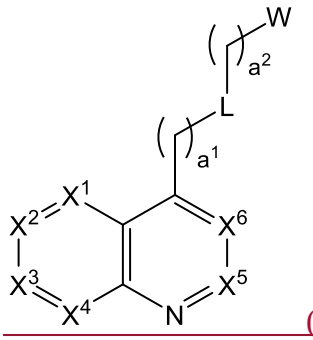
cGAMP hydrolysis. Adenosine is generated from AMP by enzymes such as CD73, and further suppresses the immune response and supports tumor survival by adenosine receptor pathways.

[0005] ENPP1 has also been implicated in bacterial or viral infections, insulin resistance and type II diabetes, chondrocalcinosis and osteoarthritis, calcium pyrophosphate deposition disorder (CPPD), hypophosphatasia, and soft-tissue calcification disorders such as cardiac calcification after heart injury. Therefore, ENPP1 inhibition can be used to treat any of these disorders.

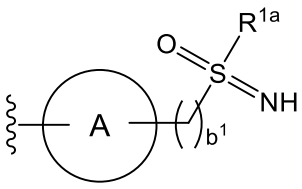
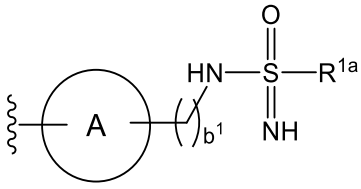
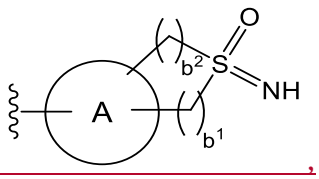
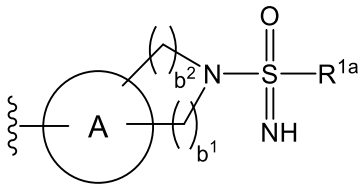
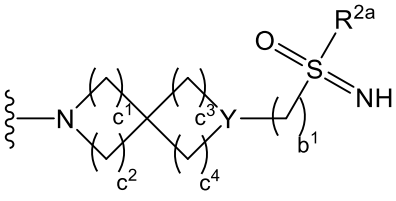
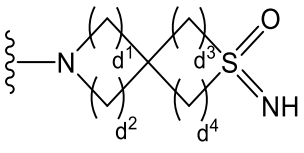
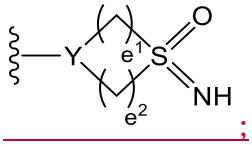
BRIEF SUMMARY

[0005a] In an aspect of the present disclosure, there is provided a compound of Formula (I)



(I),

or a pharmaceutically acceptable salt thereof, wherein:

W is  ,  ,  ,  ,  ,  , or  ;

ring A is aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is substituted or unsubstituted;

R^{1a} and R^{2a} are each independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted 3-6 membered heterocycloalkyl, or optionally substituted C_{1-6} haloalkyl;

Y is -N- or -CH-;

X^1 is $-CR^{1b}-$ or -N-;

X^2 is $-CR^{2b}-$ or -N-;

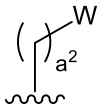
X^3 is $-CR^{3b}-$ or -N-;

X^4 is $-CR^{4b}-$ or -N-;

X^5 is $-CR^{5b}-$ or -N-;

X^6 is $-CR^{6b}-$ or -N-;

R^{1b}-R^{6b} are each independently hydrogen, halogen, hydroxyl, C_{1-4} alkoxy optionally substituted with one or more halo substituents, cyano, C_{1-3} alkyl, C_{1-3} haloalkyl, nitro, $-NR^{1c}R^{2c}$, $-NHC(O)R^{3c}$, or $-C(O)NR^{4c}R^{5c}$;

L is a bond, -O-, -C(O)-, $-NR^{6c}-$, or $-OCR^{7c}-$*, wherein * represents the point of attachment to 

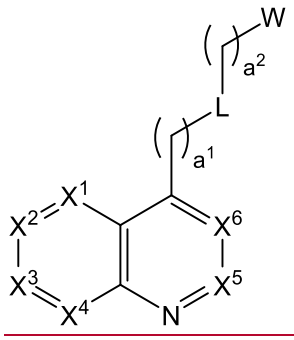
;

R^{1c}-R^{7c} are each independently hydrogen or C_{1-3} alkyl;

a^1, a^2, b^1, and c^4 are each independently 0, 1, 2, or 3; and

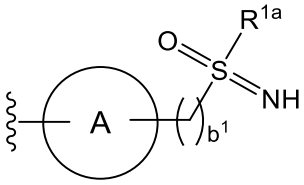
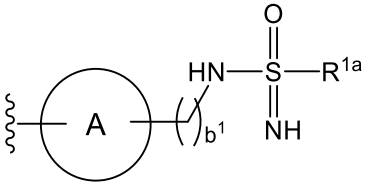
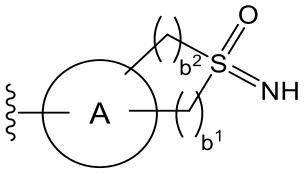
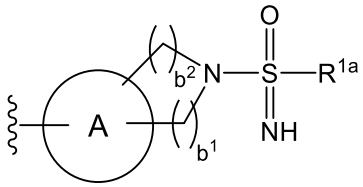
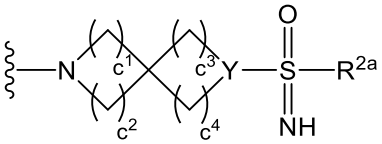
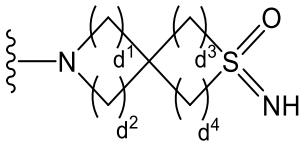
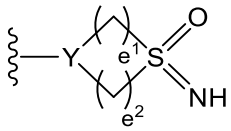
b^2, c^1-c^3, d^1-d^4, e^1, and e^2 are each independently 1, 2, or 3.

[0005b] In another aspect of the present disclosure, there is provided a compound of Formula (I-1):



(I-1),

or a pharmaceutically acceptable salt thereof, wherein:

W is  ,  ,  ,  ,  ,  , or  ;

ring A is aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is substituted or unsubstituted;

R^{1a} and R^{2a} are each independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl, or C_{1-6} haloalkyl;

Y is -N- or -CH-;

X^1 is $-CR^{1b}-$ or -N-;

X^2 is $-CR^{2b}-$ or -N-;

X^3 is $-CR^{3b}-$ or -N-;

X^4 is $-CR^{4b}-$ or -N-;

X^5 is $-CR^{5b}-$ or -N-;

X^6 is $-CR^{6b}-$ or -N-;

R^{1b}-R^{6b} are each independently hydrogen, halogen, hydroxyl, C_{1-4} alkoxy optionally substituted with one or more halo substituents, cyano, C_{1-3} alkyl, C_{1-3} haloalkyl, nitro, $-NR^{1c}R^{2c}$, $-NHC(O)R^{3c}$, or $-C(O)NR^{4c}R^{5c}$;

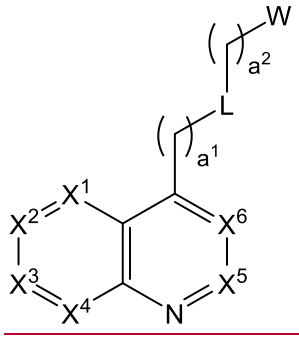
L is a bond, -O-, -C(O)-, or $-NR^{6c}-$;

R^{1c}-R^{6c} are each independently hydrogen or C_{1-3} alkyl;

a^1, a^2, and b^1 are each independently 0, 1, or 2; and

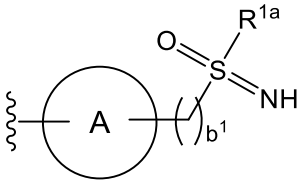
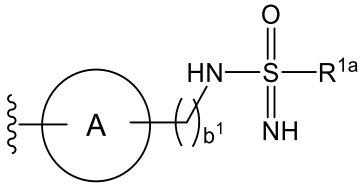
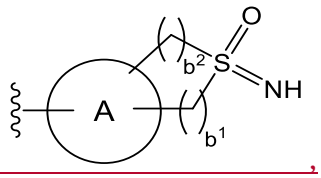
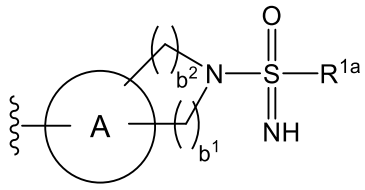
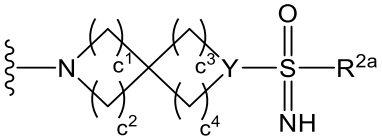
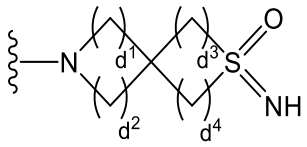
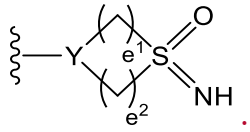
b^2, c^1-c^4, d^1-d^4, e^1, and e^2 are each independently 1, 2, or 3.

[0005c] In a further aspect of the present disclosure, there is provided a compound of Formula (I-2):



(I-2),

or a pharmaceutically acceptable salt thereof, wherein:

W is  ,  ,  ,  ,  ,  , or  ;

ring A is aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is substituted or unsubstituted;

R^{1a} and R^{2a} are each independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl, or C_{1-6} haloalkyl, wherein the C_{1-6} alkyl is optionally substituted by hydroxyl, C_{1-3} alkoxy, or C_{3-6} cycloalkyl;

Y is -N- or -CH-;

X^1 is $-CR^{1b}-$ or -N-;

X^2 is $-CR^{2b}-$ or -N-;

X^3 is $-CR^{3b}-$ or -N-;

X^4 is $-CR^{4b}-$ or -N-;

X^5 is $-CR^{5b}-$ or -N-;

X^6 is $-CR^{6b}-$ or -N-;

R^{1b}-R^{6b} are each independently hydrogen, halogen, hydroxyl, C_{1-4} alkoxy optionally substituted with one or more halo substituents, cyano, C_{1-3} alkyl, C_{1-3} haloalkyl, nitro, $-NR^{1c}R^{2c}$, $-NHC(O)R^{3c}$, or $-C(O)NR^{4c}R^{5c}$;

L is a bond, -O-, -C(O)-, or -NR^{6c}-;

R^{1c}-R^{6c} are each independently hydrogen or C_{1-3} alkyl;

a^1, a^2, and b^1 are each independently 0, 1, 2, or 3; and

b^2, c^1-c^4, d^1-d^4, e^1, and e^2 are each independently 1, 2, or 3.

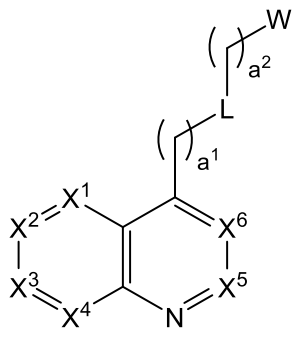
[0005d] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

[0005e] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting ENPP1.

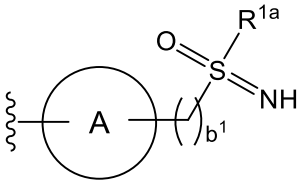
[0005f] In another apect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer, a bacterial and/or viral infection, insulin resistance, type II diabetes, chondrocalcinosis, osteoarthritis, soft-tissue calcification disorder, calcium pyrophosphate deposition disorder, or hypophosphatasia.

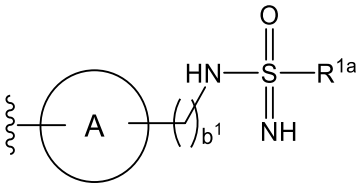
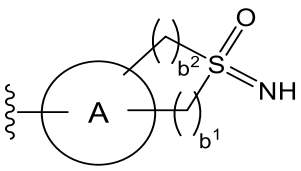
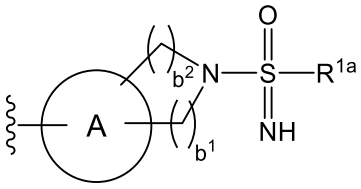
[0005g] In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for use in therapy.

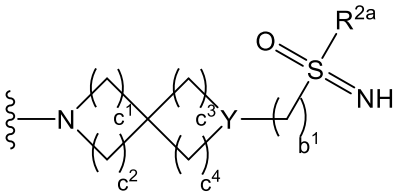
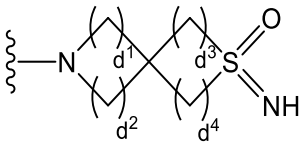
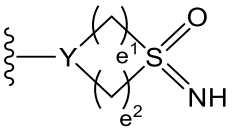
[0006] The present disclosure provides compounds of Formula (I), compositions thereof, and methods of using said compounds and compositions thereof for the treatment of diseases or conditions associated with ENPP1. In one ~~aspect~~example, provided is a compound of Formula (I)



(I),

or a pharmaceutically acceptable salt thereof, wherein W is  ,

 ,  ,  ,

 ,  , or  ;

ring A is aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is substituted or unsubstituted;

R^{1a} and R^{2a} are each independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted 3-6 membered heterocycloalkyl, or optionally substituted C_{1-6} haloalkyl;

Y is -N- or -CH-;

X^1 is $-CR^{1b}-$ or -N-;

X^2 is $-CR^{2b}-$ or -N-;

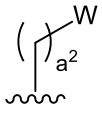
X^3 is $-CR^{3b}-$ or -N-;

X^4 is $-CR^{4b}-$ or -N-;

X^5 is $-CR^{5b}-$ or -N-;

X^6 is $-CR^{6b}-$ or -N-;

R^{1b}-R^{6b} are each independently hydrogen, halogen, hydroxyl, C_{1-4} alkoxy optionally substituted with one or more halo substituents, cyano, C_{1-3} alkyl, C_{1-3} haloalkyl, nitro, $-NR^{1c}R^{2c}$, $-NHC(O)R^{3c}$, or $-C(O)NR^{4c}R^{5c}$;

L is a bond, -O-, -C(O)-, $-NR^{6c}-$, or $-OCR^{7c}-$*, wherein * represents the point of attachment to 

;

R^{1c}-R^{7c} are each independently hydrogen or C_{1-3} alkyl;

a^1, a^2, b^1, and c^4 are each independently 0, 1, 2, or 3; and

b^2, c^1-c^3, d^1-d^4, e^1, and e^2 are each independently 1, 2, or 3.

[0007] In another ~~aspect~~example, provided is pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

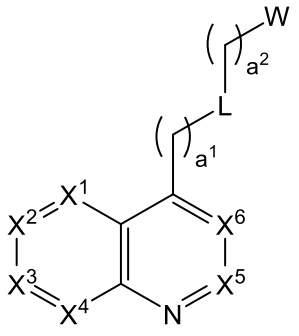
[0008] In another ~~aspect~~example, provided is a method of inhibiting ENPP1 comprising contacting a cell with an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0009] In another ~~aspect~~example, provided is a method of treating cancer, a bacterial and/or viral infection, insulin resistance, type II diabetes, chondrocalcinosis, osteoarthritis, a soft-tissue calcification disorder, calcium pyrophosphate deposition disorder, or hypophosphatasia in a

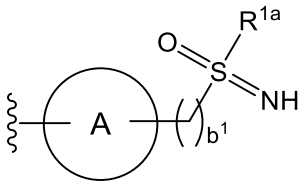
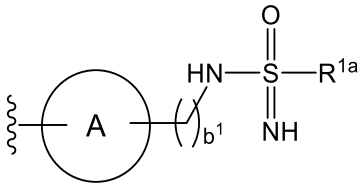
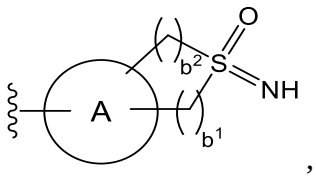
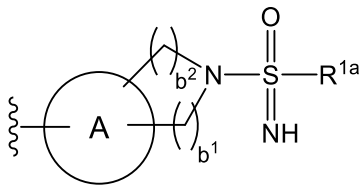
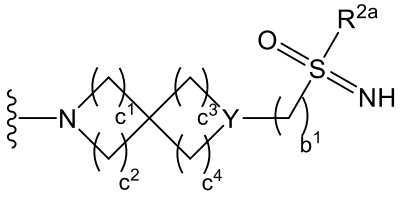
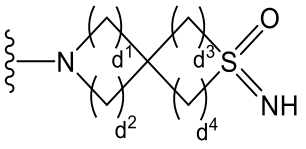
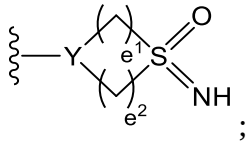
CLAIMS

What is claimed is:

1. A compound of Formula (I)


(I),

or a pharmaceutically acceptable salt thereof, wherein:

W is  ,  ,  ,  ,  ,  , or  ;

ring A is aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is substituted or unsubstituted;

R^{1a} and R^{2a} are each independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted 3-6 membered heterocycloalkyl, or optionally substituted C_{1-6} haloalkyl;

Y is -N- or -CH-;

X^1 is $-CR^{1b}-$ or -N-;

X^2 is $-CR^{2b}-$ or -N-;

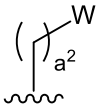
X^3 is -CR^{3b}- or -N-;

X^4 is -CR^{4b}- or -N-;

X^5 is -CR^{5b}- or -N-;

X^6 is -CR^{6b}- or -N-;

R^{1b}-R^{6b} are each independently hydrogen, halogen, hydroxyl, C_{1-4} alkoxy optionally substituted with one or more halo substituents, cyano, C_{1-3} alkyl, C_{1-3} haloalkyl, nitro, -$NR^{1c}R^{2c}$, -$NHC(O)R^{3c}$, or -$C(O)NR^{4c}R^{5c}$;

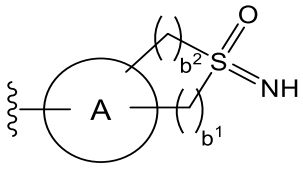
L is a bond, -O-, -C(O)-, -NR^{6c}-, or -OCR^{7c}-*, wherein * represents the point of attachment to 

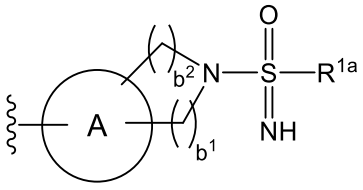
;

R^{1c}-R^{7c} are each independently hydrogen or C_{1-3} alkyl;

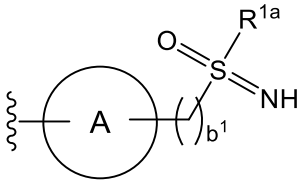
a^1, a^2, b^1, and c^4 are each independently 0, 1, 2, or 3; and

b^2, c^1-c^3, d^1-d^4, e^1, and e^2 are each independently 1, 2, or 3.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein W comprises a fused ring structure when W is 

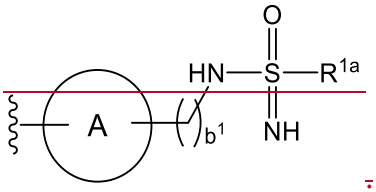
or 

.

3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein W is 

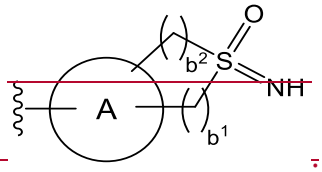
.

~~4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein W is~~



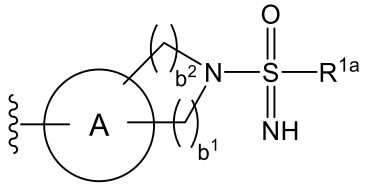
~~.~~

~~5. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein W~~



~~is~~ ~~.~~

~~6.~~4. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein W is



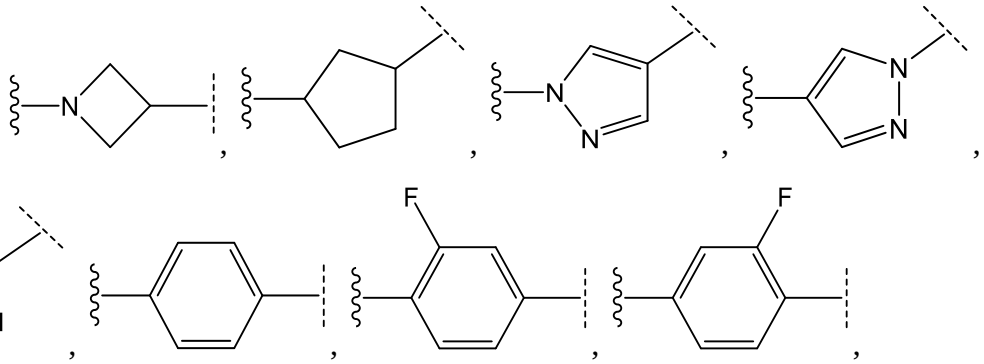
.

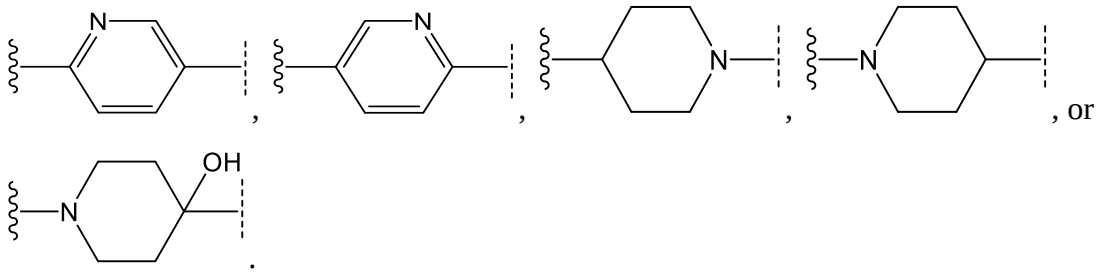
~~7.~~5. The compound of any one of claims 1-~~4~~6, or a pharmaceutically acceptable salt thereof, wherein A is aryl.

~~8. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein A is heteroaryl.~~

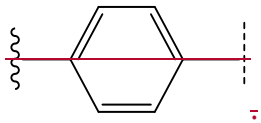
~~9.~~6. The compound of any one of claims 1-~~6~~4, or a pharmaceutically acceptable salt thereof, wherein A is heterocycloalkyl.

~~10.~~7. The compound of any one of claims 1-~~6~~4, or a pharmaceutically acceptable salt thereof, wherein A is

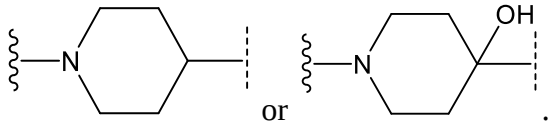




~~11. The compound of claim 10, or a pharmaceutically acceptable salt thereof, wherein A is~~



~~12.~~8. The compound of claim ~~10~~7, or a pharmaceutically acceptable salt thereof, wherein A is



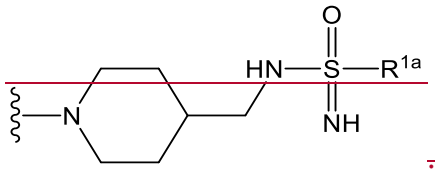
~~13.~~9. The compound of any one of claims 1-~~8~~12, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is C_{1-6} alkyl or C_{3-6} cycloalkyl.

~~14.~~10. The compound of claim ~~9~~13, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is methyl or cyclopropyl.

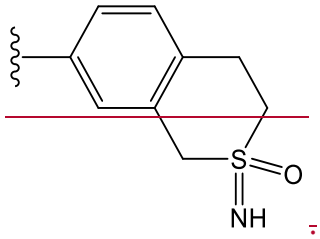
~~15.~~11. The compound of any one of claims 1-~~10~~14, or a pharmaceutically acceptable salt thereof, wherein b^1 is 0.

~~16.~~12. The compound of any one of claims 1-~~10~~14, or a pharmaceutically acceptable salt thereof, wherein b^1 is 1.

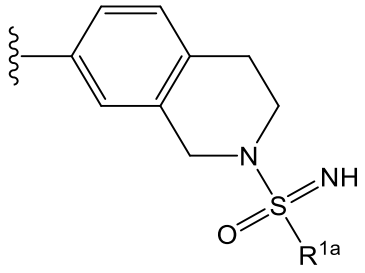
~~17. The compound of claim 4, or a pharmaceutically acceptable salt thereof, wherein W is~~



~~18. The compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein W is~~

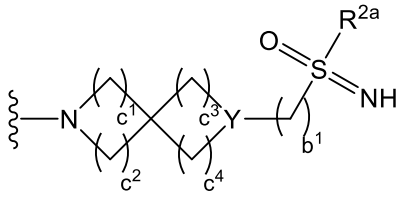


~~19.~~13. The compound of claim ~~6~~4, or a pharmaceutically acceptable salt thereof, wherein W is

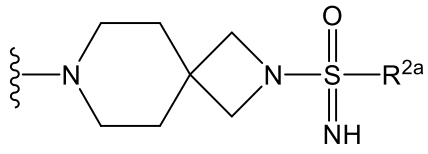
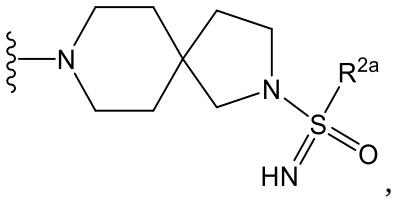
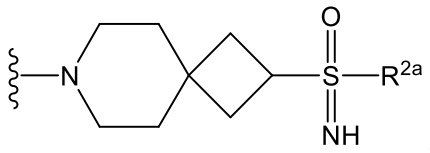
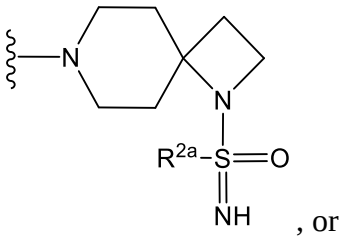
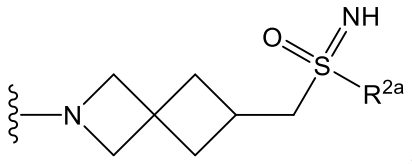


.

~~20.~~14. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein W is



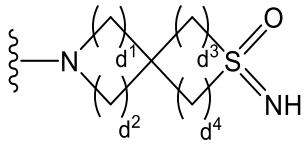
.

~~21.~~15. The compound of claim 14~~20~~, or a pharmaceutically acceptable salt thereof, wherein W is  ,  ,  ,  , or  .

~~22.~~16. The compound of claim 14~~20~~ or 15~~21~~, or a pharmaceutically acceptable salt thereof, wherein R^{2a} is C_{1-6} alkyl.

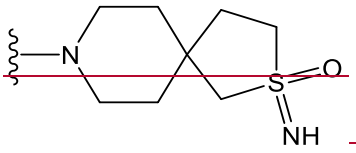
~~23. The compound of claim 22, or a pharmaceutically acceptable salt thereof, wherein R^{2a} is methyl.~~

~~24.~~17. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein W is

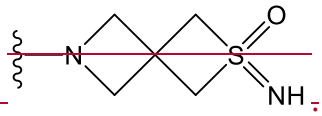


.

~~25. The compound of claim 24, or a pharmaceutically acceptable salt thereof, wherein W is~~

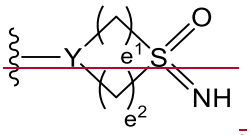


~~or~~



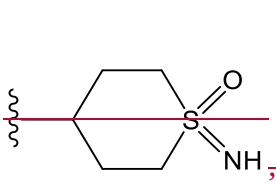
~~.~~

~~26. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein W is~~

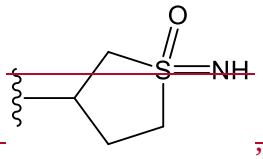


~~.~~

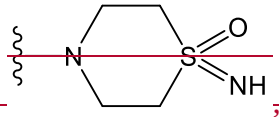
~~27. The compound of claim 26, or a pharmaceutically acceptable salt thereof, wherein W is~~



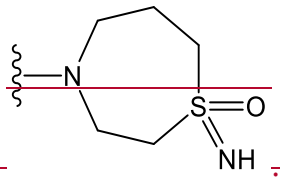
~~,~~



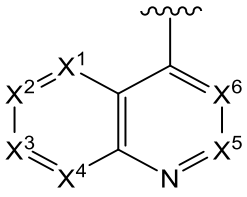
~~,~~

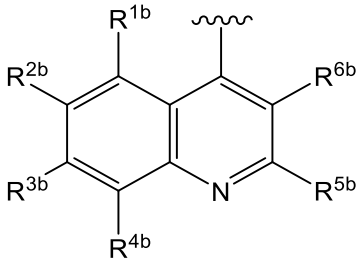


~~, or~~

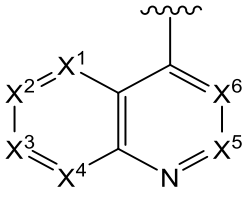


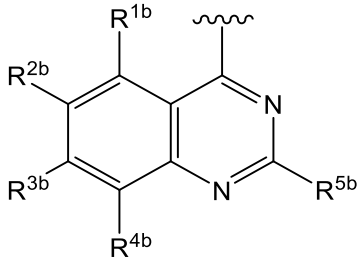
~~.~~

~~28.~~18. The compound of any one of claims 1-17~~27~~, or a pharmaceutically acceptable salt thereof, wherein the  portion of Formula (I) is

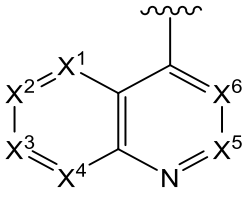


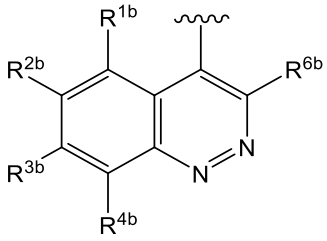
.

~~29.~~19. The compound of any one of claims 1-17~~27~~, or a pharmaceutically acceptable salt thereof, wherein the  portion of Formula (I) is

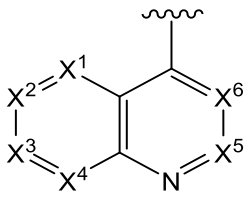
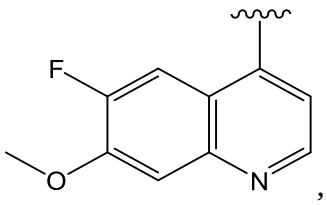
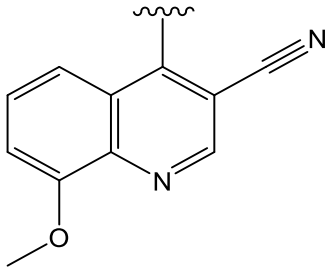
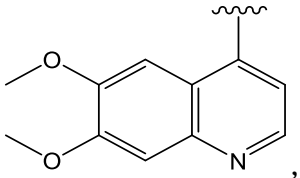
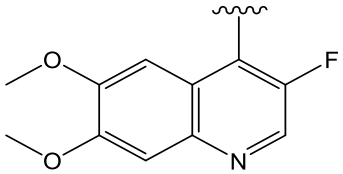


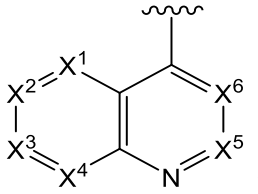
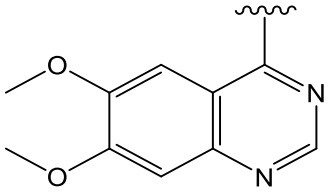
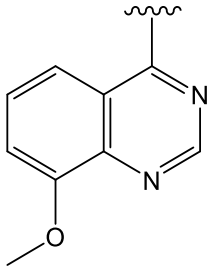
.

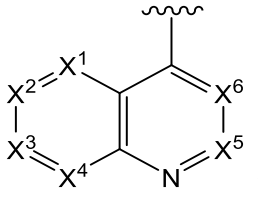
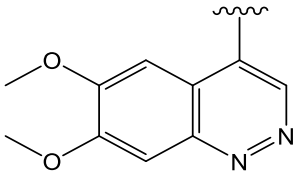
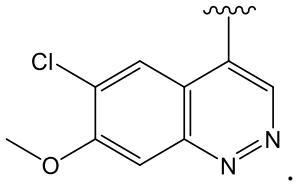
~~30.~~20. The compound of any one of claims 1-17~~27~~, or a pharmaceutically acceptable salt thereof, wherein the  portion of Formula (I) is



.

~~31.~~21. The compound of claim 18~~28~~, or a pharmaceutically acceptable salt thereof, wherein the  portion of Formula (I) is  ,  ,  , or  .

~~32.~~22. The compound of claim 19~~29~~, or a pharmaceutically acceptable salt thereof, wherein the  portion of Formula (I) is  or  .

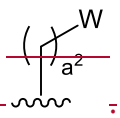
~~33.~~23. The compound of claim 20~~30~~, or a pharmaceutically acceptable salt thereof, wherein the  portion of Formula (I) is  or  .

~~34.~~24. The compound of any one of claims 1-23~~33~~, or a pharmaceutically acceptable salt thereof, wherein L is a bond.

~~35.~~25. The compound of any one of claims 1-23~~33~~, or a pharmaceutically acceptable salt thereof, wherein L is -O-.

~~36. The compound of any one of claims 1-33, or a pharmaceutically acceptable salt thereof, wherein L is -C(O)-.~~

~~37. The compound of any one of claims 1-33, or a pharmaceutically acceptable salt thereof, wherein L is -NR^{6c}-.~~

~~38. The compound of any one of claims 1-33, or a pharmaceutically acceptable salt thereof, wherein L is -OCR^{7c}-*, wherein * represents the point of attachment to~~  .

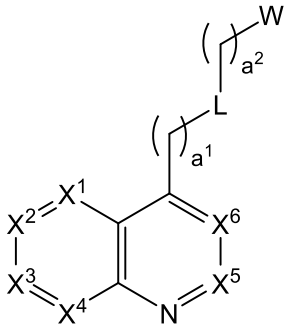
~~39.~~26. The compound of any one of claims 1-~~38~~25, or a pharmaceutically acceptable salt thereof, wherein a^1 is 0.

~~40. The compound of any one of claims 1-38, or a pharmaceutically acceptable salt thereof, wherein a^1 is 1.~~

~~41.~~27. The compound of any one of claims 1-~~40~~26, or a pharmaceutically acceptable salt thereof, wherein a^2 is 0.

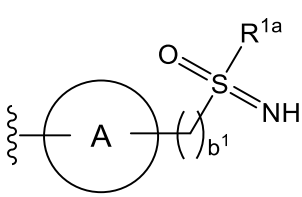
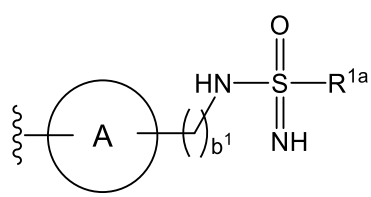
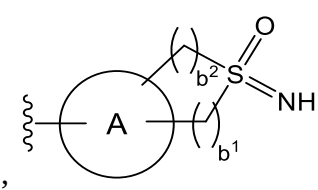
~~42.~~28. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of compounds of Table 1.

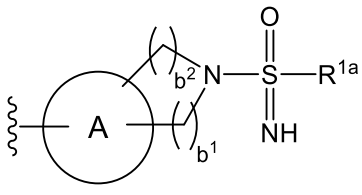
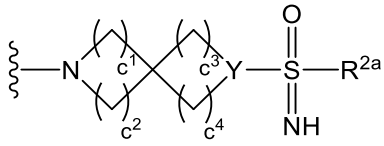
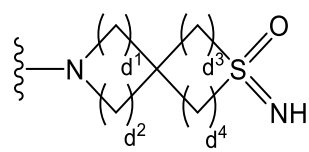
~~43.~~29. A compound of Formula (I-1):

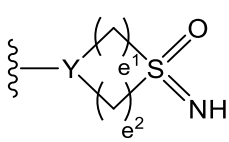


(I-1),

or a pharmaceutically acceptable salt thereof, wherein:

W is  ,  ,  ,

 ,  ,  , or

 ;

ring A is aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is substituted or unsubstituted;

R^{1a} and R^{2a} are each independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl, or C_{1-6} haloalkyl;

Y is -N- or -CH-;

X^1 is $-CR^{1b}-$ or -N-;

X^2 is $-CR^{2b}-$ or -N-;

X^3 is $-CR^{3b}-$ or -N-;

X^4 is $-CR^{4b}-$ or -N-;

X^5 is $-CR^{5b}-$ or -N-;

X^6 is $-CR^{6b}-$ or -N-;

R^{1b}-R^{6b} are each independently hydrogen, halogen, hydroxyl, C_{1-4} alkoxy optionally substituted with one or more halo substituents, cyano, C_{1-3} alkyl, C_{1-3} haloalkyl, nitro, $-NR^{1c}R^{2c}$, $-NHC(O)R^{3c}$, or $-C(O)NR^{4c}R^{5c}$;

L is a bond, -O-, -C(O)-, or $-NR^{6c}-$;

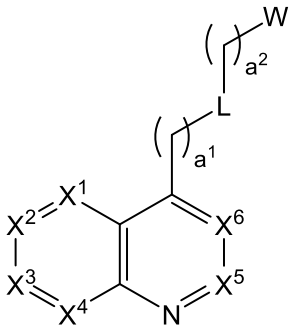
R^{1c}-R^{6c} are each independently hydrogen or C_{1-3} alkyl;

a^1, a^2, and b^1 are each independently 0, 1, or 2; and

b^2, c^1-c^4, d^1-d^4, e^1, and e^2 are each independently 1, 2, or 3.

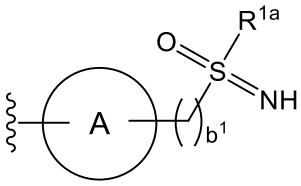
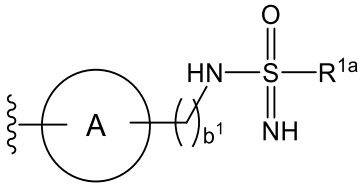
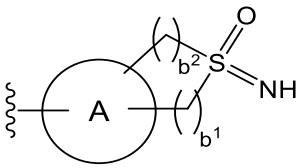
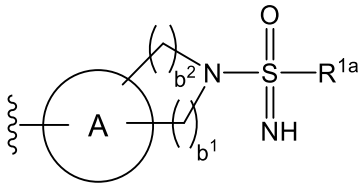
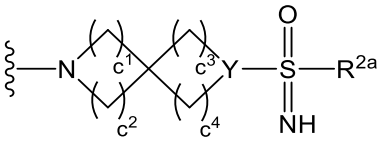
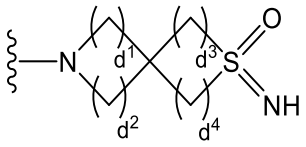
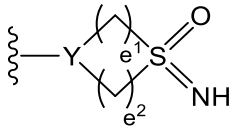
~~44.~~30. The compound of claim ~~43~~29, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of compounds 1, 2-37, 38-44, 45-52, 53, 54, 55, 56-60, 61-75, 76-80, 81-94, 95-103, and 104-113 of Table 1.

~~45.~~31. A compound of Formula (I-2):



(I-2),

or a pharmaceutically acceptable salt thereof, wherein:

W is  ,  ,  ,  ,  ,  , or  ;

ring A is aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is substituted or unsubstituted;

R^{1a} and R^{2a} are each independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl, or C_{1-6} haloalkyl, wherein the C_{1-6} alkyl is optionally substituted by hydroxyl, C_{1-3} alkoxy, or C_{3-6} cycloalkyl;

Y is -N- or -CH-;

X^1 is $-CR^{1b}-$ or -N-;

X^2 is $-CR^{2b}-$ or -N-;

X^3 is $-CR^{3b}-$ or -N-;

X^4 is $-CR^{4b}-$ or -N-;

X^5 is $-CR^{5b}-$ or -N-;

X^6 is $-CR^{6b}-$ or -N-;

R^{1b}-R^{6b} are each independently hydrogen, halogen, hydroxyl, C_{1-4} alkoxy optionally substituted with one or more halo substituents, cyano, C_{1-3} alkyl, C_{1-3} haloalkyl, nitro, $-NR^{1c}R^{2c}$, $-NHC(O)R^{3c}$, or $-C(O)NR^{4c}R^{5c}$;

L is a bond, -O-, -C(O)-, or $-NR^{6c}-$;

R^{1c}-R^{6c} are each independently hydrogen or C_{1-3} alkyl;

a^1, a^2, and b^1 are each independently 0, 1, 2, or 3; and

b^2, c^1-c^4, d^1-d^4, e^1, and e^2 are each independently 1, 2, or 3.

~~46.~~32. The compound of claim 31~~45~~, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of compounds 1-165 of Table 1.

~~47.~~33. A pharmaceutical composition comprising a compound of any one of claims 1-32~~46~~, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

~~48.~~34. ~~A method of inhibiting ENPP1 comprising contacting a cell with an effective amount~~ Use of a compound of any one of claims 1-32~~46~~, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting ENPP1.

~~49.~~35. ~~A method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount~~Use of a compound of any one of claims 1-~~46~~32, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer, a bacterial and/or viral infection, insulin resistance, type II diabetes, chondrocalcinosis, osteoarthritis, soft-tissue calcification disorder, calcium pyrophosphate deposition disorder, or hypophosphatasia.

~~50. A method of treating a bacterial and/or viral infection in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof.~~

~~51. A method of treating insulin resistance in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof.~~

~~52. A method of treating type II diabetes in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof.~~

~~53. A method of treating chondrocalcinosis in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof.~~

~~54. A method of treating osteoarthritis in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof.~~

~~55. A method of treating a soft-tissue calcification disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof.~~

~~56.~~36. The ~~method~~ use of claim ~~55~~35, wherein the soft-tissue calcification disorder is cardiac calcification after heart injury.

37. A compound of any one of claims 1-32, or a pharmaceutically acceptable salt thereof, for use in therapy.

~~57. A method of treating calcium pyrophosphate deposition disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof.~~

~~58. A method of treating hypophosphatasia in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof.~~