having elevated levels of CXCR7 with a radiolabeled or detectable form of a compound of any of claims **1** to **15** ;
- (b) determining a level of compound that is bound to CXCR7 present in said sample to determine the level of CXCR7 present in said sample; and
- (c) comparing the level determined in step (b) with a control sample to determine if elevated levels of CXCR7 are present in said sample.

2928. A method in accordance with claim 2827, wherein said compound is radiolabeled.

3029. Use of a compound of claim **1** in the manufacture of a medicament for the treatment of a disease or disorder selected from the group consisting of cancer, inflammation and ~~neural or progenitor/stem cell~~ hematopoietic disorders.

30. A compound of claim **1**, having the formula:



or a pharmaceutically acceptable salt thereof.

31. A compound of claim **1**, having the formula:

