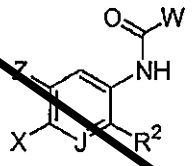
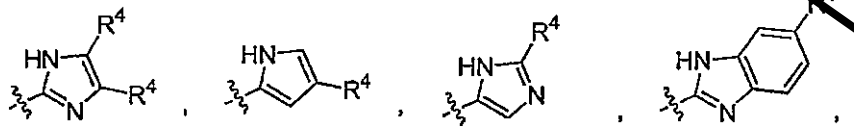
The claimed invention is:

1. The novel compounds of Formula I



I

or a solvate, hydrate, tautomer or pharmaceutically acceptable salt thereof, wherein:

W is  ;

wherein each R^4 is independently H, F, Cl, Br, I, OH, OCH_3, OCH_2CH_3, $SC_{(1-4)}$alkyl, $SOC_{(1-4)}$alkyl, $SO_2C_{(1-4)}$alkyl, $-C_{(1-3)}$alkyl, CO_2R^d, $CONR^eR^f$, $C^{=}CR^g$, or CN;

wherein R^d is H, or $-C_{(1-3)}$alkyl;

R^e is H, or $-C_{(1-3)}$alkyl;

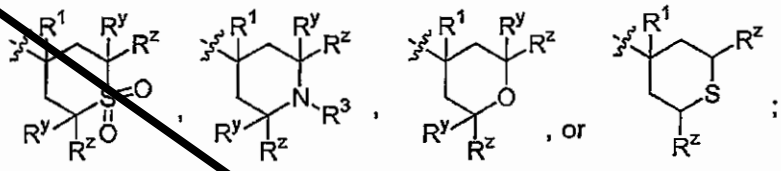
R^f is H, or $-C_{(1-3)}$alkyl; and

R^g is H, $-CH_2OH$, or $-CH_2CH_2OH$;

R^2 is cycloalkyl, spiro-substituted cycloalkenyl, heterocyclyl, spirosubstituted piperidinyl, thiophenyl, dihydrosulfonopyranyl, phenyl, furanyl, tetrahydropyridyl, or dihydropyranyl, any of which may be independently substituted with one or two of each of the following: chloro, fluoro, hydroxy, $C_{(1-3)}$alkyl, and $C_{(1-4)}$alkyl;

Z is H, F, or CH_3;

J is CH, or N;

X is 

wherein R^1 is -$C_{(1-4)}$alkyl, -OR^a, -CN, -NA^1A^2, -SO_2CH_3, -$COOR^a$, -CO_2CH_3, -CH_2-NA^1A^2, -$CONA^1A^2$, -CH_2OR^a, -$OC_{(1-4)}$alkylOR^a, -$NHCH_2CH_2CO_2R^a$, -$NHCH_2CH_2OR^a$, -$NR^aCH_2CH_2NA^1A^2$, -$OC_{(1-4)}$alkylNA^1A^2, -$OCH_2CO_2R^a$, -$CH_2CO_2R^a$, -$CH_2CH_2SO_2C_{(1-4)}$alkyl, -$SO_2CH_2CH_2NA^1A^2$, -$SOCH_2CH_2NA^1A^2$, -$SCH_2CH_2NA^1A^2$, -$NHSO_2CH_2CH_2NA^1A^2$, phenyl, imidazolyl, thiazolyl, 4H-[1,2,4]oxadiazol-5-onyl, 4H-pyrrolo[2,3-b]pyrazinyl, pyridinyl, [1,3,4]oxadiazolyl, 4H-[1,2,4]triazolyl, tetrazolyl, pyrazolyl, [1,3,5]triazinyl, and [1,3,4]thiadiazolyl;

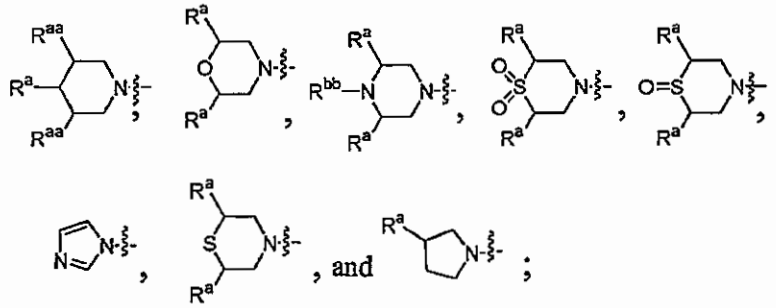
R^z and R^y are independently H or -$C_{(1-4)}$alkyl, wherein both R^z may have either *syn* or *anti* stereochemistry; alternatively both R^z in a *syn* relationship may be taken together to form –$(CH_2)_n$-, where n is 2 or 3;

R^3 is H, $C_{(1-4)}$alkyl, $C_{(1-3)}$alkyl-CF_3, $CH_2CH_2NH_2$, $CH_2CH_2OR^a$, -$COCH_3$, $CONH_2$, or CO_2R^a;

A^1 is H, –$C_{(1-4)}$alkyl, or $CH_2CH_2OR^a$;

A^2 is H, –$C_{(1-4)}$alkyl, COR^a, $CH_2CON(CH_3)_2$, -$CH_2CH_2OR^a$, -$CH_2CH_2SC_{(1-4)}$alkyl, -$CH_2CH_2SOC_{(1-4)}$alkyl, or -$CH_2CH_2SO_2C_{(1-4)}$alkyl;

alternatively, A^1 and A^2 may be taken together with their attached nitrogen to form a heterocyclic ring selected from the following:

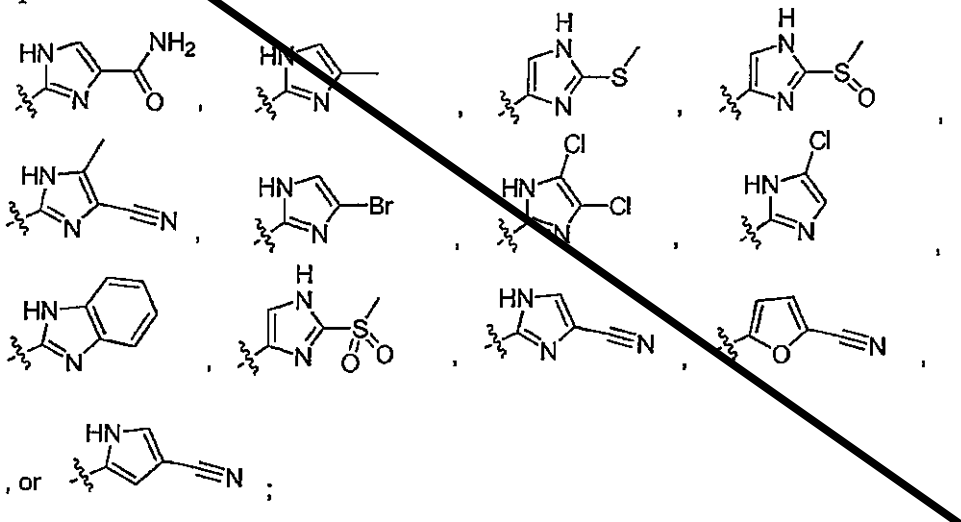


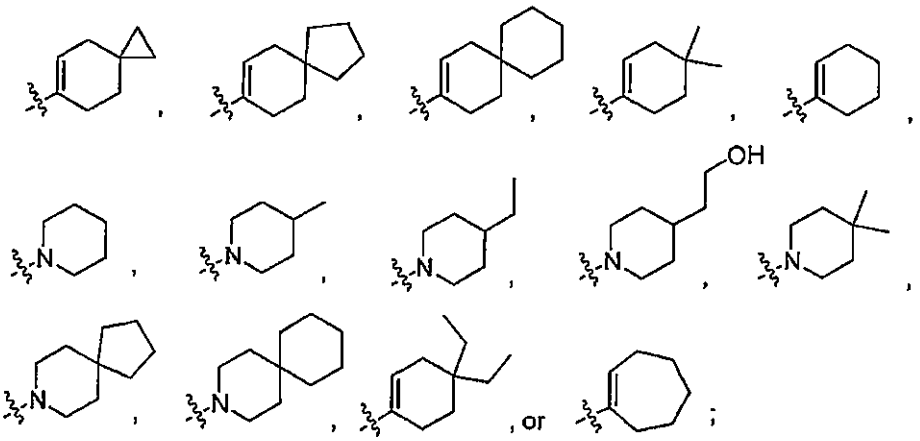
wherein R^a is H or $C_{(1-4)}$alkyl;

R^{aa} is H or $C_{(1-4)}$alkyl; and

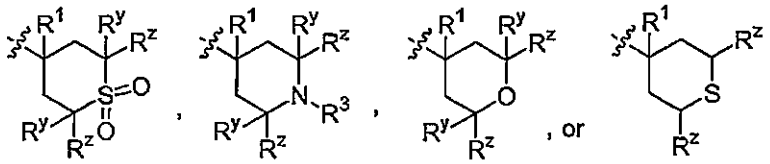
R^{bb} is H, $-C_{(1-4)}$alkyl, $-CH_2CH_2OCH_2CH_2OCH_3$, $-CH_2CO_2H$, $-C(O)C_{(1-4)}$alkyl, or $-CH_2C(O)C_{(1-4)}$alkyl.

2. A Compound of Claim 1 wherein

W is  ;

R^2 is  ;

Z is H;

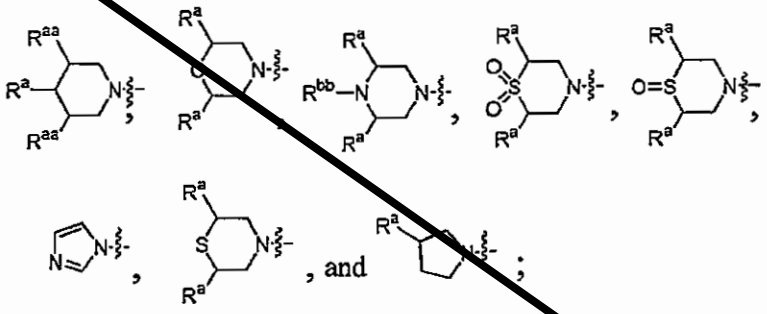
X is  ;

wherein R^1 is -OH, -CN, $-NA^1A^2$, $-SO_2CH_3$, $-COOR^a$, $-CO_2CH_3$, $-CH_2-NA^1A^2$, $-CONA^1A^2$, $-CH_2OR^a$, $-NHCH_2CH_2CO_2R^a$, $-NHCH_2CH_2OR^a$, $-NHCH_2CH_2NA^1A^2$, $-OC_{(1-4)}$alkylNA^1A^2, $-OCH_2CO_2R^a$, or tetrazolyl;

A^1 is H, or $-CH_3$;

A^2 is H, $-CH_2CH_2OCH_3$, $-COCH_3$, or $-CH_3$;

alternatively, A^1 and A^2 may be taken together with their attached nitrogen to form a heterocyclic ring selected from the following:



R^a is H, or $-C_{(1-4)}$alkyl;

R^{aa} is H, or $-C_{(1-4)}$alkyl;

R^{bb} is H, $-C_{(1-4)}$alkyl, $-CH_2CO_2H$ or $-COCH_3$;

R^y is H, or $-CH_3$;

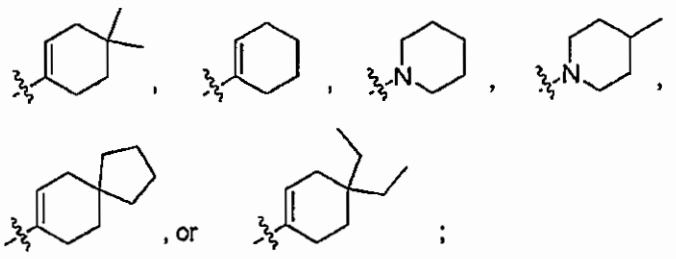
R^z is H, $-CH_3$, or may be taken together as $-CH_2CH_2-$;

R^3 is H, $-CH_2CF_3$, $-COCH_3$, $-CH_3$, $-CO_2CH_3$, $-CONH_2$, or $-CO_2H$.

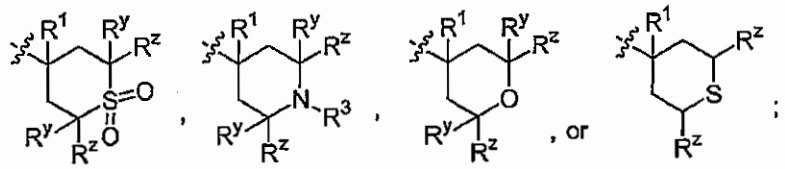
as well as solvates, hydrates, tautomers and pharmaceutically acceptable salts thereof.

3. A compound of Claim 2 wherein

R^2 is



X is



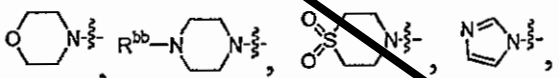
wherein R^1 is -OH, -CN, $-NA^1A^2$, $-SO_2CH_3$, -COOH, $-CO_2CH_3$, $-CH_2-NA^1A^2$, $-CONH_2$, $-CON(CH_3)_2$, $-CH_2OH$, $-OCH_2CH_2N(CH_3)_2$, $-NHCH_2CH_2CO_2CH_3$, -

$NHCH_2CH_2OCH_3$, $-NHCH_2CH_2NA^1A^2$, $-OC_{(1-4)}alkylNA^1A^2$, $-OCH_2CO_2H$, or tetrazolyl;

A^1 is H, or $-CH_3$;

A^2 is H, $-CH_2CH_2OCH_3$, $-COCH_3$, or $-CH_3$;

alternatively, A^1 and A^2 may be taken together with their attached nitrogen to form a heterocyclic ring selected from the following:



and ;

R^{bb} is H, $-C_{(1-4)}$alkyl, $-CH_2CO_2H$ or $-COCH_3$;

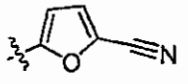
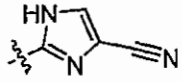
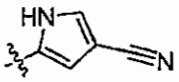
R^y is H, or $-CH_3$;

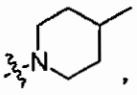
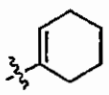
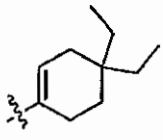
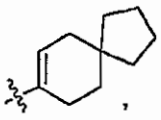
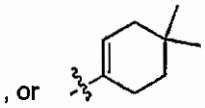
R^z is H, $-CH_3$, or may be taken together as $-CH_2CH_2-$;

R^3 is H, $-CH_2CF_3$, $-COCH_3$, $-CH_3$, $-CO_2CH_3$, $-CONH_2$, or $-CO_2H$.

as well as solvates, hydrates, tautomers and pharmaceutically acceptable salts thereof.

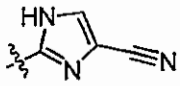
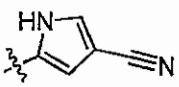
4. A compund of Claim 3 wherein

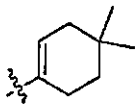
W is , , or ;

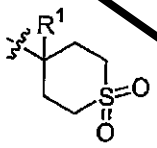
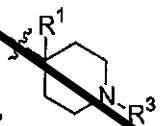
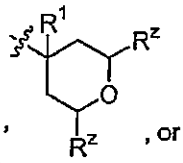
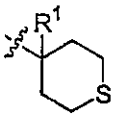
R^2 is , , , , ;

as well as solvates, hydrates, tautomers and pharmaceutically acceptable salts thereof.

5. A compund of Claim 4 wherein

W is , or ;

R^2 is  , or  ;

X is  ,  ,  , or  ;

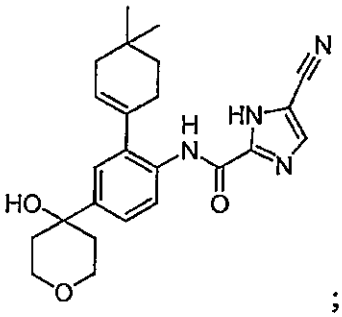
wherein R^1 is -OH, $-NH_2$, $-N(CH_3)_2$, $-SO_2CH_3$, -COOH, $-CO_2CH_3$, $-CH_2$-morpholinyl, $-CONH_2$, $-CON(CH_3)_2$, $-CH_2OH$, $-OCH_2CH_2N(CH_3)_2$, $-NHCH_2CH_2OCH_3$, $-OCH_2CO_2H$, morpholinyl, piperazinyl, N-methyl piperazinyl, piperazinyl-CH_2CO_2H, or tetrazolyl;

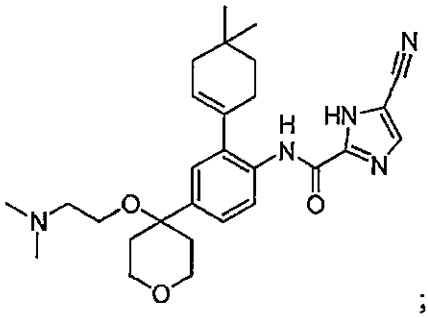
R^z is H, or $-CH_3$;

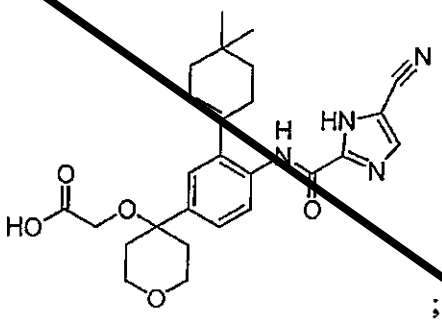
R^3 is $-COCH_3$, $-CH_2CF_3$, or $-CO_2H$;

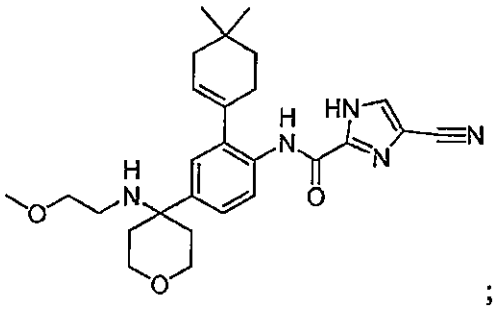
and solvates, hydrates, tautomers and pharmaceutically acceptable salts thereof

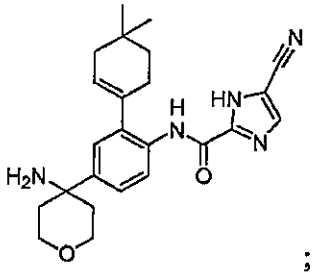
6. A compound selected from the group consisting of:

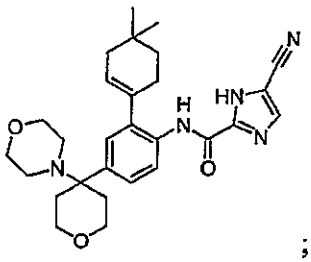
 ;

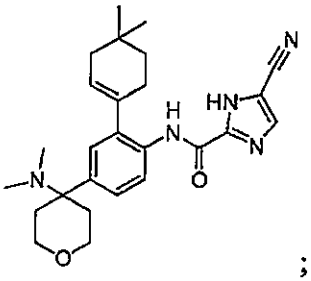
 ;

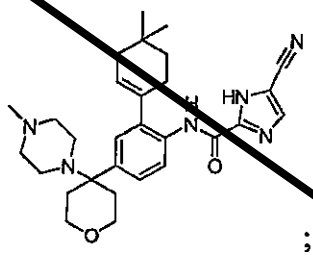

;


;

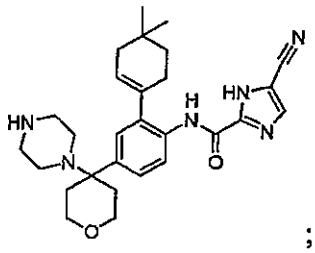

;


;

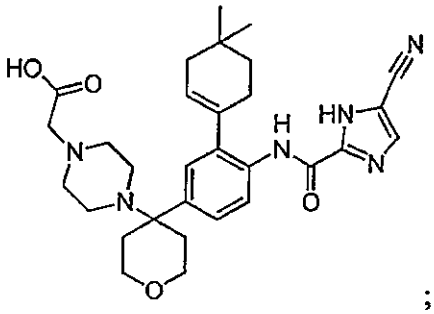

5 ;



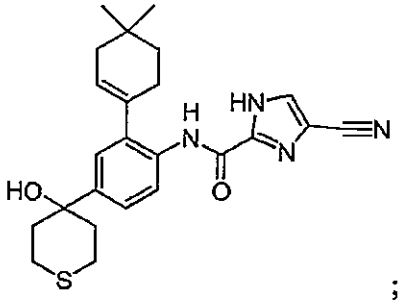
;



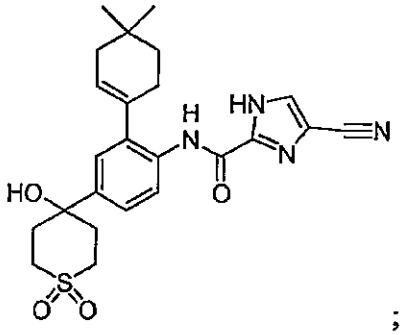
;



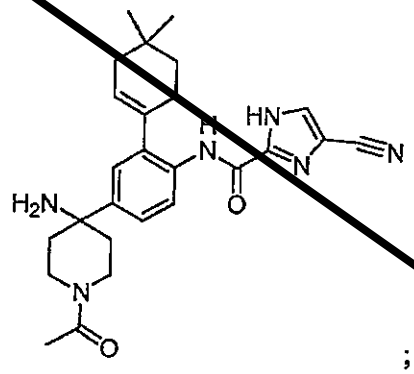
;



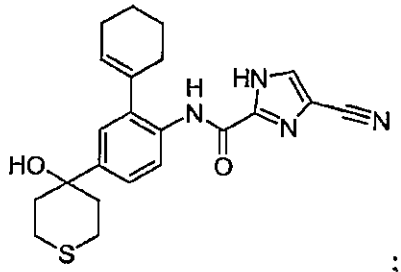
;



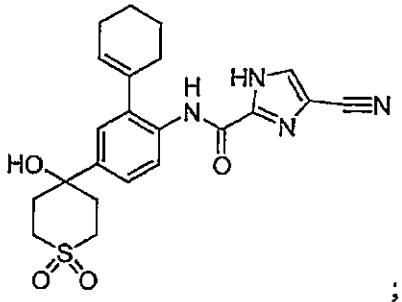
;



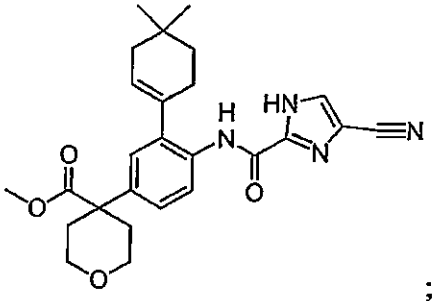
;



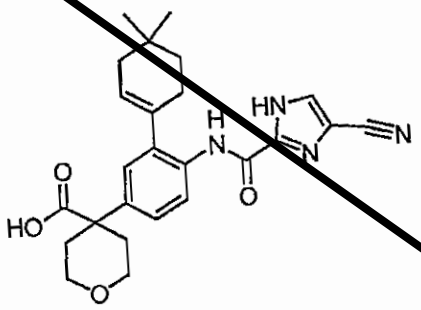
;



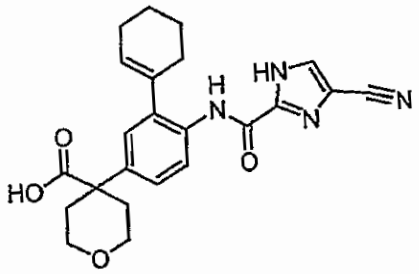
;



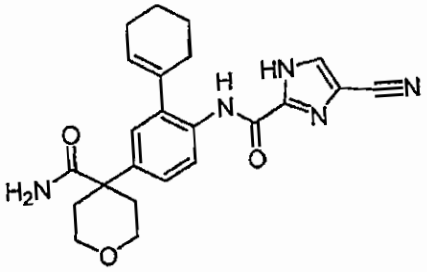
;



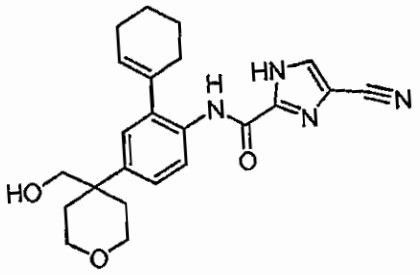
;



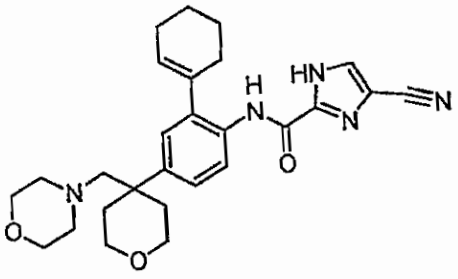
;



;

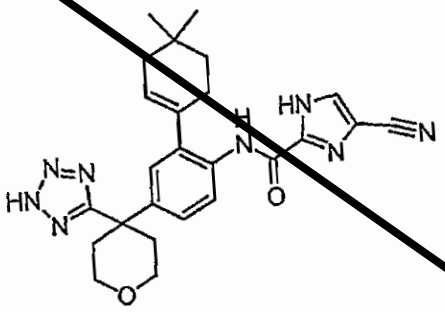


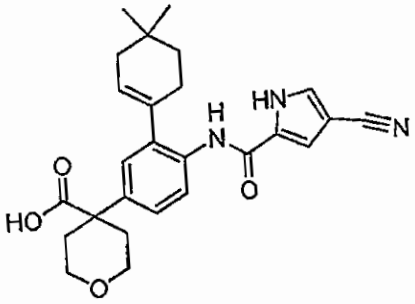
;

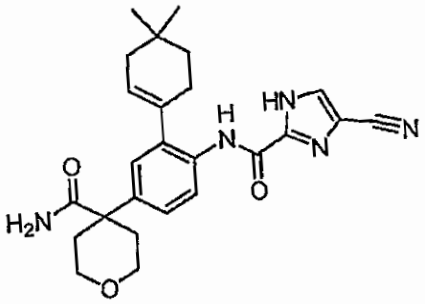


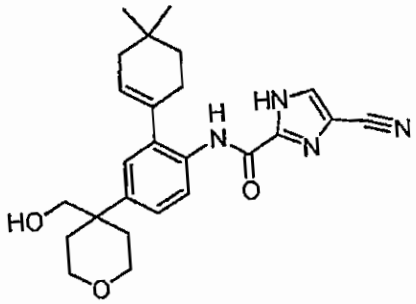
;

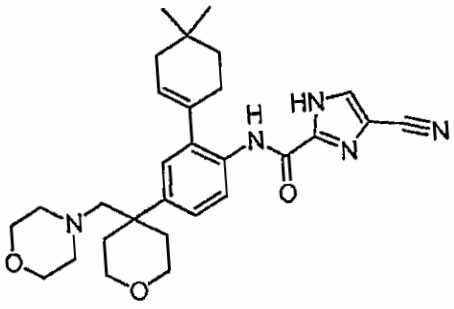
5

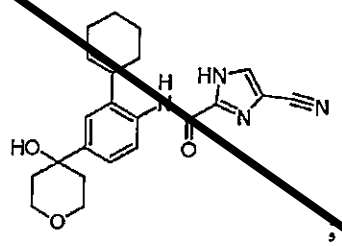

;

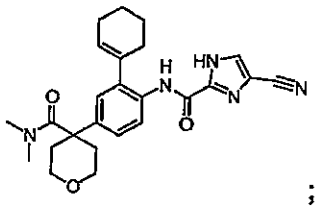

;

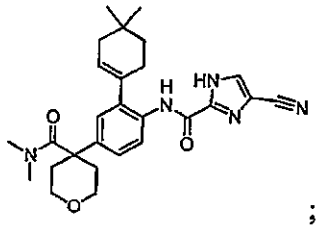

;

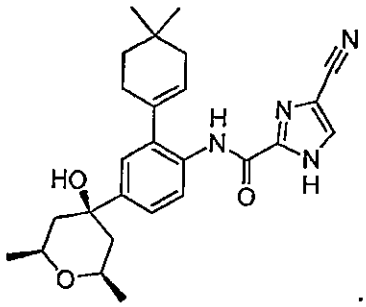

;

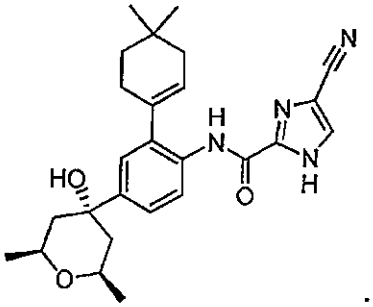

;

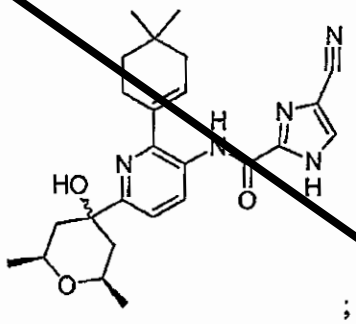

HO
O
H
N
HN
N
N
,


O
N
H
N
O
HN
N
N
;

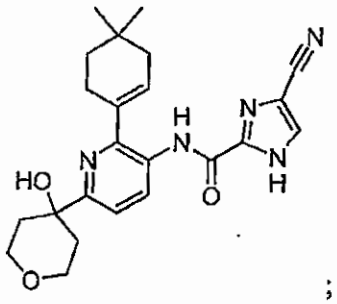

O
N
H
N
O
HN
N
N
;


HO
O
H
N
O
N
N
H
N
;

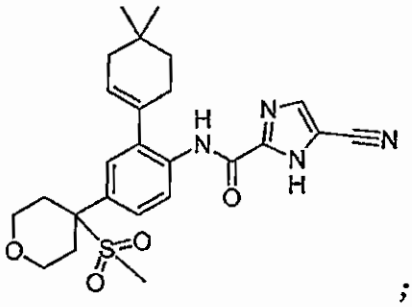

HO
O
H
N
O
N
N
H
N
;



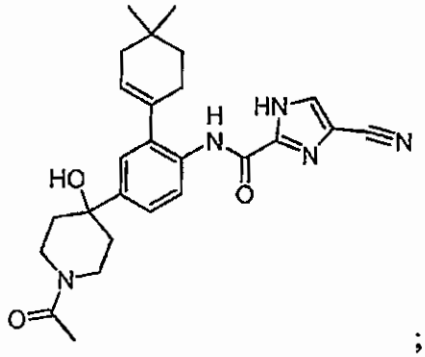
;



;



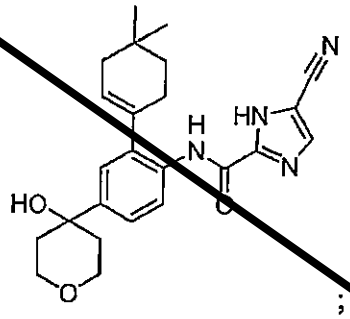
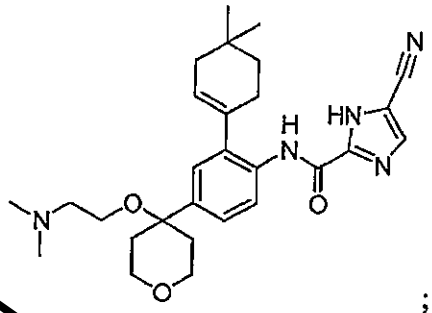
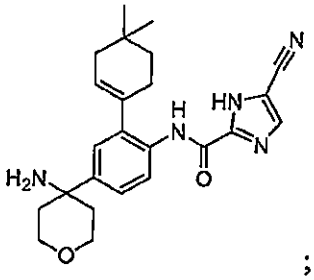
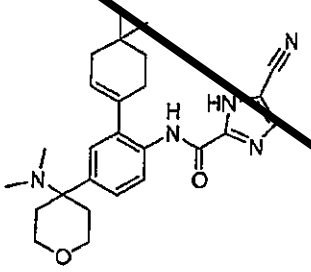
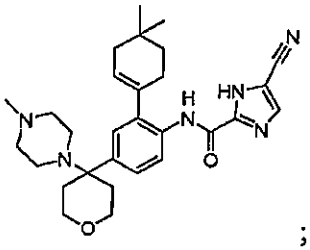
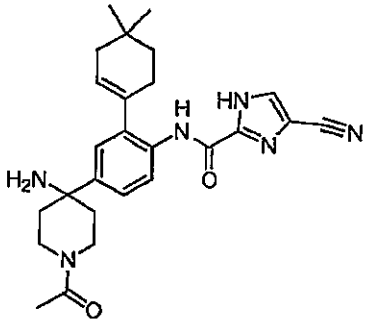
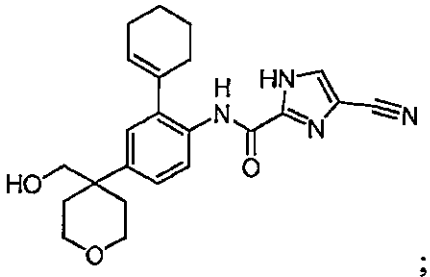
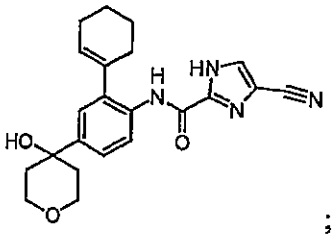
;



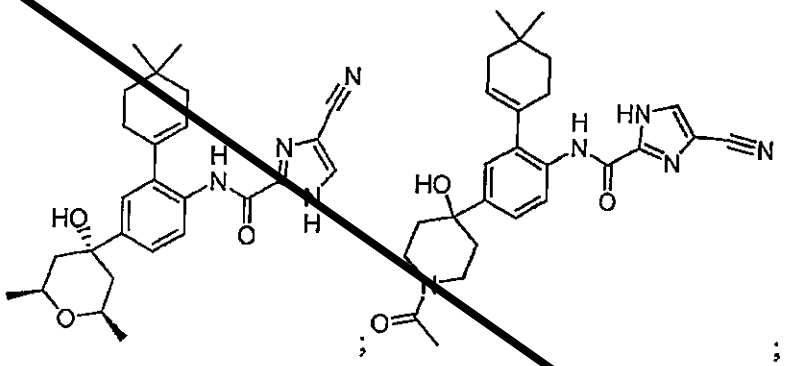
;

and solvates, hydrates, tautomers and pharmaceutically acceptable salts thereof.

7. A compound of Claim 6 selected from the group consisting of:


;

;

;

;

;

;

;

;

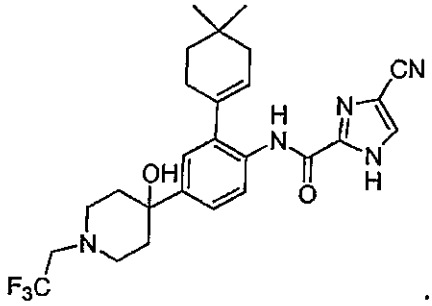
5



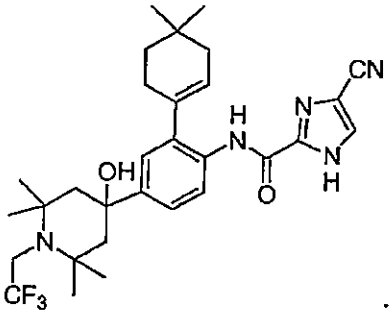
;

and solvates, hydrates, tautomers and pharmaceutically acceptable salts thereof.

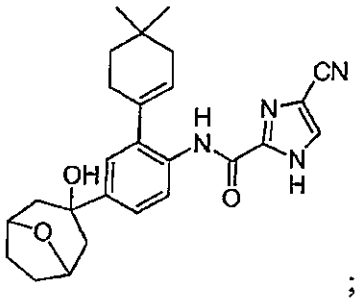
8. A compound selected from the group consisting of:



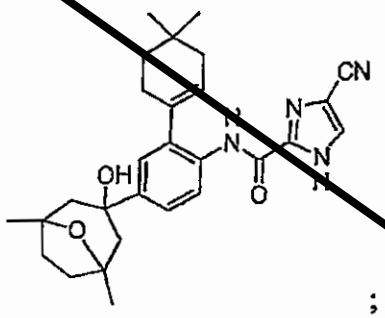
;



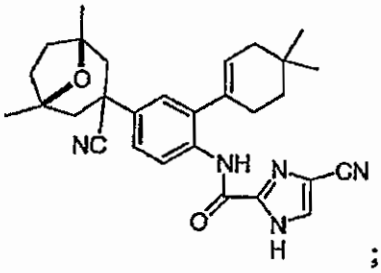
;



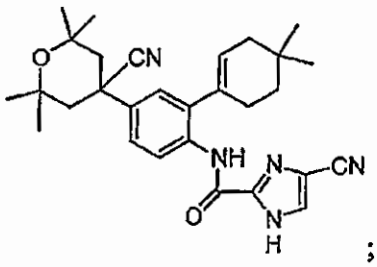
;



;



;



;

and solvates, hydrates, tautomers, and pharmaceutically acceptable salts thereof.

9. A pharmaceutical composition, comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

10. A pharmaceutical dosage form comprising a pharmaceutically acceptable carrier and from about 0.5 mg to about 10 g of at least one compound of Claim 1.

11. A method for inhibiting protein tyrosine kinase activity, comprising contacting the kinase with an effective inhibitory amount of at least one compound of Claim 1.

12. A method according to claim 11, wherein the protein tyrosine kinase is c-fms.

13. A method of treating inflammation in a mammal, comprising administering to the mammal a therapeutically effective amount of at least one compound of Claim 1.

14. A method of treating cancer in a mammal, comprising administering to the mammal a therapeutically effective amount of at least one compound of Claim 1.

15. A method of treating cardiovascular disease in a mammal, comprising administering to the mammal a therapeutically effective amount of at least one compound of Claim 1.

16. A method of treating diseases with an inflammatory component including glomerulonephritis, inflammatory bowel disease, prosthesis failure, sarcoidosis, congestive obstructive pulmonary disease, idiopathic pulmonary fibrosis, asthma, pancreatitis, HIV infection, psoriasis, diabetes, tumor related angiogenesis, age-related macular degeneration, diabetic retinopathy, restenosis, schizophrenia or Alzheimer's dementia in a mammal, comprising administering to the mammal a therapeutically effective amount of at least one compound of Claim 1.

17. A method of treating pain, including skeletal pain caused by tumor metastasis or osteoarthritis, or visceral, inflammatory, and neurogenic pain in a mammal, comprising administering to the mammal in need of such treatment a therapeutically effective amount of at least one compound of Claim 1.

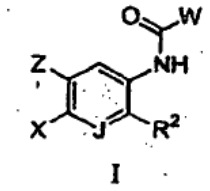
18. A method of treating osteoporosis, Paget's disease, and other diseases in which bone resorption mediates morbidity including rheumatoid arthritis, and other forms of inflammatory arthritis, osteoarthritis, prosthesis failure, osteolytic sarcoma, myeloma, and tumor metastasis to bone, comprising administering to the mammal in need of such treatment a therapeutically effective amount of at least one compound of Claim 1.

19. A method of treating and of preventing metastasis from ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, and hairy cell leukemia, comprising administering to the mammal in need of such treatment a therapeutically effective amount of at least one compound of Claim 1.

20. A method of treating autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and other forms of inflammatory arthritis, psoriasis, Sjogren's syndrome, multiple sclerosis, or uveitis, comprising administering to the mammal in need of such treatment a therapeutically effective amount of at least one compound of Claim 1.

Claims

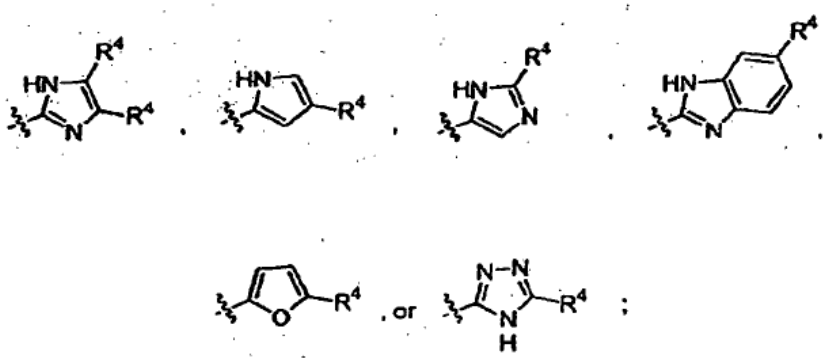
1. The compounds of Formula I



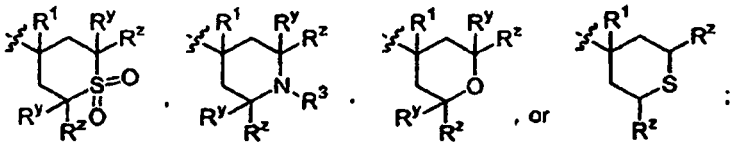
I

or a solvate, hydrate, tautomer or pharmaceutically acceptable salt thereof, wherein:

W is



wherein each R^4 is independently H, F, Cl, Br, I, OH, OCH_3, OCH_2CH_3, $SC_{(1-4)}$alkyl, $SOC_{(1-4)}$alkyl, $SO_2C_{(1-4)}$alkyl, $-C_{(1-3)}$alkyl, CO_2R^d, $CONR^eR^f$, $C{\equiv}R^g$, or CN;
wherein R^d is H, of $-C_{(1-3)}$alkyl;
R^e is H, or $-C_{(1-3)}$Alkyl;
R^f is H, or $-C_{(1-3)}$alkyl; and
R^g is H, $-CH_2OH$, or $-CH_2CH_2OH$,
R^2 is cycloalkyl, spiro-substituted cycloalkenyl, piperidinyl, or phenyl, any of which may be independently substituted with one or two of each of the following: chloro, fluoro, hydroxy, $C_{(1-3)}$alkyl, and $C_{(1-4)}$alkyl;
Z is H, F, or CH_3;
J is CH, or N;
X is



wherein R^1 is $-C_{(1-4)}$alkyl, $-OR^a$, -CN, $-NA^1A^2$, $-SO_2CH_3$, $-COOR^a$, $-CO_2CH_3$, $-CH_2-NA^1A^2$, $-CONA^1A^2$, $-CH_2OR^a$, $-OC_{(1-4)}$alkylOR^a, $-NHCH_2CH_2CO_2R^a$, $-NHCH_2CH_2OR^a$, $-NR^aCH_2CH_2NA^1A^2$, $-OC_{(1-4)}$alkylNA^1A^2, $-OCH_2CO_2R^a$, $-CH_2CO_2R^a$, $-CH_2CH_2SO_2C_{(1-4)}$alkyl, $-SO_2CH_2CH_2NA^1A^2$, $-SOCH_2CH_2NA^1A^2$, $-SCH_2CH_2NA^1A^2$, $-NHSO_2CH_2CH_2NA^1A^2$, phenyl, imidazolyl,, thiazolyl, 4H-[1,2,4]oxadiazol-5-onyl, 4H-pyrrolo[2,3-b]pyrazinyl, pyridinyl, [1,3,4]oxadiazolyl, 4H-[1,2,4]triazolyl, tetrazolyl, pyrazolyl, [1,3,5]triazinyl, and [1,3,4]thiadiazolyl;

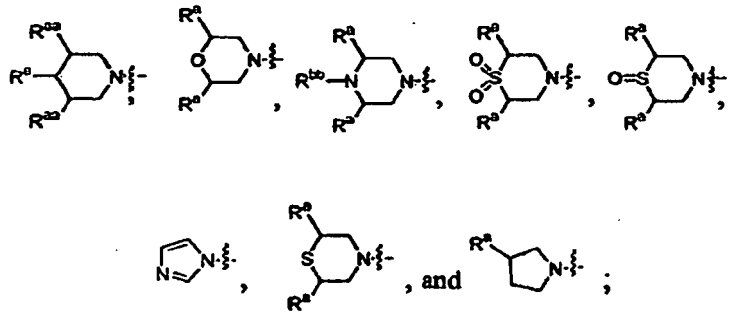
R^z and R^y are independently H or $-C_{(1-4)}$alkyl, wherein both R^z may have either *syn* or *anti* stereochemistry; alternatively both R^z in a *syn* relationship may be taken together to form $-(CH_2)_n-$, where n is 2 or 3;

R^3 is H, $C_{(1-4)}$alkyl, $C_{(1-3)}$alkyl-CF_3, $CH_2CH_2NH_2$, $CH_2CH_2OR^a$, $-COCH_3$, $CONH_2$. or CO_2R^a;

A^1 is H, $-C_{(1-4)}$alkyl, or $CH_2CH_2OR^a$;

A^2 is H, $-C_{(1-4)}$alkyl, COR^a, $CH_2CON(CH_3)_2$, $-CH_2CH_2OR^a$, $-CH_2CH_2SC_{(1-4)}$alkyl,$-CH_2CH_2SOC_{(1-4)}$alkyl, or $-CH_2CH_2SO_2C_{(1-4)}$alkyl;

alternatively, A^1 and A^2 may be taken together with their attached nitrogen to form a heterocyclic ring selected from the following:



wherein R^a is H or $C_{(1-4)}$alkyl;

R^{aa} is H or $C_{(1-4)}$alkyl; and

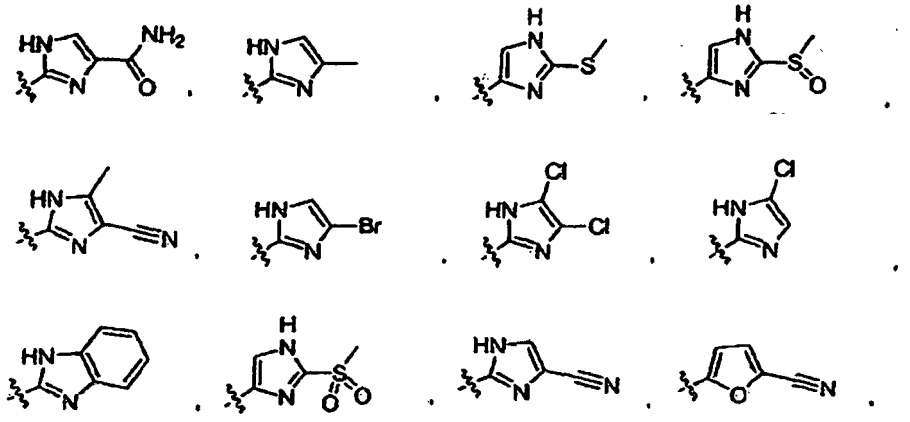
R^{bb} is H, $-C_{(1-4)}$alkyl, $-CH_2CH_2OCH_2CH_2OCH_3$, $-CH_2CO_2H$, $-C(O)C_{(1-4)}$alkyl, or-$CH_2C(O)C_{(1-4)}$alkyl

wherein cycloalkyl is a saturated or partially unsaturated ring composed of from 3 to 8 carbon atoms; and

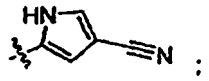
wherein spiro-substituted cycloalkenyl is a pair of cycloalkyl rings that share a single carbon atom and at least one of the rings is partially unsaturated.

2. A Compound of Claim 1 wherein

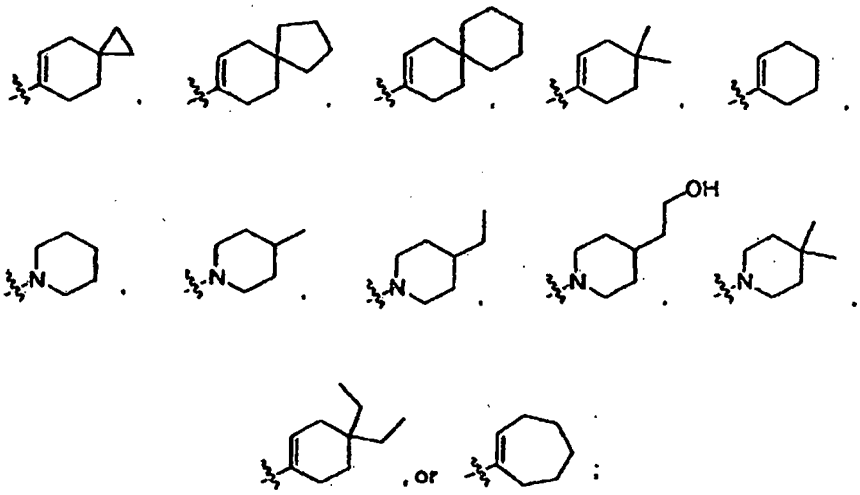
W is



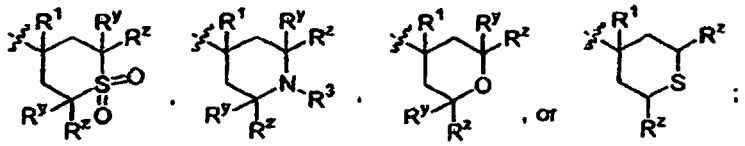
or



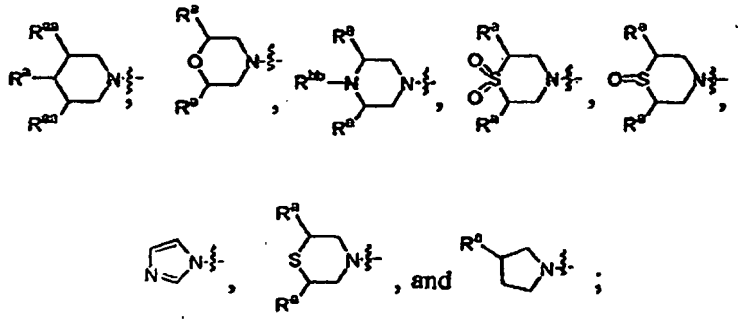
R^2 is



Z is H;
X is



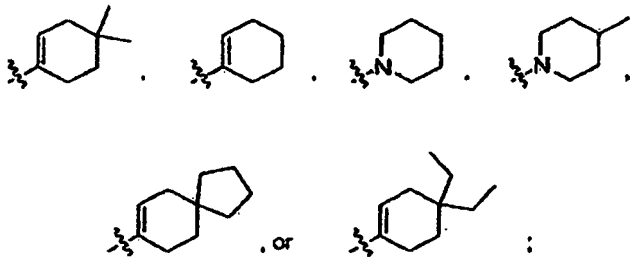
wherein R^1 is -OH, -CN, $-NA^1A^2$, $-SO_2CH_3$, $-COOR^a$, $-CO_2CH_3$, $-CH_2-A^1A^2$,$-CONA^1A^2$, $-CH_2OR^a$, $-NHCH_2CH_2CO_2R^a$, $-NHCH_2CH_2OR^a$, $-NHCH_2CH_2NA^1A^2$,$-OC_{(1-4)}alkylNA^1A^2$, $-OCH_2COR^a$, or tetrazolyl;
A^1 is H, or $-CH_3$;
A^2 is H, $-CH_2CH_2OCH_3$, $-COCH_3$, or $-CH_3$;
alternatively, A^1 and A^2 may be taken together with their attached nitrogen to form a heterocyclic ring selected from the following:



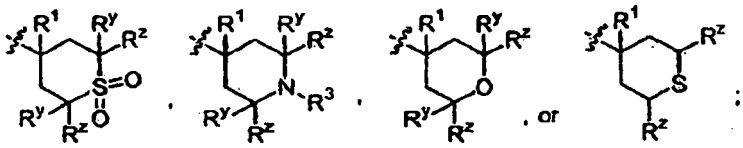
R^a is H, or $-C_{(1-4)}alkyl$;
R^{8a} is H, or $-C_{(1-4)}alkyl$;
R^{bb} is H, $-C_{(1-4)}alkyl$, $-CH_2CO_2H$ or $-COCH_3$;
R^y is H, or $-CH_3$;

R^z is H, $-CH_3$, or may be taken together as $-CH_2CH_2-$;
R^3 is H, $-CH_2CF_3$, $-COCH_3$, $-CH_3$, $-CO_2CH_3$, $-CONH_2$, or $-CO_2H$.
as well as solvates, hydrates, tautomers and pharmaceutically acceptable salts thereof.

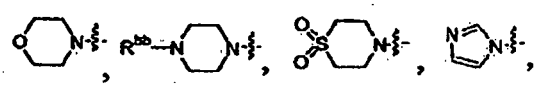
3. A compound of Claim 2 wherein
R^2 is



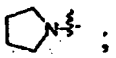
X is



wherein R^1 is -OH, -CN, $-NA^1A^2$, $-SO_2CH_3$, -COOH, $-CO_2CH_3$, $-CH_2-NA^1A^2$,$-CONH_2$, $-CON(CH_3)_2$, $-CH_2OH$, $-OCH_2CH_2N(CH_3)_z$, $-NHCH_2CH_2CO_2CH_3$,$-NHCH_2CH_2OCH_3$, $-NHCH_2CH_2NA^1A^2$, $-OC_{(1-4)}alkylNA^1A^2$, $-OCH_2CO_2H$, or tetrazolyl;
A^1 is H, or $-CH_3$;
A^2 is H,$-CH_2CH_2OCH_3$,$-COCH_3$, or$-CH_3$;
alternatively, A^1 and A^2 may be taken together with their attached nitrogen to form a heterocyclic ring selected from the following:

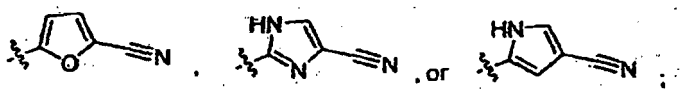


and

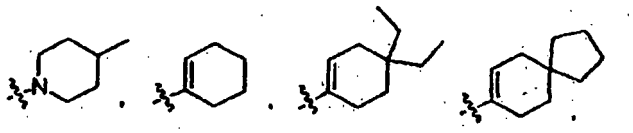


R^{bb} is H, $-C_{(1-4)}$alkyl, $-CH_2CO_2H$ or $-COCH_3$;
R^y is H, or $-CH_3$;
R^z is H, $-CH_3$, or may be taken together as $-CH_2CH_2-$;
R^3 is H. $-CH_2CF_3$, $-COCH_3$, $-CH_3$, $-CO_2CH_3$, $-CONH_2$, or $-CO_2H$.
as well as solvates, hydrates, tautomers and pharmaceutically acceptable salts thereof.

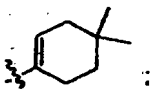
4. A compound of Claim 3 wherein
Wis



R^2 is

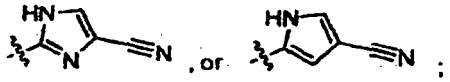


or

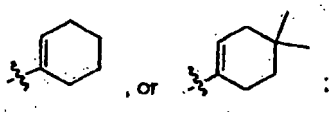


as well as solvates, hydrates, tautomers and pharmaceutically acceptable salts thereof.

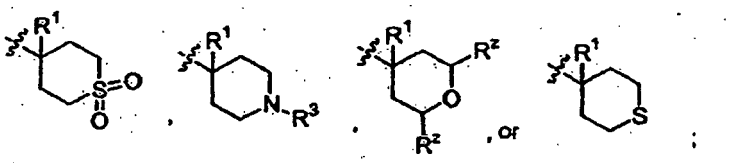
5. A compound of Claim 4 wherein
Wis



R^2 is

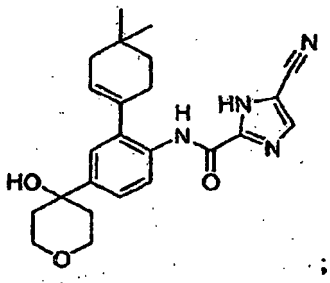


Xis

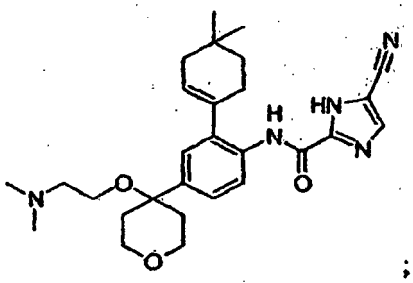


wherein R^1 is -OH, $-NH_2$, $N(CH_3)_2$, $-SO_2CH_3$, -COOH, $-CO_2CH_3$, $-CH_2$-morpholinyl, $-CONH_2$, $-CON(CH_3)_2$, $-CH_2OH$, $-OCH_2CH_2N(CH_3)_2$. $NHCH_2CH_2OCH_3$, $-OCH_2CO_2H$, morpholinyl, piperazinyl, H-methyl piperazinyl, piperazinyl-CH_2CO_2H, or tetrazolyl;
R^z is H, or $-CH_3$;
R^3 is $-CoCH_3$, $-CH_2CF_3$, or $-CO_2H$;
and solvates, hydrates, tautomers and pharmaceutically acceptable salts thereof

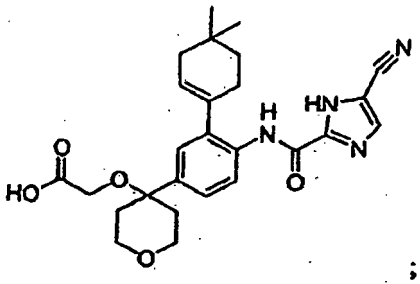
6. A compound selected from the group consisting of:



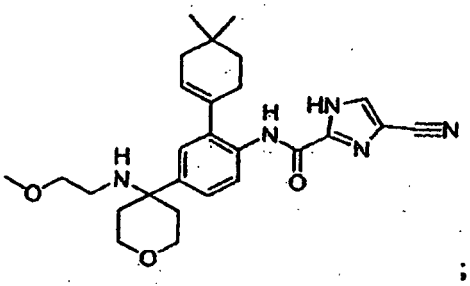
;



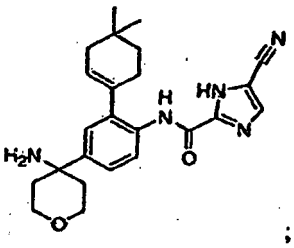
;



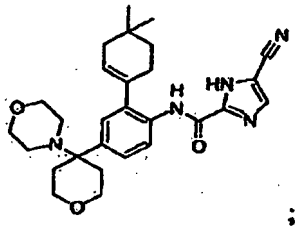
;



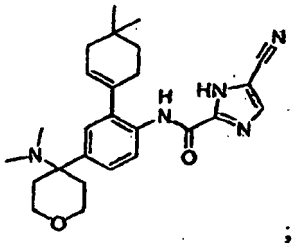
;



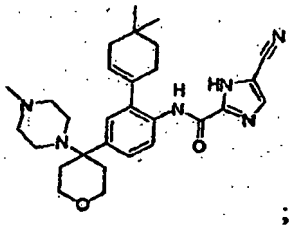
;



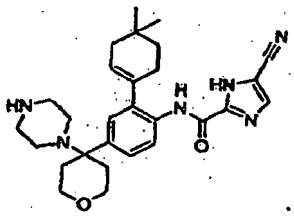
;



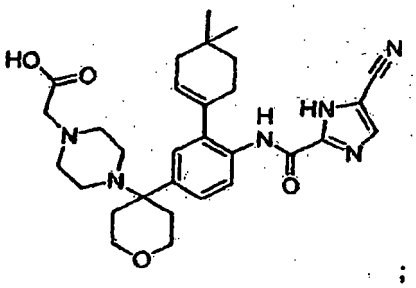
;



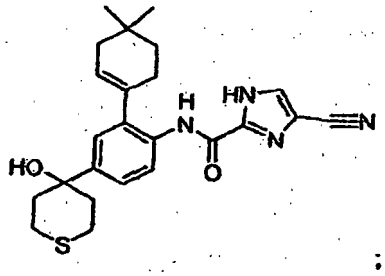
;



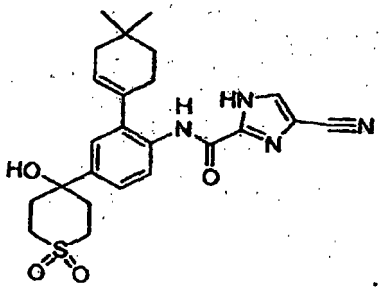
;



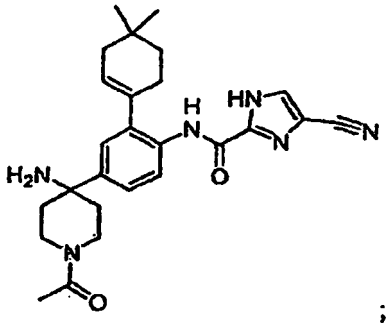
;



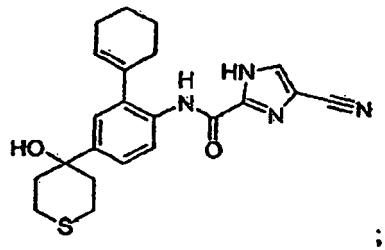
;



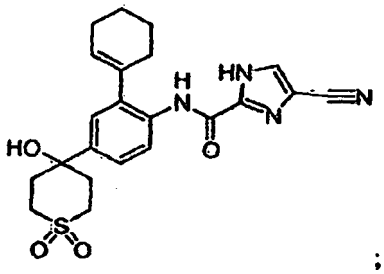
;



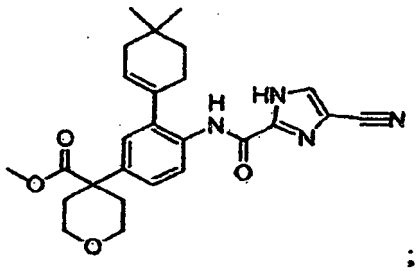
;



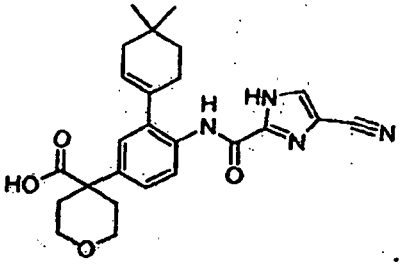
;



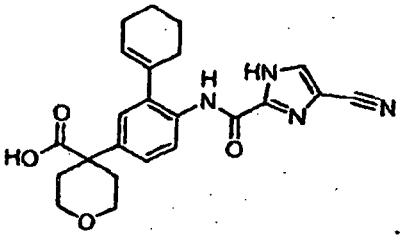
;



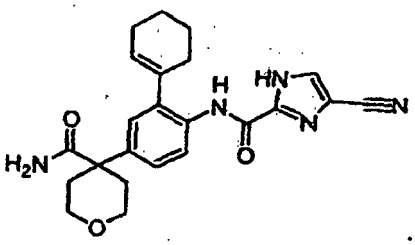
;



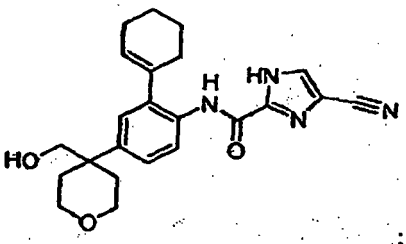
;



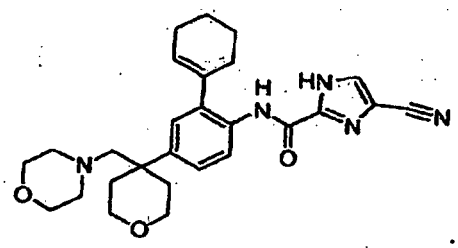
;



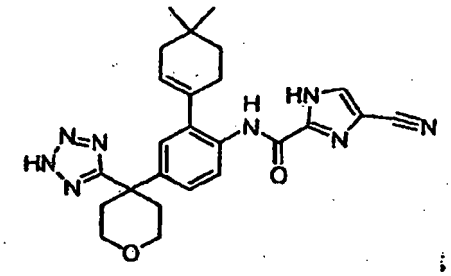
;



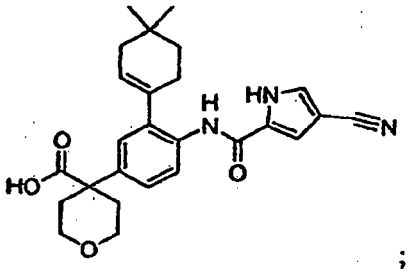
;



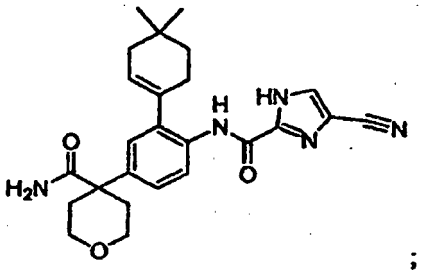
;



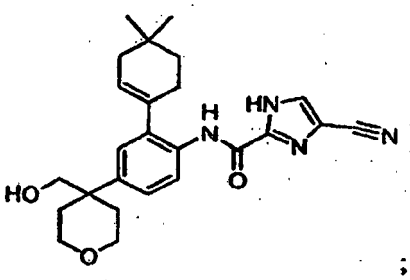
;



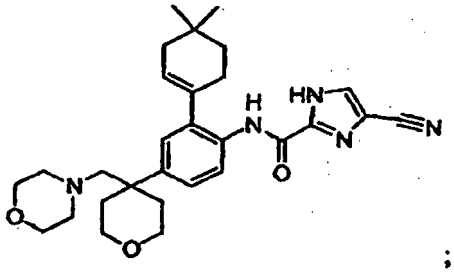
;



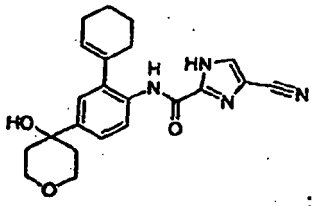
;



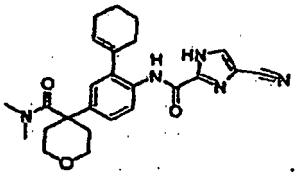
;



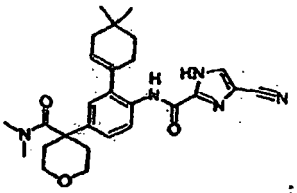
;



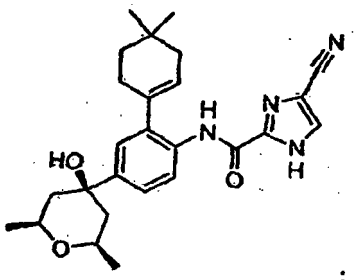
;



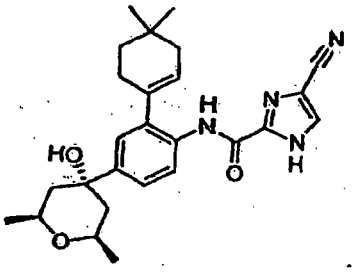
;



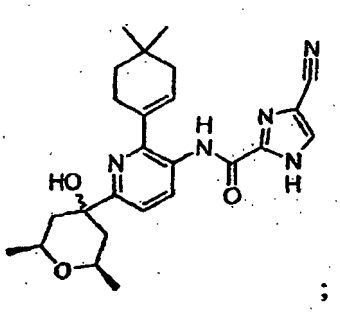
;



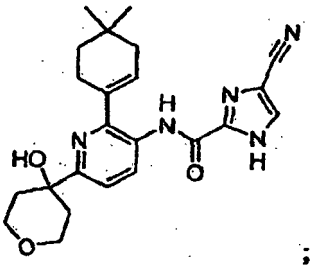
;



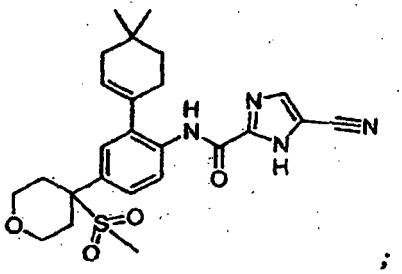
;



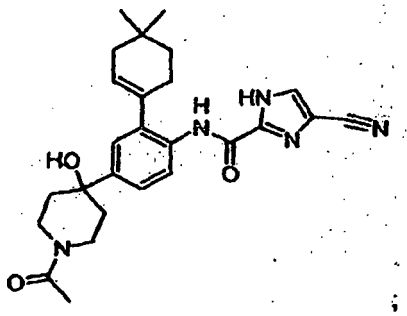
;



;



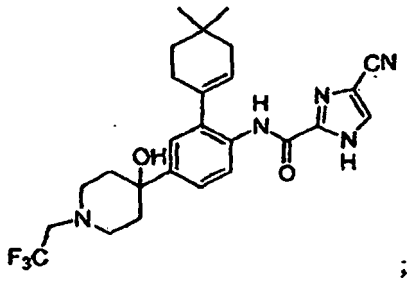
;

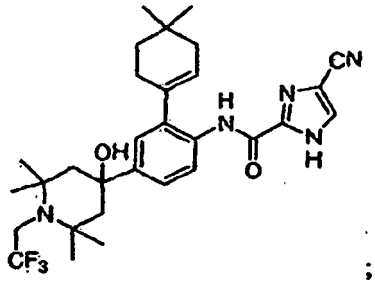


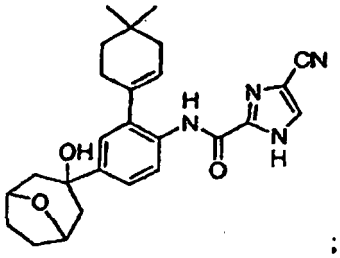
;

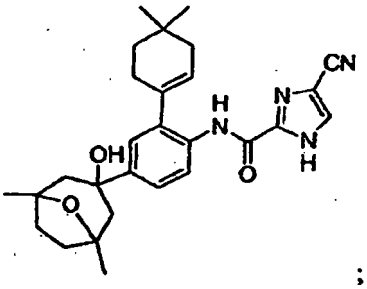
and solvates, hydrates, tautomers and pharmaceutically acceptable salts thereof.

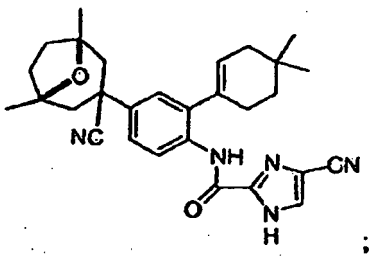
7. A compound selected from the group consisting of:

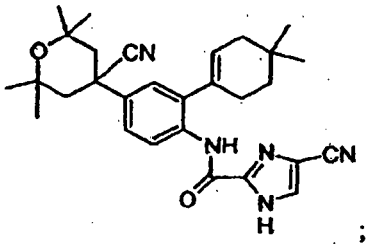

;


;


;


;


;



;

and solvates, hydrates, tautomers, and pharmaceutically acceptable salts thereof.

8. A pharmaceutical composition, comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

9. At least one compound of Claim 1, for use in a method of treating inflammation in a mammal.

10. At least one compound of Claim 1, for use in a method of treating cancer or cardiovascular disease in a mammal.

11. At least one compound of Claim 1, for use in a method of treating diseases with an inflammatory component including glomerulonephritis, inflammatory bowel disease, prosthesis failure, sarcoidosis, congestive obstructive pulmonary disease, idiopathic pulmonary fibrosis, asthma, pancreatitis, HIV infection, psoriasis, diabetes, tumor related angiogenesis, age-related macular degeneration, diabetic retinopathy, restenosis, schizophrenia or Alzheimer's dementia in a mammal.

12. At least one compound of Claim 1, for use in a method of treating pain, including skeletal pain caused by tumor metastasis or osteoarthritis, or visceral, inflammatory, and neurogenic pain in a mammal.

13. At least one compound of Claim 1, for use in a method of treating osteoporosis, Paget's disease, and other diseases in which bone resorption mediates morbidity including rheumatoid arthritis, and other forms of inflammatory arthritis, osteoarthritis, prosthesis failure, osteolytic sarcoma, myeloma, and tumor metastasis to bone.

14. At least one compound of Claim 1, for use in a method of treating and of preventing metastasis from ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, and hairy cell leukemia.

15. At least one compound of Claim 1, for use in a method of treating autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and other forms of inflammatory arthritis, psoriasis, Sjogren's syndrome, multiple sclerosis, or uveitis.