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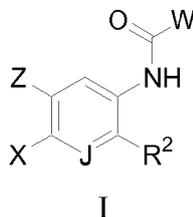
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Remarks:

- This application was filed on 08-08-2013 as a divisional application to the application mentioned under INID code 62.
- Claims filed after the date of filing of the application/ date of receipt of the divisional application (Rule 68 (4) EPC).

(54) **Inhibitors of C-FMS Kinase**

(57) The invention is directed to compounds of Formula I:



wherein Z, X, J, R² and W are set forth in the specification,

as well as solvates, hydrates, tautomers and pharmaceutically acceptable salts thereof, that inhibit protein tyrosine kinases, especially c-fms kinase. Methods of treating autoimmune diseases; and diseases with an inflammatory component; treating metastasis from ovarian cancer, uterine cancer, breast cancer, colon cancer, stomach cancer, hairy cell leukemia and non-small lung carcinoma; and treating pain, including skeletal pain caused by tumor metastasis or osteoarthritis, or visceral, inflammatory, and neurogenic pain; as well as osteoporosis, Paget's disease, and other diseases in which bone resorption mediates morbidity including arthritis, prosthesis failure, osteolytic sarcoma, myeloma, and tumor metastasis to bone with the compounds of Formula I, are also provided.

Description

CROSS REFERENCE TO RELATED APPLICATION

5 **[0001]** This application claims priority from United States Provisional Applications Serial Nos. 60/793,694, filed on April 20, 2006, and 60/871,171, filed December 21, 2006, the contents of both of which are hereby incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

10 **[0002]** The invention relates to novel compounds that function as protein tyrosine kinase inhibitors. More particularly, the invention relates to novel compounds that function as inhibitors of c-fms kinase.

15 **[0003]** Protein kinases are enzymes that serve as key components of signal transduction pathways by catalyzing the transfer of the terminal phosphate from adenosine 5'-triphosphate (ATP) to the hydroxy group of tyrosine, serine and threonine residues of proteins. As a consequence, protein kinase inhibitors and substrates are valuable tools for assessing the physiological consequences of protein kinase activation. The overexpression or inappropriate expression of normal or mutant protein kinases in mammals has been demonstrated to play significant roles in the development of many diseases, including cancer and diabetes.

20 **[0004]** Protein kinases can be divided into two classes: those which preferentially phosphorylate tyrosine residues (protein tyrosine kinases) and those which preferentially phosphorylate serine and/or threonine residues (protein serine/threonine kinases). Protein tyrosine kinases perform diverse functions ranging from stimulation of cell growth and differentiation to arrest of cell proliferation. They can be classified as either receptor protein tyrosine kinases or intracellular protein tyrosine kinases. The receptor protein tyrosine kinases, which possess an extracellular ligand binding domain and an intracellular catalytic domain with intrinsic tyrosine kinase activity, are distributed among 20 subfamilies.

25 **[0005]** Receptor tyrosine kinases of the epidermal growth factor ("EGF") family, which includes HER-1, HER-2/neu and HER-3 receptors, contain an extracellular binding domain, a transmembrane domain and an intracellular cytoplasmic catalytic domain. Receptor binding leads to the initiation of multiple intracellular tyrosine kinase dependent phosphorylation processes, which ultimately results in oncogene transcription. Breast, colorectal and prostate cancers have been linked to this family of receptors.

30 **[0006]** Insulin receptor ("IR") and insulin-like growth factor I receptor ("IGF-1R") are structurally and functionally related but exert distinct biological effects. IGF-1R over-expression has been associated with breast cancer.

[0007] Platelet derived growth factor ("PDGF") receptors mediate cellular responses that include proliferation, migration and survival and include PDGFR, the stem cell factor receptor (c-kit) and c-fms. These receptors have been linked to diseases such as atherosclerosis, fibrosis and proliferative vitreoretinopathy.

35 **[0008]** Fibroblast growth factor ("FGF") receptors consist of four receptors which are responsible for the production of blood vessels, for limb outgrowth, and for the growth and differentiation of numerous cell types.

[0009] Vascular endothelial growth factor ("VEGF"), a potent mitogen of endothelial cells, is produced in elevated amounts by many tumors, including ovarian carcinomas. The known receptors for VEGF are designated as VEGFR-1 (Flt-1), VEGFR-2 (KDR), VEGFR-3 (Flt-4). A related group of receptors, tie-1 and tie-2 kinases, have been identified in vascular endothelium and hematopoietic cells. VEGF receptors have been linked to vasculogenesis and angiogenesis.

40 **[0010]** Intracellular protein tyrosine kinases are also known as non-receptor protein tyrosine kinases. Over 24 such kinases have been identified and have been classified into 11 subfamilies. The serine/threonine protein kinases, like the cellular protein tyrosine kinases, are predominantly intracellular.

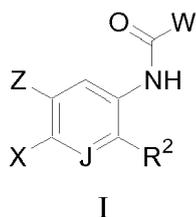
45 **[0011]** Diabetes, angiogenesis, psoriasis, restenosis, ocular diseases, schizophrenia, rheumatoid arthritis, cardiovascular disease and cancer are exemplary of pathogenic conditions that have been linked with abnormal protein tyrosine kinase activity. Thus, a need exists for selective and potent small-molecule protein tyrosine kinase inhibitors. U.S. Patent Nos. 6,383,790; 6,346,625; 6,235,746; 6,100,254 and PCT International Applications WO 01/47897, WO 00/27820 and WO 02/068406 are indicative of recent attempts to synthesize such inhibitors.

SUMMARY OF THE INVENTION

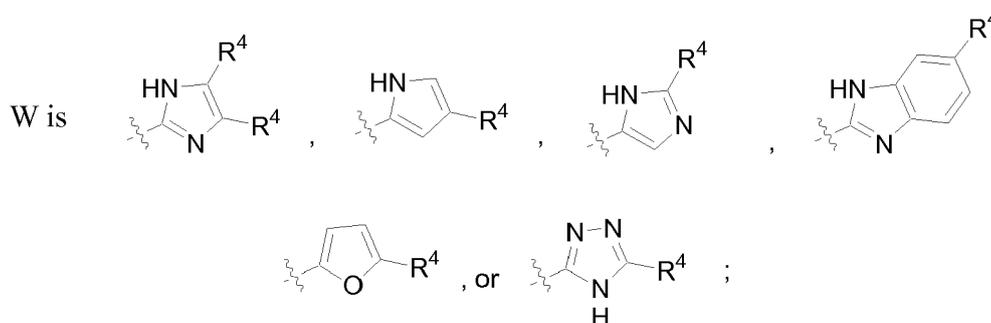
50 **[0012]** The invention addresses the current need for selective and potent protein tyrosine kinase inhibitors by providing potent inhibitors of c-fms kinase. The invention is directed to the novel compounds of Formula I:

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



25 wherein each R⁴ is independently H, F, Cl, Br, I, OH, OCH₃, OCH₂CH₃, SC₍₁₋₄₎alkyl, SOC₍₁₋₄₎alkyl, SO₂C₍₁₋₄₎alkyl, -C₍₁₋₃₎alkyl, -CO₂R^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, -CH₂OH, or -CH₂CH₂OH;

30 R² 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 CH₃;

J is CH, or N;

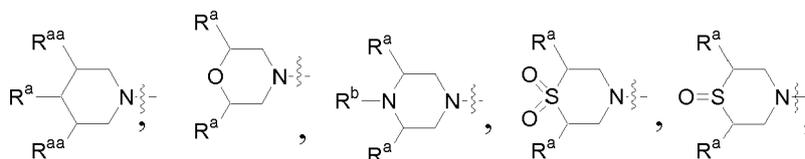
35 X is -C₍₁₋₆₎alkylR¹, alkenyl, propenyl-NA¹A², -CH=CH-CO₂R^a (including both *E* and *Z* stereochemistry for said CH=CH bond), -C₍₁₋₄₎alkylR³R^{4a}, or -CH₂-heteroaryl--C₍₁₄₎alkyl-R¹;

40 wherein R¹ is -CN, -SO₂NA¹A², -SO₂R^a, -SCH₂CH₂NA¹A², -SOCH₂CH₂NA¹A², -SO₂CH₂CH₂NA¹A², -S-C(O)C₍₁₋₄₎alkyl, -S-CH₂-4-methoxy phenyl, -OC₍₁₄₎alkylNA¹A², -NA¹A², -NHSO₂R^a, -NHCOR^a, -NHSO₂CH₂CH₂NA¹A², -NHCOCH₂CH₂NA¹A², -CONH₂, -CONHCH₂CH₂CH₂OH, CONHCH₂CH₂N(C₍₁₄₎alkyl)₂, -NHCONH₂, -NHCONHCH₂CH₂OH, -NHCOCONH₂, -NR_aCH₂CH₂NA¹A², CO₂R^a, pyridyl, 2-methyl pyridyl, -OCH₂CH₂OR^a, -OCH₂CH₂OCH₂CH₂NA¹A², -OCH₂CH₂NA¹CH₂CH₂OR^a, -NA¹CH₂CH₂OCH₂CH₂OR^a, -OCOR^a, or -CH₂OCOCH₃;

A¹ is H or -C₍₁₋₄₎alkyl;

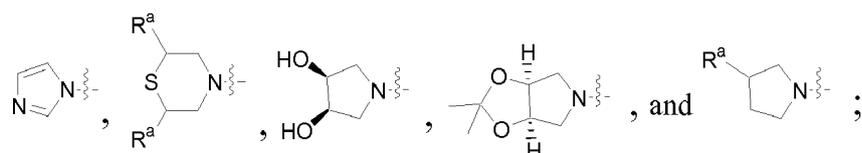
A² is -C₍₁₋₄₎alkyl, -CH₂CH₂OR^a, -COR^a, -CH₂CH₂SC₍₁₋₄₎alkyl, -CH₂CH₂SOC₍₁₋₄₎alkyl, pyridyl, -CH₂CH₂OCH₂CH₂OR^a, or -CH₂CH₂SO₂C₍₁₋₄₎alkyl;

45 alternatively, A¹ and A² may be taken together with their attached nitrogen to form a heterocyclic ring selected from the following:



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wherein:

- 10 R^3 is H or $C_{(1-4)}$ alkyl;
 R^{aa} is H or $C_{(1-4)}$ alkyl;
 R^b is H, $-C_{(1-4)}$ alkyl, alkoxyether, $-C(O)C_{(1-4)}$ alkyl, $-C_{(1-4)}$ alkyl-OH,
 $-C_{(1-4)}$ alkyl-O- $C_{(1-4)}$ alkyl, $-C_{(1-4)}$ alkyl-C(O)O- $C_{(1-4)}$ alkyl, $-C_{(1-4)}$ alkylC(O)OH, $-C_{(1-4)}$ alkylC(O)ON $_a$, or $-CH_2C(O)C_{(1-4)}$ alkyl; and

15

R^3 and R^{43} are independently $-CH_2OH$, $-OCH_3$, $-CH_2OCH_3$, $-CO_2H$, $-CO_2C_{(1-4)}$ alkyl, $-OC(O)C_{(1-4)}$ alkyl, or $-OH$.

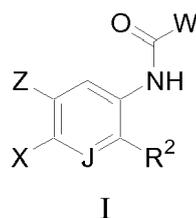
[0013] Herein and throughout this application, when two substituents appear on an alkyl group, such as $-C_{(1-4)}$ alkyl R^3R^{4a} , it is understood that the two substituents may independently be attached the same or different carbon atoms.

- 20 **[0014]** Herein and throughout this application, the terms "Me", "Et", "Pr", and "Bu" refer to methyl, ethyl, propyl, and butyl respectively.

DETAILED DESCRIPTION OF THE INVENTION

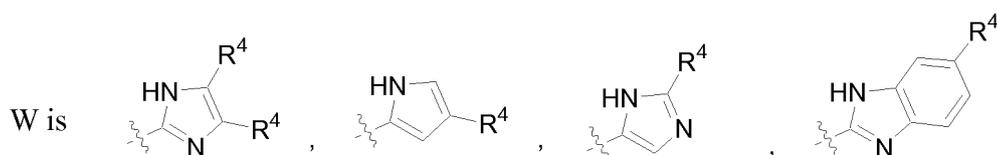
- 25 **[0015]** The invention is directed to the novel compounds of Formula I:

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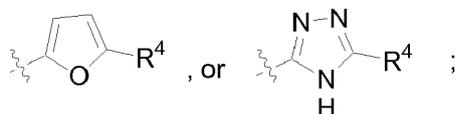


- 35 or a solvate, hydrate, tautomer or pharmaceutically acceptable salt thereof wherein:

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- 50 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, $-CO_2R^d$, $CONR^eR^f$, $C\equiv CR^g$, 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 $-CH_2CH_2OH$;

- 55 R^2 is cycloalkyl (including cyclohexenyl, and cycloheptenyl), spiro-substituted cycloalkenyl (including spiro[2.5]oct-5-enyl, spiro[3.5]non-6-enyl, spiro[4.5]dec-7-enyl, and spiro[5.5]undec-2-enyl) heterocyclyl (including piperidinyl), spiro-substituted piperidinyl (including 3-aza-spiro[5.5]undecanyl, and 8-aza-spiro[4.5]decanyl), 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₍₁₃₎alkyl, and C₍₁₋₄₎alkyl (said substituted cycloalkyls include 4,4-dimethyl cyclohexenyl, 4,4-diethyl cyclohexenyl, 4-methyl cyclohexenyl, 4-ethyl cyclohexenyl, 4-n-propyl cyclohexenyl, 4-iso-propyl cyclohexenyl, and 4-tert-butyl cyclohexenyl; said substituted piperidinyls include 4-methyl piperidinyl, 4-ethyl piperidinyl, 4-(1'hydroxyethyl-2'yl)piperidinyl, and 4,4 dimethyl piperidinyl);

Z is H, F, or CH₃;

J is CH, or N;

X is -C₍₁₋₆₎alkylR¹ (including -CH₂R¹, -CH₂CH₂R¹, and -C(C₍₁₋₄₎alkyl)₂R¹), alkenyl (including propenyl), propenyl-NA¹A², -CH=CH-CO₂R^a (including both *E* and *Z* stereochemistry for said CH=CH bond), -C₍₁₋₄₎alkylR³R^{4a}, or -CH₂-heteroaryl-C₍₁₄₎alkyl-R¹;

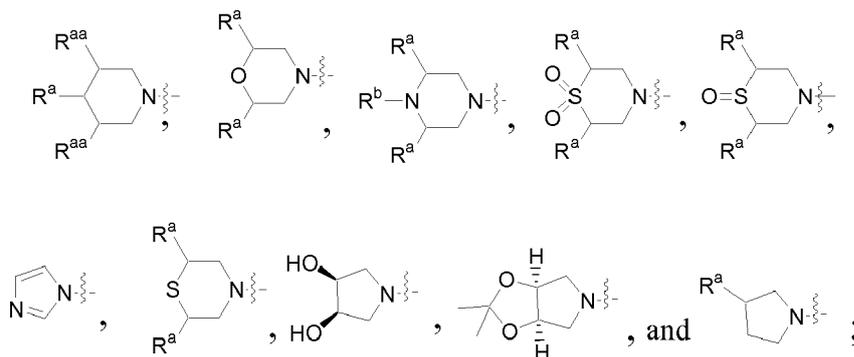
wherein:

R¹ is -CN, -SO₂NA¹A², -SO₂R^a, -SCH₂CH₂NA¹A², -SOCH₂CH₂NA¹A², -SO₂CH₂CH₂NA¹A², -S-C(O)C₍₁₋₄₎alkyl (including -S-C(O)CH₃), -S-CH₂-4-methoxy phenyl, -OC₍₁₋₄₎alkylNA¹A² (including -OCH₂CH₂NA¹A²), -NA¹A², -NHSO₂R^a (including -NHSO₂CH₃), -NHCOR^a (including -NHCONH₃, -NHSO₂CH₂CH₂NA¹A², -NHSO₂CH₂CH₂NA¹A², -CONH₂, -CONHCH₂CH₂CH₂OH, CONHCH₂CH₂N(C₍₁₋₄₎alkyl)₂ (including CONHCH₂CH₂N(CH₃)₂), -NHCONH₂, -NHCONHCH₂CH₂OH, -NHCOCONH₂, -NR_aCH₂CH₂NA¹A², CO₂R^a, pyridyl, -OCH₂CH₂OR^a, -OCH₂CH₂OCH₂CH₂NA¹A², -OCH₂CH₂NA¹CH₂CH₂OR^a, -NA¹CH₂CH₂OCH₂CH₂OR^a -OCOR^a (including -OCOCH₃), or -CH₂OCOCH₃;

A¹ is H or -C₍₁₋₄₎alkyl;

A² is -C₍₁₋₄₎alkyl, -CH₂CH₂OR^a (including -CH₂CH₂OCH₃), -COR^a (including -COCH₃), -CH₂CH₂SC₍₁₋₄₎alkyl (including -CH₂CH₂SCH₃), -CH₂CH₂SOC₍₁₋₄₎alkyl (including -CH₂CH₂SOCH₃), pyridyl, 2-methyl pyridyl, -CH₂CH₂OCH₂CH₂OR^a, or -CH₂CH₂SO₂C₍₁₋₄₎alkyl (including -CH₂CH₂SO₂CH₃);

alternatively, A¹ and A² may be taken together with their attached nitrogen to form a heterocyclic ring selected from the following:



wherein:

R³ is H or C₍₁₋₄₎alkyl;

R^{aa} is H or C₍₁₋₄₎alkyl;

R^b is H, -C₍₁₋₄₎alkyl, alkoxyether, -C(O)C₍₁₋₄₎alkyl, -C₍₁₋₄₎alkyl-OH (including -CH₂CH₂OH), -C₍₁₋₄₎alkyl-O-C₍₁₋₄₎alkyl (including -CH₂CH₂OCH₃), -C₍₁₋₄₎alkyl-C(O)O-C₍₁₋₄₎alkyl (including -CH₂C(O)OCH₂CH₃), -C₍₁₋₄₎alkylC(O)OH (including -CH₂C(O)OH), -C₍₁₋₄₎alkylC(O)ONa (including -CH₂C(O)ONa), or -CH₂C(O)C₍₁₋₄₎alkyl; and

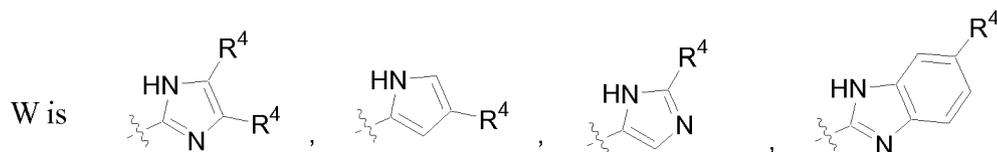
R³ and R^{4a} are independently -CH₂OH, -OCH₃, -CH₂OCH₃, -CO₂H, -CO₂C₍₁₋₄₎alkyl (including -CO₂CH₂CH₂), OC(O)C₍₁₋₄₎alkyl (including -OC(O)CH₃), or -OH.

[0016] Preferred compounds of Formula I are those wherein

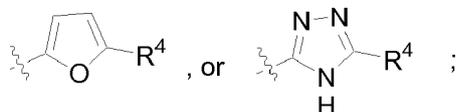
W is substituted with one -CN.

[0017] Other preferred compounds of Formula I are those wherein:

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wherein each R⁴ is independently H, F, Cl, Br, I, OH, OCH₃, OCH₂CH₃, SC₍₁₋₄₎alkyl, SOC₍₁₋₄₎alkyl, SO₂C₍₁₋₄₎alkyl, -C₍₁₋₃₎alkyl, CO₂R^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;

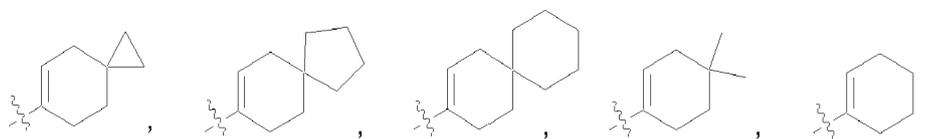
R^f is H, or -C₍₁₋₃₎alkyl; and

R^g is H, -CH₂OH, or -CH₂CH₂OH;

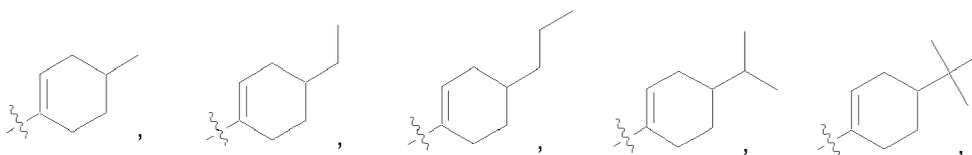
R² is

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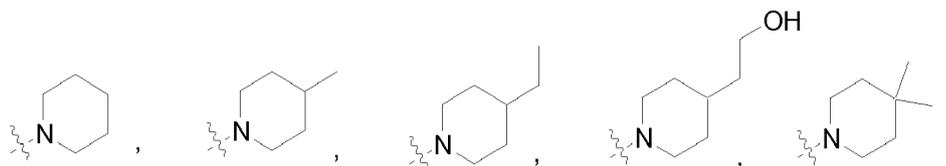
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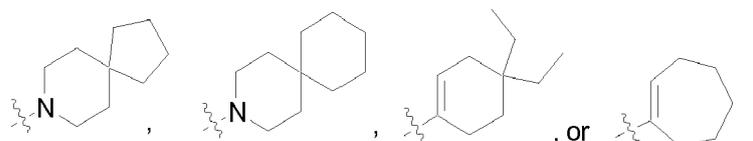


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Z is H, F, or CH₃;

J is CH, or N;

X is -C₍₁₋₆₎alkylR¹, alkenyl, propenyl-NA¹A², -CH=CH-CO₂R^a, -C₍₁₋₄₎alkylR³R^{4a}, or -CH₂-heteroaryl-C₍₁₋₄₎alkyl-R¹;

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wherein:
R¹ is -CN, -SO₂NA¹A², -SO₂R³, -SCH₂CH₂NA¹A², -SOCH₂CH₂NA¹A², -SO₂CH₂CH₂NA¹A², -S-C(O)C₍₁₋₄₎alkyl, -S-CH₂-4-methoxy phenyl, -OC₍₁₄₎alkylNA¹A², -NA¹A², -NHSO₂CH₃, -NHCOCH₃, -CONH₂, -CONHCH₂CH₂CH₂OH, -CONHCH₂CH₂N(C₍₁₋₄₎alkyl)₂, -NHCONH₂, -NHCONHCH₂CH₂OH, -NHCOCONH₂, -NR_aCH₂CH₂NA¹A², -CO₂R^a, pyridyl, -OCOCH₃, or -CH₂OCOCH₃;

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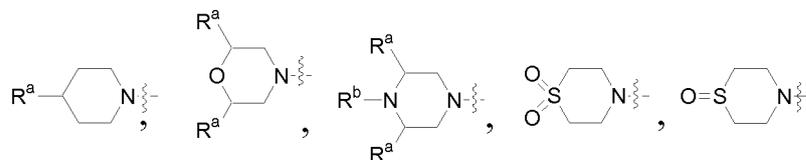
A¹ is H or -C₍₁₋₄₎alkyl;

A² is -C₍₁₋₄₎alkyl, -CH₂CH₂OR^a, -COR^a, -CH₂CH₂SC₍₁₋₄₎alkyl, -CH₂CH₂SOC₍₁₋₄₎alkyl, pyridyl, 2-methyl pyridyl, or -CH₂CH₂SO₂C₍₁₄₎alkyl;

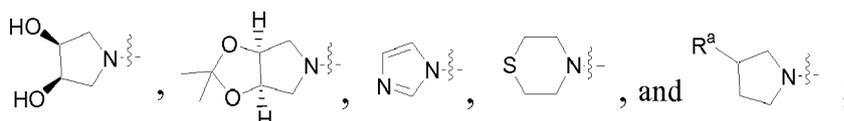
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alternatively, A¹ and A² may be taken together with their attached nitrogen to form a heterocyclic ring selected from the following:

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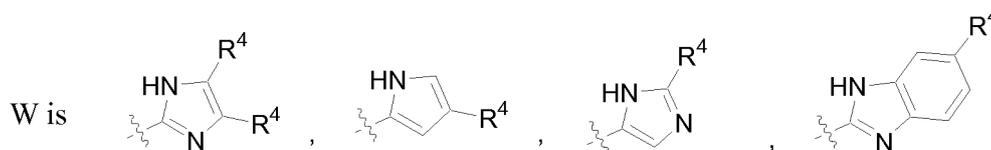
wherein:

20 R^a is H or C₍₁₋₄₎alkyl;
 R^b is H, -C₍₁₋₄₎alkyl, alkoxyether, -C(O)C₍₁₋₄₎alkyl, -C₍₁₋₄₎alkyl-OH,
 -C₍₁₋₄₎alkyl-O-C₍₁₋₄₎alkyl, -C₍₁₋₄₎alkyl-C(O)O-C₍₁₋₄₎alkyl, -C₍₁₄₎alkylC(O)OH, -C₍₁₋₄₎alkylC(O)ONa, or -CH₂C(O)
 C₍₁₋₄₎alkyl; and

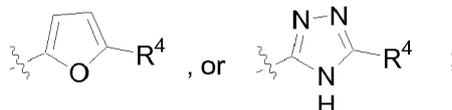
25 R³ and R^{4a} are independently -CH₂OH, -OCH₃, -CH₂OCH₃, -CO₂H, -CO₂C₍₁₋₄₎alkyl, OC(O)C₍₁₋₄₎alkyl, or -OH;
 and solvates, hydrates, tautomers and pharmaceutically acceptable salts thereof.

[0018] Other preferred compounds of Formula I are those wherein:

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40 wherein each R⁴ is independently H, F, Cl, Br, I, OH, OCH₃, OCH₂CH₃, SC₍₁₋₄₎alkyl, SOC₍₁₋₄₎alkyl, SO₂C₍₁₋₄₎alkyl,
 -C₍₁₋₃₎alkyl, CO₂R^d, CONR^eR^f, C≡CR^g, or CN;

wherein R^d is H, or -C₍₁₋₃₎alkyl;

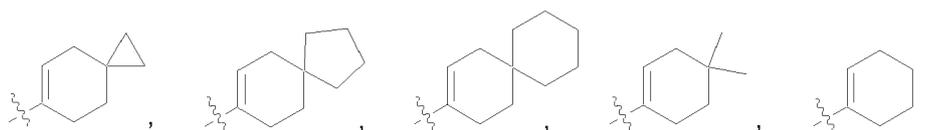
R^e is H, or -C₍₁₋₃₎alkyl;

R^f is H, or -C₍₁₋₃₎alkyl; and

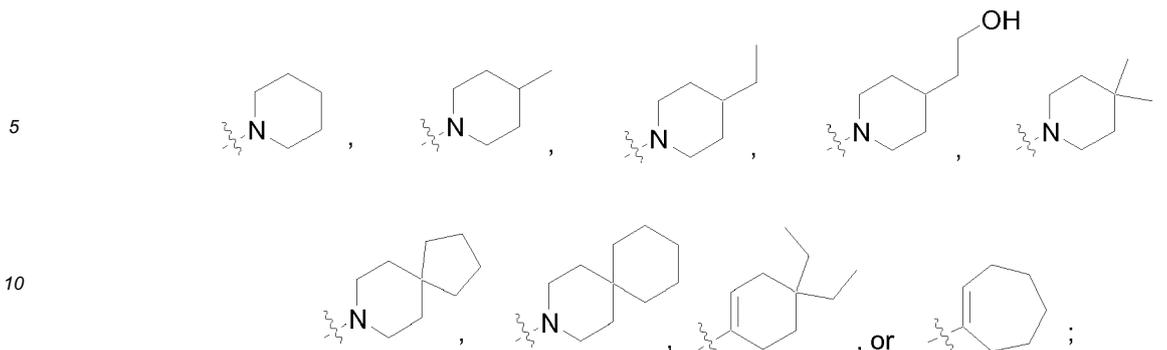
45 R^g is H, -CH₂OH, or -CH₂CH₂OH;

R² is

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55



Z is H, F, or CH₃;

15 J is CH, or N;

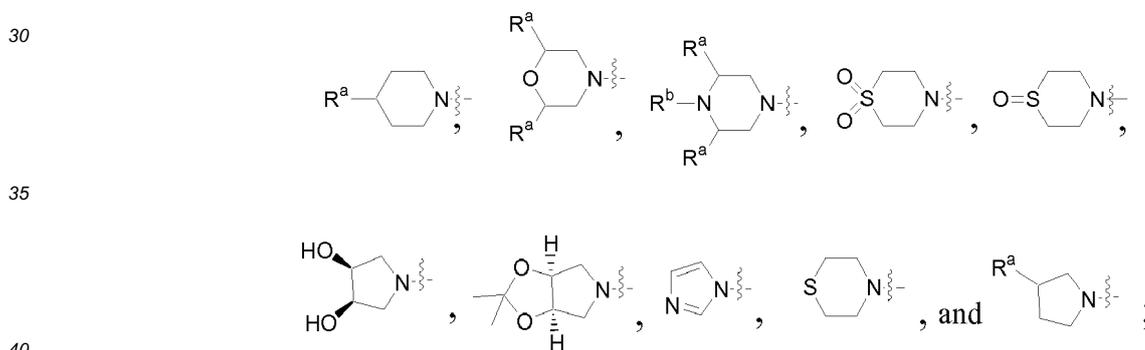
X is -C₍₁₋₅₎alkylR¹, alkenyl, propenyl-NA¹A², -CH=CH-CO₂R^a, -C₍₁₋₄₎alkylR³R^{4a}, or -CH₂-heteroaryl-C₍₁₋₄₎alkyl-R¹;
wherein:

20 R¹ is -CN, -SO₂NA¹A², -SO₂R^a, -SCH₂CH₂NA¹A², -SOCH₂CH₂NA¹A², -SO₂CH₂CH₂NA¹A², -S-C(O)C₍₁₋₄₎alkyl, -S-CH₂-4-methoxy phenyl, -OC₍₁₄₎alkylNA¹A², -NA¹A², -NHSO₂CH₃, -NHCOCH₃, -CONH₂, -CONHCH₂CH₂CH₂OH,,
-CONHCH₂CH₂N(C₍₁₋₄₎alkyl)₂, -NHCONH₂, -NHCONHCH₂CH₂OH, -NHCOCONH₂, -NR_aCH₂CH₂NA¹A², -CO₂R^a,
pyridyl, -OCOCH₃, or -CH₂OCOCH₃;

A¹ is H or -C₍₁₋₄₎alkyl;

25 A² is -C₍₁₋₄₎alkyl, -CH₂CH₂OR^a, -COR^a, -CH₂CH₂SC₍₁₋₄₎alkyl, -CH₂CH₂SOC₍₁₋₄₎alkyl, pyridyl, 2-methyl pyridyl, or
-CH₂CH₂SO₂C₍₁₄₎alkyl;

alternatively, A¹ and A² may be taken together with their attached nitrogen to form a heterocyclic ring selected from the following:



wherein:

R³ is H or C₍₁₋₄₎alkyl;

45 R^b is H, -C₍₁₋₄₎alkyl, alkoxyether, -C(O)C₍₁₋₄₎alkyl, -C₍₁₋₄₎alkyl-OH,
-C₍₁₋₄₎alkyl-O-C₍₁₋₄₎alkyl, -C₍₁₋₄₎alkyl-C(O)O-C₍₁₋₄₎alkyl, -C₍₁₄₎alkylC(O)OH, -C₍₁₋₄₎alkylC(O)ONa, or -CH₂C
(O)-C₍₁₋₄₎alkyl; and

50 R³ and R^{4a} are independently -CH₂OH, -OCH₃, -CH₂OCH₃, -CO₂H, -CO₂C₍₁₋₄₎alkyl, OC(O)C₍₁₋₄₎alkyl, or -OH;

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

[0019] Other preferred compounds of Formula I are those wherein:

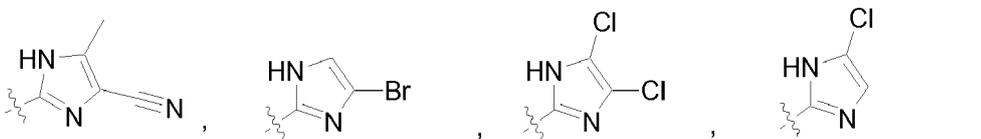
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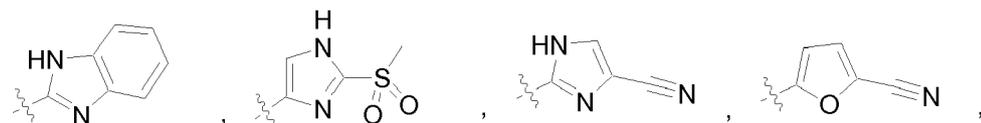
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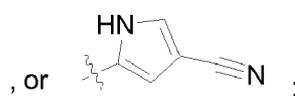
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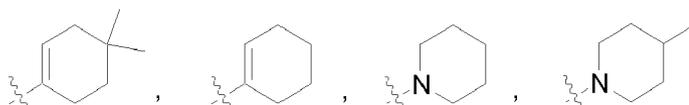
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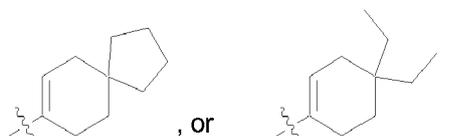
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R² is

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Z is H;

J is CH, or N;

X is -C₍₁₋₅₎alkylR¹, -CH=CH-CO₂H wherein said CH=CH bond has *E* stereochemistry, -C₍₁₋₄₎alkylR³R^{4a}, propenyl-NA¹A², or propenyl;

wherein:

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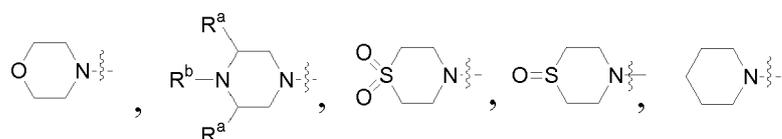
R¹ is -SO₂NA¹A², -S-C(O)CH₃, -S-CH₂-4-methoxy phenyl, -OC₍₁₋₄₎alkylNA¹A², NA¹A², NHCH₂CH₂NA¹A², NHSO₂CH₃,

NCOCH₃, CONH₂, CONHCH₂CH₂CH₂OH, CONHCH₂CH₂N(CH₃)₂, NHCONH₂, NHCONHCH₂CH₂OH, NHCOCONH₂, CO₂R^a, or pyridyl;

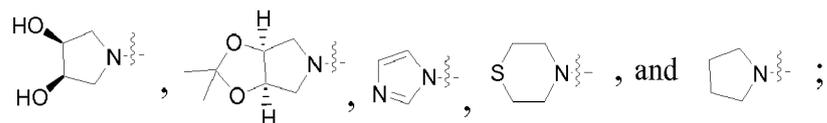
A¹ is H or -C₍₁₋₄₎alkyl;

A² is -C₍₁₋₄₎alkyl, -CH₂CH₂OR^a, -COCH₃, -CH₂CH₂SC₍₁₋₄₎alkyl, pyridyl, 2-methyl pyridyl, or -CH₂CH₂SO₂C₍₁₋₄₎alkyl; alternatively, A¹ and A² may be taken together with their attached nitrogen to form a heterocyclic ring selected from the following:

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wherein:

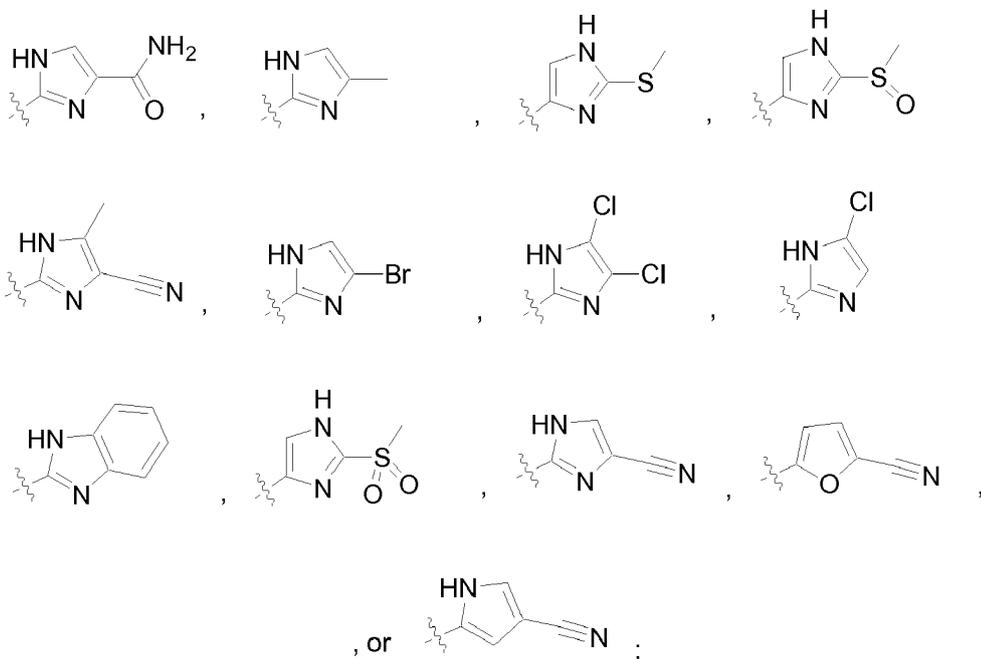
10 R^a is H or $C_{(1-4)}$ alkyl;

R^b is H, CH_2CH_2OH , $-CH_2CH_2OCH_3$, $-CH_2C(O)OCH_2CH_3$, $CH_2C(O)OH$, $-CH_2C(O)ONa$, $C(O)CH_3$, or $-C_{(1-4)}$ alkyl; and

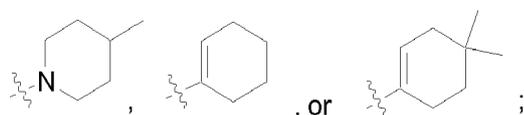
15 R^3 and R^{4a} are independently $-OCH_3$, $-CH_2OCH_3$, $-CO_2H$, $-OC(O)CH_3$, or $-OH$; and solvates, hydrates, tautomers and pharmaceutically acceptable salts thereof.

[0020] Other preferred compounds of Formula I are those wherein:

Wis



R^2 is



50 Z is H;

J is CH, or N;

X is $-CH_2R^1$, $-CH_2CH_2R^1$, $-C(CH_3)_2R^1$, $-CH=CH-CO_2H$ wherein said $CH=CH$ bond has *E* stereochemistry, $-C_{(1-4)}$ alkyl R^3R^{4a} , propenyl- NA^1A^2 , or propenyl;

wherein:

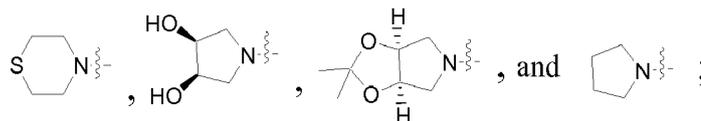
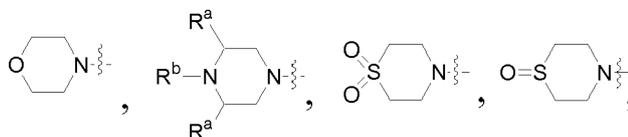
55 R^1 is $-SO_2NA^1A^2$, $-S-C(O)CH_3$, $-S-CH_2-4$ -methoxy phenyl, $-OCH_2CH_2NA^1A^2$, $-NA^1A^2$, $-NHCH_2CH_2NA^1A^2$, $-NHCOCH_3$, $-NHCOCH_3$, $-CONH_2$, $-CONHCH_2CH_2CH_2OH$, $-CONHCH_2CH_2N(CH_3)_2$, $-NHCONH_2$, $-NHCONHCH_2CH_2OH$, $-NHCOCONH_2$, or $-CO_2R^a$;

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A¹ is H or -C₍₁₋₄₎alkyl;

A² is -C₍₁₋₄₎alkyl, -C(O)CH₃, -CH₂CH₂OCH₃, -CH₂CH₂OH, -CH₂CH₂SCH₃, pyridyl, 2-methyl pyridyl, or -CH₂CH₂SO₂CH₃;

alternatively, A¹ and A² may be taken together with their attached nitrogen to form a heterocyclic ring selected from the following:



wherein:

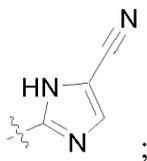
R³ is H, CH₃, or CH₂CH₃;

R^b is H, CH₂CH₂OH, -CH₂CH₂OCH₃, -CH₂C(O)OCH₂CH₃, CH₂C(O)OH, -CH₂C(O)ONa, CH₂CH₃, C(O)CH₃, or CH₃; and

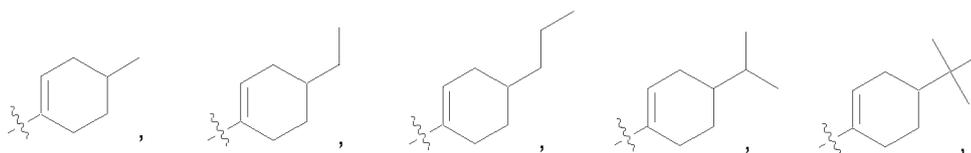
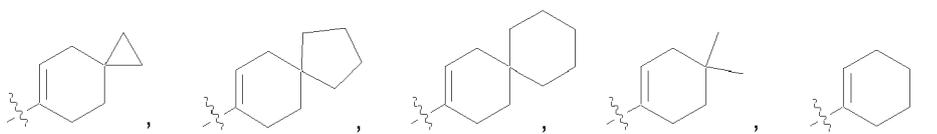
R³ and R^{4a} are independently, -OCH₃, -CH₂OCH₃, -CO₂H, -OC(O)CH₃, or -OH; and solvates, hydrates, tautomers and pharmaceutically acceptable salts thereof.

[0021] Other preferred compounds of Formula I are those wherein:

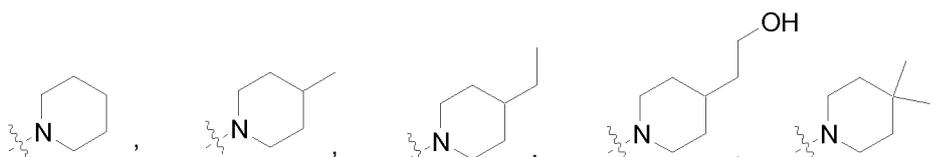
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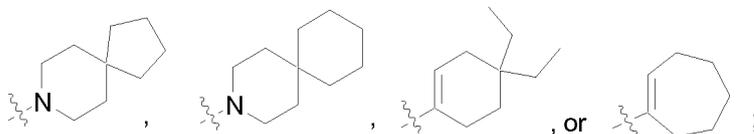
R² is



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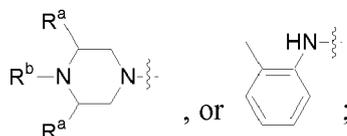
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Z is H;
J is CH, or N;
X is $-C_{(1-6)}\text{alkylR}^1$ or propenyl- NA^1A^2 , wherein:

20

R^1 is $-\text{S}-\text{C}(\text{O})\text{C}_{(1-4)}\text{alkyl}$, $-\text{S}-\text{CH}_2-4\text{-methoxy phenyl}$,

25



wherein:

30

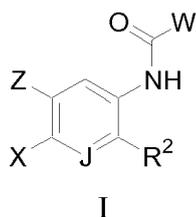
R^a is H or $\text{C}_{(1-4)}\text{alkyl}$; and
 R^b is $-\text{C}_{(1-4)}\text{alkyl}-\text{OH}$, $-\text{C}_{(1-4)}\text{alkyl}-\text{O}-\text{C}_{(1-4)}\text{alkyl}$, $-\text{C}_{(1-4)}\text{alkyl}-\text{C}(\text{O})-\text{O}-\text{C}_{(1-4)}\text{alkyl}$, $-\text{C}_{(1-4)}\text{alkylC}(\text{O})\text{OH}$, or $\text{C}_{(1-4)}\text{alkylC}(\text{O})\text{ONa}$;

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

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[0022] Other preferred compounds of Formula I

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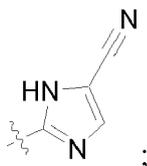


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are those wherein:

W is

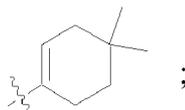
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R^2 is

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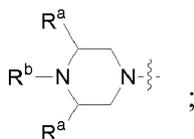
Z is H;

J is CH, or N (preferably, J is CH);

X is $-C_{(1-6)}\text{alkylR}^1$ (preferably, $-C_{(1-4)}\text{alkylR}^1$) wherein:

10

R¹ is



15

wherein:

20

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

R^b is $-C_{(1-4)}\text{alkyl-OH}$, $-C_{(1-4)}\text{alkyl-O-C}_{(1-4)}\text{alkyl}$, $-C_{(1-4)}\text{alkyl-C(O)O-C}_{(1-4)}\text{alkyl}$, $-C_{(1-4)}\text{alkylC(O)OH}$, or $-C_{(1-4)}\text{alkylC(O)ONa}$ (preferably, $-C_{(1-4)}\text{alkyl-OH}$);

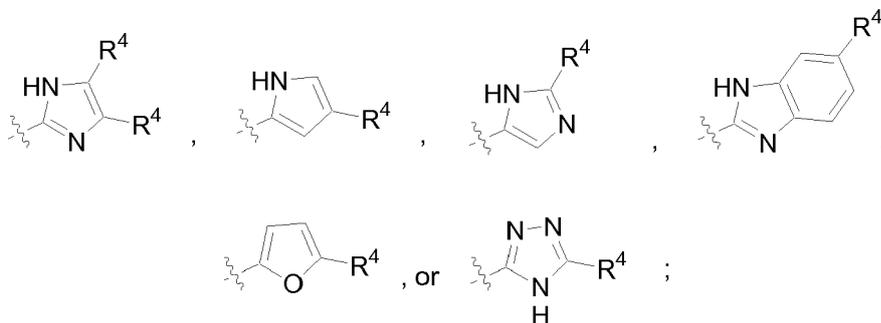
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and solvates, hydrates, tautomers or pharmaceutically acceptable salts thereof

[0023] Another embodiment is compounds of formula I wherein:

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wherein each R⁴ is independently H, F, Cl, Br, I, OH, OCH₃, OCH₂CH₃, $SC_{(1-4)}\text{alkyl}$, $SOC_{(1-4)}\text{alkyl}$, $SO_2C_{(1-4)}\text{alkyl}$, $-C_{(1-3)}\text{alkyl}$, CO_2R^d , $CONR^eR^f$, $C\equiv CR^g$, or CN;

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

45

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

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

R^g is H, $-CH_2OH$, or $-CH_2CH_2OH$; R² is cycloalkyl, spiro-substituted cycloalkenyl heterocyclyl, spirosubstituted piperidiny, thiophenyl, dihydrosulfonopyranlyl, phenyl, furanyl, tetrahydropyridyl, or dihydropyranlyl, any of which may be independently substituted with one or two of each of the following: chloro, fluoro, hydroxy, $C_{(1-3)}\text{alkyl}$, and $C_{(1-4)}\text{alkyl}$;

50

Z is H, F, or CH₃;

J is CH, or N;

X is $-C_{(1-6)}\text{alkylR}^1$, alkenyl, $-CH=CH-CO_2R^a$, $-C_{(1-4)}\text{alkylR}^3R^{4a}$, or $-CH_2\text{-heteroaryl-}C_{(14)}\text{alkyl-R}^1$;

wherein:

55

R¹ is $-CN$, $-SO_2NA^1A^2$, $-SO_2R^a$, $-SCH_2CH_2NA^1A^2$, $-SOCH_2CH_2NA^1A^2$, $-SO_2CH_2CH_2NA^1A^2$, $-OC_{(1-4)}\text{alkylINA}^1A^2$, $-NA^1A^2$, $-NHSO_2R^a$, $-NHCOR^a$, $-NHSO_2CH_2CH_2NA^1A^2$, $-NHCOCH_2CH_2NA^1A^2$, $-CONH_2$, $-CONHCH_2CH_2CH_2OH$, $CONHCH_2CH_2N(C_{(1-4)}\text{alkyl})_2$, $-NHCONH_2$, $-NHCONHCH_2CH_2OH$, $-NHCOCONH_2$,

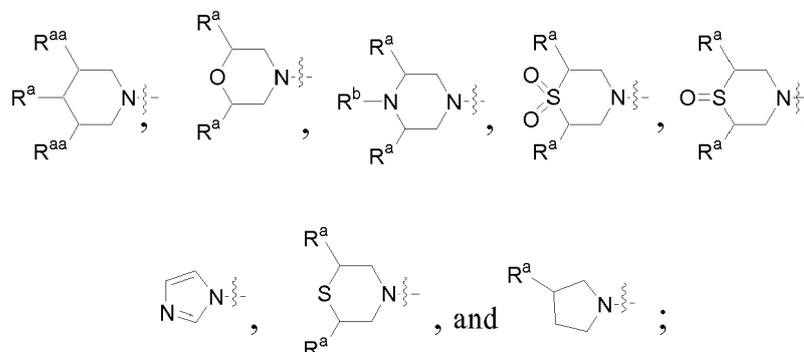
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$-NR_aCH_2CH_2NA^1A^2$, CO_2R^a , pyridyl, $-OCH_2CH_2OR^a$, $-OCH_2CH_2OCH_2CH_2NA^1A^2$,
 $OCH_2CH_2NA^1CH_2CH_2OR^a$, $-NA^1CH_2CH_2OCH_2CH_2OR^a$, $-OCOR^a$, or $-CH_2OCOCH_3$;

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

A^2 is $-C_{(1-4)}$ alkyl, $-CH_2CH_2OR^a$, $-COR^a$, $-CH_2CH_2SC_{(1-4)}$ alkyl, $-CH_2CH_2SOC_{(1-4)}$ alkyl, pyridyl,
 $-CH_2CH_2OCH_2CH_2OR^a$ 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;

R^b is H, $-C_{(1-4)}$ alkyl, alkoxyether, $-C(O)C_{(1-4)}$ alkyl, or $-CH_2C(O)C_{(14)}$ alkyl; and

R^3 and R^{4a} are independently $-CH_2OH$, $-OCH_3$, $-CH_2OCH_3$, $-CO_2H$, $-CO_2C_{(14)}$ alkyl, $OC(O)C_{(1-4)}$ alkyl, or $-OH$;

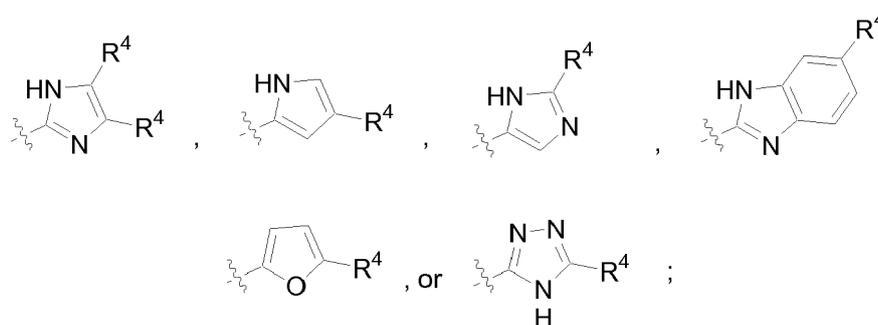
and solvates, hydrates, tautomers, and pharmaceutically acceptable salts thereof

[0024] Preferred compounds of Formula I are those wherein

W is substituted with one $-CN$.

[0025] Other preferred compounds of Formula I are those wherein:

Wis



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 , $CONR^eR^f$, $C\equiv CR^g$, or CN ;

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

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

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

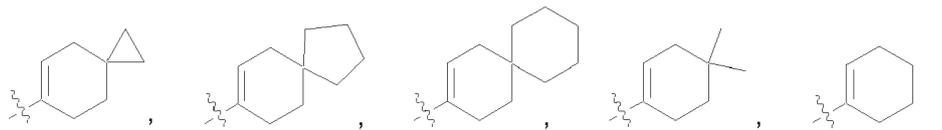
R^g is H, $-CH_2OH$, or $-$

CH_2CH_2OH ;

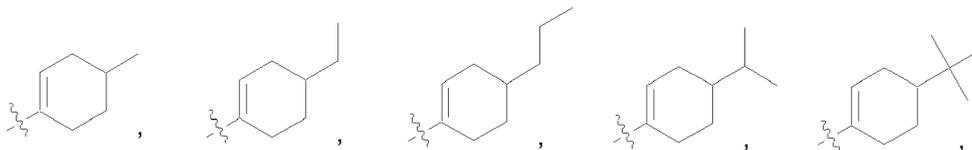
R^2 is

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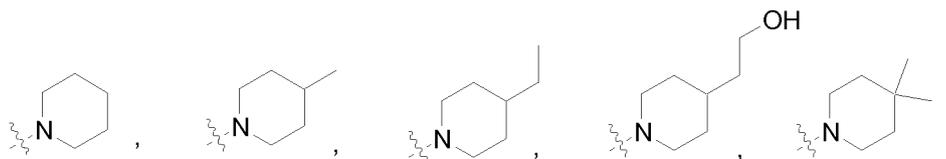
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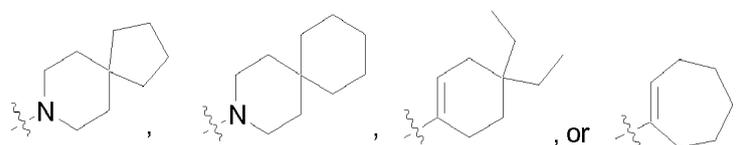


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Z is H, F, or CH₃;

J is CH, or N;

X is -C₍₁₋₆₎alkylR¹, alkenyl, -CH=CH-CO₂R^a, -C₍₁₋₄₎alkylR³R^{4a}, or -CH₂-heteroaryl-C₍₁₄₎alkyl-R¹;

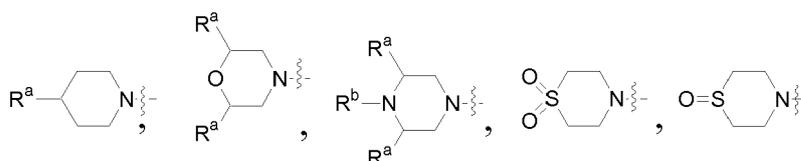
wherein:

R¹ is -CN, -SO₂NA¹A², -SO₂R³, -SCH₂CH₂NA¹A², -SOCH₂CH₂NA¹A², -SO₂CH₂CH₂NA¹A², -OC₍₁₋₄₎alkylNA¹A², -NA¹A², -NSO₂CH₃, -NCOCH₃, -CONH₂, -CONHCH₂CH₂CH₂OH, CONHCH₂CH₂N(C₍₁₋₄₎alkyl)₂, -NHCONH₂, -NHCONHCH₂CH₂OH, -NHCOCNH₂, -NR_aCH₂CH₂NA¹A², CO₂R^a, pyridyl, -OCOCH₃, or -CH₂OCOCH₃;

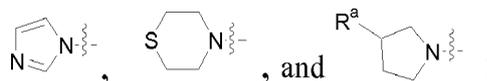
A¹ is H or -C₍₁₋₄₎alkyl;

A² is -C₍₁₋₄₎alkyl, -CH₂CH₂OR^a, -COR^a, -CH₂CH₂SC₍₁₋₄₎alkyl, -CH₂CH₂SOC₍₁₋₄₎alkyl, pyridyl, or -CH₂CH₂SO₂C₍₁₋₄₎alkyl; alternatively, A¹ and A² may be taken together with their attached nitrogen to form a heterocyclic ring selected from the following:

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wherein:

R³ is H or C₍₁₋₄₎alkyl;

R^b is H, -C₍₁₋₄₎alkyl, alkoxyether, -C(O)C₍₁₋₄₎alkyl, or -CH₂C(O)C₍₁₄₎alkyl; and

55

R³ and R^{4a} are independently -CH₂OH, -OCH₃, -CH₂OCH₃, -CO₂H, -CO₂C₍₁₋₄₎alkyl, OC(O)C₍₁₋₄₎alkyl, or -OH; and solvates, hydrates, tautomers and pharmaceutically acceptable salts thereof.

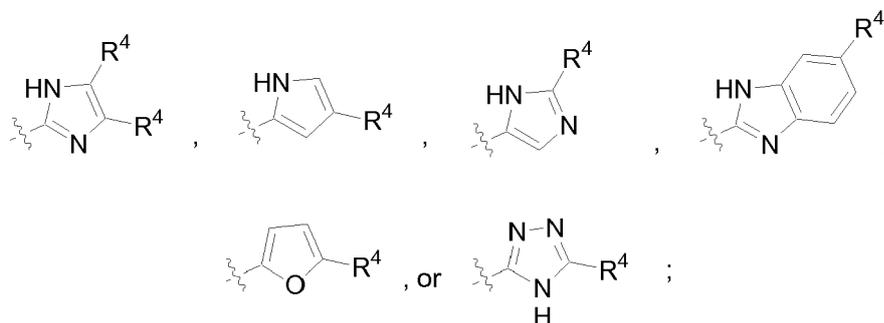
[0026] Other preferred compounds of Formula I are those wherein:

Wis

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wherein each R⁴ is independently H, F, Cl, Br, I, OH, OCH₃, OCH₂CH₃, SC₍₁₋₄₎alkyl, SOC₍₁₋₄₎alkyl, SO₂C₍₁₋₄₎alkyl, -C₍₁₋₃₎alkyl, CO₂R^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, -CH₂OH, or -CH₂CH₂OH;

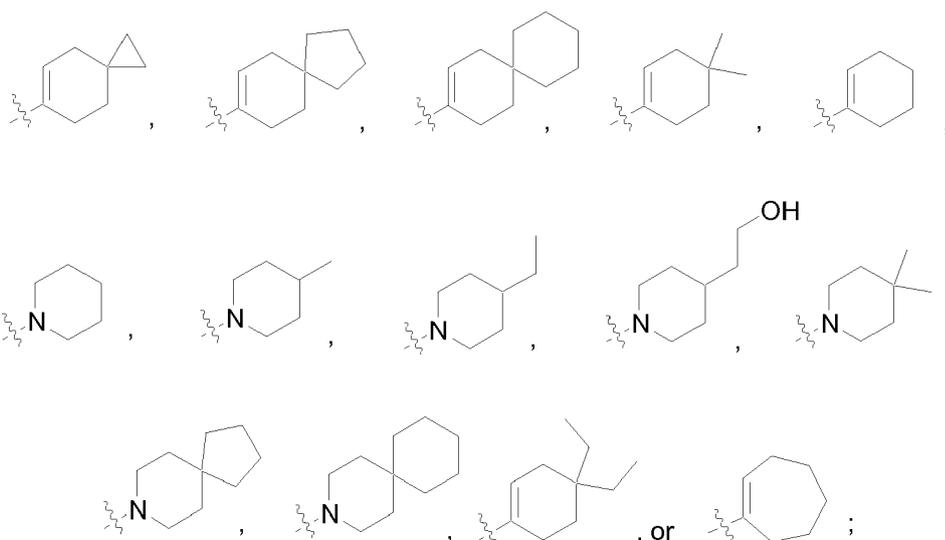
R² is

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Z is H, F, or CH₃;

J is CH, or N;

X is -C₍₁₋₅₎alkylR¹, alkenyl, -CH=CH-CO₂R^a, -C₍₁₋₄₎alkylR³R^{4a}, or -CH₂-heteroaryl-C₍₁₄₎alkyl-R¹ wherein:

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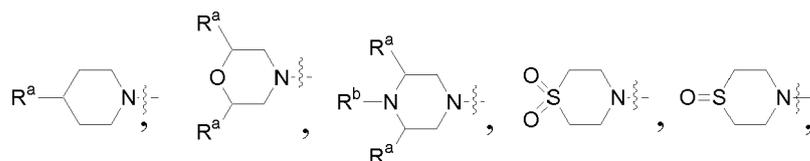
R¹ is -CN, -SO₂NA¹A², -SO₂R^a, -SCH₂CH₂NA¹A², -SOCH₂CH₂NA¹A², -SO₂CH₂CH₂NA¹A², -OC₍₁₋₄₎alkylNA¹A², -NA¹A², -NSO₂CH₃, -NCOCH₃, -CONH₂, -CONHCH₂CH₂CH₂OH, CONHCH₂CH₂N(C₍₁₋₄₎alkyl)₂, -NHCONH₂, -NHCONHCH₂CH₂OH, -NHCOCNH₂, -NR_aCH₂CH₂NA¹A², CO₂R^a, pyridyl, -OCOCH₃, or -CH₂OCOCH₃;

A¹ is H or -C₍₁₋₄₎alkyl;

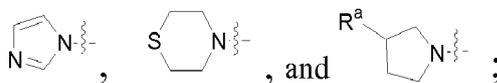
A² is -C₍₁₋₄₎alkyl, -CH₂CH₂OR^a, -COR^a, -CH₂CH₂SC₍₁₋₄₎alkyl, -CH₂CH₂SOC₍₁₋₄₎alkyl, pyridyl, or -CH₂CH₂SO₂C₍₁₋₄₎alkyl; alternatively, A¹ and A² may be taken together with their attached nitrogen to form a heterocyclic ring selected from the following:

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wherein:

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R^a is H or C₍₁₋₄₎alkyl;

R^b is H, -C₍₁₋₄₎alkyl, alkoxyether, -C(O)C₍₁₋₄₎alkyl, or -CH₂C(O) - C₍₁₋₄₎alkyl; and

R³ and R^{4a} are independently -CH₂OH, -OCH₃, -CH₂OCH₃, -CO₂H, -CO₂C₍₁₋₄₎alkyl, OC(O)C₍₁₋₄₎alkyl, or -OH;

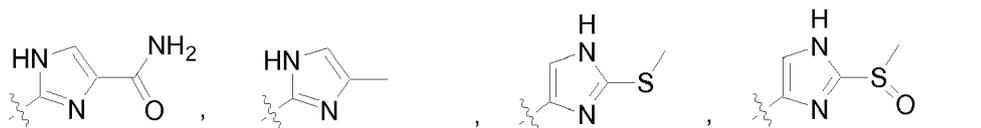
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and solvates, hydrates, tautomers and pharmaceutically acceptable salts thereof.

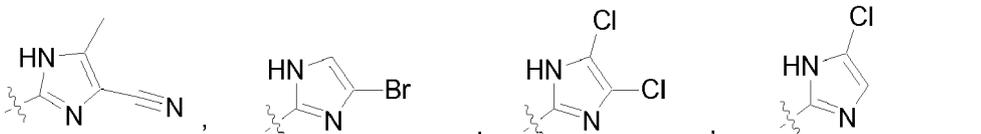
[0027] Other preferred compounds of Formula I are those wherein:

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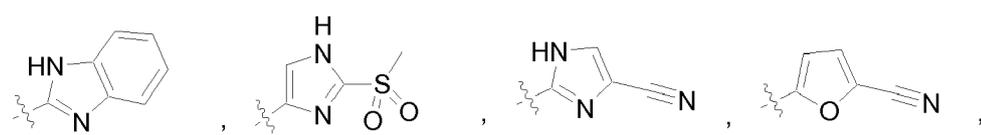
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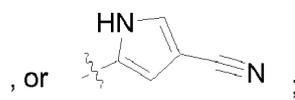


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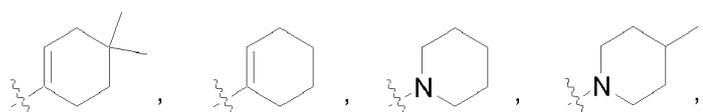
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R² is

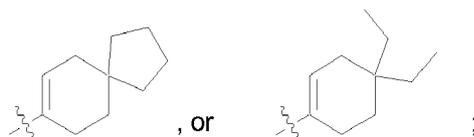
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Z is H;

J is CH, or N;

X is $-C_{(1-5)}$ alkylR¹, $-\text{CH}=\text{CH}-\text{CO}_2\text{H}$ wherein said $\text{CH}=\text{CH}$ bond has *E* stereochemistry, $-C_{(1-4)}$ alkylR³R^{4a}, or propenyl; wherein:

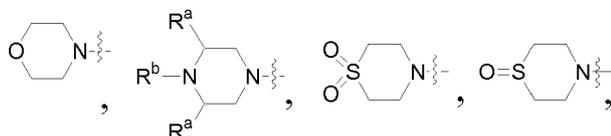
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R¹ is $-\text{SO}_2\text{NA}^1\text{A}^2$, $-\text{OC}_{(1-4)}\text{alkylNA}^1\text{A}^2$, NA^1A^2 , $\text{NHCH}_2\text{CH}_2\text{NA}^1\text{A}^2$, NHSO_2CH_3 , NCOCH_3 , CONH_2 , $\text{CONHCH}_2\text{CH}_2\text{CH}_2\text{OH}$, $\text{CONHCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, NHCONH_2 , $\text{NHCONHCH}_2\text{CH}_2\text{OH}$, NHCOCONH_2 , CO_2R^a , or pyridyl;

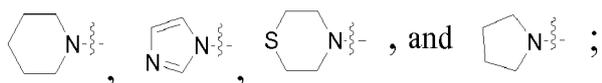
A¹ is H or $-C_{(1-4)}$ alkyl;

A² is $-C_{(1-4)}$ alkyl, $-\text{CH}_2\text{CH}_2\text{OR}^a$, $-\text{COCH}_3$, $-\text{CH}_2\text{CH}_2\text{SC}_{(1-4)}\text{alkyl}$, pyridyl, or $-\text{CH}_2\text{CH}_2\text{SO}_2\text{C}_{(1-4)}\text{alkyl}$; alternatively, A¹ and A² may be taken together with their attached nitrogen to form a heterocyclic ring selected from the following:

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wherein:

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

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

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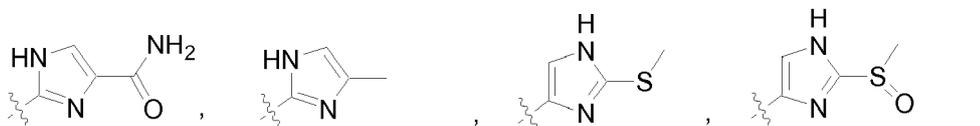
R³ and R^{4a} are independently $-\text{OCH}_3$, $-\text{CH}_2\text{OCH}_3$, $-\text{CO}_2\text{H}$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{OH}$; and solvates, hydrates, tautomers and pharmaceutically acceptable salts thereof.

[0028] Other preferred compounds of Formula I are those wherein:

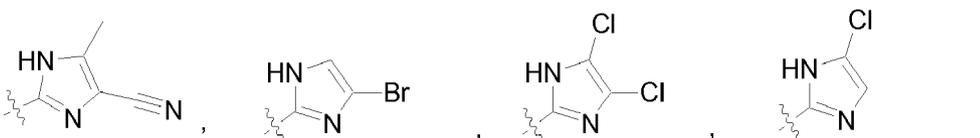
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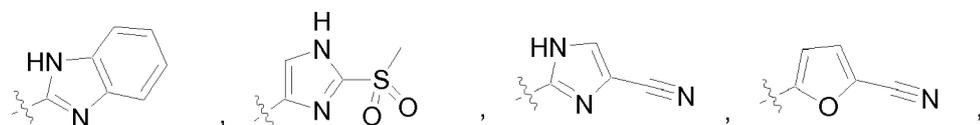
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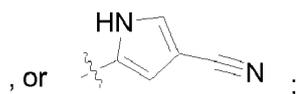
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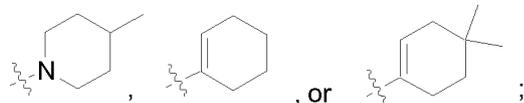
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R² is

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Z is H;

J is CH, or N;

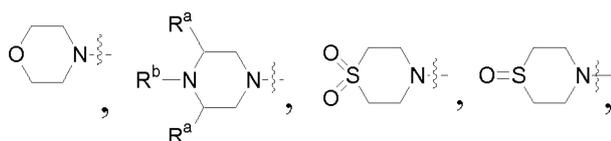
15 X is -CH₂R¹, -CH₂CH₂R¹, -C(CH₃)₂R¹, -CH=CH-CO₂H wherein said CH=CH bond has *E* stereochemistry, -C₍₁₋₄₎alkylR³R^{4a}, or propenyl; wherein:

20 R¹ is -SO₂NA¹A², -OCH₂CH₂NA¹A², NA¹A², NHCH₂CH₂NA¹A², NHSO₂CH₃, NCOCH₃, CONH₂, CONHCH₂CH₂CH₂OH, CONHCH₂CH₂N(CH₃)₂, NHCONH₂, NHCONHCH₂CH₂OH, NHCOCONH₂, or CO₂R^a;

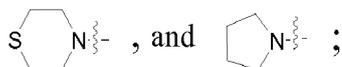
A¹ is H or -C₍₁₋₄₎alkyl;

A² is -C₍₁₋₄₎alkyl, -CH₂CH₂OCH₃, -CH₂CH₂SCH₃, or -CH₂CH₂SO₂CH₃; alternatively, A¹ and A² may be taken together with their attached nitrogen to form a heterocyclic ring selected from the following:

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wherein:

R³ is H, CH₃, or CH₂CH₃;

R^b is H, or CH₃; and

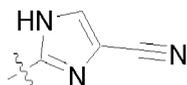
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R³ and R^{4a} are independently, -OCH₃, -CH₂OCH₃, -CO₂H, -OC(O)CH₃, or -OH; and solvates, hydrates, tautomers and pharmaceutically acceptable salts thereof.

[0029] Yet another embodiment is the compounds of Examples 1 to 122, solvates, hydrates, tautomers and pharmaceutically acceptable salts of these compounds, and any combination thereof.

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[0030] Another embodiment is compounds of Formula I wherein W is



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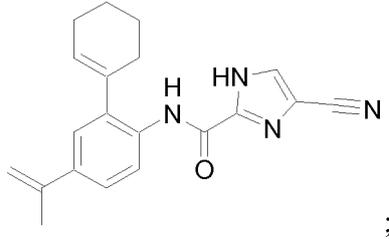
[0031] Still another embodiment is compounds selected from the group consisting of:

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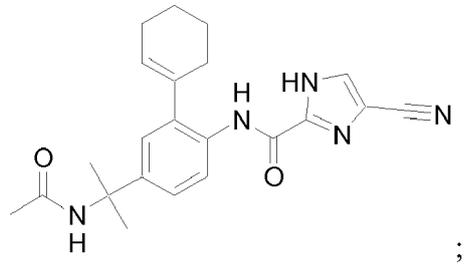


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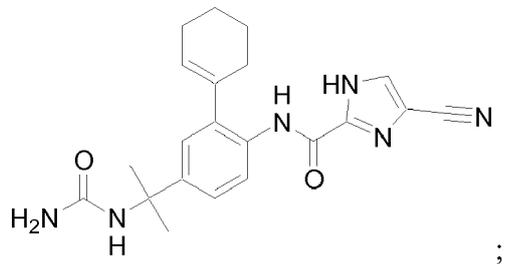
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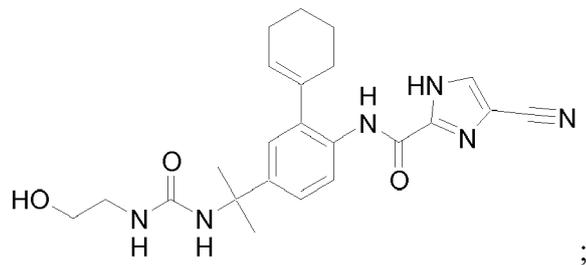
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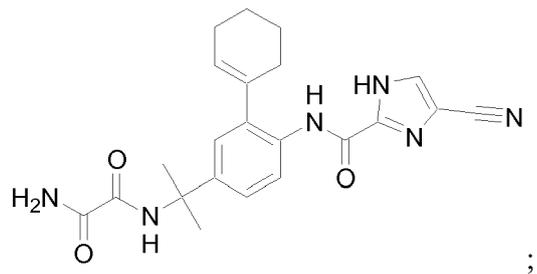
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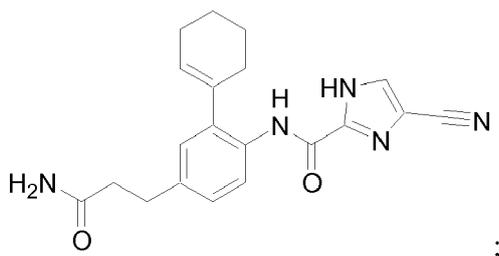
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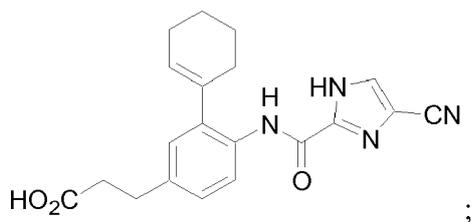


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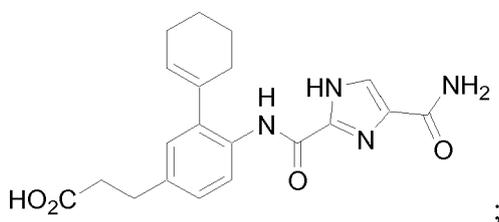


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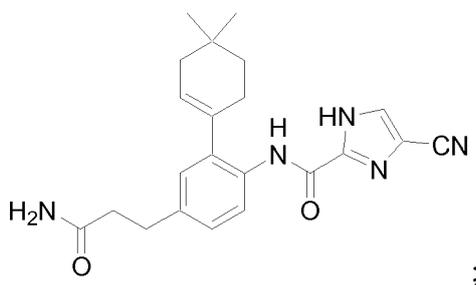
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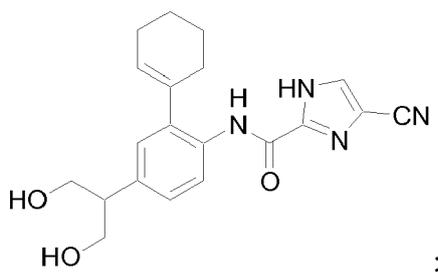
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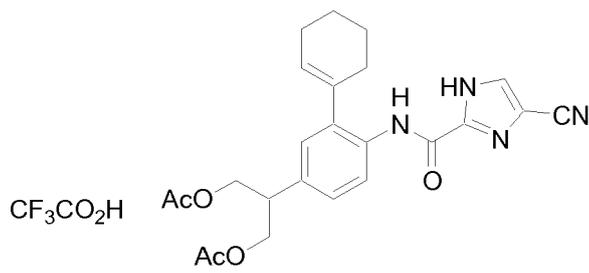
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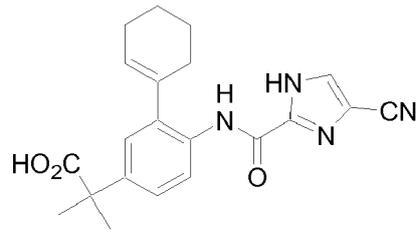
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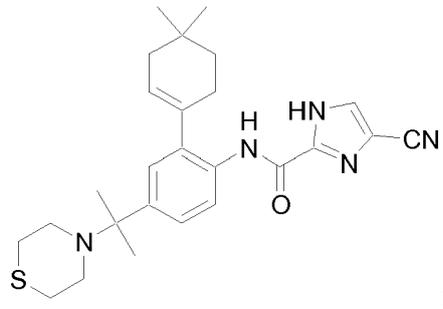


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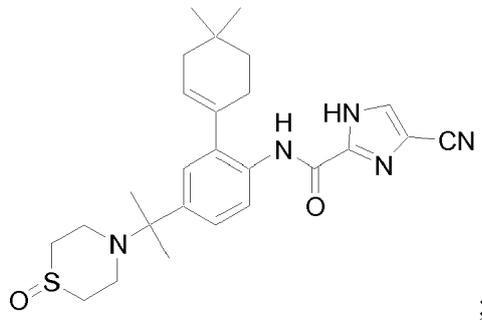


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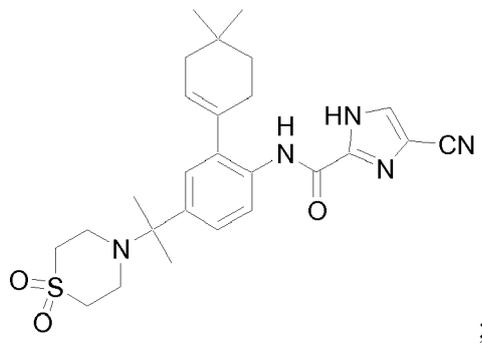
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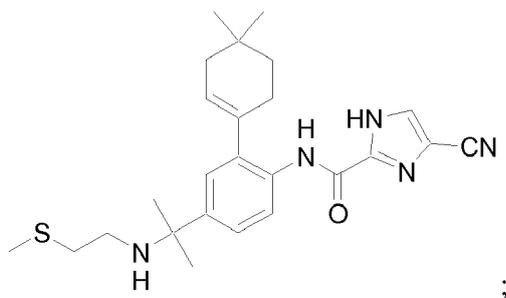
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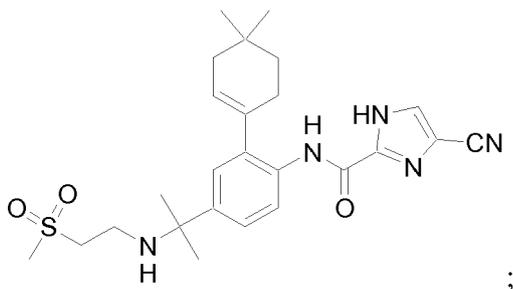
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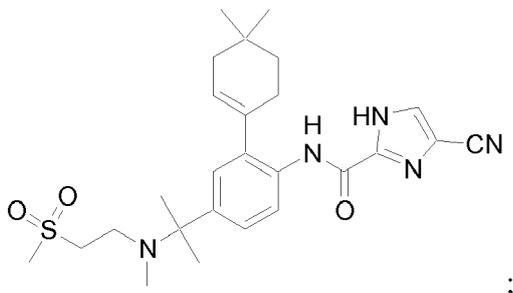
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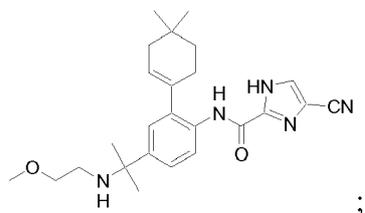
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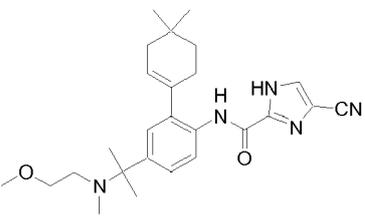
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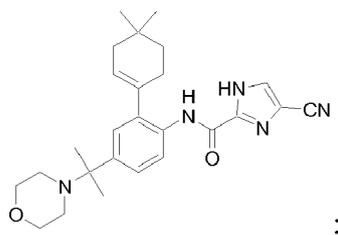
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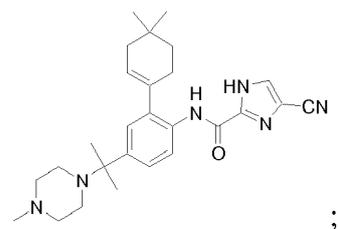
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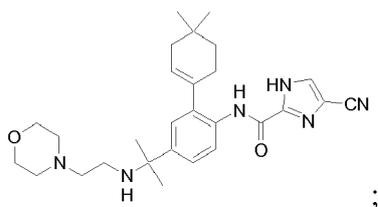


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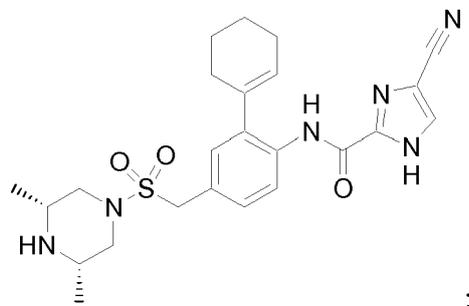
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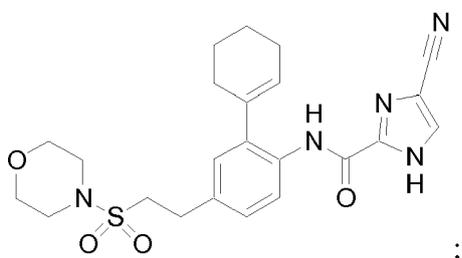


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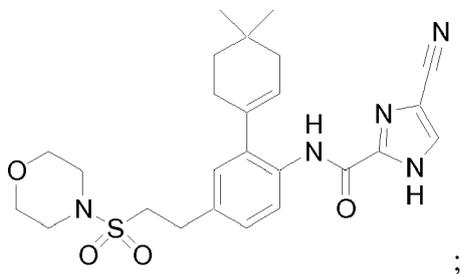
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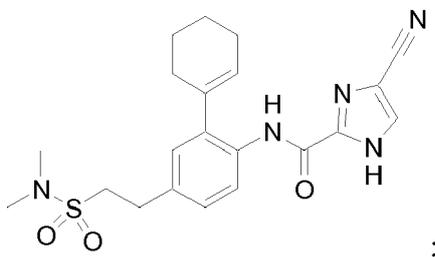
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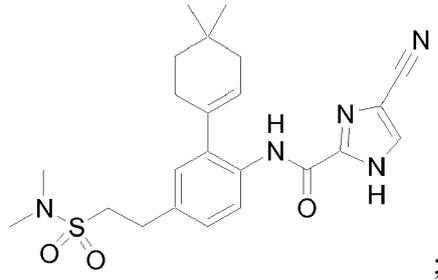
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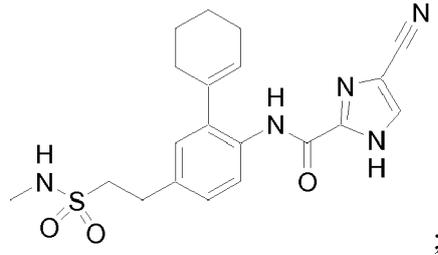
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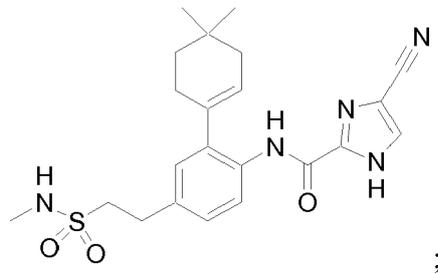


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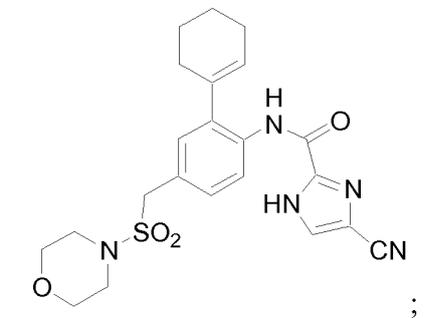
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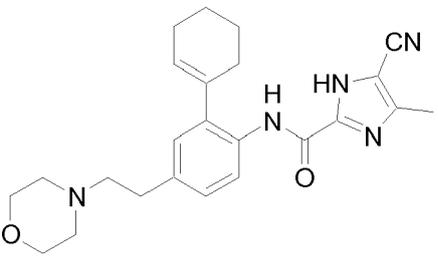
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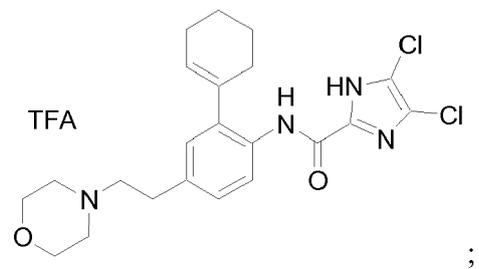
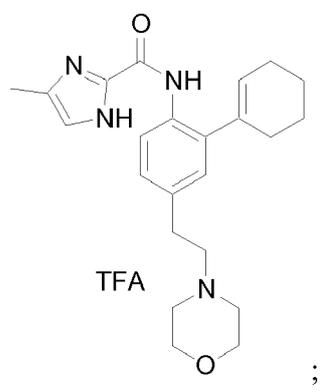
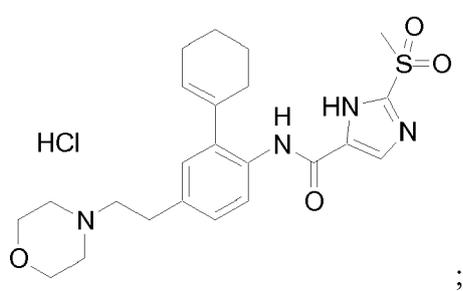
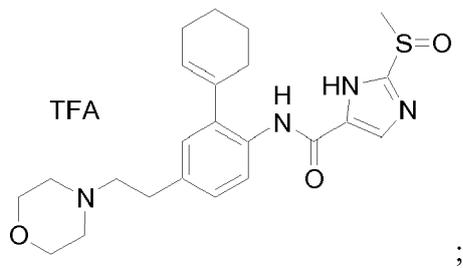
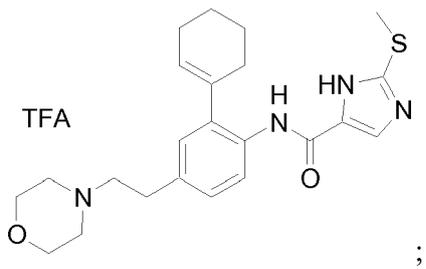


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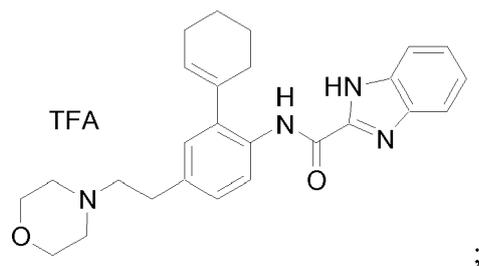
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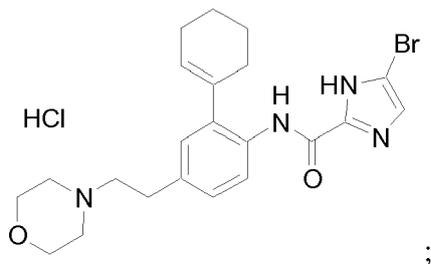


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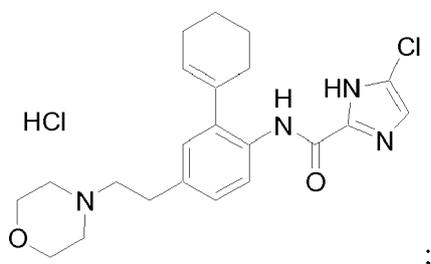
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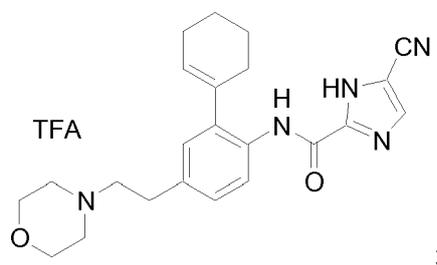
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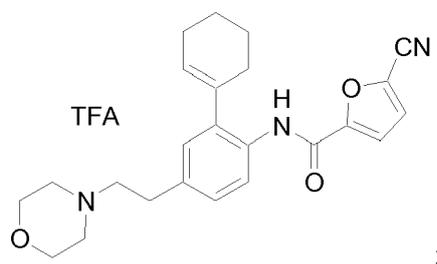
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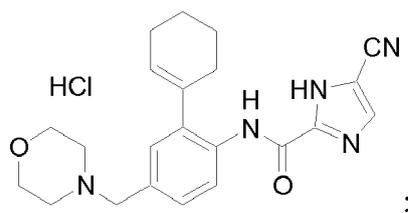
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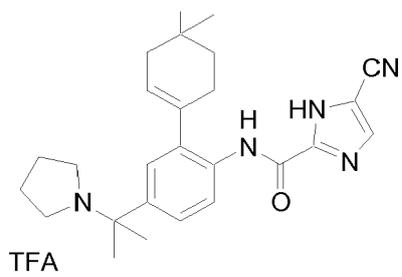


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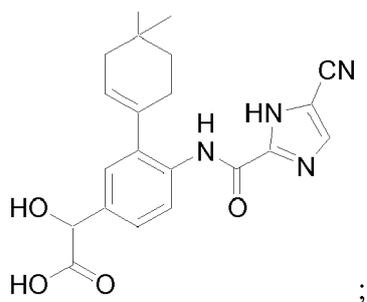


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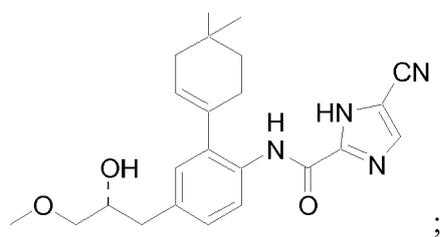
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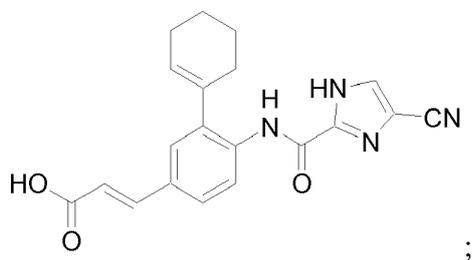
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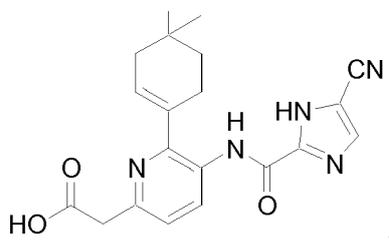
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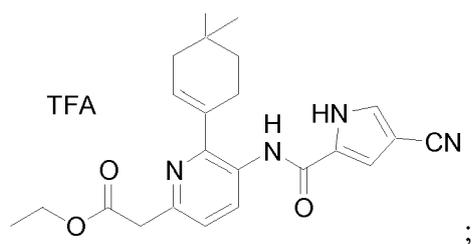
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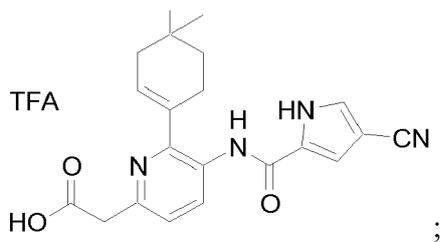


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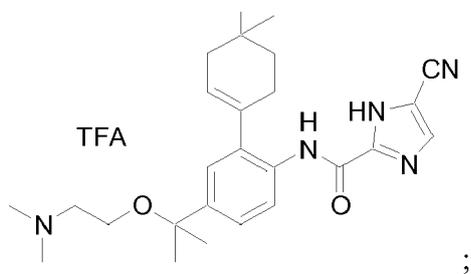
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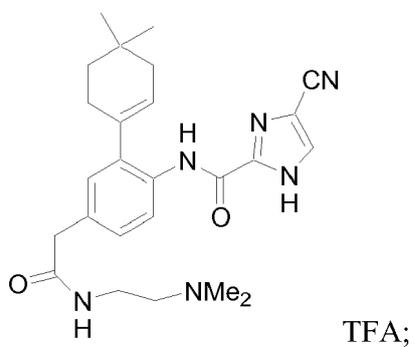


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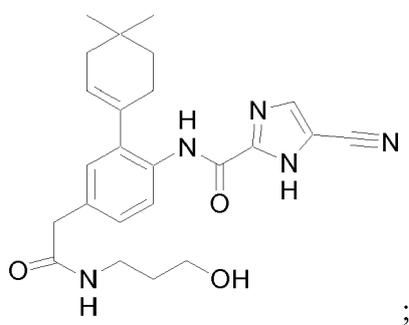
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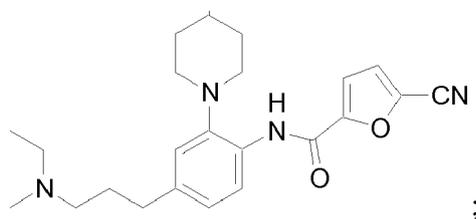
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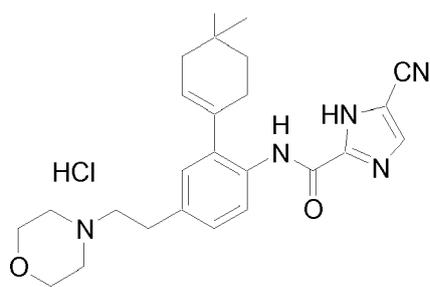
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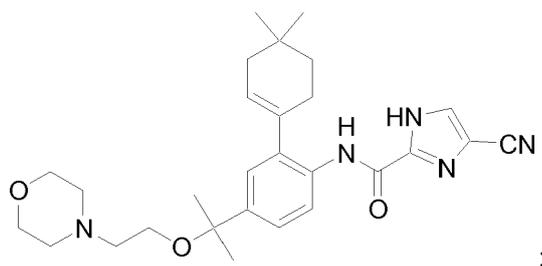


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and solvates, hydrates, tautomers and pharmaceutically acceptable salts thereof. The compounds of this embodiment are in Examples 1-55, and 60.

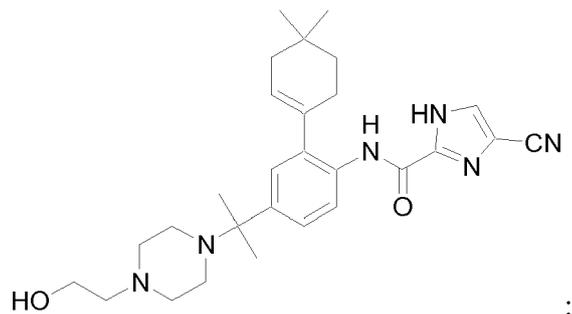
[0032] Another embodiment of the invention is a compound selected from the group consisting of:

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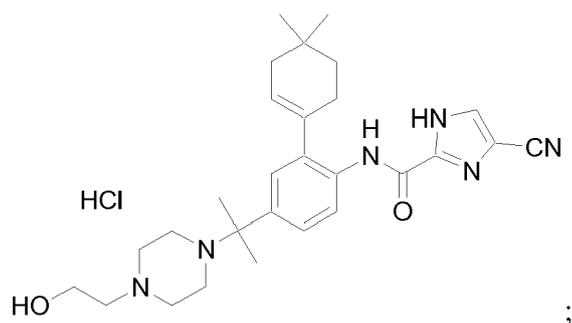
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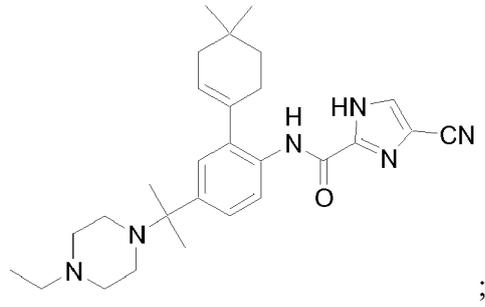
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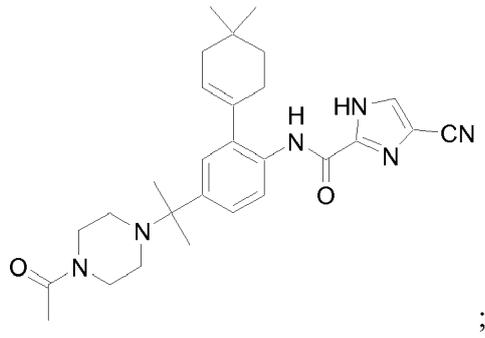
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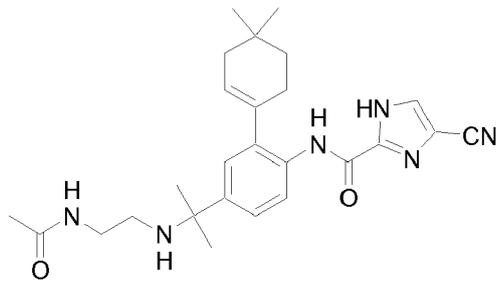
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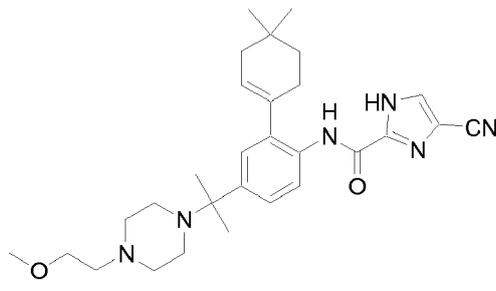
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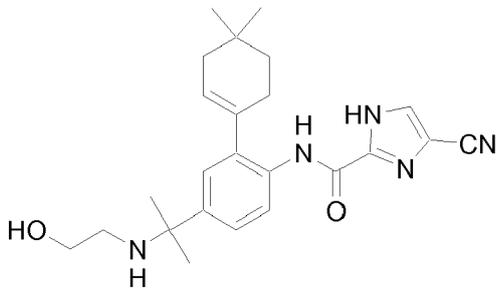
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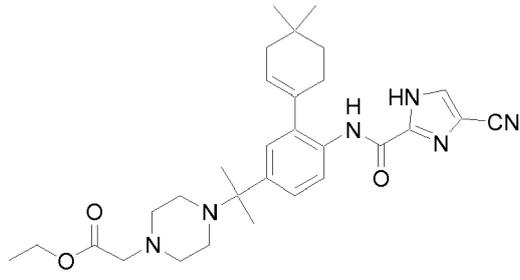
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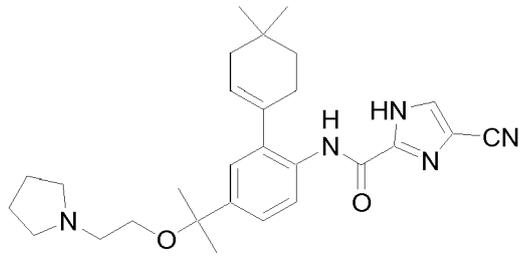
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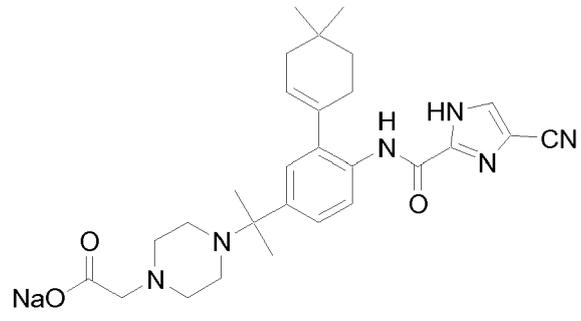
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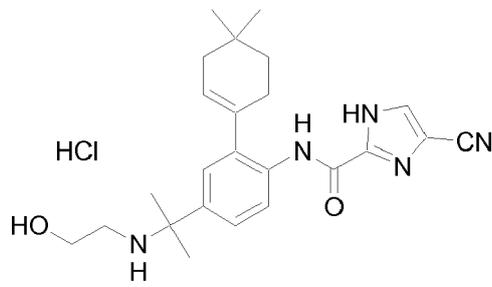
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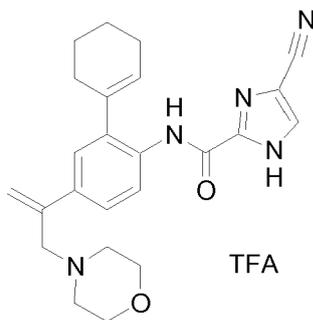
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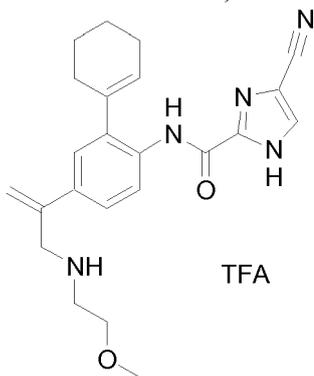
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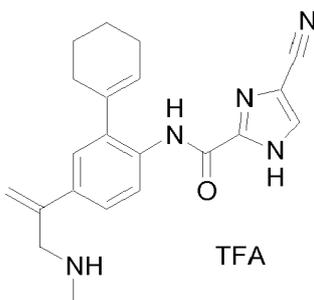


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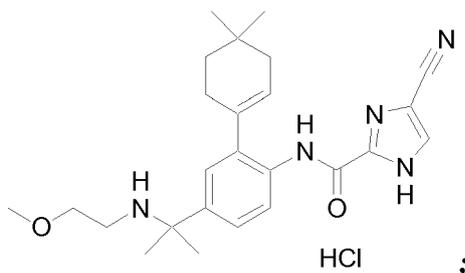
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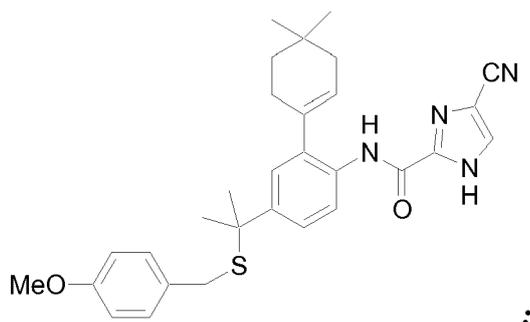
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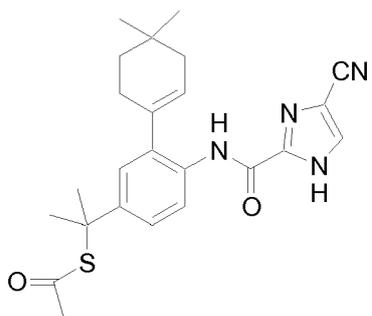
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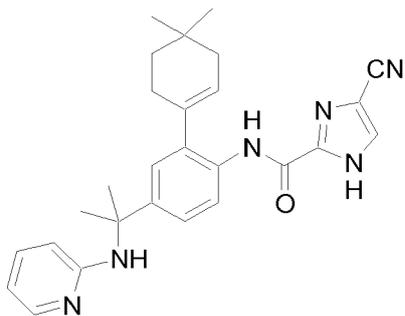
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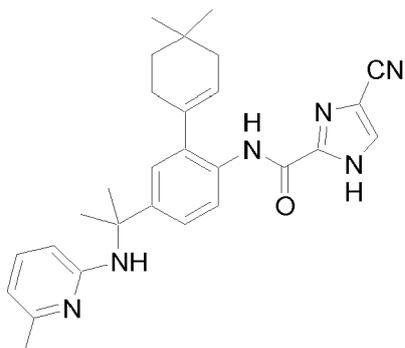
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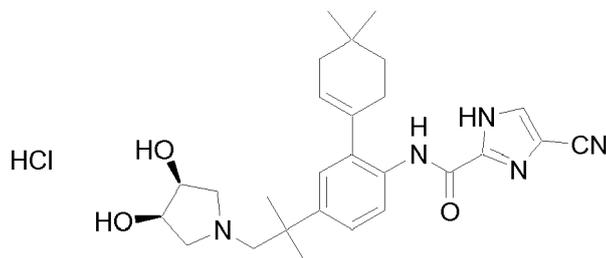
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and solvates, hydrates, tautomers and pharmaceutically acceptable salts thereof. The compounds of this embodiment are in Examples 61-80.

[0033] Another embodiment is a compound selected from the group consisting of:

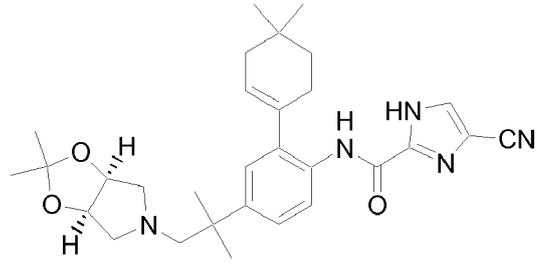
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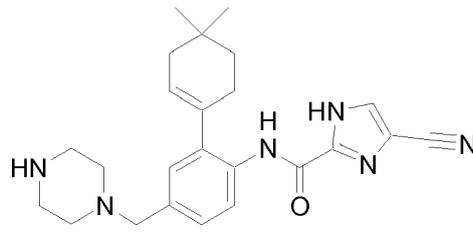
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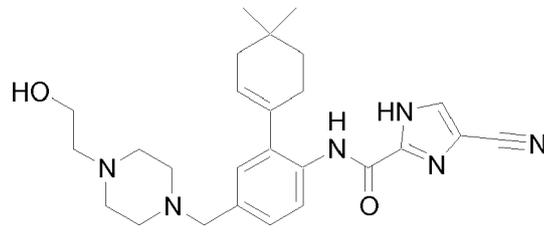
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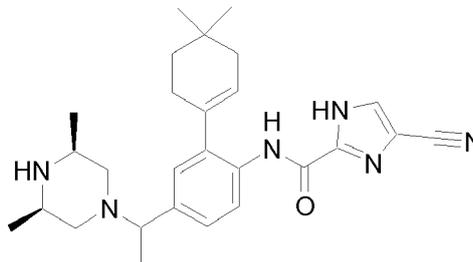
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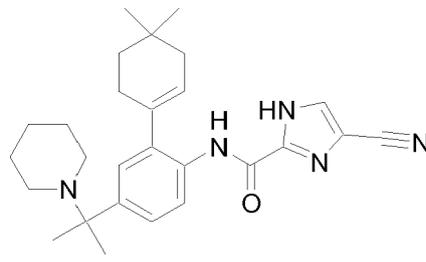
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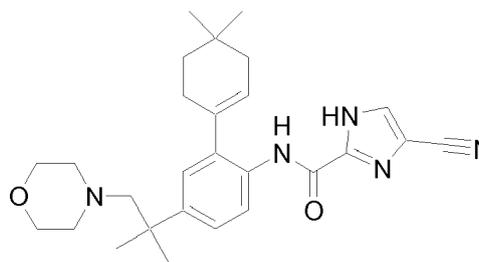
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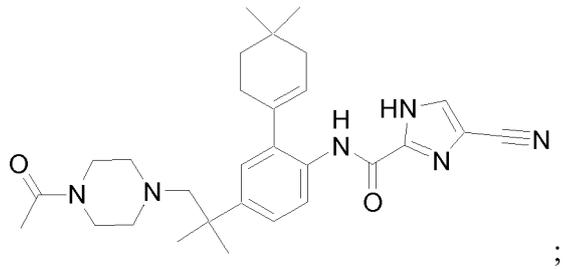


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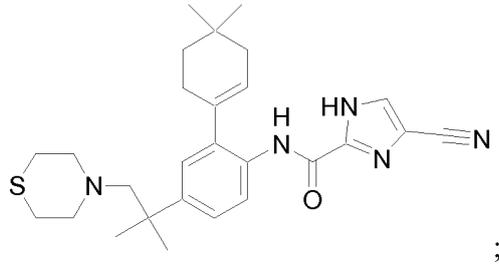
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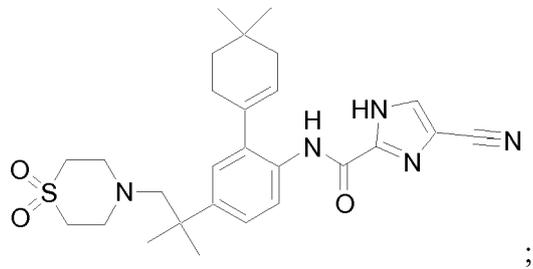


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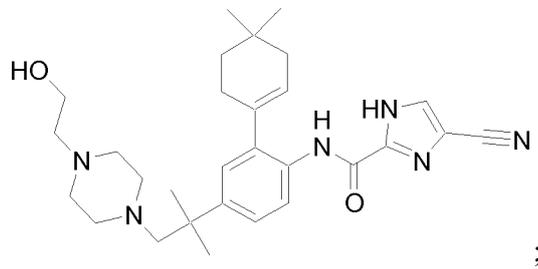
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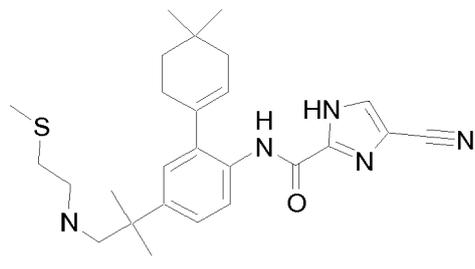
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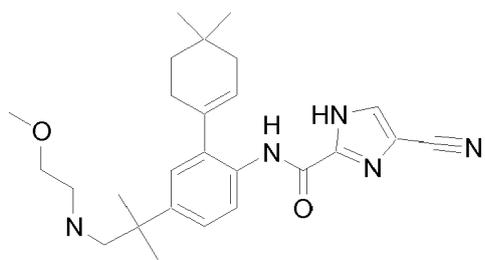


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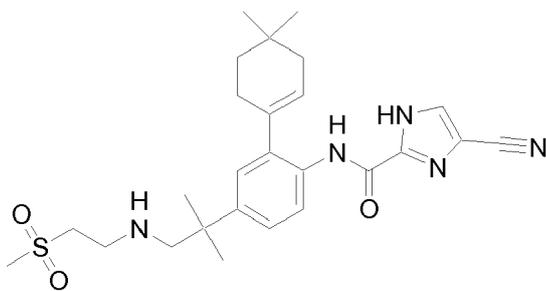
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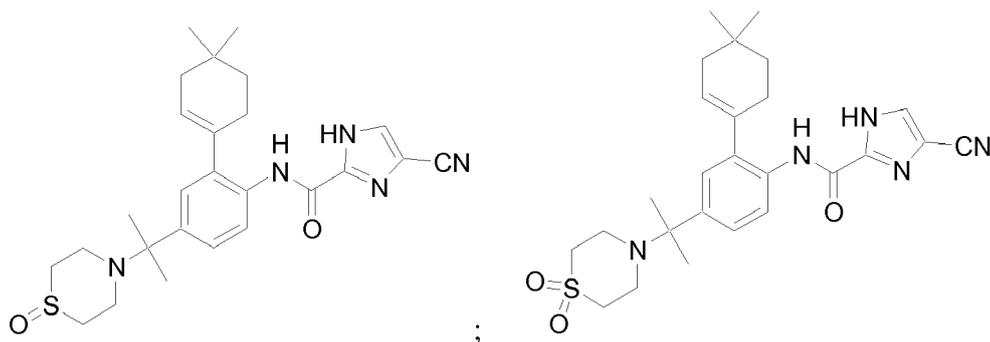
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and solvates, hydrates, tautomers and pharmaceutically acceptable salts thereof. There are the compounds of examples 138-151.

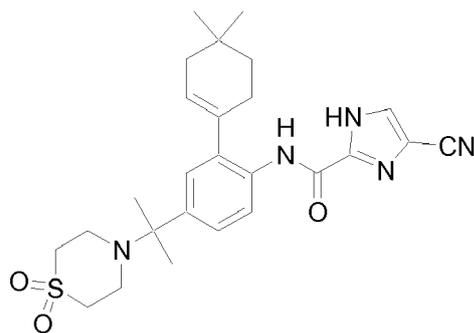
[0034] Yet another embodiment is a compound selected from the group consisting of:

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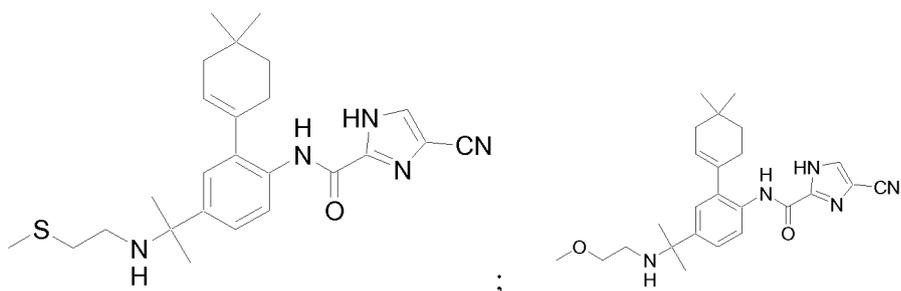
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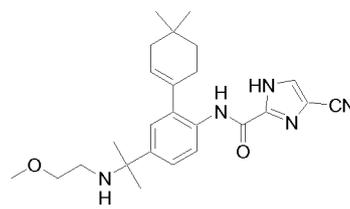
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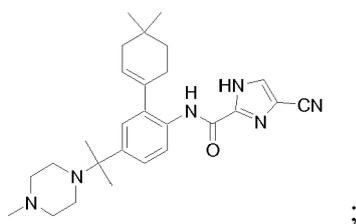
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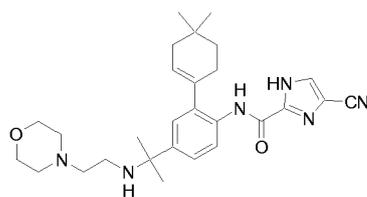
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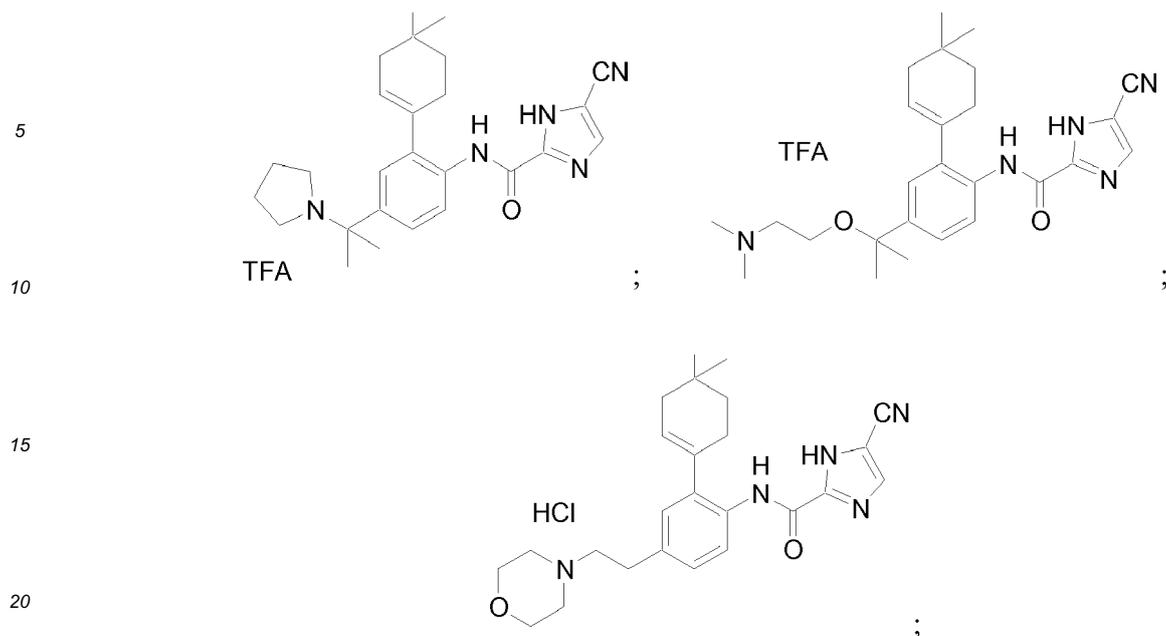
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and solvates, hydrates, tautomers and pharmaceutically acceptable salts thereof. These are the compounds of Examples 15, 16, 17, 20, 23, 24, 45, 52, and 60.

[0035] The invention also relates to methods of inhibiting protein tyrosine kinase activity in a mammal by administration of a therapeutically effective amount of at least one compound of Formula I. A preferred tyrosine kinase is c-fms.

[0036] The invention is considered to include the enantiomeric, diastereomeric and tautomeric forms of all compounds of Formula I as well as their racemic mixtures. In addition, some of the compounds represented by Formulae I may be prodrugs, *i.e.*, derivatives of an acting drug that possess superior delivery capabilities and therapeutic value as compared to the acting drug. Prodrugs are transformed into active drugs by *in vivo* enzymatic or chemical processes.

I. Definitions

[0037] The term "alkyl" refers to both linear and branched chain radicals of up to 12 carbon atoms, preferably up to 6 carbon atoms, unless otherwise indicated, and includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, hexyl, isohexyl, heptyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl and dodecyl.

[0038] The term "hydroxyalkyl" refers to both linear and branched chain radicals of up to 6 carbon atoms, in which one hydrogen atom has been replaced with an OH group.

[0039] The term "hydroxyalkylamino" refers to an hydroxyalkyl group in which one hydrogen atom from the carbon chain has been replaced with an amino group, wherein the nitrogen is the point of attachment to the rest of the molecule.

[0040] The term "cycloalkyl" refers to a saturated or partially unsaturated ring composed of from 3 to 8 carbon atoms. Up to four alkyl substituents may optionally be present on the ring. Examples include cyclopropyl, 1,1-dimethyl cyclobutyl, 1,2,3-trimethylcyclopentyl, cyclohexyl, cyclopentenyl, cyclohexenyl, and 4,4-dimethyl cyclohexenyl.

[0041] The term "aminoalkyl" refers to at least one primary or secondary amino group bonded to any carbon atom along an alkyl chain, wherein an alkyl group is the point of attachment to the rest of the molecule.

[0042] The term "alkylamino" refers to an amino with one alkyl substituent, wherein the amino group is the point of attachment to the rest of the molecule.

[0043] The term "dialkylamino" refers to an amino with two alkyl substituents, wherein the amino group is the point of attachment to the rest of the molecule.

[0044] The term "heteroaromatic" or "heteroaryl" refers to 5- to 7-membered mono- or 8- to 10-membered bicyclic aromatic ring systems, any ring of which may consist of from one to four heteroatoms selected from N, O or S where the nitrogen and sulfur atoms can exist in any allowed oxidation state. Examples include benzimidazolyl, benzothiazolyl, benzothienyl, benzoxazolyl, furyl, imidazolyl, isothiazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridyl, pyrimidinyl, pyrrolyl, quinolinyl, thiazolyl and thienyl.

[0045] The term "heteroatom" refers to a nitrogen atom, an oxygen atom or a sulfur atom wherein the nitrogen and sulfur atoms can exist in any allowed oxidation states.

[0046] The term "alkoxy" refers to straight or branched chain radicals of up to 12 carbon atoms, unless otherwise

indicated, bonded to an oxygen atom. Examples include methoxy, ethoxy, propoxy, isopropoxy and butoxy.

[0047] The term "aryl" refers to monocyclic or bicyclic aromatic ring systems containing from 6 to 12 carbons in the ring. Alkyl substituents may optionally be present on the ring. Examples include benzene, biphenyl and naphthalene.

[0048] The term "aralkyl" refers to a C₁₋₆ alkyl group containing an aryl substituent. Examples include benzyl, phenylethyl or 2-naphthylmethyl.

[0049] The term "sulfonyl" refers to the group -S(O)₂R_a, where R_a is hydrogen, alkyl, cycloalkyl, haloalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl. A "sulfonylating agent" adds the -S(O)₂R_a group to a molecule.

[0050] The term "spiro-substituted cycloalkenyl" refers to a pair of cycloalkyl rings that share a single carbon atom and wherein at least one of the rings is partially unsaturated, for example:



[0051] The term "spiro-substituted heterocyclyl" refers to a heterocyclyl and cycloalkyl ring that share a single carbon atom, for example:



II. Therapeutic Uses

[0052] The compounds of Formula I represent novel potent inhibitors of protein tyrosine kinases, such as c-fms, and may be useful in the prevention and treatment of disorders resulting from actions of these kinases.

[0053] The invention also provides methods of inhibiting a protein tyrosine kinase comprising contacting the protein tyrosine kinase with an effective inhibitory amount of at least one of the compounds of Formula I. A preferred tyrosine kinase is c-fms. The compounds of the present invention are also inhibitors of FLT3 tyrosine kinase activity. In one embodiment of inhibiting a protein tyrosine kinase, at least one of the compounds of Formula I is combined with a known tyrosine kinase inhibitor.

[0054] In various embodiments of the invention, the protein tyrosine kinases inhibited by the compounds of Formula I are located in cells, in a mammal or *in vitro*. In the case of mammals, which includes humans, a therapeutically effective amount of a pharmaceutically acceptable form of at least one of the compounds of Formula I is administered.

[0055] The invention further provides methods of treating cancer in mammals, including humans, by administration of a therapeutically effective amount of a pharmaceutically acceptable composition of least one compound of Formula I. Exemplary cancers include, but are not limited to, acute myeloid leukemia, acute lymphocytic leukemia, ovarian cancer, uterine cancer, breast cancer, colon cancer, stomach cancer, hairy cell leukemia and non-small lung carcinoma. The invention also provides methods of treating certain precancerous lesions including myelofibrosis. In one embodiment of the invention, an effective amount of at least one compound of Formula I is administered in combination with an effective amount of a chemotherapeutic agent.

[0056] The invention further provides methods of treating and of preventing metastasis arising from cancers that include, but are not limited to, ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, and hairy cell leukemia.

[0057] The invention further provides methods for the treatment 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 as occurs frequently in cancers including, but not limited to, breast cancer, prostate cancer, and colon cancer.

[0058] The invention also provides methods of treating pain, in particular skeletal pain caused by tumor metastasis or osteoarthritis, as well as visceral, inflammatory, and neurogenic pain.

[0059] The invention also provides methods of treating cardiovascular, inflammatory, and autoimmune diseases in mammals, including humans, by administration of a therapeutically effective amount of a pharmaceutically acceptable form of at least one of the compounds of Formula I. Examples of diseases with an inflammatory component include 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. These may be effectively treated with compounds of this invention. Other diseases that may be effectively treated include, but are not limited to atherosclerosis and cardiac hypertrophy.

[0060] Autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis and other forms of inflam-

matory arthritis, psoriasis, Sjogren's syndrome, multiple sclerosis, or uveitis, can also be treated with compounds of this invention.

5 [0061] The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation, prevention, treatment, or the delay of the onset or progression of the symptoms of the disease or disorder being treated.

10 [0062] When employed as protein tyrosine kinase inhibitors, the compounds of the invention may be administered in an effective amount within the dosage range of about 0.5 mg to about 10 g, preferably between about 0.5 mg to about 5 g, in single or divided daily doses. The dosage administered will be affected by factors such as the route of administration, the health, weight and age of the recipient, the frequency of the treatment and the presence of concurrent and unrelated treatments.

15 [0063] It is also apparent to one skilled in the art that the therapeutically effective dose for compounds of the present invention or a pharmaceutical composition thereof will vary according to the desired effect. Therefore, optimal dosages to be administered may be readily determined by one skilled in the art and will vary with the particular compound used, the mode of administration, the strength of the preparation, and the advancement of the disease condition. In addition, factors associated with the particular subject being treated, including subject age, weight, diet and time of administration, will result in the need to adjust the dose to an appropriate therapeutic level. The above dosages are thus exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

20 [0064] The compounds of Formula I may be formulated into pharmaceutical compositions comprising any known pharmaceutically acceptable carriers. Exemplary carriers include, but are not limited to, any suitable solvents, dispersion media, coatings, antibacterial and antifungal agents and isotonic agents. Exemplary excipients that may also be components of the formulation include fillers, binders, disintegrating agents and lubricants.

25 [0065] The pharmaceutically-acceptable salts of the compounds of Formula I include the conventional non-toxic salts or the quaternary ammonium salts which are formed from inorganic or organic acids or bases. Examples of such acid addition salts include acetate, adipate, benzoate, benzenesulfonate, citrate, camphorate, dodecylsulfate, hydrochloride, hydrobromide, lactate, maleate, methanesulfonate, nitrate, oxalate, pivalate, propionate, succinate, sulfate and tartrate. Base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamino salts and salts with amino acids such as arginine. Also, the basic nitrogen-containing groups may be quaternized with, for example, alkyl halides.

30 [0066] The pharmaceutical compositions of the invention may be administered by any means that accomplish their intended purpose. Examples include administration by parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, buccal or ocular routes. Alternatively or concurrently, administration may be by the oral route. Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, for example, water-soluble salts, acidic solutions, alkaline solutions, dextrose-water solutions, isotonic carbohydrate solutions and cyclodextrin inclusion complexes.

35 [0067] The present invention also encompasses a method of making a pharmaceutical composition comprising mixing a pharmaceutically acceptable carrier with any of the compounds of the present invention. Additionally, the present invention includes pharmaceutical compositions made by mixing a pharmaceutically acceptable carrier with any of the compounds of the present invention. As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

45 ***Polymorphs and Solvates***

[0068] Furthermore, the compounds of the present invention may have one or more polymorph or amorphous crystalline forms and as such are intended to be included in the scope of the invention. In addition, the compounds may form solvates, for example with water (i.e., hydrates) or common organic solvents. As used herein, the term "solvate" means a physical association of the compounds of the present invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. The term "solvate" is intended to encompass both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like.

50 [0069] It is intended that the present invention include within its scope solvates of the compounds of the present invention. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the means for treating, ameliorating or preventing a syndrome, disorder or disease described herein with the compounds of the present invention or a solvate thereof, which would obviously be included within the scope of the invention albeit not specifically disclosed.

Methods of Preparation

[0070]

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Scheme 1

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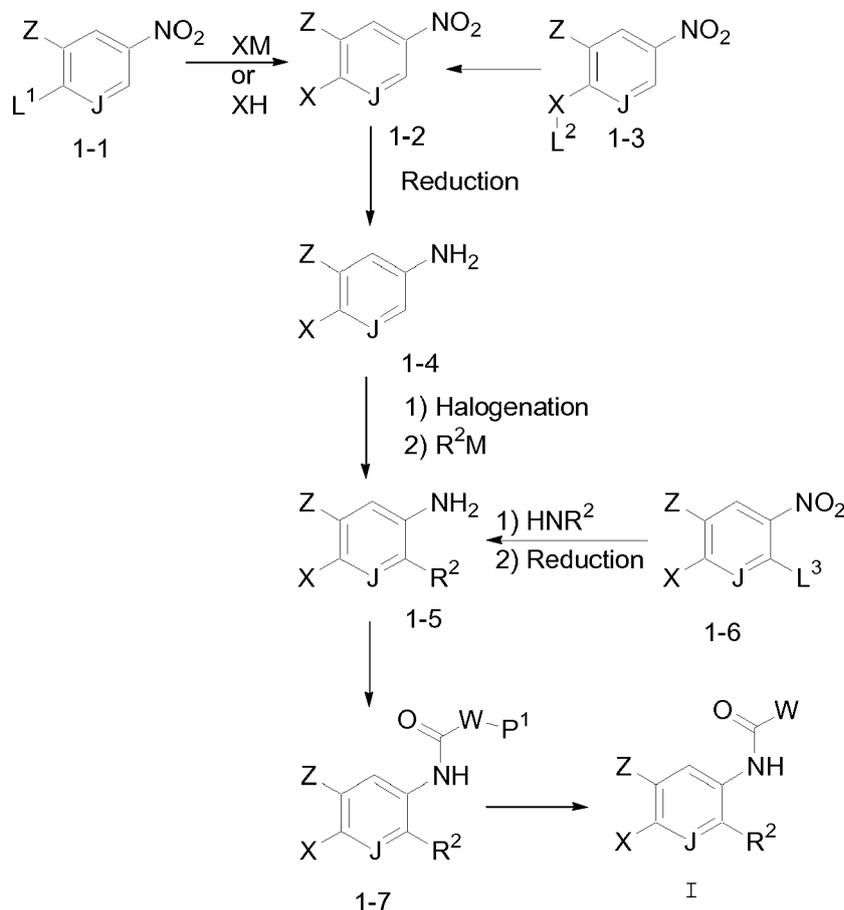
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[0071] Scheme 1 illustrates general methodology for the preparation of compounds of Formula I where X is neither CO₂H, nor -NA¹A² where A¹ is H. To illustrate the methodology of this scheme, reagents and conditions for the compounds where J is CH are defined. It is understood that where J is N, minor modifications of the reaction conditions and preferred reagents may be required.

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[0072] Anilines and aminopyridines of Formula 1-4 may be commercially available or obtained from nitro compounds of Formula 1-2 by reduction using standard synthetic methodology (see Reductions in Organic Chemistry, M. Hudlicky, Wiley, New York, 1984). The preferred conditions are catalytic hydrogenation using a palladium catalyst in a suitable solvent such as methanol or ethanol.

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[0073] In cases where the desired functionality is not present in compounds of Formula 1-2, it can be obtained from compounds of Formula 1-1 by nucleophilic aromatic substitution of leaving groups L¹ (preferably fluoro or chloro) that are activated by the nitro group with carbon nucleophiles (for example, malonate esters, where X is CH(CO₂C₍₁₋₄₎alkyl)₂) in the presence of a suitable base such as NaH. Malonate esters may then be further elaborated by, for example, hydrolysis followed by decarboxylation to acetic acid derivatives, where X is CH₂CO₂H. Additionally, when the leaving group L¹ is suitable for metal-catalyzed couplings (preferably bromo, iodo, or trifluoromethane-sulfonyloxy), a number of cross-coupling reactions, such as Heck, Stille, or Suzuki couplings, (for reviews, see N. Miyaura and A. Suzuki, Chem. Rev., 95:2457 (1995); J. K. Stille, Angew. Chem, Int. Ed. Engl., 25: 508-524 (1986); S. Braese and A. de Meijere in Metal-Catalyzed Cross-Coupling Reactions (2nd Edition), p. 217-315, A. de Meijere, F. Diederich, Eds., Wiley-VCH, Weinheim (2004); and A. Suzuki in Metal-Catalyzed Coupling Reactions, F. Deiderich, P. Stang, Eds., Wiley-VCH, Weinheim (1988)) may be performed.

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[0074] Compounds of Formula 1-2 may also be obtained from compounds of Formula 1-3 where X is a C₍₁₋₆₎alkyl by

displacement of L² (preferably iodo or bromo) with appropriate nucleophiles (for example, HNA^{1A2}) in the presence of a suitable base such as K₂CO₃, N,N-diisopropylethylamine (DIEA) or NEt₃ to obtain compounds of Formula 1-2 where, for example, X is C₍₁₋₆₎alkylINA^{1A2}.

[0075] Compounds of Formula 1-5 where R² is cycloalkyl can be obtained by ortho-halogenation, preferably bromination, of amino compounds of Formula 1-4 followed by metal-catalyzed coupling reactions with boronic acids or boronate esters (Suzuki reactions, where R²M is R²B(OH)₂ or a boronic ester) or tin reagents (Stille reactions, where R²M is R²Sn(alkyl)₃)(see above for reviews) on the intermediate halo compound. Preferred conditions for the bromination of 1-5 are N-bromosuccinimide (NBS) in a suitable solvent such as N,N-dimethylformamide (DMF), dichloromethane (DCM) or acetonitrile. Metal-catalyzed couplings, preferably Suzuki reactions, can be performed according to standard methodology, preferably in the presence of a palladium catalyst such as tetrakis(triphenylphosphine)palladium(0) (Pd(PPh₃)₄), an aqueous base such as aq. Na₂CO₃, and a suitable solvent such as toluene, ethanol, 1,4-dioxane, dimethoxyethane (DME), or DMF.

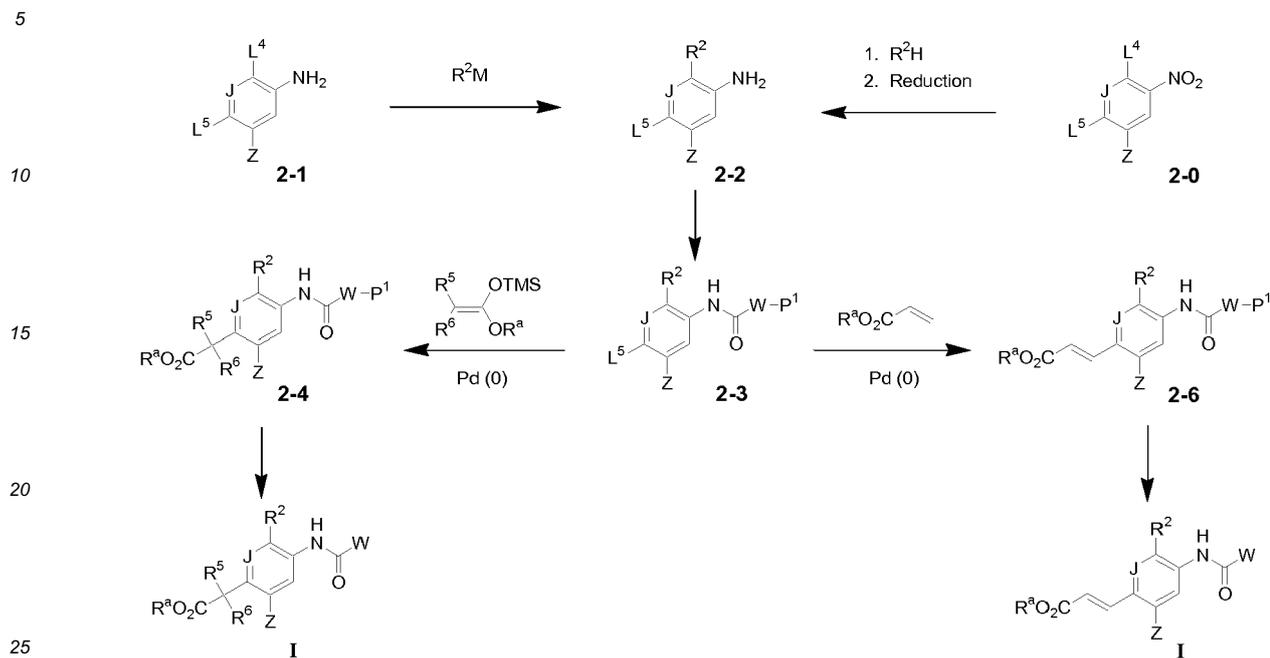
[0076] Compounds of Formula 1-5 where R² is cycloalkylamino (for example, piperidino) can be obtained by nucleophilic aromatic substitution of leaving groups L³ (preferably fluoro or chloro) from compounds of Formula 1-6 that are activated by the nitro group with cycloalkylamines (for example, piperidine) in the presence of a suitable base such as K₂CO₃, N,N-diisopropylethylamine (DIEA) or NEt₃, followed by reduction of the nitro group as described above.

[0077] The amino group in compounds of Formula 1-5 can then be coupled with a heterocyclic acid P¹-WCOOH (or a corresponding salt thereof P¹-WCOOM², where M² is Li, Na or K) where P¹ is an optional protecting group (for example 2-(trimethylsilyl)ethoxymethyl (SEM) such as when W is imidazole, triazole, pyrrole, or benzimidazole) or where P¹ is not present such as when W is furan. (For a list of protecting groups for W, see Theodora W. Greene and Peter G. M. Wuts, Protective Groups in Organic Synthesis, John Wiley and Sons, Inc., NY (1991)). The coupling can be carried out according to standard procedures for amide bond formation (for a review, see: M. Bodansky and A. Bodansky, The Practice of Peptide Synthesis, Springer-Verlag, NY (1984)) or by reaction with acid chlorides P¹-WCOCl or activated esters P¹-WCO₂R_q (where R_q is a leaving group such as pentafluorophenyl or N-succinimide) to form compounds of Formula 1-7. The preferred reaction conditions for coupling with P¹-WCOOH or P¹-WCOOM² are: when W is a furan (optional protecting group P¹ not present), oxalyl chloride in dichloromethane (DCM) with DMF as a catalyst to form the acid chloride WCOCl and then coupling in the presence of a trialkylamine such as N,N-diisopropylethylamine (DIEA); when W is a pyrrole (optional protecting group P¹ not present), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and 1-hydroxybenzotriazole (HOBt); and when W is an imidazole, pyrrole or benzimidazole (optional P¹ present) the preferred conditions are bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP) and DIEA in a solvent such as DCM or DMF.

[0078] When W in compounds of Formula 1-7 contain an optional protecting group P¹ as mentioned previously, it can be removed at this point to give compounds of Formula I. For example, when W is imidazole protected on nitrogen with a SEM group, the SEM group can be removed with either acidic reagents such as trifluoroacetic acid (TFA) or fluoride sources such as tetrabutylammonium fluoride (TBAF) (see Greene and Wuts above).

[0079] Finally it is understood that compounds of Formula I may be further derivatized. Examples of further derivatization of compounds of I include, but are not limited to: when compounds of Formula I contain a cyano group, this group may be hydrolyzed to amides or acids under acidic or basic conditions; when compounds of Formula I contain an ester, the ester may be hydrolysed to the acid, and the acid may be converted to amides by the methods described above for amide bond formation. Acids may be reduced to alcohols, and alcohols may be oxidized to aldehydes and ketones. The preferred conditions for the reduction of a carboxylic acid in the presence of a cyano group include sodium borohydride and ethyl chloroformate in tetrahydrofuran (THF); and alcohol oxidation can be performed using the Dess-Martin periodinane reagent (Adv. Syn. Catalysis, 346, 111-124 (2004)). Aldehydes and ketones may be reacted with primary or secondary amines in the presence of a reducing agent such as sodium triacetoxyborohydride (see J. Org. Chem., 61, 3849-3862, (1996)) to give amines by reductive amination. Olefins, including acrylic acids and acrylate esters (X is CH=CHCO₂R^a), may be reduced by catalytic hydrogenation or, when R² contains an alkene, by 1,4-conjugate addition such that the alkene of R² is not reduced to give alkyls (X is CH₂CH₂CO₂R^a) (see Larock, Richard C., Comprehensive Organic Transformation; VCH: New York, 1989; p 8-17). When compounds of Formula I contain a sulfide, either acyclic or cyclic, the sulfide can be further oxidized to the corresponding sulfoxides or sulfones. Sulfoxides can be obtained by oxidation using an appropriate oxidant such as one equivalent of *meta*-chloroperbenzoic acid (MCPBA) or by treatment with NaIO₄ (see, for example, J. Med. Chem., 46: 4676-86 (2003)) and sulfones can be obtained using two equivalents of MCPBA or by treatment with 4-methylmorpholine N-oxide and catalytic osmium tetroxide (see, for example, PCT application WO 01/47919). Also, both sulfoxides and sulfones can be prepared by using one equivalent and two equivalents of H₂O₂ respectively, in the presence of titanium (IV) isopropoxide (see, for example, J. Chem. Soc., Perkin Trans. 2, 1039-1051 (2002)).

Scheme 2



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[0080] Scheme 2 illustrates general methodology for the preparation of compounds of Formula I where Z is H, X is C (R^5, R^6) R^1 or $-CH=CH-R^1$, R^5 and R^6 are H or Me, and R^1 is $-CO_2A^1$.

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[0081] For the illustration of synthetic strategy in this scheme, reagents and conditions are defined for the substrate where J is CH. As previously mentioned in Scheme 1, it is understood that similar synthetic methods can be utilized with minor modifications when J is N.

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[0082] When R^2 is cycloalkyl (specifically cycloalkenyl), compound 2-2 can be obtained by metal-catalyzed coupling reactions with boronic acids or boronate esters (M is $B(OH)_2$ or a boronic ester) and the starting material 2-1 is a dihaloaniline where L^4 is bromo or preferably iodo and where L^5 is chloro or preferably bromo. The metal-catalyzed couplings, preferably Suzuki reactions, can be performed according to standard methodology as described in Scheme 1, preferably in the presence of a palladium catalyst such as tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$), an aqueous base such as aq. Na_2CO_3 , and a suitable solvent such as toluene, ethanol, 1,4-dioxane, dimethoxyethane (DME), or DMF.

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[0083] When R^2 is cycloalkylamino (for example, piperidino), compound 2-2 can be obtained from starting material 2-0 by nucleophilic aromatic substitution of leaving group L^4 (preferably fluoro or chloro) that is activated by the nitro group with a cycloalkylamine R^2H (for example, piperidine), followed by reduction of the nitro group as described in Scheme 1.

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[0084] Compound 2-3 can be prepared by reaction of compound 2-2 with carboxylic acids $P^1-WCOOH$ where P^1 is an optional protecting group according to the procedures for amide bond formation as described in Scheme 1 for the preparation of 1-7.

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[0085] Compound 2-4 can be obtained from compound 2-3 by palladium-mediated cross-coupling reaction (see, for example, J. Am. Chem. Soc. 2004, 126, 5182) with silylketene acetals in the presence of a palladium catalyst such as tris(dibenzylideneacetone)-dipalladium(0) ($Pd_2(dba)_3$) or preferably bis(dibenzylideneacetone) palladium(0) ($Pd(dba)_2$), an appropriate ligand such as tri-tert-butylphosphine ($P(t-Bu)_3$), a suitable additive such as ZnF_2 and an appropriate solvent such as DMF.

[0086] The optional protecting group P^1 in compound 2-4 can be removed as described in Scheme 1 to give compound I. For example, when W is imidazole, a SEM group can be removed by either fluoride sources, such as tetrabutylammonium fluoride (TBAF) or preferably by acidic reagents such as trifluoroacetic acid (TFA).

[0087] The ester I (where R^a is $C_{(1-4)}$ alkyl) can be hydrolyzed by an appropriate metal hydroxide reagent such as

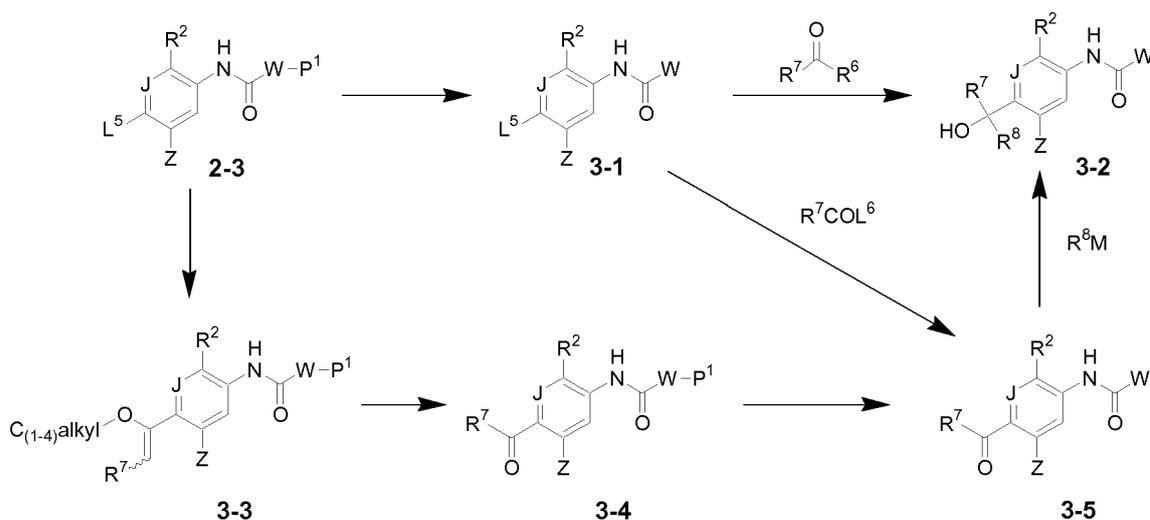
sodium hydroxide to give acid I (where R^a is H).

[0088] Compound 2-6 can be obtained from compound 2-3 by a palladium-mediated Heck reaction (for reviews, see I. Beletskaya, A. Cheprakov, *Chem. Rev.*, 100:3009 (2000)) with an alkyl acrylate in the presence of an appropriate palladium catalyst such as bis(tri-tert-butylphosphine)palladium (0) (Pd(t-Bu₃P)₂), a suitable base such as Cs₂CO₃ and an appropriate solvent such as 1,4-dioxane.

[0089] In compound 2-6, the optional protecting group P¹ can be removed by methods described in Scheme 1 and the ester group (R^a is C₍₁₋₄₎alkyl) can be hydrolyzed by base such as sodium hydroxide to afford the acid I (R^a is H). In the case of a tert-butyl ester, both the tert-butyl group and the optional protecting group can be removed to afford I (R^a is H) by acidic reagents such as hydrochloric acid or preferably trifluoroacetic acid (TFA).

[0090] It is understood that functional groups in I, especially X, can be further derivatized as outlined in Scheme 1.

Scheme 3



[0091] Scheme 3 illustrates two general syntheses for the preparation of the key intermediate compound 3-2, which will be used as a building block in Scheme 4.

[0092] For the illustration of synthetic strategy in this scheme, reagents and conditions are defined for the substrate where J is CH. As previously mentioned in Scheme 1, it is understood that similar synthetic methods can be utilized with minor modifications when J is N.

[0093] The starting material, compound 2-3, is obtained as described in Scheme 2. Its optional protecting group P¹ can be removed at this point as described in Scheme 1 to give compound 3-1.

[0094] The halo compound 3-1 can be converted to alcohol 3-2 by initial deprotonation with a suitable base, such as isopropylmagnesium chloride (i-PrMgCl) followed by lithium-halogen exchange with an appropriate lithium reagent such as n-butyllithium or preferably tert-butyllithium, and then trapping of the organo-lithium intermediate with a ketone or aldehyde R⁷R⁸CO, where R⁷ and R⁸ are independently H, or C₍₁₋₄₎alkyl.

[0095] An alternative method to prepare compound 3-2 begins with material 3-3, which is obtained by Stille coupling of an alkoxyvinyltin reagent (see, for example, *J. Org. Chem.*, 48: 1559-60 (1983)) with compound 2-3. The vinyl alkyl ether group (C₍₁₄₎alkyIOC=CH(R⁷-) in compound 3-3 can be hydrolyzed by acidic reagents, such as trifluoroacetic acid or acetic acid, to afford the ketone 3-4.

[0096] The optional protecting group P¹ in compound 3-4 can be removed at this point as described for the conversion of 2-3 to 3-1 to give compound 3-5.

[0097] The ketone in compound 3-5 can be reacted with an appropriate organometallic reagent R⁸M such as a Grignard reagent (M is MgBr or MgCl), or a suitable reducing reagent, such as NaBH₄ (where R⁸ is H, and M is NaBH₃), to form the alcohol compound 3-2.

[0098] Alternatively, 3-5 can be obtained directly from 3-1 by reaction of the organolithium intermediate as described for the conversion of 3-1 to 3-2 with an appropriate electrophile R⁷COL⁶ such as an acid chloride (where R⁷ is alkyl, and L⁶ is Cl, see, for example, *J. Med. Chem.*, 48(11): 3930-34 (2005)) or a Weinreb amide (L⁶ is N(OMe)Me, see, for example, *Bioorg. Med. Chem. Lett.*, 14(2): 455-8 (2004)).

[0099] It should be noted that the organo-lithium intermediate as described for the conversion of 3-1 to 3-2 and 3-1 to

3-5 is a versatile reagent that can react with various electrophiles.

[0100] It is understood that functional groups of compounds in this scheme can be further derivatized as outlined in Scheme 1.

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Scheme 4

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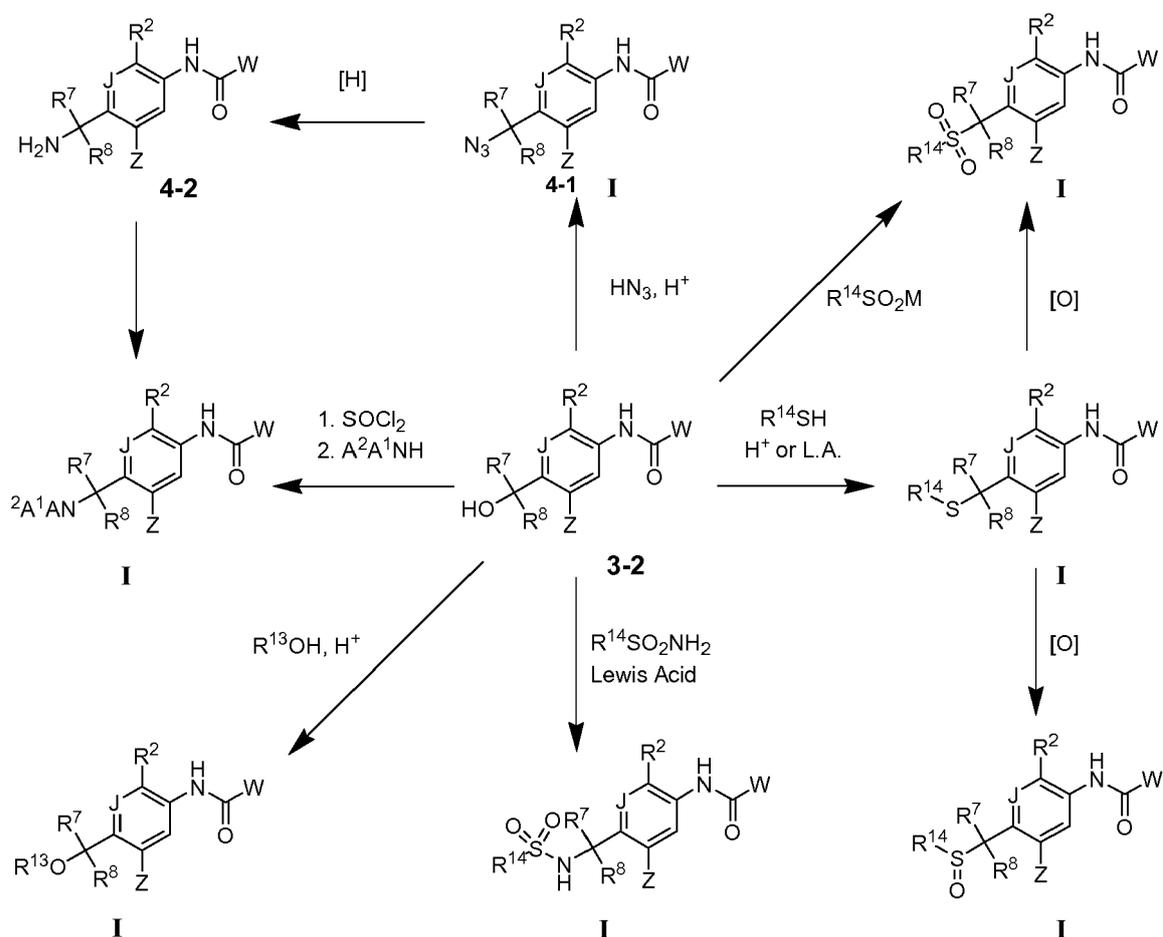
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[0101] Scheme 4 describes the use of the key intermediate 3-2, as prepared in Scheme 3, to synthesize compounds of Formula I, where X is $-\text{C}(\text{C}_{(1-4)}\text{alkyl})_2\text{R}^1$ and $-\text{CHC}_{(1-4)}\text{alkylR}^1$ and where R^1 is as defined in Formula 1.

[0102] For the illustration of synthetic strategy in this scheme, reagents and conditions are defined for the substrate where J is CH. As previously mentioned in Scheme 1, it is understood that similar synthetic methods can be utilized with minor modifications when J is N.

[0103] The azido compound 4-1 can be obtained from compound 3-2 by treatment with an azide reagent such as sodium azide or preferably hydrazoic acid (HN_3), and an appropriate acidic reagent such as TFA in a suitable solvent such as THF.

[0104] The azide group in compound 4-1 can be reduced to an amino group to form compound 4-2, preferably by a reducing agent which will not reduce an olefin when R^2 is alkenyl such as iron powder in the presence of NH_4Cl , or preferably zinc powder in the presence of acetic acid.

[0105] The tertiary hydroxyl group in compound 3-2 can also be converted to an amino group in compound I by activating 3-2 with a reagent such as thionyl chloride (SOCl_2) and trapping of the resulting intermediate(s) with a primary or secondary amine.

[0106] Compounds of Formula I where R^1 is alkoxy can be obtained from the hydroxyl compound 3-2 by treatment with acidic reagents such as sulfuric acid or preferably trifluoroacetic acid (TFA) and then trapping of the resulting tertiary cation with an alcohol R^{13}OH (where R^{13} is $\text{CH}_2\text{CH}_2\text{NA}^2$ or $\text{CH}_2\text{CH}_2\text{OR}^a$).

[0107] The hydroxyl compound 3-2 can also be reacted with a sulfonamide $\text{R}^{14}\text{SO}_2\text{NR}^a\text{H}$ in the presence of a Lewis

acid (L. A.) such as boron trifluoride diethyl etherate ($\text{BF}_3 \cdot \text{OEt}_2$) in a suitable solvent, such as THF to afford compound I (where R^{14} is $\text{CH}_2\text{CH}_2\text{NA}^1\text{A}^2$ or R^a).

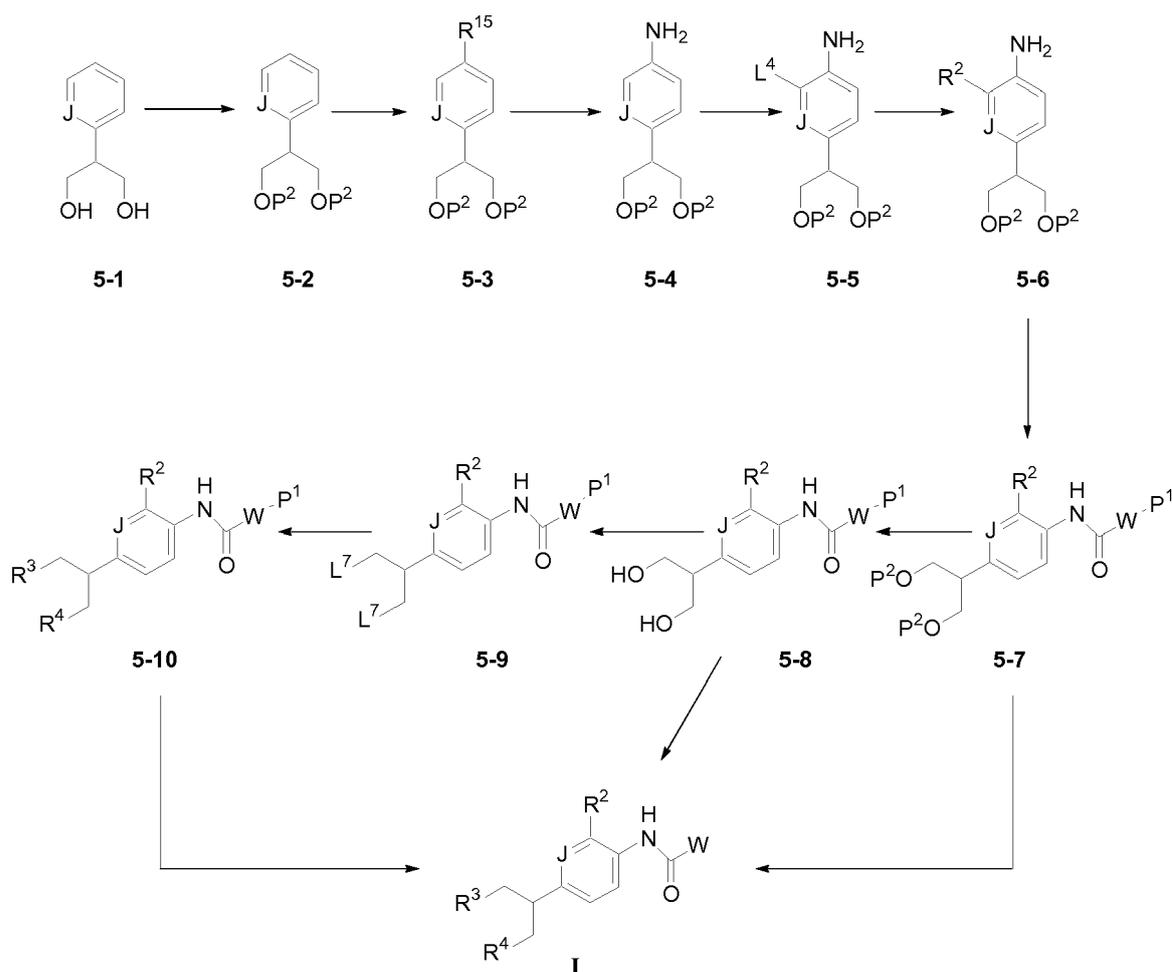
[0108] Compounds of Formula I where R^1 is a sulfide can be obtained from compound 3-2 by treatment with acidic reagents such as TFA or Lewis acids such as $\text{BF}_3 \cdot \text{OEt}_2$ and then trapping of the resulting tertiary cation with a thiol R^{14}SH (where R^{14} is $\text{CH}_2\text{CH}_2\text{NA}^1\text{A}^2$ or R^a).

[0109] Compounds of Formula I where R^1 is a sulfide can be further oxidized to the corresponding sulfoxide or sulfone of Formula I according to the sulfide oxidation procedures as described in Scheme 1.

[0110] Compounds of Formula I where R^1 is a sulfone can also be obtained directly from compound 3-2 by reaction with a metal sulfinic acid salt $\text{R}^{14}\text{SO}_2\text{M}$ (where M is Na, or K) (see, for example, B. Koutek, et al, Synth. Commun., 6 (4), 305-8 (1976)).

[0111] It is understood that functional groups in this scheme can be further derivatized as outlined in Scheme 1. For example, the amino group in compound 4-2 can be reacted with various electrophiles. The amino group can be reacted with carboxylic acids according to standard procedures for amide bond formation or by reaction with acid chlorides or activated esters to form amide compounds as described in Scheme 1. It can be also reacted with an appropriate carbonylation agent, such as phosgene, carbonyldiimidazole or preferably triphosgene, in the presence of a base, such as pyridine or DIEA. The intermediate thus formed can be trapped with a primary or secondary amine, to afford the corresponding urea compound. Similarly, the amino group in compound 4-2 can be reacted with an appropriate oxalylating agent, such as oxalyl chloride, in the presence of a base, such as pyridine or DIEA and the intermediate thus formed can be trapped with a primary or secondary amine to afford oxalamide compounds. Furthermore, the amino group can be reacted with appropriate aldehydes or ketones in the presence of suitable reducing reagents such as NaBH_4 or NaBH_3CN , or preferably $\text{NaBH}(\text{OAc})_3$ according to standard procedures for reductive amination as described in Scheme 1, to form compounds of Formula I where R^1 is $-\text{NA}^1\text{A}^2$.

Scheme 5



[0112] Scheme 5 describes the synthesis of compounds of Formula 1 where X is C₁₋₄ alkylR³R^{4a} and Z is H. To illustrate the methodology of this scheme, reagents and conditions for the substrate where J is CH are defined using commercially available 2-phenylpropane-1,2-diol as starting material 5-1. It is understood that when (2-pyridyl)propane diol (Tetrahedron: Asymmetry 8(13), 2175-2187, (1997)) where J is N, is employed as starting material 5-1, minor modifications of the reaction conditions and preferred reagents may be required.

[0113] The P²-protected 2-phenylpropane-1,2-diol 5-2 can be employed in this synthetic protocol. The examples of suitable O-protecting groups can be found in "Protective Groups in Organic Synthesis," by Theodora W. Greene and Peter G. M. Wuts, John Wiley & Sons, Inc, NY, (1999). The preferred protections of the hydroxyls include the conversion of diol 5-1 to corresponding diacetate 5-2 where P² is CH₃CO (Tetrahedron, 46 (20), 7081, (1990)).

[0114] The conversion of intermediate 5-2 to 5-4 can be accomplished via either halogenation, preferably bromination, of intermediate 5-2 to obtain intermediate 5-3 (where R¹⁵ is Br) followed by metal-catalyzed amination of halo intermediate 5-3 (for reviews, see: S. L. Buchwald, et al, Top. Curr. Chem., 219:131-209 (2001) and J. F. Hartwig in "Organopalladium Chemistry for Organic Synthesis," Wiley Interscience, NY (2002).) or by nitration of intermediate 5-2 to obtain nitro intermediate 5-3 (where R¹⁵ is NO₂) followed by reduction of the nitro group (for references see; The Nitro Group in Organic Synthesis" by Noboru Ono, John Wiley & Sons, Inc.). The preferred method for this transformation is the nitration of intermediate 5-2 with conc. HNO₃ to obtain nitro compound 5-3, followed by reduction of the nitro group, preferably by catalytic hydrogenation to obtain the corresponding amine 5-4.

[0115] The compounds of formula 5-6 can be obtained by ortho-halogenation, preferably bromination, of aniline substrate 5-4 to obtain intermediate 5-5 (L⁴ is a halogen), followed by a metal-catalyzed coupling reaction with a suitable partner as previously described in Scheme 1 to introduce R². The preferred conditions for bromination of intermediate 5-4 are NBS in a suitable solvent such as DMF, DCM or acetonitrile. The metal-catalyzed couplings, preferably Suzuki reactions, can be performed according to standard methodology, preferably in the presence of palladium (0) catalyst such as tris(dibenzylideneacetone)dipalladium (Pd₂(dba)₃) in the presence of a non-aqueous base such as K₃PO₄ and a phosphine ligand such as 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl (S-Phos) in suitable solvents such as toluene, DME or dioxane.

[0116] The amino group in compound 5-6 can then be coupled with a heterocyclic acid P¹-WCOOH (or a corresponding salt thereof P¹-WCOOM², M² is Li, Na or K), according to procedures for amide bond formation as described in Scheme 1 to form amide 5-7.

[0117] When P² is a group present in the final compound, and W in compound 5-7 contains an optional protecting group P¹, P¹ is removed at this point. For example, when W is imidazole optionally protected with SEM, the SEM group can be removed with either acidic reagents such as TFA or fluoride sources such as tetrabutylammonium fluoride (TBAF) to obtain the final product I (where R³ and R^{4a} are OP²). The preferred method of deprotection is the treatment of compound 5-7 with TFA.

[0118] When P² is not in the final product and is used only as a protecting group, P² in intermediate 5-7 can be removed at this point by standard methodology (see Green and Wuts reference above) to unmask the diol function while retaining protecting group P¹ when it is present. The preferred method of deprotection when, for example, P² is CH₃CO, involves the saponification of diacetate 5-7 with an inorganic base such as KOH in a suitable solvent such as EtOH to provide 5-8.

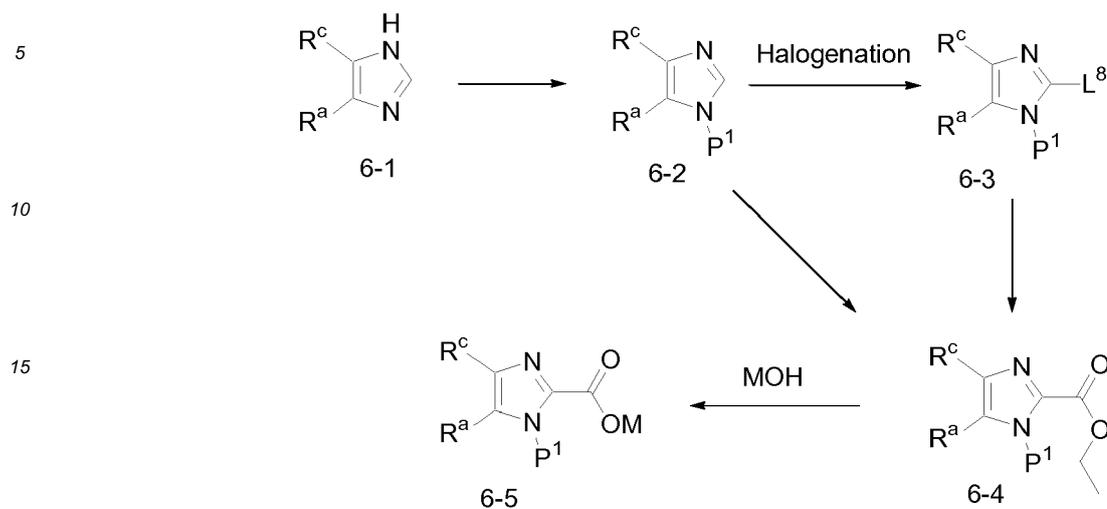
[0119] When the hydroxyl groups are present in the final compound, and W in compound 5-8 contains an optional protecting group P¹, P¹ can be removed at this point as described previously to obtain the final product I (where R³ and R^{4a} are OH).

[0120] The hydroxyl groups of diol 5-8 can also be converted to leaving groups L⁷ to obtain intermediate 5-9 using known literature methods for further functionalizations. Examples of suitable leaving groups L⁷ are mesylates, tosylates, triflates and halogens such as Br or I. The preferable leaving group is mesylate which can be prepared by the reaction of diol 5-8 with CH₃SO₂Cl and a tertiary amine bases such as Et₃N in DCM.

[0121] It is clear to those who are skilled in the art that the intermediate 5-9 can be subjected to various substitution reactions under appropriate reaction conditions with nucleophiles such as amines, alcohols and thiols to introduce R³ and R^{4a} (where R³ is R^{4a}) in intermediate 5-10. When W in compound 5-10 contains an optional protecting group P¹, it can be removed at this point to obtain the final product I as described previously.

[0122] It is understood that R³ and R^{4a} in intermediates 5-10 and I may be further functionalized as described in Scheme 1.

Scheme 6



[0123] Scheme 6 illustrates a route to the preparation of 2-imidazolecarboxylates of Formula 6-5 where R^a is H or $C_{(1-4)}$ alkyl, and R^c is H, alkyl, -CN, or -CONH₂ that are used as intermediates in the synthesis of compounds of Formula I where W is imidazole.

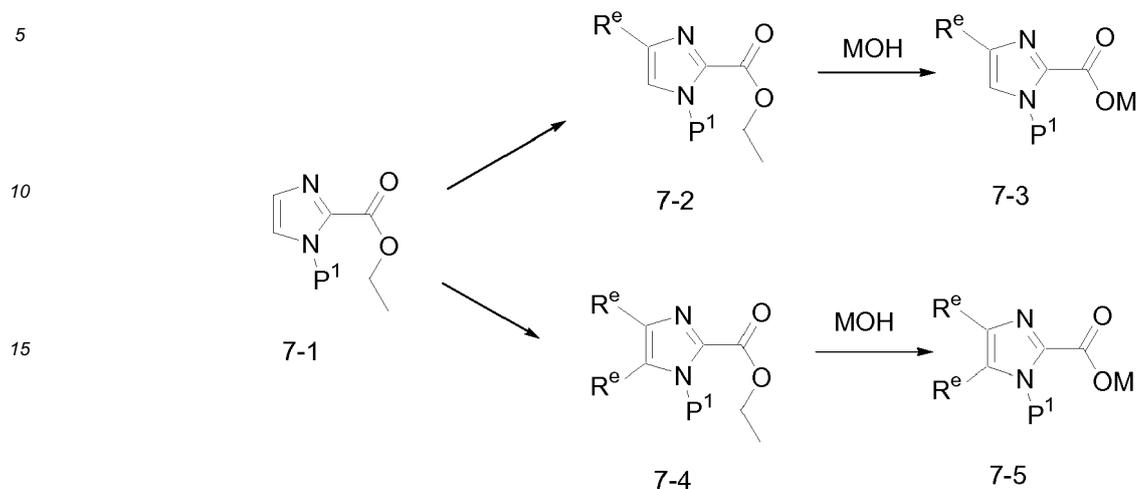
[0124] Imidazoles of Formula 6-1 where R^a is H or $C_{(1-4)}$ alkyl, and R^c is H, $C_{(1-4)}$ alkyl or -CN are either commercially available or, in the case of R^c is -CN, are readily available from commercially available aldehydes (6-1 where R^c is CHO) by reaction with hydroxylamines followed by dehydration with a suitable reagent such as phosphorus oxychloride or acetic anhydride (Synthesis, 677, 2003). Imidazoles of Formula 6-1 are protected with a suitable group (P^1) such as a methoxymethylamine (MOM), or preferably a SEM group to give compounds of Formula 6-2 (see Theodora W. Greene and Peter G. M. Wuts, Protective Groups in Organic Synthesis, John Wiley and Sons, Inc., NY (1991)).

[0125] Imidazoles of Formula 6-2, where R^c is -CN, are halogenated with a suitable reagent such as N-bromosuccinimide or N-iodosuccinimide under either electrophilic conditions in a solvent such as DCM or CH₃CN or under radical conditions in the presence of an initiator such as azobis(isobutyronitrile) (AIBN) in a solvent such as CCl₄ to give compounds of Formula 6-3 where L^8 is a leaving group (preferably bromo or iodo). Halogen-magnesium exchange on compounds of Formula 6-3 provides the organomagnesium species, which is then reacted with a suitable electrophile to provide compounds of Formula 6-4. The preferred conditions for halogen-magnesium exchange are using an alkylmagnesium reagent, preferably isopropylmagnesium chloride in a suitable solvent such as THF at temperatures between -78 °C - to 0°C. The preferred electrophiles are ethyl chloroformate or ethyl cyanoformate. For examples of halogen-magnesium exchange on cyanoimidazoles see J. Org. Chem. 65, 4618, (2000).

[0126] For imidazoles of Formula 6-2, where R^c is not -CN, these may be converted directly to imidazoles of Formula 6-4 by deprotonation with a suitable base such as an alkyllithium followed by reaction with an electrophile as described above for the organomagnesium species. The preferred conditions are treating the imidazole with n-butyllithium in THF at -78 °C and quenching the resulting organolithium species with ethyl chloroformate (for examples, see Tetrahedron Lett., 29, 3411-3414, (1988)).

[0127] The esters of Formula 6-4 may then be hydrolyzed to carboxylic acids (M is H) or carboxylate salts (M is Li, Na, or K,) of Formula 6-5 using one equivalent of an aqueous metal hydroxide (MOH) solution, preferably potassium hydroxide in a suitable solvent such as ethanol or methanol. Synthesis of compounds of Formula 6-5 where R^c is -CONH₂ is accomplished by first treating compounds of Formula 6-4 where R^c is -CN with an appropriate alkoxide such as potassium ethoxide to convert the cyano group to an imidate group (Pinner reaction) followed by hydrolysis of both the ester and imidate groups with two equivalents of an aqueous metal hydroxide solution.

Scheme 7

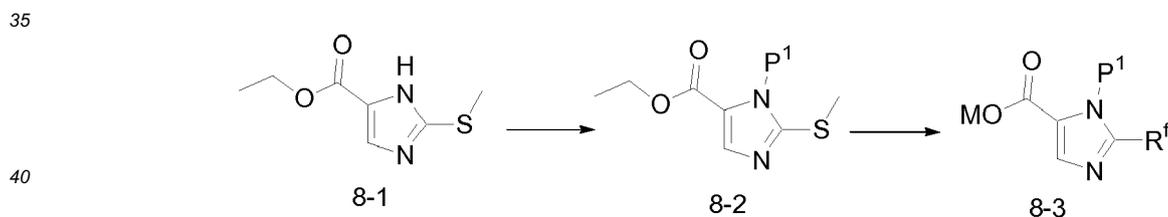


[0128] Scheme 7 illustrates a route to 2-imidazolecarboxylates of Formula 7-3 or 7-5 where R^e is chloro or bromo, and M is H, Li, K, or Na that are used as intermediates in the synthesis of compounds of Formula I where W is imidazole.

[0129] Compounds of Formula 7-1 are first prepared by protection of commercially available ethyl imidazolecarboxylate according to the methods outlined in Scheme 6, preferably with a SEM group.

[0130] Compounds of Formula 7-2 are prepared by reaction of compounds of Formula 7-1 with one equivalent of an appropriate halogenating reagent, such as NBS or N-chlorosuccinimide (NCS) in a suitable solvent such as CH₃CN, DCM or DMF at 25°C. Compounds of Formula 7-4 are prepared by reaction of compounds of Formula 7-1 with two equivalents of an appropriate halogenating reagent, such as NBS or NCS in a suitable solvent such as CH₃CN or DMF at temperatures between 30 °C to 80 °C. Imidazoles of Formula 7-3 and 7-5 are then obtained from the respective esters by hydrolysis as described in Scheme 6.

Scheme 8



[0131] Scheme 8 illustrates a method for the preparation of imidazoles of Formula 8-3 where R^f is -SCH₃, -SOCH₃, or -SO₂CH₃, and M is H, Li, K, or Na that are used as intermediates in the synthesis of compounds of Formula I where W is imidazole.

[0132] Imidazole 8-1 (WO 1996011932) is protected according to the methods described in Scheme 6, preferably with a SEM protecting group to give compounds of Formula 8-2. Ester hydrolysis according to the procedure in Scheme 6 gives compounds of Formula 8-3 where R^f is -SCH₃. Oxidation of 2-methylthioimidazoles of Formula 8-2 with one equivalent of an appropriate oxidant, followed by ester hydrolysis according to the procedure in Scheme 6 gives compounds of Formula 8-3 where R^f is -SOCH₃. Oxidation with two equivalents of an appropriate oxidant, followed by ester hydrolysis according to the procedure in Scheme 6 gives compounds of Formula 8-3 where R^f is -SO₂CH₃. The preferred reagent for oxidation is MCPBA in DCM. References for the conversion of sulfides to sulfoxides and sulfones are given in Scheme 1.

[0133] The following examples are for exemplary purposes only and are in no way meant to limit the invention.

EXAMPLES

Example 1 and Example 2

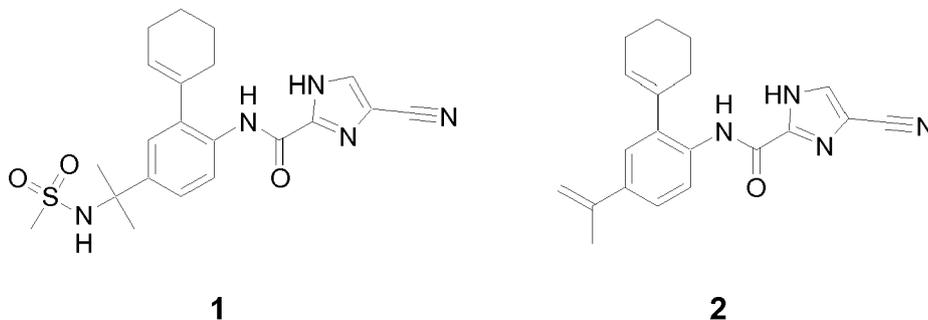
5 **4-Cyano-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(1-methanesulfonylamino-1-methyl-ethyl)-phenyl]-amide (1) and 4-Cyano-1H-imidazole-2-carboxylic acid (2-cyclohex-1-enyl-4-isopropenyl-phenyl)-amide (2)**

[0134]

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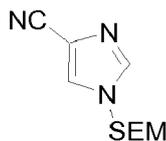


a) **1-(2-Trimethylsilylanyl-ethoxymethyl)-1H-imidazole-4-carbonitrile**

[0135]

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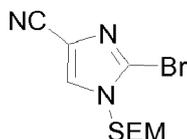
[0136] A flask charged with imidazole-4-carbonitrile (0.50 g, 5.2 mmol) (Synthesis, 677, 2003), 2-(trimethylsilyl)ethoxymethyl chloride (SEMCl) (0.95 mL, 5.3 mmol), K_2CO_3 (1.40 g, 10.4 mmol), and acetone (5 mL) was stirred for 10 h at RT. The mixture was diluted with ethyl acetate (EtOAc) (20 mL) and washed with water (20 mL) and brine (20 mL) and the organic layer was dried over $MgSO_4$. The crude product was eluted from a 20-g SPE cartridge (silica) with 30 % EtOAc/hexane to give 0.80 g (70 %) of the title compound as a colorless oil. Mass spectrum (CI (CH_4), m/z) Calcd. for $C_{10}H_{17}N_3OSi$, 224.1(M+H), found 224.1.

b) **2-Bromo-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-imidazole-4-carbonitrile**

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[0137]

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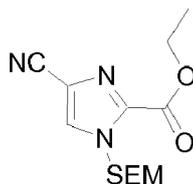
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[0138] To a solution of 1-(2-trimethylsilylanyl-ethoxymethyl)-1H-imidazole-4-carbonitrile (0.70 g, 3.1 mmol) (as prepared in the previous step) in CCl_4 (10 mL) was added N-bromosuccinimide (NBS) (0.61 g, 3.4 mmol) and azobis(isobutyronitrile) (AIBN) (cat), and the mixture was heated at 60 °C for 4 h. The reaction was diluted with EtOAc (30 mL), washed with $NaHCO_3$ (2 x 30 mL), brine (30 mL), the organic layer was dried over Na_2SO_4 and then concentrated. The title compound was eluted from a 20-g SPE cartridge (silica) with 30 % EtOAc/hexane to give 0.73 g (77 %) of a yellow solid. Mass spectrum (CI (CH_4), m/z) Calcd. for $C_{10}H_{16}BrN_3OSi$, 302.0/304.0 (M+H), found 302.1/304.1.

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c) **4-Cyano-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid ethyl ester**

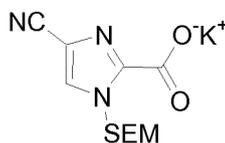
[0139]



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[0140] To a solution of 2-bromo-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-4-carbonitrile (0.55 g, 1.8 mmol) (as prepared in the previous step) in tetrahydrofuran (THF) (6 mL) at -40 °C was added dropwise a solution of 2 M i-PrMgCl in THF (1 mL). The reaction was allowed to stir for 10 min at -40 °C and then cooled to -78 °C, and ethyl cyanoformate (0.30 g, 3.0 mmol) was added. The reaction was allowed to attain RT and stirred for 1 h. The reaction was quenched with satd aq NH₄Cl, diluted with EtOAc (20 mL), washed with brine (2 x 20 mL). The organic layer was dried over Na₂SO₄ and then concentrated. The title compound was eluted from a 20-g SPE cartridge (silica) with 30 % EtOAc/hexane to give 0.40 g (74 %) of a colorless oil. Mass spectrum (ESI, m/z): Calcd. for C₁₃H₂₁N₃O₃Si, 296.1 (M+H), found 296.1.

d) 4-Cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylate potassium salt

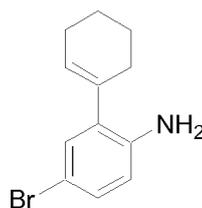
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[0141]



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[0142] To a solution of 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid ethyl ester (0.40 g, 1.3 mmol) (as prepared in the previous step) in ethanol (3 mL) was added a solution of 6M KOH (0.2 mL, 1.2 mmol) and the reaction was stirred for 10 min and then concentrated to give 0.40 g (100 %) of the title compound as a yellow solid. ¹H-NMR (CD₃OD; 400 MHz) δ 7.98 (s, 1H), 5.92 (s, 2H), 3.62 (m, 2H), 0.94 (m, 2H), 0.00 (s, 9H). Mass spectrum (ESI-neg, m/z): Calcd. for C₁₁H₁₆KN₃O₃Si, 266.1 (M-K), found 266.0.

e) 4-Bromo-2-cyclohex-1-enyl-phenylamine

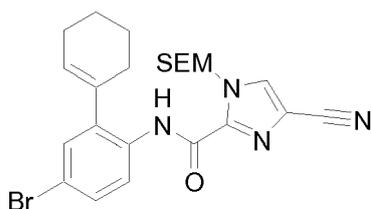
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[0143]



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[0144] To a mixture of 4-bromo-2-iodo-phenylamine (2.00 g, 6.71 mmol), 2-cyclohex-1-enyl-4,4,5,5-tetramethyl-[1,3,2] dioxaborolane (1.40 g, 6.71 mmol) and Pd(PPh₃)₄ (388 mg, 0.336 mmol) in 40 mL of 1,4-dioxane was added 2.0 M aq Na₂CO₃ solution (26.8 mL, 53.7 mmol). After stirring at 80 °C for 5 h under Ar, the reaction was cooled to room temperature (RT). The mixture was treated with EtOAc (100 mL), washed with H₂O (3 x 30 mL) and brine (20 mL). The organic layer was dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (10-20 % EtOAc/hexane) to give 1.47 g (87 %) of the title compound as a light brown oil. Mass spectrum (ESI, m/z): Calcd. for C₁₂H₁₄BrN, 252.0 (M+H), found 252.0.

f) 4-Cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid (4-bromo-2-cyclohex-1-enyl-phenyl)-amide

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[0145]



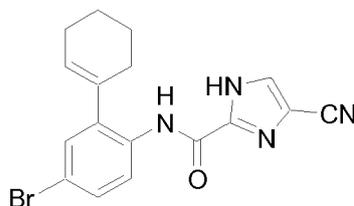
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10 **[0146]** To a mixture of 4-bromo-2-cyclohex-1-enyl-phenylamine (as prepared in the previous step, 1.23 g, 4.88 mmol), potassium 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylate (as prepared in Example 1, step (d), 1.49 g, 4.88 mmol) and bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP) (2.27 g, 4.88 mmol) in 25 mL of DMF was added N,N-diisopropylethylamine (DIEA) (2.55 mL, 14.6 mmol). After stirring at RT for 16 h, the mixture was treated with 100 mL of EtOAc and washed with H₂O (2 x 30 mL), brine (30 mL) and dried (Na₂SO₄). The organic solvent was evaporated and the residue was purified by flash chromatography on silica gel (5-10 % EtOAc/hexane) to give 2.21 g (90 %) of the title compound as a white solid. ¹H-NMR (CDCl₃; 400 MHz): δ 9.70 (s, 1H), 8.26 (d, 1H, J = 8.6 Hz), 7.78 (s, 1H), 7.36 (dd, 1H, J = 8.6, 2.3 Hz), 7.31 (d, 1H, J = 2.3 Hz), 5.94 (s, 2H), 5.86 (m, 1H), 3.66 (t, 2H, J = 8.3 Hz), 2.19-2.33 (m, 4H), 1.75-1.88 (m, 4H), 0.97 (t, 2H, J = 8.3 Hz), 0.00 (s, 9H).

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20 **g) 4-Cyano-1H-imidazole-2-carboxylic acid (4-bromo-2-cyclohex-1-enyl-phenyl)-amide**

25 **[0147]**



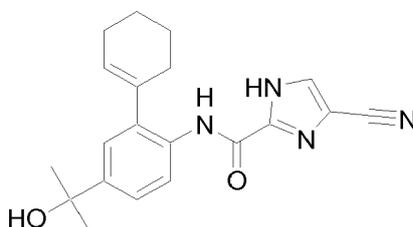
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30 **[0148]** To a solution of 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid (4-bromo-2-cyclohex-1-enyl-phenyl)-amide (as prepared in the previous step, 1.20 g, 2.39 mmol) in 10 mL of DCM (CH₂Cl₂) was added 0.30 mL of EtOH followed by 5.0 mL of TFA. After stirring at RT for 3 h, the mixture was treated with 20 mL of n-propanol and concentrated in vacuo. The residue was triturated with DCM to afford 853 mg (96 %) of the title compound as a white solid. ¹H-NMR (dimethylsulfoxide (DMSO)-d₆; 400 MHz): δ 9.80 (s, 1H), 8.30 (s, 1H), 7.94 (d, 1H, J = 8.6 Hz), 7.50 (dd, 1H, J = 8.6, 2.3 Hz), 7.39 (d, 1H, J = 2.3 Hz), 5.80 (m, 1H), 2.12-2.25 (m, 4H), 1.61-1.77 (m, 4H). Mass spectrum (ESI, m/z): Calcd. for C₁₇H₁₅BrN₄O, 371.0 (M+H), found 371.0.

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40 **h) 4-Cyano-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-amide**

45 **[0149]**



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55 **[0150]** To a solution of 4-cyano-1H-imidazole-2-carboxylic acid (4-bromo-2-cyclohex-1-enyl-phenyl)-amide (as prepared in the previous step, 50.0 mg, 0.135 mmol) in 2 mL of THF at -78 °C under Ar was added isopropyl magnesium chloride (71 μL, 0.14 mmol, 2.0 M in THF). The resulting mixture was warmed to RT and stirred for 15 min, cooled to -78 °C again. To the mixture was added tert-butyllithium (240 μL, 0.405 mmol, 1.7 M in pentane) and the resulting mixture was stirred at -78 °C for 5 min and then acetone (0.40 mL, 0.68 mmol) was added. The reaction was warmed to RT and stirred for 1 h under Ar. The mixture was treated with 1 mL of saturated NH₄Cl followed by 40 mL of EtOAc and washed with H₂O (10 mL), brine (5 mL) and dried (Na₂SO₄). Removal of the solvent under reduced pressure followed by flash

chromatography of the residue on silica gel (1-2 % MeOH/DCM) gave 32.1 mg (68 %) of the title compound as a white solid. $^1\text{H-NMR}$ (CDCl_3 ; 400 MHz): δ 11.88 (s, 1H), 9.58 (s, 1H), 8.29 (d, 1H, $J = 8.6$ Hz), 7.74 (s, 1H), 7.42 (dd, 1H, $J = 8.6, 2.2$ Hz), 7.35 (d, 1H, $J = 2.2$ Hz), 5.87 (m, 1H), 2.23-2.34 (m, 4H), 1.73-1.90 (m, 4H), 1.79 (s, 1H, OH), 1.61 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for $\text{C}_{20}\text{H}_{22}\text{N}_4\text{O}_2$, 351.2 (M+H), found 351.0.

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i) 4-Cyano-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(1-methanesulfonylamino-1-methyl-ethyl)-phenyl]-amide (1) and 4-Cyano-1H-imidazole-2-carboxylic acid (2-cyclohex-1-enyl-4-isopropenyl-phenyl)-amide (2)

[0151] To a solution of 4-cyano-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-amide (as prepared in the previous step, 30.0 mg, 0.0856 mmol) and methanesulfonamide (40.7 mg, 0.428 mmol) in 1 mL of THF at -78 °C was added $\text{BF}_3 \cdot \text{OEt}_2$ (16.0 μL , 0.128 mmol) under Ar. The resulting mixture was warmed to -10 °C and stirred for 2 h and then at RT for 16 h under Ar. The reaction was treated with 2 mL of saturated aqueous NaHCO_3 and 10 ml of brine and then extracted with EtOAc (2 x 20 mL). The combined organic layers were concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (10-20 % EtOAc/DCM) to give the title compound **1** (24.3 mg, 66 %) as a white solid and the title compound **2** (9.3 mg, 33 %) as a white solid. **1**: $^1\text{H-NMR}$ (CDCl_3 ; 400 MHz): δ 11.89 (s, 1H), 9.55 (s, 1H), 8.30 (d, 1H, $J = 8.6$ Hz), 7.72 (d, 1H, $J = 2.3$ Hz), 7.59 (dd, 1H, $J = 8.6, 2.3$ Hz), 7.29 (d, 1H, $J = 2.3$ Hz), 5.84 (m, 1H), 5.64 (s, 1H), 2.82 (s, 3H), 2.18-2.34 (m, 4H), 1.74-1.88 (m, 4H), 1.80 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for $\text{C}_{21}\text{H}_{25}\text{N}_5\text{O}_3\text{S}$, 428.2 (M+H), found 428.0. **2**: $^1\text{H-NMR}$ (CDCl_3 ; 400 MHz): δ 12.56 (s, 1H), 9.65 (s, 1H), 8.30 (d, 1H, $J = 8.6$ Hz), 7.77 (s, 1H), 7.43 (dd, 1H, $J = 8.6, 2.3$ Hz), 7.31 (d, 1H, $J = 2.3$ Hz), 5.88 (m, 1H), 5.40 (br s, 1H), 5.11 (m, 1H), 2.24-2.36 (m, 4H), 2.17 (s, 3H), 1.76-1.91 (m, 4H). Mass spectrum (ESI, m/z): Calcd. for $\text{C}_{20}\text{H}_{20}\text{N}_4\text{O}_4$, 333.2 (M+H), found 333.1.

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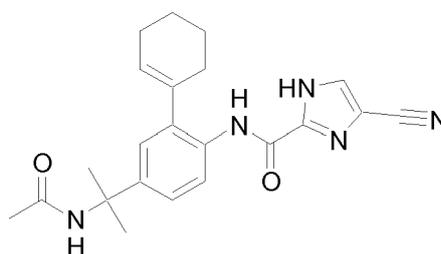
Example 3

4-Cyano-1H-imidazole-2-carboxylic acid [4-(1-acetylamino-1-methyl-ethyl)-2-cyclohex-1-enyl-phenyl]-amide

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[0152]

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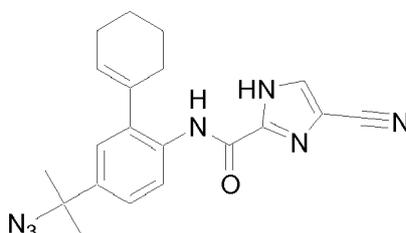
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a) 4-Cyano-1H-imidazole-2-carboxylic acid [4-(1-azido-1-methyl-ethyl)-2-cyclohex-1-enyl-phenyl]-amide

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[0153]

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[0154] To a mixture of 4-cyano-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-amide (as prepared in example 1, step (h), 15.0 mg, 0.0428 mmol) and NaN_3 (27.8 mg, 0.428 mmol) in 1 mL of chloroform at 0 °C under Ar was added TFA (49 μL , 0.64 mmol). The resulting mixture was stirred at 0 °C for 1 h under Ar. Treated with 30 mL of EtOAc, the mixture was washed with saturated aqueous NaHCO_3 (10 mL), brine (10 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (0-5 % EtOAc/DCM) gave 13.6 mg (84 %) of the title compound as a white solid. Mass spectrum (ESI, m/z): Calcd. for $\text{C}_{20}\text{H}_{21}\text{N}_7\text{O}$, 376.2 (M+H), found 376.0.

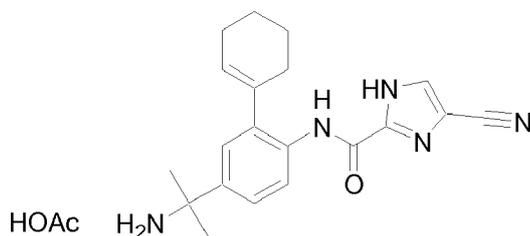
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b) 4-Cyano-1H-imidazole-2-carboxylic acid [4-(1-amino-1-methyl-ethyl)-2-cyclohex-1-enyl-phenyl]-amide acetic acid salt

[0155]

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15 [0156] To a mixture of 4-cyano-1H-imidazole-2-carboxylic acid [4-(1-amino-1-methyl-ethyl)-2-cyclohex-1-enyl-phenyl]-amide (as prepared in the previous step, 13.6 mg, 0.0362 mmol) and zinc (9.5 mg, 0.15 mmol) in 1 mL of THF was added acetic acid (0.20 mL). The resulting mixture was stirred at RT for 3 h under Ar. The solid was removed by filtration on Celite and the filtrate was concentrated in vacuo to give a light brown oil. The mixture was triturated with DCM (2 x 4 mL). The solvent was removed by filtration and the solid was dried in vacuo to give 13.5 mg (91 %) of the title compound as a white solid. ¹H-NMR (CD₃OD; 400 MHz): δ 8.27 (s, 1H), 7.70 (s, 1H), 7.43 (d, 1H, J = 7.3 Hz), 7.29 (s, 1H), 5.81 (m, 1H), 2.11-2.37 (m, 4H), 1.91 (s, 3H), 1.59-1.84 (m, 4H), 1.71 (s, 6H).

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c) 4-Cyano-1H-imidazole-2-carboxylic acid [4-(1-acetylamino-1-methyl-ethyl)-2-cyclohex-1-enyl-phenyl]-amide

25 [0157] A mixture of 4-cyano-1H-imidazole-2-carboxylic acid [4-(1-amino-1-methyl-ethyl)-2-cyclohex-1-enyl-phenyl]-amide acetic acid salt (as prepared in the previous step, 50.0 mg, 0.122 mmol) and DIEA (85.0 μL, 0.488 mmol) in 2 mL of CHCl₃ was stirred at RT for 5 min before dimethylaminopyridine (DMAP) (4.1 mg, 0.037 mmol) was added. The mixture was cooled to 0 °C and a solution of acetyl chloride (10 μL, 0.15 mmol) in 2 mL of CHCl₃ was added dropwise. The reaction was warmed to RT and stirred for 18 h under Ar. The mixture was treated with EtOAc (40 mL), washed with saturated aqueous NaHCO₃ (5 mL), brine (10 mL) and dried over Na₂SO₄. Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (1-2 % MeOH/DCM) gave 7.6 mg (16 %) of the title compound as a white solid. ¹H-NMR (CD₃OD; 400 MHz): δ 8.17 (s, 1H), 8.10 (d, 1H, J = 8.6 Hz), 7.99 (s, 1H), 7.27 (dd, 1H, J = 8.6, 2.3 Hz), 7.16 (d, 1H, J = 2.3 Hz), 5.80 (m, 1H), 2.20-2.32 (m, 4H), 1.94 (s, 3H), 1.74-1.88 (m, 4H), 1.62 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for C₂₂H₂₅N₅O₂, 392.2 (M+H), found 391.8.

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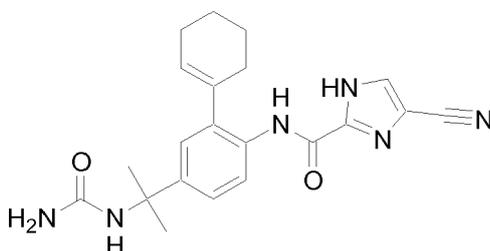
Example 4**4-Cyano-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(1-methyl-1-ureido-ethyl)-phenyl]-amide**

[0158]

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55 [0159] To a solution of triphosgene (7.2 mg, 0.024 mmol) in 2 mL of THF at 0 °C was added a solution of 4-cyano-1H-imidazole-2-carboxylic acid [4-(1-amino-1-methyl-ethyl)-2-cyclohex-1-enyl-phenyl]-amide acetic acid salt (as prepared in Example 3, step (b), 25.0 mg, 0.0611 mmol) and DIEA (32 μL, 0.18 mmol) in 2 mL of THF under Ar. The resulting mixture was stirred at RT for 20 min and cooled to 0 °C. NH₃ (g) was bubbled into the mixture for ca. 4 min and the reaction was then sealed and stirred at RT for 0.5 h. The mixture was treated with brine (10 mL) and extracted with EtOAc (2 x 25 mL). The combined organic layers were concentrated in vacuo and the residue was purified by flash chromatography on silica gel (3-6 % MeOH/DCM) to afford 7.2 mg (30 %) of the title compound as a white solid. ¹H-

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NMR (CD₃OD; 400 MHz): δ 8.11 (d, 1H, J = 8.6 Hz), 7.98 (s, 1H), 7.32 (dd, 1H, J = 8.6, 2.1 Hz), 7.22 (d, 1H, J = 2.1 Hz), 5.80 (m, 1H), 2.20-2.34 (m, 4H), 1.73-1.89 (m, 4H), 1.61 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for C₂₁H₂₄N₆O₂, 393.2 (M+H), found 393.0.

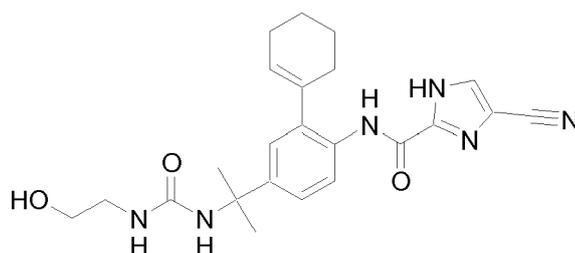
5 Example 5

4-Cyano-1H-imidazole-2-carboxylic acid (2-cyclohex-1-enyl-4-{1-[3-(2-hydroxy-ethyl)-ureido]-1-methyl-ethyl}-phenyl)-amide

10 [0160]

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[0161] To a solution of triphosgene (11.9 mg, 0.0400 mmol) in 2 mL of THF at 0 °C was added a solution of 4-cyano-1H-imidazole-2-carboxylic acid [4-(1-amino-1-methyl-ethyl)-2-cyclohex-1-enyl-phenyl]-amide acetic acid salt (as prepared in Example 3, step (b), 41.0 mg, 0.100 mmol) and DIEA (52 μ L, 0.30 mmol) in 2 mL of THF under Ar. The resulting mixture was stirred at RT for 10 min and cooled to 0 °C. 2-Amino-ethanol (60.0 μ L, 1.00 mmol) was added into the mixture and the reaction was stirred at RT for 2 h. The mixture was treated with brine (10 mL) and extracted with EtOAc (2 x 25 mL). The combined organic layers were concentrated in vacuo and the residue was purified by flash chromatography on silica gel (2-8 % MeOH/DCM) to give 15.1 mg (35 %) of the title compound as a light yellow oil. ¹H-NMR (CD₃OD; 400 MHz): δ 8.11 (d, 1H, J = 8.4 Hz), 7.99 (s, 1H), 7.31 (dd, 1H, J = 8.4, 2.4 Hz), 7.21 (d, 1H, J = 2.4 Hz), 6.48 (s, 1H), 5.80 (m, 1H), 3.52 (t, 2H, J = 5.6 Hz), 3.16 (t, 2H, J = 5.6 Hz), 2.20-2.33 (m, 4H), 1.73-1.88 (m, 4H), 1.60 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for C₂₃H₂₈N₆O₃, 437.2 (M+H), found 437.1.

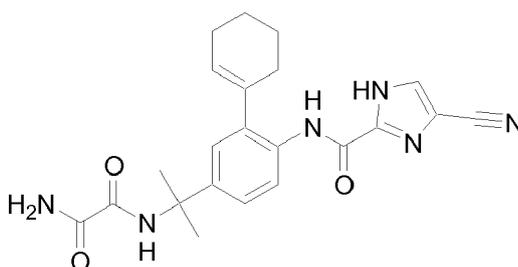
Example 6

35 **N-(1-{4-[(4-Cyano-1H-imidazole-2-carbonyl)-amino]-3-cyclohex-1-enyl-phenyl}-1-methyl-ethyl)-oxalamide**

[0162]

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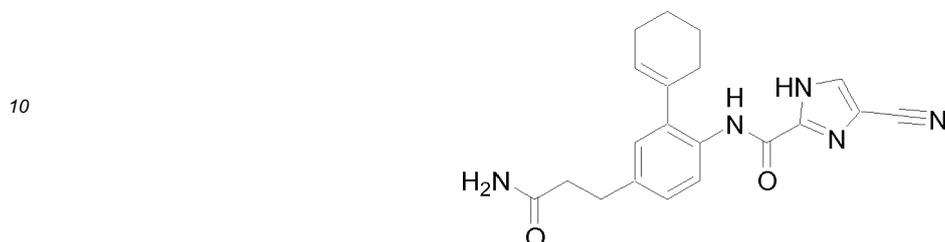
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[0163] The procedure of Example 4 was followed using 4-cyano-1H-imidazole-2-carboxylic acid [4-(1-amino-1-methyl-ethyl)-2-cyclohex-1-enyl-phenyl]-amide acetic acid salt (as prepared in Example 3, step (b), 28.0 mg, 0.0684 mmol), oxalyl chloride (51 μ L, 0.10 mmol, 2.0 M in DCM) and DIEA (36 μ L, 0.21 mmol). Flash chromatography on silica gel (1-2 % MeOH/DCM) afforded 9.2 mg (34 %) of the title compound as a white solid. ¹H-NMR (CD₃OD; 400 MHz): δ 8.14 (d, 1H, J = 8.4 Hz), 7.99 (s, 1H), 7.31 (dd, 1H, J = 8.4, 2.3 Hz), 7.20 (d, 1H, J = 2.3 Hz), 5.81 (m, 1H), 2.22-2.31 (m, 4H), 1.74-1.89 (m, 4H), 1.71 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for C₂₂H₂₄N₆O₃, 421.2 (M+H), found 421.0.

Example 7**4-Cyano-1H imidazole-2-carboxylic acid [4-(2-carbamoyl-ethyl)-2-cyclohex-1-enyl-phenyl]-amide**

5 [0164]

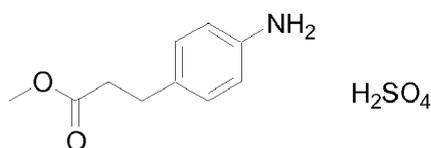


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a) 3-(4-Amino-phenyl)-propionic acid methyl ester sulfuric acid salt

[0165]

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[0166] To a mixture of 3-(4-amino-phenyl)-propionic acid (1.00 g, 6.05 mmol) in 10 mL of methyl alcohol (MeOH) was added 0.80 mL of conc H_2SO_4 . The resulting mixture was refluxed for 2 h, concentrated down to ca. half volume by distillation and then cooled to 45 °C. Methyl tert-butyl ether (MTBE, 15 mL) was added. The mixture was allowed to cool to 0 °C and stirred for 0.5 h. The solid was collected by filtration and washed with 1:4 MeOH/MTBE (2 x 10 mL), MTBE (3 x 10 mL) and dried under reduced pressure. The title compound (1.43 g, 85 %) was obtained as a white solid. $^1\text{H-NMR}$ (DMSO- d_6 ; 400 MHz): δ 8.40-11.0 (br s, 4H), 7.34 (d, 2H, $J = 8.2$ Hz), 7.23 (d, 2H, $J = 8.2$ Hz), 3.57 (s, 3H), 2.86 (t, 2H, $J = 7.4$ Hz), 2.64 (t, 2H, $J = 7.4$ Hz).

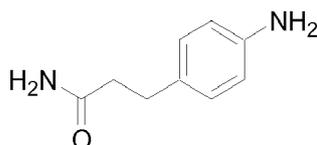
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b) 3-(4-Amino-phenyl)propionamide

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[0167]

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[0168] To a suspension of 3-(4-amino-phenyl)-propionic acid methyl ester sulfuric acid salt (as prepared in the previous step, 277 mg, 1.00 mmol) in 8 mL of conc NH_4OH was added 0.75 g of NaCl in 3 mL of H_2O . After stirring at RT for 16 h, the resulting mixture was treated with 10 mL of brine and extracted with EtOAc (5 x 25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give 133 mg (81 %) of the title compound as a white solid. Mass spectrum (ESI, m/z): Calcd. for $\text{C}_9\text{H}_{12}\text{N}_2\text{O}$, 165.1 (M+H), found 165.0.

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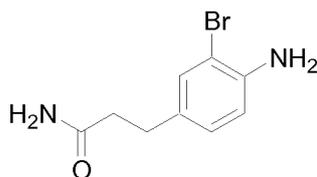
c) 3-(4-Amino-3-bromo-phenyl)-propionamide

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[0169]

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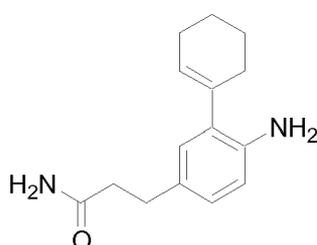
EP 2 687 516 A1



10
[0170] To a mixture of 3-(4-amino-phenyl)-propionamide (as prepared in the previous step, 123 mg, 0.749 mmol) in 10 mL of 1:1 DCM/CH₃CN at 0 °C was added N-bromosuccinimide (NBS) (133 mg, 0.749 mmol) in 4 mL of 1:1 DCM/CH₃CN. The mixture was warmed to RT and stirred for 1 h under Ar. Treated with 20 mL of brine, the mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were concentrated in vacuo and the residue was purified by flash chromatography on silica gel (1-4 % MeOH/DCM) giving 133 mg (81 %) of the title compound as a white solid. Mass spectrum (ESI, m/z): Calcd. for C₉H₁₁BrN₂O, 243.0 (M+H), found 242.9.

15 **d) 3-(4-Amino-3-cyclohex-1-enyl-phenyl)-propionamide**

[0171]

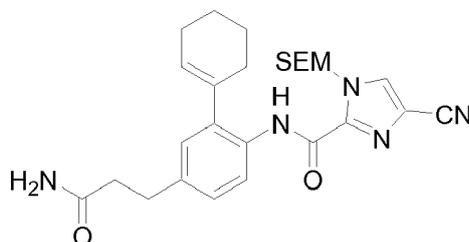


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[0172] To a mixture of 3-(4-amino-3-bromo-phenyl)-propionamide (as prepared in the previous step, 100 mg, 0.411 mmol), 2-cyclohex-1-enyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (94.1 mg, 0.452 mmol) and Pd(PPh₃)₄ (47.5 mg, 0.0411 mmol) in 3 mL of 1,4-dioxane was added 2.0 M aq Na₂CO₃ solution (1.64 mL, 3.29 mmol). After stirring at 80 °C for 16 h under Ar, the reaction was cooled to RT and treated with 15 mL of brine. The mixture was extracted with EtOAc (2 x 30 mL) and the combined organic layers were dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (1-3 % MeOH/DCM) giving 88.1 mg (88 %) of the title compound as a colorless oil. Mass spectrum (ESI, m/z): Calcd. for C₁₅H₂₀N₂O, 245.2 (M+H), found 245.1.

35

e) 4-Cyano-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [4-(2-carbamoyl-ethyl)-2-cyclohex-1-enyl-phenyl]-amide

[0173]

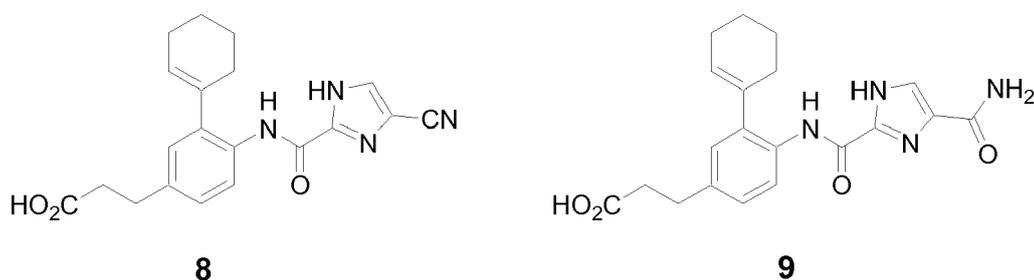


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[0174] To a mixture of 3-(4-amino-3-cyclohex-1-enyl-phenyl)-propionamide (as prepared in the previous step, 85.0 mg, 0.378 mmol), potassium 4-cyano-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazole-2-carboxylate (as prepared in Example 1, step (d), 117 mg, 0.383 mmol) and PyBroP (179 mg, 0.383 mmol) in 2.5 mL of DMF was added DIEA (182 μL, 1.04 mmol). After stirring at RT for 16 h, the mixture was treated with 30 mL of EtOAc and washed with H₂O (2 x 10 mL), brine (10 mL) and dried (Na₂SO₄). The organic solvent was evaporated in vacuo and the residue was purified by flash chromatography on silica gel (0-2 % MeOH/DCM) to give 156 mg (91 %) of the title compound as a white solid. Mass spectrum (ESI, m/z): Calcd. for C₂₆H₃₅N₅O₃Si, 494.3 (M+H), found 494.0.

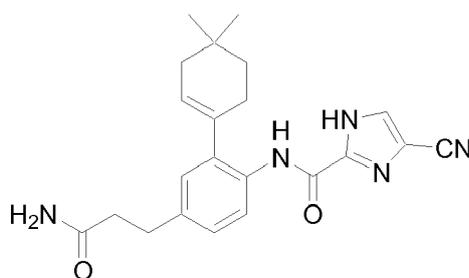
55

f) 4-Cyano-1H-imidazole-2-carboxylic acid [4-(2-carbamoyl-ethyl)-2-cyclohex-1-enyl-phenyl]-amide

[0175] To a solution of 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [4-(2-carbamoyl-ethyl)-2-cyclohex-1-enyl-phenyl]-amide (as prepared in the previous step, 150 mg, 0.304 mmol) in 2 mL of DCM was added 60 μ L of EtOH followed by 1 mL of TFA. The resulting solution was stirred at RT for 3 h. The reaction was treated with 20 mL of n-propanol and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (2-5 % MeOH/DCM) to afford 86.1 mg (78 %) of the title compound as a white solid. $^1\text{H-NMR}$ (CD_3OD ; 400 MHz): δ 8.08 (d, 1H, J = 8.3 Hz), 8.00 (s, 1H), 7.14 (dd, 1H, J = 8.3, 2.2 Hz), 7.06 (d, 1H, J = 2.2 Hz), 5.79 (m, 1H), 2.89 (t, 2H, J = 7.7 Hz), 2.50 (t, 2H, J = 7.7 Hz), 2.20-2.30 (m, 4H), 1.72-1.88 (m, 4H). Mass spectrum (ESI, m/z): Calcd. for $\text{C}_{20}\text{H}_{21}\text{N}_5\text{O}_2$, 364.2 (M+H), found 364.1.

Examples 8 and 9**3-{4-[(4-Cyano-1H-imidazole-2-carbonyl)-amino]-3-cyclohex-1-enyl-phenyl}-propionic acid (8) and 3-{4-[(4-Carbamoyl-1H-imidazole-2-carbonyl)-amino]-3-cyclohex-1-enyl-phenyl}-propionic acid (9)****[0176]**

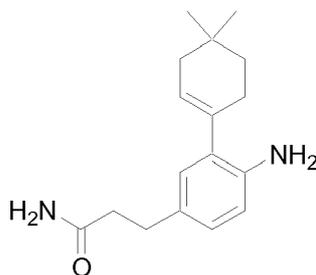
[0177] To a solution of 4-cyano-1H-imidazole-2-carboxylic acid [4-(2-carbamoyl-ethyl)-2-cyclohex-1-enyl-phenyl]-amide (as prepared in Example 7, step (f), 30.0 mg, 0.0826 mmol) in 1 mL of 1:1 MeOH/THF was added 6 N NaOH (138 μ L, 0.826 mmol). The resulting mixture was stirred at RT for 2 h and at reflux for 5 h. After cooling to RT, the mixture was treated with 10 mL of H_2O , neutralized to a pH of 6 with 15 % aqueous citric acid and extracted with EtOAc (2 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel with 1-5 % MeOH/DCM to afford 13.8 mg (46 %) of the title compound **8** as a white solid and 11.3 mg (36 %) of the title compound **9** as a white solid. **8**: $^1\text{H-NMR}$ (CD_3OD ; 400 MHz): δ 8.07 (d, 1H, J = 8.3 Hz), 8.00 (s, 1H), 7.15 (dd, 1H, J = 8.3, 2.2 Hz), 7.06 (d, 1H, J = 2.2 Hz), 5.80 (m, 1H), 2.90 (t, 2H, J = 7.6 Hz), 2.60 (t, 2H, J = 7.6 Hz), 2.26 (m, 4H), 1.74-1.88 (m, 4H). Mass spectrum (ESI, m/z): Calcd. for $\text{C}_{20}\text{H}_{20}\text{N}_4\text{O}_3$, 365.2 (M+H), found 365.2. **9**: $^1\text{H-NMR}$ (CD_3OD ; 400 MHz): δ 8.01 (d, 1H, J = 8.3 Hz), 7.81 (s, 1H), 7.16 (dd, 1H, J = 8.3, 2.0 Hz), 7.08 (d, 1H, J = 2.0 Hz), 5.82 (m, 1H), 2.90 (t, 2H, J = 7.6 Hz), 2.60 (t, 2H, J = 7.6 Hz), 2.22-2.31 (m, 4H), 1.77-1.88 (m, 4H). Mass spectrum (ESI, m/z): Calcd. for $\text{C}_{20}\text{H}_{22}\text{N}_4\text{O}_4$, 383.2 (M+H), found 383.2.

Example 10**4-Cyano-1H-imidazole-2-carboxylic acid [4-(2-carbamoyl-ethyl)-2-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-amide****[0178]**

a) 3-[4-Amino-3-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-propionamide**[0179]**

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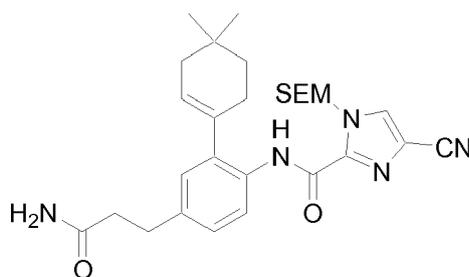
15 **[0180]** The title compound was prepared by the Suzuki coupling procedure of Example 7, step (d) using 3-(4-amino-3-bromo-phenyl)-propionamide (as prepared in Example 7, step (c), 76.0 mg, 0.351 mmol), and 4,4-dimethylcyclohexen-1-yl boronic acid (59.5 mg, 0.387 mmol). Silica gel chromatography (0-2 % MeOH/DCM) afforded the title compound (79 mg, 92 %) as a light brown oil. Mass spectrum (ESI, m/z): Calcd. for $C_{17}H_{24}N_2O$, 273.2 (M+H), found 273.2.

20 **b) 4-Cyano-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [4-(2-carbamoyl-ethyl)-2-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-amide**

[0181]

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35 **[0182]** The title compound was prepared by the coupling procedure of Example 7, step (e) using 3-[4-amino-3-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-propionamide (as prepared in the previous step, 75.0 mg, 0.307 mmol), and potassium 4-cyano-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazole-2-carboxylate (as prepared in Example 1, step (d), 103 mg, 0.338 mmol). Silica gel chromatography (0-2 % MeOH/DCM) afforded the title compound (124 mg, 82 %) as a white solid. Mass spectrum (ESI, m/z): Calcd. for $C_{28}H_{39}N_5O_3Si$, 522.3 (M+H), found 522.1.

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c) 4-Cyano-1H-imidazole-2-carboxylic acid [4-(2-carbamoyl-ethyl)-2-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-amide

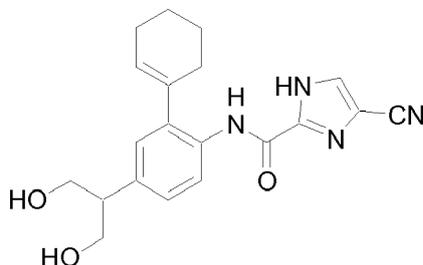
45 **[0183]** A solution of 4-cyano-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [4-(2-carbamoyl-ethyl)-2-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-amide (as prepared in the previous step, 160 mg, 0.307 mmol) and tetrabutylammonium fluoride (357 μ L, 0.357 mmol, 1.0 M in THF) in 4.5 mL of THF was stirred at reflux for 1.5 h under Ar. After cooling to RT, the mixture was treated with EtOAc (40 mL), washed with saturated aq $NaHCO_3$ (5 mL), brine (10 mL) and dried (Na_2SO_4). The organic layer was concentrated in vacuo and the residue was purified by flash chromatography on silica gel (5 % MeOH/DCM) to give 29.2 mg (24 %) of the title compound as a white solid. 1H -NMR (CD_3OD ; 400 MHz): δ 8.09 (d, 1H, J = 8.3 Hz), 7.98 (s, 1H), 7.14 (dd, 1H, J = 8.3, 2.1 Hz), 7.07 (d, 1H, J = 2.1 Hz), 5.71 (m, 1H), 2.89 (t, 2H, J = 7.7 Hz), 2.50 (t, 2H, J = 7.7 Hz), 2.29 (m, 2H), 2.06 (m, 2H), 1.57 (t, 2H, J = 6.3 Hz), 1.07 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for $C_{22}H_{25}N_5O_2$, 392.2 (M+H), found 392.2.

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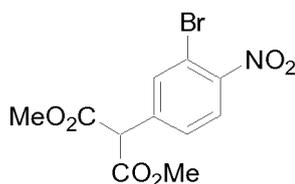
Example 11

4-Cyano-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(2-hydroxy-1-hydroxymethyl-ethyl)-phenyl]-amide

[0184]

**a) 2-(3-Bromo-4-nitro-phenyl)-malonic acid dimethyl ester**

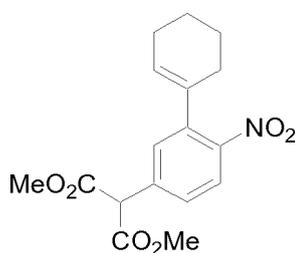
[0185]



[0186] To a suspension of NaH (364 mg, 9.08 mmol) in 10 mL of DMF at 0 °C was added malonic acid dimethyl ester (519 μ L, 4.54 mmol). The resulting mixture was warmed to RT and stirred for 0.5 h under Ar. 2-Bromo-4-fluoro-1-nitrobenzene (500 mg, 2.27 mmol) was added to the mixture and the reaction was stirred at RT for 16 h under Ar. The mixture was then treated with 2 mL of satd aq NH_4Cl followed by 10 mL of H_2O and extracted with DCM (3 x 10 mL). The combined extracts were washed with water (10 mL), brine (5 mL) and dried (Na_2SO_4). Removal of the solvent in vacuo followed by flash chromatography of the residue on silica gel (1:4 hexane-DCM) gave 604 mg (80 %) of a yellow-green oil containing the pure title compound as a mixture of di-ester (A) and its enol tautomer (B): $^1\text{H-NMR}$ (CDCl_3 ; 400 MHz): **A:** δ 8.48 (d, 1H, $J = 2.5$ Hz), 8.21 (dd, 1H, $J = 8.8, 2.5$ Hz), 7.85 (d, 1H, $J = 8.8$ Hz), 5.34 (s, 1H), 3.81 (s, 6H). **B:** δ 7.85 (d, 1H, $J = 8.4$ Hz), 7.82 (d, 1H, $J = 1.9$ Hz), 7.54 (dd, 1H, $J = 8.4, 1.9$ Hz), 4.68 (s, 1H), 3.80 (s, 6H).

b) 2-(3-Cyclohex-1-enyl-4-nitrophenyl)-malonic acid dimethyl ester

[0187]



[0188] To a mixture of 2-(3-bromo-4-nitro-phenyl)-malonic acid dimethyl ester (as prepared in the previous step, 300 mg, 0.903 mmol), cyclohex-1-enyl boronic acid (125 mg, 0.994 mmol) and dichloro[1, 1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct ($\text{Pd}(\text{dppf})\text{Cl}_2$) (66.0 mg, 0.0903 mmol) in 5 mL of DMF was added K_3PO_4 (765 mg, 3.61 mmol). The resulting mixture was stirred at 60 °C for 9 h under Ar. After cooling to RT, the mixture was treated with 50 mL of EtOAc, washed with H_2O (3 x 10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4)

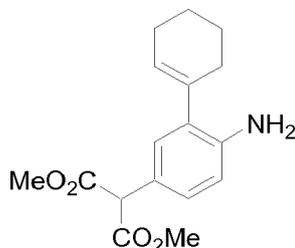
and concentrated in vacuo. The residue was purified by flash chromatography on silica gel with 10 % EtOAc-hexane to afford 210 mg (70 %) of the title compound as a yellow oil: Mass spectrum (ESI, m/z): Calcd. for $C_{17}H_{19}NO_6$, 334.1 (M+H), found 334.0.

5 **c) 2-(4-Amino-3-cyclohex-1-enyl-phenyl)-malonic acid dimethyl ester**

[0189]

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[0190] A mixture of 2-(3-cyclohex-1-enyl-4-nitro-phenyl)-malonic acid dimethyl ester (as prepared in the previous step, 200 mg, 0.600 mmol), iron powder (168 mg, 3.00 mmol) and NH_4Cl (321 mg, 6.00 mmol) in 6 mL of ethanol was stirred at 80 °C for 16 h. After cooling to RT, the mixture was treated with 30 mL of H_2O and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (30 % EtOAc-hexane) to give 129 mg (71 %) of the title compound as a faint yellow oil: Mass spectrum (ESI, m/z): Calcd. for $C_{17}H_{21}NO_4$, 304.2 (M+H), found 304.1.

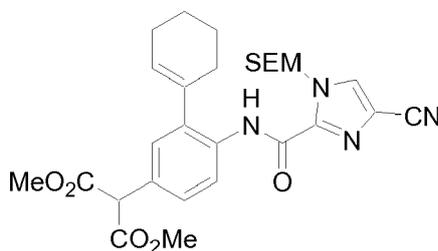
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d) 2-(4-[[4-Cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carbonyl]-amino]-3-cyclohex-1-enyl-phenyl)-malonic acid dimethyl ester

[0191]

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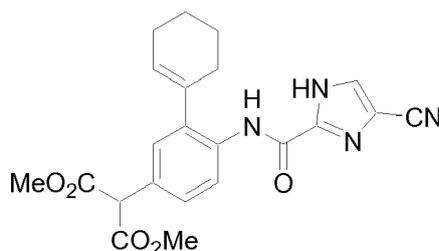
[0192] To a mixture of 2-(4-amino-3-cyclohex-1-enyl-phenyl)-malonic acid dimethyl ester (as prepared in the previous step, 100 mg, 0.330 mmol), potassium 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylate (as prepared in Example 1, step (d), 106 mg, 0.346 mmol) and bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP) (154 mg, 0.330 mmol) in 3 mL of DMF was added DIEA (0.172 mL, 0.990 mmol). After stirring at RT for 16 h, the mixture was treated with 50 mL of EtOAc and washed with H_2O (2 x 15 mL), brine (15 mL) and dried (Na_2SO_4). The organic solvent was evaporated and the residue was purified by flash chromatography on silica gel (5-10 % EtOAc-hexane) to give 118 mg (85 %) of the title compound as a colorless oil: Mass spectrum (ESI, m/z): Calcd. for $C_{28}H_{36}N_4O_6Si$, 553.2 (M+H), found 552.6.

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50 **e) 2-{4-[[4-Cyano-1H-imidazole-2-carbonyl]-amino]-3-cyclohex-1-enyl-phenyl}-malonic acid dimethyl ester**

[0193]

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[0194] To a solution of 2-(4-((4-cyano-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-imidazole-2-carbonyl)-amino)-3-cyclohex-1-enyl-phenyl)-malonic acid dimethyl ester (as prepared in the previous step, 145 mg, 0.262 mmol) in 1.0 mL of DCM (CH₂Cl₂) was added 1.0 mL of TFA. After stirring at RT for 4 h, the mixture was concentrated in vacuo. The residue was purified by flash chromatography on silica gel (20-30 % EtOAc-hexane) to give 93 mg (84 %) of the title compound as a white solid: Mass spectrum (ESI, m/z): Calcd. for C₂₂H₂₂N₄O₅, 423.1 (M+H), found 422.8.

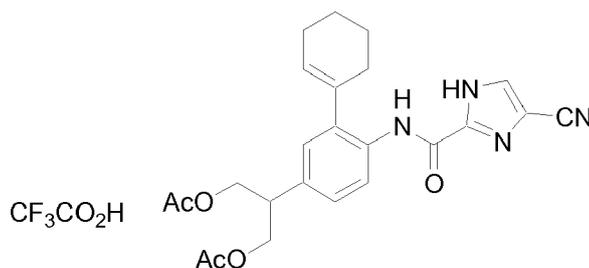
f) **4-Cyano-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(2-hydroxy-1-hydroxymethyl-ethyl)-phenyl]-amide**

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[0195] To a mixture of 2-(4-((4-cyano-1H-imidazole-2-carbonyl)-amino)-3-cyclohex-1-enyl-phenyl)-malonic acid dimethyl ester (as prepared in the previous step, 30.0 mg, 0.0710 mmol) and NaBH₄ (13.4 mg, 0.355 mmol) in 1 mL of tert-butyl alcohol (*t*-BuOH) at 80 °C was added MeOH (50 μL) over 5 min. The resulting mixture was stirred at 80 °C for 16 h under Ar. After cooling to RT, the mixture was treated with 10 % aq citric acid to a pH of 7. The mixture was then treated with 30 mL of EtOAc, washed with H₂O (5 mL) and brine (10 mL). The organic layer was dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel with 1-5 % MeOH-DCM to afford 14.1 mg (61 %) of the title compound as a white solid: ¹H-NMR (CD₃OD; 400 MHz): δ 8.00 (s, 1H), 7.54 (dd, 1H, J = 8.2, 2.3 Hz), 7.46 (d, 1H, J = 2.3 Hz), 7.27 (d, 1H, J = 8.2 Hz), 5.59 (m, 1H), 3.71-3.84 (m, 4H), 3.29 (m, 1H), 2.15-2.29 (m, 4H), 1.67-1.84 (m, 4H). Mass spectrum (ESI, m/z): Calcd. for C₂₀H₂₂N₄O₃, 367.2 (M+H), found 366.8.

30 **Example 12**

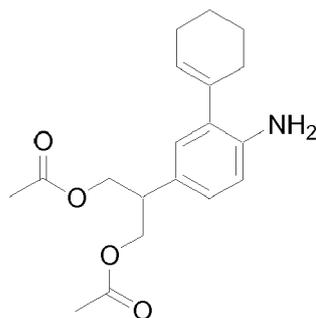
Acetic acid 3-acetoxy-2-(4-((4-cyano-1H-imidazole-2-carbonyl)-amino)-3-cyclohex-1-enyl-phenyl)-propylester trifluoroacetic acid salt

35 [0196]



40
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a) **Acetic acid 3-acetoxy-2-(4-amino-3-cyclohex-1-enyl-phenyl)-propyl ester**

50 [0197]

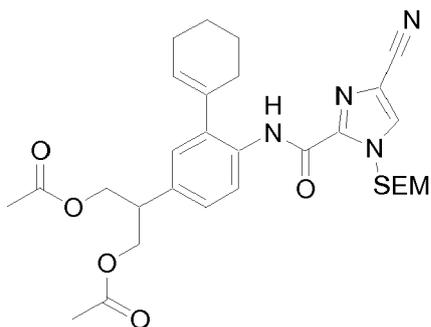


[0198] To a solution of acetic acid 3-acetoxy-2-(4-amino-phenyl)-propyl ester (Tetrahedron, 46(20), 7081, (1990), 1.2 g, 5.0 mmol) in DCM (50 mL), NBS (903 mg, 5.07 mol) was added at 0 °C. The resulting mixture was stirred at RT for 2 h and subjected to the usual work up to obtain acetic acid 3-acetoxy-2-(4-amino-3-bromo-phenyl)-propyl ester (1.4 g, 89 %) which was directly used in the next step.

[0199] The title compound was prepared according to the Suzuki coupling procedure of Example 1, step (e) using acetic acid 3-acetoxy-2-(4-amino-3-bromo-phenyl)-propyl ester (as prepared above) and cyclohex-1-enyl boronic acid: Mass spectrum, (ESI, m/z): Calcd. for $C_{19}H_{25}NO_4$, 332.1 (M+H), found 332.1.

b) Acetic acid 3-acetoxy-2-(4-[[4-cyano-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-imidazole-2-carbonyl]-amino]-3-cyclohex-1-enyl-phenyl)-propyl ester

[0200]



[0201] Acetic acid 3-acetoxy-2-(4-amino-3-cyclohex-1-enyl-phenyl)-propyl ester (as prepared in the previous step) was coupled to 4-cyano-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid, potassium salt (as prepared in Example 1, step (d)) as described in Example 1, step (f) to obtain the title compound: Mass spectrum (ESI, m/z): Calcd. for $C_{30}H_{40}N_4O_6Si$, 581.2 (M+H), found 581.0.

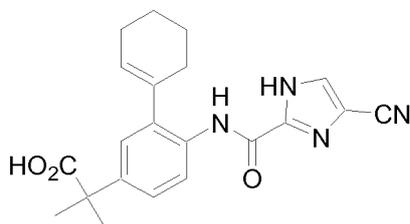
c) Acetic acid 3-acetoxy-2-(4-[[4-cyano-1H-imidazole-2-carbonyl]-amino]-3-cyclohex-1-enyl-phenyl)-propylester trifluoroacetic acid salt

[0202] A solution of acetic acid 3-acetoxy-2-(4-[[4-cyano-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-imidazole-2-carbonyl]-amino]-3-cyclohex-1-enyl-phenyl)-propyl ester (as prepared in the previous step, 102 mg, 0.175 mmol) in DCM (2 mL) was treated with ethyl alcohol (EtOH) (60 μ l) and TFA (0.6 mL) at RT for 2 h and concentrated in vacuo. The reaction mixture was dissolved in DCM (10 mL) and poured into satd aq $NaHCO_3$. The organic layer was separated, dried (Na_2SO_4) and concentrated. The solid obtained was suspended in 1:1 ether/hexane, sonicated and concentrated in vacuo. The resulting residue was dried in vacuo to obtain the title compound (57 mg, 57 %): 1H -NMR ($CDCl_3$; 400 MHz): δ 12.90 (br s, 1H), 9.75 (s, 1H), 8.32 (d, 1H, J = 8.4 Hz), 7.78 (s, 1H), 7.24 (dd, 1H, J = 8.4, 2.0 Hz), 7.06 (d, 1H, J = 2.0 Hz), 5.82 (br s, 1H), 4.38 (m, 4H), 3.35 (m, 1H), 2.23-2.35 (m, 4H), 2.10 (s, 6H), 1.75-1.92 (m, 4H): Mass spectrum, (ESI, m/z): Calcd. for $C_{24}H_{26}N_4O_5$, 451.2 (M+H), found 451.0.

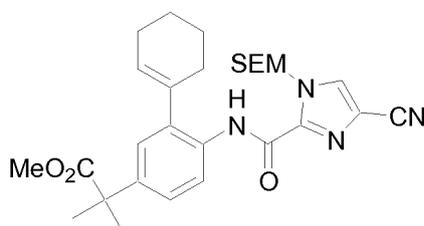
Example 13

2-{4-[(4-Cyano-1H-imidazole-2-carbonyl)-amino]-3-cyclohex-1-enyl-phenyl}-2-methyl-propionic acid

[0203]

**a) 2-(4-[(4-Cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carbonyl)-amino]-3-cyclohex-1-enyl-phenyl)-2-methyl-propionic acid methyl ester**

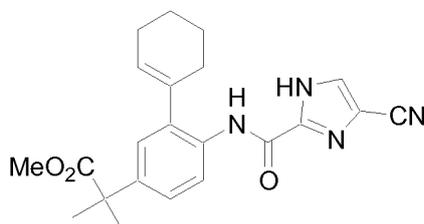
[0204]



[0205] A mixture of 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid (4-bromo-2-cyclohex-1-enyl-phenyl)-amide (as prepared in Example 1, step (f), 100 mg, 0.200 mmol), (1-methoxy-2-methyl-propenyloxy)-trimethyl-silane (61 μ L, 0.30 mmol), Pd(*t*-Bu₃P)₂ (10.2 mg, 0.0200 mmol) and ZnF₂ (10.3 mg, 0.100 mmol) in 2 mL of DMF was stirred at 80 °C for 2 d under Ar. After cooling to RT, the mixture was treated with H₂O (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with H₂O (10 mL) and brine (10 mL). After drying over Na₂SO₄ and concentrating *in vacuo*, the residue was purified by silica gel chromatography (DCM) to afford the title compound (48 mg, 46 %) as a colorless oil. LC-MS (ESI, *m/z*): Calcd. for C₂₈H₃₈N₄O₄Si, 523.3 (M+H), found 523.0.

b) 2-(4-[(4-Cyano-1H-imidazole-2-carbonyl)-amino]-3-cyclohex-1-enyl-phenyl)-2-methyl-propionic acid methyl ester

[0206]



[0207] The title compound was prepared by the procedure of Example 1, step (g) using 2-(4-[(4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carbonyl)-amino]-3-cyclohex-1-enyl-phenyl)-2-methyl-propionic acid methyl ester (as prepared in the previous step, 80.0 mg, 0.153 mmol). The title compound (60 mg, 100 %) is a white solid. Mass spectrum (ESI, *m/z*): Calcd. for C₂₂H₂₄N₄O₃, 393.2 (M+H), found 393.1.

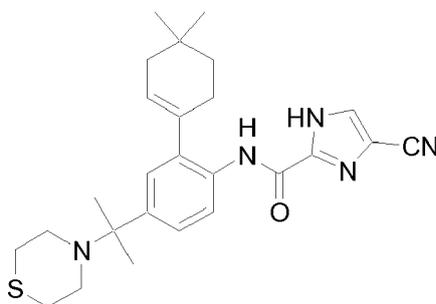
c) 2-{4-[(4-Cyano-1H-imidazole-2-carbonyl)-amino]-3-cyclohex-1-enyl-phenyl}-2-methyl-propionic acid

[0208] To a solution of 2-{4-[(4-cyano-1H-imidazole-2-carbonyl)-amino]-3-cyclohex-1-enyl-phenyl}-2-methyl-propionic acid methyl ester (as prepared in the previous step, 60.0 mg, 0.153 mmol) in 1 mL of 1:1 THF/MeOH was added 6 N NaOH (250 μ L, 1.50 mmol). After stirring at RT for 18 h, the mixture was treated with 10 mL of H₂O and washed with EtOAc (3 x 10 mL). The aqueous layer was acidified to a pH of 6 with 1 N aqueous HCl and extracted with 10:1 EtOAc-MeOH (3 x 10 mL). The combined organic layers were washed with H₂O (10 mL), brine (10 mL) and dried (Na₂SO₄). The organic solvent was evaporated in vacuo to give the title compound (48 mg, 83 %) as a white solid. ¹H-NMR (CD₃OD; 400 MHz): δ 8.19 (m, 1H), 7.90 (s, 1H), 7.31 (m, 1H), 7.20 (s, 1H), 5.84 (m, 1H), 2.17-2.40 (m, 4H), 1.76-1.92 (m, 4H), 1.57 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for C₂₁H₂₂N₄O₃, 379.2 (M+H), found 379.2.

Example 14

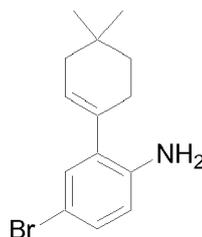
4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(1-methyl-1-thiomorpholin-4-yl-ethyl)-phenyl]-amide

[0209]



a) 4-Bromo-2-(4,4-dimethyl-cyclohex-1-enyl)-phenylamine

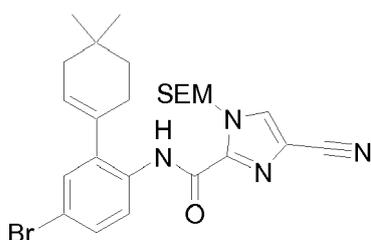
[0210]



[0211] A mixture of 4-bromo-2-iodo-phenylamine (873 mg, 2.93 mmol), 4,4-dimethylcyclohexen-1-ylboronic acid (496 mg, 3.22 mmol), Pd(PPh₃)₄ (169 mg, 0.147 mmol) and 2.0 M aq Na₂CO₃ (11.7 mL, 23.4 mmol) in 20 mL of 1,4-dioxane was stirred at 80 °C for 12 h under Ar. After cooling to RT, the reaction was treated with EtOAc (50 mL) and washed with H₂O (25 mL) and brine (20 mL). The organic layer was dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (5 % EtOAc/hexane) to afford 770 mg (91 %) of the title compound as a colorless oil. Mass spectrum (ESI, m/z): Calcd. for C₁₄H₁₈BrN, 280.1 (M+H), found 280.1.

b) 4-Cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [4-bromo-2-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-amide

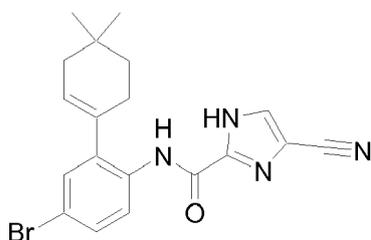
[0212]



10 **[0213]** To a mixture of 4-bromo-2-(4,4-dimethyl-cyclohex-1-enyl)-phenylamine (as prepared in the previous step, 770 mg, 2.75 mmol), potassium 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylate (as prepared in Example 1, step (d), 840 mg, 2.75 mmol) and PyBroP (1.28 g, 2.75 mmol) in 20 mL of DMF was added DIEA (1.44 mL, 8.25 mmol). The resulting mixture was stirred at RT for 16 h under Ar. Treated with 80 mL of EtOAc, the mixture was washed with H₂O (2 x 20 mL), brine (20 mL) and dried (Na₂SO₄). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (5-10 % EtOAc/hexane) gave 1.28 g (88 %) of the title compound as a white solid. Mass spectrum (ESI, m/z): Calcd. for C₂₅H₃₃ BrN₄O₂Si, 529.2 (M+H), found 528.9.

15 **c) 4-Cyano-1H-imidazole-2-carboxylic acid [4-bromo-2-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-amide**

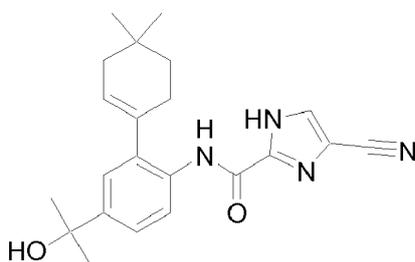
20 **[0214]**



30 **[0215]** The title compound was prepared by the procedure of Example 1, step (g) using 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [4-bromo-2-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-amide (as prepared in the previous step, 350 mg, 0.661 mmol). The title compound (253 mg, 96 %) was obtained as a white solid. ¹H-NMR (CDCl₃; 400 MHz): δ 8.19 (d, 2H, J = 8.8 Hz), 7.50 (d, 2H, J = 8.8 Hz), 6.23 (m, 1H), 4.12 (m, 2H), 3.66 (m, 2H), 2.54 (m, 2H), 1.49 (s, 9H). Mass spectrum (ESI, m/z): Calcd. for C₁₉H₁₉BrN₄O, 399.1 (M+H), found 399.1.

35 **d) 4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-amide**

40 **[0216]**



50 **[0217]** To a solution of 4-cyano-1H-imidazole-2-carboxylic acid [4-bromo-2-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-amide (as prepared in the previous step, 200 mg, 0.501 mmol) in 8 mL of THF at -78 °C under Ar was added isopropylmagnesium chloride (275 μL, 0.551 mmol, 2.0 M in THF). The resulting mixture was warmed to RT and stirred for 5 min, cooled to -78 °C again. To the mixture was added tert-butyllithium (884 μL, 1.50 mmol, 1.7 M in pentane) and the resulting mixture was stirred at -78 °C for 10 min. Acetone (736 μL, 10.0 mmol) was then added, and the reaction was warmed to RT and stirred for 0.5 h under Ar. The mixture was treated with 5 mL of saturated NH₄Cl followed by 40 mL of EtOAc, washed with brine (10 mL) and dried (Na₂SO₄). Removal of the solvent under reduced pressure followed

by flash chromatography of the residue on silica gel (1-4 % MeOH/DCM) gave 101 mg (53 %) of the title compound as a white solid. ¹H-NMR (CDCl₃; 400 MHz): δ 12.52 (s, 1H), 9.68 (s, 1H), 8.29 (d, 1H, J = 8.6 Hz), 7.72 (d, 1H, J = 2.3 Hz), 7.42 (dd, 1H, J = 8.6, 2.3 Hz), 7.35 (d, 1H, J = 2.3 Hz), 5.78 (m, 1H), 2.64 (s, 1H, OH), 2.30 (m, 2H), 2.11 (m, 2H), 1.62 (s, 6H), 1.59 (t, 2H, J = 6.5 Hz), 1.11 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for C₂₂H₂₆N₄O₂, 379.2 (M+H), found 379.3.

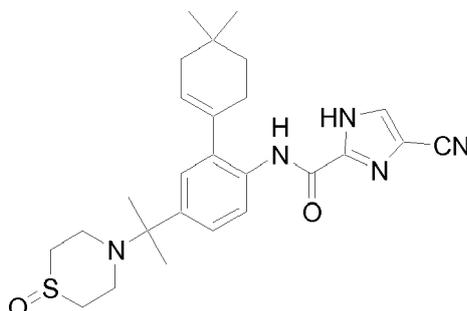
e) 4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(1-methyl-1-thiomorpholin-4-yl-ethyl)-phenyl]-amide

[0218] To a suspension of 4-cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-amide (as prepared in the previous step, 65 mg, 0.17 mmol) in 1.5 mL of DCM at 0 °C was added SOCl₂ (38 μL, 0.52 mmol) under Ar. After stirring at RT for 1 h, the mixture was cooled back to 0 °C. To the reaction was added thiomorpholine (172 μL, 1.72 mmol) and the resulting mixture was stirred at 0 °C for 1 h. After warming to RT, the mixture was treated with EtOAc (30 mL) and washed with H₂O (2 x 10 mL) and brine (10 mL). The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (5 % EtOAc/DCM then 1-2 % MeOH/DCM) to afford the title compound (70 mg, 88 %) as a white solid. ¹H-NMR (CDCl₃; 400 MHz): δ 11.90 (s, 1H), 9.65 (s, 1H), 8.28 (d, 1H, J = 8.6 Hz), 7.74 (s, 1H), 7.45 (dd, 1H, J = 8.6, 2.3 Hz), 7.33 (d, 1H, J = 2.3 Hz), 5.78 (m, 1H), 2.77 (m, 4H), 2.65 (m, 4H), 2.29 (m, 2H), 2.12 (m, 2H), 1.60 (t, 2H, J = 6.3 Hz), 1.33 (s, 6H), 1.12 (s, 6H). Mass spectrum (ESI-neg, m/z): Calcd. for C₂₆H₃₃N₅OS, 462.2 (M-H), found 462.4.

Example 15

4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1-methyl-1-(1-oxo-1,4-thiomorpholin-4-yl)-ethyl]-phenyl]-amide

[0219]



[0220] To a solution of 4-cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(1-methyl-1-thiomorpholin-4-yl-ethyl)-phenyl]-amide (as prepared in Example 14, step (e), 30.0 mg, 0.0647 mmol) in 0.5 mL of DCM at RT was added titanium (IV) isopropoxide (19 μL, 0.065 mmol). The mixture was cooled to 0 °C and H₂O₂ (13 μL, 0.13 mmol, 30 wt % in H₂O) was added. After stirring at 0 °C for 4 h, the mixture was treated with EtOAc (50 mL) and washed with H₂O (2 x 10 mL) and brine (10 mL). The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*, the residue was purified by silica gel chromatography (1-4 % MeOH/DCM) to afford the title compound (30 mg, 95 %) as a colorless oil. ¹H-NMR (CDCl₃; 400 MHz): δ 13.06 (s, 1H), 9.63 (s, 1H), 8.34 (d, 1H, J = 8.6 Hz), 7.71 (s, 1H), 7.51 (dd, 1H, J = 8.6, 2.0 Hz), 7.27 (d, 1H, J = 2.0 Hz), 5.78 (m, 1H), 3.17 (m, 2H), 2.84-3.08 (m, 4H), 2.71 (m, 2H), 2.28 (m, 2H), 2.11 (m, 2H), 1.60 (t, 2H, J = 6.3 Hz), 1.40 (s, 6H), 1.11 (s, 6H). Mass spectrum (ESI-neg, m/z): Calcd. for C₂₆H₃₃N₅O₂S, 478.2 (M-H), found 478.3.

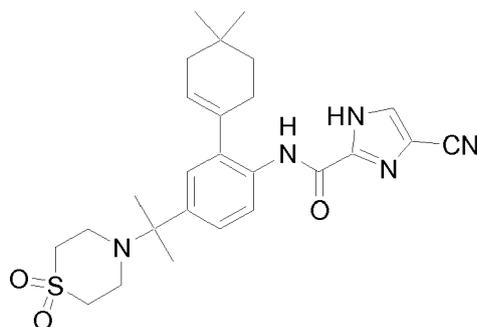
Example 16

4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1-methyl-1-(2-methylsulfanyl-ethylamino)-ethyl]-phenyl]-amide

[0221]

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[0222] To a solution of 4-cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(1-methyl-1-thiomorpholin-4-yl-ethyl)-phenyl]-amide (as prepared in Example 14, step (e), 38.0 mg, 0.0820 mmol) in 0.5 mL of DCM at RT was added titanium (IV) isopropoxide (24.0 μ L, 0.0820 mmol). The mixture was cooled to 0 °C and H₂O₂ (18 μ L, 0.16 mmol, 30 wt % in H₂O) was added. After stirring at 0 °C for 0.5 h and at -20 °C for 16 h, the mixture was treated with EtOAc (50 mL) and washed with H₂O (2 x 10 mL) and brine (10 mL). The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (15-25 % EtOAc/DCM) to afford the title compound (33 mg, 80 %) as a white solid. ¹H-NMR (CD₃OD; 400 MHz): δ 8.16 (d, 1H, J = 8.6 Hz), 7.99 (s, 1H), 7.49 (dd, 1H, J = 8.6, 2.3 Hz), 7.37 (d, 1H, J = 2.3 Hz), 5.74 (m, 1H), 2.91-3.07 (m, 8H), 2.31 (m, 2H), 2.08 (m, 2H), 1.60 (t, 2H, J = 6.3 Hz), 1.42 (s, 6H), 1.09 (s, 6H). Mass spectrum (ESI-neg, m/z): Calcd. for C₂₆H₃₃N₅O₃S, 494.2 (M-H), found 494.2.

25

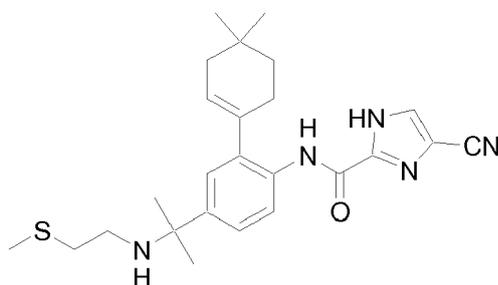
Example 17**4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1-methyl-1-(2-methylsulfanyl-ethylamino)-ethyl]-phenyl]-amide**

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[0223]

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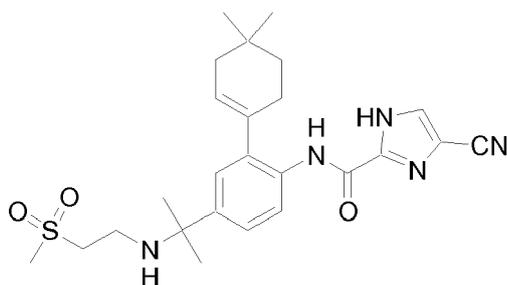
[0224] The title compound was prepared by the procedure of Example 14, step (e) using 4-cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-amide (as prepared in Example 14, step (d), 120 mg, 0.317 mmol) and 2-methylsulfanyl-ethylamine (69.0 μ L, 0.951 mmol). Silica gel chromatography (1-4 % MeOH/DCM) afforded the title compound (72 mg, 50 %) as a white solid. ¹H-NMR (CD₃OD; 400 MHz): δ 8.26 (d, 1H, J = 8.6 Hz), 7.94 (s, 1H), 7.39 (dd, 1H, J = 8.6, 2.3 Hz), 7.32 (d, 1H, J = 2.3 Hz), 5.75 (m, 1H), 2.51-2.61 (m, 4H), 2.29-2.36 (m, 2H), 2.05-2.12 (m, 2H), 1.91 (s, 3H), 1.60 (t, 2H, J = 6.3 Hz), 1.54 (s, 6H), 1.09 (s, 6H). Mass spectrum (ESI-neg, m/z): Calcd. for C₂₅H₃₃N₅OS, 450.4 (M-H), found 450.2.

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Example 18**4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1-(2-methanesulfonyl-ethylamino)-1-methyl-ethyl]-phenyl]-amide**

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[0225]

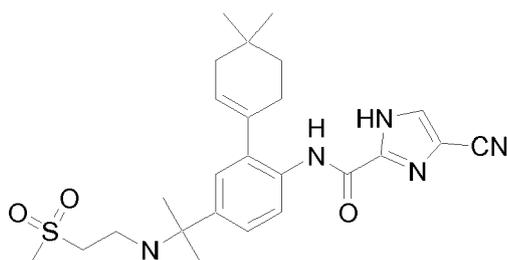


[0226] The title compound was prepared by the procedure of Example 16 using 4-cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1-methyl-1-(2-methanesulfonyl-ethyl-amino)-ethyl]-phenyl}-amide (as prepared in Example 17, 63.0 mg, 0.140 mmol). Silica gel chromatography (1-3 % MeOH/DCM) afforded the title compound (47 mg, 70 %) as a white solid. ¹H-NMR (CDCl₃; 400 MHz): δ 9.67 (s, 1H), 8.31 (d, 1H, J = 8.6 Hz), 7.75 (s, 1H), 7.40 (dd, 1H, J = 8.6, 2.3 Hz), 7.25 (d, 1H, J = 2.3 Hz), 5.78 (m, 1H), 4.23-6.25 (br s, 2H), 3.14 (t, 2H, J = 6.0 Hz), 2.98 (s, 3H), 2.89 (t, 2H, J = 6.0 Hz), 2.30 (m, 2H), 2.11 (m, 2H), 1.60 (t, 2H, J = 6.3 Hz), 1.49 (s, 6H), 1.11 (s, 6H). Mass spectrum (ESI-neg, m/z): Calcd. for C₂₅H₃₃N₅O₃S, 482.2 (M-H), found 482.4.

Example 19

4-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1-[(2-methanesulfonyl-ethyl)-methyl-amino]-1-methyl-ethyl]-phenyl}-amide

[0227]



[0228] A mixture of 4-cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1-(2-methanesulfonyl-ethyl-amino)-1-methyl-ethyl]-phenyl}-amide (as prepared in Example 18, 8.0 mg, 0.017 mmol), iodomethane (25 μL, 0.40 mmol) and solid NaHCO₃ (25 mg, 0.30 mmol) in 1.0 mL of THF was stirred at RT for 6 h. The solvent was removed by evaporation and the residue was purified by silica gel chromatography (0-2 % MeOH/DCM) to afford the title compound (5.0 mg, 61 %) as a colorless oil. ¹H-NMR (CDCl₃; 400 MHz): δ 11.90 (s, 1H), 9.63 (s, 1H), 8.31 (d, 1H, J = 8.6 Hz), 7.75 (s, 1H), 7.41 (dd, 1H, J = 8.6, 2.3 Hz), 7.28 (d, 1H, J = 2.3 Hz), 5.77 (m, 1H), 3.11 (t, 2H, J = 7.1 Hz), 2.87 (s, 3H), 2.84 (t, 2H, J = 6.0 Hz), 2.29 (m, 2H), 2.24 (s, 3H), 2.11 (m, 2H), 1.60 (t, 2H, J = 6.3 Hz), 1.40 (s, 6H), 1.11 (s, 6H). Mass spectrum (ESI-neg, m/z): Calcd. for C₂₆H₃₅N₅O₃S, 496.3 (M-H), found 496.1.

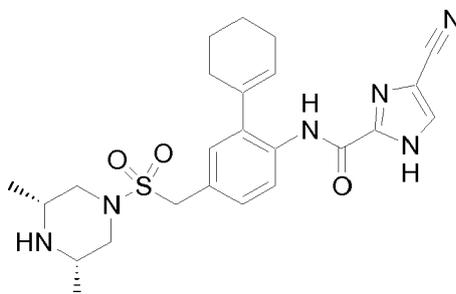
[0229] The following compounds were prepared according to the examples as indicated:

Example	Name	Structure	Procedure	Mass Spectrum (ESI-neg, m/z)
20	4-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1-(2-methoxy-ethylamino)-1-methylethyl]-phenyl}-amide		Ex. 14, step (e)	Calcd. for C ₂₅ H ₃₃ N ₅ O ₂ , 434.3 (M-H), found 434.4.
21	4-Cyano-1H-imidazole-2-carboxylic acid (2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1-(2-methoxy-ethyl)-methyl-amino]-1-methylethyl]-phenyl)-amide		Ex. 14, step (e)	Calcd. for C ₂₆ H ₃₅ N ₅ O ₂ , 448.3 (M-H), found 448.5.
22	4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(1-methyl-1-morpholin-4-yl-ethyl)-phenyl]-amide		Ex. 14, step (e)	Calcd. for C ₂₆ H ₃₃ N ₆ O ₂ , 446.3 (M-H), found 446.4.
23	4-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1-methyl-1-(4-methyl-piperazin-1-yl)-ethyl]-phenyl}-amide		Ex. 14, step (e)	Calcd. for C ₂₇ H ₃₆ N ₆ O, 459.3 (M-H), found 459.5.
24	4-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1-methyl-1-(2-morpholin-4-yl-ethylamino)-ethyl]-phenyl}-amide		Ex. 14, step (e)	Calcd. for C ₂₈ H ₃₈ N ₆ O ₂ , 489.3 (M-H), found 489.5.

Example 25

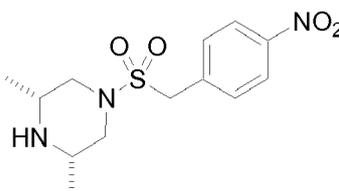
4-Cyano-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(3,5-cis-dimethyl-piperazine-1-sulfonylmethyl)-phenyl]-amide

[0230]



a) Cis-3,5-dimethyl-1-(4-nitro-phenylmethanesulfonyl)-piperazine

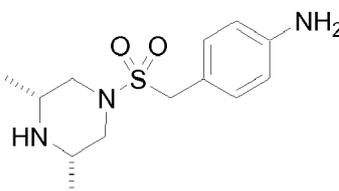
[0231]



[0232] A solution of 250 mg (1.06 mmol) of 4-nitrophenylmethanesulfonyl chloride and 133 mg (1.17 mmol) of cis-2,6-dimethylpiperazine in CH_2Cl_2 (10 mL) was treated with 325 μL (2.33 mmol) of triethylamine at RT for 20 min. The mixture was diluted with CH_2Cl_2 (15 mL) and washed with water (1 x 15 mL). The organic layer was dried (MgSO_4) and concentrated in vacuo to afford 298 mg (90 %) of the title compound as an off-white solid: $^1\text{H-NMR}$ (CDCl_3 ; 400 MHz): δ 8.25 (d, 2H, $J = 8.8$ Hz), 7.87 (d, 2H, $J = 8.8$ Hz), 4.24 (s, 1H), 3.59-3.53 (m, 2H), 2.92-2.82 (m, 2H), 2.30-2.23 (m, 2H), 1.04 (d, 6H, $J = 6.0$ Hz). Mass spectrum (ESI, m/z): Calcd. for $\text{C}_{13}\text{H}_{19}\text{N}_3\text{O}_4\text{S}$, 314.1 (M+H), found 314.1.

b) 4-(Cis-3,5-dimethyl-piperazine-1-sulfonylmethyl)-phenylamine

[0233]



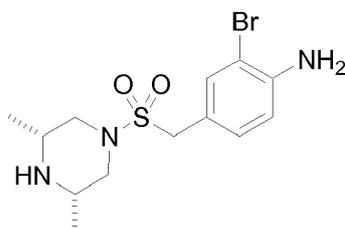
[0234] A solution of 298 mg (0.951 mmol) of cis-3,5-dimethyl-1-(4-nitrophenylmethanesulfonyl)-piperazine (as prepared in the previous step) in MeOH (15 mL) was treated with 20 mg of 10 % Pd/C (Degussa type E101-NE/W, Aldrich, 50 % by weight water) and H_2 (1 atm) at RT for 18 h. The mixture was filtered through Celite, and the filter cake was washed with MeOH. The solvent was removed in vacuo to afford 283 mg (100 %) the title compound as an off-white solid: $^1\text{H-NMR}$ (CDCl_3 ; 400 MHz): δ 7.14 (d, 2H, $J = 8.4$ Hz), 6.66 (d, 2H, $J = 8.4$ Hz), 4.08 (s, 2H), 3.75 (br s, 2H), 3.52-3.50 (m, 1H), 3.48 (s, 4H), 2.88-2.76 (m, 2H), 2.23-2.15 (m, 2H).

c) 2-Bromo-4-(cis-3,5-dimethyl-piperazine-1-sulfonylmethyl)-phenylamine

[0235]

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[0236] A solution of 283 mg (0.999 mmol) of 4-(cis-3,5-dimethyl-piperazine-1-sulfonylmethyl)-phenyl amine (as prepared in the previous step) in CH_2Cl_2 (15 mL) was cooled to -78°C and treated portionwise with 176 mg (0.989 mmol) of NBS. The mixture was stirred at -78°C for 1 h and at RT for 2 h. The mixture was diluted with CH_2Cl_2 (15 mL) and washed with saturated aqueous NaHCO_3 (1 x 20 mL) and brine (1 x 20 mL). The organic layer was dried (MgSO_4) and concentrated in vacuo to afford 356 mg (98 %) of the title compound as a tan solid: Mass spectrum (ESI, m/z): Calcd. for $\text{C}_{13}\text{H}_{20}\text{N}_3\text{O}_2\text{SBr}$, 362.0/364.0 (M+H), found 361.8/363.3.

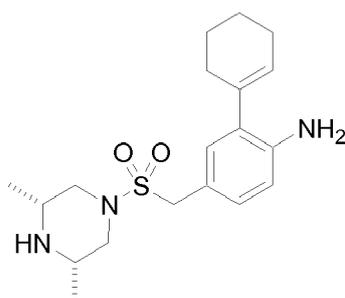
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d) 2-Cyclohex-1-enyl-4-(cis-3,5-dimethyl-piperazine-1-sulfonylmethyl)-phenylamine

[0237]

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[0238] A solution of 356 mg (0.983 mmol) of 2-bromo-4-(cis-3,5-dimethyl-piperazine-1-sulfonylmethyl)-phenylamine (as prepared in the previous step) in toluene (8 mL) and EtOH (4 mL) was treated with 3.93 mL (7.86 mmol) of 2.0 M aqueous Na_2CO_3 and 186 mg (1.47 mmol) of cyclohex-1-enylboronic acid. The mixture was degassed via sonication, placed under Ar, treated with 170 mg (0.147 mmol) of $\text{Pd}(\text{PPh}_3)_4$, and heated to 80°C for 4.3 h. The mixture was cooled to RT, diluted with EtOAc (10 mL), and washed with saturated aqueous NaHCO_3 (1 x 10 mL) and brine (1 x 10 mL). The organic layer was dried (MgSO_4) and concentrated in vacuo. Silica gel chromatography of the residue with 0-4 % $\text{MeOH}-\text{CH}_2\text{Cl}_2$ afforded 307 mg (86 %) of the title compound as a white solid: $^1\text{H-NMR}$ (CDCl_3 ; 400 MHz): δ 7.01 (dd, 1H, $J = 8.0, 2.0$ Hz), 6.99 (d, 1H, $J = 2.0$ Hz), 6.57 (d, 1H, $J = 8.0$ Hz), 5.77-5.72 (m, 1H), 4.07 (s, 2H), 3.85 (br s, 2H), 3.55-3.47 (m, 2H), 2.88-2.77 (m, 2H), 2.26-2.13 (m, 6H), 1.81-1.73 (m, 2H), 1.72-1.64 (m, 2H), 0.99 (d, 6H, $J = 6.0$ Hz).

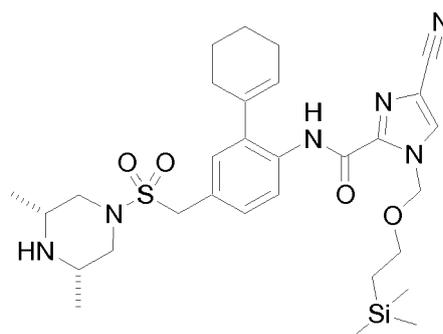
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e) 4-Cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(cis-3,5-dimethyl-piperazine-1-sulfonylmethyl)-phenyl]-amide

[0239]

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[0240] A solution of 153 mg (0.422 mmol) of 2-cyclohex-1-enyl-4-(cis-3,5-dimethylpiperazine-1-sulfonylmethyl)-phenylamine (as prepared in the previous step) in CH_2Cl_2 (10 mL) was treated with 295 mg (0.633 mmol) of PyBroP and 142 mg (0.464 mmol) of 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylate potassium salt (as prepared in Example 1, step (d)) to form a slurry, which was cooled to 0 °C, treated with 184 μL (1.06 mmol) of DIEA, and warmed to RT for 6.5 h. The mixture was diluted with CH_2Cl_2 (15 mL) and washed with saturated aqueous NaHCO_3 (1 x 15 mL) and brine (1 x 15 mL). The organic layer was dried (MgSO_4) and concentrated in vacuo to afford 163 mg (63 %) of the title compound as a white solid: Mass spectrum (ESI, m/z): Calcd. for $\text{C}_{30}\text{H}_{44}\text{N}_6\text{O}_4\text{SSi}$, 613.3 (M+H), found 612.9.

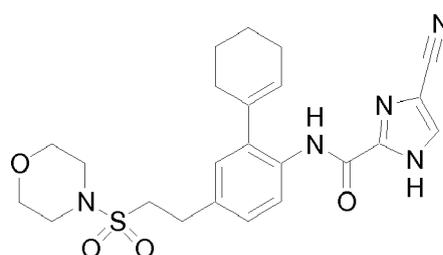
f) 4-Cyano-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(cis-3,5-dimethylpiperazine-1-sulfonylmethyl)-phenyl]-amide

[0241] A solution of 163 mg (0.266 mmol) of 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(cis-3,5-dimethylpiperazine-1-sulfonylmethyl)-phenyl]-amide (as prepared in the previous step) in CH_2Cl_2 (15 mL) was treated with EtOH (300 μL) and TFA (4.5 mL), and stirred at RT for 4 h. Solvents were evaporated in vacuo, and the residue was purified by reverse phase high pressure liquid chromatography (RP-HPLC) (C18) with 10-80 % CH_3CN in 0.1 % TFA/ H_2O over 30 min to afford 8.8 mg (7 %) of the title compound as a white solid: $^1\text{H-NMR}$ (CD_3OD ; 400 MHz): δ 8.31 (d, 1H, J = 8.4 Hz), 8.04 (s, 1H), 7.39 (dd, 1H, J = 8.4, 2.0 Hz), 7.33 (d, 1H, J = 2.0 Hz), 5.91-5.87 (m, 1H), 4.47 (s, 2H), 3.87-3.79 (m, 2H), 3.31-3.25 (m, 2H), 2.76-2.67 (m, 2H), 2.36-2.27 (m, 4H), 1.94-1.79 (m, 4H), 1.29 (d, 6H, J = 6.4 Hz). Mass spectrum (ESI, m/z): Calcd. for $\text{C}_{24}\text{H}_{30}\text{N}_6\text{O}_3\text{S}$, 483.2 (M+H), found 482.9.

Example 26

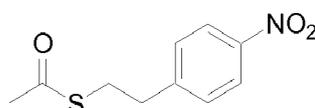
4-Cyano-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-[2-(morpholine-4-sulfonyl)-ethyl]-phenyl]-amide

[0242]



a) Thioacetic acid S-[2-(4-nitro-phenyl)-ethyl]ester

[0243]

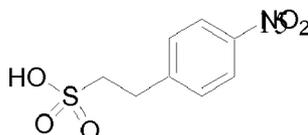


[0244] A solution of 2.00 g (8.69 mmol) of 1-(2-bromo-ethyl)-4-nitro-benzene in DMSO (10 mL) was treated with 1.99

g (17.4 mmol) of potassium thioacetate and stirred at RT for 5 h. The mixture was diluted with EtOAc (100 mL) and washed with water (6 x 60 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo to afford 1.48 g (76 %) of the title compound as a brown oil: ¹H-NMR (CD₃OD; 400 MHz): δ 8.23-8.15 (m, 2H), 7.60-7.53 (m, 2H), 3.27-3.10 (m, 4H), 3.03-2.94 (m, 3H).

b) 2-(4-Nitro-phenyl)-ethanesulfonic acid

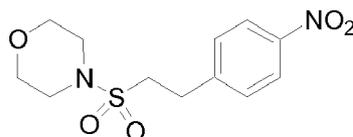
[0245]



[0246] A solution of 1.48 g (6.57 mmol) of thioacetic acid S-[2-(4-nitro-phenyl)-ethyl]ester (as prepared in the previous step) in acetic acid (30 mL) was treated with 30 % aqueous H₂O₂ (10 mL) and stirred at RT for 18 h. The mixture was diluted with water (50 mL) and solvents were removed in vacuo at <40 °C (caution: hazard). The residue was dried overnight on a high vacuum pump to afford 1.14 g (75 %) of the title compound as a pale yellow solid: Mass spectrum (ESI, negative mode, m/z): Calcd. for C₈H₉NO₅S, 230.0 (M-H), found 230.1.

c) 4-[2-(4-Nitro-phenyl)-ethanesulfonyl]-morpholine

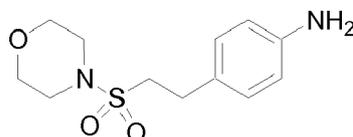
[0247]



[0248] A flask was charged with 491 mg (2.12 mmol) of solid 2-(4-nitro-phenyl)-ethanesulfonic acid (as prepared in the previous step), which was treated with 3.10 mL (42.4 mmol) of thionyl chloride and heated to 80 °C for 7 h. The volatile components were removed in vacuo, the residue was taken up in THF (20 mL), and 927 μL (10.6 mmol) of morpholine was added. The mixture was stirred at RT for 16 h, diluted with water (15 mL) and saturated aqueous NaHCO₃ (15 mL) and extracted with EtOAc (2 x 70 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo to afford 370 mg (52 %) of the title compound as a pale yellow solid: ¹H-NMR (CDCl₃; 400 MHz): δ 8.20 (d, 2H, J = 8.8 Hz), 7.40 (d, 2H, J = 8.8 Hz), 3.79-3.73 (m, 4H), 3.31-3.23 (m, 6H), 3.21-3.14 (m, 2H).

d) 4-[2-(Morpholine-4-sulfonyl)-ethyl]-phenylamine

[0249]

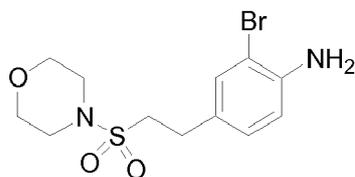


[0250] A solution of 370 mg (1.11 mmol) of 4-[2-(4-nitro-phenyl)-ethanesulfonyl]-morpholine (as prepared in the previous step) in MeOH (20 mL) was treated with 10 % Pd/C (Degussa type E101-NE/W, Aldrich, 50 % by weight water) and H₂ (1 atm) at RT for 3 h. The mixture was filtered through Celite, the filter cake was washed with MeOH, and solvents were evaporated in vacuo. Silica gel chromatography of the residue on a 50-g Varian MegaBond Elut SPE column with 50-70 % EtOAc-hexane afforded 103 mg (34 %) of the title compound as an off-white solid: Mass spectrum (ESI, m/z): Calcd. for C₁₂H₁₈N₂O₃S, 271.1 (M+H), found 270.9.

e) 2-Bromo-4-[2-(morpholine-4-sulfonyl)-ethyl]-phenylamine

[0251]

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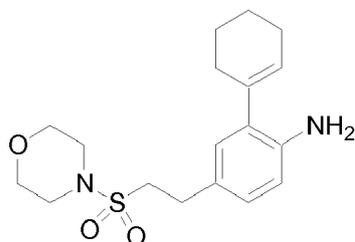
[0252] A solution of 103 mg (0.381 mmol) of 4-[2-(morpholine-4-sulfonyl)-ethyl]-phenylamine (as prepared in the previous step) in CH_2Cl_2 (15 mL) was cooled to 0 °C and treated portionwise with 67.8 mg (0.381 mmol) of solid NBS. The mixture was stirred at 0 °C for 15 min, diluted with CH_2Cl_2 (30 mL) and washed with saturated aqueous NaHCO_3 (1 x 20 mL). The organic layers were dried (MgSO_4) and concentrated in vacuo to afford 133 mg (100 %) of the title compound as a tan solid: Mass spectrum (ESI, m/z): Calcd. for $\text{C}_{12}\text{H}_{17}\text{N}_2\text{O}_3\text{SBr}$, 349.0/351.0 (M+H), found 348.7/350.8.

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f) 2-Cyclohex-1-enyl-4-[2-(morpholine-4-sulfonyl)-ethyl]-phenylamine

[0253]

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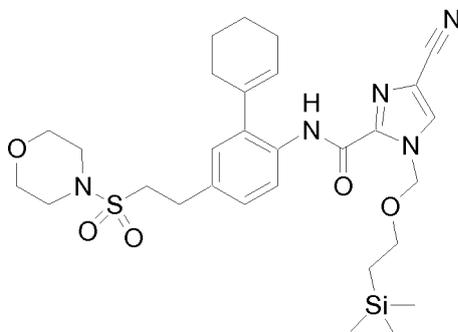
[0254] A solution of 133 mg (0.381 mmol) of 2-bromo-4-[2-(morpholine-4-sulfonyl)-ethyl]-phenylamine (as prepared in the previous step) in toluene (6 mL) and EtOH (3 mL) was treated with 1.52 mL (3.05 mmol) of 2.0 M aqueous Na_2CO_3 and 60.0 mg (0.476 mmol) of cyclohex-1-enylboronic acid. The mixture was degassed via sonication, placed under Ar, treated with 30.8 mg (0.027 mmol) of $\text{Pd}(\text{PPh}_3)_4$, and heated to 80 °C for 2.5 h. The mixture was cooled to RT, diluted with EtOAc (20 mL), and washed with saturated aqueous NaHCO_3 (1 x 15 mL) and brine (1 x 15 mL). The organic layer was dried (MgSO_4) and concentrated in vacuo to afford 132 mg (99 %) of the title compound as a tan solid: Mass spectrum (ESI, m/z): Calcd. for $\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_3\text{S}$, 351.2 (M+H), found 351.1.

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g) 4-Cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid {2-cyclohex-1-enyl-4-[2-(morpholine-4-sulfonyl)-ethyl]-phenyl}-amide

[0255]

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[0256] A solution of 132 mg (0.377 mmol) of 2-cyclohex-1-enyl-4-[2-(morpholine-4-sulfonyl)-ethyl]-phenylamine (as prepared in the previous step) in CH_2Cl_2 (15 mL) was treated with 126 mg (0.414 mmol) of 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylate potassium salt (as prepared in Example 1, step (d)), and 93.9 mg (0.565

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mmol) of PyBroP to form a slurry, which was treated with 197 μL (1.13 mmol) of DIEA. The mixture was stirred at RT for 3.5 h, diluted with CH_2Cl_2 (15 mL), and washed with saturated aqueous NaHCO_3 (1 x 20 mL). The organic layer was dried (MgSO_4) and concentrated in vacuo to afford 221 mg (98 %) of the title compound as an off-white solid: Mass spectrum (ESI, m/z): Calcd. for $\text{C}_{29}\text{H}_{41}\text{N}_5\text{O}_5\text{SSi}$, 600.3 (M+H), found 599.8.

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h) 4-Cyano-1H-imidazole-2-carboxylic acid {2-cyclohex-1-enyl-4-[2-(morpholine-4-sulfonyl)-ethyl]-phenyl}-amide

[0257] A solution of 221 mg (0.367 mmol) of 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid {2-cyclohex-1-enyl-4-[2-(morpholine-4-sulfonyl)-ethyl]-phenyl} -amide (as prepared in the previous step) in CH_2Cl_2 (20 mL) was treated with EtOH (3 drops) and TFA (1.8 mL) and stirred at RT for 2 h. Solvents were evaporated in vacuo, and the resulting residue was chromatographed on a 25-g Varian MegaBond Elut SPE column with 50-70 % EtOAc-hexane to afford 6.6 mg (4 %) of the title compound as a white solid: $^1\text{H-NMR}$ (CD_3OD ; 400 MHz): δ 8.15 (d, 1H, J = 8.0 Hz), 7.96 (s, 1H), 7.20 (dd, 1H, J = 8.0, 2.0 Hz), 7.12 (s, 1H, J = 2.0 Hz), 5.83-5.78 (m, 1H), 3.72-3.66 (m, 4H), 3.48-3.46 (m, 1H), 3.26-3.20 (m, 4H), 3.14-3.11 (m, 1H), 3.10-3.03 (m, 2H), 2.32-2.23 (m, 4H), 1.90-1.73 (m, 4H). Mass spectrum (ESI, m/z): Calcd. for $\text{C}_{23}\text{H}_{27}\text{N}_5\text{O}_4\text{S}$, 470.2 (M+H), found 469.9.

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Example 27

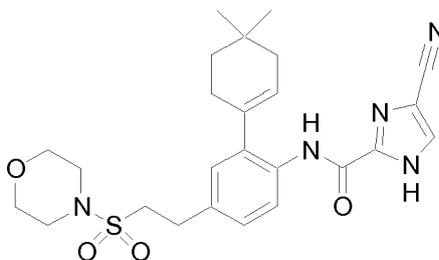
4-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[2-(morpholine-4-sulfonyl)-ethyl]-phenyl}-amide

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[0258]

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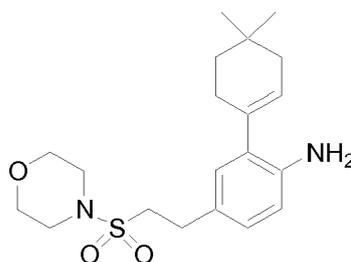
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a) 2-(4,4-Dimethyl-cyclohex-1-enyl)-4-[2-(morpholine-4-sulfonyl)-ethyl]-phenylamine

[0259]

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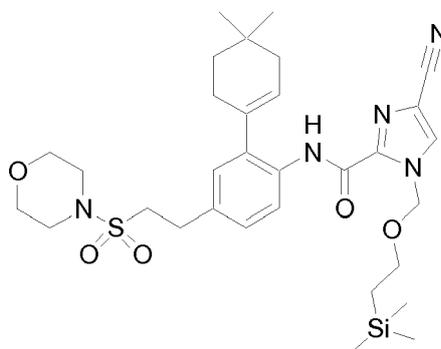


[0260] A solution of 40.0 mg (0.114 mmol) of 2-bromo-4-[2-(morpholine-4-sulfonyl)-ethyl]-phenylamine (as prepared Example 26, step (e)) in toluene (4 mL) and EtOH (2 mL) was treated with 458 μL (0.229 mmol) of 2.0 M aqueous Na_2CO_3 and 29.8 mg (0.226 mmol) of 4,4-dimethyl-cyclohex-1-enylboronic acid. The mixture was degassed via sonication, placed under Ar, treated with 13.2 mg (0.0110 mmol) of $\text{Pd}(\text{PPh}_3)_4$, and heated to 80 $^\circ\text{C}$ for 5 h. The mixture was cooled to RT, diluted with EtOAc (10 mL), and washed with saturated aqueous NaHCO_3 (1 x 10 mL) and brine (1 x 10 mL). The organic layer was dried (MgSO_4) and concentrated in vacuo to afford 60.0 mg of the title compound as a tan solid: Mass spectrum (ESI, m/z): Calcd. for $\text{C}_{20}\text{H}_{30}\text{N}_2\text{O}_3\text{S}$, 379.2 (M+H), found 379.1.

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b) 4-Cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[2-(morpholine-4-sulfonyl)-ethyl]-phenyl}-amide

[0261]



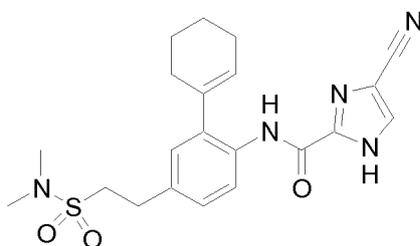
[0262] A solution of 60.0 mg of crude 2-(4,4-dimethyl-cyclohex-1-enyl)-4-[2-(morpholine-4-sulfonyl)-ethyl]-phenylamine (as prepared in the previous step) in CH_2Cl_2 (5 mL) was treated with 53.3 mg (0.174 mmol) of 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylate potassium salt (as prepared in Example 1, step (d)), and 111 mg (0.238 mmol) of PyBroP to form a slurry, which was treated with 82.8 μL (0.476 mmol) of DIEA. The mixture was stirred at RT for 4 h, diluted with CH_2Cl_2 (10 mL) and washed with saturated aqueous NaHCO_3 (1 x 10 mL). The organic layer was dried (MgSO_4) and concentrated in vacuo to afford 60.3 mg (crude) of the title compound as an off-white solid: Mass spectrum (ESI, m/z): Calcd. for $\text{C}_{31}\text{H}_{41}\text{N}_5\text{O}_5\text{SSi}$, 628.3 (M+H), found 628.0.

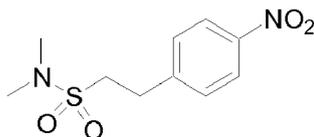
c) 4-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[2-(morpholine-4-sulfonyl)-ethyl]-phenyl}-amide

[0263] A solution of 60.3 mg of crude 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[2-(morpholine-4-sulfonyl)-ethyl]-phenyl}-amide (as prepared in the previous step) in CH_2Cl_2 (5 mL) was treated with EtOH (2 drops) and TFA (1 mL) and stirred at RT for 1.5 h. Solvents were evaporated in vacuo, and the residue was purified by RP-HPLC (C18) with 20-100 % CH_3CN in 0.1 % TFA/ H_2O over 30 min to afford 11.2 mg (20 % over three steps) of the title compound as a white solid: $^1\text{H-NMR}$ (CD_3OD ; 400 MHz): δ 8.16 (d, 1H, J = 8.4 Hz), 7.91 (s, 1H), 7.21 (dd, 1H, J = 8.4, 2.4 Hz), 5.76-5.71 (m, 1H), 3.71-3.65 (m, 4H), 3.50-3.46 (m, 1H), 3.26-3.20 (m, 4H), 3.14-3.11 (m, 1H), 3.10-3.04 (m, 2H), 3.35-2.27 (m, 2H), 2.10-2.05 (m, 2H), 1.59 (t, 2H, J = 6.4 Hz), 1.08 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for $\text{C}_{25}\text{H}_{31}\text{N}_5\text{O}_4\text{S}$, 498.2 (M+H), found 498.0.

Example 28**4-Cyano-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(2-dimethylsulfamoyl-ethyl)-phenyl]-amide**

[0264]

**a) 2-(4-Nitro-phenyl)-ethanesulfonic acid dimethylamide**



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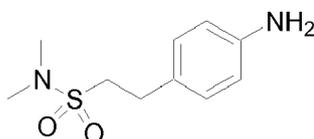
[0265] A flask was charged with 4.60 g (19.9 mmol) of solid 2-(4-nitro-phenyl)-ethanesulfonic acid (as prepared in Example 26, step (b)), which was treated with 29.0 mL (398 mmol) of thionyl chloride and heated to 80 °C for 6 h. Solvents were evaporated in vacuo, and the resulting solid was dried overnight under high vacuum. A solution of 2.12 g (8.49 mmol) of this solid sulfonyl chloride in 40 mL CH₂Cl₂ was treated with 15.0 mL (127 mmol) of 40 % w/v aqueous dimethylamine and stirred at RT for 16 h then warmed to 40 °C for 3 h. The mixture was diluted with CH₂Cl₂ (100 mL) and washed with water (2 x 50 mL). The aqueous layer was extracted with CH₂Cl₂ (50 mL). The combined organic layers were dried (MgSO₄) and concentrated in vacuo. Silica gel chromatography of the residue on a 50-g Varian MegaBond Elut SPE column with 50 % EtOAc-hexane afforded 912 mg (41 %) of the title compound as an off-white solid: ¹H-NMR (CD₃OD; 400 MHz): δ 8.20 (d, 2H, J = 8.8 Hz), 7.41 (d, 2H, J = 8.8 Hz), 3.29-3.14 (m, 4H), 2.89 (s, 6H).

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b) 2-(4-Amino-phenyl)-ethanesulfonic acid dimethylamide

[0266]

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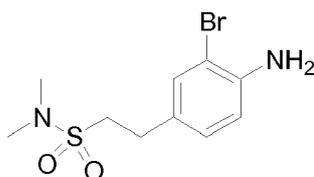
[0267] A suspension of 912 mg (3.53 mmol) of 2-(4-nitro-phenyl)-ethanesulfonic acid dimethylamide (as prepared in the previous step) in MeOH (30 mL) was hydrogenated with 10 % Pd/C (Degussa type E101-NE/W, Aldrich, 50 % by weight water) at 20 psi H₂ at RT for 2 days. The mixture was filtered through Celite, the filter cake was washed with MeOH, and the solvents were evaporated in vacuo. Silica gel chromatography of the residue on a 25-g Varian MegaBond Elut SPE column with 50 % EtOAc-hexane afforded 737 mg (91 %) of the title compound as a white solid: ¹H-NMR (CD₃CN; 400 MHz): δ 7.01 (d, 2H, J = 8.4 Hz), 6.61 (d, 2H, J = 8.4 Hz), 4.06 (br s, 2H), 3.19-3.13 (m, 2H), 2.95-2.88 (m, 2H), 2.84 (s, 6H).

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c) 2-(4-Amino-3-bromo-phenyl)-ethanesulfonic acid dimethylamide

[0268]

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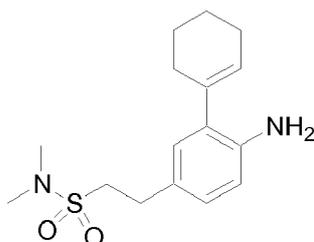
[0269] A solution of 737 mg (3.23 mmol) of 2-(4-amino-phenyl)-ethanesulfonic acid dimethylamide (as prepared in the previous step) in CH₂Cl₂ (20 mL) was cooled to 0 °C and treated with 574 mg (3.23 mmol) of NBS. The ice bath was removed and the mixture stirred at RT for 25 min. The mixture was diluted with CH₂Cl₂ (40 mL) and washed with saturated aqueous NaHCO₃ (2 x 30 mL). The aqueous layer was extracted with CH₂Cl₂ (1 x 30 mL) the combined organic layers were dried (MgSO₄) and concentrated in vacuo to afford 955 mg (96 %) of the title compound as a white solid: ¹H-NMR (CD₃OD; 400 MHz): δ 7.35 (d, 1H, J = 2.0 Hz), 7.04 (dd, 1H, J = 8.0, 2.0 Hz), 4.44 (br s, 2H), 3.21-3.14 (m, 2H), 2.96-2.89 (m, 2H), 2.84 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for C₁₀H₁₅N₂OSBr, 307.0/309.0 (M+H), found 307.0/309.0.

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d) 2-(4-Amino-3-cyclohex-1-enyl-phenyl)-ethanesulfonic acid dimethylamide

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[0270]



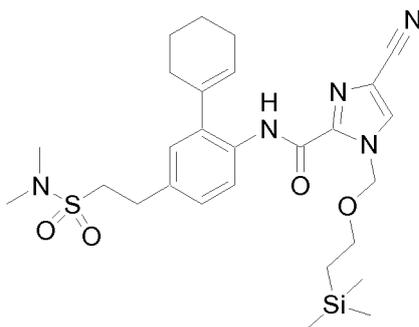
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10 **[0271]** A solution of 477 mg (1.55 mmol) of 2-(4-amino-3-bromo-phenyl)-ethanesulfonic acid dimethylamide (as prepared in the previous step) in toluene (13 mL) and EtOH (6.5 mL) was treated with 215 mg (1.71 mg) of cyclohex-1-enylboronic acid and 6.21 mL (12.4 mmol) of 2.0 M aqueous Na₂CO₃. The mixture was degassed via sonication, placed under Ar, treated with 179 mg (0.155 mmol) of Pd(PPh₃)₄, and heated to 80 °C for 17.5 h. The mixture was cooled to RT, diluted with EtOAc (50 mL), and washed with water (2 x 25 mL). The aqueous layer was extracted with EtOAc (30 mL). The combined organic layers were dried (MgSO₄) and concentrated in vacuo. Silica gel chromatography of the residue on a 50-g Varian MegaBond Elut SPE column with 50 % EtOAc-hexane afforded 365 mg (76 %) of the title compound as a white solid: ¹H-NMR (CD₃CN; 400 MHz): δ 6.90 (dd, 1H, J = 8.4, 2.4 Hz), 6.84 (d, 1H, J = 2.4 Hz), 6.62 (d, 1H, J = 8.4 Hz), 5.70-5.66 (m, 1H), 4.03 (br s, 2H), 3.20-3.13 (m, 2H), 2.93-2.87 (m, 2H), 2.83 (s, 6H), 2.24-2.17 (m, 4H), 1.82-1.74 (m, 2H), 1.74-1.66 (m, 2H). Mass spectrum (ESI, m/z): Calcd. for C₁₆H₂₄N₂O₂S, 309.2 (M+H), found 309.1.

15 **e) 4-Cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(2-dimethylsulfamoyl-ethyl)-phenyl]-amide**

25 **[0272]**

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40 **[0273]** A solution of 365 mg (1.18 mmol) of 2-(4-amino-3-cyclohex-1-enyl-phenyl)-ethanesulfonic acid dimethylamide (as prepared in the previous step) in CH₂Cl₂ (10 mL) was treated with 827 mg (1.78 mmol) of PyBroP, 398 mg (1.30 mmol) of 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylate potassium salt (as prepared in Example 1, step (d)), and 618 μL (3.55 mmol) of DIEA at RT for 16.5 h. The mixture was diluted with CH₂Cl₂ (20 mL) and washed with water (1 x 20 mL). The aqueous layer was extracted with CH₂Cl₂ (1 x 20 mL) and the combined organic layers dried (MgSO₄) and concentrated in vacuo. Silica gel chromatography of the residue on a 50-g Varian MegaBond Elut SPE column with 25-40 % EtOAc-hexane afforded 660 mg (100 %) of the title compound as a white solid: Mass spectrum (ESI, m/z): Calcd. for C₂₇H₃₉N₅O₄SSi, 558.2 (M+H), found 557.9.

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f) 4-Cyano-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(2-dimethylsulfamoyl-ethyl)-phenyl]-amide

50 **[0274]** A solution of 660 mg (1.19 mmol) of 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(2-dimethylsulfamoyl-ethyl)-phenyl]-amide (as prepared in the previous step) in CH₂Cl₂ (30 mL) was treated with EtOH (600 μL) and TFA (3 mL) and stirred at RT for 24 h. MeOH (20 mL) was added, and the solvents were evaporated in vacuo. The solid was triturated with acetonitrile to afford 342 mg (67 %) of the title compound as a white solid: ¹H-NMR (CD₃CN; 400 MHz): δ 8.20-8.09 (m, 1H), 7.92 (s, 1H), 7.24-7.16 (m, 1H), 7.13 (s, 1H), 5.84-5.75 (m, 1H), 3.30-3.19 (m, 4H), 3.08-2.96 (m, 2H), 2.82 (s, 6H), 2.29-2.17 (m, 4H), 1.85-1.68 (m, 4H). Mass spectrum (ESI, m/z): Calcd. for C₂₁H₂₅N₅O₃S, 428.2 (M+H), found 428.1.

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Example 29

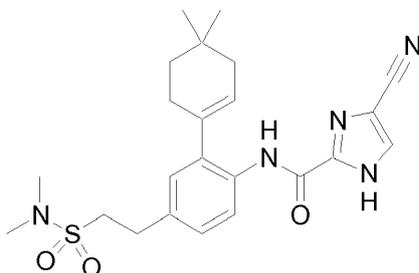
4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(2-dimethylsulfamoyl-ethyl)-phenyl]-amide

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[0275]

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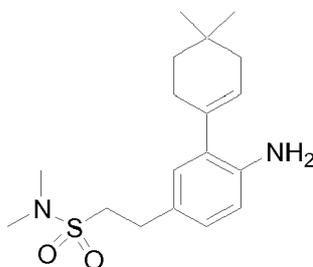
**a) 2-[4-Amino-3-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-ethanesulfonic acid dimethylamide**

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[0276]

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[0277] A solution of 477 mg (1.55 mmol) of 2-(4-amino-3-bromo-phenyl)-ethanesulfonic acid dimethylamide (as prepared in Example 28, step (c)) in toluene (13 mL) and EtOH (6.5 mL) was treated with 6.21 mL (12.4 mmol) of 2.0 M aqueous Na₂CO₃ and 403 mg (1.71 mmol) of 2-(4,4-dimethyl-cyclohex-1-enyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane. The mixture was degassed via sonication, placed under Ar, treated with 179 mg (0.155 mmol) of Pd(PPh₃)₄ and heated to 80 °C for 18 h. The mixture was cooled to RT, diluted with EtOAc (50 mL) and washed with water (1 x 50 mL). The aqueous layer was extracted with EtOAc (1 x 50 mL). The combined organic layers were dried (MgSO₄) and concentrated in vacuo. Silica gel chromatography of the residue on a 50-g Varian MegaBond Elut SPE column with 50 % EtOAc-hexane afforded 215 mg (41 %) of the title compound as a white solid: Mass spectrum (ESI, m/z): Calcd. for C₁₈H₂₈N₂O₂S, 337.2 (M+H), found 337.1.

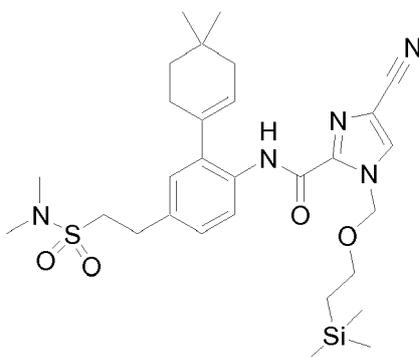
b) 4-Cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(2-dimethylsulfamoyl-ethyl)-phenyl]-amide

45

[0278]

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[0279] A solution of 215 mg (0.638 mmol) of 2-[4-amino-3-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-ethanesulfonic acid dimethylamide (as prepared in the previous step) in CH_2Cl_2 (10 mL) was treated with 446 mg (0.957 mmol) of PyBroP, 214 mg (0.701 mmol) of 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylate potassium salt (as prepared in Example 1, step (d)) and 333 μL (1.91 mmol) of DIEA and stirred at RT for 18 h. The mixture was diluted with CH_2Cl_2 (20 mL) and washed with water (1 x 20 mL). The aqueous layer was extracted with CH_2Cl_2 (1 x 20 mL). The combined organic layers were dried (MgSO_4) and concentrated in vacuo. Silica gel chromatography of the residue on a 50-g Varian MegaBond Elut SPE column with 25 % EtOAc-hexane afforded 355 mg (95 %) of the title compound as a white solid: Mass spectrum (ESI, m/z): Calcd. for $\text{C}_{29}\text{H}_{43}\text{N}_5\text{O}_4\text{SSi}$, 586.3 (M+H), found 585.9.

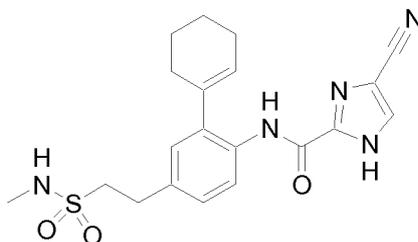
c) 4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(2-dimethylsulfamoyl-ethyl)phenyl]-amide

[0280] A solution of 355 mg (0.606 mmol) of 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(2-dimethylsulfamoyl-ethyl)-phenyl]-amide (as prepared in the previous step) in CH_2Cl_2 (15 mL) was treated with EtOH (300 μL) and TFA (1.5 mL) at RT for 24 h. MeOH (20 mL) was added, and the solvents were evaporated in vacuo. The solid was triturated with acetonitrile to afford 169 mg (61 %) of the title compound as a white solid: $^1\text{H-NMR}$ (CD_3CN ; 400 MHz): δ 9.41 (s, 1H), 8.23 (d, 1H, J = 8.0 Hz), 7.91 (s, 1H), 7.22 (d, 1H, J = 8.0 Hz), 7.18 (s, 1H), 5.80-5.71 (m, 1H), 3.31-3.21 (m, 2H), 3.10-3.00 (m, 2H), 2.85 (s, 6H), 2.37-2.27 (m, 2H), 2.10-2.04 (m, 2H), 1.64-1.55 (m, 2H), 1.10 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for $\text{C}_{23}\text{H}_{29}\text{N}_5\text{O}_3\text{S}$, 456.2 (M+H), found 456.1.

Example 30

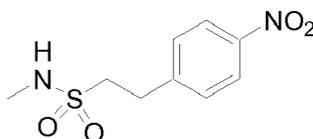
4-Cyano-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(2-methylsulfamoyl-ethyl)-phenyl]-amide

[0281]



a) 2-(4-Nitro-phenyl)-ethanesulfonic acid methylamide

[0282]

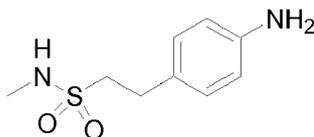


[0283] A suspension of 2.12 g (8.49 mmol) of 2-(4-nitro-phenyl)-ethanesulfonyl chloride (as prepared in Example 26, step (c)) in MeOH (40 mL) was cooled to 0 °C and treated with 21.2 mL (42.4 mmol) of methylamine (2.0 M in MeOH). The mixture was slowly warmed to RT, stirred for 16 h, and warmed to 40 °C for 3 days. Solvents were evaporated in vacuo. Silica gel chromatography of the residue on a 50-g Varian MegaBond Elut SPE column with 50 % EtOAc-hexane afforded 402 mg (19 %) of the title compound as a white solid: $^1\text{H-NMR}$ (CD_3CN ; 400 MHz): δ 8.19 (d, 2H, J = 8.8 Hz), 7.54 (d, 2H, J = 8.8 Hz), 5.15-5.05 (br s, 1H), 3.39-3.32 (m, 2H), 3.22-3.15 (m, 2H), 2.70 (d, 3H, J = 5.2 Hz).

b) 2-(4-Aminophenyl)-ethanesulfonic acid methylamide

[0284]

EP 2 687 516 A1



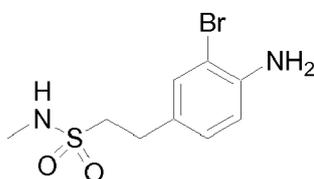
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[0285] A solution of 402 mg (1.65 mmol) of 2-(4-nitro-phenyl)-ethanesulfonic acid methylamide (as prepared in the previous step) in MeOH (30 mL) was hydrogenated over 10 % Pd/C (Degussa type E101-NE/W, Aldrich, 50 % by weight water) at 20 psi of H₂ for 19 h. The reaction mixture was filtered through Celite, and the filter cake was washed with MeOH. Solvents were evaporated in vacuo. Silica gel chromatography of the residue on a 25-g Varian MegaBond Elut SPE column with 50 % EtOAc-hexane afforded 318 mg (90 %) of the title compound as a white solid: ¹H-NMR (CD₃CN; 400 MHz): δ 7.01 (d, 2H, J = 8.4 Hz), 6.61 (d, 2H, J = 8.4 Hz), 5.00-4.92 (br s, 1H), 4.12-4.02 (br s, 2H), 3.24-3.17 (m, 2H), 2.92-2.86 (m, 2H), 2.67 (s, 3H, J = 5.2 Hz).

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15 **c) 2-(4-Amino-3-bromo-phenyl)-ethanesulfonic acid methylamide**

[0286]



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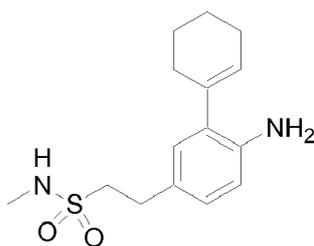
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[0287] A solution of 318 mg (1.48 mmol) of 2-(4-aminophenyl)-ethanesulfonic acid methylamide (as prepared in the previous step) in CH₂Cl₂ (20 mL) was cooled to 0 °C and treated with 251 mg (1.41 mmol) of NBS at that temperature for 1 h. The mixture was diluted with CH₂Cl₂ (30 mL) and washed with saturated aqueous NaHCO₃ (1 x 30 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo. Silica gel chromatography of the residue on a 25-g Varian MegaBond Elut SPE column with 50 % EtOAc-hexane afforded 354 mg (81 %) of the title compound as a white solid: ¹H-NMR (CD₃CN; 400 MHz): δ 7.34 (d, 1H, J = 2.0 Hz), 7.03 (dd, 1H, J = 8.0, 2.0 Hz), 6.77 (d, 1H, J = 8.0 Hz), 5.06-4.97 (m, 1H), 4.48-4.40 (br s, 2H), 3.25-3.18 (m, 2H), 2.93-2.86 (m, 2H), 2.67 (d, 3H, J = 5.2 Hz). Mass spectrum (ESI, m/z): Calcd. for C₉H₁₃N₂O₂SBr, 293.0/295.0 (M+H), found 293.0/295.0.

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35 **d) 2-(4-Amino-3-cyclohex-1-enyl-phenyl)-ethanesulfonic acid methylamide**

[0288]



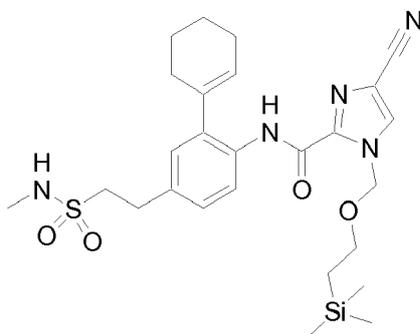
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[0289] A solution of 177 mg (0.604 mmol) of 2-(4-amino-3-bromo-phenyl)-ethanesulfonic acid methylamide (as prepared in the previous step) in toluene (5 mL) and EtOH (2.5 mL) was treated with 83.7 mg (0.664 mmol) of cyclohex-1-enylboronic acid and 2.40 mL (4.83 mmol) of 2.0 M aqueous Na₂CO₃. The mixture was degassed via sonication, placed under Ar, treated with 67.3 mg (0.0604 mmol) of Pd(PPh₃)₄, and heated to 80 °C for 19 h. The mixture was diluted with EtOAc (15 mL) and washed with water (1 x 10 mL). The aqueous layer was extracted with EtOAc (1 x 10 mL), and the combined organic layers were dried (MgSO₄) and concentrated in vacuo. Silica gel chromatography of the residue on a 25-g Varian MegaBond Elut SPE column with 50 % EtOAc-hexane afforded 123 mg (69 %) of the title compound as a white solid: ¹H-NMR (CD₃CN; 400 MHz): δ 6.90 (dd, 1H, J = 8.0, 2.0 Hz), 6.83 (d, 1H, J = 2.0 Hz), 6.32 (d, 1H, J = 8.0 Hz), 5.70-5.66 (m, 1H), 4.97-4.90 (m, 2H), 4.08-3.99 (br s, 2H), 3.24-3.17 (m, 2H), 2.91-2.84 (m, 2H), 2.66 (d, 3H, J = 5.2 Hz), 2.24-2.15 (m, 4H), 1.82-1.74 (m, 2H), 1.74-1.66 (m, 2H).

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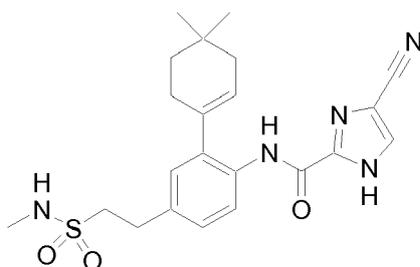
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e) 4-Cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(2-methylsulfamoyl-ethyl)-phenyl]-amide**[0290]**

[0291] A solution of 123 mg (0.418 mmol) of 2-(4-amino-3-cyclohex-1-enyl-phenyl)-ethanesulfonic acid methylamide (as prepared in the previous step) in CH_2Cl_2 (10 mL) was treated with 292 mg (0.627 mmol) of PyBroP, 140 mg (0.460 mmol) of 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylate potassium salt (as prepared in Example 1, step (d)), and 218 μL (1.25 mmol) of DIEA. The mixture was stirred at RT for 2 h, diluted with CH_2Cl_2 (20 mL) and washed with saturated aqueous NaHCO_3 (1 x 20 mL). The organic layer was dried (MgSO_4) and concentrated in vacuo. Silica gel chromatography of the residue on a 50-g Varian MegaBond Elut SPE column with 50 % EtOAc-hexane afforded 177 (71 %) of the title compound as a white solid: Mass spectrum (ESI, m/z): Calcd. for $\text{C}_{26}\text{H}_{37}\text{N}_5\text{O}_4\text{SSi}$, 544.2 (M+H), found 543.9.

f) 4-Cyano-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(2-methylsulfamoyl-ethyl)-phenyl]-amide

[0292] A solution of 177 mg (0.326 mmol) of 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(2-methylsulfamoyl-ethyl)-phenyl]-amide (as prepared in the previous step) in CH_2Cl_2 (10 mL) was treated with MeOH (300 μL) and TFA (3 mL) at RT for 45 min. MeOH (10 mL) was added, and solvents were evaporated in vacuo. The solid residue was triturated with a minimum amount of acetonitrile with sonication, but further purification was needed. Silica gel chromatography of the solid with 50 % EtOAc-hexane also afforded impure material. The solid was purified by RP-HPLC (C18) with 40-100 % CH_3CN in 0.1 % TFA/ H_2O over 30 min to afford 14.9 mg (11 %) of the title compound as a white solid: $^1\text{H-NMR}$ (CD_3CN ; 400 MHz): δ 9.38 (s, 1H), 8.27-8.20 (m, 1H), 7.93 (s, 1H), 7.27-7.20 (m, 1H), 7.18-7.14 (m, 1H), 5.89-5.82 (m, 1H), 5.09-5.01 (m, 1H), 3.36-3.26 (m, 2H), 3.08-3.00 (m, 2H), 2.70 (d, 3H, $J = 5.2$ Hz), 2.32-2.25 (m, 4H), 1.90-1.74 (m, 4H). Mass spectrum (ESI, m/z): Calcd. for $\text{C}_{20}\text{H}_{23}\text{N}_5\text{O}_3\text{S}$, 414.1 (M+H), found 414.1.

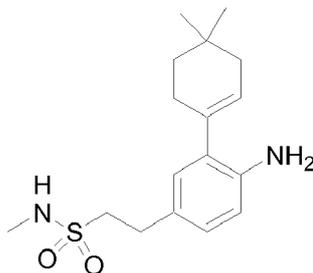
Example 31**4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(2-methylsulfamoyl-ethyl)-phenyl]-amide****[0293]**

a) 2-[4-Amino-3-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-ethanesulfonic acid methylamide

[0294]

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10



15 **[0295]** A solution of 177 mg (0.604) of 2-(4-amino-3-bromo-phenyl)-ethanesulfonic acid methylamide (as prepared in Example 30, step (c)) in toluene (5 mL) and EtOH (2.5 mL) was treated with 157 mg (0.664 mmol) of 2-(4,4-dimethyl-cyclohex-1-enyl)-4,4,5,5-tetramethyl-[1,3,2] dioxaborolane and 2.40 mL (4.83 mmol) of 2.0 M aqueous Na₂CO₃. The mixture was degassed via sonication, placed under Ar, treated with 70.0 mg (0.0604 mmol) of Pd(PPh₃)₄, and heated to 80 °C for 17 h. The mixture was diluted with EtOAc (15 mL) and washed with water (1 x 10 mL). The aqueous layer
20 was extracted with EtOAc (1 x 10 mL), and the combined organic layers were dried (MgSO₄) and concentrated in vacuo. Silica gel chromatography of the residue on a 50-g Varian MegaBond Elut SPE column with 50 % EtOAc-hexane afforded 65.0 mg (33 %) of the title compound as a white solid: ¹H-NMR (CD₃CN; 400 MHz): δ 6.90 (dd, 1H, J = 8.0, 2.0 Hz), 6.85 (d, 1H, J = 2.0 Hz), 6.63 (d, 1H, J = 8.0 Hz), 5.65-5.59 (m, 1H), 5.00-4.91 (m, 1H), 4.06-3.97 (br s, 2H), 3.26-3.18 (m, 2H), 2.93-2.85 (m, 2H), 2.67 (d, 3H, J = 5.2 Hz), 2.29-2.21 (m, 2H), 2.18 (s, 2H), 2.02-1.96 (m, 2H), 1.58-1.50 (m, 2H), 1.02 (s, 6H).

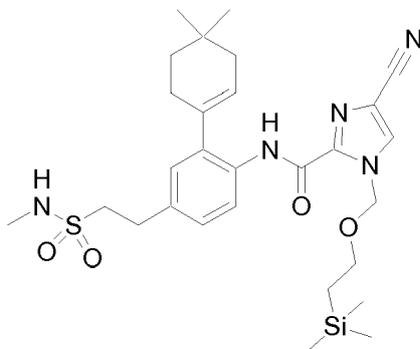
25

b) 4-Cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(2-methylsulfamoyl-ethyl)-phenyl]-amide

[0296]

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40



45 **[0297]** A solution of 65.0 mg (0.202 mmol) of 2-[4-amino-3-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-ethanesulfonic acid methylamide (as prepared in the previous step) in CH₂Cl₂ (5 mL) was treated with 141 mg (0.303 mmol) of PyBroP, 67.7 mg (0.222 mmol) of 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylate potassium salt (as prepared in Example 1, step (d)), and 105 μL (0.605 mmol) of DIEA at RT for 2 h. The mixture was diluted with CH₂Cl₂ (10 mL) and washed with saturated aqueous NaHCO₃ (1 x 10 mL). The organic layer was dried (MgSO₄) and concentrated
50 in vacuo. Silica gel chromatography of the residue on a 50-g Varian MegaBond Elut SPE column with 50 % EtOAc-hexane afforded 96.0 mg (83 %) of the title compound as a white solid: Mass spectrum (ESI, m/z): Calcd. for C₂₈H₄₁N₅O₄SSi, 572.3 (M+H), found 572.0.

c) 4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(2-methylsulfamoyl-ethyl)-phenyl]-amide

55

[0298] A solution of 97.0 mg (0.170 mmol) of 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(2-methylsulfamoyl-ethyl)-phenyl]-amide (as prepared in the previous step) in

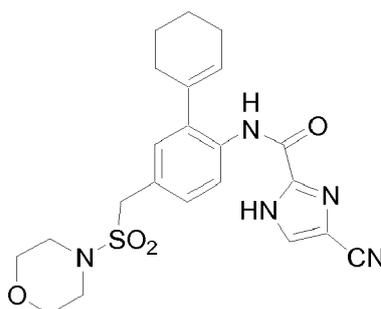
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CH₂Cl₂ (30 mL) was treated with MeOH (1 mL) and TFA (10 mL) at RT for 1 h. MeOH (10 mL) was added and the solvents were removed in vacuo. The residue was purified by RP-HPLC (C 18) with 40-100 % CH₃CN in 0.1 % TFA/H₂O over 30 min to afford 19.8 mg (26 %) of the title compound as a white solid: ¹H-NMR (CD₃CN; 400 MHz): δ 9.41 (s, 1H), 8.24 (d, 1H, J = 8.0 Hz), 7.91 (s, 1H), 7.22 (dd, 1H, J = 8.0, 2.0 Hz), 5.79-5.74 (m, 1H), 5.08-5.00 (m, 1H), 3.34-3.27 (m, 2H), 3.06-2.99 (m, 2H), 2.70 (d, 3H, J = 5.2 Hz), 2.35-2.28 (m, 2H), 2.10-2.05 (m, 2H), 1.59 (t, 2H, J = 6.4 Hz), 1.10 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for C₂₂H₂₇N₅O₃S, 442.2 (M+H), found 442.1.

Example 32

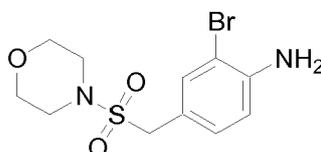
4-Cyano-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(morpholine-4-sulfonylmethyl)-phenyl]-amide

[0299]



a) 2-Bromo-4-(morpholine-4-sulfonylmethyl)-phenylamine

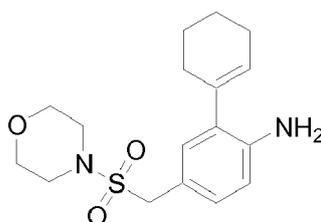
[0300]



[0301] To a solution of 4-(morpholine-4-sulfonylmethyl)-phenylamine (437 mg, 1.70 mmol, WO 9720822) in DCM (10 mL) was added NBS (304 mg, 1.70 mmol) at 0 °C. The solution was allowed to stir at RT for 15 min. Satd aq NaHCO₃ (20 mL) was then added and the organic layer was separated, dried (Na₂SO₄) and concentrated to afford the title compound (564 mg, 98 %). ¹H-NMR (CDCl₃; 400 MHz): δ 7.47 (d, 1H, J = 1.9 Hz), 7.15 (dd, 1H, J = 8.2, 1.9 Hz), 6.77 (d, 1H, J = 8.2 Hz), 4.23 (br s, 2H), 4.12 (s, 2H), 3.65-3.68 (m, 4H), 3.14-3.17 (m, 4H).

b) 2-Cyclohex-1-enyl-4-(morpholine-4-sulfonylmethyl)-phenylamine

[0302]



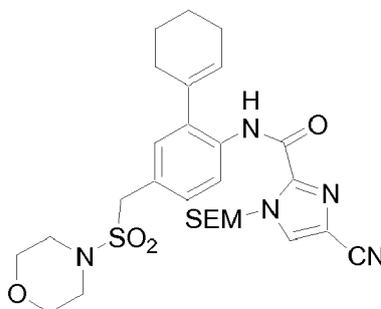
[0303] The title compound was prepared according to the Suzuki coupling procedure of the Example 1, step (e) using cyclohex-1-enyl boronic acid (157 mg, 1.25 mmol) and 2-bromo-4-(morpholine-4-sulfonylmethyl)-phenylamine (as prepared in the previous step, 335 mg, 1.00 mmol) and purified on silica (20 % EtOAc/hexanes) (276 mg, 82 %). ¹H-NMR

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(CDCl₃; 400 MHz): δ 7.05 (dd, 1H, J = 8.2, 1.9 Hz), 6.95 (d, 1H, J = 1.9 Hz) 6.67 (d, 1H, J = 8.2 Hz), 5.76 (br s, 1H), 4.12 (s, 2H), 3.90 (br s, 2H), 3.60-3.62 (m, 4H), 3.09-3.12 (m, 4H), 2.19-2.23 (m, 4H), 1.24-1.62 (m, 4H).

c) **4-Cyano-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(morpholine-4-sulfonylmethyl)-phenyl]-amide**

[0304]



[0305] A mixture of 4-cyano-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid, potassium salt (as prepared in the Example 1, step (d), 33.6 mg, 0.110 mmol), DIEA (34 μL, 0.20 mmol), 2-cyclohex-1-enyl-4-(morpholine-4-sulfonylmethyl)-phenylamine (as prepared in the previous step, 33.6 mg, 0.110 mmol) and PyBroP (69.9 mg, 0.150 mmol) in DCM (2 mL) was stirred at RT for 12 h. The reaction mixture was diluted with DCM (10 mL) and washed with satd aq NaHCO₃ (10 mL) and water (10 mL). The organic layer was separated, dried (Na₂SO₄) and concentrated in vacuo. The residue was purified on silica (20-40 % EtOAc/hexane) to afford 4-cyano-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(morpholine-4-sulfonylmethyl)-phenyl]-amide (56 mg, 95 %). Mass spectrum (ESI, m/z): Calcd. for C₂₈H₃₉N₅O₅SSi, 586.2 (M+H), found 586.1.

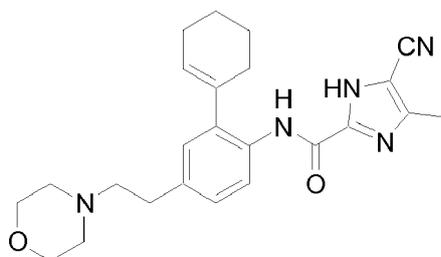
d) **4-Cyano-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(morpholine-4-sulfonylmethyl)phenyl]-amide**

[0306] To a solution of 4-cyano-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(morpholine-4-sulfonylmethyl)-phenyl]-amide (as prepared in the previous step, 33.7 mg, 0.057 mmol) in DCM (0.5 mL) and EtOH (10 μL), TFA (0.10 mL) was added. The resulting solution was stirred at RT for 6 h and concentrated in vacuo. The residue obtained was dried and purified on silica (30% EtOAc/hexane) to obtain the title compound (11 mg, 95 %): ¹H-NMR (CDCl₃; 400 MHz): δ 9.63 (s, 1H), 8.43 (d, 1H, J = 8.4 Hz), 7.73 (s, 1H), 7.36 (dd, 1H, J = 8.4, 1.9 Hz), 7.25 (d, 1H, J = 1.9 Hz), 5.85 (br s, 1H), 4.12 (s, 2H), 3.66-3.68 (m, 4H), 3.17-3.19 (m, 4H), 2.19-2.23 (m, 4H), 1.62-1.85 (m, 4H). Mass spectrum (ESI, m/z): Calcd. for C₂₂H₂₅N₅O₄S, 456.2 (M+H), found 455.9.

Example 33

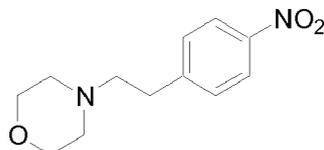
5-Cyano-4-methyl-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(2-morpholin-4-yl-ethyl)-phenyl]-amide hydrochloride

[0307]



a) 4-[2-(4-Nitro-phenyl)-ethyl]-morpholine**[0308]**

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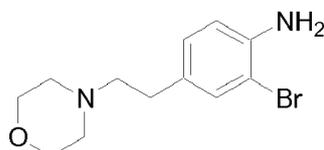
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[0309] A mixture of 1-(2-bromo-ethyl)-4-nitro-benzene (0.740 g, 3.22 mmol), morpholine (0.840 mL, 9.65 mmol), and sodium iodide (0.480 g, 3.22 mmol) in N,N-dimethylacetamide (3 mL) was heated at 80 °C for 10 min. The mixture was diluted with 30 mL EtOAc and washed with H₂O (2 x 30 mL) and brine (30 mL) and dried over Na₂SO₄ to give the title compound as a yellow oil of sufficient purity to use in the next step. Mass spectrum (ESI, m/z): Calcd. for C₁₂H₁₆N₂O₃, 237.1 (M+H), found 237.2.

15

b) 2-Bromo-4-(2-morpholin-4-yl-ethyl)-phenylamine**[0310]**

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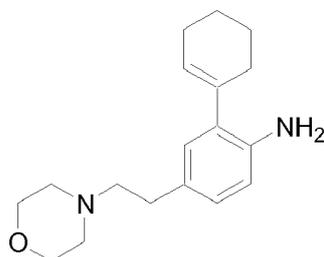
[0311] To a solution 4-[2-(4-nitro-phenyl)-ethyl]-morpholine (0.70 g, 2.97 mmol) (as prepared in the previous step) in 15 mL of MeOH was added 10% Pd/C (30 mg) and the mixture hydrogenated under 20 psi of H₂ for 2 h. The mixture was filtered through Celite and concentrated. The residue was dissolved in DCM (20 mL) and NBS (0.53 g, 2.97 mmol) was added and the reaction stirred for 20 min at RT. The reaction was diluted with DCM (20 mL) and washed with NaHCO₃ (2 x 40 mL) and the organic layer dried over Na₂SO₄ and concentrated. The title compound was eluted from a 20-g SPE with 100% EtOAc to give 0.49 g (58%) of a light yellow oil. Mass spectrum (ESI, m/z): Calcd. for C₁₂H₁₇BrN₂O, 285.0 (M+H), found 285.0.

30

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c) 2-Cyclohex-1-enyl-4-(2-morpholin-4-yl-ethyl)-phenylamine**[0312]**

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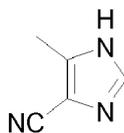
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[0313] This compound is prepared by Suzuki coupling of 2-bromo-4-(2-morpholin-4-yl-ethyl)-phenylamine (as prepared in the previous step) and 1-cyclohex-1-enyl-boronic acid according to the procedure in Example 1, step(e). Mass spectrum (ESI, m/z): Calcd. for C₁₈H₂₆N₂O, 287.2 (M+H), found 287.0.

55

d) 5-Methyl-1H-imidazole-4-carbonitrile**[0314]**



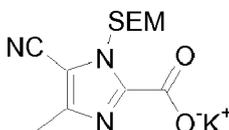
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[0315] To a suspension of 5-methyl-1*H*-imidazole-4-carbaldehyde (9.0 g, 82 mmol) in 24 mL of pyridine was added hydroxylamine hydrochloride (6.3 g, 91 mmol) and the mixture was stirred for 1 hour at RT and then heated to 85 °C. Acetic anhydride (15 mL, 159 mmol) was added over 10 min and then the mixture heated to 110 °C for 30 min. The mixture was cooled to RT, concentrated and the residue dissolved in EtOAc (100 mL) and neutralized with aqueous NaHCO₃. The aqueous layer was extracted with EtOAc (4 x 200 mL), then the combined organic fractions were dried (Na₂SO₄) and concentrated to give 8.7 g (99%) of a white solid. ¹H-NMR (400 MHz, DMSO-*d*₆): δ 12.80 (s, 1H), 7.76 (s, 1H), 2.32 (s, 3H).

15 **e) 5-Cyano-4-methyl-1-(2-trimethylsilyl-ethoxymethyl)-1*H*-imidazole-2-carboxylate potassium salt.**

[0316]

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25 **[0317]** This compound was prepared from 5-methyl-1*H*-imidazole-4-carbonitrile (as prepared in the previous step) according to the procedures in Example 1, steps (a), (b), (c), and (d). Mass spectrum (ESI, *m/z*): Calcd. for C₁₂H₁₈KN₃O₃Si, 282.1 (M-K+2H), found 281.6.

30 **f) 5-Cyano-4-methyl-1*H*-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(2-morpholin-4-yl-ethyl)-phenyl]-amide hydrochloride**

[0318] The title compound was prepared by coupling 5-cyano-4-methyl-1-(2-trimethylsilyl-ethoxymethyl)-1*H*-imidazole-2-carboxylate potassium salt (as prepared in the previous step) and 2-cyclohex-1-enyl-4-(2-morpholin-4-yl-ethyl)-phenylamine (prepared in step (c)) according to the procedure in Example 34, step (c), followed by SEM deprotection according to the procedure in Example 34, step (d). The hydrochloride salt was then obtained by ion-exchange of the trifluoroacetic acid salt using a BioRad AG-2X8 resin, Cl⁻ ion form. ¹H-NMR (400 MHz, DMSO-*d*₆): δ 14.05 (s, 1H), 10.78 (s, 1H), 9.64 (s, 1H), 8.92 (d, *J* = 8.3 Hz, 1H), 7.20 (m, 1H), 7.08 (m, 1H), 5.78 (m, 1H), 4.05-3.70 (m, 4H), 3.52-3.46 (m, 2H), 3.18-2.98 (m, 4H), 2.40 (s, 3H), 2.22-2.16 (m, 4H), 1.80-1.65 (m, 4H). Mass spectrum (ESI, *m/z*): Calcd. for C₂₄H₂₉N₅O₂, 420.2 (M+H), found 420.2.

40

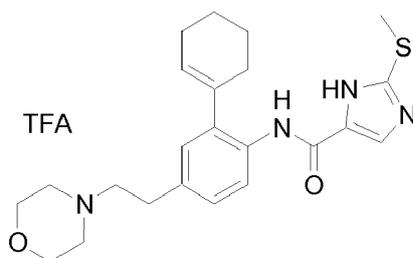
Example 34

2-Methylsulfanyl-3*H*-imidazole-4-carboxylic acid [2-cyclohex-1-enyl-4-(2-morpholin-4-yl-ethyl)-phenyl]-amide trifluoroacetic acid salt

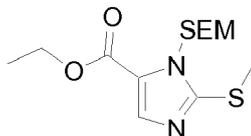
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[0319]

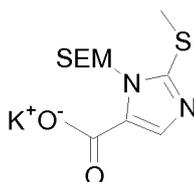
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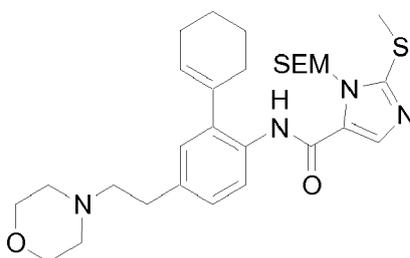
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a) 2-Methylsulfanyl-3-(2-trimethylsilylanyl-ethoxymethyl)-3H-imidazole-4-carboxylic acid ethyl ester**[0320]**

[0321] To a solution of 2-mercapto-3H-imidazole-4-carboxylic acid ethyl ester (1.0 g, 5.8 mmol) in 15 mL of DCM was added triethylamine (NEt₃) (1.0 mL, 7.2 mmol) and iodomethane (0.4 mL, 6.4 mmol) and the mixture stirred for 3 h at RT. The mixture was cooled in an ice bath, NEt₃ (1.0 mL, 7.2 mmol) and SEM-Cl (1.2 mL, 6.4 mmol) was added, the mixture stirred for 3 hours at RT and then an additional portion of NEt₃ (0.5 mL, 3.6 mmol) and SEM-Cl (0.6 mL, 3.2 mmol) was added and the mixture stirred for 8 h at RT. The mixture was diluted with 50 mL of DCM and washed with NaHCO₃ (2 x 60 mL) and brine (60 mL) and dried over Na₂SO₄. Flash chromatography of the residue on Si gel with 30% EtOAc/hexanes gave the title compound as a colorless oil (1.0 g, 55%). Mass spectrum (ESI, m/z): Calcd. for C₁₃H₂₄N₂O₃SSi, 317.1 (M+H), found 316.7.

b) 2-Methylsulfanyl-3-(2-trimethylsilylanyl-ethoxymethyl)-3H-imidazole-4-carboxylate potassium salt**[0322]**

[0323] To a solution of 2-methylsulfanyl-3-(2-trimethylsilylanyl-ethoxymethyl)-3H-imidazole-4-carboxylic acid ethyl ester (99 mg, 0.31 mmol) (as prepared in the previous step) was added 2 N KOH (0.16 mL, 0.32 mmol) and the mixture heated to 60 °C for 3 h. The mixture was concentrated and dried under vacuum to give the title compound as a white solid. Mass spectrum (ESI, m/z): Calcd. for C₁₁H₁₉KN₂O₃SSi, 289.1 (M-K+2H), found 288.7.

c) 2-Methylsulfanyl-3-(2-trimethylsilylanyl-ethoxymethyl)-3H-imidazole-4-carboxylic acid [2-cyclohex-1-enyl-4-(2-morpholin-4-yl-ethyl)-phenyl]-amide**[0324]**

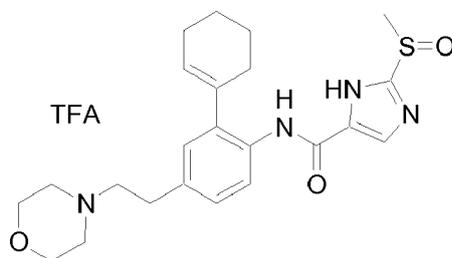
[0325] A mixture of 2-methylsulfanyl-3-(2-trimethylsilylanyl-ethoxymethyl)-3H-imidazole-4-carboxylate potassium salt (90 mg, 0.28 mmol) (as prepared in the previous step), 2-cyclohex-1-enyl-4-(2-morpholin-4-yl-ethyl)-phenylamine (81 mg, 0.28 mmol) (as prepared in Example 33, step(c)), PyBrOP (170 mg, 0.37 mmol), and DIEA (0.10 mL, 0.57 mmol) in 1.5 mL of DCM was stirred for 8 h at RT. The mixture was diluted with 20 mL of DCM and washed with NaHCO₃ (2 x 30 mL) and brine (30 mL) and dried over Na₂SO₄. Flash chromatography of the residue on Si gel with 100% EtOAc gave the title compound as a white solid (107 mg, 70%). Mass spectrum (ESI, m/z): Calcd. for C₂₉H₄₄N₄O₃SSi, 557.3 (M+H), found 556.8.

d) 2-Methylsulfonyl-3H-imidazole-4-carboxylic acid [2-cyclohex-1-enyl-4-(2-morpholin-4-yl-ethyl)-phenyl]-amide trifluoroacetic acid salt

[0326] To a solution of 2-methylsulfonyl-3-(2-trimethylsilyl-ethoxymethyl)-3H-imidazole-4-carboxylic acid [2-cyclohex-1-enyl-4-(2-morpholin-4-yl-ethyl)-phenyl]-amide (100 mg, 0.18 mmol) (as prepared in the previous step) in 1 mL of DCM was added 1 mL of TFA and the mixture stirred at RT for 6 h. The mixture was concentrated and the title compound purified by RP-HPLC on a C18 column eluting with a linear gradient of 35-55% CH₃CN in 0.1% TFA/H₂O over 8 min to give 35 mg (36%) of a white solid. ¹H-NMR (400 MHz, CD₃OD): δ 8.22 (d, *J* = 8.4 Hz, 1H), 7.71 (s, 1H), 7.20 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.12 (d, *J* = 2.2 Hz, 1H), 5.79 (m, 1H), 4.07 (m, 2H), 3.82 (m, 2H), 3.57 (m, 2H), 3.40 (m, 2H), 3.20 (m, 2H), 3.15 (m, 2H), 2.65 (s, 3H), 2.30-2.22 (m, 4H), 1.88-1.72 (m, 4H). Mass spectrum (ESI, *m/z*): Calcd. for C₂₃H₃₀N₄O₂S, 427.2 (M+H), found 427.1.

Example 35**2-Methanesulfonyl-3H-imidazole-4-carboxylic acid [2-cyclohex-1-enyl-4-(2-morpholin-4-yl-ethyl)-phenyl]-amide trifluoroacetic acid salt**

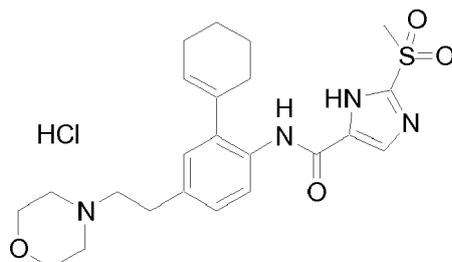
[0327]



[0328] To a solution of 2-methylsulfonyl-3-(2-trimethylsilyl-ethoxymethyl)-3H-imidazole-4-carboxylic acid [2-cyclohex-1-enyl-4-(2-morpholin-4-yl-ethyl)-phenyl]-amide (85 mg, 0.15 mmol) (as prepared in Example 34) in 1.4 mL of DCM was added MCPBA (77%, 34 mg, 0.15 mmol) and the mixture stirred at RT for 10 min. The mixture was diluted with 20 mL of DCM and washed with NaHCO₃ (2 x 30 mL) and brine (30 mL) and dried over Na₂SO₄. The residue was dissolved in 2 mL of DCM, 1 mL of TFA was added and the mixture stirred at RT for 1 h. The mixture was concentrated and the title compound purified by RP-HPLC on a C18 column eluting with a linear gradient of 30-50% CH₃CN in 0.1% TFA/H₂O over 9 min to give 55 mg (65%) of a white solid. ¹H-NMR (400 MHz, DMSO-*d*₆): δ 12.82 (s, 1H), 9.41 (s, 1H), 8.34 (d, *J* = 8.3 Hz, 1H), 7.79 (s, 1H), 7.18 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.11 (d, *J* = 2.1 Hz, 1H), 5.76 (m, 1H), 4.05-3.86 (m, 6H), 3.78-3.68 (m, 4H), 3.14-3.05 (m, 2H), 2.60 (s, 3H), 2.22-2.16 (m, 4H), 1.80-1.65 (m, 4H). Mass spectrum (ESI, *m/z*): Calcd. for C₂₃H₃₀N₄O₃S, 443.2 (M+H), found 443.0.

Example 36**2-Methanesulfonyl-3H-imidazole-4-carboxylic acid [2-cyclohex-1-enyl-4-(2-morpholin-4-yl-ethyl)-phenyl]-amide hydrochloride**

[0329]



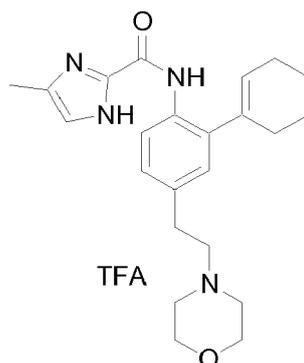
[0330] The title compound was prepared according to the procedure in Example 35 using 2 eq of MCPBA. The

hydrochloride salt was then obtained by ion-exchange of the trifluoroacetic acid salt using a BioRad AG-2X8 resin, Cl⁻ ion form. ¹H-NMR (400 MHz, DMSO-d₆): δ 14.10 (s, 1H), 12.38 (s, 1H), 9.44 (s, 1H), 8.32 (d, *J* = 8.3 Hz, 1H), 8.08 (s, 1H), 7.24 (m, 1H), 7.18 (m, 1H), 5.80 (m, 1H), 4.05-3.86 (m, 6H), 3.80-3.64 (m, 4H), 3.18-3.05 (m, 2H), 3.02 (s, 3H), 2.22-2.16 (m, 4H), 1.80-1.65 (m, 4H). Mass spectrum (ESI, *m/z*): Calcd. for C₂₃H₃₀N₄O₄S, 459.2 (M+H), found 459.0.

Example 37

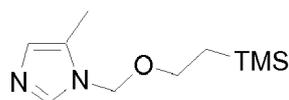
4-Methyl-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(2-morpholin-4-yl-ethyl)-phenyl]-amide trifluoroacetic acid salt

[0331]



a) 5-Methyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole

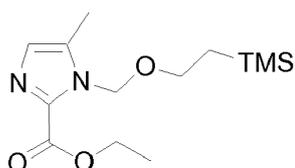
[0332]



[0333] To a solution of 4-methylimidazole (2.70 g, 33.0 mmol) in 10 mL of acetonitrile at 0 °C was added NEt₃ (4.00 g, 39.6 mmol) and acetyl chloride (2.80 g, 36.3 mmol). The mixture was allowed to attain RT then filtered to remove the ppt and the filtrate was concentrated to give 1-(4-methyl-imidazol-1-yl)-ethanone, which was used without further purification in the next step. To a solution of 1-(4-methyl-imidazol-1-yl)-ethanone (4.10 g, 33.0 mmol) in 15 mL acetonitrile was added SEM-C1 (5.80 g, 35.0 mmol) and the solution was stirred at 25 °C for 10 h. The solvents were removed by evaporation and to the residue was added 100 mL of 2.5 M NaOH and the mixture was stirred at 25 °C for 1 h. The reaction mixture was then extracted with ether (3 x 100 mL), dried over Na₂SO₄ and concentrated. The title compound was purified by chromatography on Silica gel eluting with 75% EtOAc/hexanes to give 4.30 g (61%) of a colorless oil: Mass spectrum (ESI, *m/z*): Calcd. for C₁₀H₂₀N₂O₄Si, 213.1 (M+H), found 213.1.

b) 5-Methyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid ethyl ester

[0334]



[0335] To a solution of 5-methyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole (0.320 g, 1.50 mmol) in 5 mL of THF at -78 °C was added *n*-BuLi (0.80 mL, 1.60 mmol, 2 M in cyclohexane) and the mixture was allowed to attain RT and stirred for 30 min. The mixture was cooled to -78 °C and ethyl cyanofornate (0.160 g, 1.65 mmol) was added and the

mixture allowed to stir for 10 h at RT. The reaction was diluted with 15 mL of EtOAc and washed with NaHCO₃ (2 x 15 mL) and brine (15 mL). The title compound was eluted from a 20-g SPE with 50% EtOAc/hexanes to give 0.160 g (38%) of a light brown oil: Mass spectrum (ESI, m/z): Calcd. for C₁₃H₂₄N₂O₃Si, 285.2 (M+H), found 284.9.

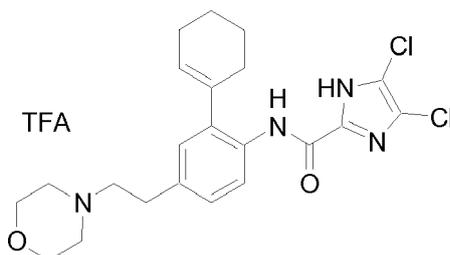
5 **c) 4-Methyl-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(2-morpholin-4-yl-ethyl)-phenyl]-amide trifluoroacetic acid salt**

10 **[0336]** To a solution of 5-methyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid ethyl ester (0.090 g, 0.32 mmol) in 2 mL of EtOH at RT was added 0.16 mL of 2N KOH and the mixture stirred for 1 h and then concentrated and dried under vacuum. DCM (3 mL) was added followed by 2-cyclohex-1-enyl-4-(2-morpholin-4-yl-ethyl)-phenylamine (0.090 g, 0.31 mmol) (Example 33, step (c)), DIEA (0.11 mL, 0.64 mmol), and PyBroP (0.16 g, 0.34 mmol) and the mixture stirred for 10 h at RT. The reaction was diluted with 15 mL of DCM and washed with NaHCO₃ (2 x 15 mL) and brine (15 mL), dried over Na₂SO₄ and concentrated. The residue was dissolved in 1.0 mL of DCM and 0.040 mL of EtOH and 1.0 mL of TFA were added and the reaction stirred at RT for 3 h and then concentrated. The title compound was purified by RP-HPLC, eluting with a linear gradient of 30% to 50% acetonitrile in 0.1% TFA/H₂O over 9 min on a C18 column giving 0.015 g (10%) of a light yellow solid. ¹H-NMR (400 MHz, CD₃OD): δ 7.69 (d, J = 8.2 Hz, 1H), 7.27 (s, 1H), 7.24 (dd, J = 2.1, 8.2 Hz, 1H), 7.19 (d, J = 2.1 Hz, 1H), 5.73 (s, 1H), 4.10 (m, 2H), 3.78 (m, 2H), 3.58 (m, 2H), 3.42 (m, 2H), 3.19 (m, 2H), 3.08 (m, 2H), 2.40 (s, 3H), 2.24 (m, 2H), 2.15 (m, 2H), 1.80 - 1.60 (m, 4H). Mass spectrum (ESI, m/z): Calcd. for C₂₃H₃₀N₄O₂ 395.2, (M+H), found 395.2.

20 **Example 38**

25 **4,5-Dichloro-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(2-morpholin-4-yl-ethyl)-phenyl]-amide trifluoroacetic acid salt**

30 **[0337]**

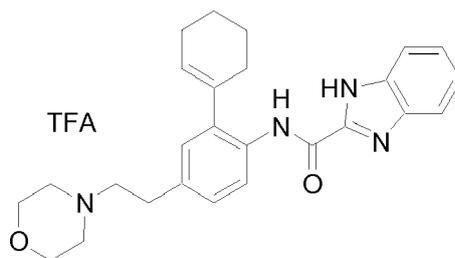


40 **[0338]** The title compound was prepared by coupling 4,5-dichloro-1H-imidazole-2-carboxylic acid (*J. Heterocyclic Chem*, 17, 409, (1980)) and 2-cyclohex-1-enyl-4-(2-morpholin-4-yl-ethyl)-phenylamine (as prepared in Example 33, step (c)) according to the procedure in Example 34, step (c). ¹H-NMR (400 MHz, CD₃OD) δ 8.19 (d, J = 8.3 Hz, 1H), 7.23 (dd, J = 8.3, 2.1 Hz, 1H), 7.16 (d, J = 2.1 Hz, 1H), 5.83 (m, 1H), 4.14 (m, 2H), 3.80 (m, 2H), 3.60 (m, 2H), 3.42 (m, 2H), 3.22 (m, 2H), 3.07 (m, 2H), 2.34-2.23 (m, 4H), 1.90-1.75 (m, 4H). Mass spectrum (ESI, m/z): Calcd. for C₂₂H₂₆Cl₂N₄O₂ 449.1 (M+H), found 449.0

45 **Example 39**

50 **1H-Benzoimidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(2-morpholin-4-yl-ethyl)-phenyl]-amide trifluoroacetic acid salt**

55 **[0339]**



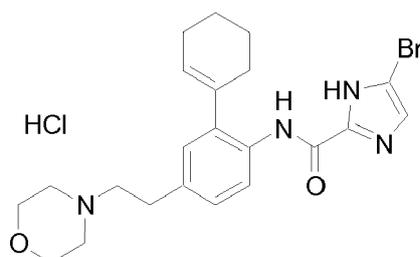
[0340] The title compound was prepared by coupling 1*H*-benzimidazole-2-carboxylic acid and 2-cyclohex-1-enyl-4-(2-morpholin-4-yl-ethyl)-phenylamine (as prepared in Example 33, step (c)) according to the procedure in Example 34, step (c). ¹H-NMR (400 MHz, CD₃OD): δ 8.27 (d, *J* = 8.3 Hz, 1H), 7.69 (dd, *J* = 6.2, 3.2 Hz, 1H), 7.41-7.35 (m, 1H), 7.28 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.21 (d, *J* = 2.0 Hz, 1H), 5.89 (s, 1H), 4.16 (m, 2H), 3.82 (m, 2H), 3.62 (m, 2H), 3.48 (m, 2H), 3.22 (m, 2H), 3.09 (m, 2H), 2.40-2.33 (m, 4H), 1.96-1.80 (m, 4H). Mass spectrum (ESI, *m/z*): Calcd. for C₂₆H₃₀N₄O₂, 431.2 (M+H), found 431.2

15

Example 40

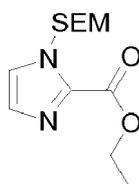
20 5-Bromo-1*H*-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(2-morpholin-4-yl-ethyl)-phenyl]-amide hydrochloride

[0341]



35 a) 1-(2-Trimethylsilyl-ethoxymethyl)-1*H*-imidazole-2-carboxylic acid ethyl ester

[0342]

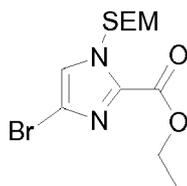


[0343] A flask charged with 1*H*-imidazole-2-carboxylic acid ethyl ester (1.03 g, 7.36 mmol), K₂CO₃ (2.00 g, 14.5 mmol), SEM-Cl (1.56 mL, 8.89 mmol), and 20 mL of acetone was stirred for 10 h at RT. The reaction was diluted with EtOAc (100 mL), washed with NaHCO₃ (2 x 100 mL), brine (100 mL), and the organic layer dried over Na₂SO₄ and concentrated. The title compound was eluted from a 20-g SPE with 50% EtOAc/hexanes to give 1.50 g (76%) of a colorless oil. Mass spectrum (ESI, *m/z*): Calcd. for C₁₂H₂₂N₃O₃Si, 271.1 (M+H), found 271.1.

50

b) 4-Bromo-1-(2-trimethylsilyl-ethoxymethyl)-1*H*-imidazole-2-carboxylic acid ethyl ester

[0344]



10 **[0345]** To a solution of 1-(2-trimethylsilyl-ethoxymethyl)-1*H*-imidazole-2-carboxylic acid ethyl ester (0.20 g, 0.74 mmol)(as prepared in the previous step) in 2 mL of CH₃CN was added NBS (0.13 g, 0.74 mmol) and the mixture heated to 60 °C for 2 h. The mixture was concentrated and the title compound purified by elution from a 20-g SPE column with 20% EtOAc/hexanes to give 0.1 g (39%) of a colorless oil. Mass spectrum (ESI, m/z): Calcd. for C₁₂H₂₁BrN₂O₃Si, 349.0 (M+H), found 348.7.

15 **c) 4-Bromo-1-(2-trimethylsilyl-ethoxymethyl)-1*H*-imidazole-2-carboxylate potassium salt**

[0346]



25 **[0347]** The title compound was prepared from 4-bromo-1-(2-trimethylsilyl-ethoxymethyl)-1*H*-imidazole-2-carboxylic acid ethyl ester (as prepared in the previous step) according to the procedure in Example 1, step (d). Mass spectrum (ESI, m/z): Calcd. for C₁₀H₁₆BrKN₂O₃Si, 321.0/323.0 (M-K+2H), found 320.6/322.6.

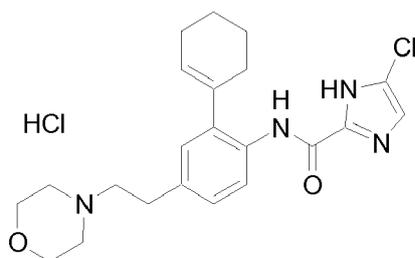
30 **d) 5-Bromo-1*H*-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(2-morpholin-4-yl-ethyl)-phenyl]-amide hydrochloride**

35 **[0348]** The title compound was prepared by coupling 4-bromo-1-(2-trimethylsilyl-ethoxymethyl)-1*H*-imidazole-2-carboxylate potassium salt (as prepared in the previous step) and 2-cyclohex-1-enyl-4-(2-morpholin-4-yl-ethyl)-phenylamine (as prepared in Example 33, step (c)) according to the procedure in Example 34, step(c), followed by SEM deprotection according to the procedure in Example 34, step (d). The hydrochloride salt was prepared from the trifluoroacetic acid salt using a BioRad AG2-X8 resin, Cl⁻ ion form. ¹H-NMR (400 MHz, CD₃OD) δ 8.18 (d, *J* = 8.3 Hz, 1H), 7.33 (s, 1H), 7.23 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.16 (d, *J* = 2.1 Hz, 1H), 5.83 (m, 1H), 4.08 (m, 2H), 3.81 (m, 2H), 3.60 (m, 2H), 3.42 (m, 2H), 3.22 (m, 2H), 3.08 (m, 2H), 2.34-2.23 (m, 4H), 1.91-1.76 (m, 4H). Mass spectrum (ESI, m/z): Calcd. for C₂₂H₂₇BrN₄O₂, 459.1/461.1 (M+H), found 459.0./461.0

40 **Example 41**

45 **5-Chloro-1*H*-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(2-morpholin-4-yl-ethyl)-phenyl]-amide hydrochloride**

[0349]



a) 4-Chloro-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid ethyl ester

[0350]

5



10

[0351] This was prepared according to the procedure in Example 40, step (b) substituting N-chlorosuccinimide for NBS. Mass spectrum (ESI, m/z): Calcd. for $C_{12}H_{21}ClN_2O_3Si$, 305.1 (M+H), found 304.7.

15

b) 4-Chloro-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylate potassium salt

[0352]

20



25

[0353] This compound was prepared from 4-chloro-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid ethyl ester (as prepared in the previous step) according to the procedure in Example 1, step (d). Mass spectrum (ESI, m/z): Calcd. for $C_{10}H_{16}ClKN_2O_3Si$, 277.1 (M-K+2H), found 276.7.

30

c) 5-Chloro-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(2-morpholin-4-yl-ethyl)-phenyl]-amide hydrochloride

[0354] The title compound was prepared by coupling 4-chloro-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylate potassium salt and (as prepared in the previous step) and 2-cyclohex-1-enyl-4-(2-morpholin-4-yl-ethyl)-phenylamine (as prepared in Example 33, step (c)) according to the procedure in Example 34, step (c), followed by SEM deprotection according to the procedure in Example 34, step (d). The hydrochloride salt was prepared from the trifluoroacetic acid salt using a BioRad AG2-X8 resin, Cl^- ion form. 1H -NMR (400 MHz, $DMSO-d_6$): δ 13.73 (s, 1H), 10.52 (s, 1H), 9.58 (s, 1H), 8.00 (d, $J = 8.1$ Hz, 1H), 7.53 (s, 1H), 7.20 (dd, $J = 8.1, 2.1$ Hz, 1H), 7.14 (d, $J = 2.1$ Hz, 1H), 5.77 (m, 1H), 4.00 (m, 2H), 3.74 (m, 2H), 3.57-3.41 (m, 4H), 3.19-2.93 (m, 4H), 2.27-2.13 (m, 4H), 1.79-1.65 (m, 4H). Mass spectrum (ESI, m/z): Calcd. for $C_{22}H_{27}ClN_4O_2$, 415.2 (M+H), found 415.1

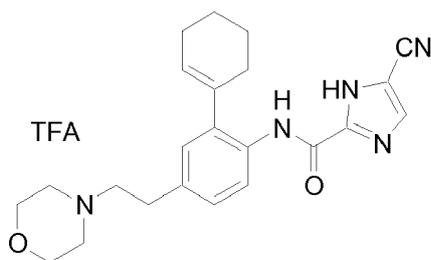
40

Example 42**5-Cyano-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(2-morpholin-4-yl-ethyl)-phenyl]-amide trifluoroacetic acid salt**

45

[0355]

50



55

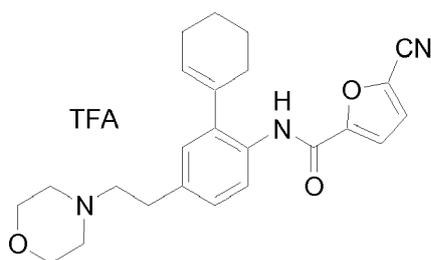
EP 2 687 516 A1

[0356] The title compound was prepared by coupling 4-cyano-1-(2-trimethylsilylanyl-ethoxymethyl)-1*H*-imidazole-2-carboxylate potassium salt (as prepared in Example 1, step (d)) and 2-cyclohex-1-enyl-4-(2-morpholin-4-yl-ethyl)-phenylamine (as prepared in Example 33, step (c)) according to the procedure in Example 34, step (c), followed by SEM deprotection according to the procedure in Example 34, step (d). ¹H-NMR (400 MHz, CD₃OD) δ 8.19 (d, *J* = 8.3 Hz, 1H), 8.02 (s, 1H), 7.23 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.17 (d, *J* = 2.1 Hz, 1H), 5.83 (m, 1H), 4.17-4.01 (m, 2H), 3.89-3.76 (m, 2H), 3.66-3.50 (m, 2H), 3.47-3.36 (m, 2H), 3.28-3.15 (m, 2H), 3.12-3.03 (m, 2H), 2.35-2.22 (m, 4H), 1.90-1.75 (m, 4H). Mass spectrum (ESI, *m/z*): Calcd. for C₂₃H₂₇N₅O₂, 406.2 (M+H), found 406.2.

Example 43

5-Cyano-furan-2-carboxylic acid [2-cyclohex-1-enyl-4-(2-morpholin-4-yl-ethyl)-phenyl]-amide trifluoroacetic acid salt

[0357]

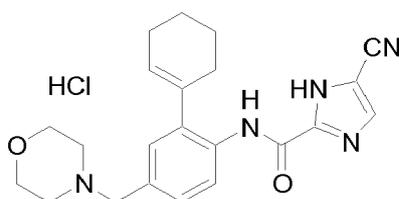


[0358] The title compound was prepared by coupling 5-cyano-furan-2-carboxylic acid (W02004096795) and 2-cyclohex-1-enyl-4-(2-morpholin-4-yl-ethyl)-phenylamine (as prepared in Example 33, step (c)) according to the procedure in Example 34, step (c). ¹H-NMR (400 MHz, CD₃OD): δ 7.81 (d, *J* = 8.2 Hz, 1H), 7.50 (d, *J* = 3.8 Hz, 1H), 7.34 (d, *J* = 3.8 Hz, 1H), 7.26 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.22 (d, *J* = 2.1 Hz, 1H), 5.81 (m, 1H), 4.18-4.05 (m, 2H), 3.84-3.73 (m, 2H), 3.63-3.53 (m, 2H), 3.48-3.39 (m, 2H), 3.29-3.17 (m, 2H), 3.14-3.04 (m, 2H), 2.35-2.17 (m, 4H), 1.86-1.68 (m, 4H). Mass spectrum (ESI, *m/z*): Calcd. for C₂₄H₂₇N₃O₃, 406.2 (M+H), found 406.2.

Example 44

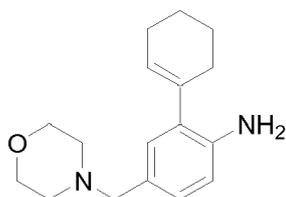
5-Cyano-1*H*-imidazole-2-carboxylic acid (2-cyclohex-1-enyl-4-morpholin-4-ylmethyl-phenyl)-amide hydrochloride

[0359]



a) 2-Cyclohex-1-enyl-4-morpholin-4-ylmethyl-phenylamine

[0360]



EP 2 687 516 A1

[0361] This compound was prepared from 4-morpholin-4-ylmethyl-phenylamine by brominating according to the procedure in Example 33, step (b), followed by Suzuki coupling to cyclohex-1-yl-boronic acid according to the procedure in Example 1, step (e). Mass spectrum (ESI, m/z): Calcd. for $C_{17}H_{24}N_2O$, 273.2 (M+H), found 272.7

5 **b) 5-Cyano-1H-imidazole-2-carboxylic acid (2-cyclohex-1-enyl-4-morpholin-4-ylmethyl-phenyl)-amide hydrochloride**

[0362] The title compound was prepared by coupling 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylate potassium salt (as prepared in Example 1, step (d)) and 2-cyclohex-1-enyl-4-morpholin-4-ylmethyl-phenylamine (as prepared in the previous step) according to the procedure in Example 34, step (c), followed by SEM deprotection according to the procedure in Example 34, step (d). The hydrochloride salt was prepared from the trifluoroacetic acid salt using a BioRad AG2-X8 resin, Cl⁻ ion form. ¹H-NMR (400 MHz, DMSO-d₆): δ 14.34 (br s, 1H), 10.45 (br s, 1H), 9.85 (s, 1H), 8.37 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.48 (dd, J = 8.4, 1.9 Hz, 1H), 7.44 (d, J = 1.9 Hz, 1H), 5.84 (m, 1H), 4.32 (s, 2H), 4.01-3.92 (m, 2H), 3.77-3.65 (m, 2H), 3.31-3.23 (m, 2H), 3.15-3.03 (m, 2H), 2.29-2.15 (m, 4H), 1.80-1.64 (m, 4H). Mass spectrum (ESI, m/z): Calcd. for $C_{22}H_{25}N_5O_2$, 392.2 (M+H), found 391.9

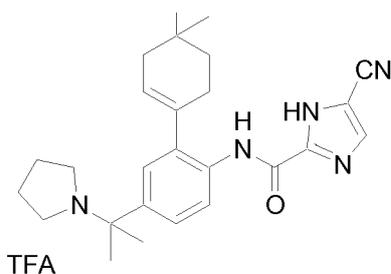
Example 45

20 **5-Cyano-1H-imidazole-2-carboxylic acid [2-(dimethyl-cyclohex-1-enyl)4-(1-methyl-1-pyrrolidin-1-yl-ethyl)-phenyl]-amide trifluoroacetic acid salt**

[0363]

25

30



35

[0364] The title compound was prepared according to the procedure in Example 46 step (a) using N-isopropylidene-pyrrolidinium perchlorate, (J. Org. Chem., 28, 3021, (1963)) as the electrophile. ¹H-NMR (400 MHz, CD₃O D₂O): δ 8.43 (d, J = 8.7 Hz, 1H), 8.04 (s, 1H), 7.61 (dd, J = 8.7, 2.5 Hz, 1H), 7.52 (d, J = 2.5 Hz, 1H), 5.84 (m, 1H), 3.30-3.22 (m, 4H), 2.36 (m, 2H), 2.13 (m, 2H), 2.08-1.93 (m, 4H), 1.86 (s, 6H), 1.64 (t, J = 6.3 Hz, 2H), 1.13 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for $C_{26}H_{33}N_5O$, 432.3 (M+H), found 431.9.

40

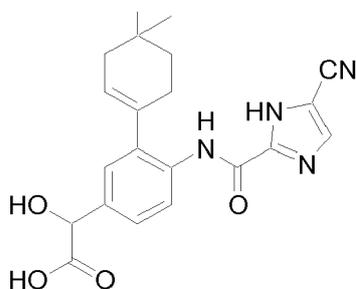
Example 46

45 **[4-[(5-Cyano-1H-imidazole-2-carbonyl)-amino]-3-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-hydroxy-acetic acid**

[0365]

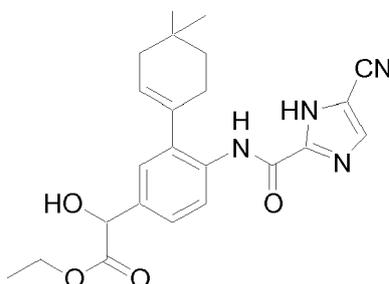
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55



a) **[4-[(5-Cyano-1H-imidazole-2-carbonyl)-amino]-3-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-hydroxy-acetic acid ethyl ester**

[0366]



[0367] To a suspension of 4-cyano-1H-imidazole-2-carboxylic acid [4-bromo-2-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-amide (71 mg, 0.18 mmol) (as prepared in Example 14, step(c)) in 3 mL THF at -40 °C was added a 2M solution of isopropylmagnesium chloride (i-PrMgCl) in THF (0.23 mL, 0.46 mmol) and the solution was then warmed to 0 °C and stirred for 10 min. The solution was then cooled to -78 °C and a 1.7 M solution of t-BuLi in pentane (0.28 mL, 0.48 mmol) was added dropwise and then a 40% solution of ethyl glyoxalate in toluene (0.23 mL, 0.90 mmol) was added immediately thereafter. After 5 min at -78 °C the reaction was quenched with satd NH₄Cl (10 mL) and extracted with EtOAc (3 x 10 mL) and dried over Na₂SO₄ and concentrated in vacuo. The title compound was purified by flash chromatography (silica gel) eluting with 50-100% EtOAc/hexanes to give 37 mg (50%) of the title compound as a white solid. Mass spectrum (ESI, m/z): Calcd. for C₂₃H₂₆N₄O₂, 423.2 (M+H), found 423.1.

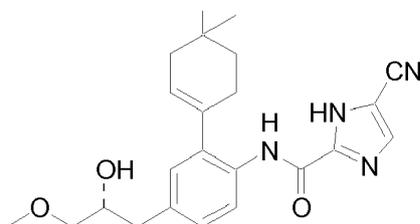
b) **[4-[(5-Cyano-1H-imidazole-2-carbonyl)-amino]-3-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-hydroxy-acetic acid**

[0368] To a solution of [4-[(5-cyano-1H-imidazole-2-carbonyl)-amino]-3-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-hydroxy-acetic acid ethyl ester (as prepared in the previous step)(30.0 mg, 71 μmol) in 0.2 mL of EtOH at RT was added a 2N KOH solution (71 μL, 14.2 μmol) and the reaction stirred for 2 h. The pH was then adjusted to 2 with a 2 M TFA solution and the title compound was purified by RP-HPLC, eluting with a linear gradient of 20% to 50% CH₃CN in 0.1%TFA/H₂O over 10 min to give 20 mg (71%) of a white solid. ¹H-NMR (400 MHz, CD₃OD): δ 8.24 (d, J = 8.4 Hz, 1H), 8.00 (s, 1H), 7.40 (dd, J = 8.4, 2.1 Hz, 1H), 7.33 (d, J = 2.1 Hz, 1H), 5.78 (m, 1H), 5.15 (s, 1H), 2.33 (m, 2H), 2.10 (m, 2H), 1.62 (t, J = 6.3, 6.3 Hz, 2H), 1.11 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for C₂₁H₂₂N₄O₂, 395.2 (M+H), found 395.1.

Example 47

5-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-((R)-2-hydroxy-3-methoxy-propyl)-phenyl]-amide

[0369]



[0370] This compound was prepared from 4-cyano-1H-imidazole-2-carboxylic acid [4-bromo-2-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-amide (as prepared in Example 14, step(c)) according to the procedure in Example 46 step (a) using (S)-glycidyl methyl ether as the electrophile. ¹H-NMR (400 MHz, CD₃OD): δ 8.10 (d, J = 8.3 Hz, 1H), 7.98 (s, 1H), 7.15 (dd, J = 8.3, 2.1 Hz, 1H), 7.07 (d, J = 2.1 Hz, 1H), 5.73 (m, 1H), 3.91 (m, 1H), 3.36 (s, 3H), 2.80 (dd, J = 13.7, 5.7 Hz, 1H), 2.69 (dd, J = 13.7, 7.5 Hz, 1H), 2.31 (m, 2H), 2.07 (m, 2H), 1.58 (t, J = 6.3 Hz, 2H), 1.07 (s, 6H). Mass spectrum

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(ESI, m/z): Calcd. for $C_{23}H_{28}N_4O_3$, 409.2 (M+H), found 409.1.

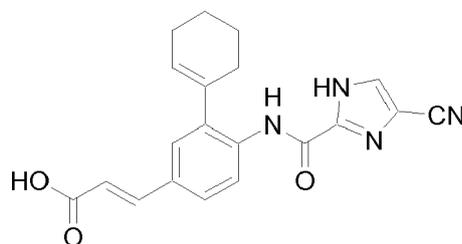
Example 48

5 **3-{4-[(4-Cyano-1H-imidazole-2-carbonyl)-amino]-3-cyclohex-1-enyl-phenyl}-acrylic acid**

[0371]

10

15



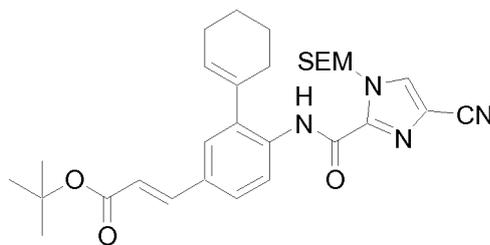
20 **a) 3-(4-[(4-Cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carbonyl)-amino]-3-cyclohex-1-enyl-phenyl)-acrylic acid tert-butyl ester**

20

[0372]

25

30



35 [0373] A flask was charged with 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid (4-bromo-2-cyclohex-1-enyl-phenyl)-amide (79 mg, 0.16 mmol)(as prepared in Example 1, step (f)), t-butyl acrylate (41 mg, 0.32 mmol), cesium carbonate (57 mg, 0.18mmol), (t-Bu₃P)₂Pd(O) (8.2 mg, 0.016 mmol), and 1 mL of dioxane and heated in a microwave reactor for 30 min at 135 °C. The crude reaction mixture was loaded on a 10-g SPE column and the title compound was eluted with 10% EtOAc/hexanes to give 30 mg (34%) of a white solid. Mass spectrum (ESI, m/z): Calcd. for $C_{30}H_{40}N_4O_4Si$, 549.2 (M+H), found 548.9.

35

40 **b) 3-{4-[(4-Cyano-1H-imidazole-2-carbonyl)-amino]-3-cyclohex-1-enyl-phenyl}-acrylic acid**

40

45 [0374] To a solution of 3-(4-[(4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carbonyl)-amino]-3-cyclohex-1-enyl-phenyl)-acrylic acid tert-butyl ester (30 mg, 0.055 mmol)(as prepared in the previous step) in 1.0 mL of DCM was added 0.30 mL of TFA, 0.026 mL of EtOH and stirred at RT for 2 h. The mixture was concentrated and the residue triturated with MeOH to give 19 mg (95%) of the title compound as a white solid. ¹H-NMR (400 MHz, DMSO-d₆): δ 14.39 (br s, 1H), 9.83 (s, 1H), 8.38 (d, J = 2.5 Hz, 1H), 8.15 (d, J = 8.5 Hz, 1H), 7.65 (dd, J = 8.5, 1.9 Hz, 1H), 7.57 (d, J = 1.9 Hz, 1H), 7.56 (d, J = 16.0 Hz, 1H), 6.53 (d, J = 16.0 Hz, 1H), 5.83 (m, 1H), 2.31-2.14 (m, 4H), 1.81-1.65 (m, 4H). Mass spectrum (ESI, m/z): Calcd. for $C_{20}H_{18}N_4O_3$, 363.1 (M+H), found 363.0.

45

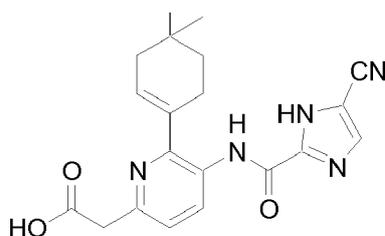
50 Example 49

50

[5-[(5-Cyano-1H-imidazole-2-carbonyl)-amino]-6-(4,4-dimethyl-cyclohex-1-enyl)-pyridin-2-yl]-acetic acid

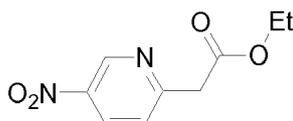
[0375]

55



a) (5-Nitro-pyridin-2-yl)-acetic acid ethyl ester

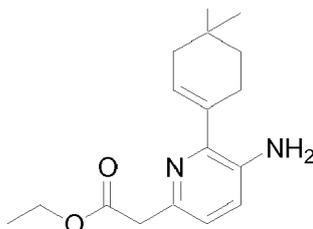
[0376]



[0377] To a suspension of NaH (60% dispersion, 0.900 g, 22.5 mmol) in 40 mL of THF was added malonic acid tert-butyl ester ethyl ester (4.00 mL, 21.1 mmol) and the mixture stirred for 15 min at RT. To this mixture was then added 2-chloro-5-nitro-pyridine (2.56 g, 16.0 mmol) and the reaction stirred for 10 h at RT. The mixture was diluted with 100 mL of EtOAc and washed with NH_4Cl (2 x 100 mL) and brine (100 mL) and dried over Na_2SO_4 and concentrated in vacuo. The residue was dissolved in DCM (20 mL), TFA (10 mL) was added and the mixture stirred for 2 h at RT. The mixture was concentrated, the residue dissolved in 100 mL of EtOAc and washed with NaHCO_3 (2 x 100 mL) and brine (100 mL) and again dried over Na_2SO_4 and concentrated in vacuo. The title compound was purified by flash chromatography eluting with 30% EtOAc/hexanes to give 2.35 g (70%) of a light yellow solid. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 9.38 (d, J = 2.6 Hz, 1H), 8.46 (dd, J = 8.6, 2.6 Hz, 1H), 7.55 (d, J = 8.6 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.99 (s, 2H), 1.28 (t, J = 7.1 Hz, 3H).

b) [5-Amino-6-(4,4-dimethyl-cyclohex-1-enyl)-pyridin-2-yl]-acetic acid ethyl ester

[0378]

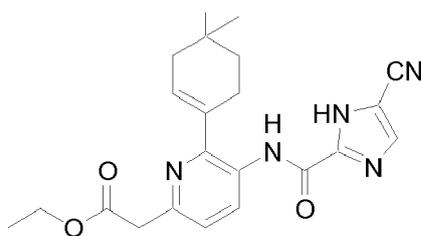


[0379] This compound was prepared from (5-nitro-pyridin-2-yl)-acetic acid ethyl ester (as prepared in the previous step) according to the procedure for nitro reduction and bromination in Example 33, step (b), followed by Suzuki coupling to 4,4-dimethyl-1-cyclohexen-1-ylboronic acid according to the procedure in Example 1, step (e). Mass spectrum (APCI, m/z): Calcd. for $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_2$, 289.2 (M+H), found 289.2.

c) [5-[(5-Cyano-1H-imidazole-2-carbonyl)-aminol-6-(4,4-dimethyl-cyclohex-1-enyl)-pyridin-2-yl]-acetic acid ethyl ester

[0380]

5



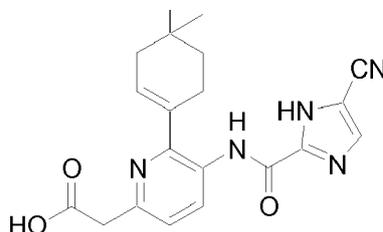
10 **[0381]** The title compound was prepared by coupling 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylate potassium salt (as prepared in Example 1, step (d)) and [5-amino-6-(4,4-dimethyl-cyclohex-1-enyl)-pyridin-2-yl]-acetic acid ethyl ester (as prepared in the previous step) according to the procedure in Example 34, step (c), followed by SEM deprotection according to the procedure in Example 34, step (d). Mass spectrum (ESI, m/z): Calcd. for $C_{22}H_{25}N_5O_3$, 408.2 (M+H), found 408.2.

15

d) [5-[(5-Cyano-1H-imidazole-2-carbonyl)-amino]-6-(4,4-dimethyl-cyclohex-1-enyl)-pyridin-2-yl]-acetic acid

[0382]

20



25

30 **[0383]** The title compound was prepared from [5-[(5-cyano-1H-imidazole-2-carbonyl)-amino]-6-(4,4-dimethyl-cyclohex-1-enyl)-pyridin-2-yl]-acetic acid ethyl ester (as prepared in the previous step) by hydrolysis of the ethyl ester according to the procedure in Example 46, step (b). 1H -NMR (400 MHz, DMSO- d_6): δ 14.28 (s, 1H), 12.47 (s, 1H), 10.08 (s, 1H), 8.34 (d, $J = 2.4$ Hz, 1H), 8.12 (d, $J = 8.2$ Hz, 1H), 7.28 (d, $J = 8.2$ Hz, 1H), 5.87 (m, 1H), 3.74 (s, 2H), 2.39 (m, 2H), 1.91 (m, 2H), 1.47 (t, $J = 6.3$ Hz, 2H), 0.97 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for $C_{20}H_{21}N_5O_3$, 380.2 (M+H), found 380.2.

35

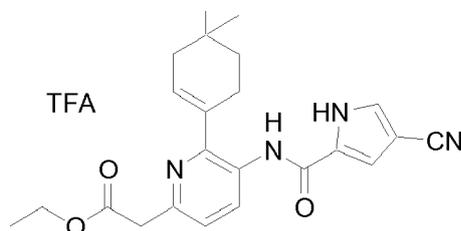
Example 50

[5-[(4-Cyano-1H-pyrrole-2-carbonyl)-amino]-6-(4,4-dimethyl-cyclohex-1-enyl)-pyridin-2-yl]-acetic acid ethyl ester trifluoroacetic acid salt

40

[0384]

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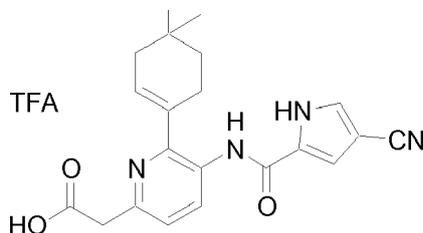
50

55 **[0385]** The title compound was prepared by coupling 4-cyano-1H-pyrrole-2-carboxylic acid (Can. J. Chem., 59(17), 2673-6, (1981)) and [5-amino-6-(4,4-dimethyl-cyclohex-1-enyl)-pyridin-2-yl]-acetic acid ethyl ester (as prepared in Example 49, step (b)) according to the procedure in Example 34, step (c). 1H -NMR (400 MHz, DMSO- d_6) δ 12.48 (s, 1H), 9.51 (s, 1H), 7.57 (m, 2H), 7.09 (d, $J = 8.2$ Hz, 1H), 7.07 (m, 1H), 5.65 (m, 1H), 3.93 (q, $J = 7.1$ Hz, 2H), 3.66 (s, 2H), 2.19 (m, 2H), 1.64 (m, 2H), 1.22 (t, $J = 6.4$ Hz, 2H), 1.01 (t, $J = 7.1$ Hz, 3H), 0.70 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for $C_{23}H_{26}N_4O_3$, 407.2 (M+H), found 407.2.

Example 51

[5-[(4-Cyano-1H-pyrrole-2-carbonyl)-amino]-6-(4,4-dimethyl-cyclohex-1-enyl)-pyridin-2-yl]-acetic acid trifluoroacetic acid salt

[0386]

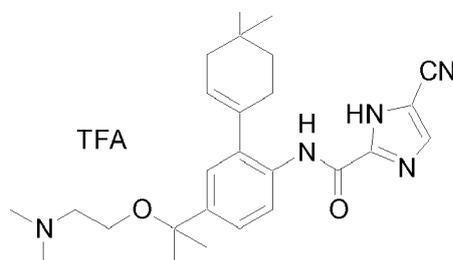


[0387] The title compound was prepared from [5-[(4-cyano-1H-pyrrole-2-carbonyl)-amino]-6-(4,4-dimethyl-cyclohex-1-enyl)-pyridin-2-yl]-acetic acid ethyl ester (as prepared in the previous step) by hydrolysis of the ethyl ester according to the procedure in Example 46, step (b). ¹H-NMR(400 MHz, DMSO-d₆): δ 12.70 (br s, 1H), 9.74 (s, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.78 (dd, *J* = 3.2, 1.5 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.29 (m, 1H), 5.87 (m, 1H), 3.80 (s, 2H), 2.40 (m, 2H), 1.86 (m, 2H), 1.43 (t, *J* = 6.4 Hz, 2H), 0.92 (s, 6H). Mass spectrum (ESI, *m/z*): Calcd. for C₂₁H₂₂N₄O₃, 379.2 (M+H), found 379.2.

Example 52

5-Cyano-1H-imidazole-2-carboxylic acid [4-[1-(2-dimethylamino-ethoxy)-1-methyl-ethyl]-2-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-amide trifluoroacetic acid salt

[0388]



[0389] To a suspension of 5-cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-amide (60 mg, 0.16 mmol) (as prepared in Example 14, step (d)) in 1 mL of DCM was added 2-dimethylamino-ethanol (0.32 mL, 3.20 mmol), TFA (0.37 mL, 4.80 mmol), and the mixture heated to 60 °C for 6 h. The mixture was concentrated and the title compound purified by RP-HPLC on a C 18 column eluting with a linear gradient of 30-55% CH₃CN in 0.1% TFA/H₂O over 9 min to give 10 mg (11%) of a white solid. ¹H-NMR (400 MHz, CD₃OD): δ 8.26 (d, *J* = 8.5 Hz, 1H), 8.09 (s, 1H), 7.44 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.30 (d, *J* = 2.2 Hz, 1H), 5.77 (m, 1H), 3.52 (m, 2H), 3.30 (m, 2H), 2.91 (s, 6H), 2.34 (m, 2H), 2.11 (m, 2H), 1.64 (s, 6H), 1.60 (m, 2H), 1.12 (s, 6H). Mass spectrum (ESI, *m/z*): Calcd. for C₂₆H₃₅N₅O₂, 450.3 (M+H), found 450.0.

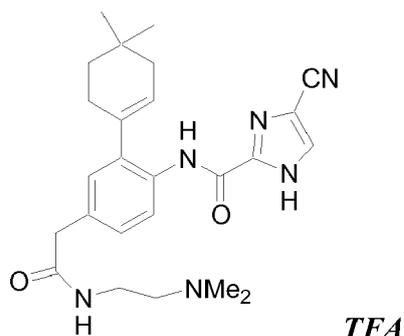
Example 53

4-Cyano-1H-imidazole-2-carboxylic acid [4-[(2-dimethylamino-ethylcarbamoyl)-methyl]-2-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-amide trifluoroacetic acid salt

[0390]

5

10

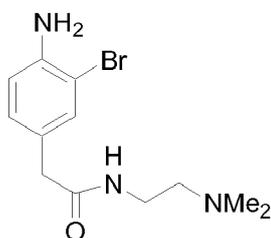


a) 2-(4-Amino-3-bromo-phenyl)-N-(2-dimethylamino-ethyl)-acetamide

15

[0391]

20



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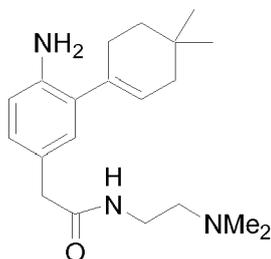
[0392] To a solution of (4-amino-phenyl)-acetic acid (320 mg, 2.10 mmol) in CH₃CN (4 mL) and AcOH (2 mL) at 0 °C was added NBS (373 mg, 2.10 mmol) in CH₃CN (3 mL). The reaction was allowed to warm to room temperature over 1 h and then concentrated in vacuo to give a mixture of (4-amino-3-bromo-phenyl)-acetic acid and starting material which was used without further purification. The crude (4-amino-3-bromo-phenyl)-acetic acid (490 mg, 2.12 mmol), EDCI (487 mg, 2.54 mmol), HOBt (343 mg, 2.54 mmol), and N¹,N¹-dimethyl-ethane-1,2-diamine (281 mg, 3.19 mmol) were slurried in DCM (10 mL), treated with NEt₃ (910 μL, 6.36 mmol) and stirred overnight. The reaction was diluted with DCM (50 mL), washed with water (2 x 50 mL), dried (Na₂SO₄) and concentrated in vacuo. The crude residue was purified by preparative TLC (10 % MeOH-CHCl₃) to afford 70 mg (11 %) of the title compound. ¹H-NMR (CDCl₃; 400 MHz) δ 7.25 (s, 1H, J = 2.0 Hz), 6.93 (dd, 1H, J = 8.1, 2.0 Hz), 6.65 (d, 1H, J = 8.1 Hz), 6.04 (br s, 1H), 4.03 (br s, 2H), 3.32 (s, 2H), 3.24-3.19 (m, 2H), 2.30-2.27 (m, 2H), 2.11 (s, 6H).

b) 2-[4-Amino-3-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-N-(2-dimethylamino-ethyl)-acetamide

40

[0393]

45



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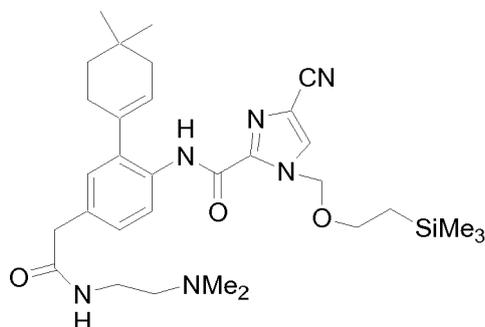
55

[0394] To a flask containing 2-(4-amino-3-bromo-phenyl)-N-(2-dimethylamino-ethyl)-acetamide (as prepared in the previous step, 83 mg, 0.27 mmol), tris(dibenzylideneacetone)dipalladium (0) (4.0 mg, 0.0080 mmol), 2-(dicyclohexylphosphino)-2',6'-dimethoxy-1,1'-biphenyl (5.6 mg, 0.010 mmol) and K₃PO₄ (0.17 g, 0.82 mmol) was charged dioxane (3 mL) and the reaction was heated to 100 °C for 48 h. At this time the reaction was diluted with EtOAc (25 mL) and washed with water (25 mL). The organic layer was dried (Na₂SO₄) and concentrated in vacuo. The crude residue was purified by preparative TLC (10 % MeOH-CHCl₃) to afford 26 mg (28 %) of the title compound as a tan solid. ¹H-NMR (CDCl₃; 400 MHz): δ 6.85 (dd, 1H, J = 8.0, 2.1 Hz), 6.79 (d, 1H, J = 2.1 Hz), 6.59 (d, 1H, J = 8.0 Hz), 6.01 (br s, 1H), 5.60 (m, 1H), 3.66 (br s, 2H), 3.35 (s, 2H), 3.23-3.18 (m, 2H), 2.27 (t, 1H, J = 6.1 Hz), 2.20-2.14 (m, 2H), 2.09 (s, 6H),

1.90-1.88 (m, 2H), 1.44 (t, 2H, J = 6.3 Hz), 0.92 (s, 6H).

c) **4-Cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [4-[(2-dimethylamino-ethylcarbamoyl)-methyl]-2-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-amide**

[0395]



[0396] The title compound was prepared from 2-[4-amino-3-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-N-(2-dimethylamino-ethyl)-acetamide (as prepared in the previous step) and potassium 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylate (as prepared in Example 1, step (d)) according to the procedure in Example 1, step (f). Mass spectrum (ESI, m/z): Calcd. for $C_{31}H_{46}N_6O_3Si$, 579.3 (M+H), found 579.3.

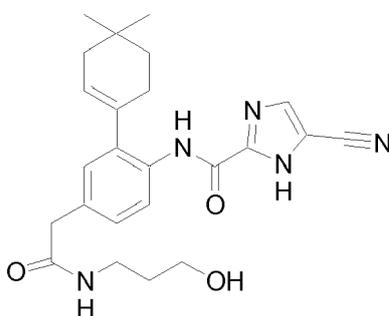
d) **4-Cyano-1H-imidazole-2-carboxylic acid [4-[(2-dimethylamino-ethylcarbamoyl)-methyl]-2-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-amide trifluoroacetic acid salt**

[0397] The title compound was prepared from 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [4-[(2-dimethylamino-ethylcarbamoyl)-methyl]-2-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-amide (as prepared in the previous step) according to the procedure in Example 1, step (g). 1H -NMR (CD_3OD ; 400 MHz): δ 8.17 (d, 1 H, J = 8.3 Hz), 7.99 (s, 1 H), 7.22 (dd, 1 H, J = 8.3, 2.0 Hz), 7.15 (1 H, d, J = 2.0 Hz), 5.74 (m, 1 H), 3.57-3.54 (m, 4H), 3.25 (t, 2H, J = 5.9 Hz), 2.92 (s, 6H), 2.32-2.28 (m, 2H), 2.07-2.06 (m, 2H), 1.58 (t, 2H, J = 6.3 Hz), 1.08 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for $C_{25}H_{32}N_6O_2$, 449.2 (M+H), found 449.3.

Example 54

5-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[(3-hydroxy-propylcarbamoyl)-methyl]-phenyl}-amide

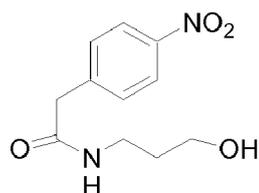
[0398]



a) **N-(3-Hydroxy-propyl)-2-(4-nitro-phenyl)-acetamide**

[0399]

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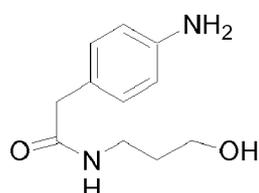


10 [0400] To a stirred solution of 3-hydroxypropylamine (507 mg, 6.76 mmol) and triethylamine (1.88 mL, 0.013 mol) in DCM (10 mL) at 0 °C was added (4-nitro-phenyl)-acetyl chloride (1.35 g, 6.76 mmol) in DCM (10 mL) dropwise. The dark red solution was allowed to warm to room temperature and then poured into water (50 mL). The layers were separated and the organic layer was dried (Na₂SO₄) and concentrated in vacuo. The crude material was purified by preparative thin layer chromatography (TLC) (5%-MeOH-CHCl₃) to afford 183 mg (11 %) of the title compound as a solid.

15 ¹H-NMR (CDCl₃; 400 MHz): δ 8.12 (d, 2H, J = 8.7 Hz), 7.39 (d, 1H, J = 8.7 Hz), 6.09 (br s, 1H), 3.58 (s, 2H), 3.57-3.54 (m, 2H), 3.40 (br s, 1H), 3.36-3.31 (m, 2H), 1.63-1.57 (m, 2H).

b) 2-(4-Amino-phenyl)-N-(3-hydroxy-propyl)-acetamide

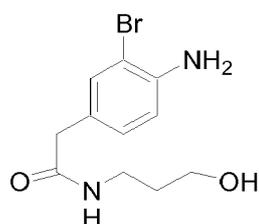
20 [0401]



30 [0402] A slurry of N-(3-hydroxy-propyl)-2-(4-nitro-phenyl)-acetamide (as prepared in the previous step, 183 mg, 0.768 mmol) and 5 % Pd-C (130 mg) in EtOH-EtOAc (5 mL, 4:1 v/v) was stirred under 1 atm H₂ for 2 h. The reaction was filtered and concentrated to afford 152 mg (95 %) of the title compound. ¹H- NMR (DMSO-d₆; 400 MHz): δ 7.78 (br s, 1H), 6.88 (d, 2H, J = 8.3 Hz), 6.47 (d, 2H, J = 8.3 Hz), 4.88 (br s, 2H), 4.39 (t, 1H, J = 5.2 Hz), 3.43-3.34 (m, 2H), 3.16 (s, 2H), 3.08-3.03 (m, 2H), 1.55-1.48 (m, 2H).

35 **c) 2-(4-Amino-3-bromo-phenyl)-N-(3-hydroxy-propyl)-acetamide**

[0403]



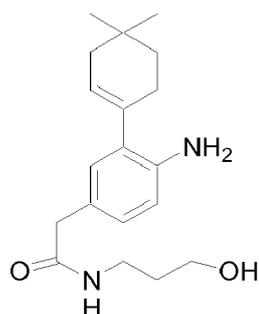
50 [0404] The title compound was prepared from 2-(4-amino-phenyl)-N-(3-hydroxy-propyl)-acetamide (as prepared in the previous step) and NBS according to the procedure in Example 7, step (c). Mass spectrum (ESI, m/z): Calcd. for C₁₁H₁₅BrN₂O₂, 287.0 (M+H), found 287.0.

d) 2-[4-Amino-3-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-N-(3-hydroxy-propyl)-acetamide

55 [0405]

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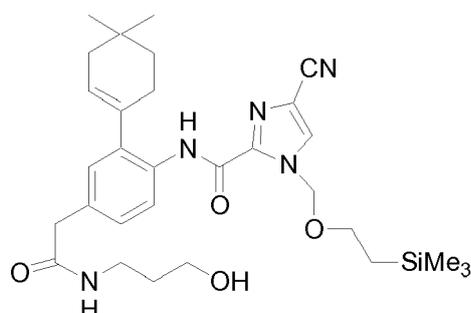
[0406] The title compound was prepared from 2-(4-amino-3-bromo-phenyl)-N-(3-hydroxy-propyl)-acetamide (as prepared in the previous step), 4,4-dimethylcyclohex-1-yl boronic acid and Pd(PPh₃)₄ according to the procedure in Example 1, step (e). Mass Spectrum (ESI, m/z): Calcd. for C₁₉H₂₈N₂O₂, 317.2 (M+H), found 317.1.

20

e) 4-Cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[(3-hydroxy-propylcarbamoyl)-methyl]-phenyl}-amide

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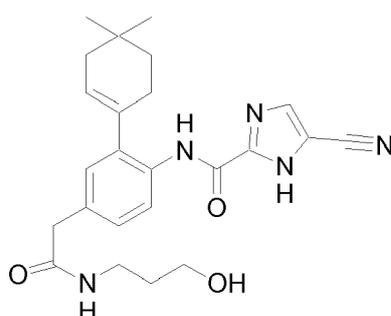
[0408] The title compound was prepared from 2-[4-amino-3-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-N-(3-hydroxy-propyl)-acetamide (as prepared in the previous step), potassium 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylate (as prepared in Example 1, step (d)), PyBroP and DIEA according to the procedure in Example 1, step (f). ¹H-NMR (CDCl₃; 400 MHz): δ 9.74 (s, 1H), 8.31 (d, 1H, J = 8.3 Hz), 7.78 (s, 1H), 7.20 (dd, 1H, J = 8.4, 1.9 Hz), 7.11 (d, 1H, J = 1.9 Hz), 7.03 (br s, 1H), 5.94 (s, 2H), 5.75 (s, 1H), 4.22 (t, 1H, J = 6.1 Hz), 3.67-3.63 (m, 2H), 3.61-3.56 (m, 2H), 3.52 (s, 2H), 3.38-3.33 (m, 2H), 2.27-2.23 (m, 2H), 2.08-2.07 (m, 2H), 1.67-1.61 (m, 2H), 1.57 (t, 2H, J = 6.2 Hz), 1.09 (s, 6H), 0.98-0.94 (m, 2H), 0.00 (s, 9H).

45

f) 5-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[(3-hydroxy-propylcarbamoyl)-methyl]-phenyl}-amide

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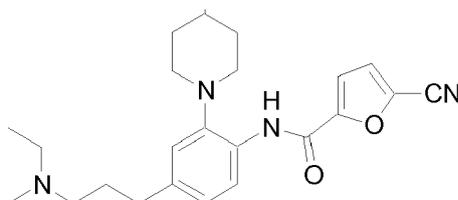
EP 2 687 516 A1

[0410] The title compound was prepared from 4-cyano-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[(3-hydroxy-propylcarbamoyl)-methyl]-phenyl}-amide (as prepared in the previous step) according to the procedure in Example 1, step (g). ¹H NMR (CD₃OD; 400 MHz): d 8.05 (d, 1H, J = 7.9 Hz), 7.87 (s, 1H), 7.11 (dd, 1H, J = 8.2, 1.8 Hz), 7.04 (d, 1H, J = 1.9 Hz), 5.64 (m, 1H), 3.45 (t, 2H, J = 6.3 Hz), 3.37 (s, 2H), 3.20 (m, 2H), 2.21-2.18 (m, 2H), 1.97-1.96 (m, 1H), 1.60 (m, 2H), 1.48 (t, 2H, J = 6.2 Hz), 0.97 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for C₂₄H₂₉N₅O₃, 436.2 (M+H), found 436.2.

Example 55

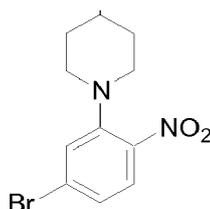
5-Cyano-furan-2-carboxylic acid [4-[3-(ethyl-methyl-amino)-propyl]-2-(4-methyl-piperidin-1-yl)-phenyl]-amide

[0411]



a) 1-(5-Bromo-2-nitro-phenyl)-4-methyl-piperidine

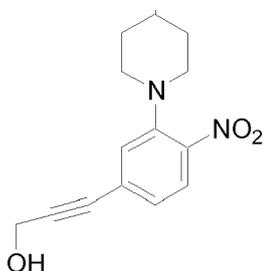
[0412]



[0413] To a round bottom flask containing 4-bromo-2-fluoro-1-nitro-benzene (640 mg, 2.92 mmol) was added 4-methyl piperidine (4 mL) and the reaction was stirred at 40 °C overnight. At this time the dark solution was poured into water (25 mL) and extracted with DCM (2 x 25 mL). The combined organic layers were washed with water (2 x 25 mL), dried (Na₂SO₄) and concentrated in vacuo to afford 556 mg (64 %) of 1-(5-bromo-2-nitro-phenyl)-4-methyl-piperidine as an orange oil which was used without further purification.

b) 3-[3-(4-Methyl-piperidin-1-yl)-4-nitro-phenyl]-prop-2-yn-1-ol

[0414]



[0415] To a round bottom flask containing 1-(5-bromo-2-nitro-phenyl)-4-methyl-piperidine (as prepared above, 400 mg, 1.33 mmol) in 8 mL of dioxane was added propargyl alcohol (155 μL, 2.64 mmol), bis-dichloro(triphenylphosphiny) palladium (II) (56.3 mg, 0.0798 mmol), copper (I) iodide (5.0 mg, 0.02 mmol) and triethylamine (741 μL, 5.32 mmol). The result was heated at 80 °C for 16 h. The reaction was then diluted with EtOAc (50 mL), washed with water (2 x 50 mL), dried (Na₂SO₄), and concentrated in vacuo. Purification of the crude material by preparative thin layer chromatog-

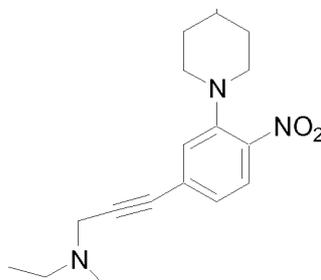
raphy (75% EtOAc-hexanes) afforded 280 mg (77 %) of the title compound as a reddish oil. $^1\text{H-NMR}$ (CDCl_3 ; 400 MHz): δ 7.73 (d, 1H, $J = 8.6$ Hz), 7.17 (d, 1H, $J = 1.6$ Hz), 6.98 (dd, 1H, $J = 8.6, 1.6$ Hz), 3.23-3.26 (m, 2H), 4.53 (s, 2H), 1.73-1.42 (m, 5H), 2.86-2.79 (m, 2H), 1.00 (d, 3H, $J = 6.4$ Hz).

5 **c) Ethyl-methyl-{3-[3-(4-methyl-piperidin-1-yl)-4-nitro-phenyl]-prop-2-ynyl}-amine**

[0416]

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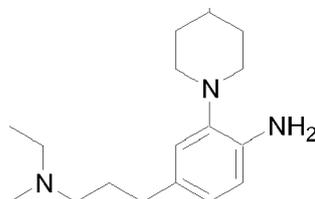
20 **[0417]** To a stirred solution of 3-[3-(4-methyl-piperidin-1-yl)-4-nitro-phenyl]-prop-2-yn-1-ol (as prepared in the previous step, 47 mg, 0.17 mmol) in 4 mL of DCM at 0 °C was added triethylamine (71 μL , 0.51 mmol) followed by methanesulfonyl chloride (17 μL , 0.22 mmol). The reaction was allowed to stir for 10 min, at which time ethylmethylamine (4 drops) was added. The result was heated at reflux for 20 min. and then poured into water (20 mL). The aqueous layer was extracted with DCM (2 x 25 mL), the organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by preparative TLC (10%-MeOH- CHCl_3) to afford 59 mg (100 %) of the title compound as an oil. Mass spectrum (ESI, m/z) Calcd for $\text{C}_{18}\text{H}_{25}\text{N}_3\text{O}_2$, 316.1 (M+H), found 316.2.

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d) **4-[3-(Ethyl-methyl-amino)-propyl]-2-(4-methyl-piperidin-1-yl)-phenylamine**

30 **[0418]**

35



40 **[0419]** The title compound was prepared from ethyl-methyl-1-{3-[3-(4-methyl-piperidin-1-yl)-4-nitro-phenyl]-prop-2-ynyl}-amine (as prepared in the previous step) according to the procedure in Example 54, step (b). Mass spectrum (ESI, m/z) Calcd for $\text{C}_{18}\text{H}_{31}\text{N}_3$, 290.2 (M+H), found 290.2.

e) **5-Cyano-furan-2-carboxylic acid [4-[3-(ethyl-methyl-amino)-propyl]-2-(4-methyl-piperidin-1-yl)-phenyl]-amide**

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[0420] To a mixture of 5-cyano-furan-2-carboxylic acid (WO 2004096795-A2, 23 mg, 0.16 mmol) in DCM (2 mL) at 0 °C was added DMF (10 μL) followed by oxalyl chloride (15 μL , 0.17 mmol) and stirred for 1 h. The reaction was concentrated in vacuo, azeotroped with toluene (2 x 5 mL) and used immediately without further purification. To a solution of 4-[3-(ethyl-methyl-amino)-propyl]-2-(4-methyl-piperidin-1-yl)-phenylamine (as prepared in the previous step, 32 mg, 0.11 mmol) in DCM (2 mL) at 0 °C was added DIEA (48 μL , 0.27 mmol) followed by 5-cyano-furan-2-carbonyl chloride (as prepared above, 22 mg, 0.16 mmol). The reaction was allowed to warm to RT overnight, at which time it was diluted with DCM (20 mL), washed with saturated aqueous NaHCO_3 (10 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification by preparative TLC (10 % MeOH- CHCl_3) afforded 20 mg (45 %) of the title compound as an oily amber solid. $^1\text{H-NMR}$ (CDCl_3 ; 400 MHz): δ 9.69 (s, 1H), 8.38 (d, 1H, $J = 8.4$ Hz), 7.26 (d, 1H, $J = 3.6$ Hz), 7.05 (d, 1H, $J = 2.0$ Hz), 7.00-6.97 (m, 1H), 6.91 (d, 1H, $J = 4.0$ Hz), 3.01-2.98 (m, 2H), 2.78-2.64 (m, 7H), 2.50 (s, 3H), 2.04-1.98 (m, 2H), 1.89-1.85 (m, 2H), 1.63-1.46 (m, 5H), 1.25 (t, 3H, $J = 4.6$ Hz), 1.10 (d, 3H, $J = 6.4$ Hz), 0.93-0.89 (m, 2H). Mass spectrum (ESI, m/z) calcd for $\text{C}_{24}\text{H}_{32}\text{N}_4\text{O}_2$, 409.2 (M+H), found 409.3.

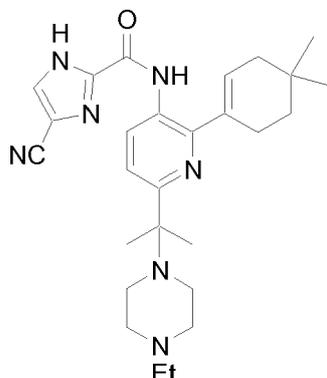
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Example 56

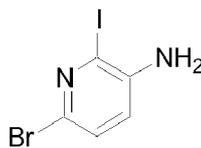
4-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-6-[1-(4-ethyl-piperazin-1-yl)-1-methyl-ethyl]pyridin}-3-yl)-amide

[0421]



a) 6-Bromo-2-iodo-pyridin-3-ylamine

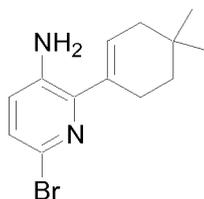
[0422]



[0423] To a stirred solution of 6-bromo-pyridin-3-ylamine (10.2 g, 0.0580 mol) and Ag_2SO_4 (18.1 g, 0.0580 mol) in EtOH (150 mL) was added I_2 (7.59 g, 0.0580 mol) and the reaction was allowed to stir overnight. At this time hexane (200 mL) was added and the resultant mixture was filtered through Celite. The solvent was removed in vacuo, dissolved in CHCl_3 (200 mL), washed with aqueous saturated $\text{Na}_2\text{S}_2\text{O}_3$ (100 mL), water (1 x 100 mL), and dried (Na_2SO_4). The solvent was concentrated in vacuo and the residue was dissolved in hot EtOAc (100 mL), filtered and treated with hexanes (100 mL). Filtration gave 11.2 g (65 %) of the title compound as a white crystalline material. $^1\text{H-NMR}$ (CDCl_3 ; 400 MHz): δ 7.10 (d, 1H, J = 8.2 Hz), 6.74 (d, 1H, J = 8.2 Hz), 4.06 (br s, 2H).

b) 6-Bromo-2-(4,4-dimethyl-cyclohex-1-enyl)-pyridin-3-ylamine

[0424]



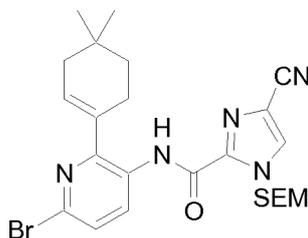
[0425] The title compound was prepared from 6-bromo-2-iodo-pyridin-3-ylamine (as prepared in the previous step, 348 mg, 1.17 mmol), 4,4-dimethylcyclohexen-1-yl boronic acid (198 mg, 1.28 mmol), $\text{Pd}(\text{PPh}_3)_4$ (135 mg, 0.117 mol) and 2M Na_2CO_3 (15.2 mL, 30.5 mmol) according to the procedure in Example 34, step (b) (417 mg, 46 %). $^1\text{H-NMR}$ (CDCl_3 ; 400 MHz): δ 7.06 (d, 1H, J = 8.3 Hz), 6.85 (d, 1H, J = 8.3 Hz), 5.95 (m, 1H), 3.86 (br s, 2H), 2.43-2.39 (m, 2H), 1.99-1.97 (m, 2H), 1.51 (t, 2H, J = 6.4 Hz), 0.99 (s, 6H).

c) 4-Cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [6-bromo-2-(4,4-dimethyl-cyclohex-1-enyl)-pyridin-3-yl]-amide

[0426]

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[0427] The title compound was prepared from 6-bromo-2-(4,4-dimethyl-cyclohex-1-enyl)-pyridin-3-ylamine (as prepared in the previous step, 60 mg, 0.21 mmol), potassium 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylate (as prepared in Example 1, step (d), 91.0 mg, 0.290 mmol), PyBroP (157 mg, 0.330 mmol) and DIEA (91.0 μ L, 0.520 mmol) according to the procedure in Example 1, step (f) (84 mg, 78 %). $^1\text{H-NMR}$ (CDCl_3 ; 400 MHz): δ 9.91 (s, 1H), 8.64 (d, 1H, $J = 8.6$ Hz), 7.79 (s, 1H), 7.38 (d, 1H, $J = 8.6$ Hz), 6.00 (m, 1H), 5.92 (s, 2H), 3.67 (m, 2H), 2.46 (m, 2H), 2.14 (m, 2H), 1.62 (t, 2H, $J = 6.3$ Hz), 1.12 (s, 6H), 0.98 (m, 2H).

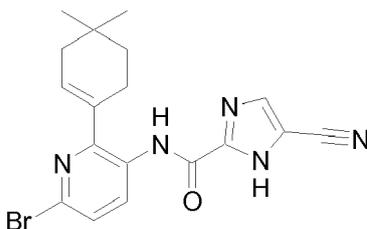
20

d) 5-Cyano-1H-imidazole-2-carboxylic acid [6-bromo-2-(4,4-dimethyl-cyclohex-1-enyl)-pyridin-3-yl]-amide

[0428]

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[0429] The title compound was prepared from 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [6-bromo-2-(4,4-dimethyl-cyclohex-1-enyl)-pyridin-3-yl]-amide (as prepared in the previous step) according to the procedure in Example 1, step (g). Mass spectrum (ESI, m/z): Calcd. for $\text{C}_{18}\text{H}_{18}\text{BrN}_5\text{O}$, 400.0 ($\text{M}+\text{H}$), found 400.0.

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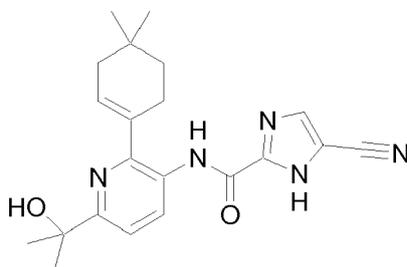
e) 5-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-6-(1-hydroxy-1-methyl-ethyl)-pyridin-3-yl]-amide

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[0430]

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[0431] The title compound is prepared from 5-cyano-1H-imidazole-2-carboxylic acid [6-bromo-2-(4,4-dimethyl-cyclohex-1-enyl)-pyridin-3-yl]-amide (as prepared in the previous step) according to the procedure in Example 1, step (h).

55

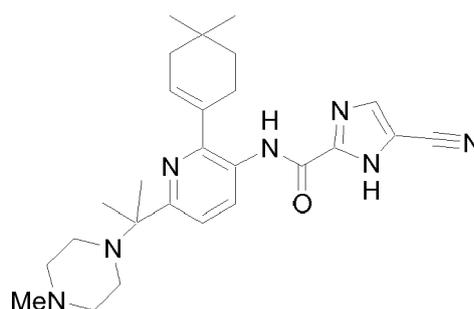
f) 4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-6-[1-(4-ethyl-piperazin-1-yl)-1-methyl-ethyl]-pyridin-3-yl]-amide

[0432] The title compound is prepared from 5-cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-6-(1-hydroxy-1-methyl-ethyl)-pyridin-3-yl]-amide (as prepared in the previous step), N-ethylpiperazine, and thionyl chloride in DCM solvent according to the procedure in Example 14, step (e).

Example 57

5-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-6-[1-methyl-1-(4-methyl-piperazin-1-yl)-ethyl]-pyridin-3-yl]-amide

[0433]



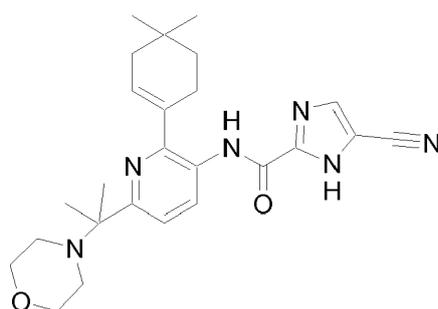
a) 5-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-6-[1-methyl-1-(4-methyl-piperazin-1-yl)-ethyl]-pyridin-3-yl]-amide

[0434] The title compound is prepared from 5-cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-6-(1-hydroxy-1-methyl-ethyl)-pyridin-3-yl]-amide (as prepared in Example 56, step (e)), N-methylpiperazine and thionyl chloride in DCM solvent according to the procedure in Example 14, step (e).

Example 58

5-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-6-(1-methyl-1-morpholin-4-yl-ethyl)-pyridin-3-yl]-amide

[0435]



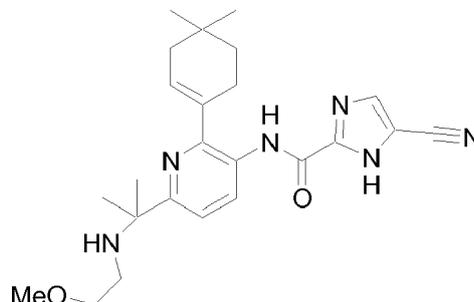
a) 5-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-6-(1-methyl-1-morpholin-4-yl-ethyl)-pyridin-3-yl]-amide

[0436] The title compound is prepared from 5-cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-6-(1-hydroxy-1-methyl-ethyl)-pyridin-3-yl]-amide (as prepared in Example 56, step (e)), morpholine, and thionyl chloride in DCM solvent according to the procedure in Example 14, step (e).

Example 59

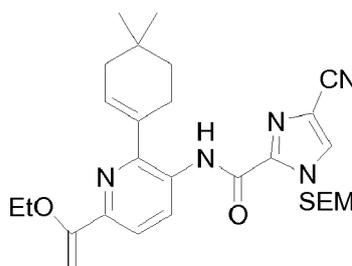
5-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-6-[1-(2-methoxy-ethylamino)-1-methyl-ethyl]-pyridin-3-yl}-amide

[0437]



a) 4-Cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-6-(1-ethoxy-vinyl)-pyridin-3-yl]-amide

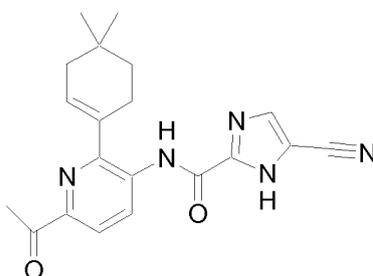
[0438]



[0439] To a round bottom flask containing 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [6-bromo-2-(4,4-dimethyl-cyclohex-1-enyl)-pyridin-3-yl]-amide (as prepared in Example 56, step (c), 32 mg, 0.060 mmol), Pd(PPh₃)₄ (7 mg, 0.006 mmol), and tributyl-(1-ethoxy-vinyl)-stannane (30 mg, 0.080 mmol) was added DMF (0.7 mL) and the resultant solution was allowed to stir at 100 °C overnight. The reaction was diluted with EtOAc (25 mL), washed with water (2 x 25 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification of the residue by preparative TLC (20% EtOAc-hexanes) afforded 12 mg (43 %) of the title compound as an oil. Mass spectrum (ESI, m/z): Calcd. for C₂₈H₃₉N₅O₃Si, 522.2 (M+H), found 522.3.

b) 5-Cyano-1H-imidazole-2-carboxylic acid [6-acetyl-2-(4,4-dimethyl-cyclohex-1-enyl)-pyridin-3-yl]-amide

[0440]

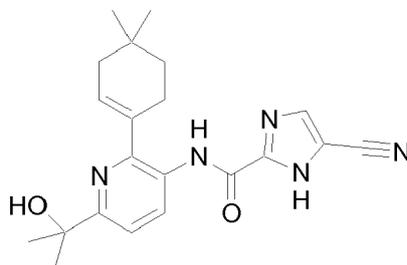


[0441] The title compound was prepared from 5-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-6-(1-ethoxy-vinyl)-pyridin-3-yl]-amide (as prepared in the previous step, 12 mg, 0.023 mmol) according to the procedure in Example 1, step (g) (4.4 mg, 52 %). Mass spectrum (ESI, m/z): Calcd. for

$C_{20}H_{21}N_5O_2$, 364.1 (M+H), found 364.1.

c) 5-Cyano-1H-imidazole-2-carboxylic acid [2-(dimethyl-cyclohex-1-enyl)-6-(1-hydroxy-1-methyl-ethyl)-pyridin-3-yl]-amide

[0442]



[0443] To a solution of 5-cyano-1H-imidazole-2-carboxylic acid [6-acetyl-2-(4,4-dimethyl-cyclohex-1-enyl)-pyridin-3-yl]-amide (as prepared in the previous step, 6 mg, 0.016 mmol) in THF (1 mL) was added methylmagnesium bromide (MeMgBr) (3 M in THF, 41 μ L, 0.072 mmol). After 20 min another 2.5 equivalents of MeMgBr was added and the reaction was allowed to warm to room temperature and quenched with saturated aqueous $NaHCO_3$ (2 mL). The slurry was filtered through a 5-g Sep-Pak and concentrated in vacuo. The crude product was purified by silica gel chromatography (250-mg, 3-mL Supelco Si-tube, gradient $CHCl_3$ -2% $CHCl_3$ -MeOH) to afford 2.6 mg (43 %) of the title compound as a white solid. 1H -NMR (CD_3OD ; 400 MHz): δ 8.44 (d, 1H, J = 8.5 Hz), 7.90 (s, 1H), 7.42 (d, 1H, J = 8.5 Hz), 5.86 (s, 1H), 2.39-2.37 (m, 2H), 1.99-1.94 (m, 2H), 1.51 (t, 1H, J = 6.3 Hz), 1.43 (s, 6H), 0.99 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for $C_{21}H_{25}N_5O_2$, 380.2 (M+H), found 380.1.

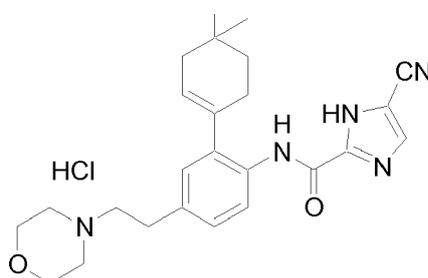
d) 5-Cyano-1H-imidazole-2-carboxylic acid [2-(dimethyl-cyclohex-1-enyl)-6-[1-(2-methoxy-ethylamino)-1-methyl-ethyl]-pyridin-3-yl]-amide

[0444] The title compound is prepared from 5-cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-6-(1-hydroxy-1-methyl-ethyl)-pyridin-3-yl]-amide (as prepared in Example 59, step (e)), methoxyethylamine and thionyl chloride in DCM solvent according to the procedure in Example 14, step (e).

Example 60

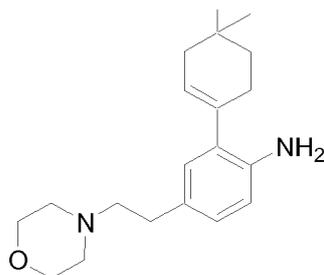
5-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(2-morpholin-4-yl-ethyl)-phenyl]-amide hydrochloride

[0445]



a) 2-(4,4-Dimethyl-cyclohex-1-enyl)-4-(2-morpholin-4-yl-ethyl)-phenylamine

[0446]



[0447] The title compound was prepared by Suzuki coupling of 2-bromo-4-(2-morpholin-4-yl-ethyl)-phenylamine (as prepared in Example 33, step (b)) and 4,4-dimethyl-1-cyclohexen-1-ylboronic acid according to the procedure in Example 1, step (e). Mass spectrum (ESI, m/z): Calcd. for $C_{20}H_{30}N_2O$, 315.2 (M+H), found 315.1.

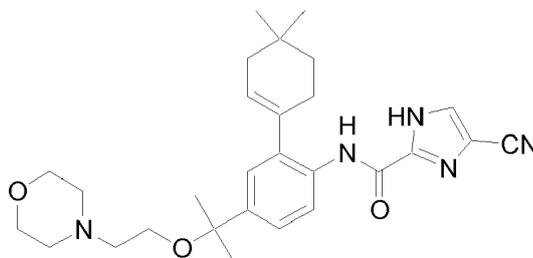
b) 5-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(2-morpholin-4-yl-ethyl)-phenyl]-amide hydrochloride

[0448] The title compound was prepared by coupling 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylate potassium salt (as prepared in Example 1, step (d)) and 2-(4,4-dimethyl-cyclohex-1-enyl)-4-(2-morpholin-4-yl-ethyl)-phenylamine (as prepared in the previous step) according to the procedure in Example 34, step (c), followed by SEM deprotection according to the procedure in Example 34, step (d). The hydrochloride salt was prepared from the trifluoroacetic acid salt using a BioRad AG2-X8 resin, Cl⁻ ion form. ¹H-NMR (400 MHz, DMSO-d₆) δ 14.27 (br s, 1H), 10.58 (br s, 1H), 9.77 (s, 1H), 8.34 (s, 1H), 7.95 (d, J = 8.2 Hz, 1H), 7.21 (dd, J = 8.2, 1.9 Hz, 1H), 7.17 (d, J = 1.9 Hz, 1H), 5.68 (m, 1H), 4.04-3.96 (m, 2H), 3.82-3.70 (m, 2H), 3.54-3.46 (m, 2H), 3.15-2.98 (m, 6H), 2.31-2.22 (m, 2H), 1.96 (m, 2H), 1.49 (t, J = 6.2 Hz, 2H), 1.01 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for $C_{23}H_{31}N_5O_2$, 434.2 (M+H), found 434.2.

Example 61

4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1-methyl-1-(2-morpholin-4-ylethoxy)-ethyl]-phenyl]-amide

[0449]

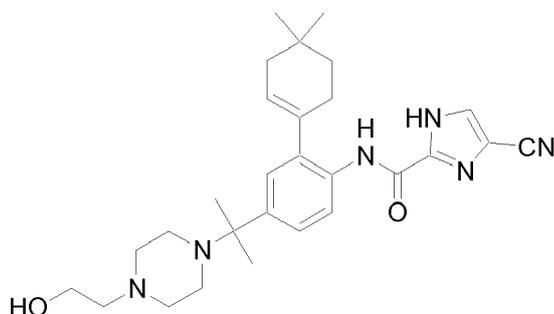


[0450] To a suspension of 4-cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-amide (as prepared in Example 14, step (d), 50.0 mg, 0.132 mmol) in 1 mL of DCM at -15 °C was added oxalyl chloride (16 μL, 0.20 mmol) under Ar. After stirring at RT for 1 h, the mixture was cooled back to -15 °C. To the reaction was added 2-hydroxyethylmorpholine (80 μL, 0.66 mmol) and the resulting mixture was warmed to RT and stirred for 16 h under Ar. Treated with EtOAc (30 mL), the mixture was washed with aqueous saturated NH₄Cl (10 mL), H₂O (10 mL) and brine (10 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by silica gel chromatography (1-3 % MeOH/DCM) to afford the title compound (29 mg, 44 %) as a white solid. ¹H-NMR (CDCl₃; 400 MHz): δ 9.68 (s, 1H), 8.31 (d, 1H, J = 8.6 Hz), 7.72 (s, 1H), 7.37 (dd, 1H, J = 8.6, 2.3 Hz), 7.21 (d, 1H, J = 2.3 Hz), 5.77 (m, 1H), 3.71 (t, 4H, J = 4.7 Hz), 3.34 (t, 2H, J = 6.2 Hz), 2.61 (t, 2H, J = 6.2 Hz), 2.54 (m, 4H), 2.25-2.31 (m, 2H), 2.07-2.13 (m, 2H), 1.59 (t, 2H, J = 6.3 Hz), 1.52 (s, 6H), 1.11 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for $C_{28}H_{37}N_5O_3$, 492.3 (M+H), found 492.0.

Example 62

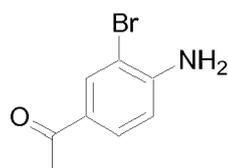
4-Cyano-1H-imidazole-2-carboxylic acid (2-(4,4-dimethyl-cyclohex-1-enyl)-4-{1-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-1-methyl-ethyl }-phenyl)-amide

[0451]



a) 1-(4-Amino-3-bromo-phenyl)-ethanone

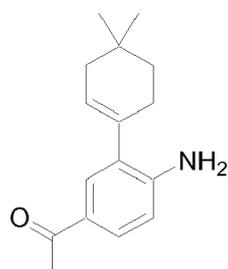
[0452]



[0453] To a solution of 4-aminoacetophenone (5.67 g, 0.0419 mol) in 30 mL of CH₃CN at 0 °C was added N-bromosuccinimide (7.83 g, 0.0439 mol) in 20 mL of CH₃CN dropwise. The reaction was allowed to warm to room temperature and concentrated in vacuo after stirring 16 h. The crude residue was dissolved in EtOAc (100 mL), washed with saturated aqueous NaHCO₃ (1 x 100 mL), brine (1 x 100 mL) and dried (Na₂SO₄). The solvent was removed under vacuum to afford the title compound (7.62 g, 85 %) as a yellow solid. Mass spectrum (ESI, m/z): Calcd. for C₈H₈BrNO, 213.9 (M + H), found 214.0.

b) 1-[4-Amino-3-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-ethanone

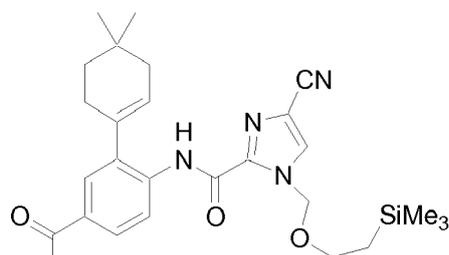
[0454]



[0455] To a slurry of 1-(4-amino-3-bromo-phenyl)-ethanone (20.5 g, 0.960 mol, as prepared in the previous step), 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl (3.94 g, 9.60 mmol), and K₃PO₄ (61.0 g, 0.280 mol) in 250 mL of toluene was added 2-(4,4-dimethyl-cyclohex-1-enyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (24.9 g, 0.100 mol) followed by Pd₂(dba)₃ (4.39 g, 4.80 mmol). The resultant mixture was heated to 100 °C with vigorous stirring. After 3 h, the reaction was filtered and concentrated in vacuo. Purification of the residue by column chromatography (20 % EtOAc-hexane) afforded the title compound (15.0 g, 64 %). Mass spectrum (ESI, m/z): Calcd. for C₁₆H₂₁NO, 244.1 (M + H), found 244.2.

c) 4-Cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [4-acetyl-2-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-amide

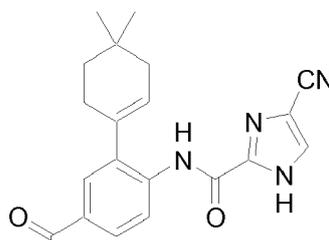
[0456]



[0457] To a solution of 1-[4-amino-4,4-dimethyl-cyclohex-1-enyl]-phenyl]-ethanone (7.86 g, 0.0320 mol, as prepared in the previous step), 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylate potassium salt (13.7 g, 0.0450 mol, as prepared in Example 1, step (d)), and PyBroP (22 g, 0.048 mol) in 120 mL of DMF was added DIEA (13.9 mL, 0.0800 mol) and the reaction was allowed to stir overnight. The reaction was then poured into 300 mL of water and stirred vigorously at 0 °C for 30 min and filtered. The solids were azeotropically dried by evaporation from 100 mL of toluene and then under vacuum. The crude oil was dissolved in 100 mL of DCM and triturated with hexanes to afford 8.20 g of the title compound. The mother liquor was concentrated and dissolved in 50 mL of DCM followed by trituration with hexanes to afford another 3.50 g affording a total of 11.7 g (75 %) of the title compound. Mass spectrum (ESI, m/z): Calcd. for $C_{27}H_{36}N_4O_3Si$, 493.2 (M + H), found 493.1

d) 4-Cyano-1H-imidazole-2-carboxylic acid [4-acetyl-2-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-amide

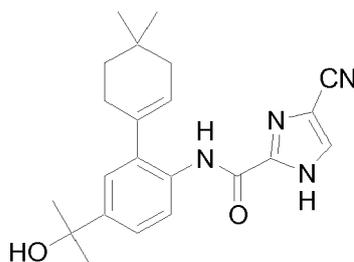
[0458]



[0459] A solution of 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [4-acetyl-2-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-amide (8.2 g, 0.016 mol, as prepared in the previous step) in 50 mL of DCM was treated with 6 mL of EtOH followed by 42 mL of TFA. The reaction was stirred for h 45 min, at which time it was diluted with MeOH (100 mL), concentrated to half of the volume and diluted with diethyl ether (80 mL). The result was concentrated in vacuo and dried under vacuum overnight to afford the title compound as a yellow solid (6.00 g, 100 %). Mass spectrum (ESI, m/z): Calcd. for $C_{21}H_{22}N_4O_2$, 363.1 (M + H), found 363.1.

e) 4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-amide

[0460]



[0461] To a slurry of 4-cyano-1H-imidazole-2-carboxylic acid [4-acetyl-2-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-amide (6.00 g, 0.0160 mol) in 100 mL of THF at -78 °C was added a solution of MeMgBr (3.0 M in THF, 22 mL, 0.066 mol) via syringe over a 20-min period. The reaction was allowed to warm to ca. 0 °C over a 30-min period at which point there was no starting material evident by thin layer chromatography (10 % MeOH-CHCl₃). The reaction was cooled to -78 °C, quenched by the addition of saturated aqueous NH₄Cl (100 mL) and allowed to warm to 0 °C. The mixture was extracted with ether (2 x 150 mL) and dried (Na₂SO₄). The solvent was concentrated to afford the title compound as a white solid (6.40 g, 100 %). The NMR and mass spectral data were identical to those for the compound produced in Example 14, step (d).

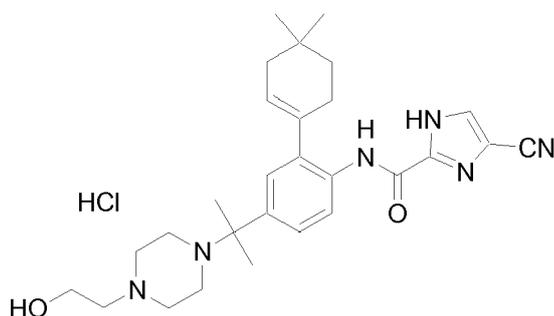
f) **4-Cyano-1H-imidazole-2-carboxylic acid (2-(4,4-dimethyl-cyclohex-1-enyl)-4-{1-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-1-methyl-ethyl}-phenyl)-amide**

[0462] To a suspension of 4-cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-amide (as prepared in the previous step, 50.0 mg, 0.132 mmol) in 2 mL of DCM at -15 °C was added SOCl₂ (29 μL, 0.40 mmol) under Ar. After stirring at RT for h, the mixture was cooled back to -15 °C. To the reaction was added 2-hydroxyethylpiperazine (162 μL, 1.32 mmol). After stirring at -15 °C for h, the resulting mixture was warmed to RT and stirred for 16 h under Ar. Treated with EtOAc (30 mL), the mixture was washed with H₂O (2 x 10 mL) and brine (10 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by silica gel chromatography (2-6 % MeOH/DCM) to afford the title compound (37.5 mg, 58 %) as a white solid. ¹H-NMR (CD₃OD; 400 MHz): δ 8.12 (d, 1H, J = 8.6 Hz), 7.93 (s, 1H), 7.42 (dd, 1H, J = 8.6, 2.3 Hz), 7.34 (d, 1H, J = 2.3 Hz), 5.72 (m, 1H), 3.70 (t, 2H, J = 6.1 Hz), 2.52-2.77 (m, 10H), 2.25-2.32 (m, 2H), 2.04-2.10 (m, 2H), 1.59 (t, 2H, J = 6.2 Hz), 1.38 (s, 6H), 1.08 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for C₂₈H₃₈N₆O₂, 491.3 (M+H), found 491.0.

Example 63

4-Cyano-1H-imidazole-2-carboxylic acid (2-(4,4-dimethyl-cyclohex-1-enyl)-4-{1-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-1-methyl-ethyl}-phenyl)-amide hydrochloride

[0463]



[0464] To a solution of 4-cyano-1H-imidazole-2-carboxylic acid (2-(4,4-dimethyl-cyclohex-1-enyl)-4-{1-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-1-methyl-ethyl}-phenyl)-amide (as prepared in Example 62, 162.0 mg, 0.330 mmol) in 2 mL of EtOH was added a 2 N HCl ether solution (165 μL, 0.330 mmol). The mixture was stirred at RT for 0.5 h, mL of diethyl ether (Et₂O) was added and the resulting mixture was heated at 60 °C for min until the solution turned clear. The mixture was cooled down to RT and the solid was collected by filtration and washed with Et₂O. Upon drying in vacuo, the title compound (92 mg, 53 %) was obtained as an off-white solid. ¹H-NMR (CD₃OD; 400 MHz): δ 8.42 (d, 1H, J = 8.6 Hz),

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8.04 (s, 1H), 7.70 (dd, 1H, J = 8.6, 2.0 Hz), 7.64 (br s, 1H), 5.83 (m, 1H), 3.91 (m, 2H), 3.40-3.93 (m, 4H), 3.37 (m, 2H), 2.33-2.40 (m, 2H), 2.05-2.12 (m, 2H), 1.72-2.00 (br s, 6H), 1.62 (t, 2H, J = 6.5 Hz), 1.07 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for C₂₈H₃₈N₆O₂, 491.3 (M+H), found 491.1.

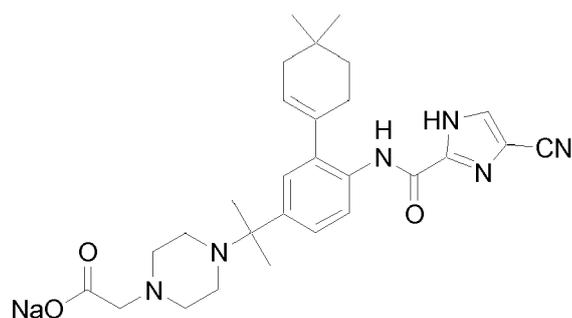
5 **Example 64**

(4-{1-[4-[(4-Cyano-1H-imidazole-2-carbonyl)-amino]-3-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-1-methyl-ethyl}-piperazin-1-yl)-acetic acid, sodium salt

10 **[0465]**

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[0466] To a solution of 4-{1-[4-[(4-cyano-1H-imidazole-2-carbonyl)-amino]-3-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-1-methyl-ethyl}-piperazin-1-yl)-acetic acid ethyl ester (as prepared in Example 79, 72.0 mg, 0.135 mmol) in 5 mL of 1:1 THF/MeOH was added 6 N NaOH (225 μ L, 1.35 mmol). After stirring at RT for 16 h, the mixture was washed with 1:2 EtOAc/hexane (3x10 mL). The aqueous layer was treated with 50 mL of brine and extracted with EtOAc (5 x 30 mL). The combined organic layers were washed with H₂O (4 x 20 mL) and dried (Na₂SO₄). The organic solvent was evaporated in vacuo to give the title compound (66 mg, 92 %) as a white solid. ¹H-NMR (CD₃OD; 400 MHz): δ 8.14 (d, 1H, J = 8.6 Hz), 7.85 (s, 1H), 7.44 (dd, 1H, J = 8.6, 2.0 Hz), 7.34 (d, 1H, J = 2.0 Hz), 5.72 (m, 1H), 3.43 (s, 2H), 3.00-3.19 (br s, 4H), 2.74 (br s, 4H), 2.24-2.34 (m, 2H), 2.05-2.11 (m, 2H), 1.58 (t, 2H, J = 6.3 Hz), 1.41 (s, 6H), 1.07 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for C₂₈H₃₅N₆NaO₃, 505.3 (M-Na+2H), found 504.9.

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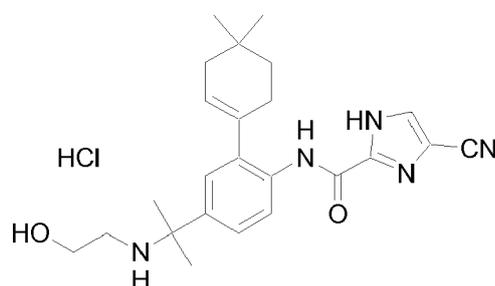
Example 65

4-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1-(2-hydroxy-ethylamino)-1-methyl-ethyl]-phenyl}-amide hydrochloride

40 **[0467]**

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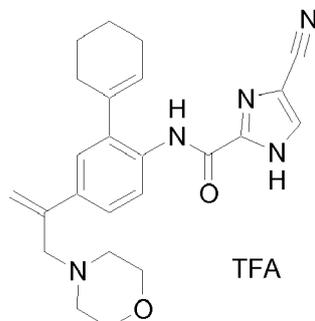


[0468] The title compound was prepared from 4-cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1-(2-hydroxy-ethylamino)-1-methyl-ethyl]-phenyl}-amide (as prepared in Example 78) and 2N HCl in ether according to the procedure as described in Example 63. ¹H-NMR (CD₃OD; 400 MHz): δ 8.37 (d, 1H, J = 8.6 Hz), 8.02 (s, 1H), 7.50 (dd, 1H, J = 8.6, 2.3 Hz), 7.44 (d, 1H, J = 2.3 Hz), 5.81 (m, 1H), 3.70 (t, 2H, J = 5.1 Hz), 2.83 (t, 2H, J = 5.1 Hz), 2.31-2.38 (m, 2H), 2.07-2.13 (m, 2H), 1.81 (s, 6H), 1.62 (t, 2H, J = 6.3 Hz), 1.11 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for C₂₄H₃₁N₅O₂, 422.3 (M+H), found 421.9.

Example 66

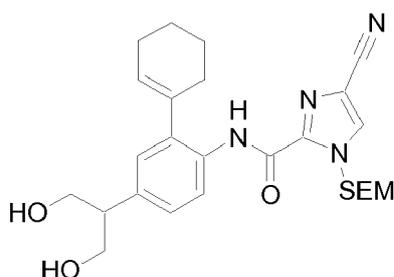
4-Cyano-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(1-morpholin-4-ylmethyl-vinyl)phenyl]-amide trifluoroacetic acid salt

[0469]



a) 4-Cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(2-hydroxy-1-hydroxymethyl-ethyl)-phenyl]-amide

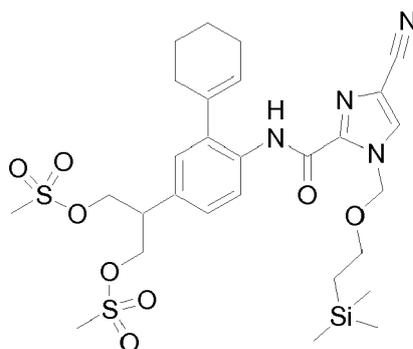
[0470]



[0471] To a solution of acetic acid 3-acetoxy-2-(4-[[4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxyl]-amino]-3-cyclohex-1-enyl-phenyl)-propyl ester (580 mg, 1.00 mmol, as prepared in Example 12, step (c)) in isopropylalcohol (i-PrOH) (15 mL), 2N NaOH (1 mL, 2 mmol) was added. The reaction mixture was stirred at RT for 1 h, and DCM (200 mL) and water (200 mL) were added. The organic layer was separated, dried (Na₂SO₄) and concentrated. The residue was purified on silica (40 % EtOAc-hexane) to obtain the title compound (312 mg, 63 %). Mass spectrum (ESI, m/z): Calcd. for C₂₆H₃₆N₄O₄Si, 497.2 (M+H), found 497.0.

b) Methanesulfonic acid 2-(4-[[4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxyl]-amino]-3-cyclohex-1-enyl-phenyl)-3-methanesulfonyloxy-propyl ester

[0472]



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[0473] A solution of 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(2-hydroxy-1-hydroxymethyl-ethyl)-phenyl]-amide (0.600 g, 1.21 mmol, as prepared in the previous step) in CH_2Cl_2 (25 mL) was cooled to 0 °C and was treated with Et_3N (421 μL , 3.02 mmol) and methanesulfonyl chloride (190 μL , 2.42 mmol). The mixture was stirred at 0 °C for 2 h, diluted with CH_2Cl_2 , and washed with water. The organic layer was dried over MgSO_4 and concentrated in vacuo. Silica gel chromatography of the residue with 25-50 % EtOAc-hexane afforded the title compound (0.551 g, 70 %) as a white solid. Mass spectrum (APCI, m/z): Calcd. for $\text{C}_{28}\text{H}_{40}\text{N}_4\text{O}_8\text{S}_2\text{Si}$, 653.2 (M+H), found 652.8.

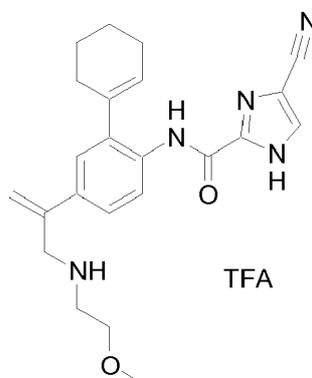
c) 4-Cyano-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(1-morpholin-4-ylmethyl-vinyl)-phenyl]-amide trifluoroacetic acid salt

[0474] A solution of methanesulfonic acid 2-(4-[[4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carbonyl]-amino]-3-cyclohex-1-enyl-phenyl)-3-methanesulfonyloxy-propyl ester (30.0 mg, 0.0460 mmol, as prepared in the previous step) in THF (1 mL) was treated with morpholine (200 μL , 2.29 mmol) and heated to 50 °C for 19 h. The mixture was diluted with EtOAc and washed with water. The organic layer was dried over MgSO_4 and concentrated in vacuo. The residue was treated with a solution of 20 % TFA in CH_2Cl_2 (1 mL) at room temperature overnight. Purification of the residue by RP-HPLC (C18) with 10-80 % CH_3CN in 0.1 % TFA/ H_2O over 25 min afforded 4.0 mg (15 %) of the title compound as a white solid. $^1\text{H-NMR}$ (CD_3OD ; 400 MHz): δ 8.24 (d, 1H, J = 8.0 Hz), 7.93 (s, 1H), 7.39 (dd, 1H, J = 8.0, 2.0 Hz), 7.31 (d, 1H, 2.0 Hz), 5.80-5.76 (m, 1H), 5.74 (s, 1H), 5.56 (s, 1H), 4.22 (s, 2H), 3.96-3.55 (m, 4H), 3.37-3.04 (m, 4H), 2.26-2.16 (m, 4H), 1.82-1.67 (m, 4H). Mass spectrum (ESI, m/z): Calcd. for $\text{C}_{24}\text{H}_{27}\text{N}_5\text{O}_2$, 418.2 (M+H), found 418.4.

Example 67

4-Cyano-1H-imidazole-2-carboxylic acid (2-cyclohex-1-enyl-4-{1-[(2-methoxy-ethylamino)-methyl]-vinyl}-phenyl)-amide trifluoroacetic acid salt

[0475]



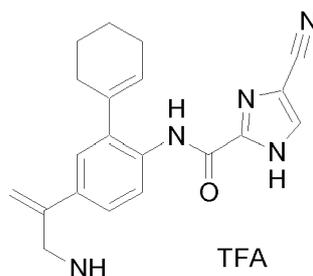
[0476] The title compound was prepared from methanesulfonic acid 2-(4-[[4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carbonyl]-amino]-3-cyclohex-1-enyl-phenyl)-3-methanesulfonyloxy-propyl ester (as prepared in Example 66, step (b)) and 2-methoxy-ethylamine according to the procedure of Example 66, step (c). $^1\text{H-NMR}$ (CD_3OD ; 400 MHz): δ 8.33 (d, 1H, J = 8.8 Hz), 8.04 (s, 1H), 7.47 (dd, 1H, J = 8.8 Hz, 2.0 Hz), 7.38 (dd, 1H, J = 2.0 Hz), 5.93-5.86 (m, 1H), 5.76 (s, 1H), 5.53 (s, 1H), 4.19 (s, 2H), 3.71-3.65 (m, 2H), 3.42 (s, 3H), 3.30-3.25 (m, 2H), 2.37-2.28 (m, 4H), 1.95-1.79 (m, 4H). Mass spectrum (APCI, m/z): Calcd. for $\text{C}_{23}\text{H}_{27}\text{N}_5\text{O}_2$, 406.2 (M+H), found 406.2.

Example 68

4-Cyano-1H-imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(1-methylaminomethyl-vinyl)-phenyl]-amide trifluoroacetic acid salt

[0477]

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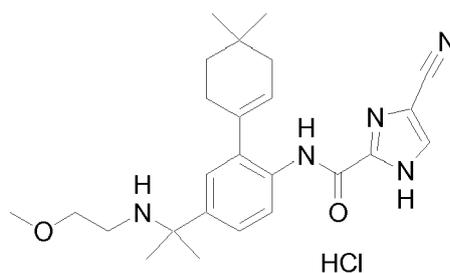


[0478] The title compound was prepared from methanesulfonic acid 2-(4-[[4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carbonyl]-amino]-3-cyclohex-1-enyl-phenyl)-3-methanesulfonyloxy-propyl ester (as prepared in Example 66, step (b)) and methylamine solution in THF according to the procedure of Example 66, step (c). ¹H-NMR (CD₃OD; 400 MHz): δ 8.33 (d, 1H, J = 8.4 Hz), 8.03 (s, 1H), 7.46 (dd, 1H, J = 8.4 Hz, 2.4 Hz), 7.37 (d, 1H, J = 2.4 Hz), 5.91-5.85 (m, 1H), 5.74 (s, 1H), 5.49 (s, 1H), 4.14 (s, 2H), 2.73 (s, 3H), 2.35-2.26 (m, 4H), 1.93-1.77 (m, 4H). Mass spectrum (ESI, m/z): Calcd. for C₂₁H₂₃N₅O, 362.2 (M+H), found 362.3.

Example 69

4-Cyano-1H imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1-(2-methoxy-ethylamino)-1-methyl-ethyl]-phenyl}-amide hydrochloride salt

[0479]



[0480] A solution of 4-cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1-(2-methoxy-ethylamino)-1-methyl-ethyl]-phenyl}-amide (750 mg, 1.72 mmol, as prepared in Example 20) in isopropanol (dissolved with heating) was treated with HCl (331 μL, 1.72 mmol, 5.2 M in isopropanol) at RT for 1 h. The resulting precipitate was filtered, washed with cold hexanes, and dried under high vacuum to afford the title compound (438 mg, 54 %) as a white solid. ¹H-NMR (CD₃OD; 400 MHz): δ 8.40 (d, 1H, J = 9.2 Hz), 8.04 (s, 1H), 7.50 (dd, 1H, J = 9.2, 2.8 Hz), 7.43 (d, 1H, J = 2.8 Hz), 5.86-5.80 (m, 1H), 3.59-3.52 (m, 2H), 3.38 (s, 3H), 2.97-2.89 (m, 2H), 2.40-2.32 (m, 2H), 2.16-2.10 (m, 2H), 1.82 (s, 6H), 1.68-1.60 (m, 2H), 1.13 (s, 6H). Mass spectrum (APCI, m/z): Calcd. for C₂₅H₃₃N₅O₂, 436.3 (M+H), found 435.8.

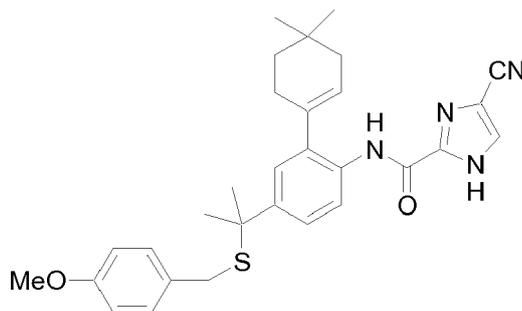
Example 70

4-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1-(4-methoxy-benzylsulfanyl)-1-methyl-ethyl]-phenyl}-amide

[0481]

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[0482] To a mixture of 4-cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-amide (as prepared in Example 14, step (d), 86 mg, 0.22 mmol) and (4-methoxy-phenyl)-methanethiol (157 μ L, 1.13 mmol) in 2 mL of DCM at 0 °C was added 175 μ L (2.27 mmol) of TFA. The mixture was allowed to warm to room temperature overnight, at which time it was diluted with DCM (20 mL), washed with water (1 x 20 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by preparative TLC on silica gel (5 % methanol- CHCl_3) to afford the title compound (63 mg, 54 %). $^1\text{H-NMR}$ (CDCl_3 ; 400 MHz): δ 12.78 (br s, 1H), 9.75 (s, 1H), 8.32 (d, 1H, J = 8.6 Hz), 7.75 (s, 1H), 7.51 (dd, 1H, J = 7.5, 2.1 Hz), 7.41 (d, 1H, J = 2.1 Hz), 7.04 (d, 2H, J = 8.6 Hz), 6.75 (d, 2H, J = 8.6 Hz), 5.80 (m, 1H), 3.75 (s, 3H), 3.41 (s, 2H), 2.31 (m, 2H), 2.13 (m, 2H), 1.72 (s, 6H), 1.61 (t, 2H, J = 6.2 Hz), 1.12 (s, 6H).

Example 71

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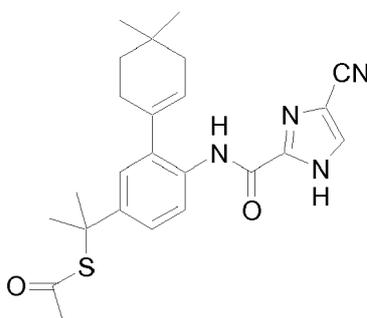
Thioacetic acid S-{1-[4-[(4-cyano-1H-imidazole-2-carbonyl)-amino]-3-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-1-methyl-ethyl} ester

[0483]

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[0484] The title compound was prepared from 4-cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-amide (as prepared in Example 14, step (d)) and thioacetic acid using the conditions described in Example 70. $^1\text{H-NMR}$ (CDCl_3 ; 400 MHz): δ 9.73 (s, 1H), 8.29 (d, 1H, J = 8.6 Hz), 7.74 (s, 1H), 7.49-7.47 (m, 1H), 7.35 (d, 1H, J = 2.2 Hz), 5.79 (m, 1H), 2.32-2.28 (m, 2H), 2.20 (s, 3H), 2.11 (m, 2H), 1.86 (s, 6H), 1.59 (t, 2H, J = 6.2 Hz), 1.11 (s, 6H).

Example 72

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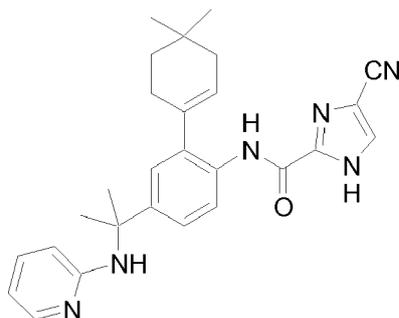
4-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1-methyl-1-(pyridin-2-ylamino)-ethyl]-phenyl}-amide

[0485]

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[0486] To a mixture of 4-cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-amide (as prepared in Example 14, step (d), 120 mg, 0.317 mmol) and 2-aminopyridine (448 mg, 4.76 mmol) in 5 mL of DCM at 0 °C was added 244 μ L (3.17 mmol) of TFA. The mixture was allowed to warm to room temperature, at which time it was cooled in an ice bath and filtered. The filtrate was concentrated in vacuo with MeOH (10 mL) and purified by preparative thin layer chromatography ((2 x) with 10 % MeOH-CHCl₃) to afford 2.5 mg (2 %) of the title compound as a white solid. ¹H-NMR (CDCl₃-CD₃OD; 400 MHz): δ 8.16 (d, 1H, J = 8.6 Hz), 7.88 (m, 1H), 7.64 (s, 1H), 7.29 (m, 1H), 7.18 (d, 1H, J = 2.0 Hz), 7.16-7.11 (m, 1H), 7.47-7.44 (m, 1H), 5.81 (d, 1H, J = 8.6 Hz), 5.66 (m, 1H), 2.16-2.13 (m, 2H), 1.99 (m, 2H), 1.59 (s, 6H), 1.52-1.44 (m, 2H), 0.99 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for C₂₇H₃₀N₆O 455.2 (M+H), found 455.1.

Example 73

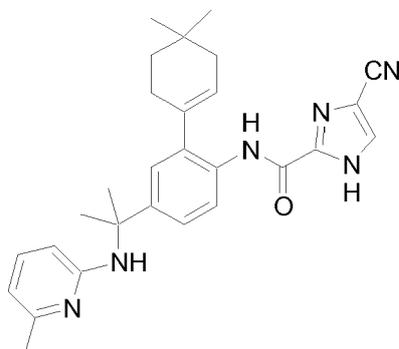
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4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1-methyl-1-(6-methyl-pyridin-2-ylamino)-ethyl]-phenyl]-amide

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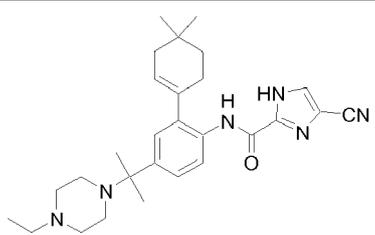
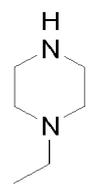
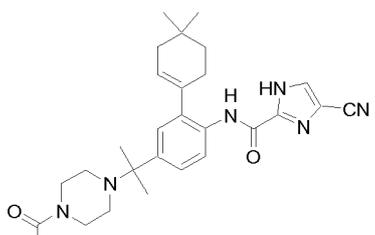
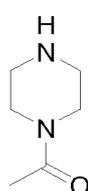
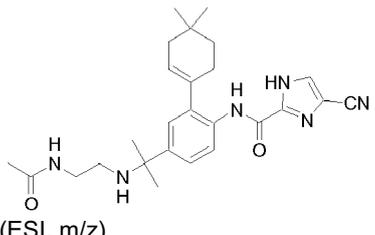
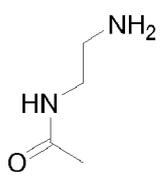
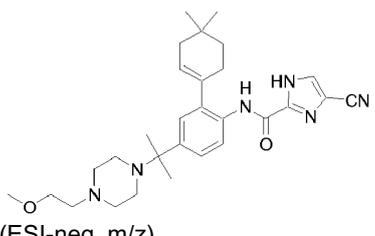
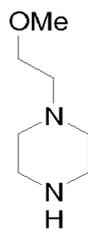
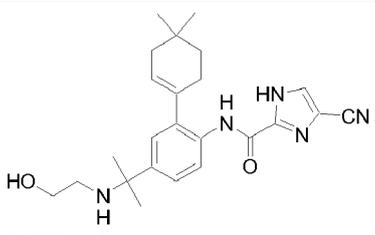
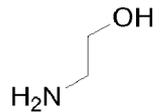
[0488] The title compound was prepared from 4-cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-amide (as prepared in Example 14, step (d)) and 2-amino-6-methylpyridine using the conditions described in Example 72. ¹H-NMR (CDCl₃-CD₃OD; 400 MHz): δ 8.26 (dd, 1H, J = 8.6, 2.0 Hz), 7.76 (s, 1H), 7.54-7.49 (m, 1H), 7.28-7.22 (m, 1H), 7.14 (d, 1H, J = 2.2 Hz), 6.58 (d, 1H, J = 7.3 Hz), 6.07 (m, 1H), 5.67 (m, 1H), 2.46 (s, 3H), 2.20-2.14 (m, 2H), 2.00 (m, 2H), 1.71 (s, 6H), 1.51-1.48 (m, 2H), 1.00 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for C₂₈H₃₂N₆O, 469.2 (M+H), found 469.1.

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[0489] The following examples were produced according to procedures of previous examples with the corresponding reagents as indicated in the table below:

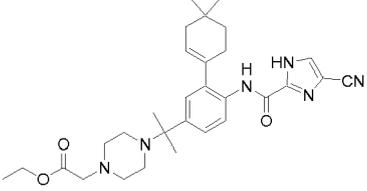
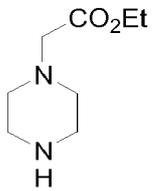
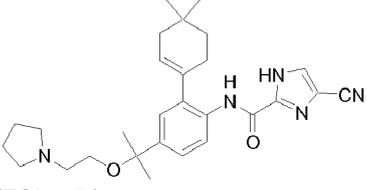
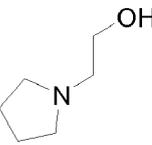
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Example	Name	Structure	Procedure	Reagents
5 10 74	4-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1-(4-ethyl-piperazin-1-yl)-1-methyl-ethyl]-phenyl}-amide	 <p>(ESI-neg, m/z) Calcd. for C₂₈H₃₈N₆O, 473.3 (M-H), found 473.5.</p>	62	
15 20 75	4-Cyano-1H-imidazole-2-carboxylic acid [4-[1-(4-acetyl-piperazin-1-yl)-1-methyl-ethyl]-2-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-amide	 <p>(ESI-neg, m/z) Calcd. for C₂₈H₃₆N₆O₂, 487.3 (M-H), found 487.5.</p>	62	
25 30 76	4-Cyano-1H-imidazole-2-carboxylic acid [4-[1-(2-acetylamino-ethylamino)-1-methyl-ethyl]-2-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-amide	 <p>(ESI, m/z) Calcd. for C₂₆H₃₄N₆O₂, 463.3 (M+H), found 463.0.</p>	62	
35 40 77	4-Cyano-1H-imidazole-2-carboxylic acid (2-(4,4-dimethyl-cyclohex-1-enyl)-4-{1-[4-(2-methoxy-ethyl)-piperazin-1-yl]-1-methyl-ethyl}-phenyl)-amide	 <p>(ESI-neg, m/z) Calcd. for C₂₉H₄₀N₆O₂, 503.3 (M-H), found 503.5.</p>	62	
45 50 55 78	4-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1-(2-hydroxy-ethylamino)-1-methyl-ethyl]-phenyl}-amide	 <p>(APCI, m/z) Calcd. for C₂₄H₃₁N₅O₂, 422.3 (M+H), found 421.7.</p>	62	

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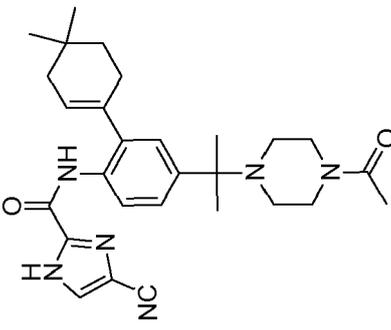
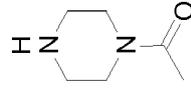
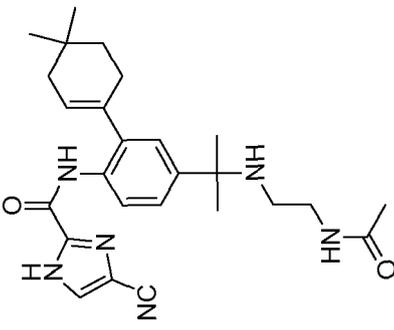
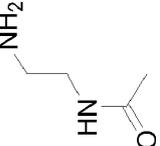
(continued)

Example	Name	Structure	Procedure	Reagents
5 10 79	(4-{1-[4-[4-Cyano-1H-imidazole-2-carbonyl]-amino]-3-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-1-methyl-ethyl}-piperazin-1-yl)-acetic acid ethyl ester	 <p>(ESI, m/z) Calcd. for C₃₀H₄₀N₆O₃, 533.3 (M+H), found 533.0.</p>	62	
15 20 80	4-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1-methyl-1-(2-pyrrolidin-1-yl-ethoxy)-ethyl]-phenyl}-amide	 <p>(ESI, m/z) Calcd. for C₂₈H₃₇N₅O₂, 476.3 (M+H), found 476.1.</p>	61	

[0490] The following examples are produced according to procedures of previous examples with the corresponding reagents as indicated in the table below:

Example No.	Name	Structure	Procedure Reference	Reagents
61	4-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1-methyl-1-(2-morpholin-4-yl-ethoxy)-ethyl]-phenyl}-amide		Example 52	
74	4-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1-(4-ethyl-piperazin-1-yl)-1-methyl-ethyl]-phenyl}-amide		Example 14, step (e)	

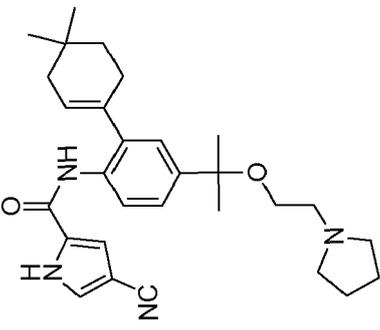
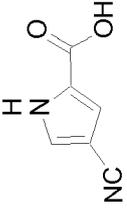
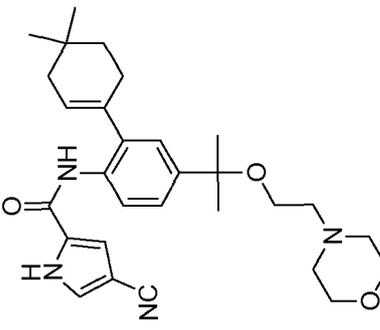
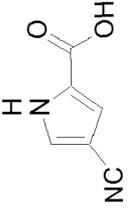
(continued)

Example No.	Name	Structure	Procedure Reference	Reagents
75	4-Cyano-1H-imidazole-2-carboxylic acid [4-[1-(4-acetyl-piperazin-1-yl)-1-methyl-ethyl]-2-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-amide		Example 14, step (e)	
76	4-Cyano-1H-imidazole-2-carboxylic acid [4-[1-(2-acetylamino-ethylamino)-1-methyl-ethyl]-2-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-amide		Example 14, step (e)	

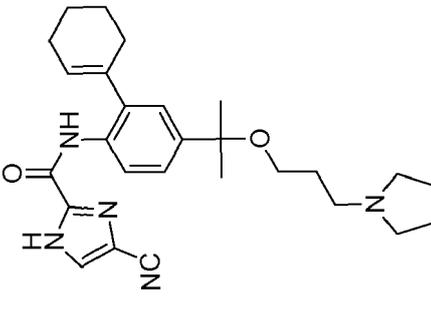
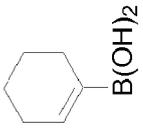
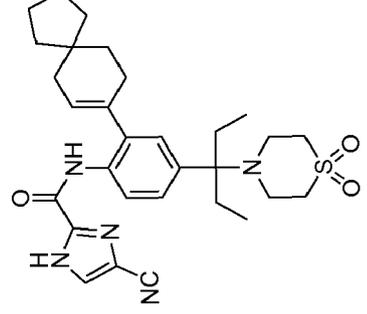
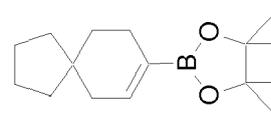
(continued)

Example No.	Name	Structure	Procedure Reference	Reagents
80	4-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1-methyl-1-(2-pyrrolidin-1-yl-ethoxy)-ethyl]-phenyl}-amide		Example 52	
81	4-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1-methyl-1-(2-pyrrolidin-1-yl-ethylamino)-ethyl]-phenyl}-amide		Example 14, step (e)	

(continued)

Example No.	Name	Structure	Procedure Reference	Reagents
82	4-Cyano-1H-pyrrole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1-methyl-1-(2-pyrrolidin-1-yl-ethoxy)-ethyl]-phenyl}-amide		Example 14, steps (b),(d); Example 52	 (Canadian J. Chem. 59, 2673 (1981));
83	4-Cyano-1H-pyrrole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1-methyl-1-(2-morpholin-4-yl-ethoxy)-ethyl]-phenyl}-amide		Example 14, steps (b),(d); Example 52	 (Canadian J. Chem. 59, 2673 (1981));

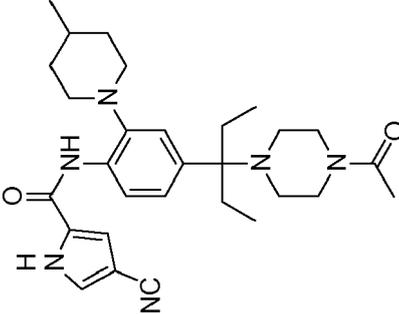
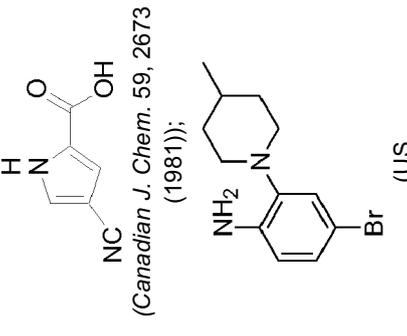
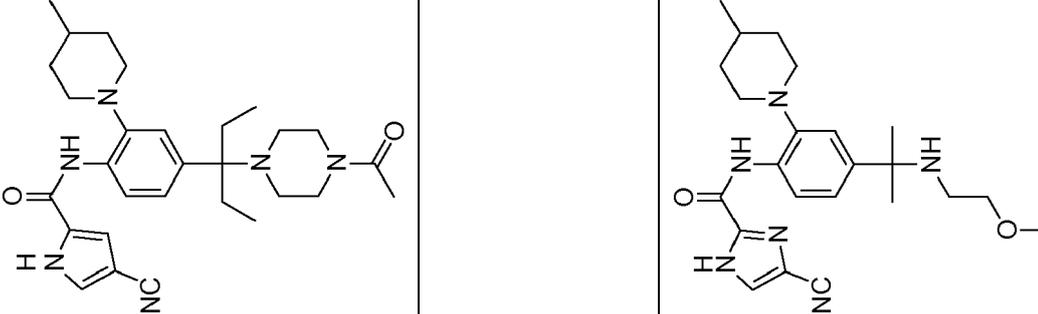
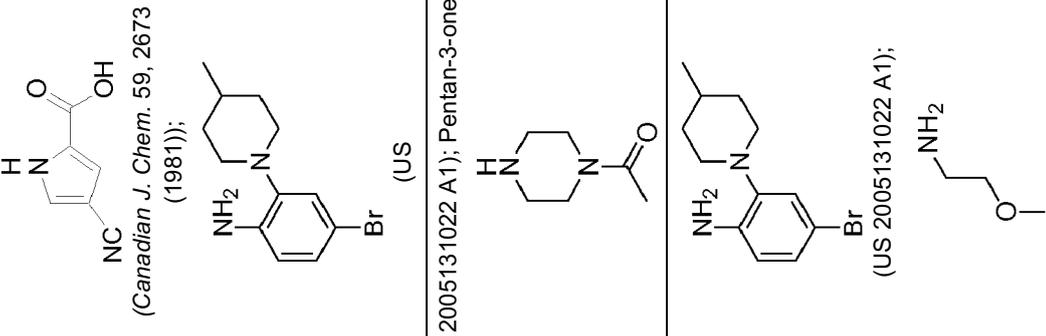
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Example No.	Name	Structure	Procedure Reference	Reagents
84	4-Cyano-1H-imidazole-2-carboxylic acid {2-cyclohex-1-enyl-4-[1-methyl-1-(3-pyrrolidin-1-yl-propoxy)-ethyl]-phenyl}-amide		Example 14, step (a)-(d); Example 52	 Bioorg Med Chem Lett, 15(1), 107-113; (2005)
85	4-Cyano-1H-imidazole-2-carboxylic acid {4-[1-(1,1-dioxo-1,2,6-thiomorpholin-4-yl)-1-ethyl-propyl]-2-spiro[4.5]dec-7-en-8-yl-phenyl}-amide		Example 14, steps (a)-(e); Example 16	Pentan-3-one;  (WO 2005063705)

(continued)

Example No.	Name	Structure	Procedure Reference	Reagents
86	4-Cyano-1H-imidazole-2-carboxylic acid [4-[1-(4-ethyl-piperazin-1-yl)-1-methyl-ethyl]-2-(4-methyl-piperidin-1-yl)-phenyl]-amide		Example 14, Steps (b)-(e),	<p>(US 2005131022 A1)</p>
87	4-Cyano-1H-imidazole-2-carboxylic acid {2-(4-methyl-piperidin-1-yl)-4-[1-methyl-1-(2-pyrrolidin-1-yl-ethoxy)-ethyl]-phenyl}-amide		Example 14, steps (b)-(d); Example 52	<p>(US 2005131022 A1);</p>

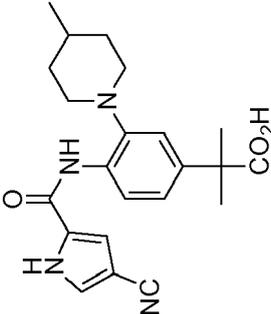
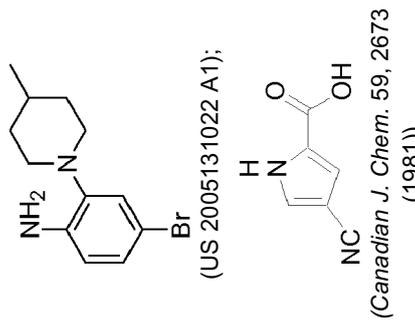
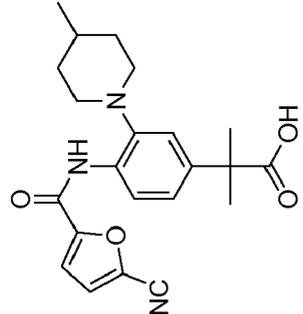
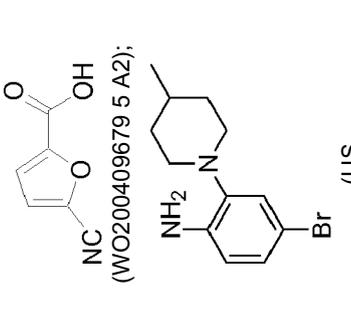
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Example No.	Name	Structure	Procedure Reference	Reagents
88	4-Cyano-1H-pyrrole-2-carboxylic acid [4-[1-(4-acetyl-piperazin-1-yl)-1-ethyl-propyl]-2-(4-methyl-piperidin-1-yl)-phenyl]-amide		Example 14, Steps (b),(d),(e)	
89	4-Cyano-1H-imidazole-2-carboxylic acid [4-[1-(2-methoxy-ethylamino)-1-methyl-ethyl]-2-(4-methyl-piperidin-1-yl)-phenyl]-amide		Example 14, Steps (b)-(e)	

(continued)

Example No.	Name	Structure	Procedure Reference	Reagents
90	4-Cyano-1H-pyrrole-2-carboxylic acid [4-[1-(2-methoxy-ethylamino)-1-methyl-ethyl]-2-(4-methyl-piperidin-1-yl)-phenyl]-amide		Example 14, Steps (b),(d),(e)	<p>(Canadian J. Chem. 59, 2673 (1981)); (US 2005131022 A1);</p>
91	2-[4-[4-Cyano-1H-imidazole-2-carbonyl]-amino]-3-(4-methyl-piperidin-1-yl)-phenyl]-2-methyl-propionic acid		Example 14, step (b); Example 13, step (a)-(c).	<p>(US 2005131022 A1)</p>

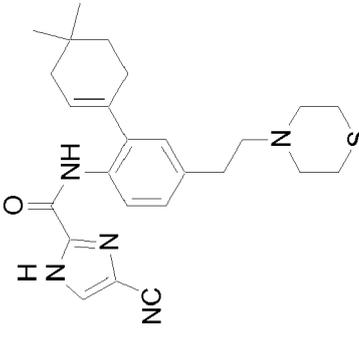
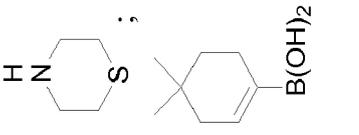
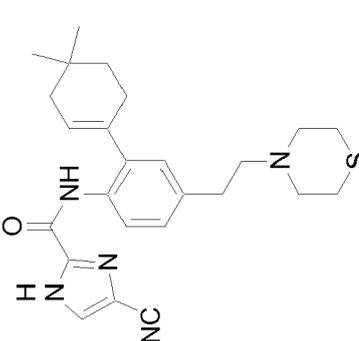
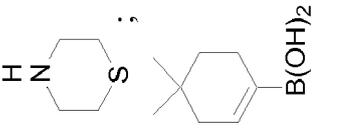
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Example No.	Name	Structure	Procedure Reference	Reagents
92	2-[4-[(4-Cyano-1H-pyrrole-2-carbonyl)-amino]-3-(4-methylpiperidin-1-yl)-phenyl]-2-methylpropionic acid		Example 14, step (b); Example 13, step (a),(c).	 <p>(US 2005131022 A1); (Canadian J. Chem. 59, 2673 (1981))</p>
93	2-[4-[(5-Cyano-furan-2-carbonyl)-amino]-3-(4-methylpiperidin-1-yl)-phenyl]-2-methylpropionic acid		Example 14, step (b); Example 13, step (a),(c).	 <p>(WO200409679 5 A2); (US 2005131022 A1)</p>

(continued)

Example No.	Name	Structure	Procedure Reference	Reagents
94	2-[4-[(4-Cyano-1H-pyrrole-2-carbonyl)-amino]-3-(4,4-dimethylcyclohex-1-enyl)-phenyl]-2-methylpropionic acid		Example 14, step (b); Example 13, step (a),(c).	 (Canadian J. Chem. 59, 2673 (1981))
95	2-[4-[(5-Cyano-furan-2-carbonyl)-amino]-3-(4,4-dimethylcyclohex-1-enyl)-phenyl]-2-methylpropionic acid		Example 14, step (b); Example 13, step (a),(c).	
96	4-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethylcyclohex-1-enyl)-4-[2-(4-ethyl-piperazin-1-yl)-ethyl]-phenyl}-amide		Example 33, steps (a)-(c); Example 25, steps (e) and (f)	 B(OH) ₂ ;

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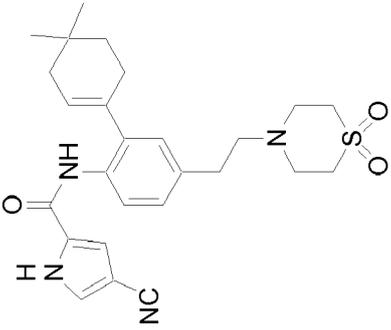
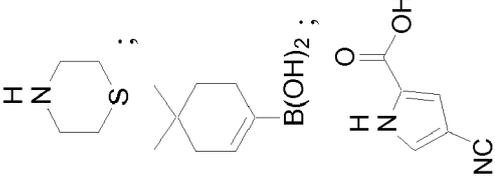
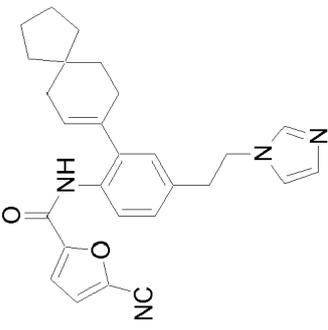
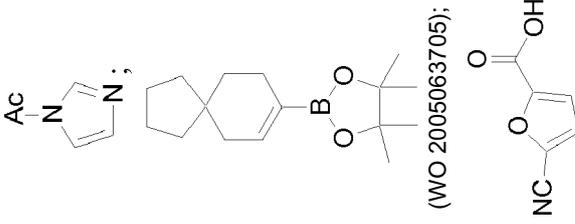
Example No.	Name	Structure	Procedure Reference	Reagents
97	4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(2-thiomorpholin-4-ylethyl)-phenyl]-amide		Ex. 33, steps (a)-(c); Ex. 25, steps (e) and (f)	
98	4-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[2-(1-oxo-1,4-thiomorpholin-4-yl)-ethyl]-phenyl}-amide		Ex. 33, steps (a)-(c); Ex. 25, steps (e) and (f); Ex. 15	

(continued)

Example No.	Name	Structure	Procedure Reference	Reagents
99	4-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[2-(1,1-dioxo-1,2-thiomorpholin-4-yl)-ethyl]-phenyl}-amide		Ex. 33, steps (a)-(c); Ex. 25, steps (e) and (f); Ex. 15; Ex. 16	
100	4-Cyano-1H-imidazole-2-carboxylic acid [4-(2-imidazol-1-yl-ethyl)-2-spiro[4.5]dec-7-en-8-yl-phenyl]-amide		Ex. 33, steps (a)-(c); Ex. 25, steps (e) and (f)	

(WO 2005063705)

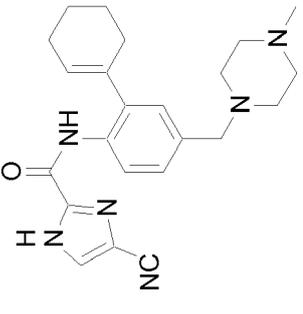
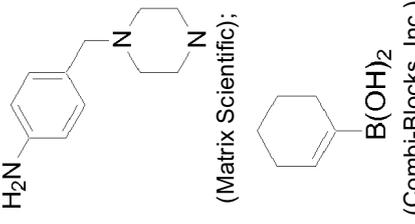
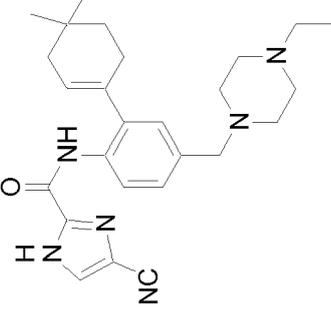
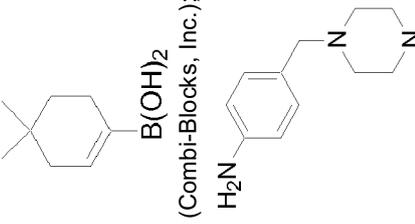
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Example No.	Name	Structure	Procedure Reference	Reagents
101	4-Cyano-1H-pyrrole-2- carboxylic acid {2-(4,4- dimethyl-cyclohex-1-enyl)- 4-[2-(1,1-dioxo-1λ⁶- thiomorpholin-4-yl)- ethyl]-phenyl}-amide		Ex. 33, steps (a)-(c); Ex. 34, step (c); Ex. 15; Ex. 16	 (Can. J. Chem. 59,2673 (1981))
102	5-Cyano-furan-2- carboxylic acid [4-(2- imidazol-1-yl-ethyl)-2- spiro [4.5]dec-7-en-8-yl-phenyl]-amide		Ex. 33, steps (a)-(c); Ex. 43	 (WO 2005063705);

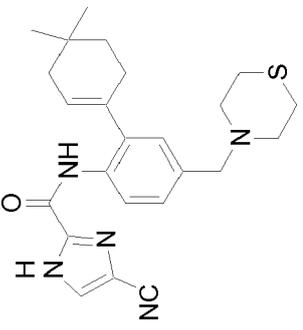
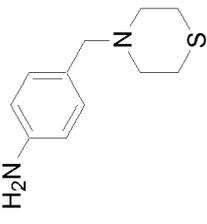
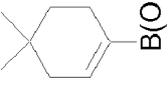
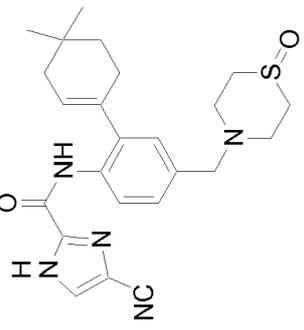
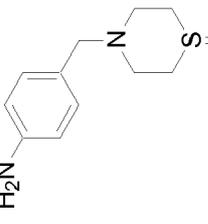
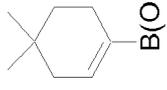
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Example No.	Name	Structure	Procedure Reference	Reagents
103	4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(2-pyridin-2-ylethyl)-phenyl]-amide		Example 25, steps (c)-(f)	<p>(WO200409679 5 A2); (EP 0 356 234 A2);</p>
104	4-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[2-(pyridin-2-ylamino)-ethyl]-phenyl}-amide		Example 33, steps (a)-(c); Example 25, steps (e) and (f)	

(continued)

Example No.	Name	Structure	Procedure Reference	Reagents
105	4-Cyano-1H imidazole-2-carboxylic acid [2-cyclohex-1-enyl-4-(4-methylpiperazin-1-ylmethyl)-phenyl]-amide		Example 44, steps (a)-(b)	 (Matrix Scientific); (Combi-Blocks, Inc.)
106	4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(4-ethyl-piperazin-1-ylmethyl)-phenyl]-amide		Ex. 44, steps (a)-(b)	 (Combi-Blocks, Inc.); (Matrix Scientific)

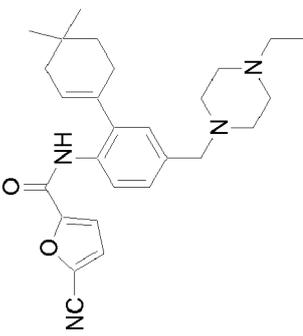
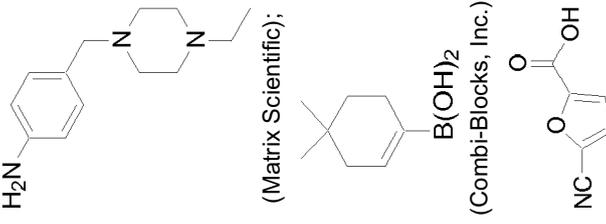
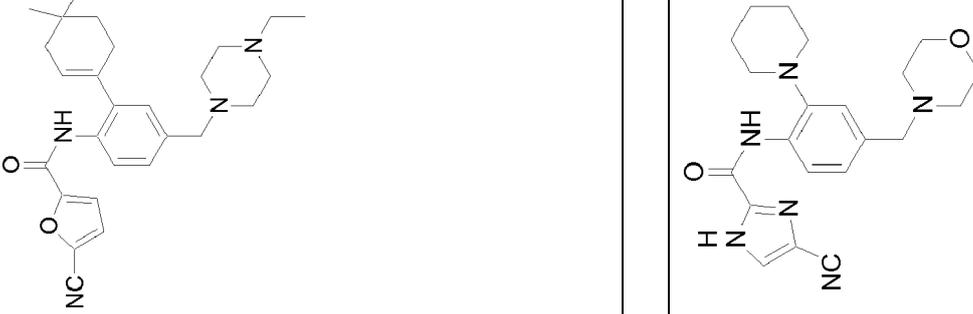
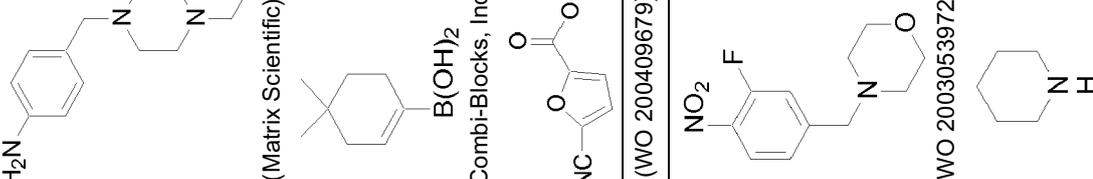
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Example No.	Name	Structure	Procedure Reference	Reagents
107	4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-thiomorpholin-4-ylmethyl]-amide		Ex. 44, steps (a)-(b)	 Bioorganic & Medicinal Chemistry Letters, 8(12), 1493-1498, (1998);  B(OH) ₂ (Combi-Blocks, Inc.)
108	4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(1-oxo-1,4-thiomorpholin-4-ylmethyl)-phenyl]-amide		Ex. 44, steps (a)-(b)	 (WO 2000018734);  B(OH) ₂ (Combi-Blocks, Inc.)

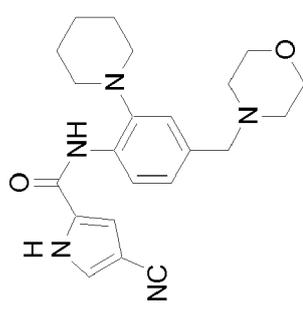
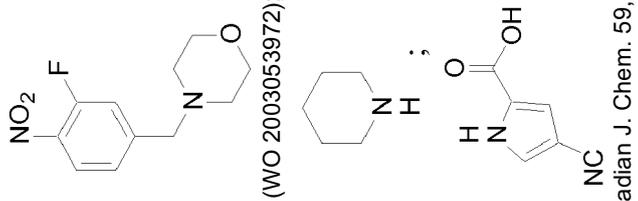
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Example No.	Name	Structure	Procedure Reference	Reagents
109	4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(1,1-dioxo-1λ6-thiomorpholin-4-ylmethyl)-phenyl]-amide		Ex. 44, steps (a)-(b)	<p>(Ryan Scientific); B(OH)₂ (Combi-Blocks, Inc.)</p>
110	4-Cyano-1H-pyrrole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(4-ethyl-piperazin-1-ylmethyl)-phenyl]-amide		Ex. 44, steps (a) Ex. 1, step (f)	<p>(Matrix Scientific); NC (Canadian J. Chem. 59, 2673 (1981))</p>

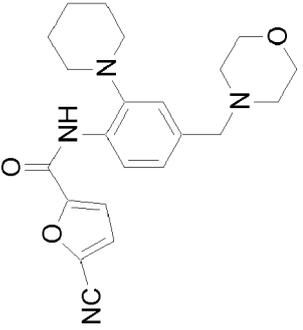
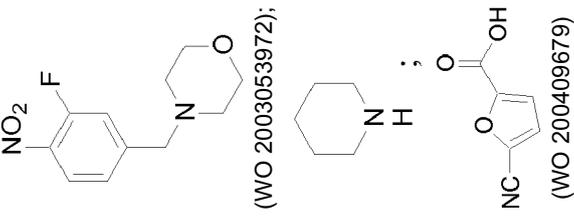
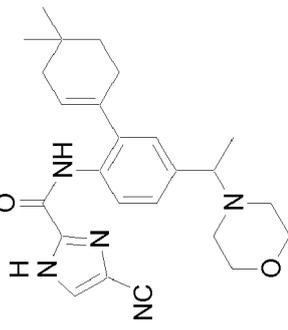
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Example No.	Name	Structure	Procedure Reference	Reagents
111	5-Cyano-furan-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)- 4-(4-ethyl-piperazin-1-ylmethyl)-phenyl]-amide		Ex. 44, steps (a) Ex. 1, step (f)	 (Matrix Scientific); B(OH) ₂ (Combi-Blocks, Inc.) NC
112	4-Cyano-1H-imidazole-2-carboxylic acid (4-morpholin-4-ylmethyl-2-piperidin-1-yl-phenyl)-amide		Ex. 55 step (a), Ex. 54 step (b), Ex. 1 steps (f)-(g)	 (WO 200409679); (WO 2003053972);

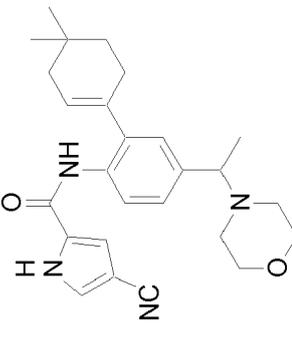
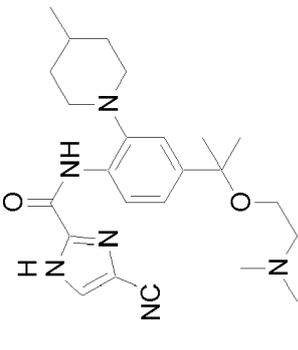
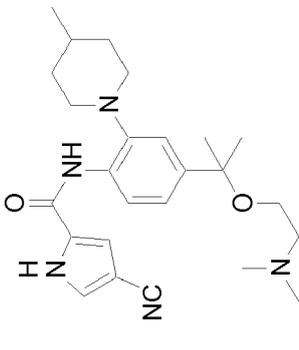
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Example No.	113	Name	4-Cyano-1H-pyrrole-2-carboxylic acid (4-morpholin-4-ylmethyl-2-piperidin-1-yl-phenyl)-amide	Structure		Procedure Reference	Ex. 55 step (a), Ex. 54 step (b), Ex. 1 step (f)	Reagents	 <p>(WO 2003053972);</p> <p>;</p> <p>(Canadian J. Chem. 59, 2673 (1981))</p>
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(continued)

Example No.	Name	Structure	Procedure Reference	Reagents
114	5-Cyano-furan-2-carboxylic acid (4-morpholin-4-ylmethyl-2-piperidin-1-yl-phenyl)-amide		Ex. 55 step (a), Ex. 54 step (b), Ex. 1 step (f)	 (WO 2003053972); ; (WO 200409679)
115	4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(1-morpholin-4-ylethyl)-phenyl]-amide		Ex 14, steps (d),(e).	Acetaldehyde, morpholine

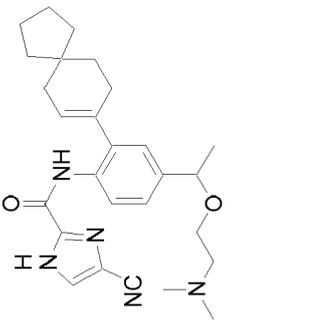
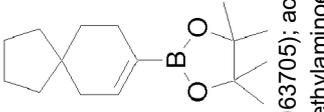
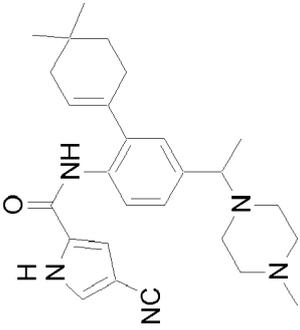
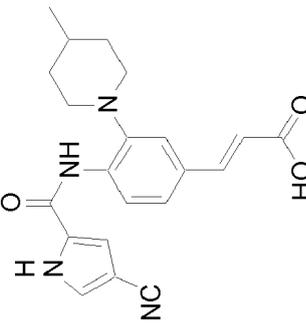
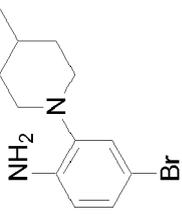
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Example No.	Name	Structure	Procedure Reference	Reagents
116	4-Cyano-1H-pyrrole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(1-morpholin-4-ylethyl)-phenyl]-amide		Ex 50, Ex 14, steps (a),(d),(e).	Acetaldehyde, morpholine
117	4-Cyano-1H-imidazole-2-carboxylic acid [4-[1-(2-dimethylaminoethoxy)-1-methyl-ethyl]-2-(4-methyl-piperidin-1-yl)-phenyl]-amide		Ex 1, steps (f)-(h), Ex. 52	(US 2005131022 A1); 2-dimethylaminoethanol
118	4-Cyano-1H-pyrrole-2-carboxylic acid [4-[1-(2-dimethylaminoethoxy)-1-methyl-ethyl]-2-(4-methyl-piperidin-1-yl)-phenyl]-amide		Ex 50, Ex 1, step (h), Ex 52	(US 2005131022 A1); 2-dimethylaminoethanol

(continued)

Example No.	Name	Structure	Procedure Reference	Reagents
119	4-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1-(2-imidazol-1-yl-ethoxy)-propyl]-phenyl}-amide		Ex. 14, steps (d); Ex 52	Propionaldehyde; 1-(2-hydroxyethyl) imidazole
120	4-Cyano-1H-imidazole-2-carboxylic acid {4-[1-(4-ethyl-piperazin-1-yl)-ethyl]-2-spiro[4.5]dec-7-en-8-yl-phenyl}-amide		Ex. 1, steps (e)-(h); Ex 14 (e)	 (WO 2005063705); acetaldehyde; 1-ethyl-piperazine
121	4-Cyano-1H-imidazole-2-carboxylic acid [4-(1-dimethylamino-ethyl)-2-spiro[4.5]dec-7-en-8-yl-phenyl]-amide		Ex. 1, steps (e)-(h); Ex 14 (e)	 (WO 2005063705); acetaldehyde; dimethylamine

(continued)

Example No.	Name	Structure	Procedure Reference	Reagents
122	4-Cyano-1H-imidazole-2-carboxylic acid {4-[1-(2-dimethylaminoethoxy)-ethyl]-2-spiro[4.5]dec-7-en-8-yl-phenyl}-amide		Ex. 1, steps (e)-(h); Ex 52	 (WO 2005063705); acetaldehyde; 2-dimethylaminoethanol
123	4-Cyano-1H-pyrrole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1-(4-methyl-piperazin-1-yl)-ethyl]-phenyl}-amide		Ex 50, Ex 14 step (a),(d),(e)	Acetaldehyde; 1-methyl-piperazine
124	3-[4-(4-Cyano-1H-pyrrole-2-carbonyl)-amino]-3-(4-methyl-piperidin-1-yl)-phenyl]-acrylic acid		Ex 50, Ex 48 step (a), (b)	 (US 2005131022 A1)

(continued)

Example No.	Name	Structure	Procedure Reference	Reagents
125	3-[4-[(4-Cyano-1H-imidazole-2-carbonyl)-amino]-3-(4-methyl-piperidin-1-yl)-phenyl]-acrylic acid		Ex 1, steps (f), (g) Ex 48, steps (a), (b).	 (US 2005131022 A1)
126	3-{3'-[(4-Cyano-1H-imidazole-2-carbonyl)-amino]-4-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-yl}-acrylic acid		Ex 1, steps(f), (g) Ex 48, steps (a), (b).	 (Org. Prep. Proc. Int., 30, 709, (1998))
127	3-{3'-[(4-Cyano-1H-pyrrole-2-carbonyl)-amino]-4-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-yl}-acrylic acid		Ex 50 Ex 48, steps (a), (b).	 (Org. Prep. Proc. Int., 30, 709, (1998))

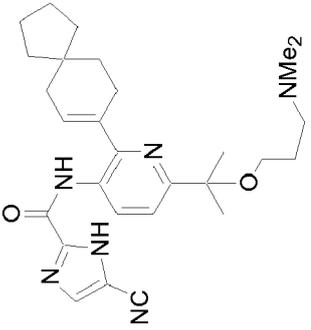
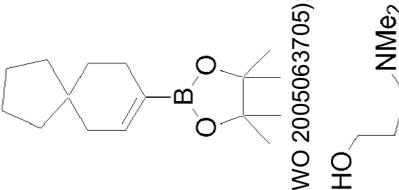
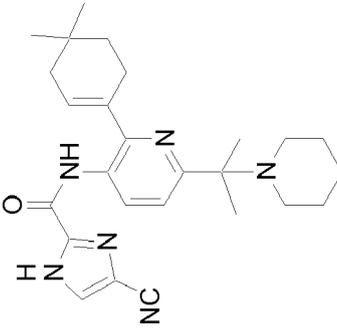
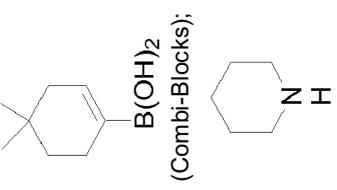
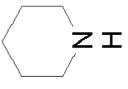
(continued)

Example No.	Name	Structure	Procedure Reference	Reagents
128	4-Cyano-1H-imidazole-2-carboxylic acid {2-cyclohex-1-enyl-6-[1-methyl-1-(2-pyrrolidin-1-yl-ethoxy)-ethyl]-pyridin-3-yl}-amide		Ex. 56, steps (a-e); Ex. 52	
129	4-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-6-[1-methyl-1-(2-morpholin-4-yl-ethoxy)-ethyl]-pyridin-3-yl}-amide		Ex. 56, steps (a-e); Ex. 14, step (e)	

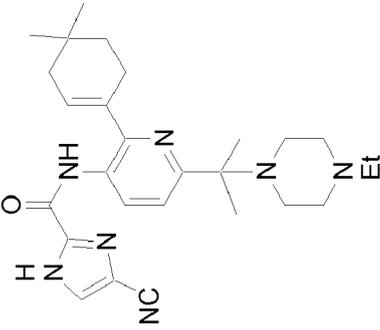
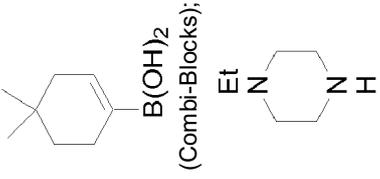
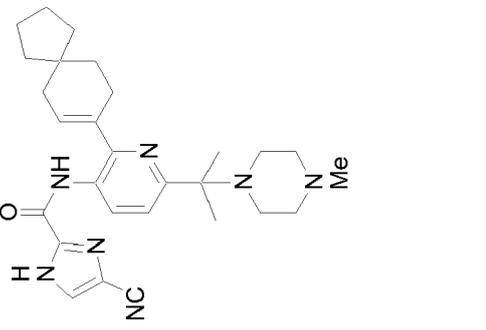
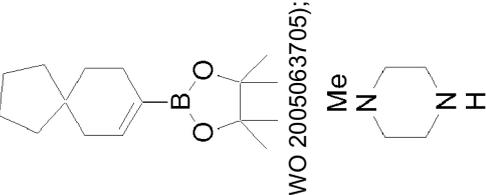
(continued)

Example No.	Name	Structure	Procedure Reference	Reagents
130	4-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-diethyl-cyclohex-1-enyl)-6-[1-(3-dimethylamino-propoxy)-1-methyl-ethyl]-pyridin-3-yl}-amide		Ex. 56, steps (a-e) Ex. 52	<p>(WO 2005063705)</p>
131	4-Cyano-1H-imidazole-2-carboxylic acid {6'-[1-(3-dimethylamino-propoxy)-1-methyl-ethyl]-3,4,5,6-tetrahydro-2H [1,2']bipyridinyl-3'-yl}-amide		Ex. 56, steps (c-e) Ex. 52	<p>(Org. Prep. and Proc. Int., 30 (6), 709-713 (1998));</p>

(continued)

Example No.	Name	Structure	Procedure Reference	Reagents
132	4-Cyano-1H-imidazole-2-carboxylic acid {6-[1-(3-dimethylamino-propoxy)-1-methyl-ethyl]-2-spiro [4.5]dec-7-en-8-yl-pyridin-3-yl}-amide		Ex. 56, steps (a), (b),(e); Ex. 55, step (d); Ex. 52	 (WO 2005063705); HO-CH ₂ -CH ₂ -CH ₂ -NMe ₂
133	4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-6-(1-methyl-1-piperidin-1-ylethyl)-pyridin-3-yl]-amide		Ex. 56, steps (a-e); Ex. 14, step (e)	 B(OH) ₂ (Combi-Blocks); 

(continued)

Example No.	Name	Structure	Procedure Reference	Reagents
134	4-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-6-[1-(4-ethyl-piperazin-1-yl)-1-methyl-ethyl]-pyridin-3-yl}-amide		Ex. 56, steps (a)-(e); Ex. 14, step (e)	
135	4-Cyano-1H-imidazole-2-carboxylic acid {6-[1-methyl-1-(4-methyl-piperazin-1-yl)-ethyl]-2-spiro[4.5] dec-7-en-8-yl-pyridin-3-yl}-amide		Ex. 56, steps (a)-(e); Ex. 14, step (e)	

(continued)

Example No.	Name	Structure	Procedure Reference	Reagents
136	4-Cyano-1H-pyrrole-2-carboxylic acid {6'-[1-methyl-1-(4-methylpiperazin-1-yl)-ethyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl}-amide		Ex. 56, step (c); Ex. 14, step (e).	<p>(Org. Prep. Proc. Int. 30 (6), 709-713, (1998));</p> <p>(Can. J. Chem. 59,2673 (1981));</p>

(continued)

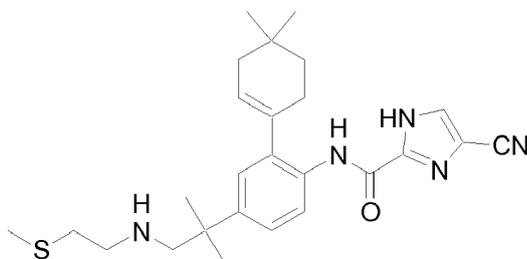
Example No.	Name	Structure	Procedure Reference	Reagents
137	4-Cyano-1H-imidazole-2-4-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-6-[1-methyl-1-(4-methyl-piperazin-1-yl)-ethyl]-pyridin-3-yl}-amide		Ex. 56, steps (a)-(e); Ex. 14, step	 B(OH)₂ (Combi-Blocks)

[0491] The following examples were made according to procedures described in this document, and other procedures known to those skilled in the art.

Example 138

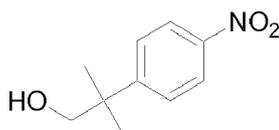
4-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1,1-dimethyl-2-(2-methylsulfanyl-ethylamino)-ethyl]-phenyl}-amide

[0492]



a) 2-Methyl-2-(4-nitro-phenyl)-propan-1-ol

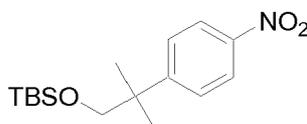
[0493]



[0494] To a suspension of lithium aluminum hydride (1.00 g, 26.3 mmol) in 50 mL of THF at 0 °C was added 2-methyl-2-(4-nitro-phenyl)-propionic acid methyl ester (2.20 g, 9.86 mmol, Hartwig, et al, J. Am. Chem. Soc, 2004, 126, 5182) in 10 mL of THF dropwise. The resulting mixture was stirred at 0 °C for 3 h and treated with 1 mL of H₂O followed by 1 mL of 15 % aq NaOH and 3 mL of H₂O. The solid was removed by filtration on Celite and the filtrate was concentrated in vacuo to give a light yellow oil (1.56 g, 81 %). The product was used in the next step without further purification. ¹H-NMR (CDCl₃; 400 MHz): δ 7.92 (d, 2H, J = 8.6 Hz), 7.55 (d, 2H, J = 8.6 Hz), 3.69 (s, 2H), 1.40 (s, 6H).

b) tert-Butyl-dimethyl-[2-methyl-2-(4-nitro-phenyl)-propoxy]-silane

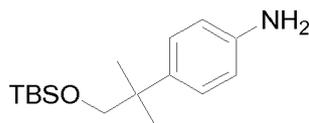
[0495]



[0496] To a mixture of 2-methyl-2-(4-nitro-phenyl)-propan-1-ol (as prepared in the previous step, 1.50 g, 7.68 mmol) and t-butyl-dimethylsilyl chloride (1.51 g, 9.99 mmol) in 60 mL of DCM was slowly added imidazole (3.09 g, 45.4 mmol). After stirring at RT for 16 h, the mixture was treated with 40 mL of DCM and washed with H₂O (30 mL), 15 % aqueous citric acid (30 mL) and brine (20 mL). The organic layer was dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (0-5 % EtOAc/hexane) to give 1.82 g (65 %) of the title compound as a light brown oil. ¹H-NMR (CDCl₃; 400 MHz): δ 7.85 (d, 2H, J = 8.8 Hz), 7.52 (d, 2H, J = 8.8 Hz), 3.59 (s, 2H), 1.35 (s, 6H), 0.86 (s, 9H), -0.04 (s, 6H).

c) 4-[2-(tert-Butyl-dimethyl-silanyloxy)-1,1-dimethyl-ethyl]-phenylamine

[0497]



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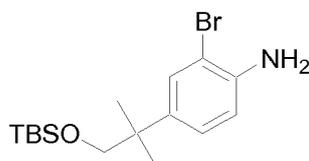
[0498] A mixture of tert-butyl-dimethyl-[2-methyl-2-(4-nitro-phenyl)-propoxy]-silane (as prepared in the previous step, 1.70 g, 5.49 mmol) and 10 % Pd/C (850 mg, 50 wt %) in 30 mL of EtOAc was stirred at RT under H₂ (balloon pressure) for 6 h. The Pd catalyst was removed by filtration on Celite and the filtrate was concentrated. The residue was purified by flash chromatography on silica gel (5-10 % EtOAc/DCM) to give 1.43 g (93 %) of the title compound as a light brown oil. Mass spectrum (ESI, m/z): Calcd. for C₁₆H₂₉NOSi, 280.2 (M+H), found 280.4.

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d) 2-Bromo-4-[2-(tert-butyl-dimethyl-silyloxy)-1,1-dimethyl-ethyl]-phenylamine

15

[0499]



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[0500] To a solution of 4-[2-(tert-butyl-dimethyl-silyloxy)-1,1-dimethyl-ethyl]-phenylamine (as prepared in the previous step, 1.41 g, 5.04 mmol) in 25 mL of DCM at 0 °C was slowly added N-bromosuccinimide (NBS) (898 mg, 5.04 mmol) in three portions over five minutes. After stirring at RT for 2 h, the mixture was treated with 50 mL of EtOAc and washed with H₂O (2 x 30 mL) and brine H₂O (20 mL). The organic layer was dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (DCM) to give 1.59 g (88 %) of the title compound as a light yellow oil. Mass spectrum (ESI, m/z): Calcd. for C₁₆H₂₈BrNOSi, 358.1 (M+H), found 358.4.

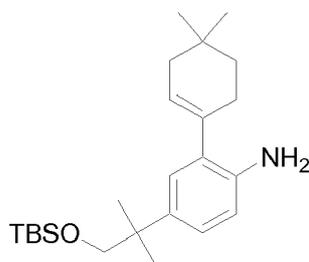
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e) 4-[2-(tert-Butyl-dimethyl-silyloxy)-1,1-dimethyl-ethyl]-2-(4,4-dimethyl-cyclohex-1-enyl)-phenylamine

[0501]

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[0502] To a mixture of 2-bromo-4-[2-(tert-butyl-dimethyl-silyloxy)-1,1-dimethyl-ethyl]-phenylamine (as prepared in the previous step, 1.50 g, 4.19 mmol), 4,4-dimethylcyclohexen-1-ylboronic acid (1.09 g, 4.61 mmol) and Pd(PPh₃)₄ (484 mg, 0.419 mmol) in 50 mL of 1,4-dioxane was added aqueous Na₂CO₃ (16.8 mL, 33.5 mmol, 2.0 M). The resulting mixture was stirred at 90 °C for 16 h under Ar. After cooling to RT, the mixture was treated with 150 mL of EtOAc and washed with H₂O (3 x 30 mL) and brine (30 mL). The organic layer was dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (5-10 % EtOAc/hexane) to afford 1.46 g (90 %) of the title compound as a colorless oil. Mass spectrum (ESI, m/z): Calcd. for C₂₄H₄₁NOSi, 388.3 (M+H), found 388.3.

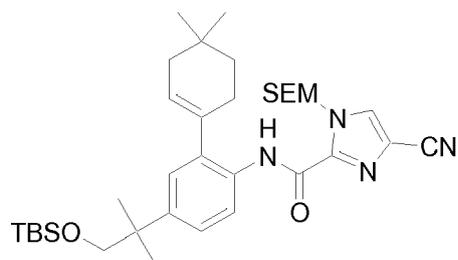
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f) 4-Cyano-1-(2-trimethylsilyanyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [4-[2-(tert-butyl-dimethyl-silyloxy)-1,1-dimethyl-ethyl]-2-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-amide

55

[0503]

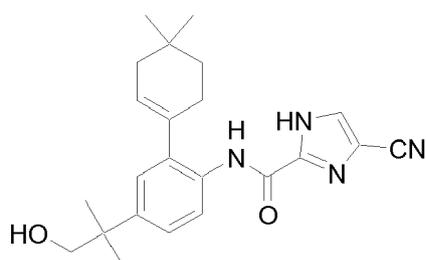


15 **[0504]** To a mixture of potassium 4-cyano-1-(2-trimethylsilyanyl-ethoxymethyl)-1H-imidazole-2-carboxylate (as prepared in Example 1, step (d), 1.37 g, 4.49 mmol) and pyridine (363 μ L, 4.49 mmol) in 15 mL of DCM at 0°C was added SOCl_2 (328 μ L, 4.49 mmol). After stirring at 0°C for 0.5 h under Ar, the resulting mixture was warmed to RT and added to a solution of 4-[2-(tert-butyl-dimethyl-silyloxy)-1,1-dimethyl-ethyl]-2-(4,4-dimethyl-cyclohex-1-enyl)-phenylamine

20 (as prepared in the previous step, 1.45 g, 3.74 mmol) in 15 mL of DCM at 0°C. After stirring at 0°C for 2 h under Ar, the reaction was warmed to RT. Treated with 100 mL of EtOAc, the mixture was washed with H_2O (20 mL), 10 % aqueous citric acid (20 mL), aqueous saturated NaHCO_3 (20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (0-5 % EtOAc/hexane) to afford the title compound (2.22 g, 93 %) as a light brown oil. Mass spectrum (ESI, m/z): Calcd. for $\text{C}_{35}\text{H}_{56}\text{N}_4\text{O}_3\text{Si}_2$, 637.4 (M+H), found 637.2.

25 **g) 4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(2-hydroxy-1,1-dimethyl-ethyl)-phenyl]-amide**

30 **[0505]**



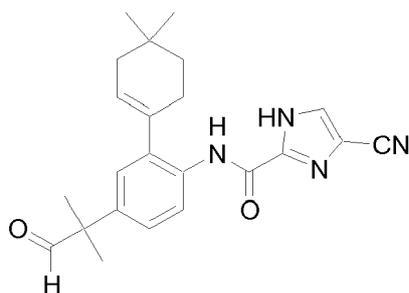
40 **[0506]** A solution of 4-cyano-1-(2-trimethylsilyanyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [4-[2-(tert-butyl-dimethyl-silyloxy)-1,1-dimethyl-ethyl]-2-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-amide (as prepared in the previous step, 2.20 g, 3.45 mmol) and tetrabutylammonium fluoride hydrate (4.52 g, 17.3 mmol) in 25 mL of THF was stirred at 50°C for 3 h. After cooling to RT, the mixture was treated with 100 mL of EtOAc and washed with saturated aqueous NH_4Cl (20 mL), H_2O (20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (0-4 % MeOH/DCM) to afford the title compound (1.25 g, 92 %) as a white solid. Mass spectrum (ESI, m/z): Calcd. for $\text{C}_{23}\text{H}_{28}\text{N}_4\text{O}_2$, 393.2 (M+H), found 393.2.

45 **h) 4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(1,1-dimethyl-2-oxo-ethyl)-phenyl]-amide**

50 **[0507]**

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[0508] To a mixture of 4-cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(2-hydroxy-1,1-dimethyl-ethyl)-phenyl]-amide (as prepared in the previous step, 1.00 g, 2.55 mmol) and NaHCO_3 (1.07 g, 12.8 mmol) in 40 mL of DCM at 0 °C was added Dess-Martin periodinane (Adv. Syn. Chem., 2004, 346, 111-124, 2.16 g, 5.10 mmol). After stirring at 0 °C for 0.5 h, the reaction was warmed to RT and continued to stir for 2 h. The mixture was treated with 100 mL of EtOAc and washed with 10 % aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (2 x 20 mL), aqueous saturated NaHCO_3 (20 mL), H_2O (20 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (0-3 % MeOH/DCM) to afford the title compound (876 mg, 88 %) as a white solid. Mass spectrum (ESI, m/z): Calcd. for $\text{C}_{23}\text{H}_{26}\text{N}_4\text{O}_2$, 391.2 (M+H), found 391.1.

i) 4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1,1-dimethyl-2-(2-methylsulfonyl-ethylamino)-ethyl]-phenyl]-amide

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[0509] To a mixture of 4-cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(1,1-dimethyl-2-oxo-ethyl)-phenyl]-amide (as prepared in the previous step, 60.0 mg, 0.154 mmol) and 2-methylsulfonyl-ethylamine (84 mg, 0.92 mmol) in 2 mL of 1,2-dichloroethane was added sodium triacetoxyborohydride (49.0 mg, 0.231 mmol). After stirring at RT for 3 h, the mixture was treated with EtOAc (40 mL) and washed with aqueous saturated NaHCO_3 (10 mL), H_2O (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (1-3 % MeOH/DCM) to afford the title compound (45.0 mg, 63 %) as a white solid. $^1\text{H-NMR}$ (1:1 $\text{CD}_3\text{OD}/\text{CDCl}_3$; 400 MHz): δ 8.22 (d, 1H, J = 8.6 Hz), 7.78 (s, 1H), 7.27 (dd, 1H, J = 8.6, 2.0 Hz), 7.14 (d, 1H, J = 2.0 Hz), 5.73 (m, 1H), 2.77 (s, 2H), 2.68 (t, 2H, J = 6.3 Hz), 2.55 (t, 2H, J = 6.3 Hz), 2.27 (m, 2H), 2.06 (m, 2H), 1.92 (s, 3H), 1.57 (t, 2H, J = 6.3 Hz), 1.35 (s, 6H), 1.07 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for $\text{C}_{26}\text{H}_{35}\text{N}_5\text{OS}$, 466.3 (M+H), found 466.2.

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Example 139

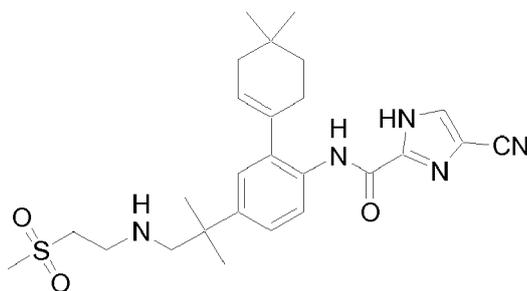
4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-[2-(2-methanesulfonyl-ethylamino)-1,1-dimethyl-ethyl]-phenyl]-amide

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[0510]

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[0511] To a solution of 4-cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1,1-dimethyl-2-(2-methylsulfonyl-ethylamino)-ethyl]-phenyl]-amide (as prepared in Example 138, step (i), 38.0 mg, 0.0816 mmol) in 2 mL of DCM and 50 μL of i-PrOH at RT was added titanium (IV) isopropoxide (24.0 μL , 0.0816 mmol). The mixture was cooled to 0°C and H_2O_2 (18.0 μL , 0.163 mmol, 30 wt % in H_2O) was added. After stirring at 0°C for 0.5 h and at RT for 2 h, the mixture was treated with EtOAc (50 mL) and washed with aqueous saturated NaHCO_3 (10 mL), aqueous saturated NH_4Cl (10 mL), brine (10 mL) and dried (Na_2SO_4). The organic layer was concentrated in vacuo and the

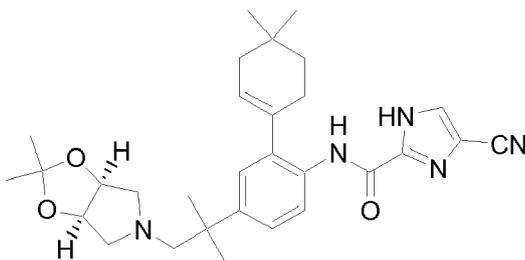
EP 2 687 516 A1

residue was purified by silica gel chromatography (1-3 % MeOH/DCM) to afford the title compound (39.8 mg, 98 %) as a white solid. ¹H-NMR (1:1 CD₃OD/CDCl₃; 400 MHz): δ 8.17 (d, 1H, J = 8.6 Hz), 7.86 (s, 1H), 7.27 (d, 1H, J = 8.6 Hz), 7.14 (br s, 1H), 5.73 (m, 1H), 3.12 (t, 2H, J = 5.9 Hz), 2.99 (t, 2H, J = 5.9 Hz), 2.86 (s, 3H), 2.76 (s, 2H), 2.28 (m, 2H), 2.07 (m, 2H), 1.58 (t, 2H, J = 6.3 Hz), 1.33 (s, 6H), 1.07 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for C₂₆H₃₅N₅O₃S, 498.3(M+H), found 498.2.

Example 140

4-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[2-(2,2-dimethyl-tetrahydro-[1,3]dioxolo[4,5-c]pyrrol-5-yl)-1,1-dimethyl-ethyl]-phenyl}-amide

[0512]

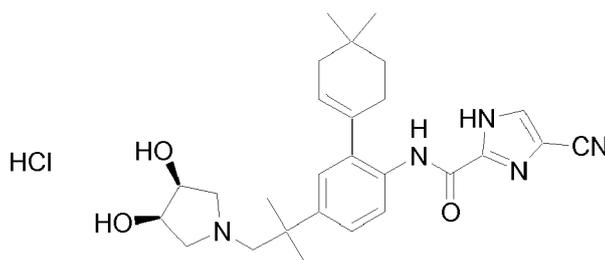


[0513] The title compound was prepared by the procedure of Example 138, step (i) using 4-cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-(1,1-dimethyl-2-oxo-ethyl)-phenyl]-amide (as prepared in Example 138, step (h), 60.0 mg, 0.154 mmol) and 2,2-dimethyl-tetrahydro-[1,3]dioxolo[4,5-c]pyrrole (Couturier, M. et al, Organic Process Research & Development, 2002, 6, 42-48, 132 mg, 0.924 mmol). Silica gel chromatography (1-3 % MeOH/DCM) afforded the title compound (49.3 mg, 63 %) as a white solid. ¹H-NMR(1:1 CD₃OD; 400 MHz): 8.13 (d, 1H, J = 8.6 Hz), 7.98 (s, 1H), 7.32 (dd, 1H, J = 8.6, 2.3 Hz), 7.21 (d, 1H, J = 2.3 Hz), 5.73 (m, 1H), 4.48 (m, 2H), 2.70 (d, 2H, J = 11.4 Hz), 2.59 (s, 2H), 2.31 (m, 2H), 2.08 (m, 2H), 1.98-2.04 (m, 2H), 1.59 (t, 2H, J = 6.3 Hz), 1.44 (s, 3H), 1.34 (s, 6H), 1.23 (s, 3H), 1.09 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for C₃₀H₃₉N₅O₃, 518.3 (M+H), found 518.3.

Example 141

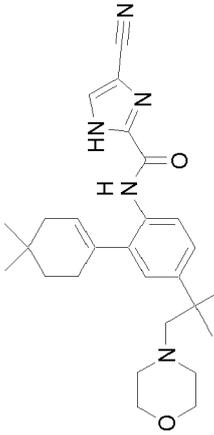
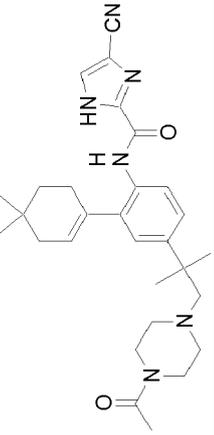
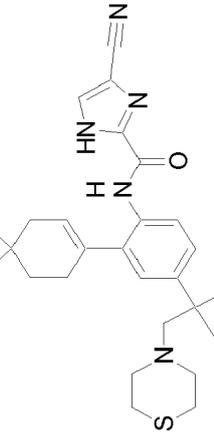
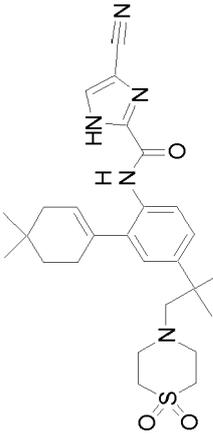
4-Cyano-1H-imidazole-2-carboxylic acid [4-[2-(3,4-dihydroxy-pyrrolidin-1-yl)-1,1-dimethyl-ethyl]-2-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-amide hydrochloride

[0514]



[0515] A solution of 4-cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[2-(2,2-dimethyl-tetrahydro-[1,3]dioxolo[4,5-c]pyrrol-5-yl)-1,1-dimethyl-ethyl]-phenyl}-amide (as prepared in Example 140, 42.0 mg, 0.0811 mmol) in 2 mL of 1:1 1N HCl/THF was stirred at 80°C for 0.5 h. After cooling to RT, the mixture was treated with 40 mL of EtOAc and concentrated in vacuo to give the title compound (38.8 mg, 91 %) as a colorless oil. ¹H-NMR (1:1 CD₃OD; 400 MHz): 8.29 (d, 1H, J = 8.6 Hz), 8.00 (s, 1H), 7.43 (dd, 1H, J = 8.6, 2.3 Hz), 7.32 (d, 1H, J = 2.3 Hz), 5.77 (m, 1H), 4.17 (m, 2H), 3.64 (s, 2H), 3.31-3.37 (m, 2H), 2.98-3.07 (m, 2H), 2.34 (m, 2H), 2.09 (m, 2H), 1.61 (t, 2H, J = 6.3 Hz), 1.51 (s, 6H), 1.10 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for C₂₇H₃₅N₅O₃, 478.3 (M+H), found 478.3.

[0516] The following compounds were prepared according to the examples as indicated:

Example Number	Name	Structure	Procedure Reference	Mass Spectrum
142	4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethylcyclohex-1-enyl)-4-(1,1-dimethylethyl)-phenyl]-amide		Ex 138, step (i)	(ESI, m/z) Calcd. for C ₂₇ H ₃₅ N ₅ O ₂ , 462.3 (M+H), found 462.3.
143	4-Cyano-1H-imidazole-2-carboxylic acid [4-[2-(4-acetylpiperazin-1-yl)-1,1-dimethyl-ethyl]-cyclohex-1-enyl]-phenyl]-amide		Ex 138, step (i)	(ESI, m/z) Calcd. for C ₂₉ H ₃₈ N ₆ O ₂ , 503.3 (M+H), found 503.3.
144	4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethylcyclohex-1-enyl)-4-(1,1-dimethyl-2-thiomorpholin-4-ylethyl)-phenyl]-amide		Ex 138, step (i)	(ESI, m/z) Calcd. for C ₂₇ H ₃₅ N ₅ OS, 478.3 (M+H), found 478.3.
145	4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethylcyclohex-1-enyl)-4-[2-(1,1-dioxo-1λ ⁶ -thiomorpholin-4-yl)-1,1-dimethyl-ethyl]-phenyl]-amide		Ex 144, Ex 139	(ESI, m/z) Calcd. for C ₂₇ H ₃₅ N ₅ O ₃ S, 510.3 (M+H), found 510.2.

(continued)

Example Number	Name	Structure	Procedure Reference	Mass Spectrum
146	4-Cyano-1H-imidazole-2-carboxylic acid (2-(4,4-dimethylcyclohex-1-enyl)-4-[2-[4-(2-hydroxy-ethyl)piperazin-1-yl]-1,1-dimethylethyl]-phenyl)-amide		Ex 138, step (i)	(ESI, m/z) Calcd. for C ₂₉ H ₄₀ N ₆ O ₂ , 505.3 (M+H), found 505.3.
147	4-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethylcyclohex-1-enyl)-4-[2-(2-methoxyethyl)-1,1-dimethyl-ethyl]-phenyl}-amide		Ex 138, step (i)	(ESI, m/z) Calcd. for C ₂₆ H ₃₅ N ₅ O ₂ , 450.3 (M+H), found 450.2.

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[0517] The following examples were made according to procedures described in this document, and other procedures known to those skilled in the art.

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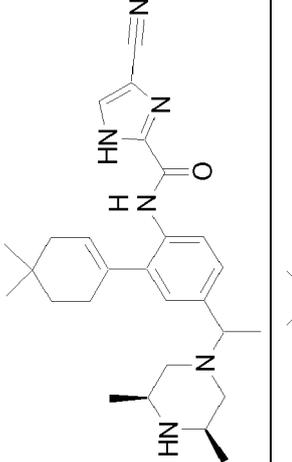
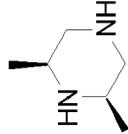
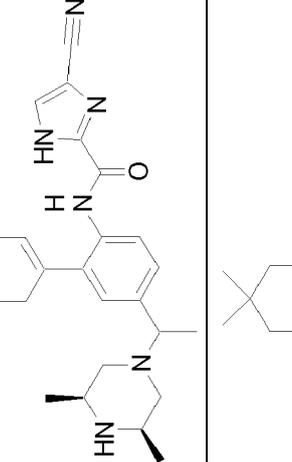
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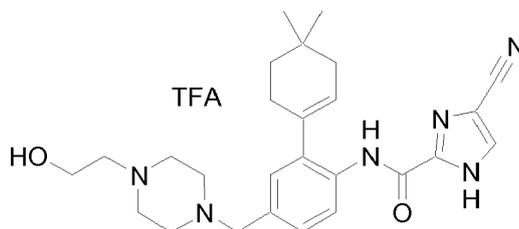
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Example Number	Name	Structure	Procedure Reference	Reagents
148	<p>4-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[1-(3,5-dimethyl-piperazin-1-yl)-ethyl]-phenyl}-amide</p>		<p>Ex. 62, step (c); Ex. 138, step (i); Ex. 62, step (d)</p>	 <p>piperidine</p>
149	<p>4-Cyano-1H-imidazole-2-carboxylic acid [2-(dimethyl-cyclohex-1-enyl)-4-(1-methyl-1-piperidin-1-yl-ethyl)-phenyl]-amide</p>		<p>Ex. 14, step (e)</p>	<p>piperidine</p>

Example 150

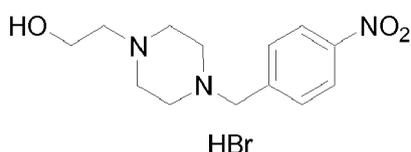
4-Cyano-1H-imidazole-2-carboxylic acid {2-(4,4-dimethyl-cyclohex-1-enyl)-4-[4-(2-hydroxy-ethyl)-piperazin-1-ylmethyl]-phenyl}-amide trifluoroacetic acid salt

[0518]



a) 2-[4-(4-Nitro-benzyl)-piperazin-1-yl]-ethanol hydrobromide

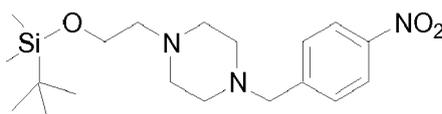
[0519]



[0520] A solution of 2-piperazin-1-yl-ethanol (5.10 g, 38.4 mmol) in EtOH (30 mL) was cooled to 0 °C and treated portionwise with 1-bromomethyl-4-nitro-benzene (8.30 g, 38.4 mmol). The mixture was allowed to warm to RT and stir at that temperature for 3 h. The mixture was filtered, and the solid was washed with EtOH and air-dried to afford the title compound (9.72 g, 73 %) as a white solid. Mass spectrum (ESI, m/z): Calcd. for C₁₃H₁₉N₃O₃, 266.1 (M+H), found 266.2.

b) 1-[2-(tert-Butyl-dimethyl-silyloxy)-ethyl]-4-(4-nitro-benzyl)-piperazine

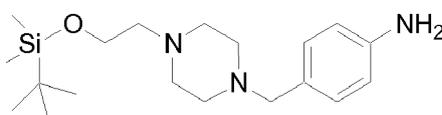
[0521]



[0522] A suspension of 2-[4-(4-nitro-benzyl)-piperazin-1-yl]-ethanol hydrobromide (as prepared in the previous step, 1.00 g, 2.89 mmol) in DMF (3 mL) was treated with imidazole (688 mg, 10.1 mmol) and tert-butyl-chloro-dimethyl-silane (566 mg, 3.76 mmol) at RT for 3 h. The mixture was partitioned between EtOAc (50 mL) and brine (50 mL), and the layers were separated. The organic layer was washed with brine (3 x 40 mL). The combined aqueous layers were extracted with EtOAc (1 x 50 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Purification of the residue on a 50-g Isolute SPE column on a FlashMaster system with 50 % EtOAc-hexane afforded the title compound (1.03 g, 94 %) as a pale yellow oil which solidified upon standing. Mass spectrum (ESI, m/z): Calcd. for C₁₉H₃₃N₃O₃Si, 380.2 (M+H), found 380.2.

c) 4-[4-[2-(tert-Butyl-dimethyl-silyloxy)-ethyl]-piperazin-1-ylmethyl]-phenylamine

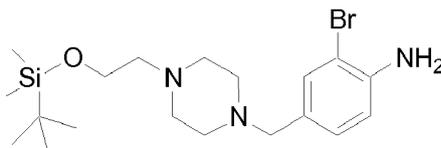
[0523]



[0524] A solution of 1-[2-(tert-butyl-dimethyl-silyloxy)-ethyl]-4-(4-nitro-benzyl)-piperazine (as prepared in the previous step, 279 mg, 0.735 mmol) in MeOH (4 mL) and water (4 mL) was treated with solid NH₄Cl (393 mg, 7.35 mmol) and Zn powder (240 mg, 3.67 mmol). The mixture was stirred at 50 °C for 2 h and at RT for 16 h. The mixture was partitioned between EtOAc and water. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Purification of the residue on a 20-g Isolute SPE column on a FlashMaster system with EtOAc afforded the title compound (204 mg, 79 %) as a yellow solid. Mass spectrum (ESI, m/z): Calcd. for C₁₉H₃₅N₃OSi, 350.3 (M+H), found 350.2.

d) 2-Bromo-4-{4-[2-(tert-butyl-dimethyl-silyloxy)-ethyl]-piperazin-1-ylmethyl}-phenylamine

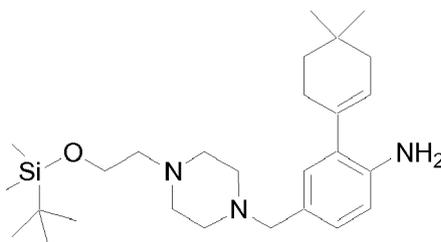
[0525]



[0526] A solution of 4-{4-[2-(tert-butyl-dimethyl-silyloxy)-ethyl]-piperazin-1-ylmethyl}-phenylamine (as prepared in the previous step, 204 mg, 0.582 mmol) in CH₃CN (6 mL) was cooled to 0 °C and treated dropwise with NBS as a solution in CH₃CN (6 mL). The solvents were evaporated in vacuo. The residue was taken up in EtOAc and washed with satd aq NaHCO₃. The organic layer was dried over MgSO₄ and concentrated in vacuo. Purification of the residue on a 20-g Isolute SPE column on a FlashMaster system with 25-50 % EtOAc-hexane afforded the title compound (80.9 mg, 32 %) as an off-white solid. Mass spectrum (ESI, m/z): Calcd. for C₁₉H₃₄N₃OSiBr, 428.2/430.2 (M+H), found 428.1/430.0.

e) 4-{4-[2-(tert-Butyl-dimethyl-silyloxy)-ethyl]-piperazin-1-ylmethyl}-2-(4,4-dimethyl-cyclohex-1-enyl)-phenylamine

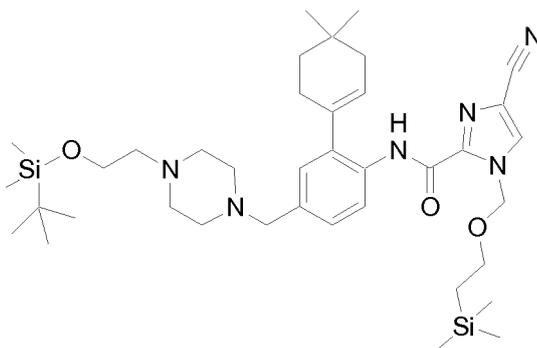
[0527]



[0528] A solution of 2-bromo-4-{4-[2-(tert-butyl-dimethyl-silyloxy)-ethyl]-piperazin-1-ylmethyl}-phenylamine (as prepared in the previous step, 305 mg, 0.712 mmol) in DME (15 mL) was treated with LiCl (36.2 mg, 0.854 mmol), 4,4-dimethyl-cyclohex-1-enyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (202 mg, 8.54 mmol), and aqueous Na₂CO₃ (2.85 mL, 5.69 mmol, 2.0 M). The mixture was degassed via sonication, placed under Ar, treated with Pd(PPh₃)₄ (82.2 mg, 0.0712 mmol), and heated to 80 °C for 21 h. The mixture was concentrated in vacuo, and the residue was partitioned between EtOAc (60 mL) and water (60 mL). The layers were separated, and the organic layer was washed with brine (1 x 20 mL). The combined aqueous layers were extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Purification of the residue on a 20-g Isolute SPE column on a FlashMaster system with 50 % EtOAc-hexane afforded the title compound (233 mg, 72 %) as a light tan glassy solid. Mass spectrum (ESI, m/z): Calcd. for C₂₇H₄₇N₃OSi, 458.4 (M+H), found 458.1.

f) 4-Cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [4-{4-[2-(tert-butyl-dimethyl-silyloxy)-ethyl]-piperazin-1-ylmethyl}-2-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-amide

[0529]



[0530] A solution of 4-{4-[2-(tert-butyl-dimethyl-silyloxy)-ethyl]-piperazin-1-ylmethyl}-2-(4,4-dimethyl-cyclohex-1-enyl)-phenylamine (as prepared in the previous step, 233 mg, 0.590 mmol) in CH_2Cl_2 (10 mL) was treated with 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid potassium salt (as prepared in Example 1, step (d), 188 mg, 0.610 mmol), PyBroP (332 mg, 0.713 mmol), and DIEA (177 μL , 10.2 mmol) at RT for 1 h. The mixture was diluted with CH_2Cl_2 (40 mL) and washed with water (1 x 30 mL) and satd aq NaHCO_3 (1 x 30 mL). The combined aqueous layers were extracted with CH_2Cl_2 (1 x 30 mL). The combined organic layers were dried over MgSO_4 and concentrated in vacuo. Purification of the residue on a 20-g Isolute SPE column on a FlashMaster system with 10-25 % EtOAc-hexane afforded the title compound (223 mg, 62 %) as an off-white solid. Mass spectrum (ESI, m/z): Calcd. for $\text{C}_{38}\text{H}_{62}\text{N}_6\text{O}_3\text{Si}_2$, 707.4 (M+H), found 707.4.

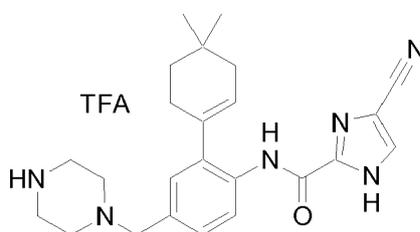
g) 4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-[4-(2-hydroxy-ethyl)-piperazin-1-ylmethyl]-phenyl]-amide trifluoroacetic acid salt

[0531] A suspension of 4-cyano-1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazole-2-carboxylic acid [4-{4-[2-(tert-butyl-dimethyl-silyloxy)-ethyl]-piperazin-1-ylmethyl}-2-(4,4-dimethyl-cyclohex-1-enyl)-phenyl]-amide (78.0 mg, 0.110 mmol) in DMF (2 mL) was heated to 60 °C and treated with tetrabutylammonium fluoride (TBAF) monohydrate (144 mg, 0.552 mmol). The mixture was stirred at 60 °C for 16 h, diluted with EtOAc (60 mL), and washed with brine (3 x 40 mL). The combined aqueous layers were extracted with EtOAc (1 x 20 mL). The combined organic layers were dried over MgSO_4 and concentrated in vacuo. Purification of the residue by RP-HPLC (C18) with 10-80 % CH_3CN in 0.1 % TFA/ H_2O over 25 min afforded the title compound (59.1 mg, 93 %) as a white solid. $^1\text{H-NMR}$ (CD_3OD ; 400 MHz): δ 8.27 (d, 1H, J = 8.8 Hz), 8.03 (s, 1H), 7.34 (dd, 1H, J = 8.8, 2.8 Hz), 7.27 (d, 1H, J = 2.8 Hz), 5.81-5.75 (m, 1H), 3.90-3.81 (m, 4H), 3.44-3.25 (br s, 4H), 3.23-3.16 (m, 2H), 3.10-2.85 (br s, 4H), 2.38-2.29 (m, 2H), 2.14-2.06 (m, 2H), 1.66-1.58 (m, 2H), 1.11 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for $\text{C}_{26}\text{H}_{34}\text{N}_6\text{O}_2$, 463.3 (M+H), found 463.2.

Example 151

4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-piperazin-1-ylmethyl-phenyl]-amide trifluoroacetic acid salt

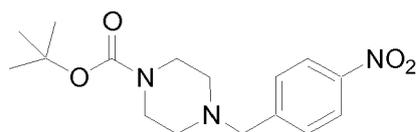
[0532]



a) 4-(4-Nitro-benzyl)-piperazine-1-carboxylic acid tert-butyl ester

[0533]

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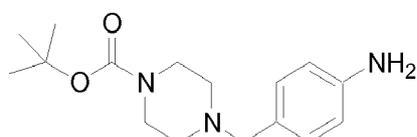
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[0534] A solution of piperazine-1-carboxylic acid tert-butyl ester (1.90 g, 10.2 mmol) and triethylamine (1.55 mL, 11.1 mmol) in CH₃CN (9 mL) was treated with 1-bromomethyl-4-nitro-benzene (2.00 g, 9.26 mmol) as a solution in CH₃CN (15 mL) at RT for 20 min. The mixture was concentrated in vacuo. The residue was taken up in CH₂Cl₂ (20 mL) and washed with water (1 x 20 mL). The aqueous layer was extracted with CH₂Cl₂ (2 x 20 mL), and the combined organic layers were washed with water (1 x 40 mL), dried over MgSO₄ and concentrated in vacuo. Purification of the residue on a 50-g Isolute SPE column on a FlashMaster system with 10-25 % EtOAc-hexane afforded the title compound (2.82 g, 95 %) as a white solid. Mass spectrum (ESI, m/z): Calcd. for C₁₆H₂₃N₃O₄, 322.2 (M+H), found 321.9.

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15 **b) 4-(4-Amino-benzyl)-piperazine-1-carboxylic acid tert-butyl ester**

[0535]



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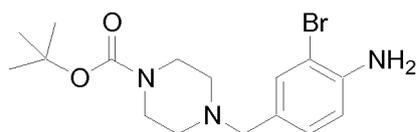
[0536] A solution of 4-(4-nitro-benzyl)-piperazine-1-carboxylic acid tert-butyl ester (2.82 g, 8.77 mmol) was hydrogenated on an H-Cube apparatus with a 5 % Pd/C cartridge under the following conditions: flow rate = 1 mL/min, heating column temperature = 30 °C, H₂ pressure = 40 bar. The material was passed through the column twice more in order to complete the reaction. Solvents were evaporated in vacuo. Purification of the residue on a 50-g Isolute SPE column on a FlashMaster system with 25-50 % EtOAc-hexane afforded the title compound (1.70 g, 67 %) as a yellow solid. Mass spectrum (ESI, m/z): Calcd. for C₁₆H₂₅N₃O₂, 292.2 (M+H), found 292.1.

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c) 4-(4-Amino-3-bromo-benzyl)-piperazine-1-carboxylic acid tert-butyl ester

[0537]



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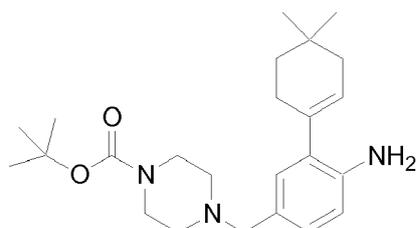
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[0538] The title compound was prepared as described in Example 150, step (d) using 4-(4-amino-benzyl)-piperazine-1-carboxylic acid tert-butyl ester (as prepared in the previous step). Mass spectrum (APCI, m/z): Calcd. for C₁₆H₂₄N₃O₂Br, 370.1/372.1 (M+H), found 370.3/372.0.

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d) 4-[4-Amino-3-(4,4-dimethyl-cyclohex-1-enyl)-benzyl]-piperazine-1-carboxylic acid tert-butyl ester

[0539]



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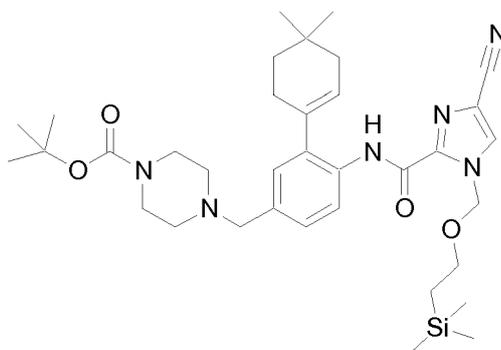
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[0540] The title compound was prepared as described in Example 150, step (e) using 4-(4-amino-3-bromo-benzyl)-piperazine-1-carboxylic acid tert-butyl ester (as prepared in the previous step). Mass spectrum (ESI, m/z): Calcd. for $C_{24}H_{37}N_3O_2$, 400.3 (M+H), found 400.1.

5 **e) 4-[4-{[4-Cyano-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-imidazole-2-carbonyl]-amino}3-(4,4-dimethyl-cyclohex-1-enyl)-benzyl]-piperazine-1-carboxylic acid tert butyl ester**

[0541]



[0542] The title compound was prepared as described in Example 150, step (f) using 4-[4-amino-3-(4,4-dimethyl-cyclohex-1-enyl)-benzyl]-piperazine-1-carboxylic acid tert-butyl ester (as prepared in the previous step). Mass spectrum (APCI, m/z): Calcd. for $C_{35}H_{52}N_6O_4Si$, 649.4 (M+H), found 649.2.

25 **f) 4-Cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-4-piperazin-1-ylmethyl-phenyl]-amide trifluoroacetic acid salt**

30 [0543] The title compound was prepared as described in Example 150, step (g) using 4-[4-{[4-cyano-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-imidazole-2-carbonyl]-amino}3-(4,4-dimethyl-cyclohex-1-enyl)-benzyl]-piperazine-1-carboxylic acid tert-butyl ester (as prepared in the previous step). 1H -NMR (CD_3OD ; 400 MHz): δ 8.31-8.23 (m, 1H), 8.03 (s, 1H), 7.37-7.29 (m, 1H), 7.29-7.23 (m, 1H), 5.81-5.74 (m, 1H), 3.85 (s, 2H), 3.39-3.28 (m, 4H), 3.04-2.85 (m, 4H), 2.38-2.27 (m, 2H), 2.14-2.03 (m, 2H), 1.66-1.56 (m, 2H), 1.11 (s, 6H). Mass spectrum (ESI, m/z): Calcd. for $C_{24}H_{30}N_6O$, 419.3 (M+H), found 419.1.

IV. Results

Fluorescence Polarization Competition Immunoassay

40 [0544] A fluorescence polarization competition immunoassay was used to measure compound inhibition of CSF-1R phosphorylation of tyrosine on a synthetic CSF-1R₅₅₅₋₅₆₈ peptide (SYEGNSYTFIDPTQ). The assay was performed in black 96-well microplates (Cat # 42-000-0117, Molecular Devices, Sunnyvale, CA). To each well, 5 μ L of compound (in 4% DMSO) were mixed with 2 μ L of 3.5 nM CSF-1R, 25 mM $MgCl_2$ in assay buffer (100 mM HEPES (hydroxyethyl-piperazineethanesulfonate), pH 7.5, 1 mM DTT (dithiothreitol), 0.01% Tween-20), and 2 μ L of 1540 μ M peptide in assay buffer. The kinase reaction was initiated by adding 1 μ L of 10 mM ATP in assay buffer. The final concentrations in the 10 μ L reaction mixture were 100 mM HEPES, pH 7.5, 1 mM DTT, 0.01% Tween-20, 2% DMSO, 308 μ M SYEGNSYTFIDPTQ, 1 mM ATP, 5 mM $MgCl_2$, and 0.7 nM CSF-1R. Positive and negative control wells were included on each plate, where 4% DMSO in assay buffer was substituted for the compound; in addition, positive control wells received 1.2 μ L of 50 mM EDTA (ethylenediaminetetraacetic acid) before the start of the reaction.

50 [0545] The plates were covered and incubated at room temperature for 80 min. Reactions were stopped by addition of 1.2 μ L of 50 mM EDTA. Each well then received 10 μ L of a 1:1:3 mixture of 10X anti-phosphotyrosine antibody, 10X PTK green tracer, and FP dilution buffer, respectively (Cat. # P2837, Invitrogen, Carlsbad, CA). The plates were covered, incubated for 30 min at room temperature, and the fluorescence polarization was read on an Analyst plate reader (Molecular Devices). Instrument settings were: 485 nm excitation, 530 nm emission, with a 505 nm cut-off filter; Z height: middle of well; G factor: 0.93. Under these conditions, the fluorescence polarization values for positive and negative controls were approximately 290 and 160, respectively, and were used to define 100% and 0% inhibition of the CSF-1R reaction. Reported IC_{50} values are the mean of three of at least three determinations.

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CSF-1-Driven Mouse Bone-Marrow Derived Macrophages Assay

[0546] Macrophages are derived by culturing mouse bone marrow in alpha-MEM supplemented with 10% FCS and 50 ng/ml recombinant mouse CSF-1 in bacteriologic dishes. On the sixth day, macrophages are detached from dishes, washed, and resuspended to 0.05 million cells/ml in alpha-MEM containing 10% FCS (fetal calf serum). One hundred ul of cell suspension are distributed per well into 96 well culture plates. Wells are further supplemented with the addition of 50 ul media containing 15 ng/ml CSF-1, 3 uM Indomethacin, and 3X of a dilution series of test compounds. The cells are cultured for 30 hrs at 37 degrees and 5%CO₂. During the final six hours, cultures are supplemented with an additional 30 ul of media containing a 1:500 dilution of bromodeoxyuridine (BrDU). At the end of the culture period, the plates are spun at 1000 RPM for 1 minute and 130 ul of media is removed with a pipet and replaced with 150 ul of fixative solution for 1 hour @ room temperature. The fixative is then dispelled from the plates and the plates allowed to air dry. Incorporation of BrDU into the fixed, dried cells is quantified using a specific ELISA.

[0547] Table 1 lists the assay results for representative compounds of the invention.

TABLE 1

Example	1 nM c-fms; peptide Pi assay - IC-50 (μM)	mCSF driven proliferation BMDM (Mouse) - IC-50 (μM)
1	0.0047	0.0579
2	0.0329	N/A
3	0.0061	0.077
4	0.0124	>0.3
5	0.0317	>0.15
6	0.0086	0.0239
7	0.0027	>0.05
8	0.0059	>0.3
9	0.079	N/A
10	0.0017	0.0246
11	>0.06	N/A
12	0.0044	0.0442
13	0.008	>0.3
14	0.0093	0.059
15	0.0011	0.0058
16	0.0033	0.0085
17	0.0014	0.005
18	0.0018	0.0148
19	0.0072	0.04
20	0.00044	0.0113
21	0.0026	0.0047
21	0.0017	0.0048
22	0.00094	0.0119
22		0.0143
22		0.02
22		0.0129
23	0.0029	0.0033
23	0.0051	0.0031
23		0.0033
24	0.0012	0.0072
25	0.00774	0.1014

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(continued)

Example	1 nM c-fms; peptide Pi assay - IC-50 (μM)	mCSF driven proliferation BMDM (Mouse) - IC-50 (μM)	
5		0.0059	
	0.0032	0.0049	
26	0.0037	0.04613	
	0.0036	0.046	
		0.0059	
10		0.085	
27	0.0045	0.042	
28	0.0094	0.0394	
29	0.0029	0.0317	
30	0.0056	0.0226	
15	31	0.0026	0.0209
	32	0.0128	0.0482
	33	>0.06	N/A
	34	0.373	N/A
20	35	>0.5	N/A
	36	>0.5	N/A
	37	~0.3	N/A
	38	>0.06	N/A
	39	>0.06	N/A
25	40	0.0279	N/A
	41	0.0082	0.3205
			0.0027
	42	0.00143	0.0012
30	43	N/A	N/A
			0.01636
	44	0.0046	0.0146
	45	0.0006	0.0032
	46	0.0025	>0.3
35	47	0.0015	0.03388
		0.0039	>0.1
	48	0.0053	>1
	49	0.026	>0.3
40	50	0.06	N/A
	51	0.0362	N/A
		0.0056	0.001
		0.0008	0.0033
	53	0.0029	>0.1
45	54	0.0024	>0.1
	55	0.05@0.002-2 (10 nM c-fms auto-Pi assay - IC-50)	N/A
	60	0.0008	0.0026
	61	0.0019	0.024
50	62	0.00088	0.0057
	63	0.00069	0.0087
	64	0.00093	0.2
	65	N/A	0.0081
	66	0.0039	0.044
55	67	0.0013	0.018
	68	0.0016	0.0093
	69	0.00051	0.0019

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(continued)

Example	1 nM c-fms; peptide Pi assay - IC-50 (μ M)	mCSF driven proliferation BMDM (Mouse) - IC-50 (μ M)
5	70	0.14
	71	0.033
	72	0.019
	73	0.0088
	74	0.0015
10	75	0.0017
	76	0.00068
	77	0.0013
	78	N/A
15	79	0.002
	80	0.0012
	138	0.0013
20	139	0.0016
	140	>0.1
	141	0.018
	142	0.008
25	143	0.0057
	144	0.036
	145	0.0035
	146	0.002
30	147	0.00064
	148	0.0017
	149	0.0015
35	150	0.00075
	151	0.00082

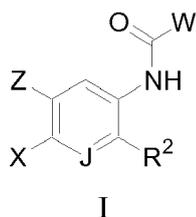
40 **[0548]** The term "N/A" in Table 1 means "not available".
[0549] While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.
45 **[0550]** All publications disclosed in the above specification are hereby incorporated by reference in full.

Embodiments

[0551]

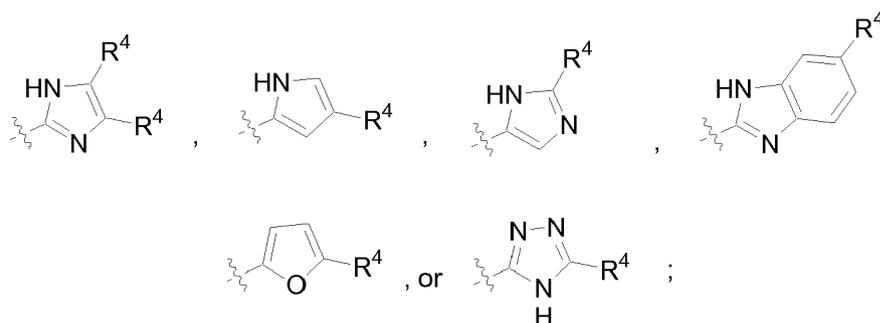
50 1. The compounds of Formula I

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

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wherein each R^4 is independently H, F, Cl, Br, I, OH, OCH₃, OCH₂CH₃, SC₍₁₋₄₎alkyl, SOC₍₁₋₄₎akyl, SO₂C₍₁₋₄₎alkyl, -C₍₁₋₃₎alkyl, CO₂R^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, -CH₂OH, or -CH₂CH₂OH;

R² is cycloalkyl, spiro-substituted cycloalkenyl, heterocyclyl, spirosubstituted piperidinyl, thiophenyl, dihydro-sulfonopyranyl, 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 CH₃;

J is CH, or N;

X is -C₍₁₋₆₎alkylR¹, alkenyl, propenyl-NA¹A², -CH=CH-CO₂R^a wherein said CH=CH bond includes both E and Z stereochemistry, -C₍₁₋₄₎alkylR³R^{4a}, or -CH₂-heteroaryl-C₍₁₄₎alkyl-R¹;

wherein:

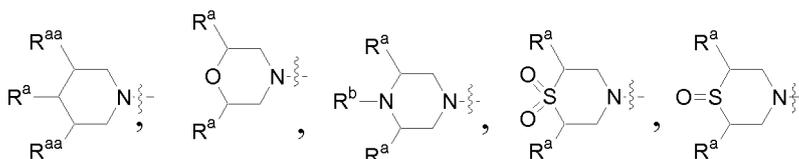
R¹ is -CN, -SO₂NA¹A², -SO₂R^a, -SCH₂CH₂NA¹A², -SOCH₂CH₂NA¹A², -SO₂CH₂CH₂NA¹A², -S-C(O)C₍₁₋₄₎alkyl, -S-CH₂-4-methoxy phenyl, -OC₍₁₄₎alkylNA¹A², -NA¹A², -NHCO₂R^a, -NHCOR^a, -NHCO₂CH₂CH₂NA¹A², -NHCOCH₂CH₂NA¹A², -CONH₂, -CONHCH₂CH₂CH₂OH, -CONHCH₂CH₂N(C₍₁₋₄₎alkyl)₂, -NHCONH₂, -NHCONHCH₂CH₂OH, -NHCOCONH₂, -NR^aCH₂CH₂NA¹A², CO₂R^a, pyridyl, -OCH₂CH₂OR^a, -OCH₂CH₂OCH₂CH₂NA¹A², -OCH₂CH₂NA¹CH₂CH₂OR^a,

-NA¹CH₂CH₂OCH₂CH₂OR^a, -OCOR^a, or -CH₂OCOCH₃;

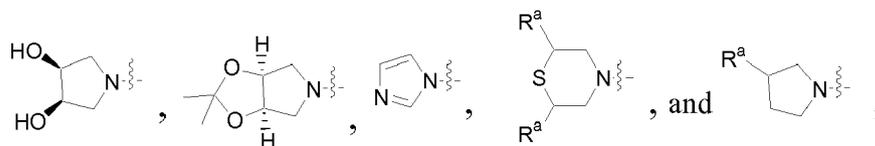
A¹ is H or -C₍₁₋₄₎alkyl;

A² is -C₍₁₋₄₎alkyl, -CH₂CH₂OR^a, -COR^a, -CH₂CH₂SC₍₁₋₄₎alkyl, -CH₂CH₂SOC₍₁₋₄₎alkyl, pyridyl, 2-methyl pyridyl, -CH₂CH₂OCH₂CH₂OR^a, or -CH₂CH₂SO₂C₍₁₋₄₎alkyl;

alternatively, A¹ and A² may be taken together with their attached nitrogen to form a heterocyclic ring selected from the following:



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wherein:

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

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

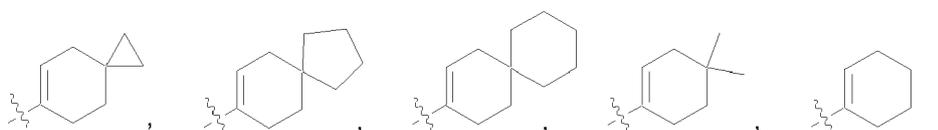
R^b is H, $-C_{(1-4)}$ alkyl, alkoxyether, $-C(O)C_{(1-4)}$ alkyl, $-C_{(1-4)}$ alkyl-OH, $-C_{(1-4)}$ alkyl-O- $C_{(1-4)}$ alkyl, $-C_{(1-4)}$ alkyl-C(O)- $C_{(1-4)}$ alkyl, $-C_{(14)}$ alkylC(O)OH, $-C_{(1-4)}$ alkylC(O)ONa, or $-CH_2C(O)C_{(1-4)}$ alkyl; and R^3 and R^{4a} are independently $-CH_2OH$, $-OCH_3$, $-CH_2OCH_3$, $-CO_2H$, $-CO_2C_{(14)}$ alkyl, $OC(O)C_{(1-4)}$ alkyl, or $-OH$.

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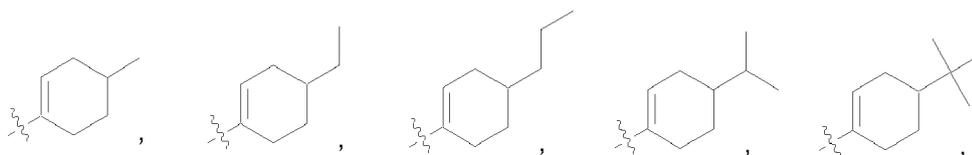
2. A compound of embodiment 1, wherein:

$\text{à}R^2$ is

20

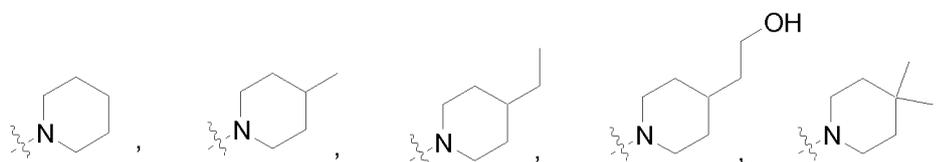


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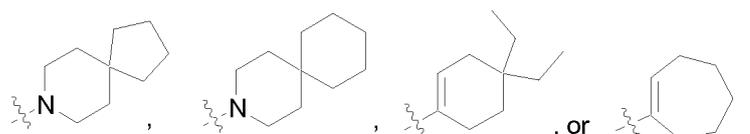


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X is $-C_{(1-6)}$ alkyl R^1 , alkenyl, propenyl- NA^1A^2 , $-CH=CH-CO_2R^a$, $-C_{(1-4)}$ alkyl R^3R^{4a} , or $-CH_2$ -heteroaryl- $C_{(1-4)}$ alkyl- R^1 ;

wherein:

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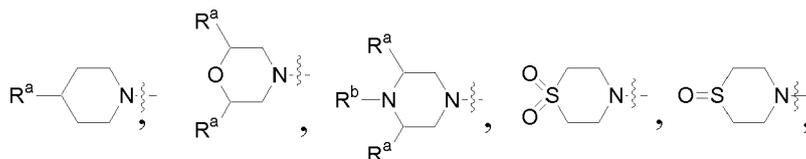
R^1 is $-CN$, $-SO_2NA^1A^2$, $-SO_2R^a$, $-SCH_2CH_2NA^1A^2$, $-SOCH_2CH_2NA^1A^2$, $-SO_2CH_2CH_2NA^1A^2$, $-S-C(O)C_{(1-4)}$ alkyl, $-S-CH_2-4$ -methoxy phenyl, $-OC_{(14)}$ alkyl NA^1A^2 , $-NA^1A^2$, $-NHCOCH_3$, $-CONH_2$, $-CONHCH_2CH_2CH_2OH$, $-CONHCH_2CH_2N(C_{(1-4)})_2$, $-NHCONH_2$, $-NHCONHCH_2CH_2OH$, $-NHCOCNH_2$, $-NR_aCH_2CH_2NA^1A^2$, $-CO_2R^a$, pyridyl, $-OCOCH_3$, or $-CH_2OCOCH_3$;

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

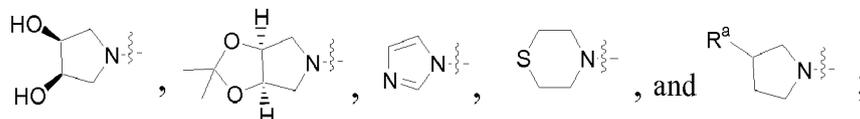
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A^2 is $-C_{(1-4)}$ alkyl, $-CH_2CH_2OR^a$, $-COR^a$, $-CH_2CH_2SC_{(1-4)}$ alkyl, $-CH_2CH_2SOC_{(1-4)}$ alkyl, pyridyl, 2-methyl pyridyl, or $-CH_2CH_2SO_2C_{(14)}$ alkyl; alternatively, A^1 and A^2 may be taken together with their attached nitrogen to form a heterocyclic ring selected from the following:

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wherein:

R³ is H or C₍₁₋₄₎alkyl;

R^b is H, -C₍₁₋₄₎alkyl, alkoxyether, -C(O)C₍₁₋₄₎alkyl, -C₍₁₋₄₎alkyl-OH, -C₍₁₋₄₎alkyl-O-C₍₁₋₄₎alkyl, -C₍₁₋₄₎alkyl-C(O)O-C₍₁₋₄₎alkyl, -C₍₁₄₎alkylC(O)OH, -C₍₁₋₄₎alkylC(O)ONa, or -CH₂C(O)C₍₁₋₄₎alkyl; and

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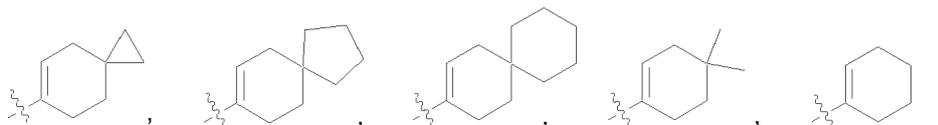
R³ and R^{4a} are independently -CH₂OH, -OCH₃, -CH₂OCH₃, -CO₂H, -CO₂C₍₁₋₄₎alkyl, -OC(O)C₍₁₋₄₎alkyl, or -OH.

3. A compound of embodiment 2 wherein:

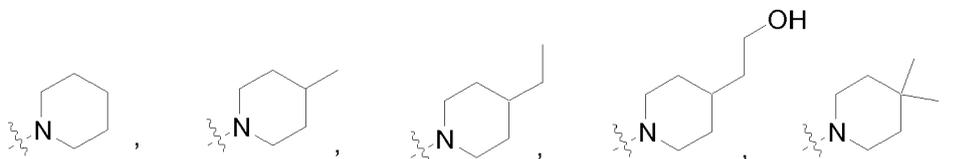
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R² is

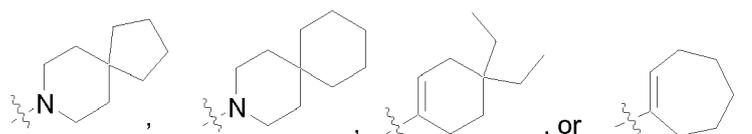
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X is -C₍₁₋₅₎alkylR¹, alkenyl, propenyl-NA¹A², -CH=CH-CO₂R^a, -C₍₁₋₄₎alkylR³R^{4a}, or -CH₂-heteroaryl-C₍₁₋₄₎alkyl-R¹;

wherein:

50

R¹ is -CN, -SO₂NA¹A², -SO₂R^a, -SCH₂CH₂NA¹A², -SOCH₂CH₂NA¹A², -SO₂CH₂CH₂NA¹A², -S-C(O)C₍₁₋₄₎alkyl, -S-CH₂-4-methoxy phenyl, -OC₍₁₄₎alkylNA¹A², -NA¹A², -NH₂SO₂CH₃, -NHCOCH₃, -CONH₂, -CONHCH₂CH₂CH₂OH, CONHCH₂CH₂N(C₍₁₋₄₎alkyl)₂, -NHCONH₂, -NHCONHCH₂CH₂OH, -NHC(O)CONH₂, -NR_aCH₂CH₂NA¹A², -CO₂R^a, pyridyl, -OCOCH₃, or -CH₂OCOCH₃;

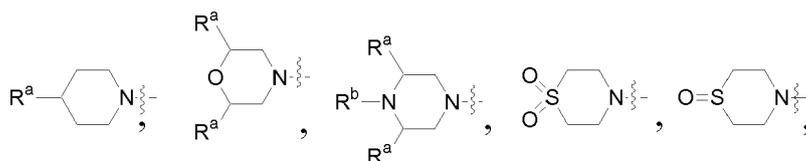
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A¹ is H or -C₍₁₋₄₎alkyl;

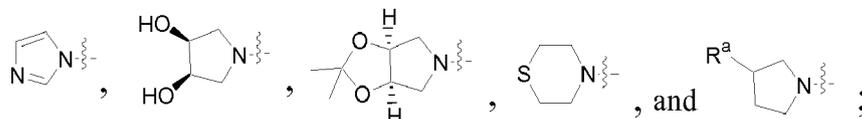
A² is -C₍₁₋₄₎alkyl, -CH₂CH₂OR^a, -COR^a, -CH₂CH₂SC₍₁₋₄₎alkyl, -CH₂CH₂SOC₍₁₋₄₎alkyl, pyridyl, 2-methyl pyridyl, or -CH₂CH₂SO₂C₍₁₄₎alkyl;

alternatively, A¹ and A² may be taken together with their attached nitrogen to form a heterocyclic ring selected from the following:

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wherein:

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

R^b is H, $-C_{(1-4)}$ alkyl, alkoxyether, $-C(O)C_{(1-4)}$ alkyl, $-C_{(1-4)}$ alkyl-OH, $-C_{(1-4)}$ alkyl-O- $C_{(1-4)}$ alkyl, $-C_{(1-4)}$ alkyl-C(O)- $C_{(1-4)}$ alkyl, $-C_{(14)}$ alkylC(O)OH, $-C_{(1-4)}$ alkylC(O)ONa, or $-CH_2C(O)-C_{(1-4)}$ alkyl; and

20

R^3 and R^{4a} are independently $-CH_2OH$, $-OCH_3$, $-CH_2OCH_3$, $-CO_2H$, $-CO_2C_{(1-4)}$ alkyl, $OC(O)C_{(1-4)}$ alkyl, or $-OH$.

4. A compound of embodiment 3 wherein:

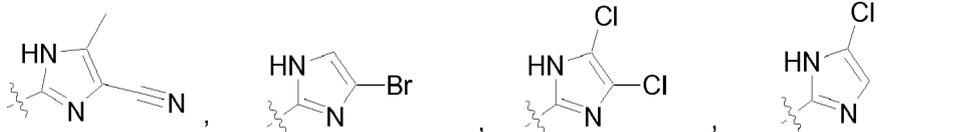
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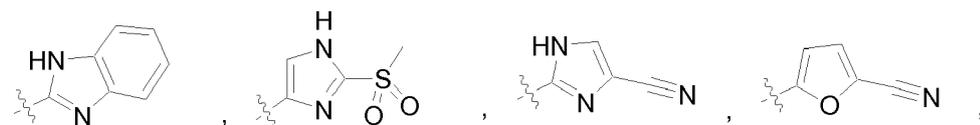
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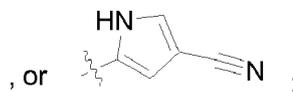
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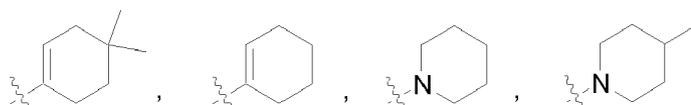
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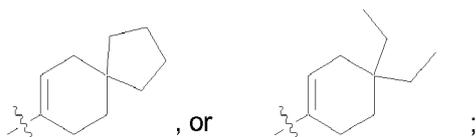
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R^2 is

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Z is H;

X is $-C_{(1-5)}$ alkylR¹, $-\text{CH}=\text{CH}-\text{CO}_2\text{H}$ wherein said $\text{CH}=\text{CH}$ bond has *E* stereochemistry, $-C_{(1-4)}$ alkylR³R^{4a}, propenyl-NA¹A², or propenyl;

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wherein:

R¹ is $-\text{SO}_2\text{NA}^1\text{A}^2$, $-\text{S}-\text{C}(\text{O})\text{CH}_3$, $-\text{S}-\text{CH}_2-4\text{-methoxy phenyl}$, $-\text{OC}_{(1-4)}$ alkylNA¹A², $-\text{NA}^1\text{A}^2$, $-\text{NHCH}_2\text{CH}_2\text{NA}^1\text{A}^2$, $-\text{NH}\text{SO}_2\text{CH}_3$, $-\text{NHCOCH}_3$, $-\text{CONH}_2$, $-\text{CONHCH}_2\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CONHCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, $-\text{NHCONH}_2$, $-\text{NHCONHCH}_2\text{CH}_2\text{OH}$, $-\text{NHCOCNH}_2$, $-\text{CO}_2\text{R}^a$, or pyridyl;

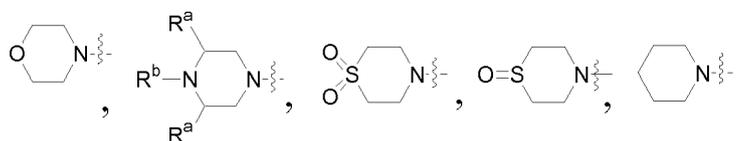
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A¹ is H or $-\text{C}_{(1-4)}$ alkyl;

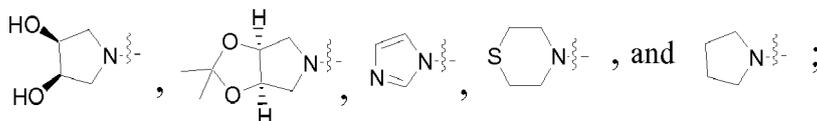
A² is $-\text{C}_{(1-4)}$ alkyl, $-\text{CH}_2\text{CH}_2\text{OR}^a$, $-\text{COCH}_3$, $-\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{CH}_2\text{SC}_{(1-4)}$ alkyl, pyridyl, 2-methyl pyridyl, or $-\text{CH}_2\text{CH}_2\text{SO}_2\text{C}_{(1-4)}$ alkyl;

alternatively, A¹ and A² may be taken together with their attached nitrogen to form a heterocyclic ring selected from the following:

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wherein:

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R³ is H or $\text{C}_{(1-4)}$ alkyl;

R^b is H, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{C}(\text{O})\text{OCH}_2\text{CH}_3$, $-\text{CH}_2\text{C}(\text{O})\text{OH}$, $-\text{CH}_2\text{C}(\text{O})\text{ONa}$, $-\text{C}(\text{O})\text{CH}_3$, or $-\text{C}_{(1-4)}$ alkyl; and

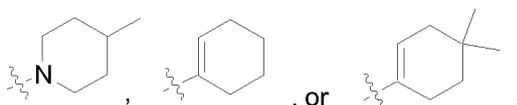
R³ and R^{4a} are independently $-\text{OCH}_3$, $-\text{CH}_2\text{OCH}_3$, $-\text{CO}_2\text{H}$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{OH}$.

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5. A compound of embodiment 4 wherein:

R² is

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X is $-\text{CH}_2\text{R}^1$, $-\text{CH}_2\text{CH}_2\text{R}^1$, $-\text{C}(\text{CH}_3)_2\text{R}^1$, $-\text{CH}=\text{CH}-\text{CO}_2\text{H}$ wherein said $\text{CH}=\text{CH}$ bond has *E* stereochemistry, $-C_{(1-4)}$ alkylR³R^{4a}, propenyl-NA¹A², or propenyl;

wherein:

55

R¹ is $-\text{SO}_2\text{NA}^1\text{A}^2$, $-\text{S}-\text{C}(\text{O})\text{CH}_3$, $-\text{S}-\text{CH}_2-4\text{-methoxy phenyl}$, $-\text{OCH}_2\text{CH}_2\text{NA}^1\text{A}^2$, $-\text{NA}^1\text{A}^2$, $-\text{NHCH}_2\text{CH}_2\text{NA}^1\text{A}^2$, $-\text{NH}\text{SO}_2\text{CH}_3$, $-\text{NHCOCH}_3$, $-\text{CONH}_2$, $-\text{CONHCH}_2\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CONHCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, $-\text{NHCONH}_2$, $-\text{NHCONHCH}_2\text{CH}_2\text{OH}$, $-\text{NHCOCNH}_2$, or $-\text{CO}_2\text{R}^a$;

A¹ is H or $-\text{C}_{(1-4)}$ alkyl;

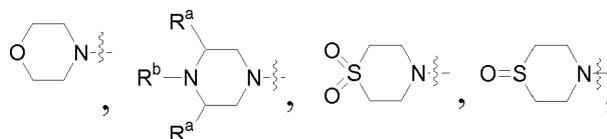
A² is $-\text{C}_{(1-4)}$ alkyl, $-\text{C}(\text{O})\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{SCH}_3$, pyridyl, 2-methyl pyridyl, or

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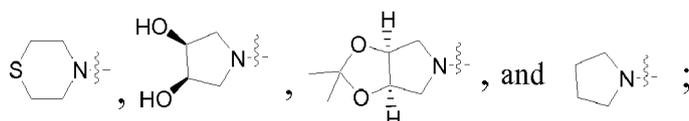
-CH₂CH₂SO₂CH₃;

alternatively, A¹ and A² may be taken together with their attached nitrogen to form a heterocyclic ring selected from the following:

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wherein:

R^a is H, CH₃, or -CH₂CH₃;

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R^b is H, CH₂CH₂OH, -CH₂CH₂OCH₃, -CH₂C(O)OCH₂CH₃, -CH₂C(O)OH, -CH₂C(O)ONa, CH₂CH₃, C(O)CH₃, or CH₃; and

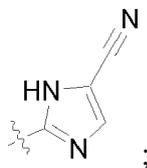
R³ and R^{4a} are independently, -OCH₃, -CH₂OCH₃, -CO₂H, -OC(O)CH₃, or -OH.

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6. A compound of embodiment 1, wherein

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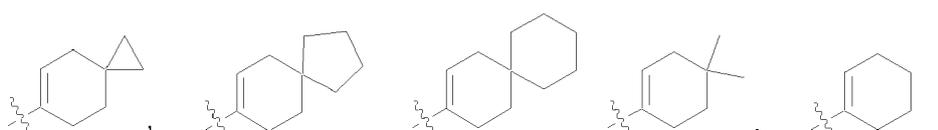
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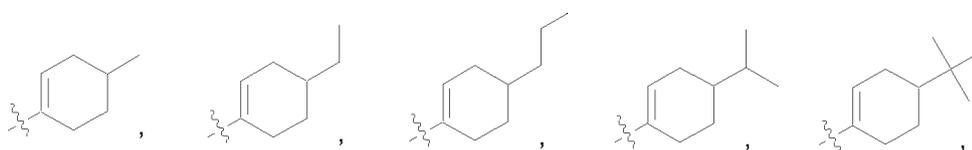
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R² is

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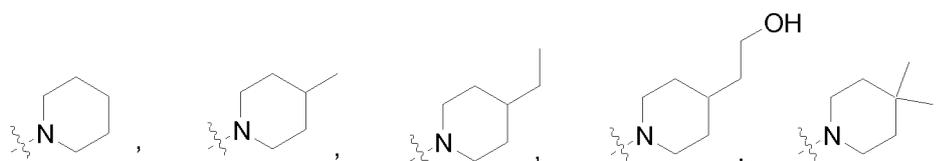


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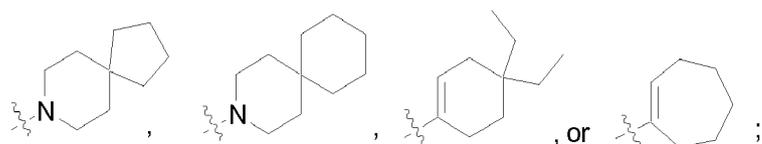
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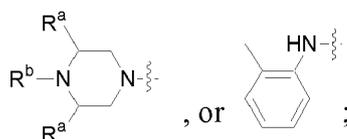
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Z is H;

X is $-C_{(1-6)}\text{alkyl}R^1$, or propenyl- NA^1A^2 , wherein:

R^1 is $-NA^1A^2$, $-S-C(O)C_{(1-4)}\text{alkyl}$, or $-S-CH_2-4\text{-methoxy phenyl}$, wherein A^1 and A^2 are taken together with their attached nitrogen to form a heterocyclic ring selected from

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wherein:

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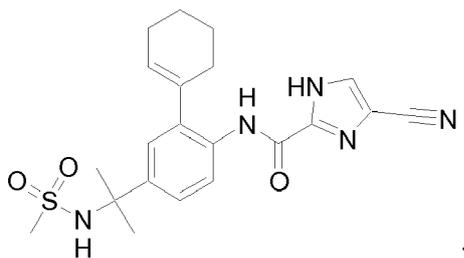
R^a is H or $C_{(1-4)}\text{alkyl}$; and

R^b is $-C_{(1-4)}\text{alkyl-OH}$, $-C_{(1-4)}\text{alkyl-O-C}_{(1-4)}\text{alkyl}$, $-C_{(1-4)}\text{alkyl-C(O)O-C}_{(1-4)}\text{alkyl}$, $-C_{(1-4)}\text{alkylC(O)OH}$, or $-C_{(1-4)}\text{alkylC(O)ONa}$

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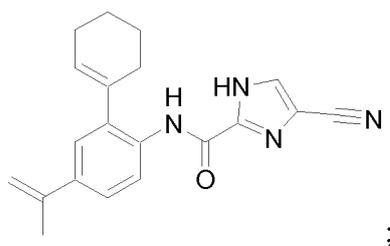
7. A compound selected from the group consisting of:

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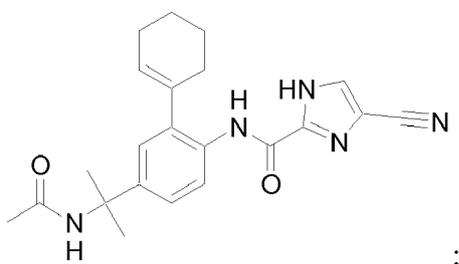
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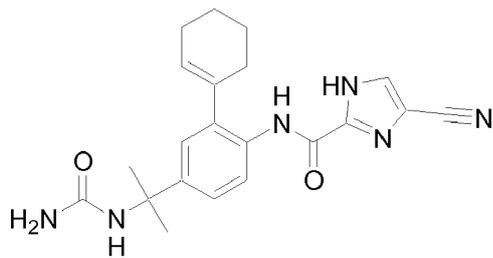
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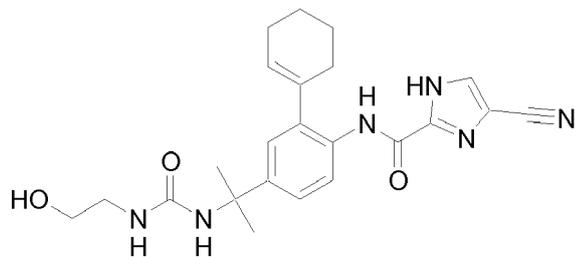
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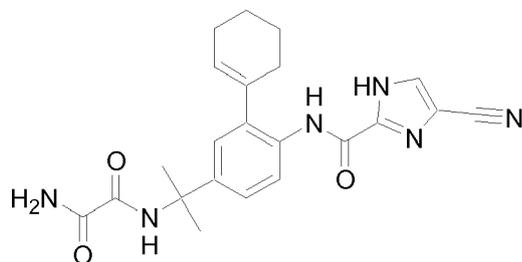
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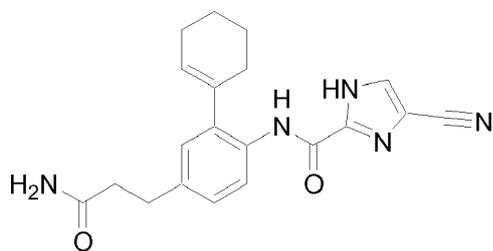
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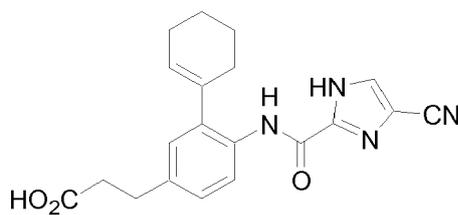
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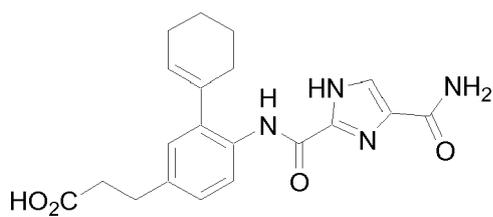
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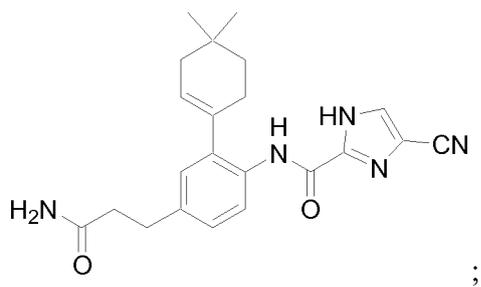
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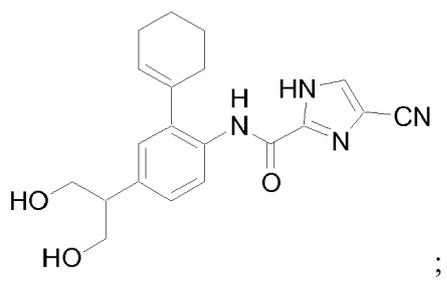
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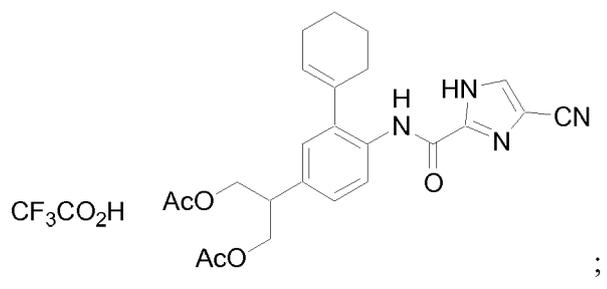
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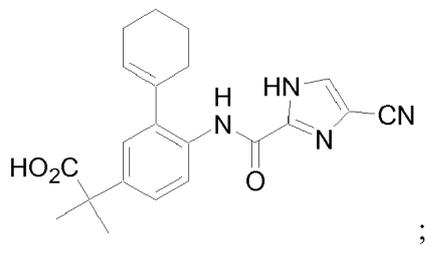
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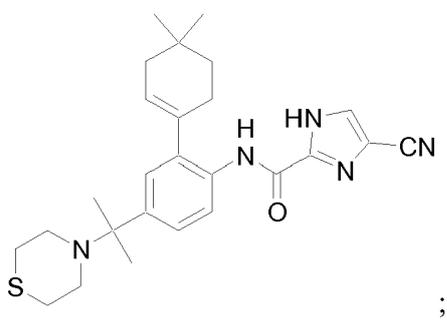
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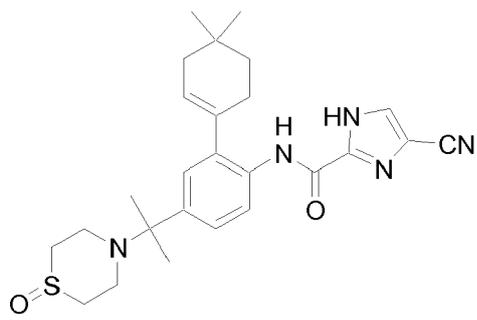
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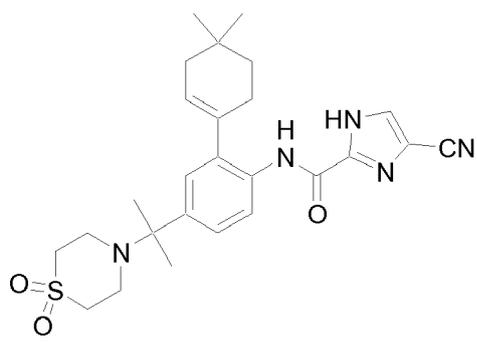
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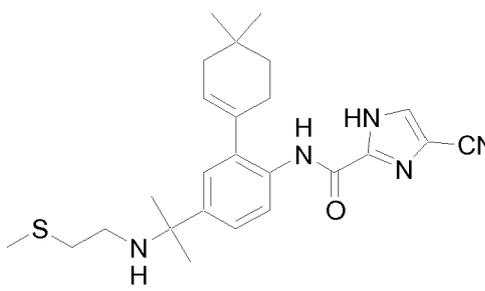
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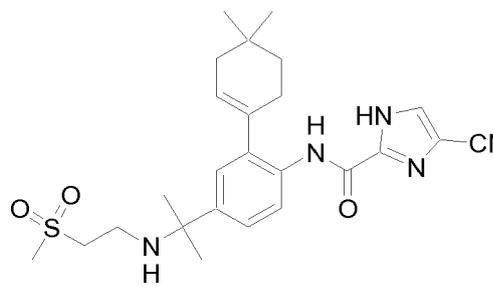
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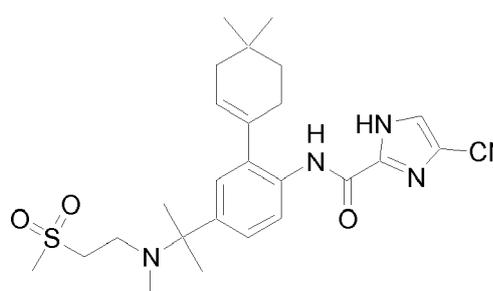
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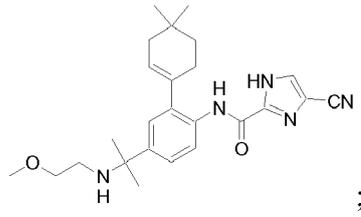
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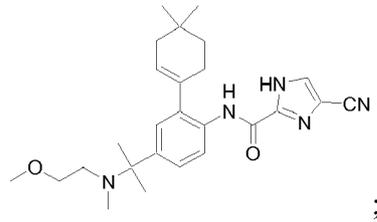
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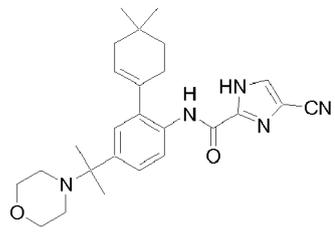


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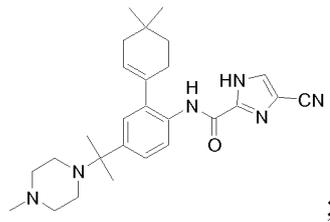
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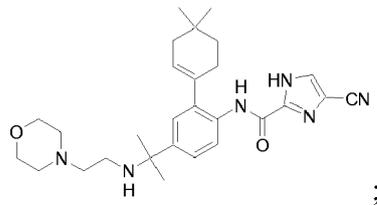
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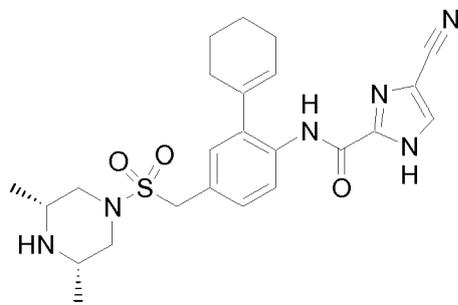
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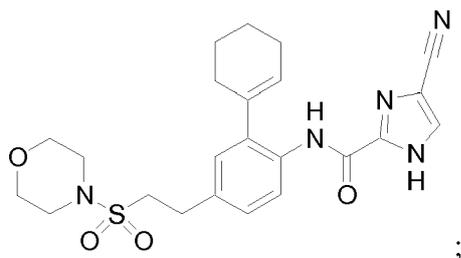
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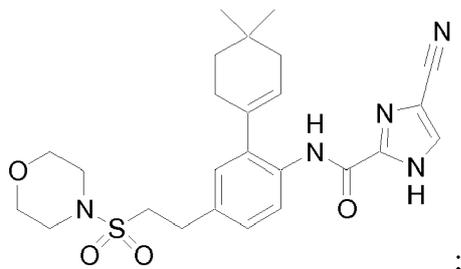


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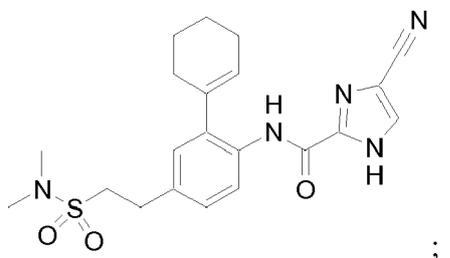
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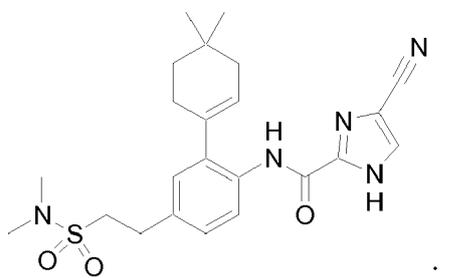
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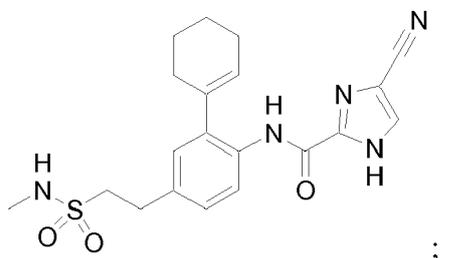
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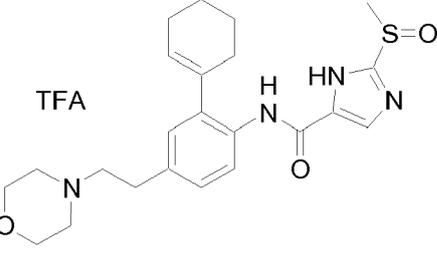
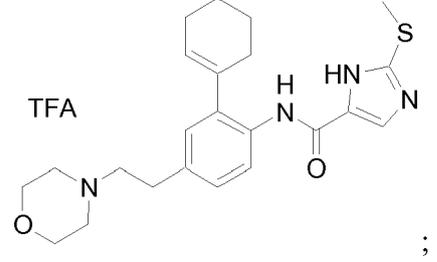
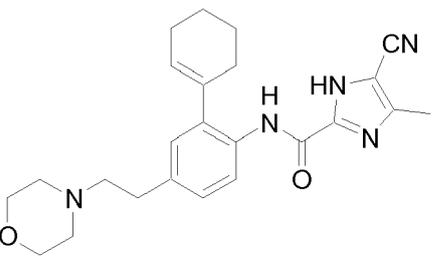
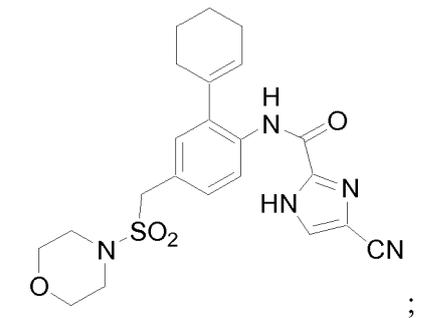
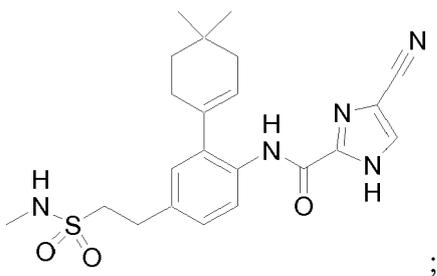
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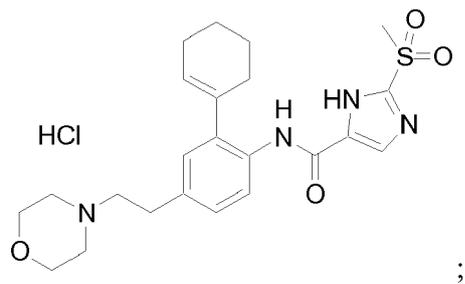
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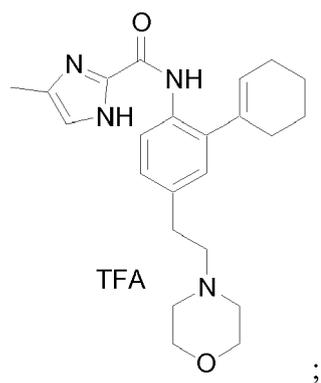


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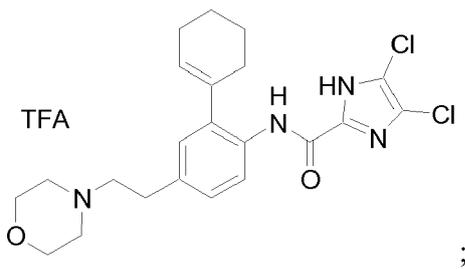
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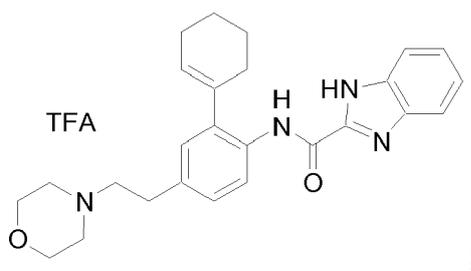
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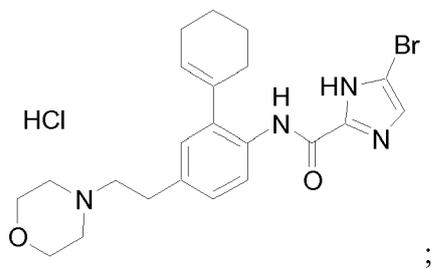
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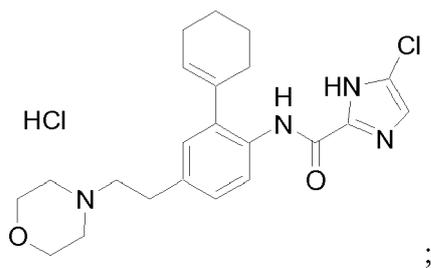
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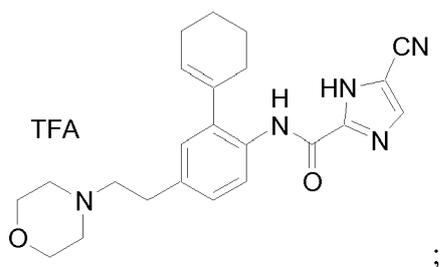


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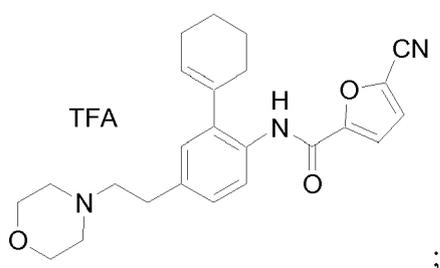
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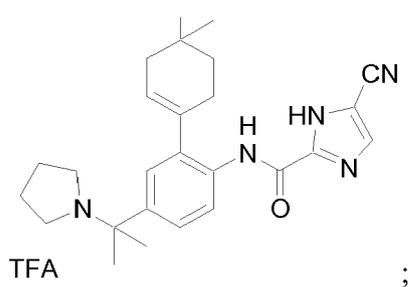
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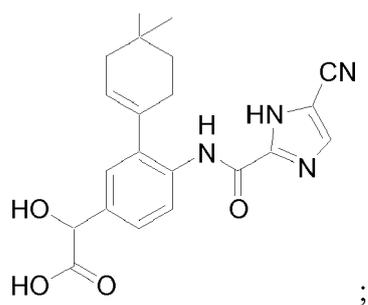
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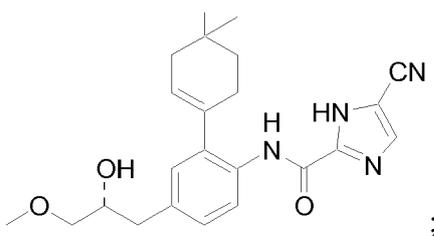


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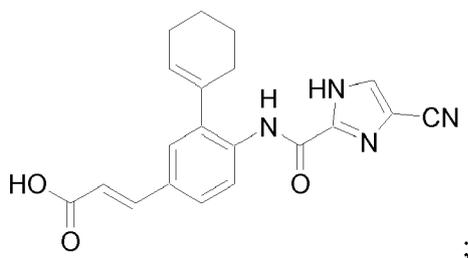
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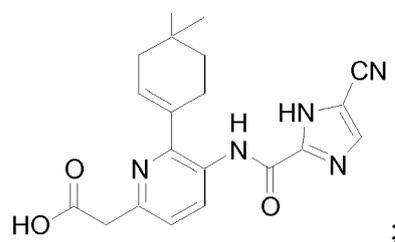


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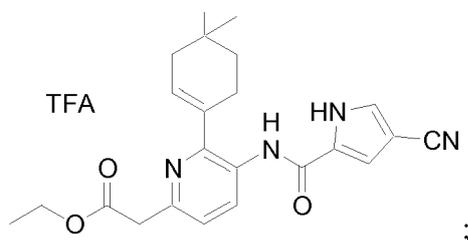
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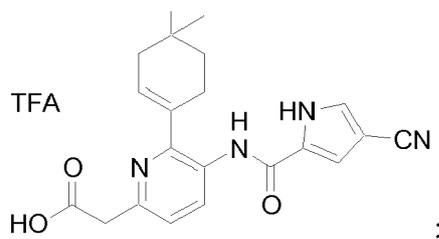
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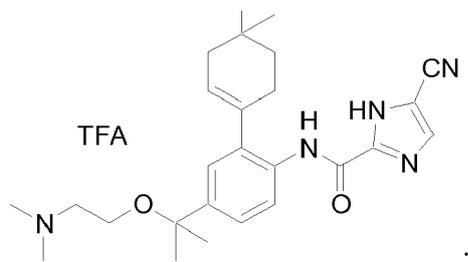
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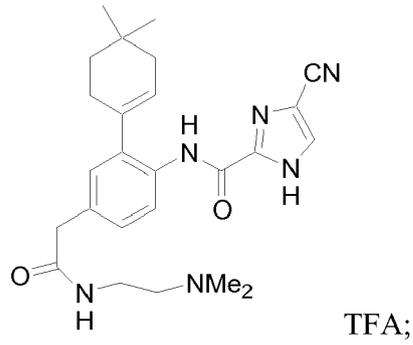
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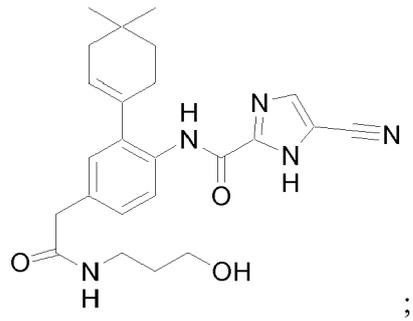
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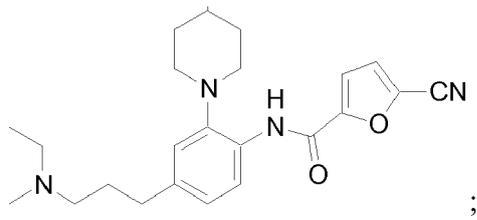
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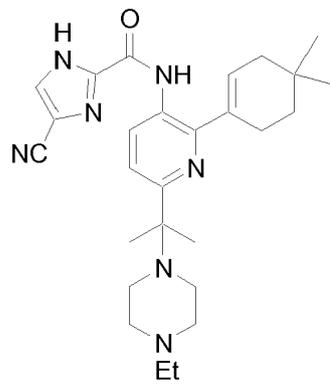
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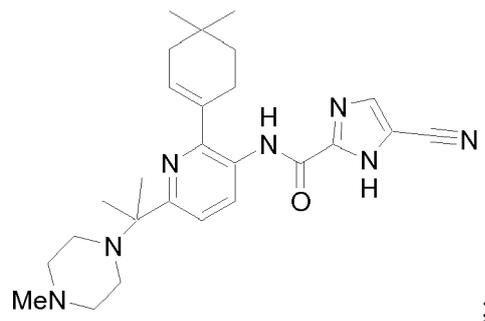
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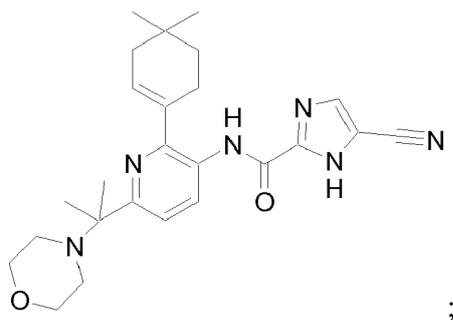


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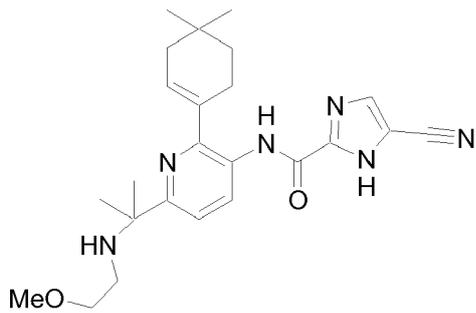


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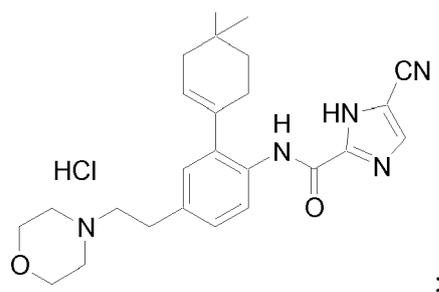
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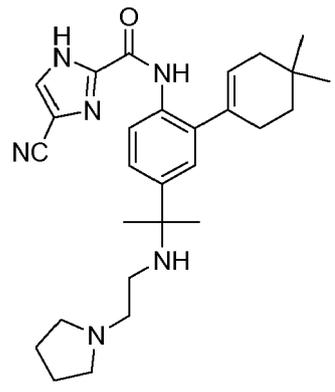
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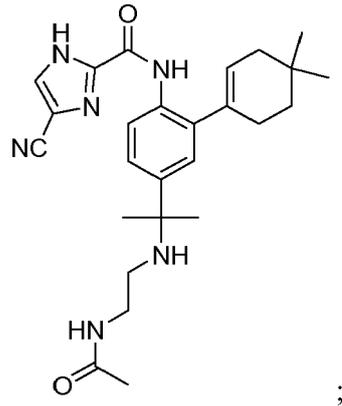


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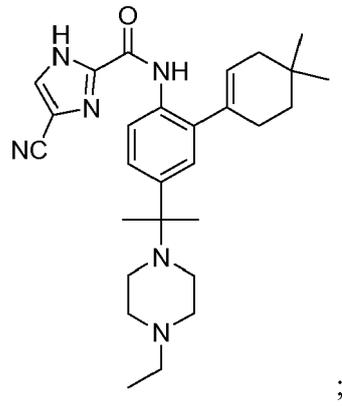
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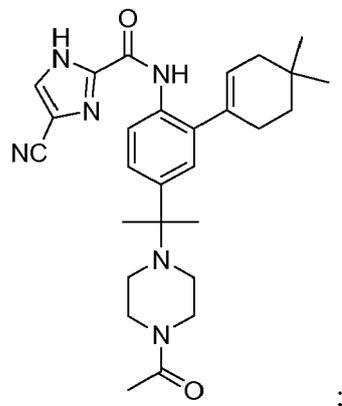
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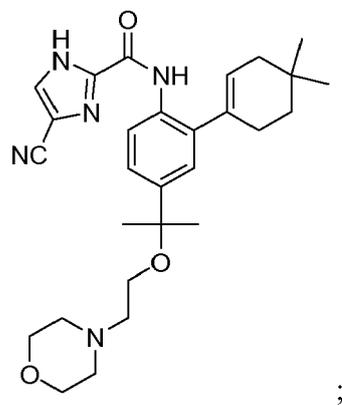
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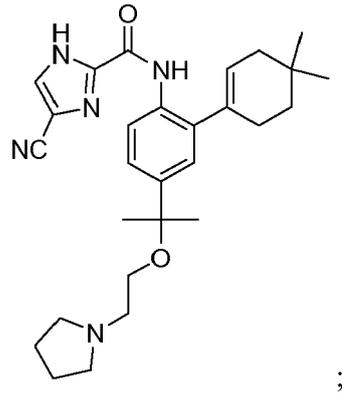
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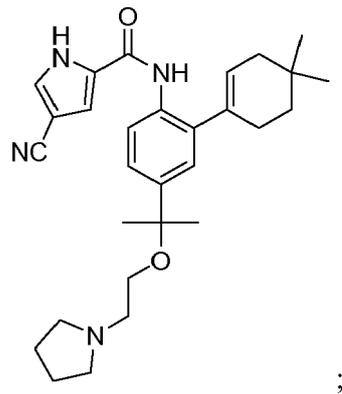
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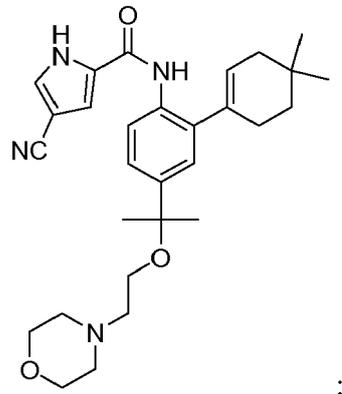
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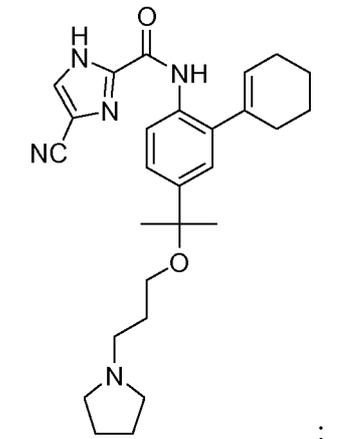
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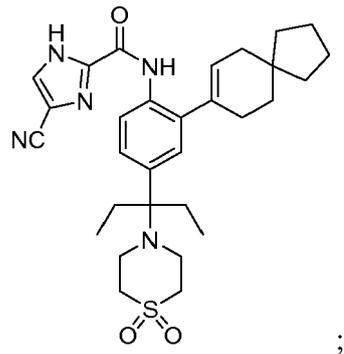


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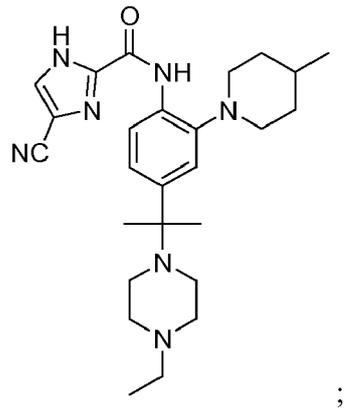
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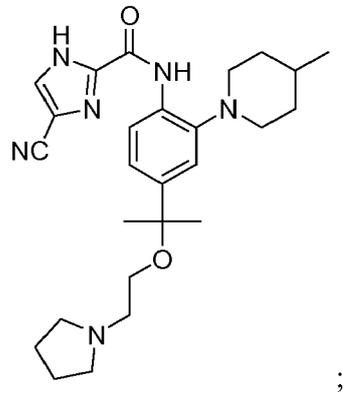
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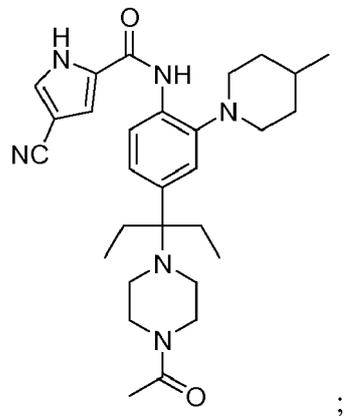
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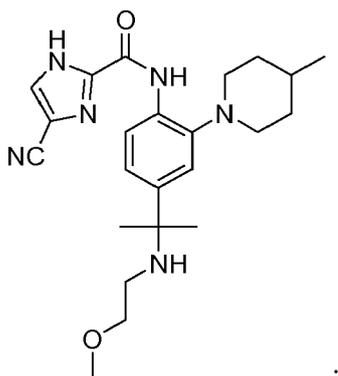
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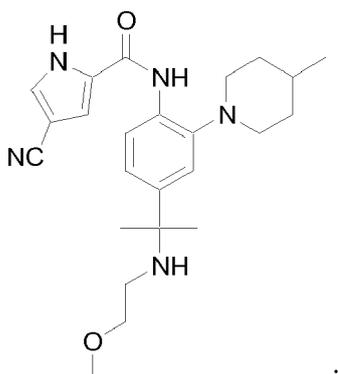
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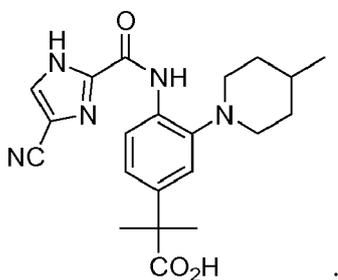


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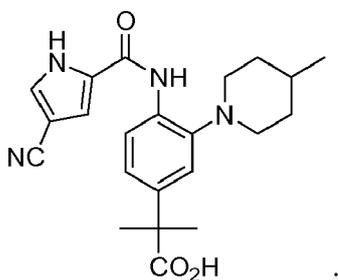
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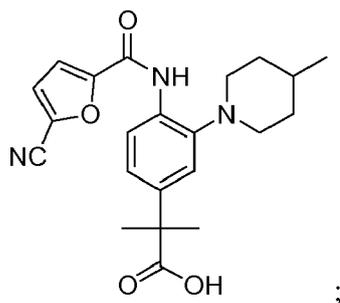
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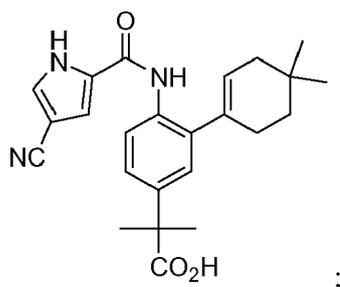
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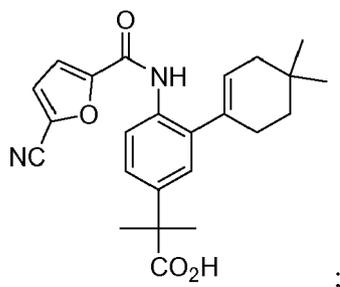
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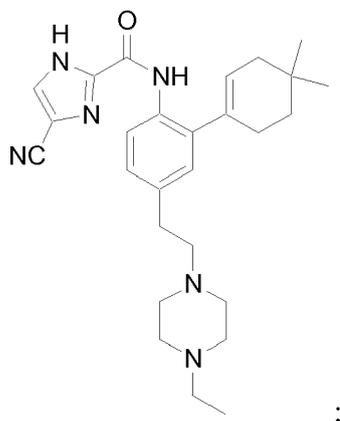
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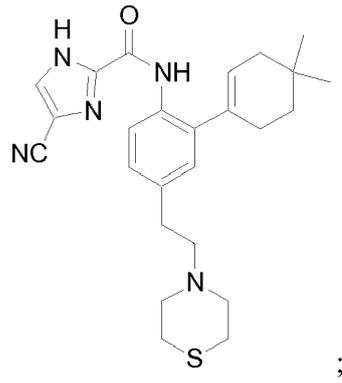
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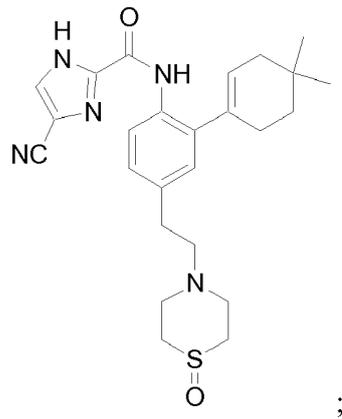
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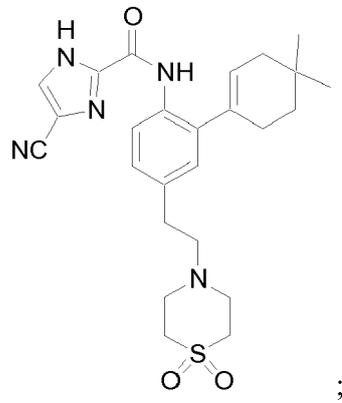
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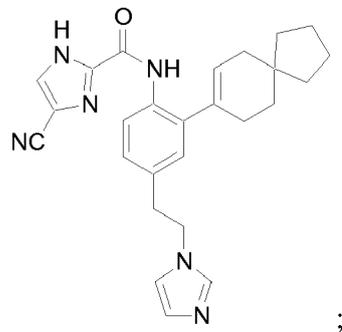
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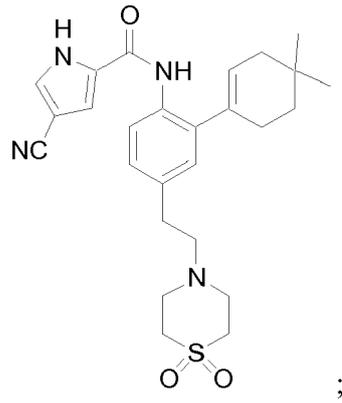
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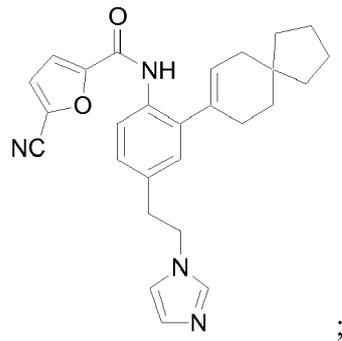
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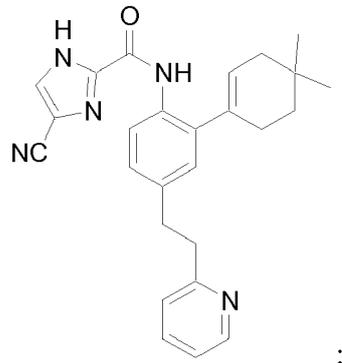
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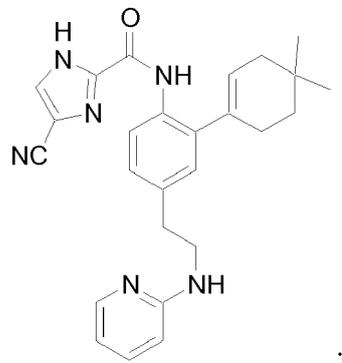
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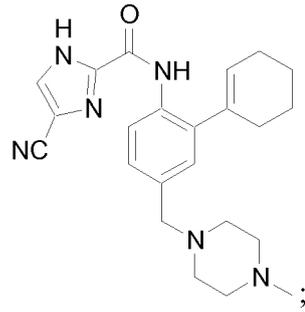
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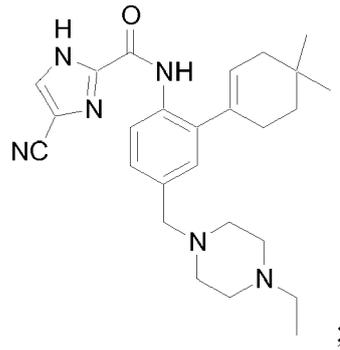
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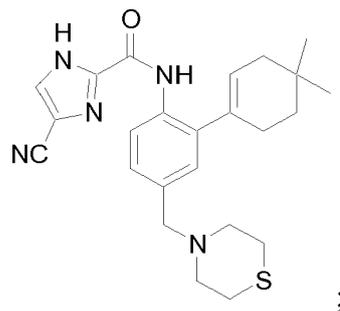
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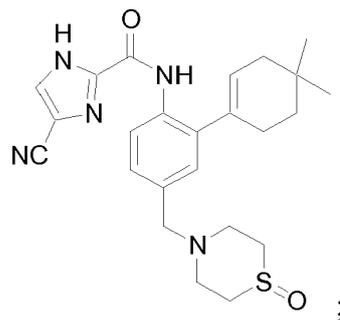
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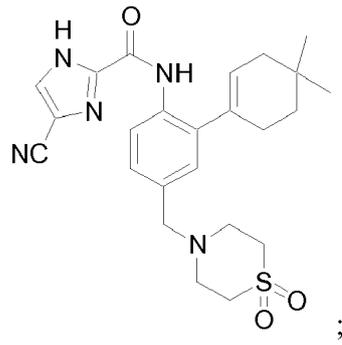


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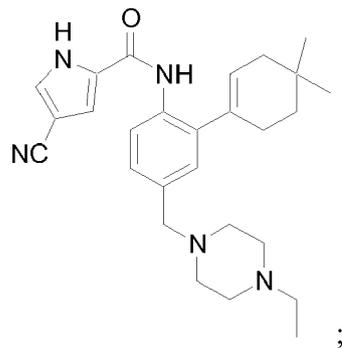
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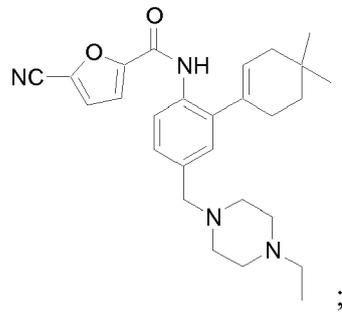
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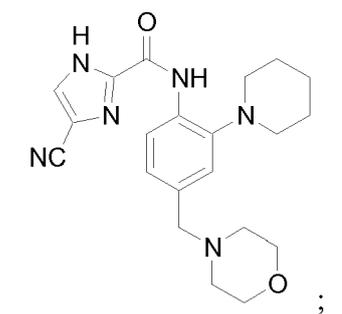
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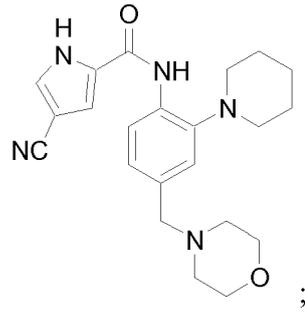


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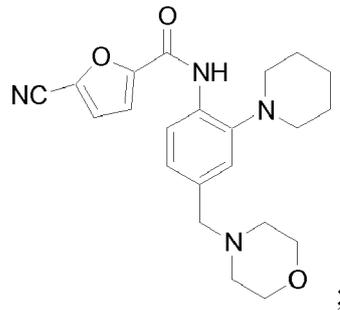
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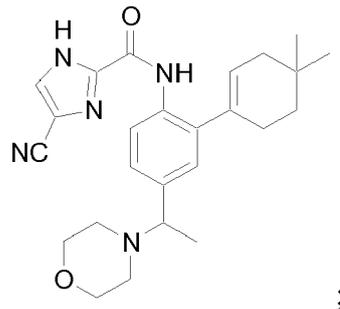
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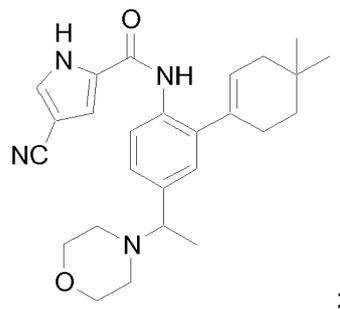
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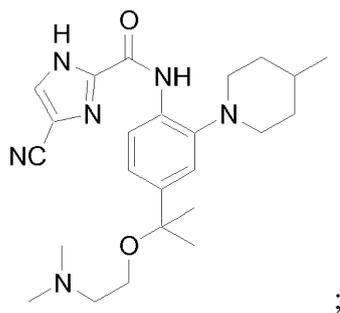


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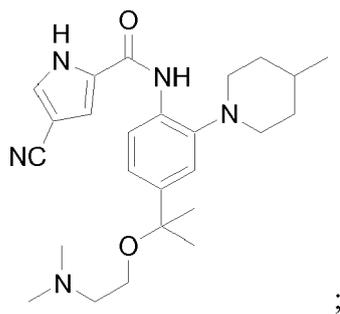
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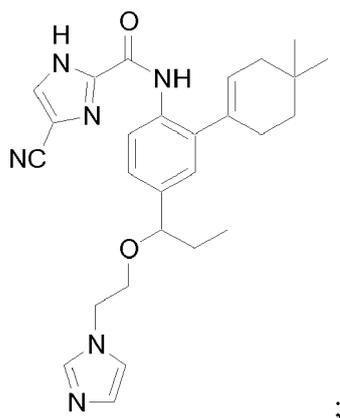
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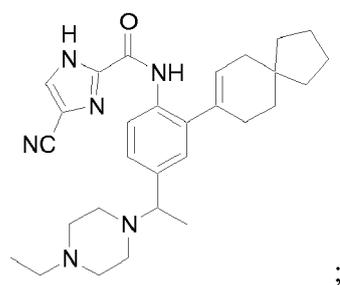
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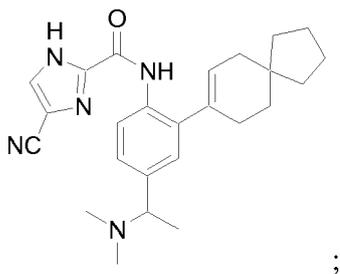
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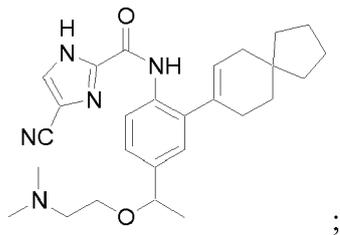
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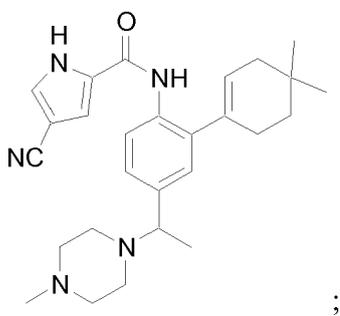


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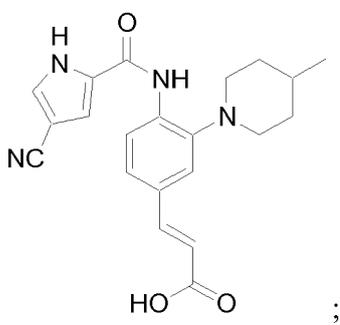
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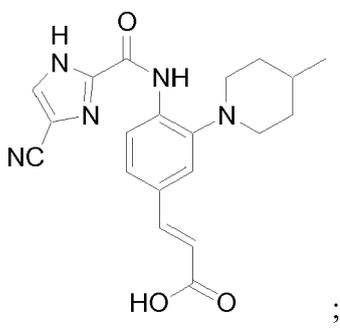
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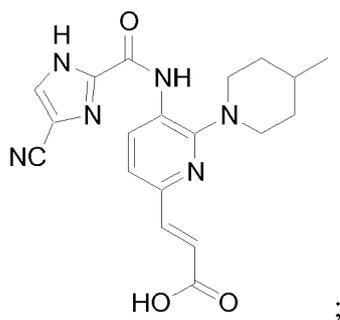


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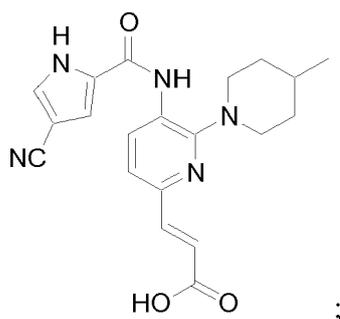
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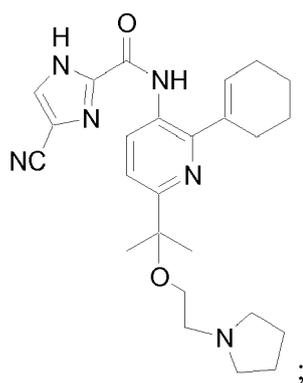
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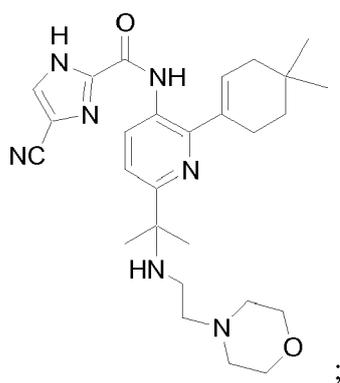
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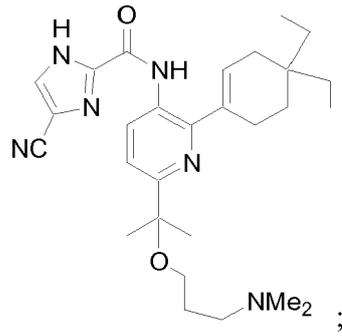
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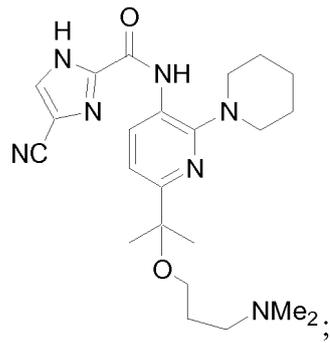
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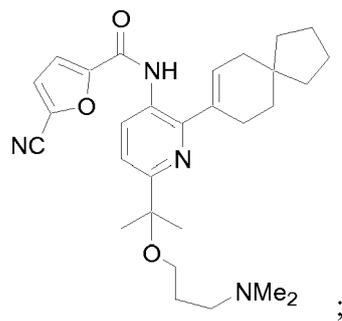
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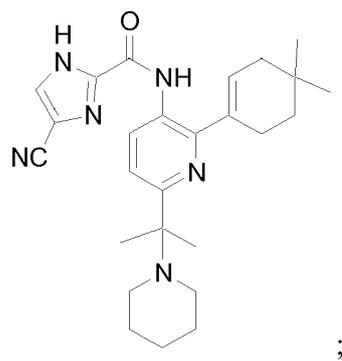
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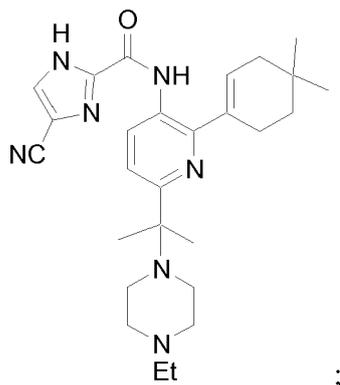
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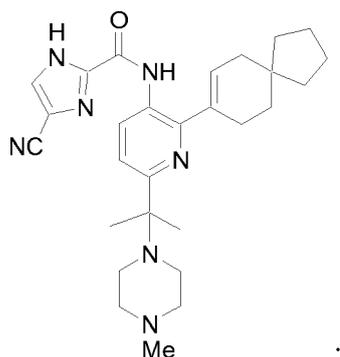
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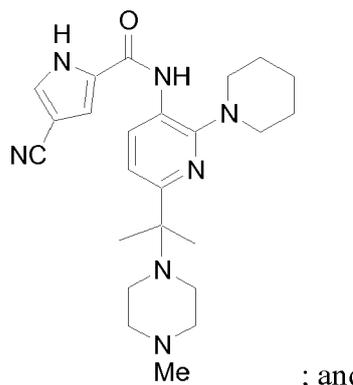
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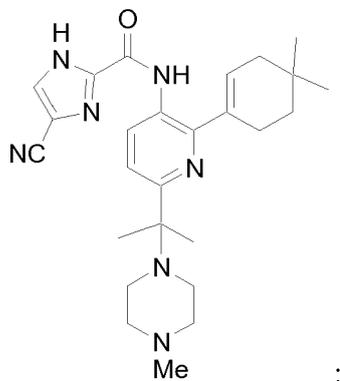
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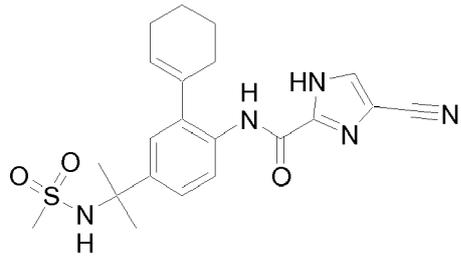
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and solvates, hydrates, tautomers and pharmaceutically acceptable salts thereof.

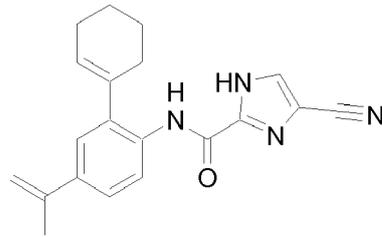
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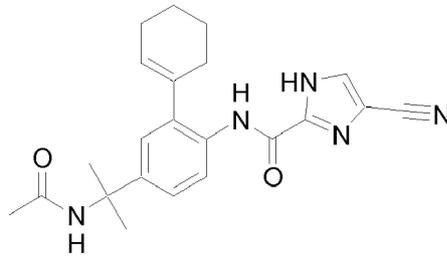
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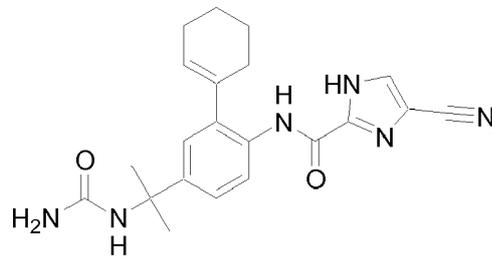
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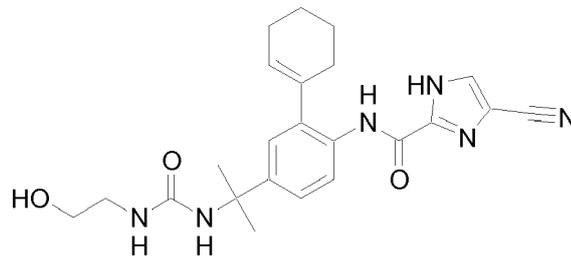
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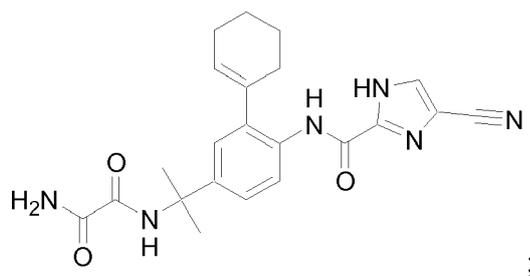
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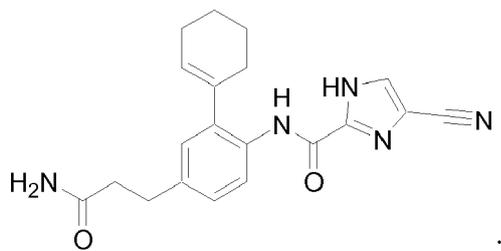
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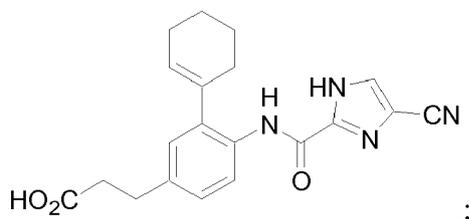


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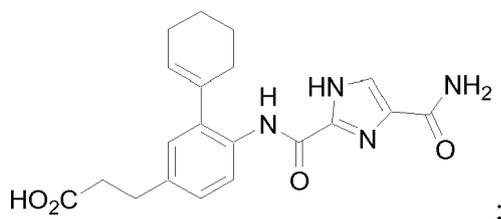
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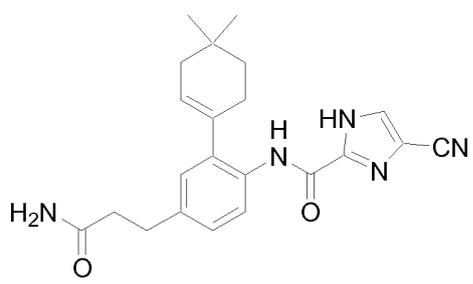
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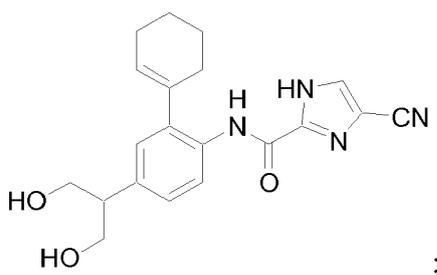
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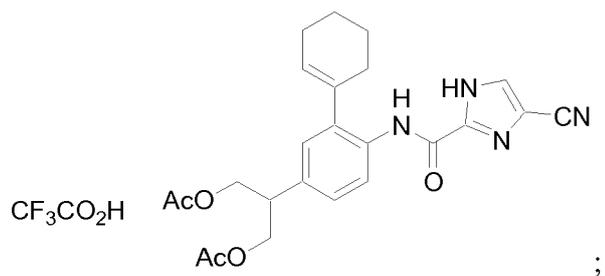
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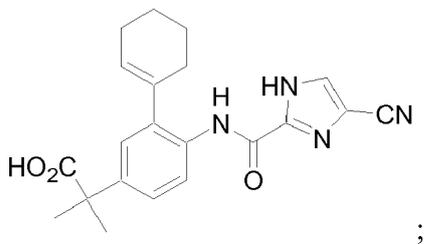
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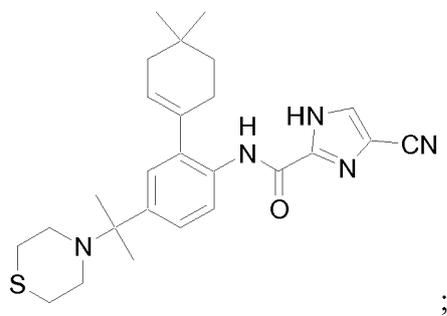
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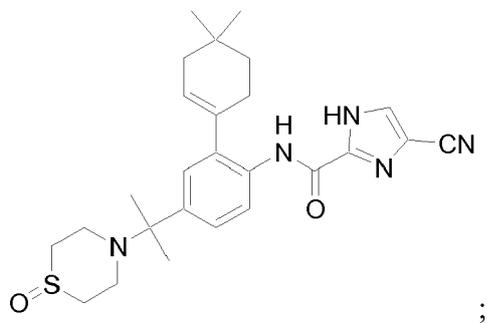
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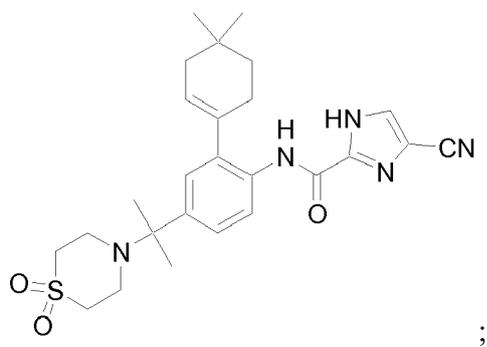
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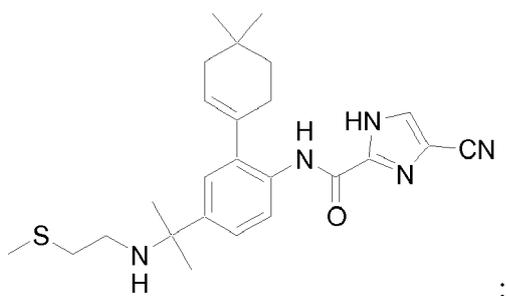
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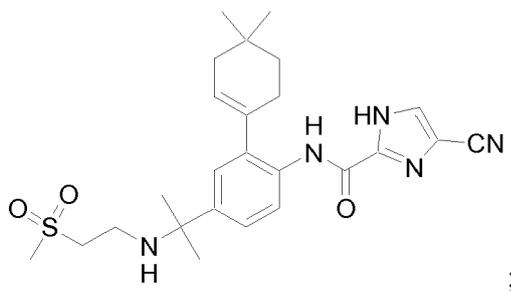


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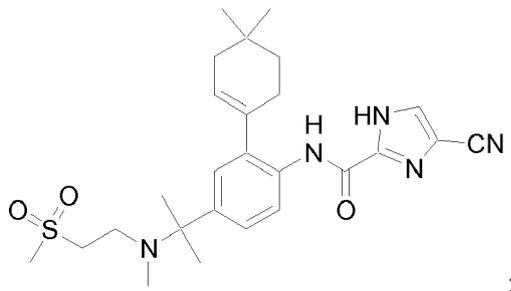
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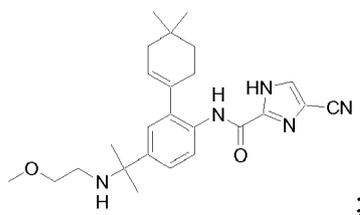
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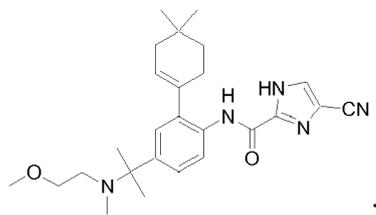
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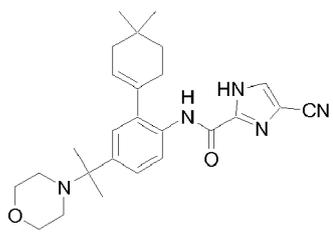
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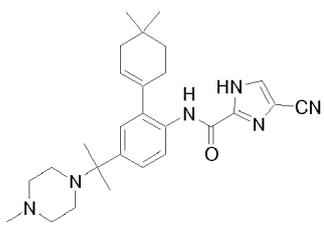


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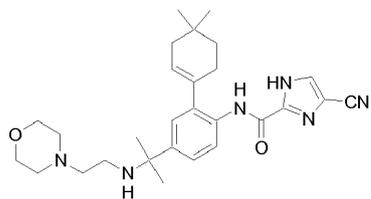


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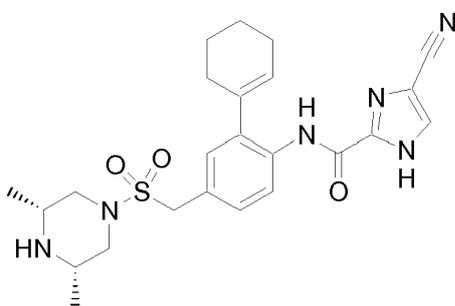
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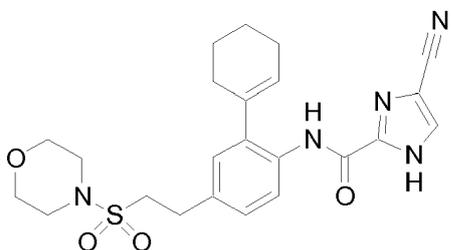
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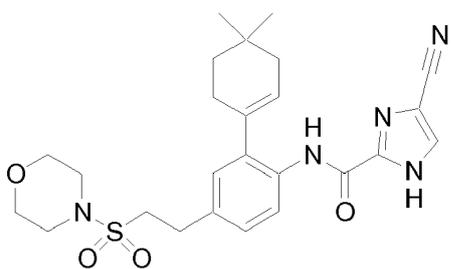
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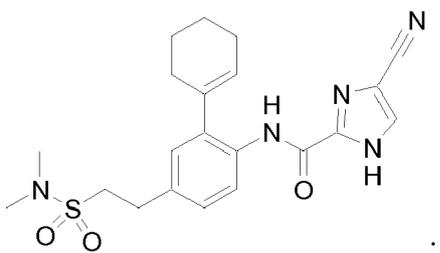
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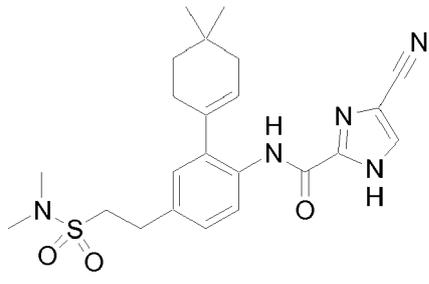
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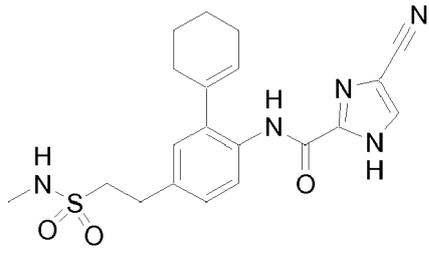
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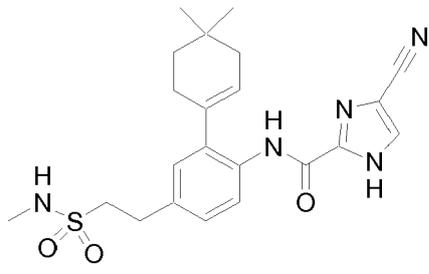
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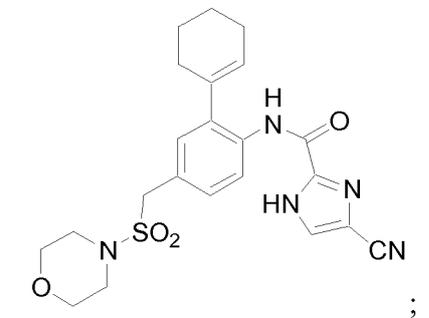
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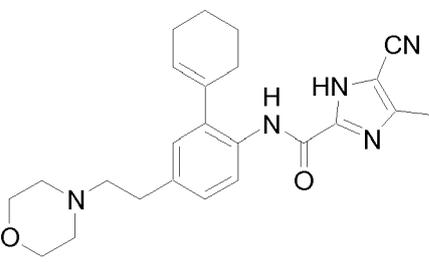
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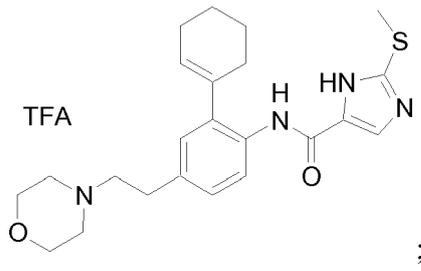
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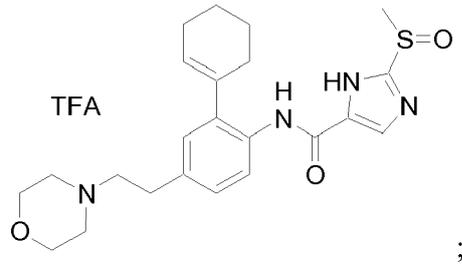
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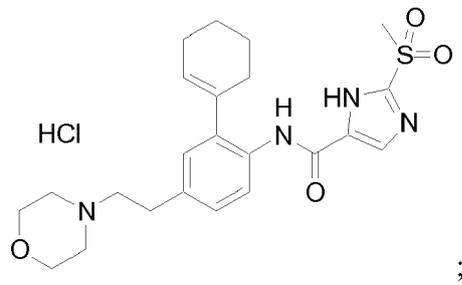


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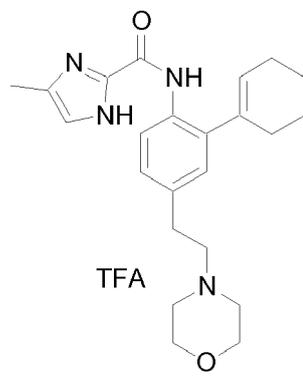
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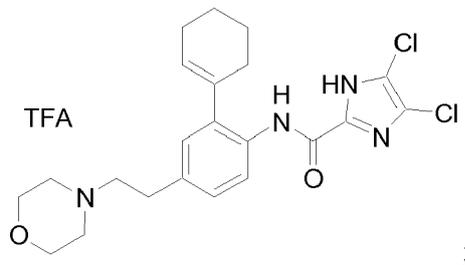
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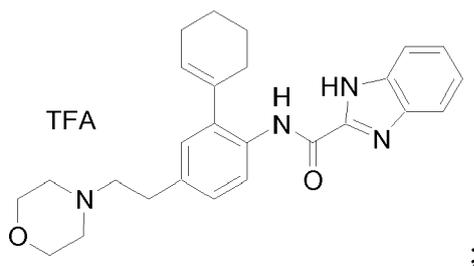
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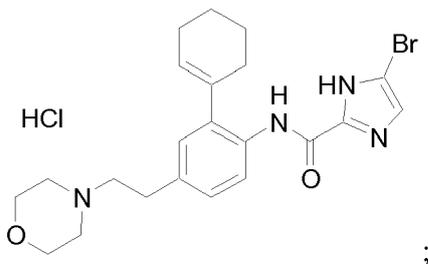
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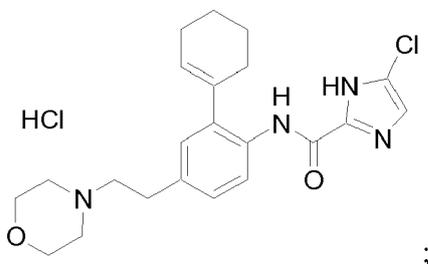
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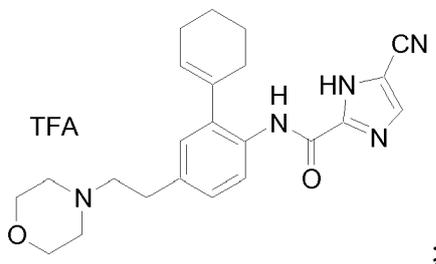
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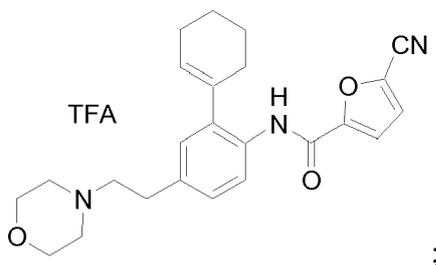
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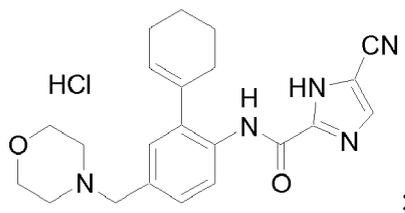
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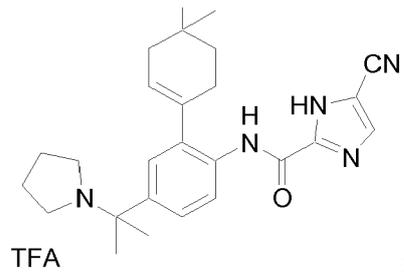


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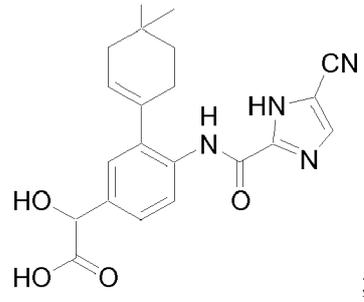


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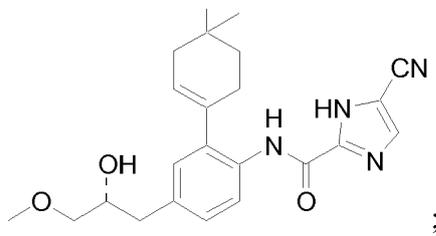
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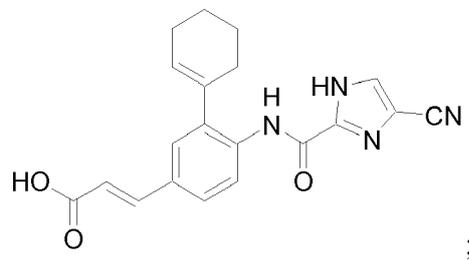
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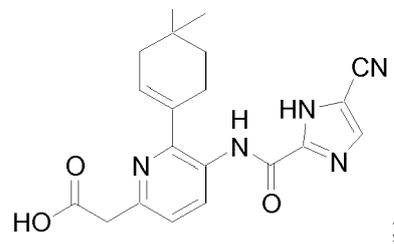
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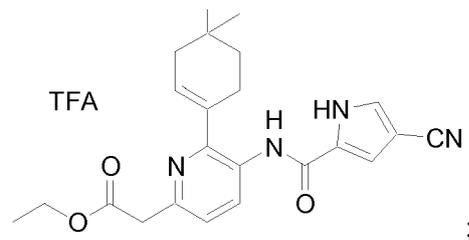
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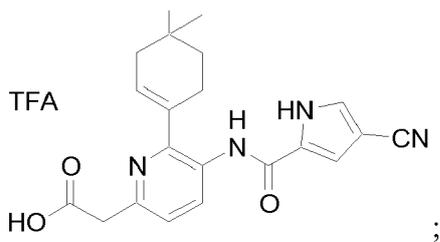


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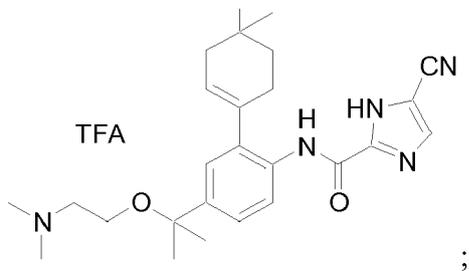
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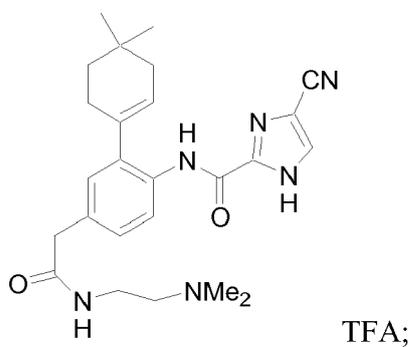


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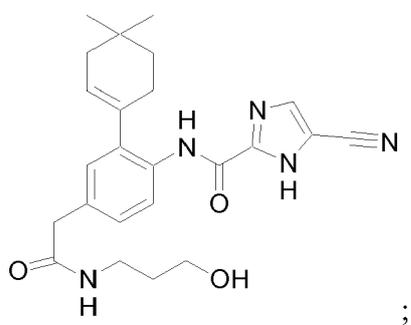
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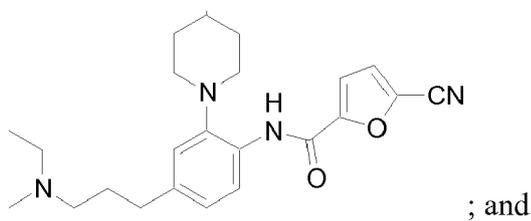
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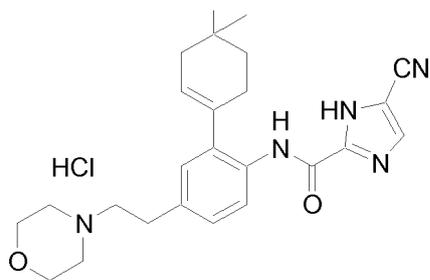
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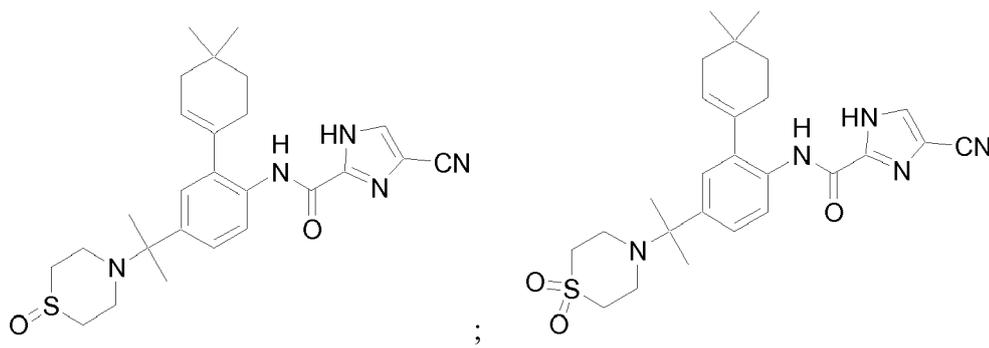
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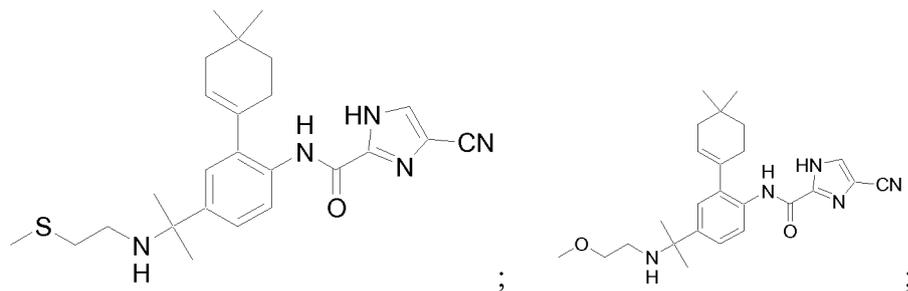
9. A compound of embodiment 8 selected from the group consisting of:

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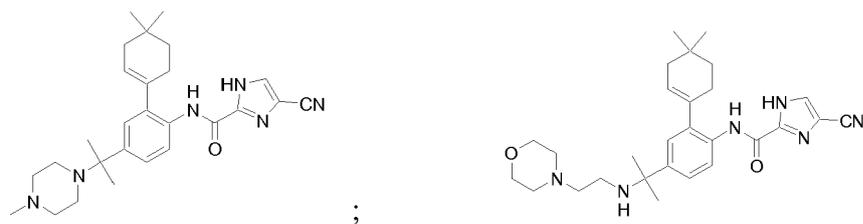
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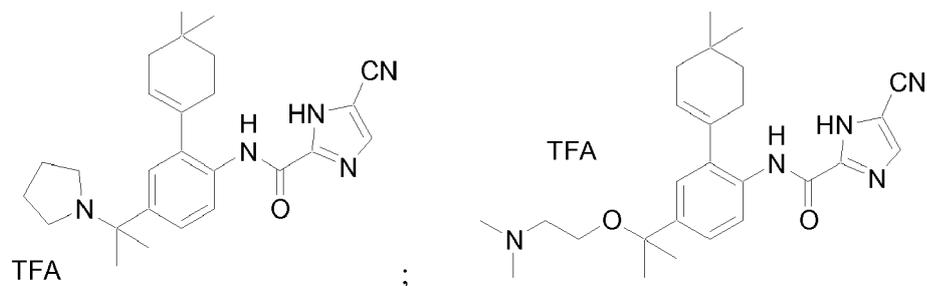
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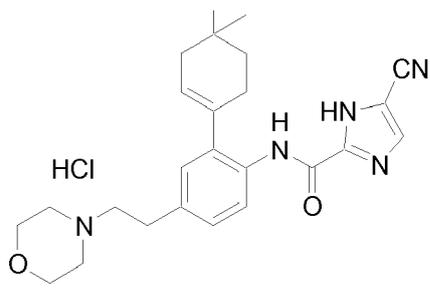
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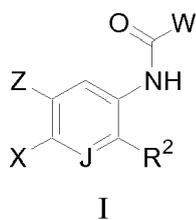


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and solvates, hydrates, tautomers, and pharmaceutically acceptable salts thereof.

10. A compound of Formula I

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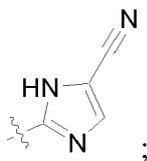
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wherein

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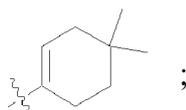
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R² is

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Z is H;

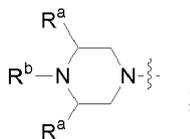
J is CH, or N;

X is -C₍₁₋₆₎alkylR¹ wherein:

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R¹ is

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wherein:

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R^a is H or C₍₁₋₄₎alkyl; and

R^b is -C₍₁₋₄₎alkyl-OH, -C₍₁₋₄₎alkyl-O-C₍₁₋₄₎alkyl, -C₍₁₋₄₎alkyl-C(O)O-C₍₁₋₄₎alkyl, -C₍₁₋₄₎alkylC(O)OH, or -C₍₁₋₄₎alkylC(O)ONa;

and solvates, hydrates, tautomers or pharmaceutically acceptable salts thereof

11. A compound of embodiment 10, wherein

J is CH;

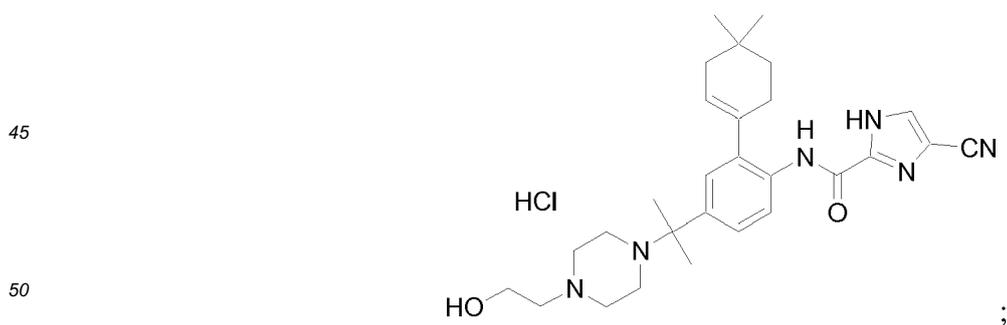
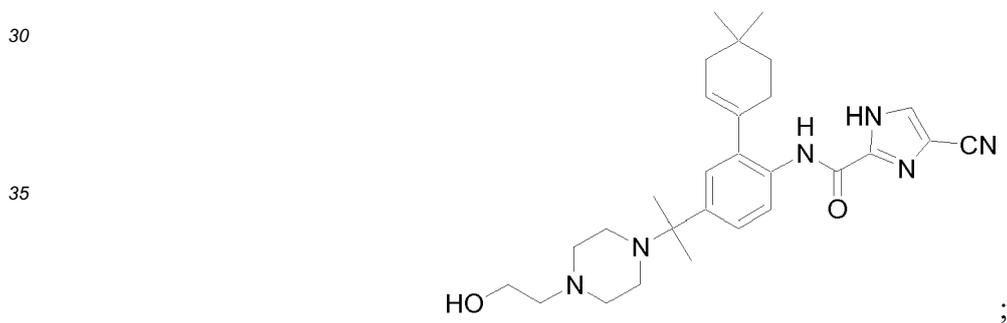
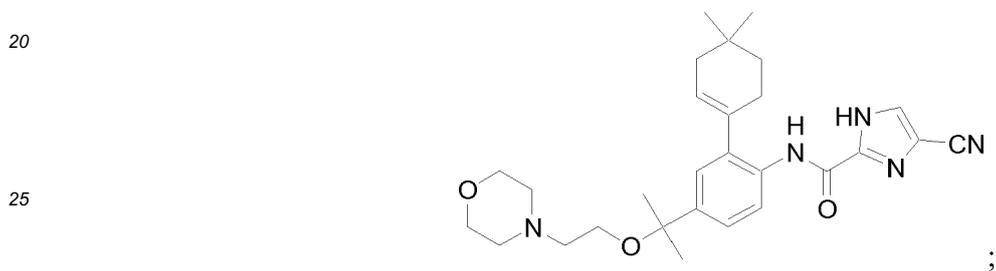
5 X is -C₍₁₋₄₎alkylR¹ wherein:



wherein:

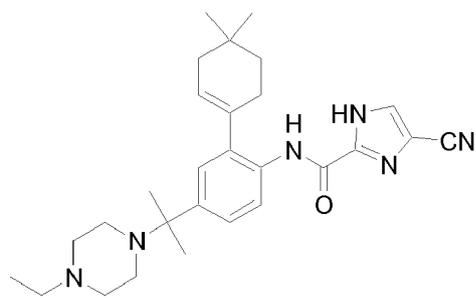
15 R^a is H; and R^b is -C₍₁₋₄₎alkyl-OH.

12. A compound selected from the group consisting of:



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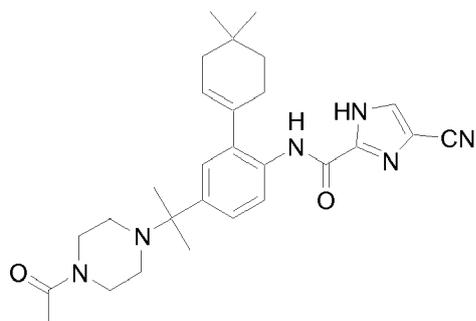
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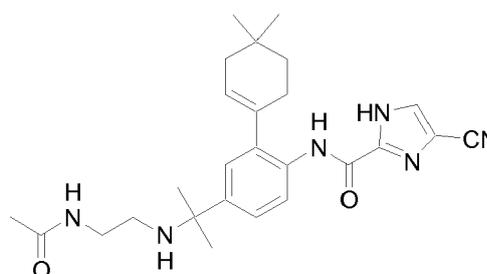
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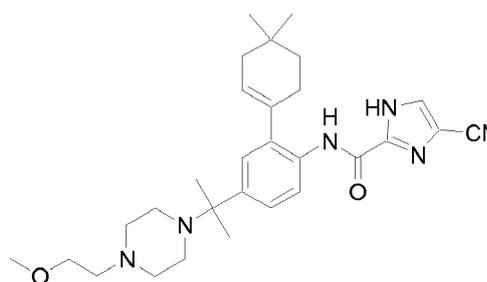
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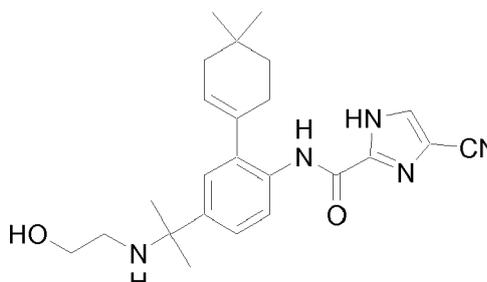
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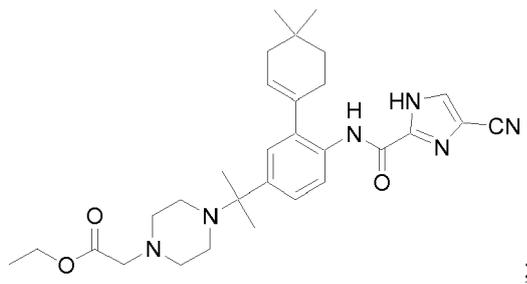


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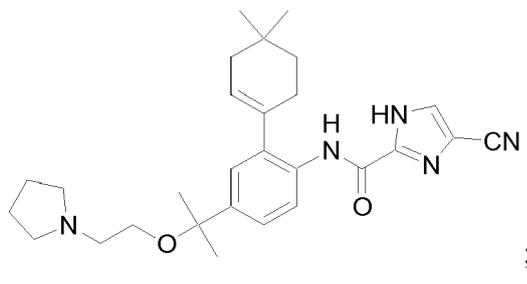
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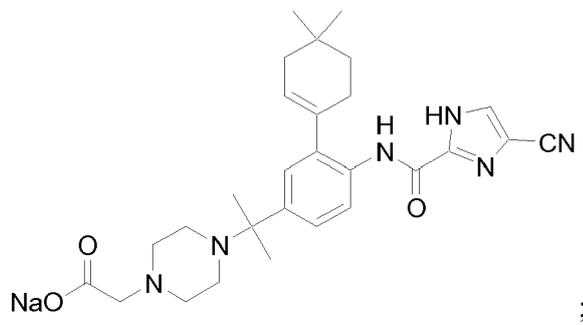
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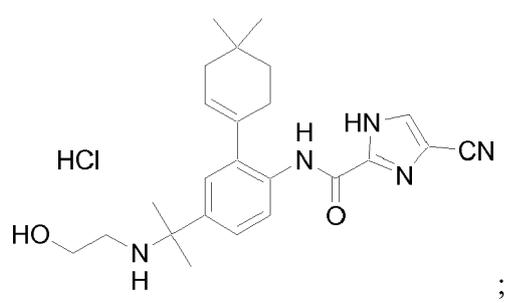
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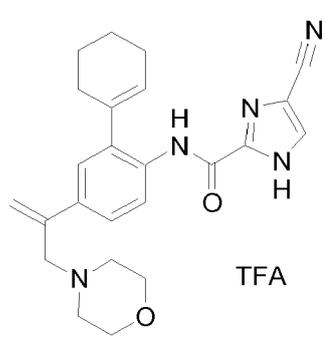
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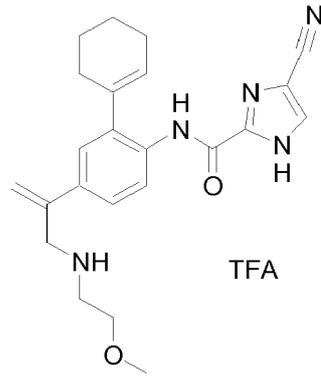
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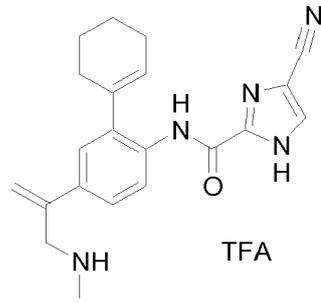
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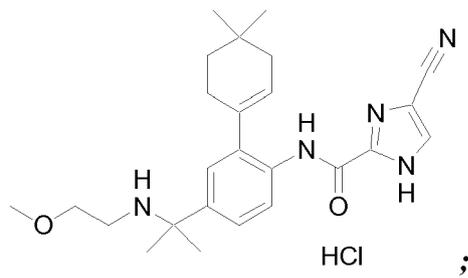
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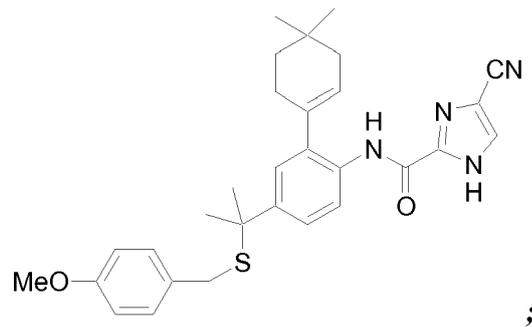
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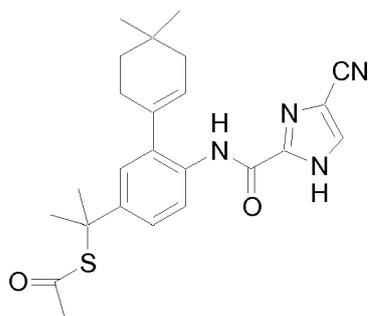


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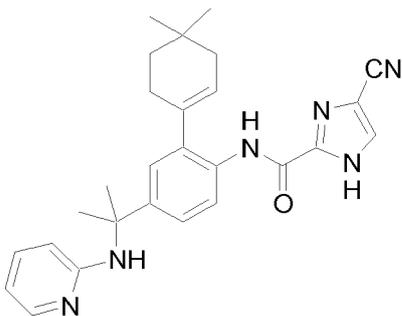
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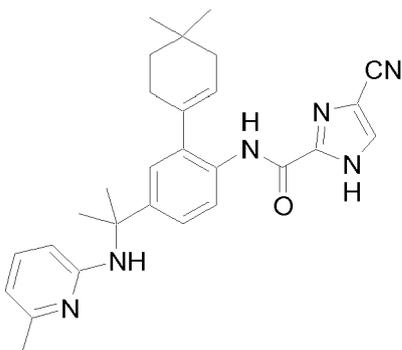
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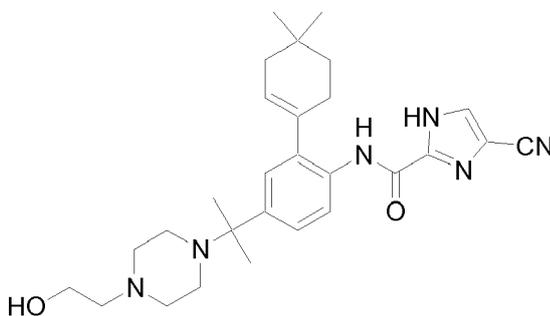
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and solvates, hydrates, tautomers, and pharmaceutically acceptable salts thereof

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13. A compound which is

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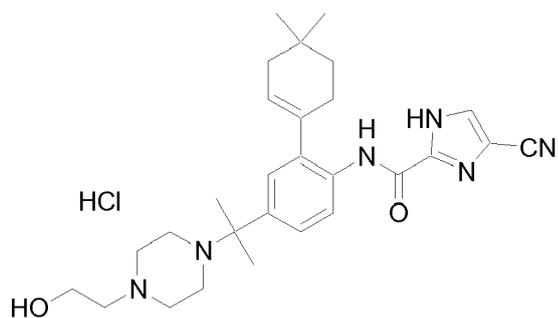
and solvates, hydrates, tautomers, and pharmaceutically acceptable salts thereof

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14. A compound which is

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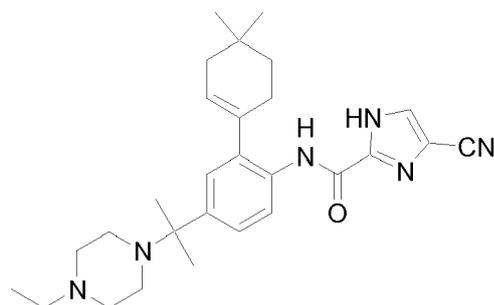
and solvates, hydrates, and tautomers thereof.

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15. A compound which is

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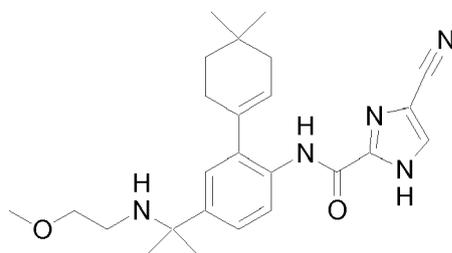
and solvates, hydrates, tautomers, and pharmaceutically acceptable salts thereof.

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16. A compound which is

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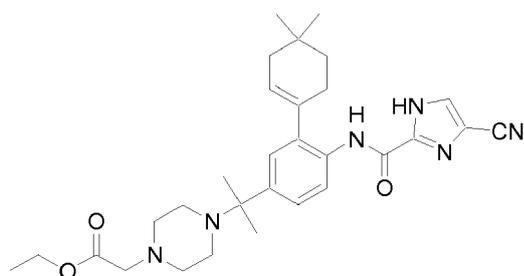
and solvates, hydrates, tautomers, and pharmaceutically acceptable salts thereof.

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17. A compound which is

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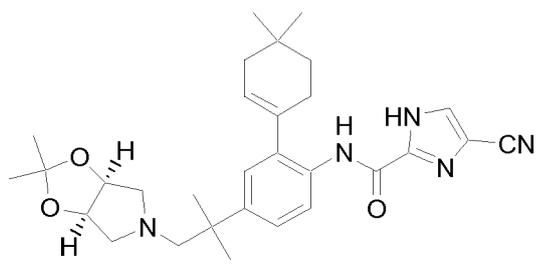
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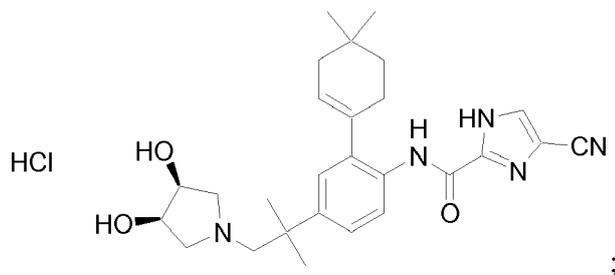
and solvates, hydrates, tautomers, and pharmaceutically acceptable salts thereof.

18. A compound selected from the group consisting of:

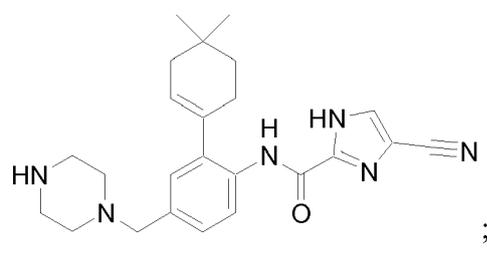
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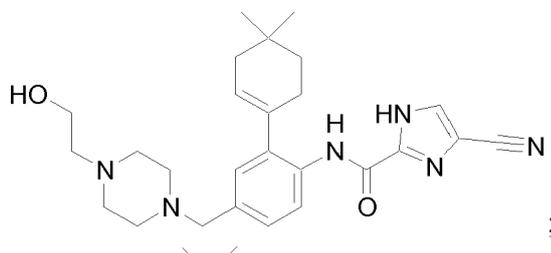


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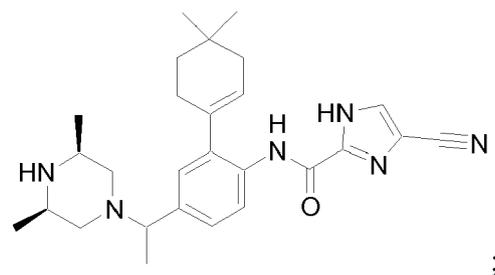
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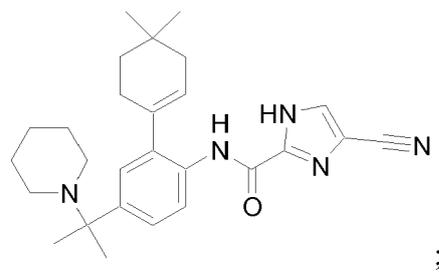
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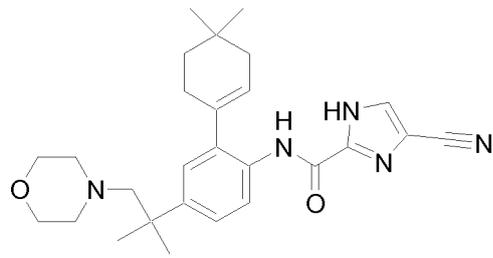
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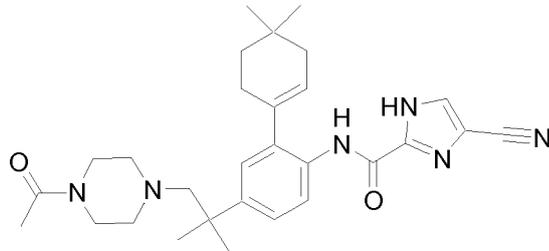
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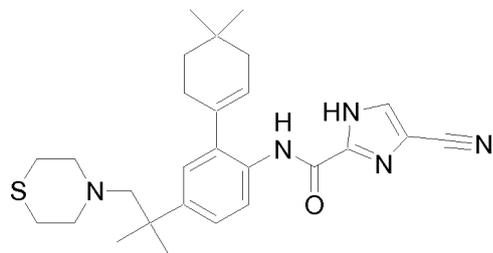
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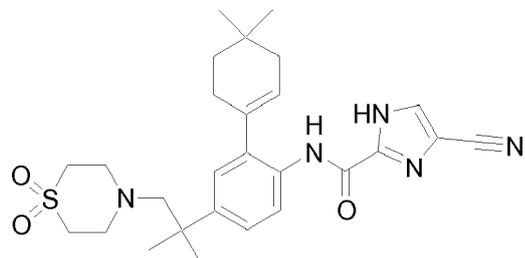
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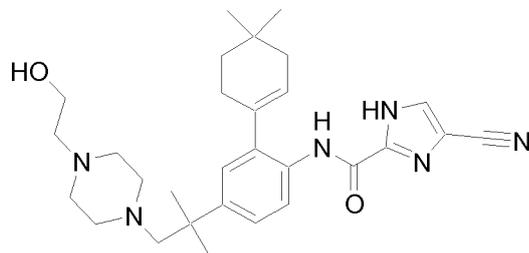
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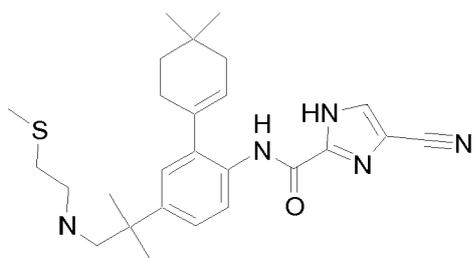
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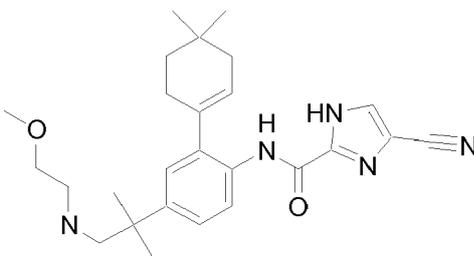
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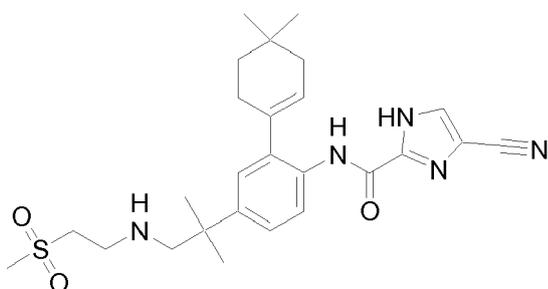
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and solvates, hydrates, tautomers, and pharmaceutically acceptable salts thereof.

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19. A pharmaceutical composition, comprising a compound of embodiment 1 and a pharmaceutically acceptable carrier.

20. 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 embodiment 1.

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21. A dosage form according to embodiment 20 adapted for parenteral or oral administration.

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

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23. A method according to embodiment 22, wherein the protein tyrosine kinase is c-fms.

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

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

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

55

27. A method of treating diseases with an inflammatory component selected from the group consisting of: 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 and Alzheimer's dementia in a mammal, comprising administering to the mammal a therapeutically effective amount of at least one compound of embodiment 1.

5 28. A method of treating pain selected from the group consisting of: skeletal pain caused by tumor metastasis, osteoarthritis, and 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 embodiment 1.

10 29. 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 in a mammal, comprising administering to the mammal in need of such treatment a therapeutically effective amount of at least one compound of embodiment 1.

15 30. 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 in a mammal, comprising administering to the mammal in need of such treatment a therapeutically effective amount of at least one compound of embodiment 1.

20 31. 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 in a mammal, comprising administering to the mammal in need of such treatment a therapeutically effective amount of at least one compound of embodiment 1.

25 32. A pharmaceutical composition, comprising a compound of embodiment 10 and a pharmaceutically acceptable carrier.

33. 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 embodiment 10.

30 34. A dosage form according to embodiment 33 adapted for parenteral or oral administration.

35 35. A method for inhibiting protein tyrosine kinase activity, comprising contacting the kinase with an effective inhibitory amount of at least one compound of embodiment 10.

36. A method according to embodiment 35, wherein the protein tyrosine kinase is c-fms.

37. A method of treating inflammation in a mammal, comprising administering to the mammal a therapeutically effective amount of at least one compound of embodiment 10.

40 38. A method of treating cancer in a mammal, comprising administering to the mammal a therapeutically effective amount of at least one compound of embodiment 10.

45 39. A method of treating cardiovascular disease in a mammal, comprising administering to the mammal a therapeutically effective amount of at least one compound of embodiment 10.

50 40. A method of treating diseases with an inflammatory component selected from the group consisting of: 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 and Alzheimer's dementia in a mammal, comprising administering to the mammal a therapeutically effective amount of at least one compound of embodiment 10.

55 41. A method of treating pain selected from the group consisting of: skeletal pain caused by tumor metastasis, osteoarthritis, and 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 embodiment 10.

42. 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,

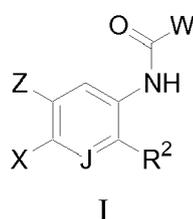
osteolytic sarcoma, myeloma, and tumor metastasis to bone in a mammal, comprising administering to the mammal in need of such treatment a therapeutically effective amount of at least one compound of embodiment 10.

43. 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 in a mammal, comprising administering to the mammal in need of such treatment a therapeutically effective amount of at least one compound of embodiment 10.

44. 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 in a mammal, comprising administering to the mammal in need of such treatment a therapeutically effective amount of at least one compound of embodiment 10.

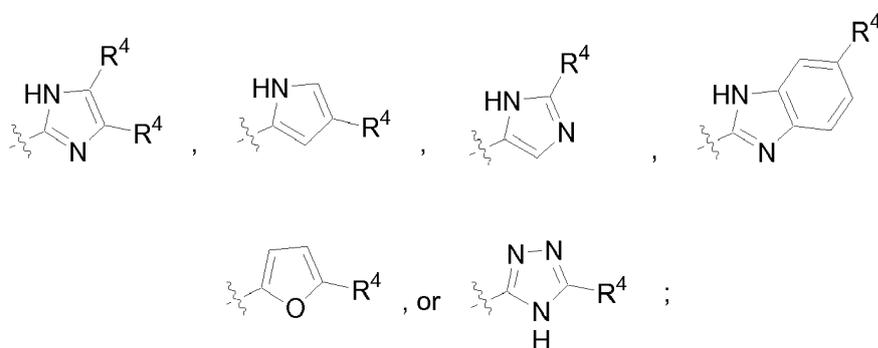
Claims

1. The compounds of Formula I



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

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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 , $CONR^eR^f$, $C\equiv CR^g$, 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, dihydro-sulfonopyranyl, 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 $-C_{(1-6)}alkylR^1$, alkenyl, propenyl- NA^1A^2 , $-CH=CH-CO_2R^a$ wherein said $CH=CH$ bond includes both E and Z stereochemistry, $-C_{(1-4)}alkylR^3R^{4a}$, or $-CH_2-heteroaryl-C_{(14)}alkyl-R^1$;

wherein:

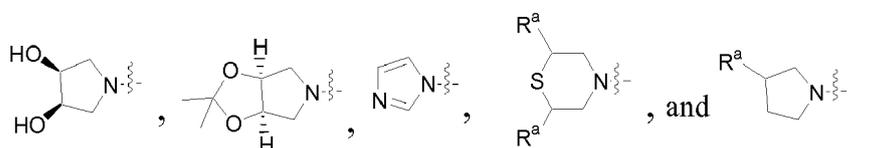
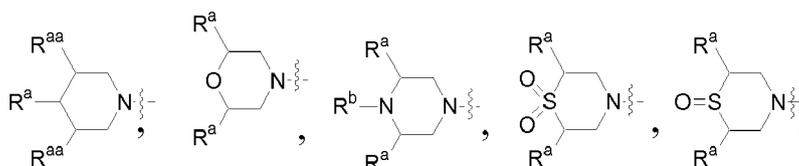
EP 2 687 516 A1

R¹ is -CN, -SO₂NA¹A², -SO₂R^a, -SCH₂CH₂NA¹A², -SOCH₂CH₂NA¹A², -SO₂CH₂CH₂NA¹A², -S-C(O)
 C₍₁₋₄₎alkyl, -S-CH₂-4-methoxy phenyl, -OC₍₁₄₎alkylNA¹A², -NA¹A², -NHCO₂R^a, -NHCOR^a,
 -NHCO₂CH₂CH₂NA¹A², -NHCOCH₂CH₂NA¹A², -CONH₂, -CONHCH₂CH₂CH₂OH, -CONHCH₂CH₂N
 (C₍₁₋₄₎alkyl)₂, -NHCONH₂, -NHCONHCH₂CH₂OH, -NHCOCNH₂, -NR_aCH₂CH₂NA¹A², CO₂R^a, pyri-
 5 dyl, -OCH₂CH₂OR^a, -OCH₂CH₂OCH₂CH₂NA¹A², -OCH₂CH₂NA¹CH₂CH₂OR^a,
 -NA¹CH₂CH₂OCH₂CH₂OR^a, -OCOR^a, or -CH₂OCOCH₃;

A¹ is H or -C₍₁₋₄₎alkyl;

A² is -C₍₁₋₄₎alkyl, -CH₂CH₂OR^a, -COR^a, -CH₂CH₂SC₍₁₋₄₎alkyl, -CH₂CH₂SOC₍₁₋₄₎alkyl, pyridyl, 2-methyl py-
 10 ridyl, -CH₂CH₂OCH₂CH₂OR^a, or -CH₂CH₂SO₂C₍₁₋₄₎alkyl;

alternatively, A¹ and A² 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;

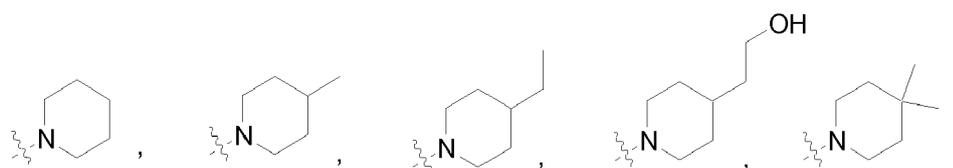
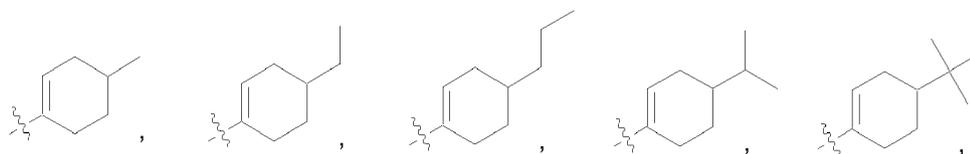
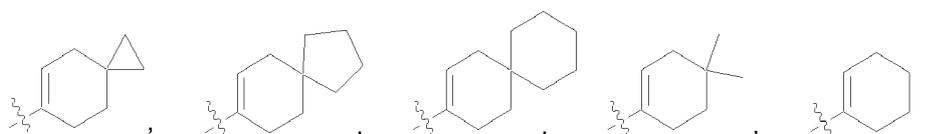
R^{aa} is H or C₍₁₋₄₎alkyl;

R^b is H, -C₍₁₋₄₎alkyl, alkoxyether, -C(O)C₍₁₋₄₎alkyl, -C₍₁₋₄₎alkyl-OH, -C₍₁₋₄₎alkyl-O-C₍₁₋₄₎alkyl, -C₍₁₋₄₎alkyl-
 C(O)O-C₍₁₋₄₎alkyl, -C₍₁₄₎alkylC(O)OH, -C₍₁₋₄₎alkylC(O)ONa, or -CH₂C(O)C₍₁₋₄₎alkyl; and

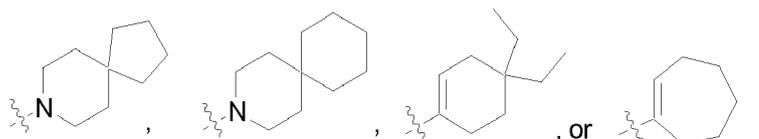
R³ and R^{4a} are independently -CH₂OH, -OCH₃, -CH₂OCH₃, -CO₂H, -CO₂C₍₁₄₎alkyl, OC(O)C₍₁₋₄₎alkyl, or -OH.

2. A compound of claim 1, wherein:

R² is



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X is $-C_{(1-6)}\text{alkylR}^1$, alkenyl, propenyl- NA^1A^2 , $-\text{CH}=\text{CH}-\text{CO}_2\text{R}^a$, $-C_{(1-4)}\text{alkylR}^3\text{R}^{4a}$, or $-\text{CH}_2\text{-heteroaryl-}C_{(1-4)}\text{alkyl-}$
 R^1 ;

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wherein:

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R^1 is $-\text{CN}$, $-\text{SO}_2\text{NA}^1\text{A}^2$, $-\text{SO}_2\text{R}^a$, $-\text{SCH}_2\text{CH}_2\text{NA}^1\text{A}^2$, $-\text{SOCH}_2\text{CH}_2\text{NA}^1\text{A}^2$, $-\text{SO}_2\text{CH}_2\text{CH}_2\text{NA}^1\text{A}^2$, $-\text{S-C(O)}$
 $\text{C}_{(1-4)}\text{alkyl}$, $-\text{S-CH}_2\text{-4-methoxy phenyl}$, $-\text{OC}_{(14)}\text{alkylNA}^1\text{A}^2$, $-\text{NA}^1\text{A}^2$, $-\text{NHSO}_2\text{CH}_3$, $-\text{NHCOCH}_3$, $-\text{CONH}_2$,
 $-\text{CONHCH}_2\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CONHCH}_2\text{CH}_2\text{N}(\text{C}_{(1-4)}\text{alkyl})_2$, $-\text{NHCONH}_2$, $-\text{NHCONHCH}_2\text{CH}_2\text{OH}$,
 $-\text{NHCOCNH}_2$, $-\text{NR}_a\text{CH}_2\text{CH}_2\text{NA}^1\text{A}^2$, $-\text{CO}_2\text{R}^a$, pyridyl, $-\text{OCOCH}_3$, or $-\text{CH}_2\text{OCOCH}_3$;

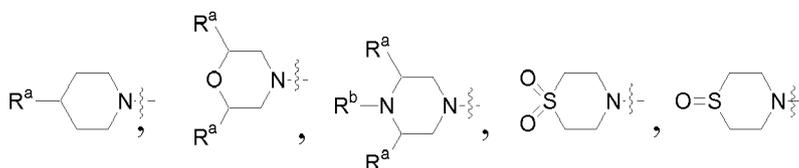
A^1 is H or $-\text{C}_{(1-4)}\text{alkyl}$;

A^2 is $-\text{C}_{(1-4)}\text{alkyl}$, $-\text{CH}_2\text{CH}_2\text{OR}^a$, $-\text{COR}^a$, $-\text{CH}_2\text{CH}_2\text{SC}_{(1-4)}\text{alkyl}$, $-\text{CH}_2\text{CH}_2\text{SOC}_{(1-4)}\text{alkyl}$, pyridyl, 2-methyl py-
 ridyl, or $-\text{CH}_2\text{CH}_2\text{SO}_2\text{C}_{(14)}\text{alkyl}$;

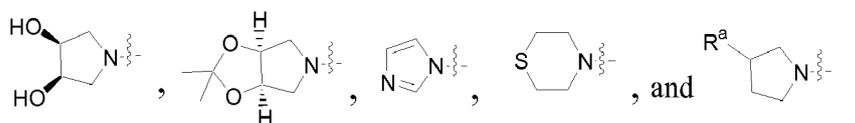
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alternatively, A^1 and A^2 may be taken together with their attached nitrogen to form a heterocyclic ring
 selected from the following:

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wherein:

R^3 is H or $\text{C}_{(1-4)}\text{alkyl}$;

R^b is H, $-\text{C}_{(1-4)}\text{alkyl}$, alkoxyether, $-\text{C(O)C}_{(1-4)}\text{alkyl}$, $-\text{C}_{(1-4)}\text{alkyl-OH}$, $-\text{C}_{(1-4)}\text{alkyl-O-C}_{(1-4)}\text{alkyl}$, $-\text{C}_{(1-4)}\text{alkyl-}$
 $\text{C(O)O-C}_{(1-4)}\text{alkyl}$, $-\text{C}_{(14)}\text{alkylC(O)OH}$, $-\text{C}_{(1-4)}\text{alkylC(O)ONa}$, or $-\text{CH}_2\text{C(O)C}_{(1-4)}\text{alkyl}$; and

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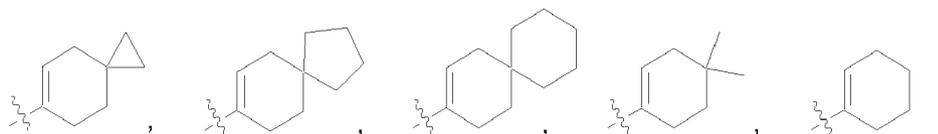
R^3 and R^{4a} are independently $-\text{CH}_2\text{OH}$, $-\text{OCH}_3$, $-\text{CH}_2\text{OCH}_3$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{C}_{(1-4)}\text{alkyl}$, $-\text{OC(O)C}_{(1-4)}\text{alkyl}$, or $-\text{OH}$.

3. A compound of claim 2 wherein:

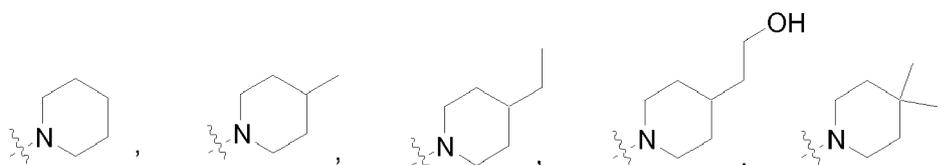
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R^2 is

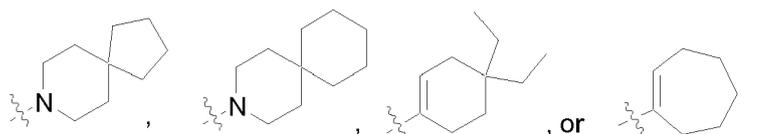
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X is $-C_{(1-5)}$ alkylR¹, alkenyl, propenyl-NA¹A², $-\text{CH}=\text{CH}-\text{CO}_2\text{R}^a$, $-C_{(1-4)}$ alkylR³R^{4a}, or $-\text{CH}_2$ -heteroaryl- $C_{(1-4)}$ alkyl-R¹;

wherein:

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R¹ is $-\text{CN}$, $-\text{SO}_2\text{NA}^1\text{A}^2$, $-\text{SO}_2\text{R}^a$, $-\text{SCH}_2\text{CH}_2\text{NA}^1\text{A}^2$, $-\text{SOCH}_2\text{CH}_2\text{NA}^1\text{A}^2$, $-\text{SO}_2\text{CH}_2\text{CH}_2\text{NA}^1\text{A}^2$, $-\text{S}-\text{C}(\text{O})$
 $C_{(1-4)}$ alkyl, $-\text{S}-\text{CH}_2$ -4-methoxy phenyl, $-\text{OC}_{(14)}$ alkylNA¹A², $-\text{NA}^1\text{A}^2$, $-\text{NHSO}_2\text{CH}_3$, $-\text{NHCOCH}_3$, $-\text{CONH}_2$,
 $-\text{CONHCH}_2\text{CH}_2\text{CH}_2\text{OH}$, $\text{CONHCH}_2\text{CH}_2\text{N}(\text{C}_{(1-4)}\text{alkyl})_2$, $-\text{NHCONH}_2$, $-\text{NHCONHCH}_2\text{CH}_2\text{OH}$,
 $-\text{NHCOCNH}_2$, $-\text{NR}_a\text{CH}_2\text{CH}_2\text{NA}^1\text{A}^2$, $-\text{CO}_2\text{R}^a$, pyridyl, $-\text{OCOCH}_3$, or $-\text{CH}_2\text{OCOCH}_3$;

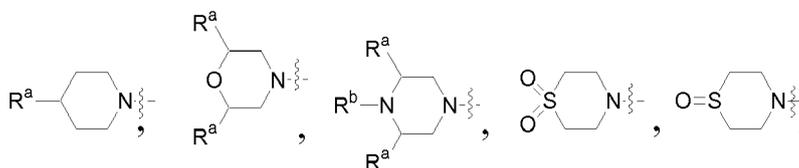
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A¹ is H or $-\text{C}_{(1-4)}$ alkyl;

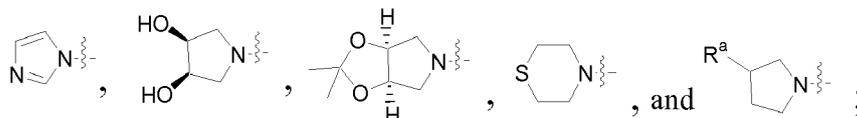
A² is $-\text{C}_{(1-4)}$ alkyl, $-\text{CH}_2\text{CH}_2\text{OR}^a$, $-\text{COR}^a$, $-\text{CH}_2\text{CH}_2\text{SC}_{(1-4)}$ alkyl, $-\text{CH}_2\text{CH}_2\text{SOC}_{(1-4)}$ alkyl, pyridyl, 2-methyl py-
ridyl, or $-\text{CH}_2\text{CH}_2\text{SO}_2\text{C}_{(14)}$ alkyl;

alternatively, A¹ and A² may be taken together with their attached nitrogen to form a heterocyclic ring
selected from the following:

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wherein:

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

R^b is H, $-\text{C}_{(1-4)}$ alkyl, alkoxyether, $-\text{C}(\text{O})\text{C}_{(1-4)}$ alkyl, $-\text{C}_{(1-4)}$ alkyl-OH, $-\text{C}_{(1-4)}$ alkyl-O- $C_{(1-4)}$ alkyl, $-\text{C}_{(1-4)}$ alkyl-
 $\text{C}(\text{O})\text{O}-\text{C}_{(1-4)}$ alkyl, $-\text{C}_{(14)}$ alkyl $\text{C}(\text{O})\text{OH}$, $-\text{C}_{(1-4)}$ alkyl $\text{C}(\text{O})\text{ONa}$, or $-\text{CH}_2\text{C}(\text{O})-\text{C}_{(1-4)}$ alkyl; and

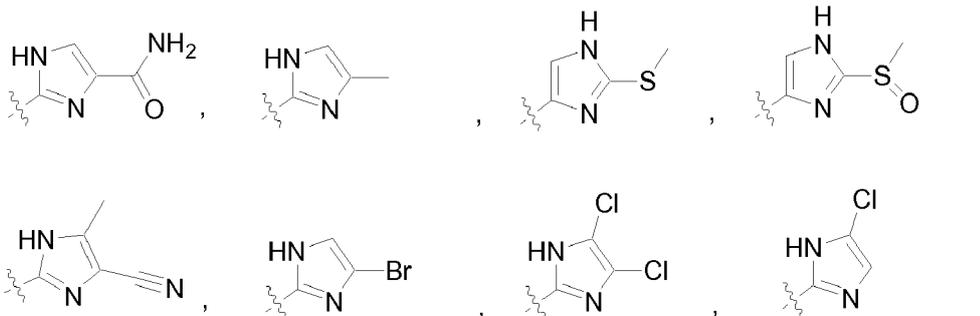
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R³ and R^{4a} are independently $-\text{CH}_2\text{OH}$, $-\text{OCH}_3$, $-\text{CH}_2\text{OCH}_3$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{C}_{(1-4)}$ alkyl, $\text{OC}(\text{O})\text{C}_{(1-4)}$ alkyl, or $-\text{OH}$.

4. A compound of claim 3 wherein:

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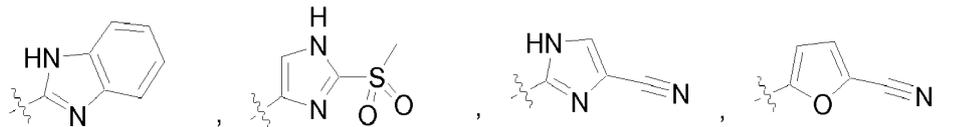
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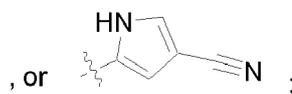
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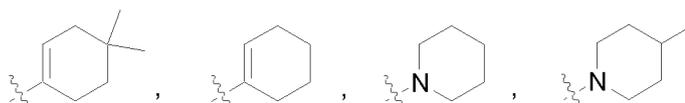


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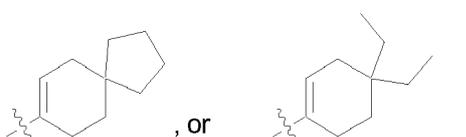


R² is

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Z is H;

X is -C₍₁₋₅₎alkylR¹, -CH=CH-CO₂H wherein said CH=CH bond has E stereochemistry, -C₍₁₋₄₎alkylR³R^{4a}, propenyl-NA¹A², or propenyl;

wherein:

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R¹ is -SO₂NA¹A², -S-C(O)CH₃, -S-CH₂-4-methoxy phenyl, -OC₍₁₋₄₎alkylNA¹A², -NA¹A², -NHCH₂CH₂NA¹A², -NHSO₂CH₃, -NHCOCH₃, -CONH₂, -CONHCH₂CH₂CH₂OH, -CONHCH₂CH₂N(CH₃)₂, -NHCONH₂, -NHCONHCH₂CH₂OH, -NHCOCONH₂, -CO₂R^a, or pyridyl;

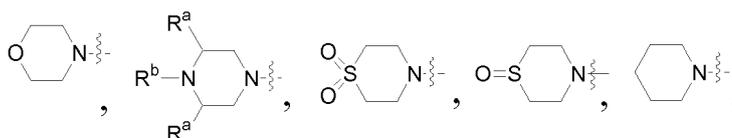
A¹ is H or -C₍₁₋₄₎alkyl;

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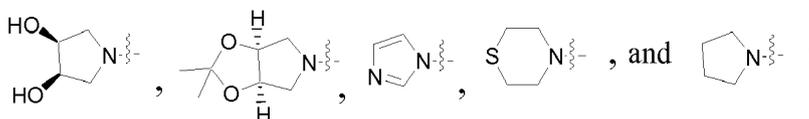
A² is -C₍₁₋₄₎alkyl, -CH₂CH₂OR³, -COCH₃, -CH₂OCH₃, -CH₂CH₂SC₍₁₋₄₎alkyl, pyridyl, 2-methyl pyridyl, or -CH₂CH₂SO₂C₍₁₋₄₎alkyl;

alternatively, A¹ and A² may be taken together with their attached nitrogen to form a heterocyclic ring selected from the following:

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wherein:

R³ is H or C₍₁₋₄₎alkyl;

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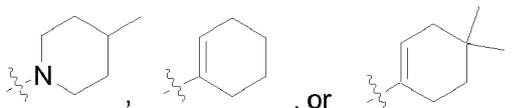
R^b is H, -CH₂CH₂OH, -CH₂CH₂OCH₃, -CH₂C(O)OCH₂CH₃, -CH₂C(O)OH, -CH₂C(O)ONa, -C(O)CH₃, or -C₍₁₋₄₎alkyl; and

R³ and R^{4a} are independently -OCH₃, -CH₂OCH₃, -CO₂H, -OC(O)CH₃, or -OH.

5. A compound of claim 4 wherein:

R² is

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X is -CH₂R¹, -CH₂CH₂R¹, -C(CH₃)₂R¹, -CH=CH-CO₂H wherein said CH=CH bond has E stereochemistry, -C₍₁₋₄₎alkylR³R^{4a}, propenyl-NA¹A², or propenyl; wherein:

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R¹ is -SO₂NA¹A², -S-C(O)CH₃, -S-CH₂-4-methoxy phenyl, -OCH₂CH₂NA¹A², -NA¹A², -NHCH₂CH₂NA¹A², -NHSO₂CH₃, -NHCOCH₃, -CONH₂, -CONHCH₂CH₂CH₂OH, -CONHCH₂CH₂N(CH₃)₂, -NHCONH₂, -NHCONHCH₂CH₂OH, -NHCOCONH₂, or -CO₂R^a;

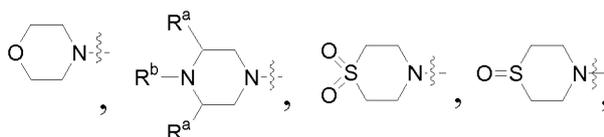
A¹ is H or -C₍₁₋₄₎alkyl;

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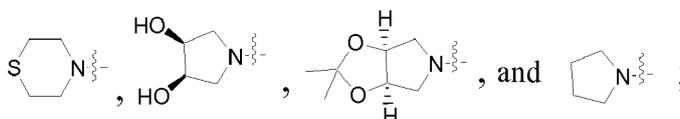
A² is -C₍₁₋₄₎alkyl, -C(O)CH₃, -CH₂CH₂OCH₃, -CH₂CH₂OH, -CH₂CH₂SCH₃, pyridyl, 2-methyl pyridyl, or -CH₂CH₂SO₂CH₃;

alternatively, A¹ and A² may be taken together with their attached nitrogen to form a heterocyclic ring selected from the following:

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wherein:

R^a is H, CH₃, or -CH₂CH₃;

R^b is H, CH₂CH₂OH, -CH₂CH₂OCH₃, -CH₂C(O)OH, -CH₂C(O)ONa, CH₂CH₃, C(O)CH₃, or CH₃; and

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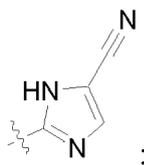
R³ and R^{4a} are independently, -OCH₃, -CH₂OCH₃, -CO₂H, -OC(O)CH₃, or -OH.

6. A compound of claim 1, wherein

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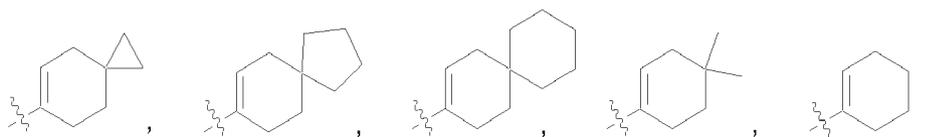
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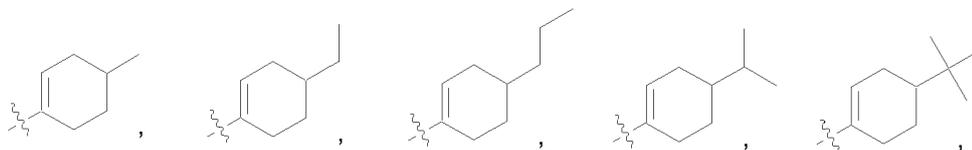
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R² is

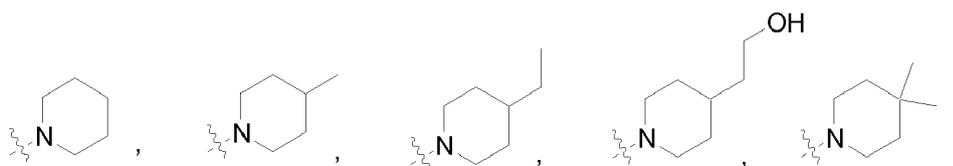
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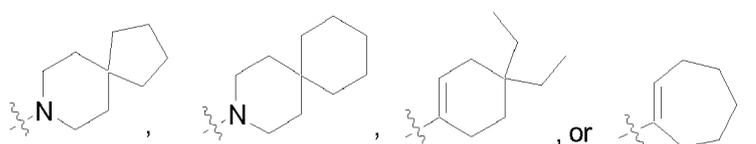


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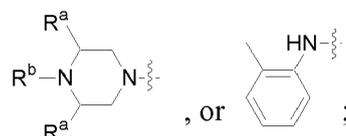
Z is H;

X is $-C_{(1-6)}\text{alkyl}R^1$, or propenyl- NA^1A^2 , wherein:

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R^1 is $-NA^1A^2$, $-S-C(O)C_{(1-4)}\text{alkyl}$, or $-S-CH_2-4\text{-methoxy phenyl}$, wherein A^1 and A^2 are taken together with their attached nitrogen to form a heterocyclic ring selected from

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wherein:

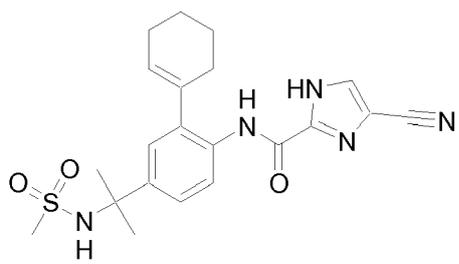
R^a is H or $C_{(1-4)}\text{alkyl}$; and

R^b is $-C_{(1-4)}\text{alkyl-OH}$, $-C_{(1-4)}\text{alkyl-O-C}_{(1-4)}\text{alkyl}$, $-C_{(1-4)}\text{alkyl-C(O)O-C}_{(1-4)}\text{alkyl}$, $-C_{(1-4)}\text{alkylC(O)OH}$, or $-C_{(1-4)}\text{alkylC(O)ONa}$.

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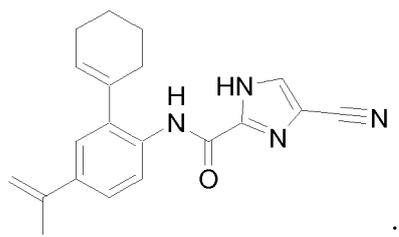
7. A compound selected from the group consisting of:

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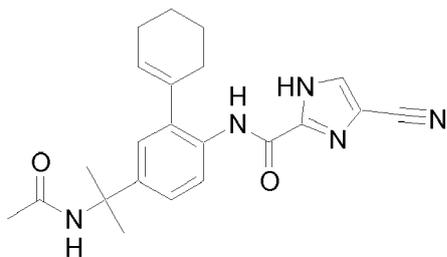
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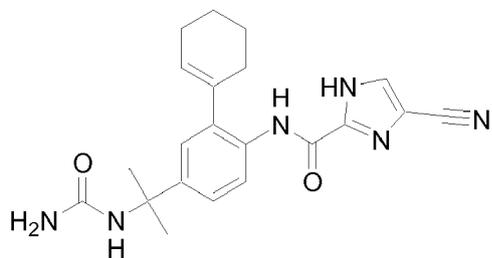
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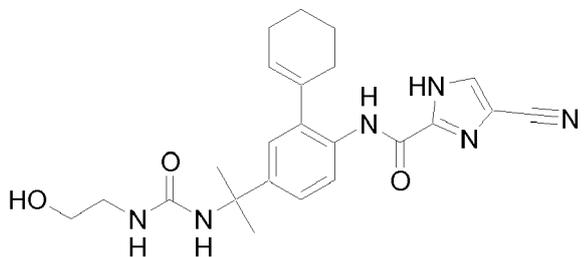
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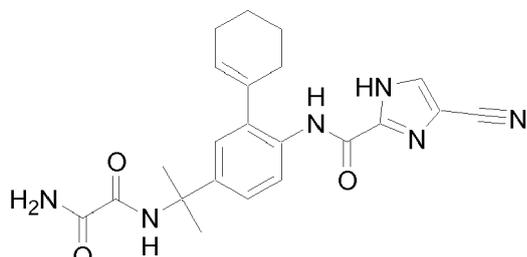
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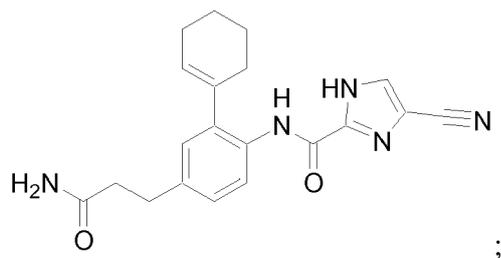
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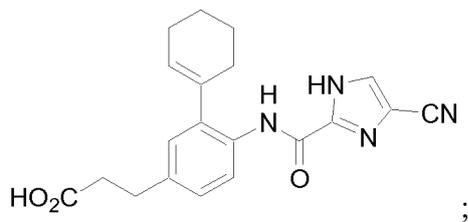
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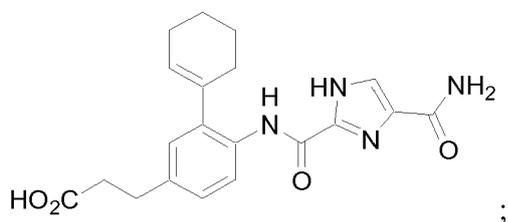
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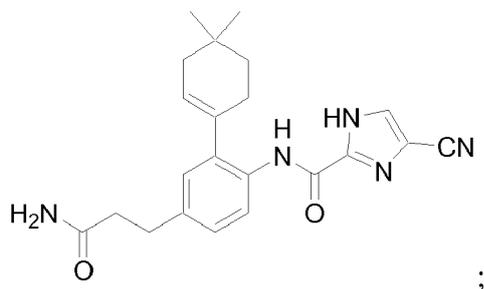
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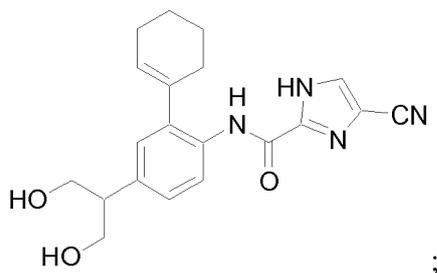
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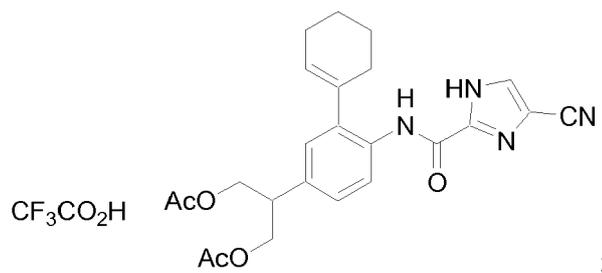
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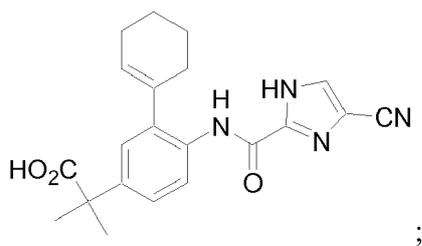
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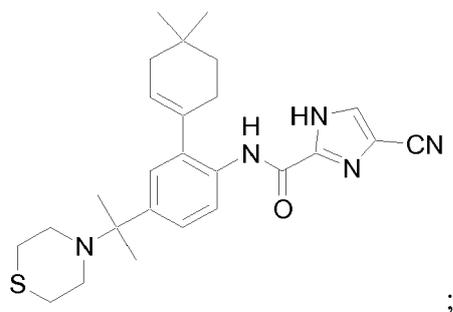
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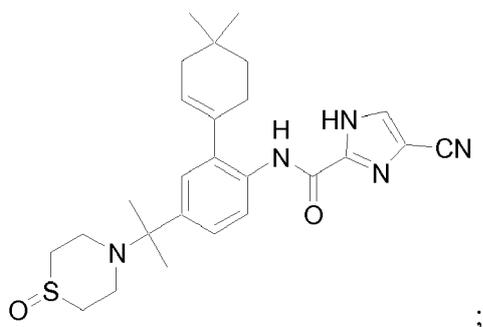
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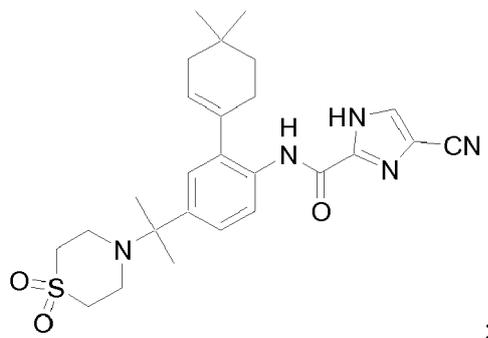
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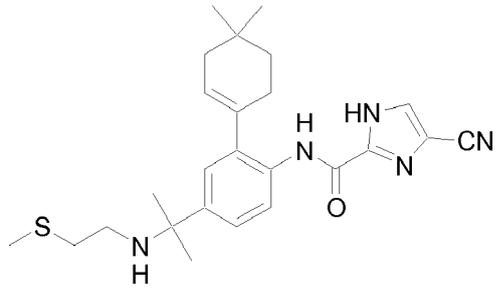
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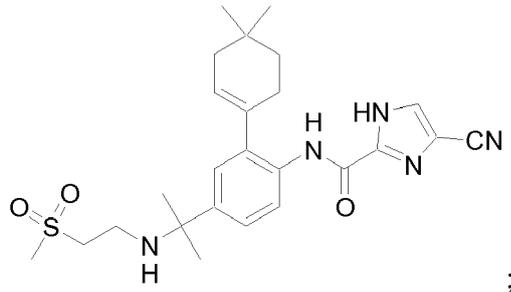
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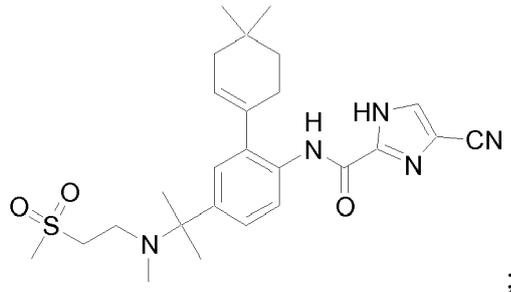
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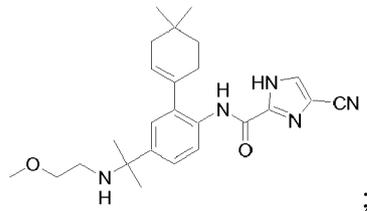
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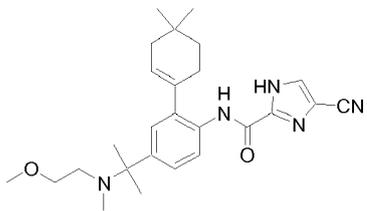
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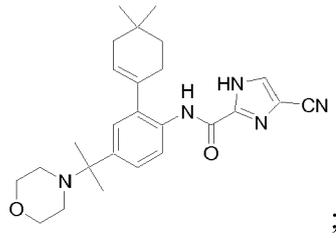
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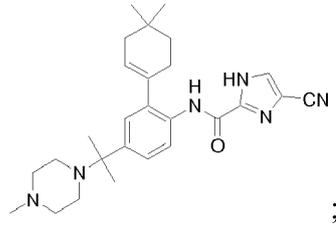
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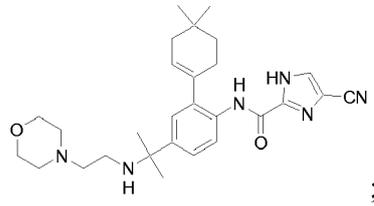


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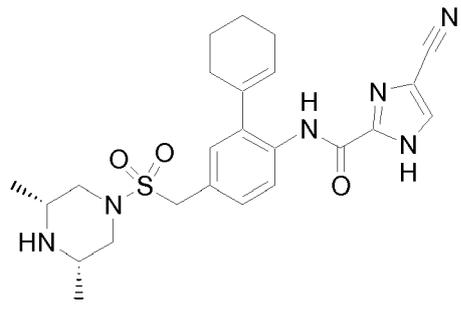
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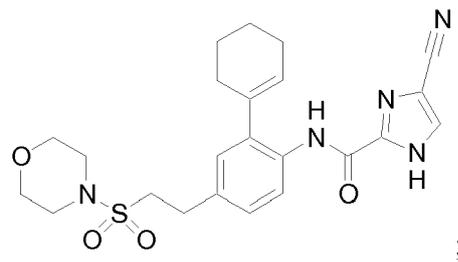
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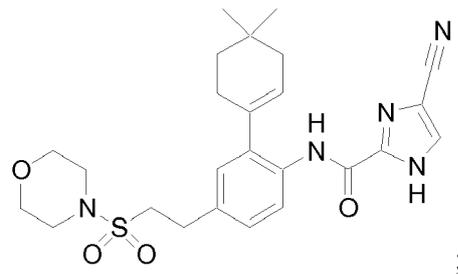
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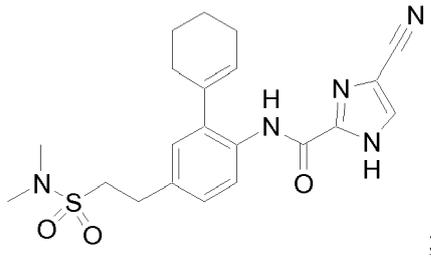
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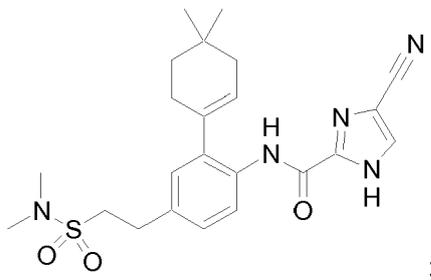


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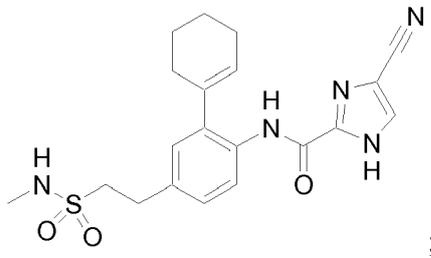
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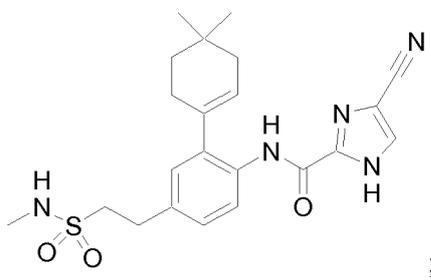
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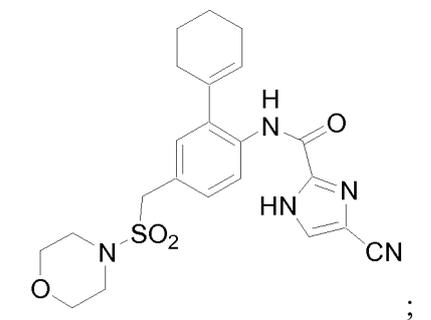
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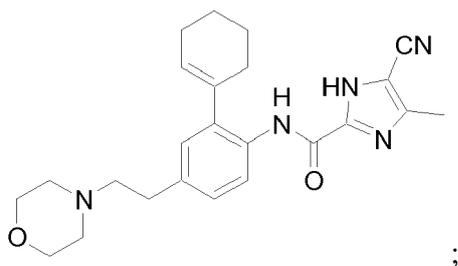
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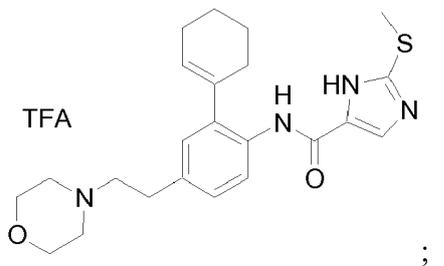
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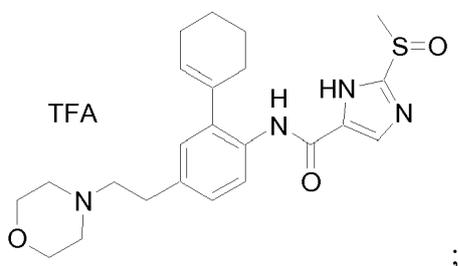
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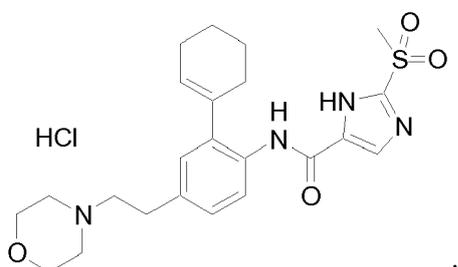
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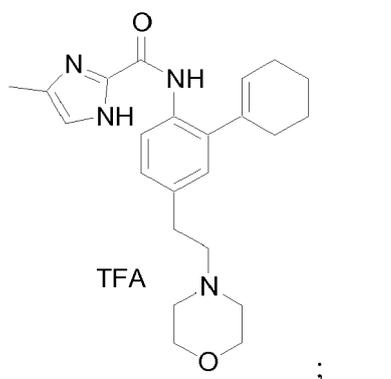
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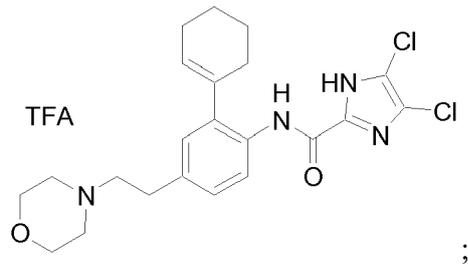
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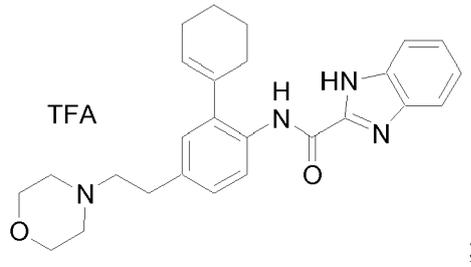
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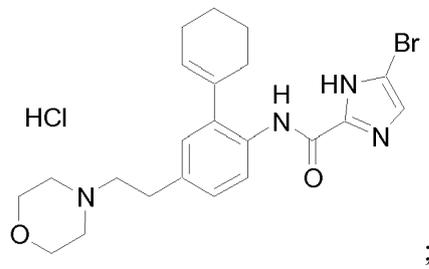
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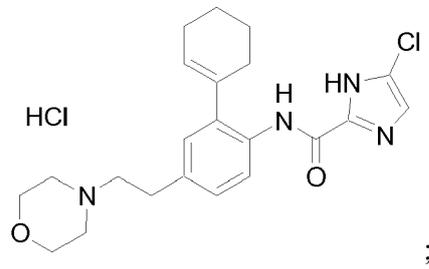
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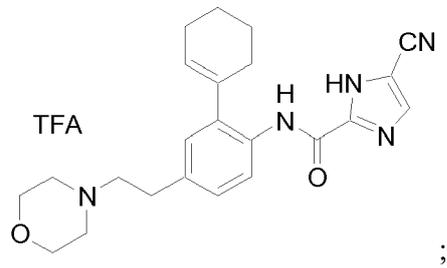
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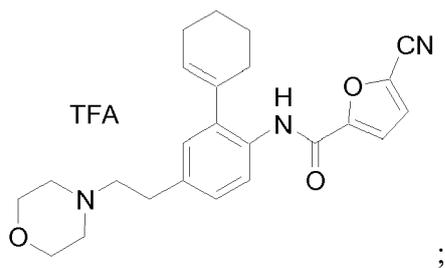
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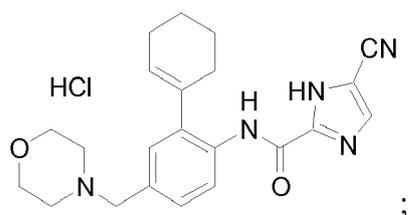
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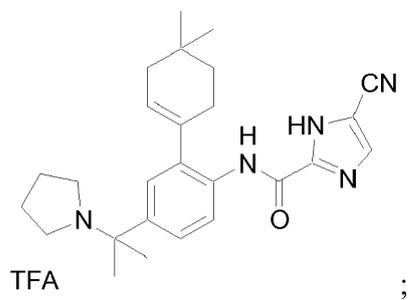
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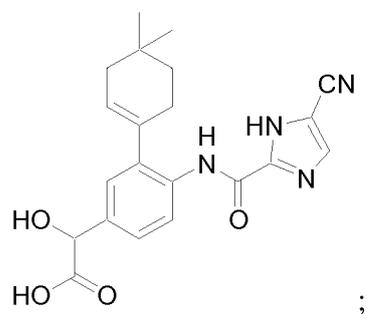
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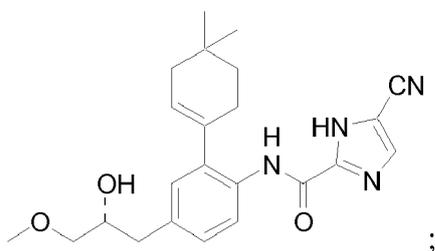
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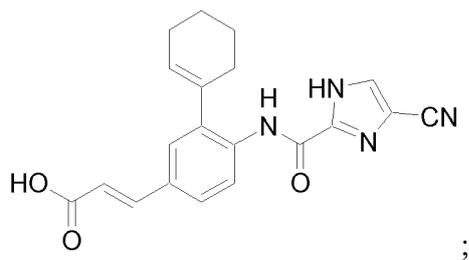
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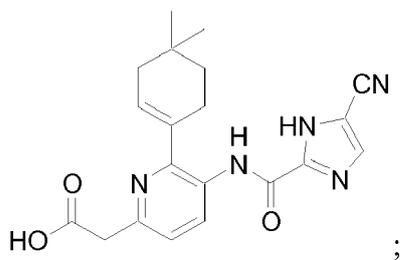
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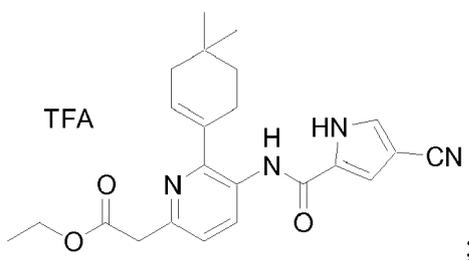
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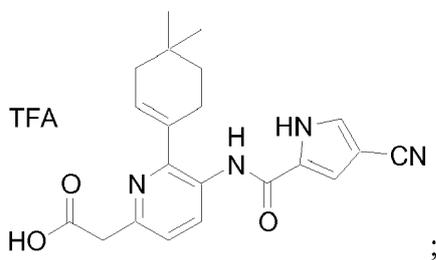
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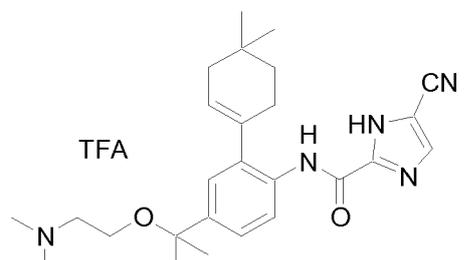
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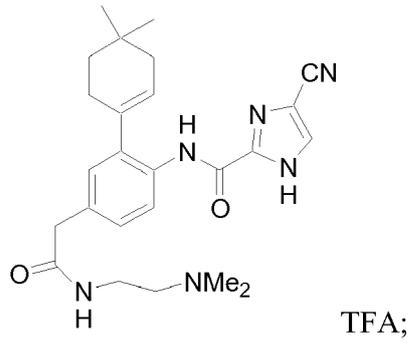


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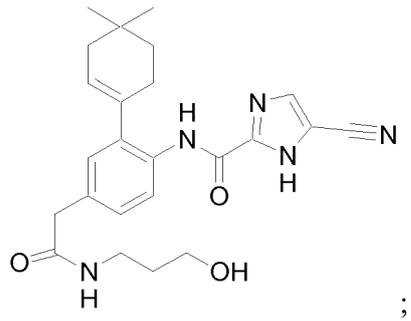
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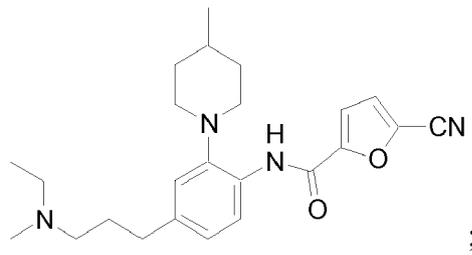
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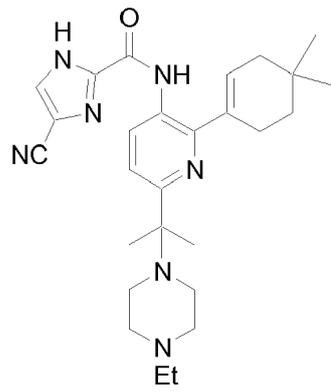
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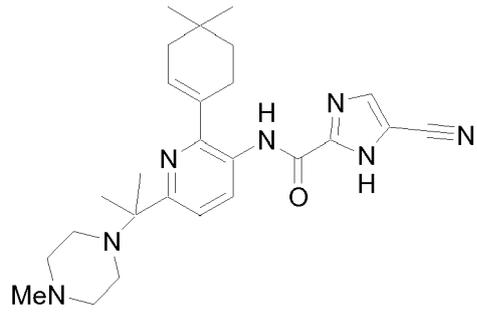


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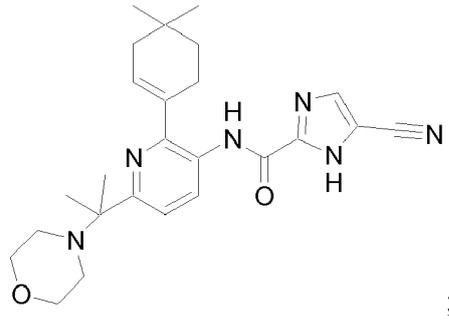
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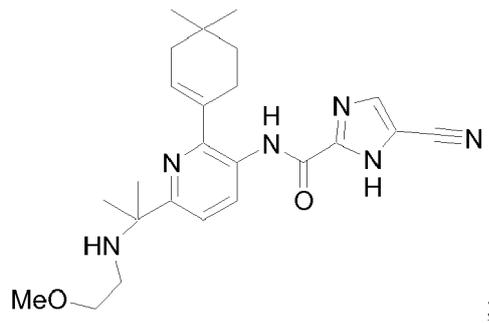
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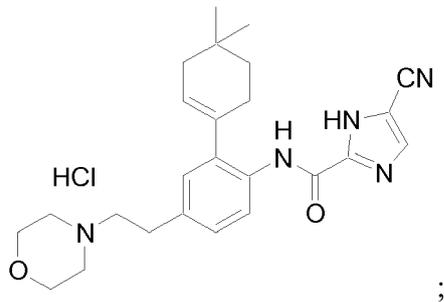
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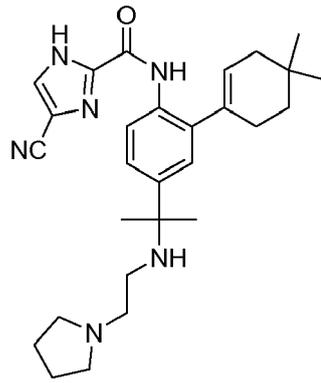


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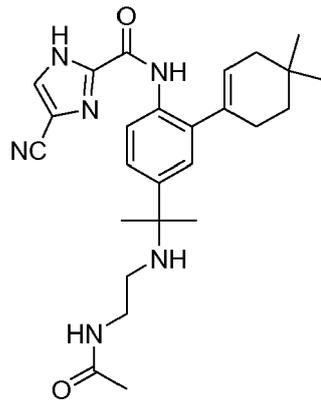
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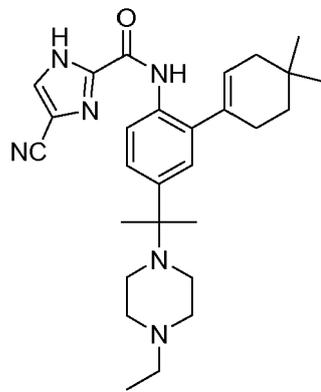
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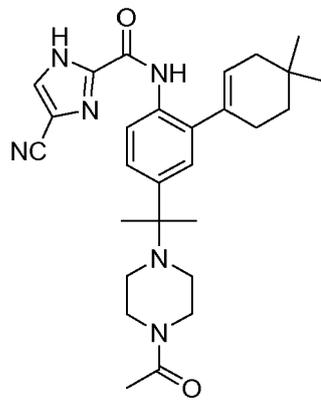
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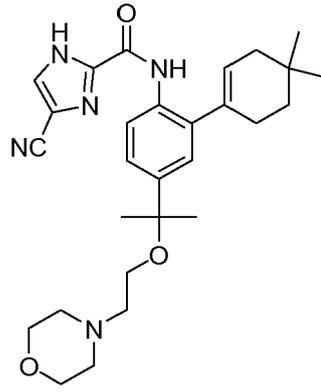
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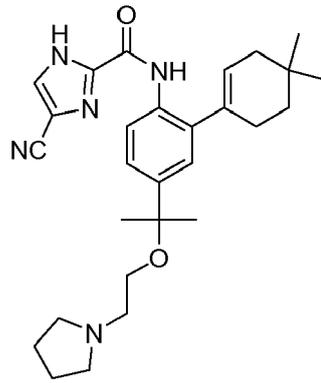


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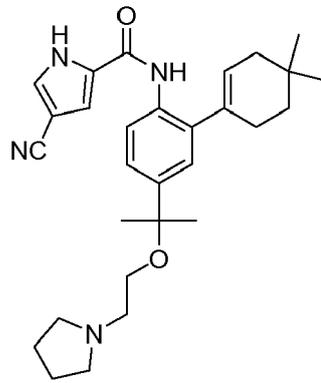
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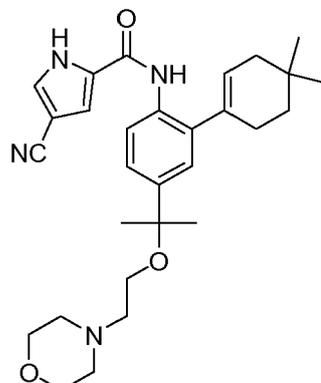
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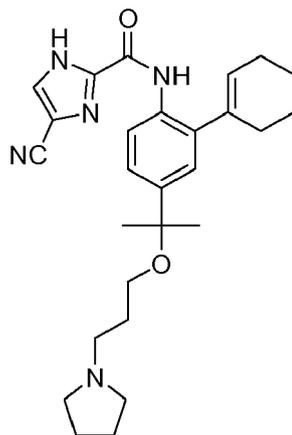


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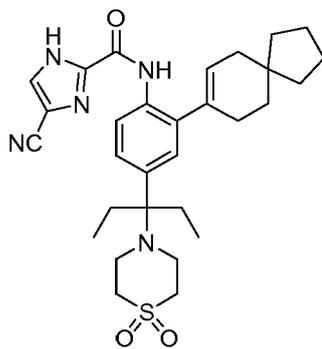
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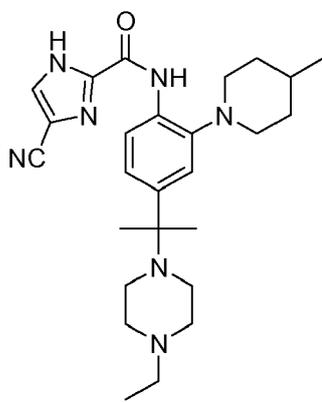
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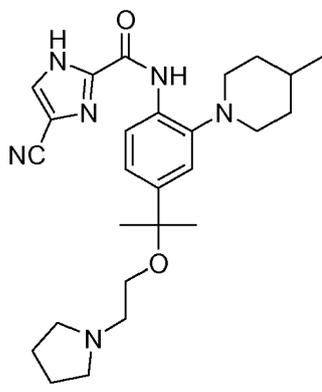
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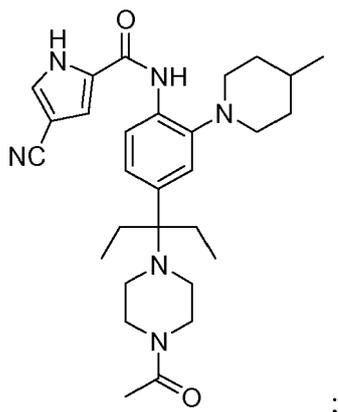
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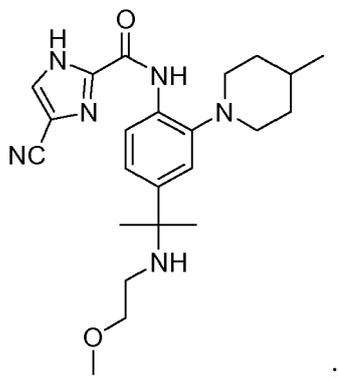
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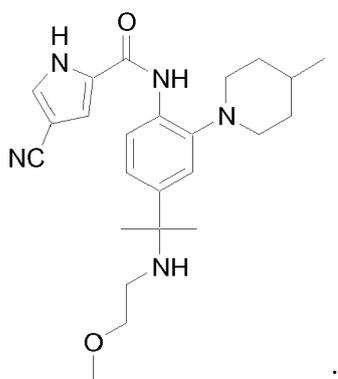
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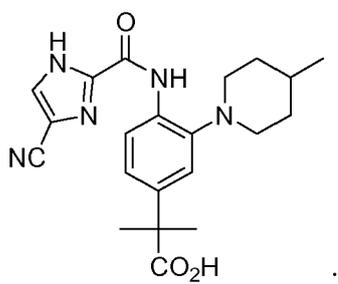
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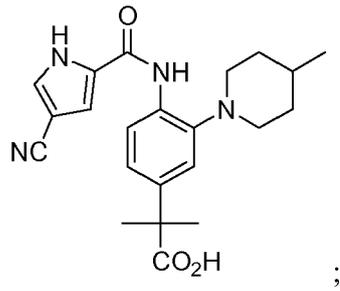
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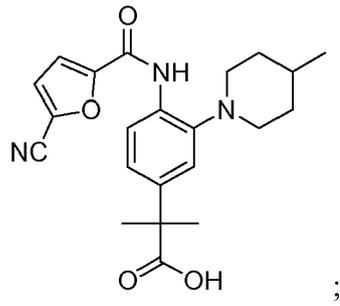
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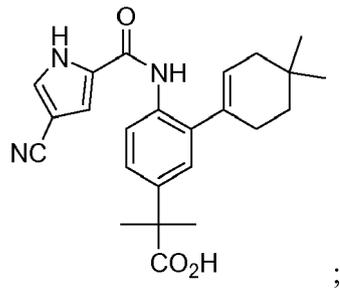
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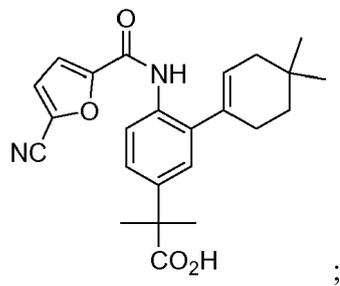
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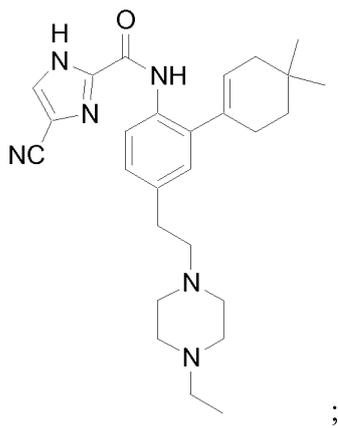
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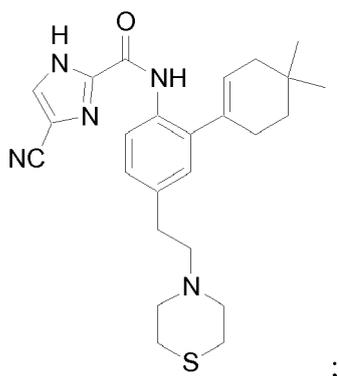


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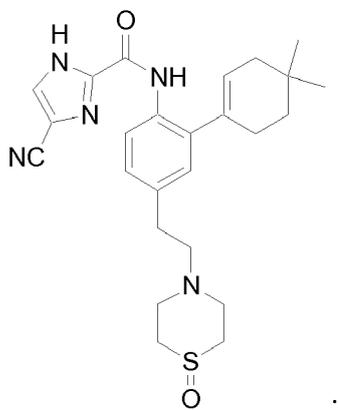
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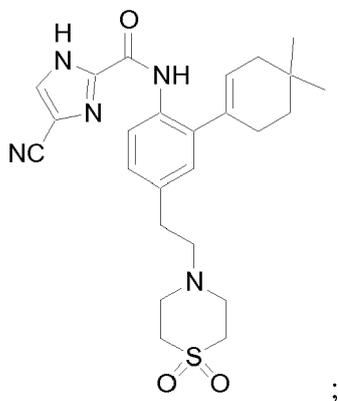
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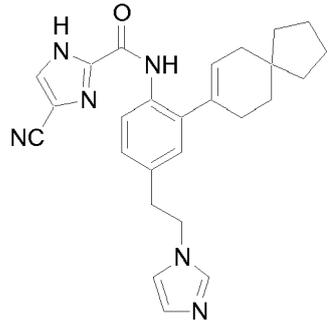


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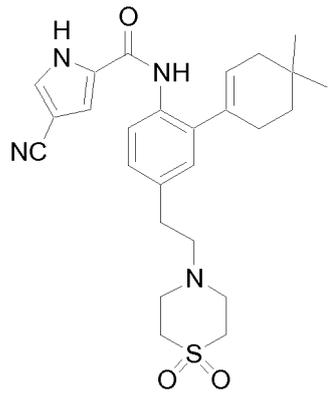
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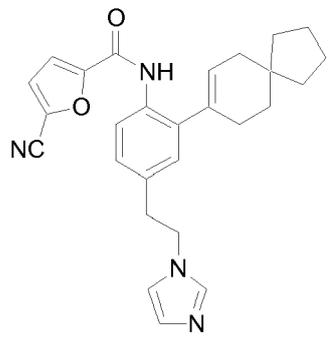
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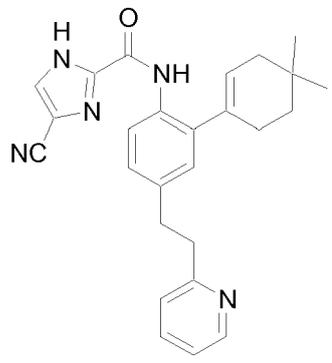
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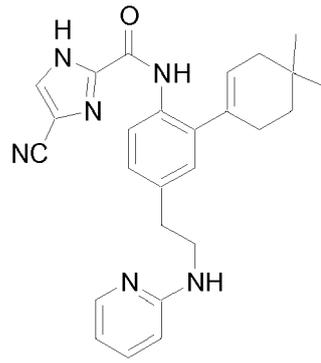
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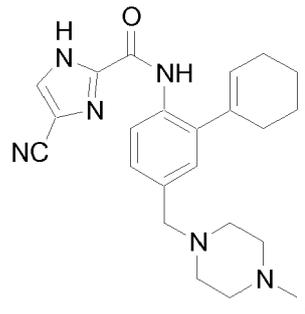
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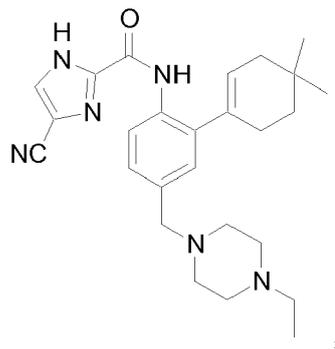
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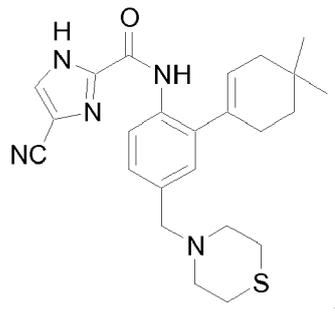
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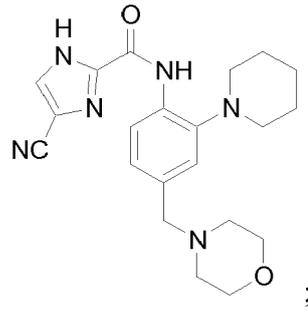


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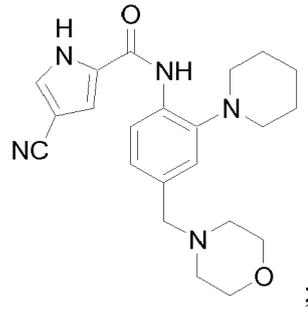
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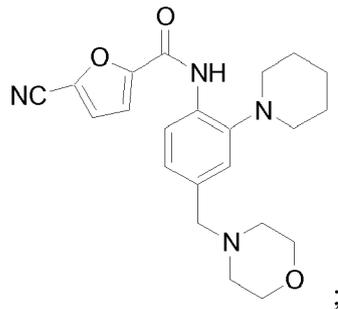
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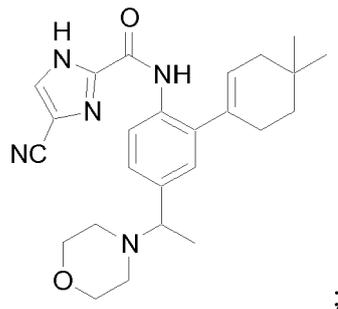
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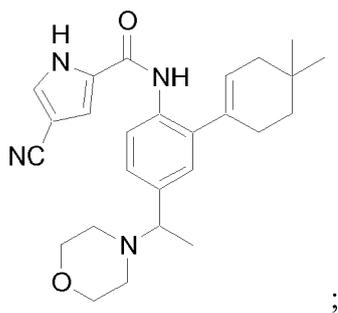


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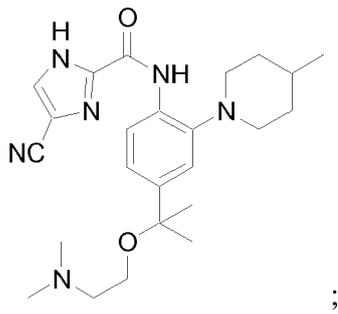
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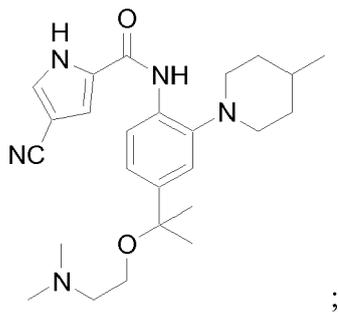
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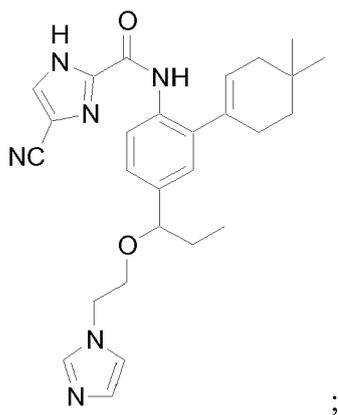
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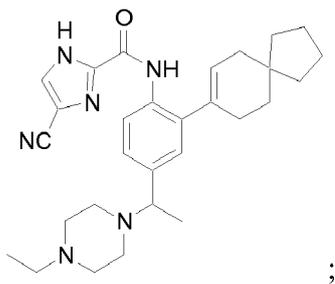
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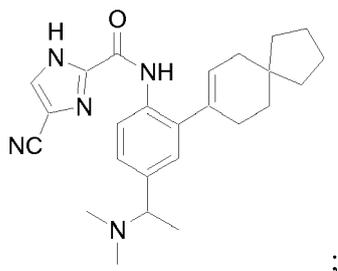
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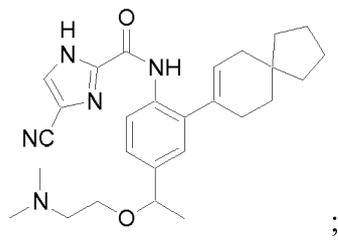
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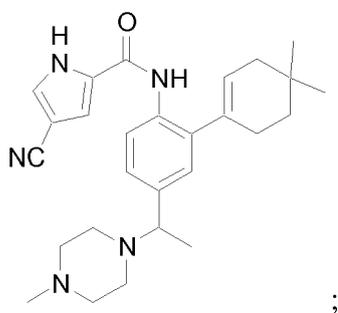
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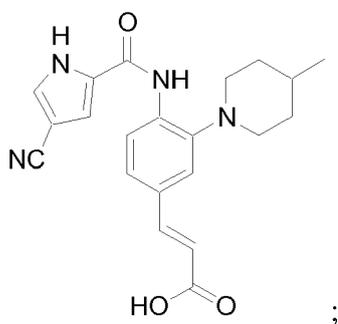
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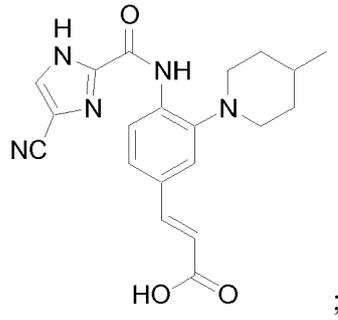


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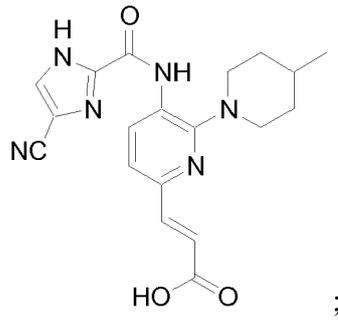
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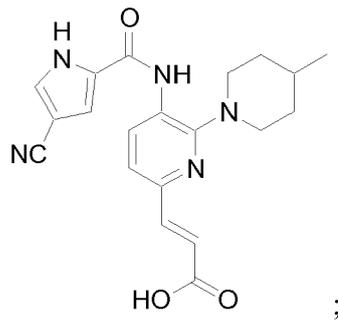
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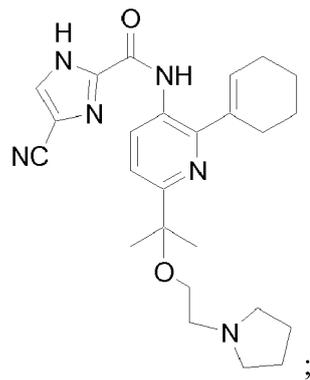
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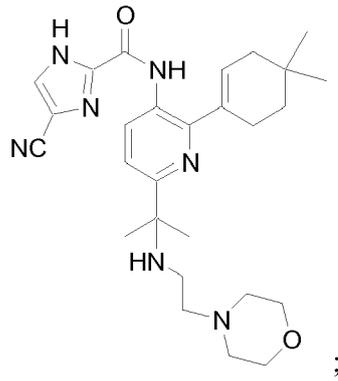
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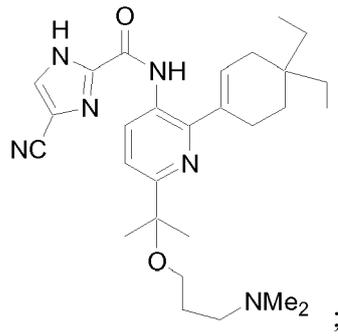
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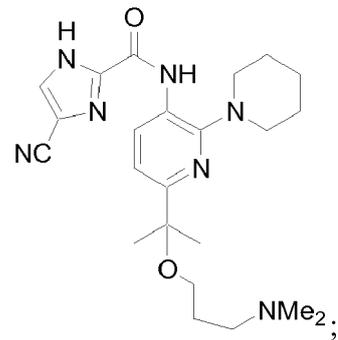
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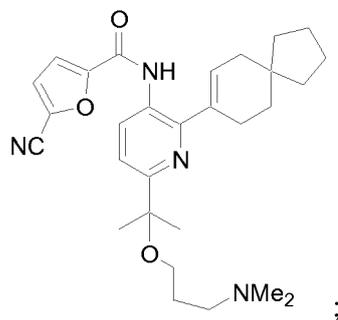
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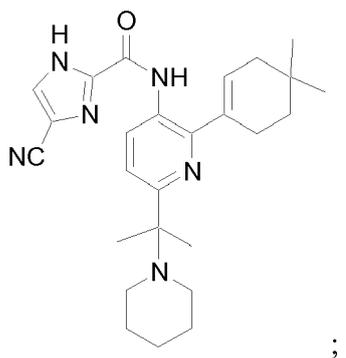
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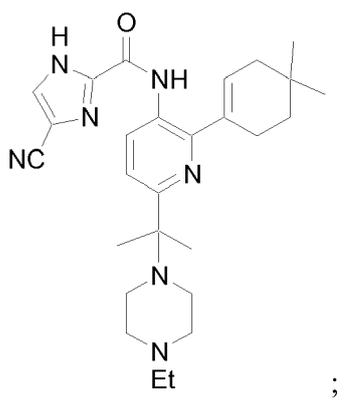
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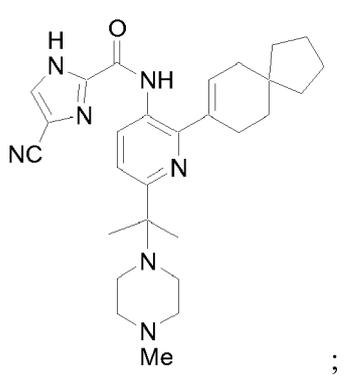
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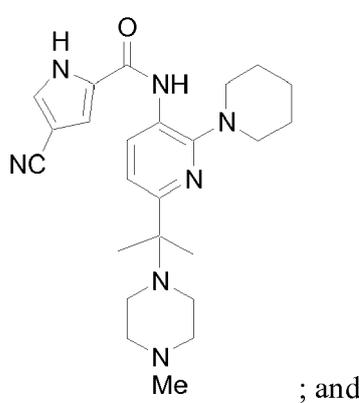
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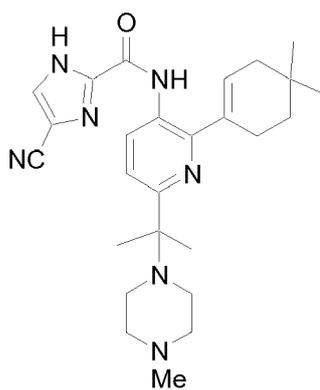
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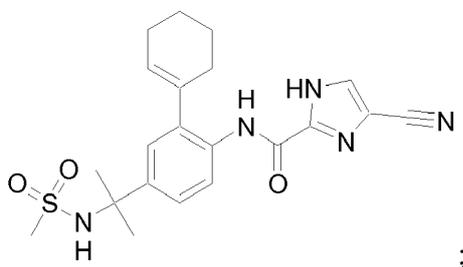
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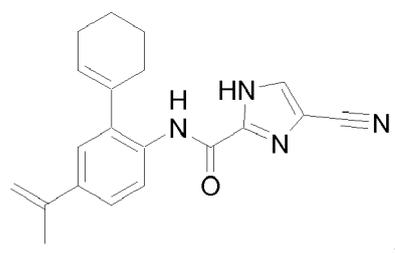
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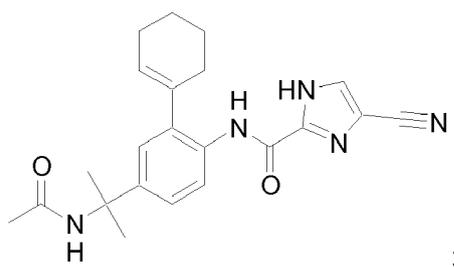
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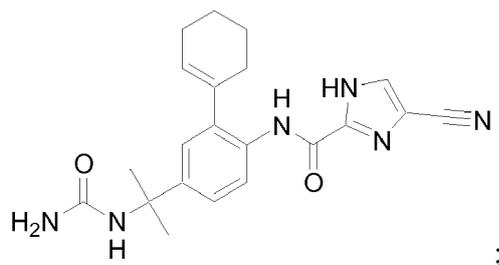
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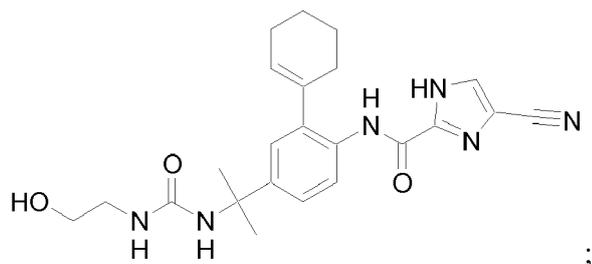
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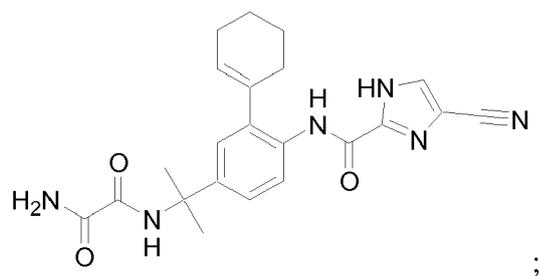
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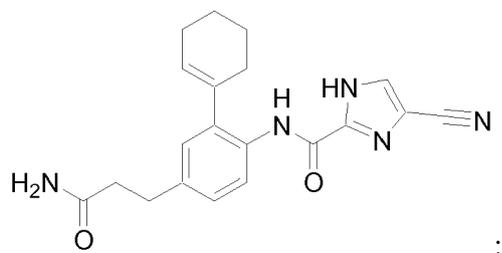
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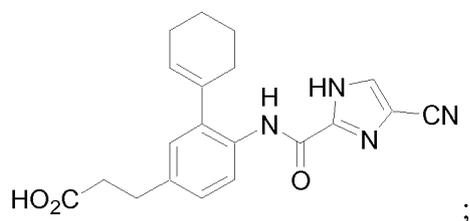
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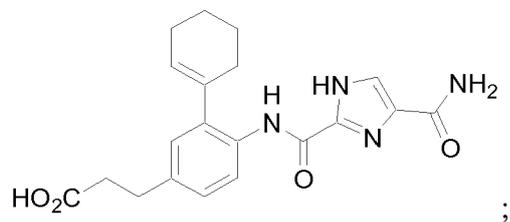
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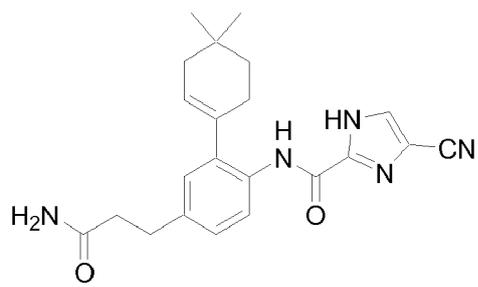
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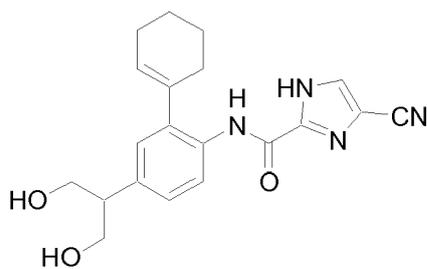
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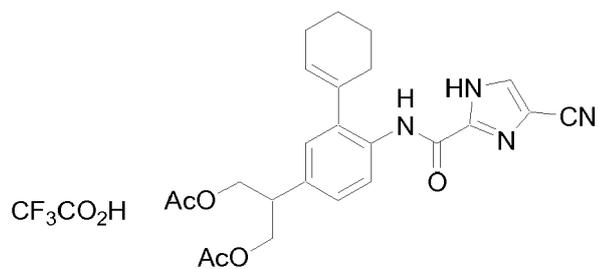
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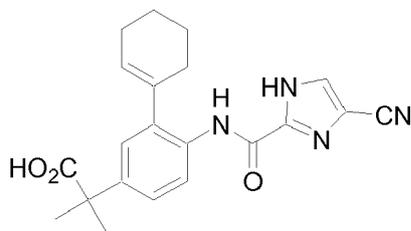
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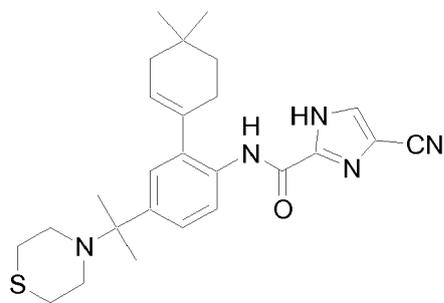
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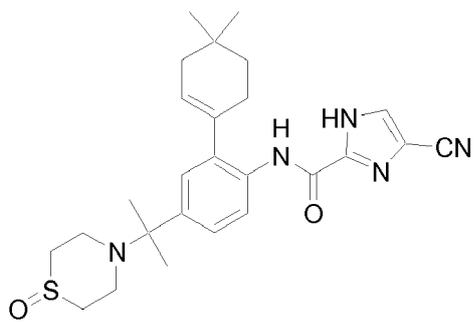


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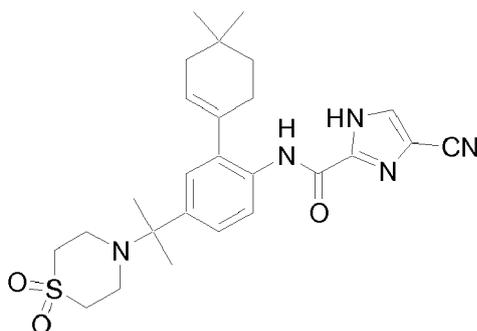
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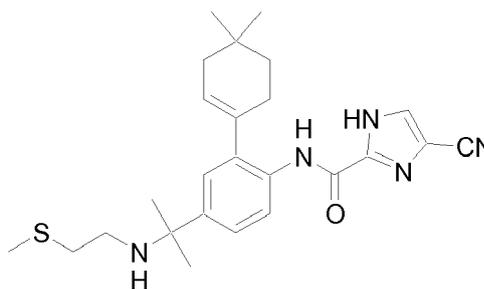
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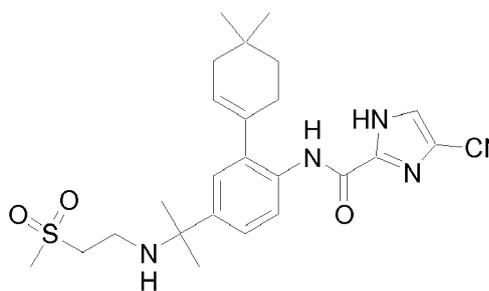
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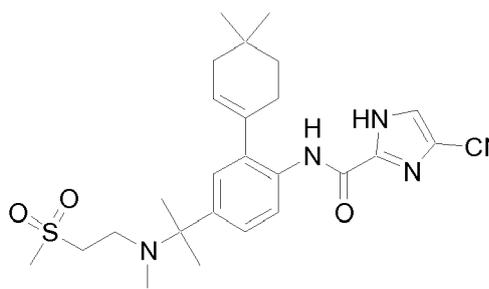
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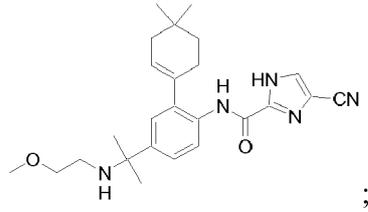
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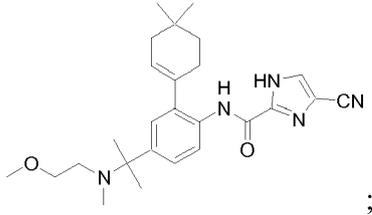
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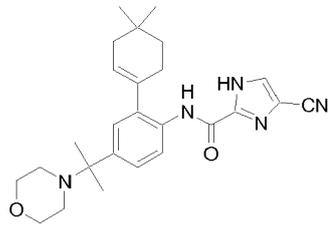


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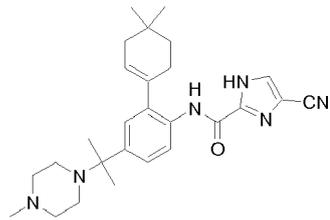
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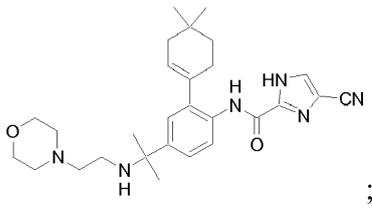
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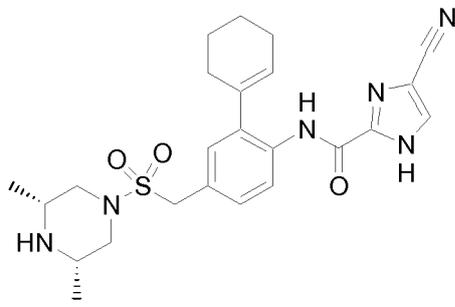
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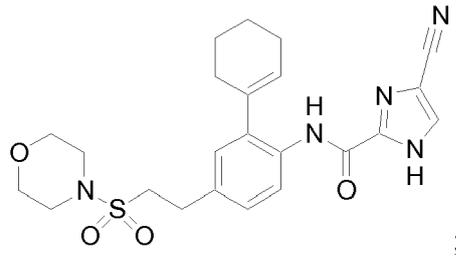
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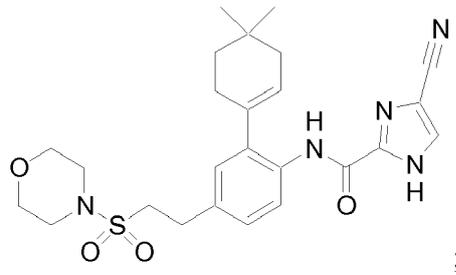


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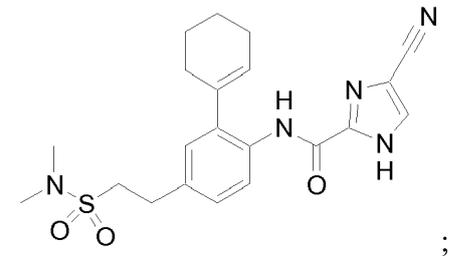
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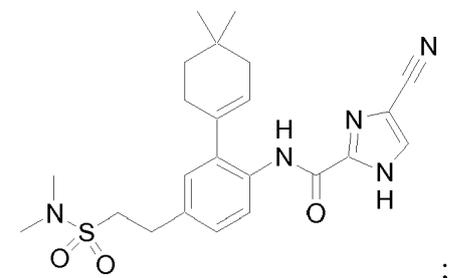
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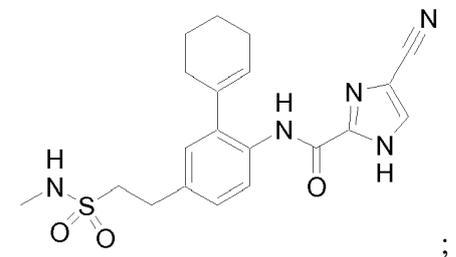
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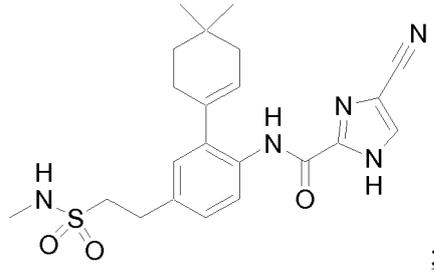
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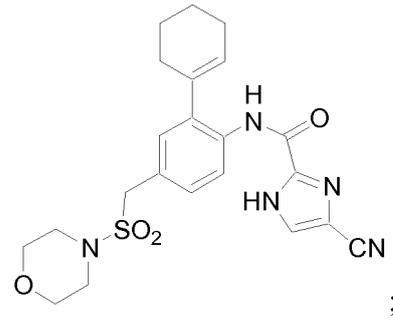
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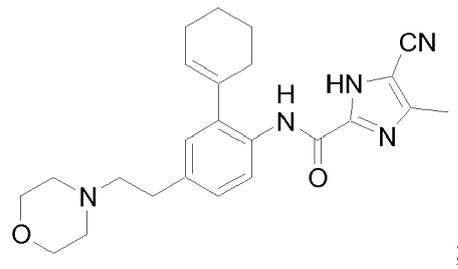
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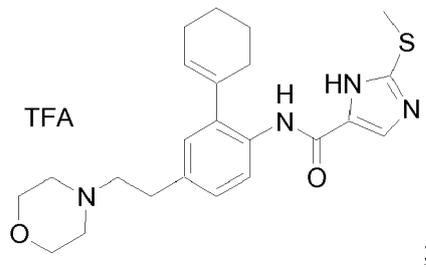
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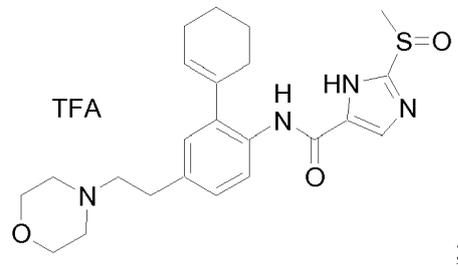
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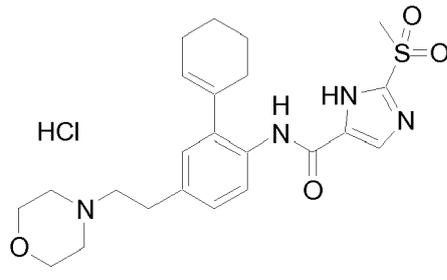
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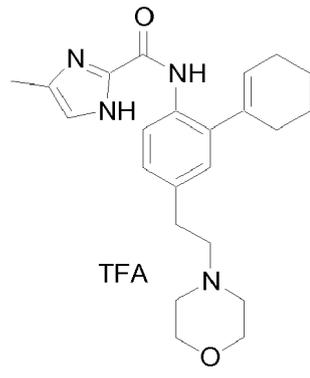
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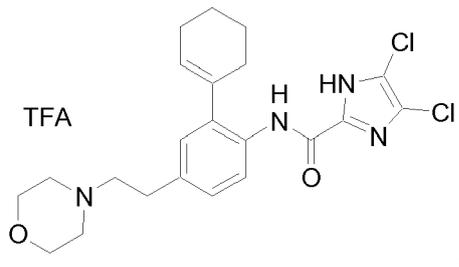
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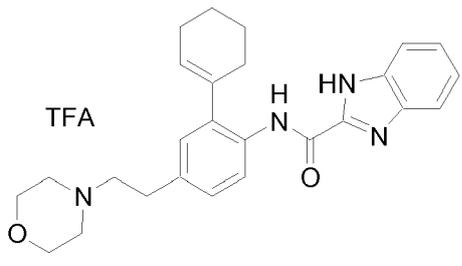
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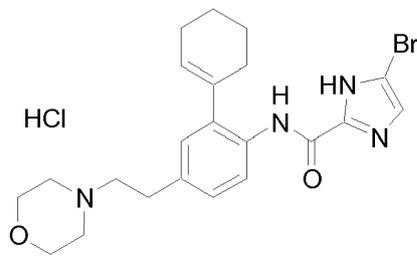
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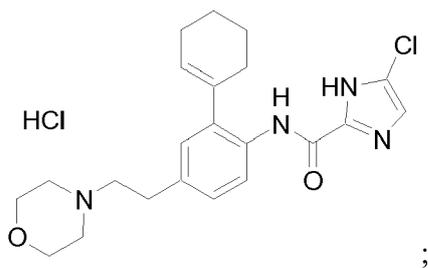
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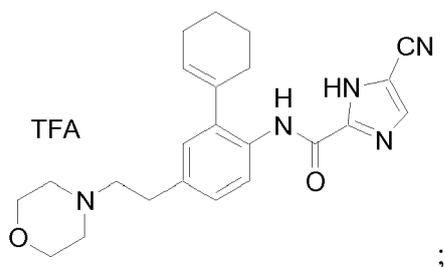


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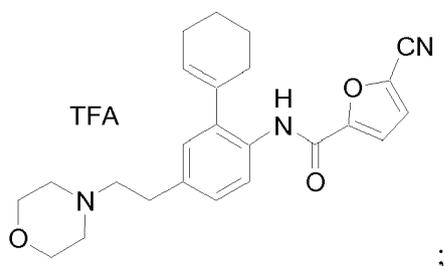


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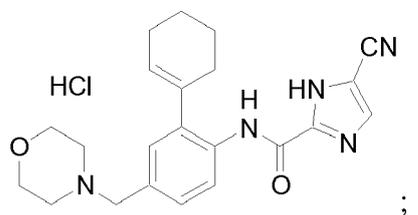
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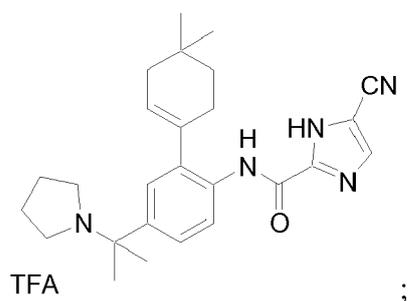
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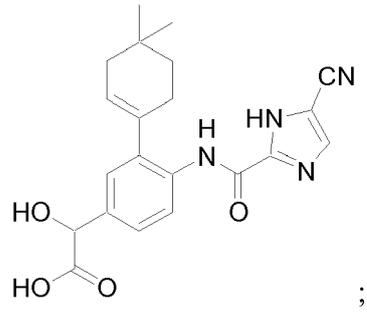


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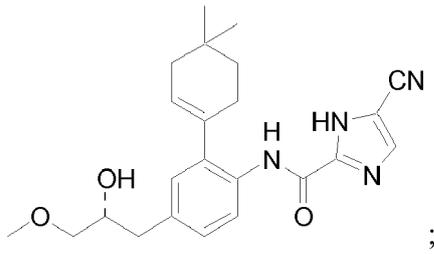
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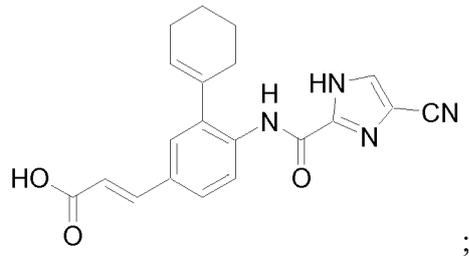
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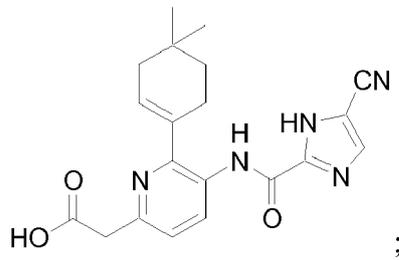
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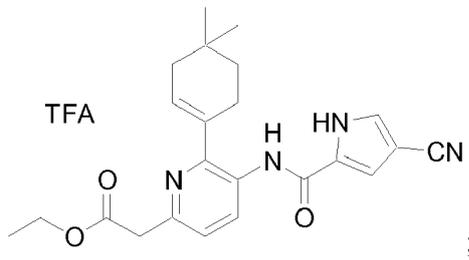
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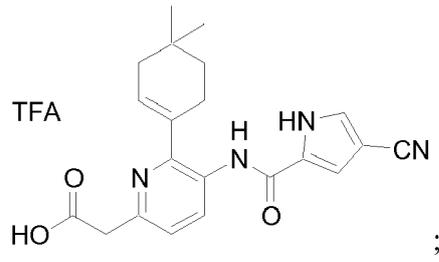
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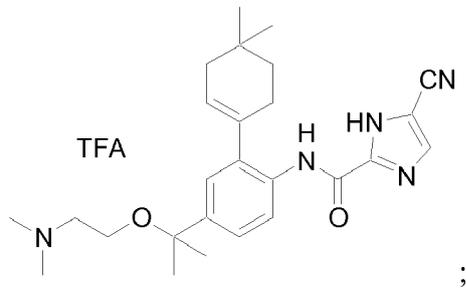
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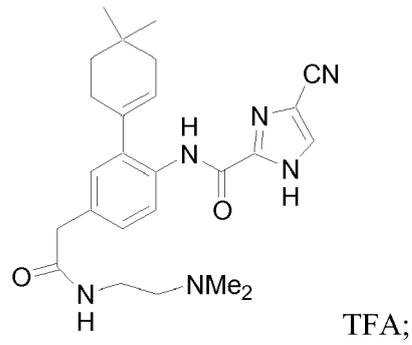
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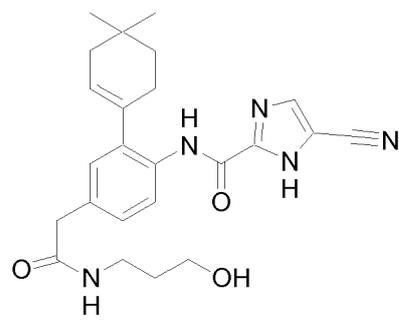
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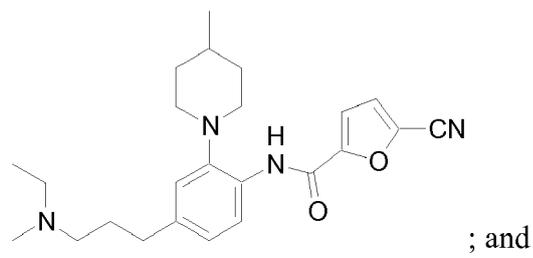
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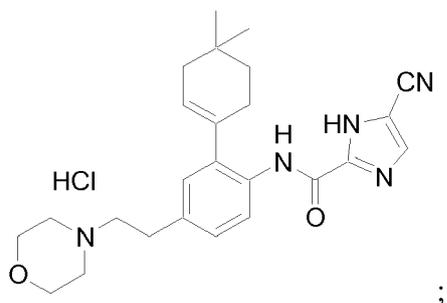
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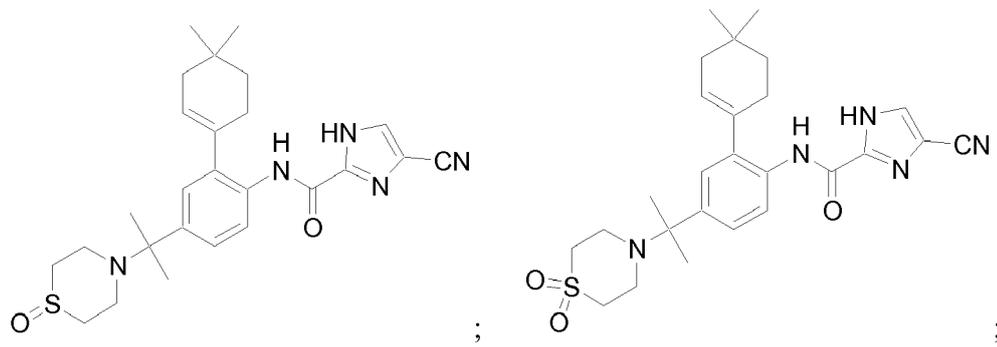
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in particular a compound selected from the group consisting of:

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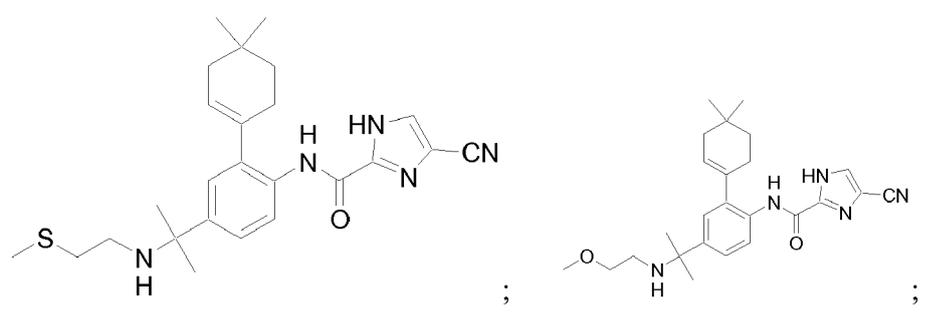
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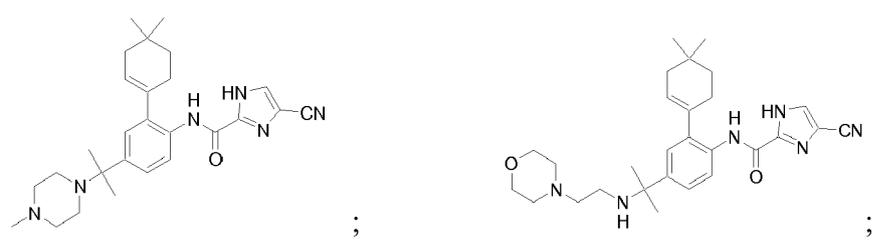
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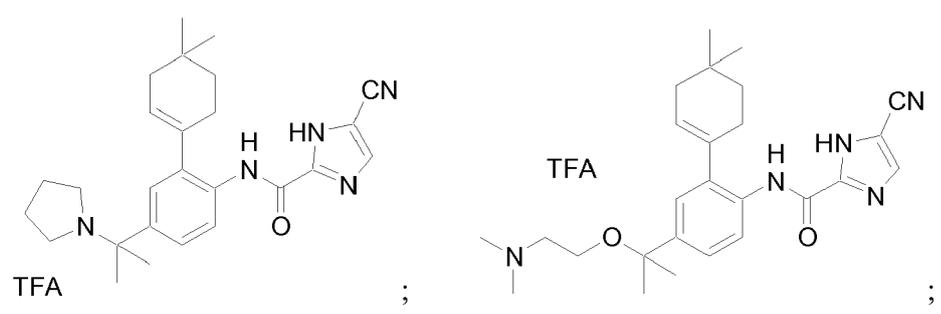
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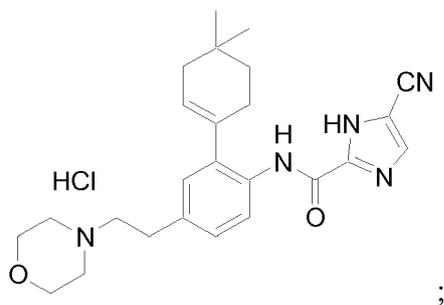
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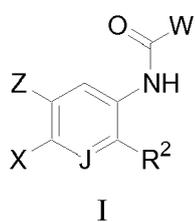


and solvates, hydrates, tautomers, and pharmaceutically acceptable salts thereof

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9. A compound of Formula I

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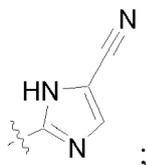


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wherein

W is

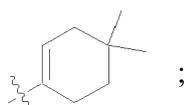
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R² is

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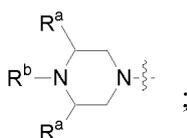


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Z is H;
J is CH, or N;
X is -C₍₁₋₆₎alkylR¹ wherein:

R¹ is

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wherein:

R^a is H or C₍₁₋₄₎alkyl; and

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R^b is -C₍₁₋₄₎alkyl-OH, -C₍₁₋₄₎alkyl-O-C₍₁₋₄₎alkyl, -C₍₁₋₄₎alkyl-C(O)O-C₍₁₋₄₎alkyl, -C₍₁₋₄₎alkylC(O)OH, or -C₍₁₋₄₎alkylC(O)ONa;

and solvates, hydrates, tautomers or pharmaceutically acceptable salts thereof

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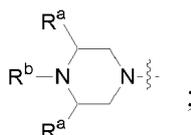
10. A compound of claim 9, wherein

J is CH;

X is -C₍₁₋₄₎alkylR¹ wherein:

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R¹ is



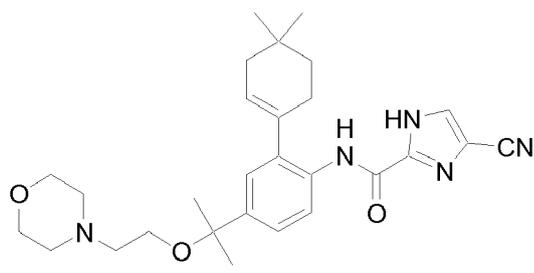
wherein:

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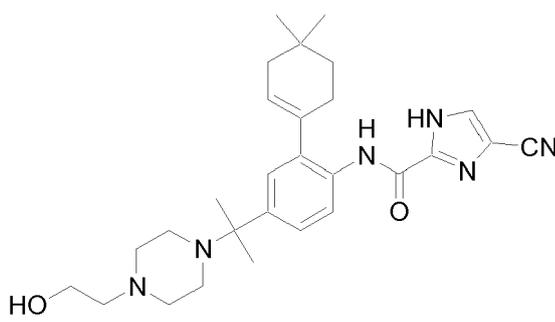
R^a is H; and R^b is -C₍₁₋₄₎alkyl-OH.

11. A compound selected from the group consisting of:

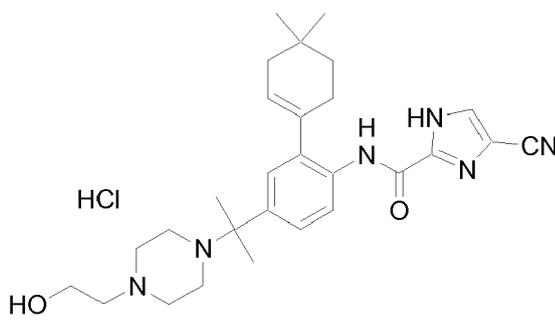
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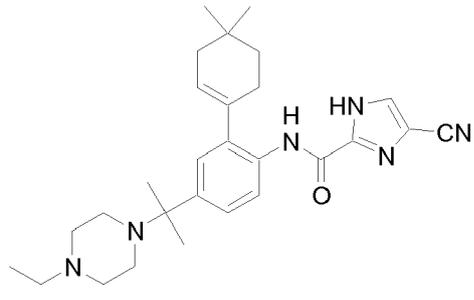


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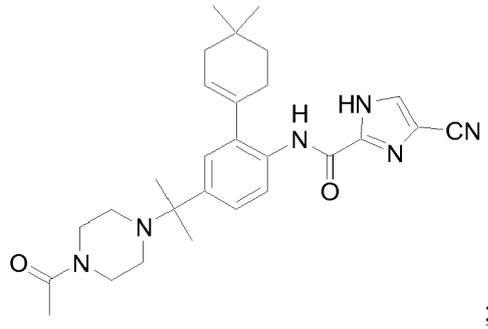
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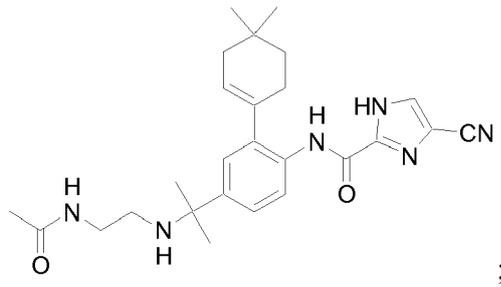
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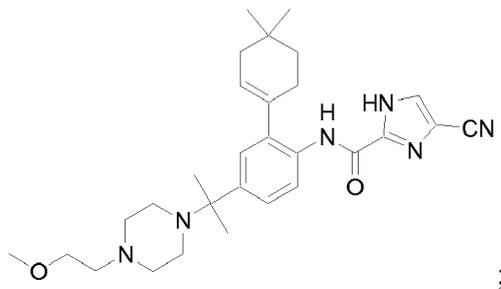
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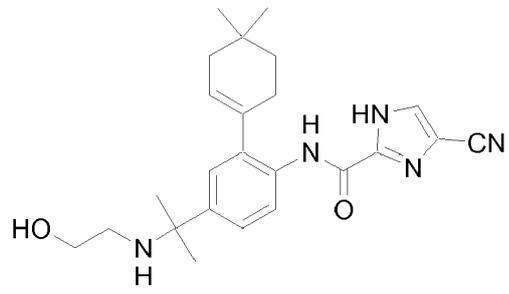
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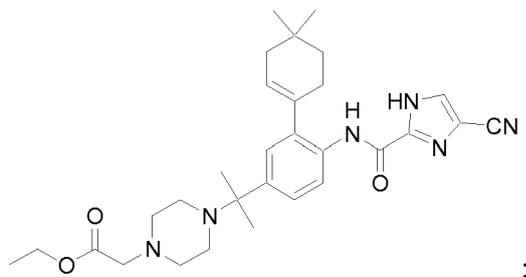
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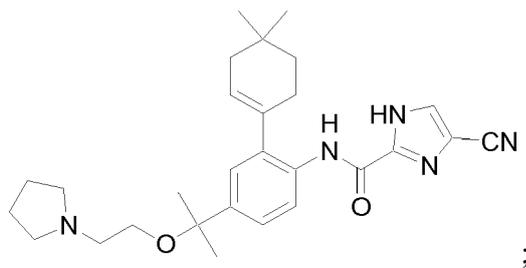
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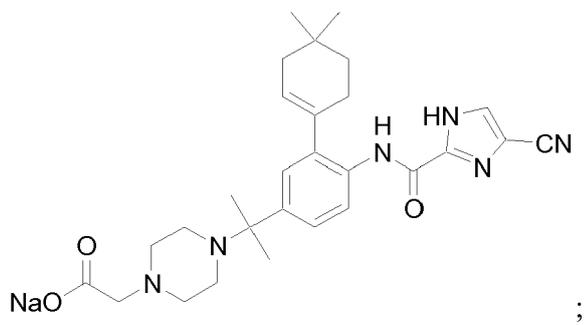
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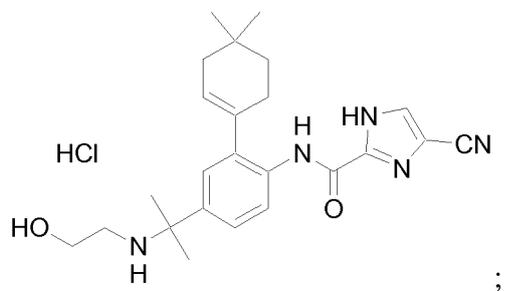
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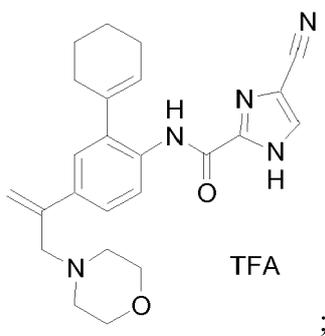
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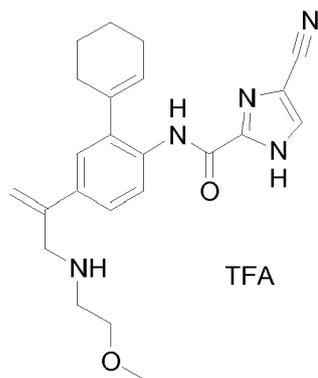
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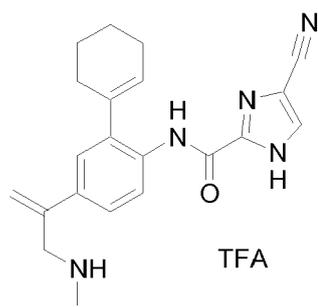
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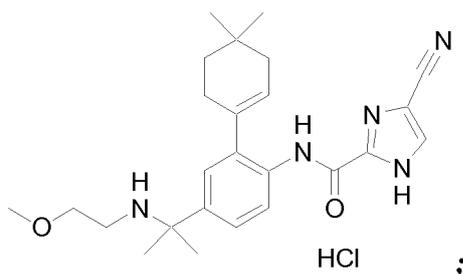
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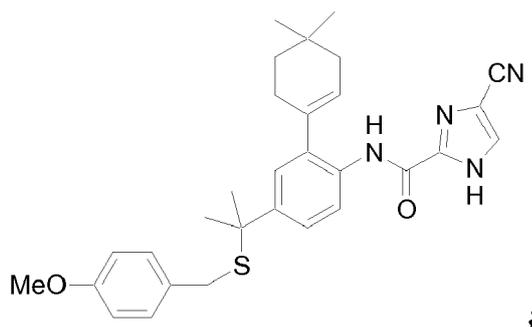
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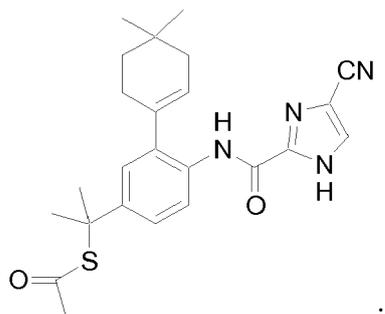


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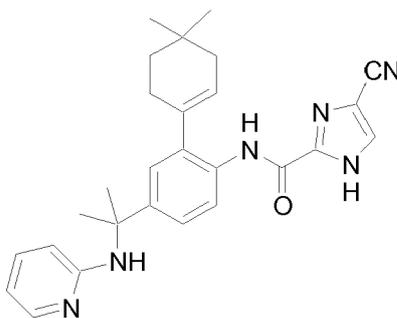
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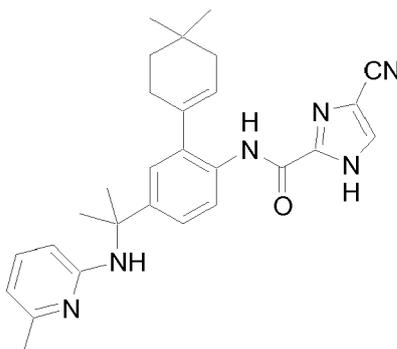
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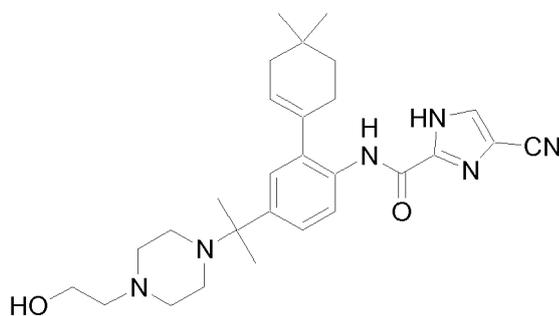
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and solvates, hydrates, tautomers, and pharmaceutically acceptable salts thereof; or a compound which is

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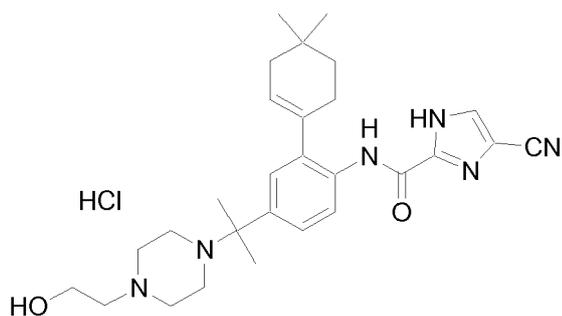
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and solvates, hydrates, tautomers, and pharmaceutically acceptable salts thereof; or a compound which is

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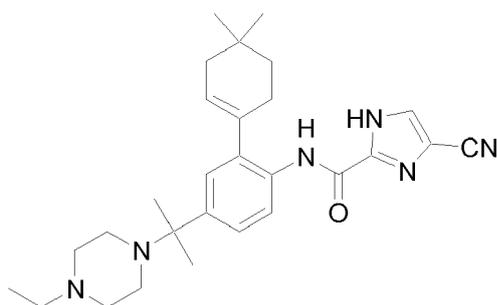


and solvates, hydrates, and tautomers thereof; or
a compound which is

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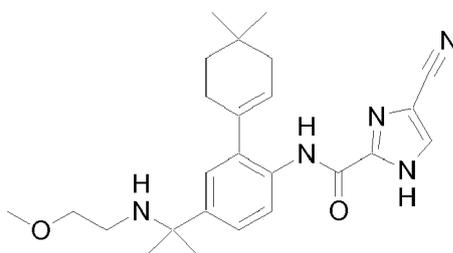


and solvates, hydrates, tautomers, and
pharmaceutically acceptable salts thereof; or
a compound which is

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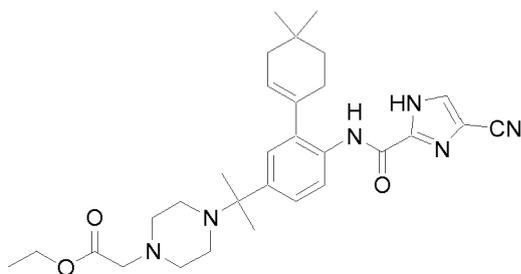


and solvates, hydrates, tautomers, and
pharmaceutically acceptable salts thereof; or
a compound which is

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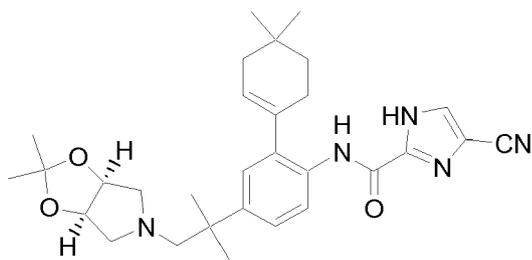
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and solvates, hydrates, tautomers, and
pharmaceutically acceptable salts thereof; or

a compound selected from the group consisting of:

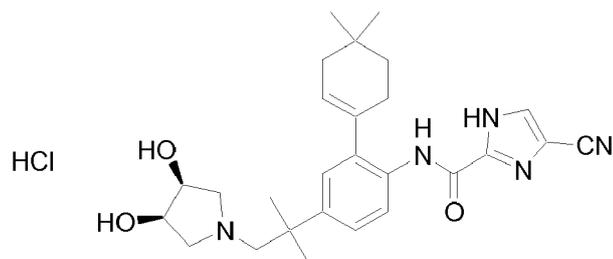
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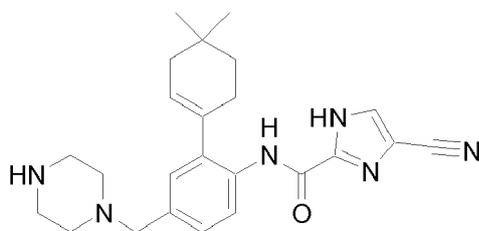
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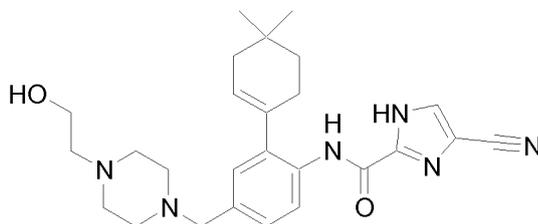
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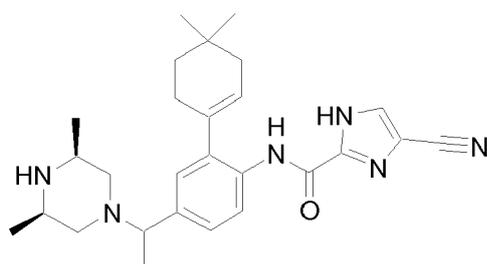
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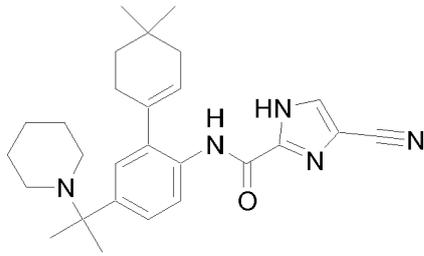


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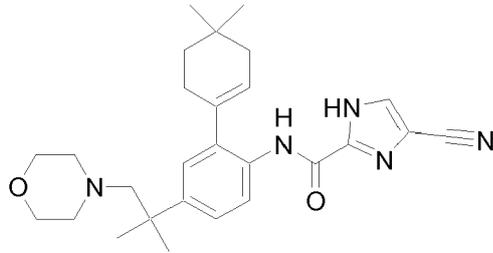
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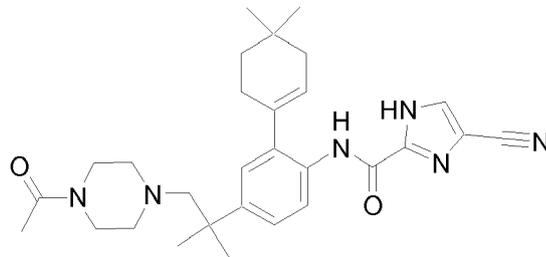
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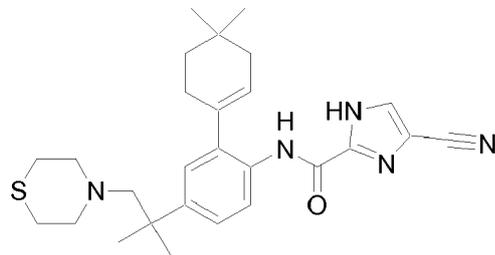
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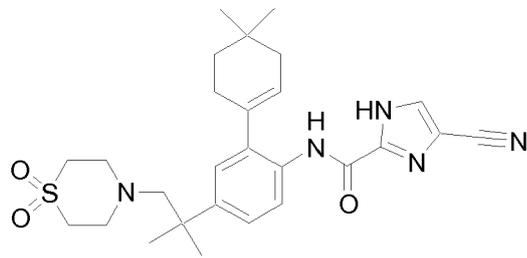
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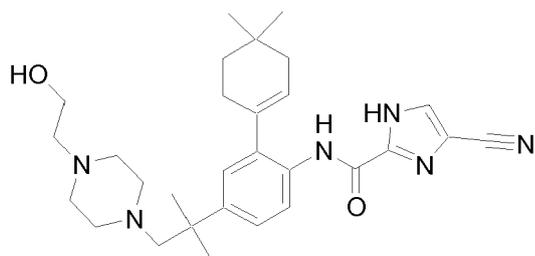
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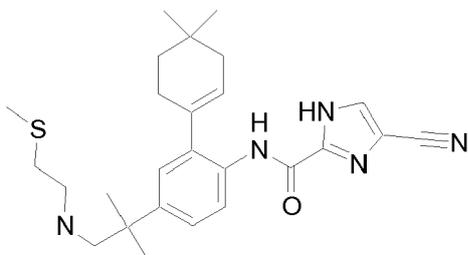
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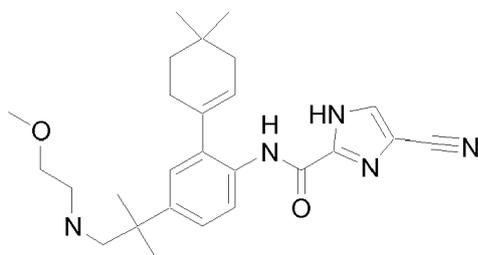
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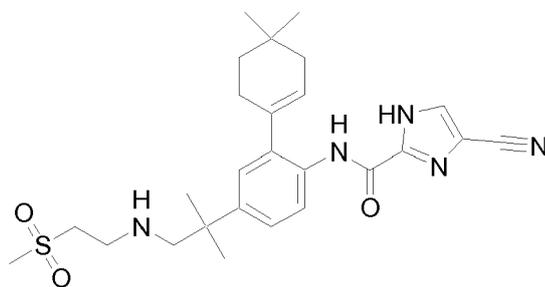
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and solvates, hydrates, tautomers, and pharmaceutically acceptable salts thereof

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12. A pharmaceutical composition, comprising a compound of claim 1 or a compound of claim 9 and a pharmaceutically acceptable carrier.

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13. 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 or of at least one compound of claim 9; in particular, wherein the dosage form is adapted for parenteral or oral administration.

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14. 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 or of at least one compound of claim 9; in particular wherein the protein tyrosine kinase is c-fms.

15. A compound for use in a method of treating an indication or indications in a mammal, comprising administering to the mammal a therapeutically effective amount of at least one compound of claim 1 or of at least one compound of claim 9; wherein the indication is inflammation; or

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wherein the indication is cancer; or wherein the indication is cardiovascular disease; or
wherein the indications are diseases with an inflammatory component selected from the group consisting of: glomer-
ulonephritis, inflammatory bowel disease, prosthesis failure, sarcoidosis, congestive obstructive pulmonary disease,
5 idiopathic pulmonary fibrosis, asthma, pancreatitis, HIV infection, psoriasis, diabetes, tumor related angiogenesis,
age-related macular degeneration, diabetic retinopathy, restenosis, schizophrenia and Alzheimer's dementia; or
wherein the indication is pain selected from the group consisting of: skeletal pain caused by tumor metastasis,
osteoarthritis, and visceral, inflammatory, and neurogenic pain; or
10 wherein the indication is 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 in a mammal; or
wherein the indications are autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis and
other forms of inflammatory arthritis, psoriasis, Sjogren's syndrome, multiple sclerosis, or uveitis; or
15 a compound 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 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 or of at least one compound of claim 9.

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EUROPEAN SEARCH REPORT

Application Number
EP 13 17 9745

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	WO 2004/096795 A (DIMENSIONAL PHARM INC [US]; PLAYER MARK R [US]; BAINBUR NAND [US]; BRA) 11 November 2004 (2004-11-11) * page 40; claims 5, 10-18 * -----	1-15	INV. C07D233/90 C07D235/16 C07D307/68 C07D401/12
X	US 2005/113566 A1 (PLAYER MARK R [US] ET AL) 26 May 2005 (2005-05-26) * claims 1-4 * -----	1-15	C07D403/12 C07D407/12 A61K31/4178 A61P11/00
X,P	US 2006/258666 A1 (PLAYER MARK R [US] ET AL) 16 November 2006 (2006-11-16) * the whole document * -----	1-15	A61P25/00 A61P35/00
			TECHNICAL FIELDS SEARCHED (IPC)
			C07D A61K A61P
The present search report has been drawn up for all claims			
Place of search Munich		Date of completion of the search 16 December 2013	Examiner Gregoire, Ariane
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

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EPO FORM 1503 03.82 (P04C01)

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 13 17 9745

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
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16-12-2013

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004096795 A	11-11-2004	CA 2536964 A1	11-11-2004
		EP 1631560 A2	08-03-2006
		JP 2007525460 A	06-09-2007
		MX PA05011503 A	31-05-2006
		US 2005004112 A1	06-01-2005
		WO 2004096795 A2	11-11-2004
US 2005113566 A1	26-05-2005	AU 2005299500 A1	04-05-2006
		CN 101087773 A	12-12-2007
		EP 1807406 A2	18-07-2007
		JP 2008517944 A	29-05-2008
		US 2005113566 A1	26-05-2005
		WO 2006047503 A2	04-05-2006
US 2006258666 A1	16-11-2006	NONE	

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

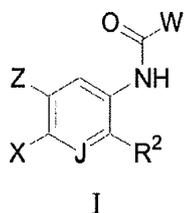
- US 60793694 B [0001]
- US 60871171 B [0001]
- US 6383790 B [0011]
- US 6346625 B [0011]
- US 6235746 B [0011]
- US 6100254 B [0011]
- WO 0147897 A [0011]
- WO 0027820 A [0011]
- WO 02068406 A [0011]
- WO 0147919 A [0079]
- WO 1996011932 A [0132]
- WO 9720822 A [0301]
- WO 2004096795 A [0358]
- WO 2004096795 A2 [0420] [0490]
- WO 2005063705 A [0490]
- US 2005131022 A1 [0490]
- WO 2005131022 A1 [0490]
- US 2005131022 A [0490]
- EP 0356234 A2 [0490]
- WO 2000018734 A [0490]
- WO 200409679 A [0490]
- WO 2003053972 A [0490]

Non-patent literature cited in the description

- **M. HUDLICKY.** Reductions in Organic Chemistry. Wiley, 1984 [0072]
- **N. MIYaura ; A. SUZUKI.** *Chem. Rev.*, 1995, vol. 95, 2457 [0073]
- **J. K. STILLE.** *Angew. Chem, Int. Ed. Engl.*, 1986, vol. 25, 508-524 [0073]
- **S. BRAESE ; A. DE MEIJERE.** Metal-Catalyzed Cross-Coupling Reactions. Wiley-VCH, 2004, 217-315 [0073]
- **A. SUZUKI.** Metal-Catalyzed Coupling Reactions. Wiley-VCH, 1988 [0073]
- **THEODORA W. GREENE ; PETER G. M. WUTS.** Protective Groups in Organic Synthesis. John Wiley and Sons, Inc, 1991 [0077] [0124]
- *Adv. Syn. Catalysis*, 2004, vol. 346, 111-124 [0079]
- *J. Org. Chem.*, 1996, vol. 61, 3849-3862 [0079]
- **LAROCK, RICHARD C.** Comprehensive Organic Transformation. VCH, 1989, 8-17 [0079]
- *J. Med. Chem.*, 2003, vol. 46, 4676-86 [0079]
- *J. Chem. Soc., Perkin Trans. 2*, 2002, 1039-1051 [0079]
- *J. Am. Chem. Soc.*, 2004, vol. 126, 5182 [0085]
- *J. Org. Chem.*, 1983, vol. 48, 1559-60 [0095]
- *J. Med. Chem.*, 2005, vol. 48 (11), 3930-34 [0098]
- *Bioorg. Med. Chem. Lett.*, 2004, vol. 14 (2), 455-8 [0098]
- **B. KOUTEK et al.** *Synth. Commun.*, 1976, vol. 6 (4), 305-8 [0110]
- *Tetrahedron: Asymmetry*, 1997, vol. 8 (13), 2175-2187 [0112]
- Protective Groups in Organic Synthesis. **THEODORA W. GREENE ; PETER G. M. WUTS.** Protective Groups in Organic Synthesis. John Wiley & Sons. Inc, 1999 [0113]
- *Tetrahedron*, 1990, vol. 46 (20), 7081 [0113] [0198]
- **S. L. BUCHWALD et al.** *Top. Curr. Chem.*, 2001, vol. 219, 131-209 [0114]
- **J. F. HARTWIG.** Organopalladium Chemistry for Organic Synthesis. Wiley Interscience, 2002 [0114]
- **NOBORU ONO,** The Nitro Group in Organic Synthesis. John Wiley & Sons. Inc [0114]
- *Synthesis*, 2003, 677 [0124] [0136]
- *J. Org. Chem.*, 2000, vol. 65, 4618 [0125]
- *Tetrahedron Lett*, 1988, vol. 29, 3411-3414 [0126]
- *J. Org. Chem.*, 1963, vol. 28, 3021 [0364]
- *Can. J. Chem.*, 1981, vol. 59 (17), 2673-6 [0385]
- *Canadian J. Chem*, 1981, vol. 59, 2673 [0490]
- *Bioorg Med Chem Lett*, 2005, vol. 15 (1), 107-113 [0490]
- *Canadian J. Chem.*, 1981, vol. 59, 2673 [0490]
- *Can. J. Chem.*, 1981, vol. 59, 2673 [0490]
- *Bioorganic & Medicinal Chemistry Letters*, 1998, vol. 8 (12), 1493-1498 [0490]
- *Org. Prep. Proc. Int.*, 1998, vol. 30, 709 [0490]
- *Org. Prep. and Proc. Int.*, vol. 30 (6), 709-713 [0490]
- *Org. Prep. Proc. Int.*, 1998, vol. 30 (6), 709-713 [0490]
- **HARTWIG et al.** *J. Am. Chem. Soc*, 2004, vol. 126, 5182 [0494]
- *Adv. Syn. Chem*, 2004, vol. 346, 111-124 [0508]
- **COUTURIER, M.** *Organic Process Research & Development*, 2002, vol. 6, 42-48 [0513]

发明名称：C-FMS 激酶的抑制剂

摘要：本发明涉及以下通式的化合物及其溶剂合物、水合物、互变异构体和药学上可接受的盐：



其中 Z、X、J、R² 和 W 如说明书中所述，其抑制蛋白酪氨酸激酶，特别是 c-fms 激酶。还公开了用式 I 的化合物治疗免疫疾病和具有炎性元素的疾病的方法；治疗来自卵巢癌、子宫癌、乳腺癌、结肠癌、胃癌、毛细胞白血病和非小细胞肺癌的转移；和治疗疼痛，包括肿瘤转移或骨关节炎引起的骨骼痛、或内脏、炎性和神经性疼痛；以及骨质疏松症、Paget's 疾病和其中骨骼再吸收介导致病的其它疾病，包括关节炎、修复失败、溶骨性骨肉瘤、骨髓瘤和肿瘤到骨的转移。