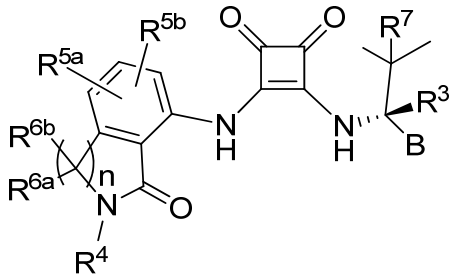
Claims

1. A compound having the Formula (A):



(A)

wherein

B is selected from the group consisting of furanyl, thiophenyl, oxazolyl, phenyl, pyridyl, pyrimidinyl and pyrazinyl, each of which is optionally substituted with R^{1a}, R^{1b}, and R^2 which are independently selected from the group consisting of halogen, CN, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-4} haloalkyl;

R^3 is a member selected from the group consisting of H and D;

R^4 is a member selected from the group consisting of H, C_{1-8} alkyl, OH, - NR^aR^b, -C_{1-4} alkoxy, and Y; wherein the C_{1-8} alkyl is optionally substituted with halogen, -CN, -CO_2R^a, -$CONR^aR^b$, -$C(O)R^a$, $OC(O)NR^aR^b$, -$NR^aC(O)R^b$, -$NR^aC(O)_2R^c$, -$NR^aC(O)NR^aR^b$, -NR^aR^b, -OR^a, -$S(O)_2NR^aR^b$, -$NR^aS(O)_2R^b$ and Y, wherein Y is a 4 to 8 membered cycloheteroalkyl group or a 3 to 8 membered cycloalkyl group or a 5- or 6-membered aryl or heteroaryl group any of which is optionally substituted with from 1 to four substituents selected from halogen, oxo, -CN, -C_{1-6} alkyl, -C_{1-6} alkoxy, -C_{1-6} hydroxyalkyl, -C_{1-6} haloalkyl, O- C_{1-6} haloalkyl, -C_{1-4}alkyl-O-C_{1-4} alkyl, -C_{1-6} alkyl-NR^aR^b , -C_{1-6} alkyl-CO_2H, -C_{1-6} alkyl-CO_2R^a, -C_{1-6} alkyl-$CONR^aR^b$, -C_{1-6} alkyl-$C(O)R^a$, -C_{1-6} alkyl-$OC(O)NR^aR^b$, -C_{1-6} alkyl-$NR^aC(O)R^b$, -C_{1-6} alkyl-$NR^aC(O)_2R^c$, -C_{1-6} alkyl-$NR^aC(O)NR^aR^b$, -C_{1-6} alkyl-OR^a, -C_{1-6} alkyl-$S(O)_2NR^aR^b$, -C_{1-6} alkyl-$NR^aS(O)_2R^b$, -CO_2R^a, -$CONR^aR^b$, -$C(O)R^a$, -$OC(O)NR^aR^b$, -$NR^aC(O)R^b$, -$NR^aC(O)_2R^c$, -$NR^aC(O)NR^aR^b$, -NR^aR^b, -OR^a, -$S(O)_2NR^aR^b$, -$NR^aS(O)_2R^b$,-$CH_2CO_2R^a$; each R^a and R^b is independently selected from hydrogen, C_{1-4} alkyl, C_{1-4} hydroxyalkyl and C_{1-4} haloalkyl, and R^c is selected from C_{1-4} alkyl, C_{1-4} hydroxyalkyl and C_{1-4} haloalkyl; and wherein the 4

to 8 membered cycloheteroalkyl group and the 3 to 8 membered cycloalkyl group may additionally be optionally substituted with oxo;

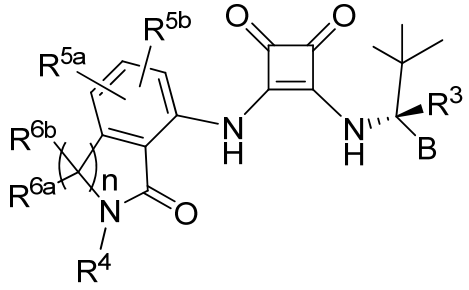
R^{5a} and R^{5b} are each members independently selected from the group consisting of H, halogen, C_{1-4} alkyl, -C_{1-4} haloalkyl, O-C_{1-4} haloalkyl, C_{1-4} alkoxy, CO_2H and CN;

R^{6a} and R^{6b} are each members independently selected from the group consisting of H, C_{1-4} alkyl, C_{1-4} hydroxyalkyl and C_{1-4} haloalkyl; or optionally R^{6a} and R^{6b} are taken together to form oxo (=O) or a 4 to 6 membered cycloheteroalkyl group or a 3 to 6 membered cycloalkyl group;

R^7 is a member selected from the group consisting of methyl, ethyl and C_{1-2} haloalkyl; and the subscript n is 1 or 2;

or any pharmaceutically acceptable salts, solvates, hydrates, N-oxides, tautomers or rotamers thereof.

2. A compound of claim 1 having the Formula (I):



(I)

wherein

B is selected from the group consisting of furanyl, oxazolyl, phenyl, pyridyl, pyrimidinyl and pyrazinyl, each of which is optionally substituted with R^{1a}, R^{1b}, and R^2 which are independently selected from the group consisting of halogen, CN, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-4} haloalkyl;

R^3 is a member selected from the group consisting of H and D;

R^4 is a member selected from the group consisting of H, C_{1-8} alkyl, and Y; wherein the C_{1-8} alkyl is optionally substituted with halogen, -CN, -CO_2R^a, -$CONR^aR^b$, -$C(O)R^a$, $OC(O)NR^aR^b$, -$NR^aC(O)R^b$, -$NR^aC(O)_2R^c$, -$NR^aC(O)NR^aR^b$, -NR^aR^b, -OR^a, -$S(O)_2NR^aR^b$, -$NR^aS(O)_2R^b$ and Y, wherein Y is a 5- or 6-membered aryl or heteroaryl group with from one to four substituents selected from halogen, -CN, -C_{1-4} alkyl, -C_{1-4} alkoxy, -C_{1-4} hydroxyalkyl, -C_{1-4} haloalkyl, OCF_3, -CO_2R^a, -$CONR^aR^b$, -$C(O)R^a$, -

$OC(O)NR^aR^b$, $-NR^aC(O)R^b$, $-CH_2CO_2R^a$; and each R^a and R^b is independently selected from hydrogen, C_{1-4} alkyl, C_{1-4} hydroxyalkyl and C_{1-4} haloalkyl, and R^c is selected from C_{1-4} alkyl, C_{1-4} hydroxyalkyl and C_{1-4} haloalkyl;

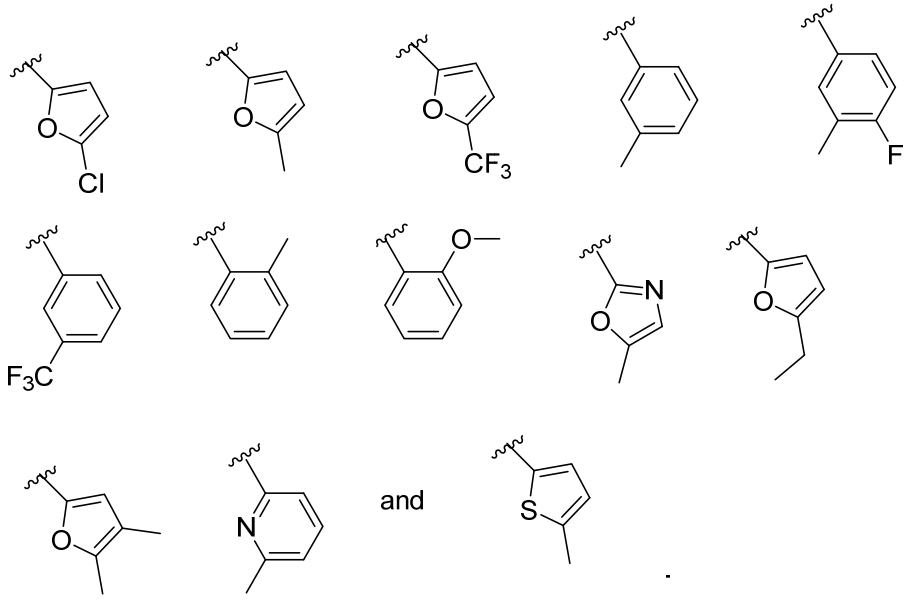
R^{5a} and R^{5b} are each members independently selected from the group consisting of H, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, CO_2H and CN;

R^{6a} and R^{6b} are each members independently selected from the group consisting of H, C_{1-4} alkyl, C_{1-4} hydroxyalkyl and C_{1-4} haloalkyl; or optionally R^{6a} and R^{6b} are taken together to form oxo (=O); and

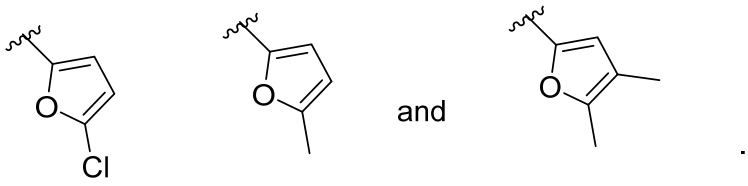
the subscript n is 1 or 2;

or any salts, solvates, hydrates, N-oxides, tautomers or rotamers thereof.

3. A compound of claim 1, or any pharmaceutically acceptable salts, solvates, hydrates, N-oxides, tautomers or rotamers thereof, wherein B is selected from the group consisting of:



4. A compound of any one of claims 1 to 3, or any pharmaceutically acceptable salts, solvates, hydrates, N-oxides, tautomers or rotamers thereof, wherein B is selected from the group consisting of:



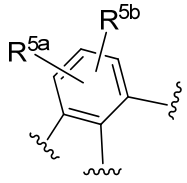
5. A compound of any one of claims 1 or 2, or any pharmaceutically acceptable salts, solvates, hydrates, N-oxides, tautomers or rotamers thereof, wherein B is furanyl or oxazolyl, each of which is optionally substituted with R^{1a} and R^{1b}, which are independently selected from the group consisting of halogen, CN, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-4} haloalkyl.

6. A compound of claim 5 or any pharmaceutically acceptable salts, solvates, hydrates, N-oxides, tautomers or rotamers thereof, wherein B is furanyl substituted with R^{1a} which is CH_3 or Cl and optionally substituted with R^{1b} which is CH_3.

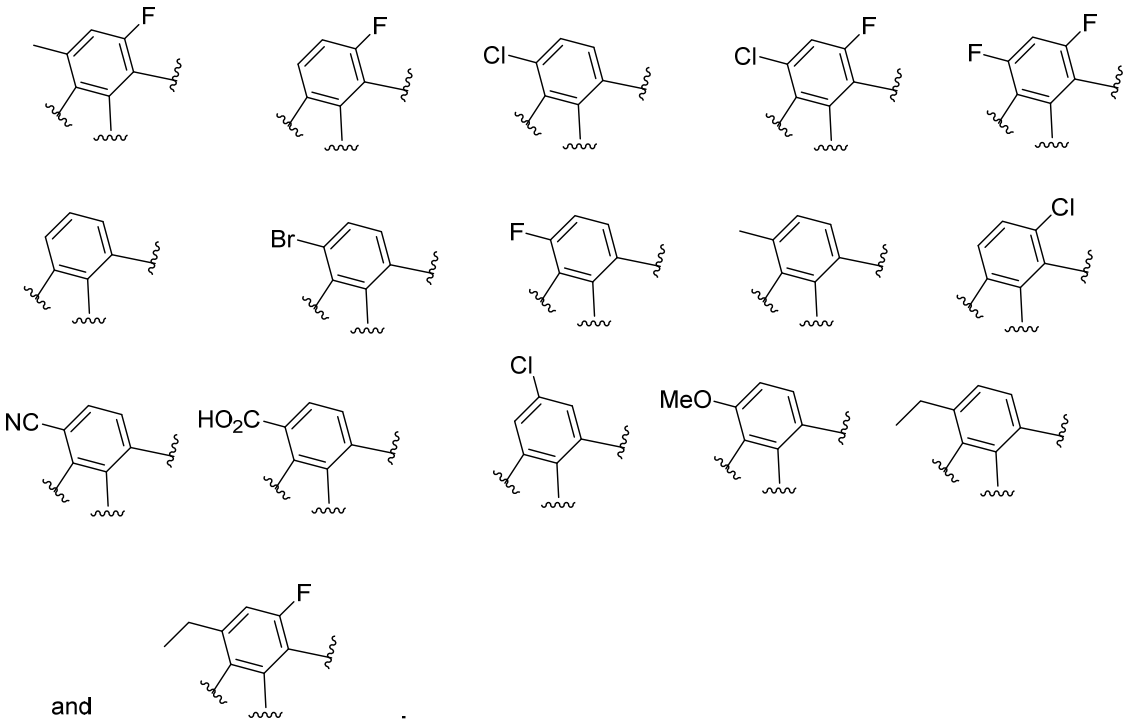
7. A compound of any one of claims 1 to 6, or any pharmaceutically acceptable salts, solvates, hydrates, N-oxides, tautomers or rotamers thereof, wherein R^3 is H.

8. A compound of any one of claims 1 to 7, or any pharmaceutically acceptable salts, solvates, hydrates, N-oxides, tautomers or rotamers thereof, wherein each of R^{5a} and R^{5b} is independently selected from the group consisting of H, CH_3, Cl and F.

9. A compound of any one of claims 1 to 7, or any pharmaceutically acceptable salts, solvates, hydrates, N-oxides, tautomers or rotamers thereof, wherein

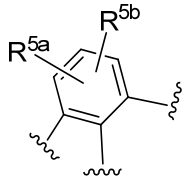


is selected from the group consisting of:

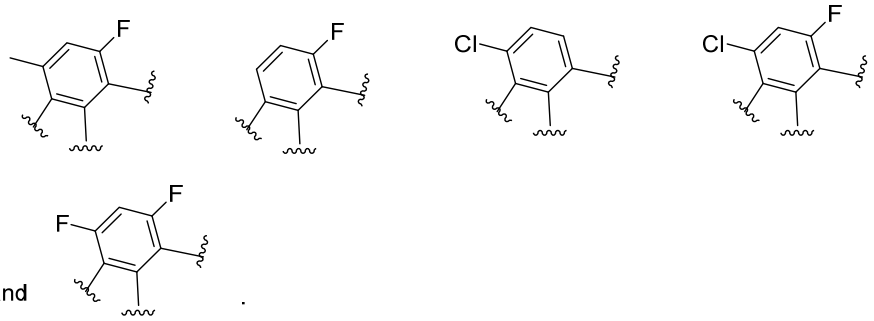


and .

10. A compound of any one of claims 1 to 7, or any pharmaceutically acceptable salts, solvates, hydrates, N-oxides, tautomers or rotamers thereof, wherein



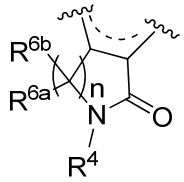
is selected from the group consisting of:



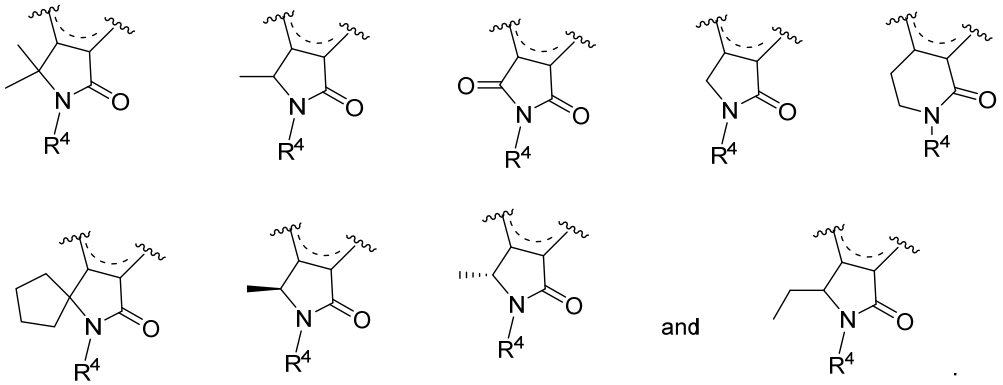
and .

11. A compound of any one of claims 1 to 10, or any pharmaceutically acceptable salts, solvates, hydrates, N-oxides, tautomers or rotamers thereof, wherein each of R^{6a} and R^{6b} is independently selected from the group consisting of H and C_{1-2} alkyl.

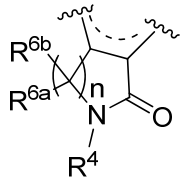
12. A compound of any one of claims 1 or 3 to 10, or any pharmaceutically acceptable salts, solvates, hydrates, N-oxides, tautomers or rotamers thereof, wherein



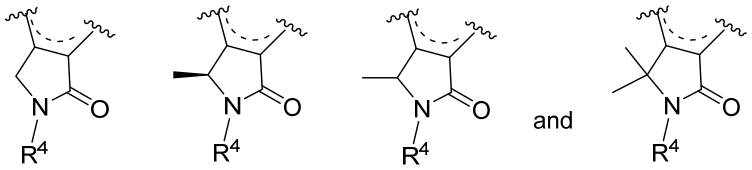
is independently selected from the group consisting of



13. A compound of any one of claims 1 to 10 or 12, or any pharmaceutically acceptable salts, solvates, hydrates, N-oxides, tautomers or rotamers thereof, wherein



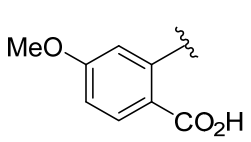
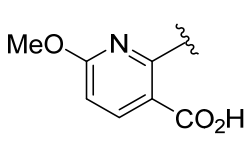
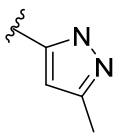
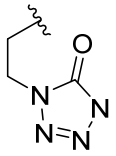
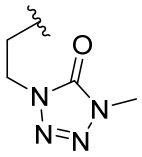
is independently selected from the group consisting of



14. A compound of any one of claims 1 or 3 to 13, or any pharmaceutically acceptable salts, solvates, hydrates, N-oxides, tautomers or rotamers thereof, wherein R^4 is H, C_{1-3} alkyl or Y, wherein the C_{1-3} alkyl is substituted with tetrazolyl or tetrazolonyl, wherein the tetrazolyl or tetrazolonyl is optionally substituted with C_{1-6} alkyl, C_{1-6} hydroxyalkyl, or C_{1-4}alkyl-O-C_{1-4}alkyl wherein Y is selected from the group consisting of pyridinyl, pyrazolyl, and phenyl

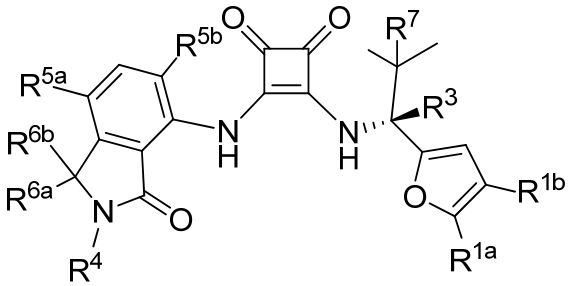
wherein the pyridinyl, pyrazolyl, and phenyl have from one to three substituents each of which is independently selected from -C_{1-4} alkyl, -C_{1-4} alkoxy and -CO_2H.

15. A compound of any one of claims 1 or 3 to 14, or any pharmaceutically acceptable salts, solvates, hydrates, N-oxides, tautomers or rotamers thereof, wherein R^4 is selected from the group consisting of:






and H .

16. A compound of any one of claims 1 or 3 to 15, or any pharmaceutically acceptable salts, solvates, hydrates, N-oxides, tautomers or rotamers thereof, wherein R^7 is selected from the group consisting of methyl, ethyl and CF_3.

17. A compound of claim 1, having the formula (A1):


(A1)

wherein R^{1a} is selected from CH_3 and Cl; R^{1b} is absent or is CH_3; R^3 is H or D; R^4 is H or Y; R^{5a} and R^{5b} are each independently selected from H, F, Cl, Br and CH_3; R^{6a} and R^{6b} are each independently selected from H and CH_3; and R^7 is methyl or ethyl; or a pharmaceutically acceptable salt, solvate or hydrate, thereof.

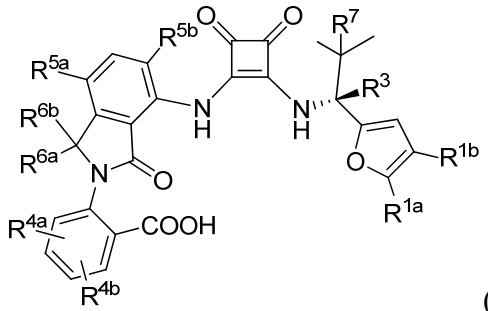
18. A compound of claim 17, or any pharmaceutically acceptable salts, solvates, hydrates, N-oxides, tautomers or rotamers thereof, wherein R^{1a} is CH_3; R^{1b} is absent or is CH_3; R^3 is

H or D; R^4 is H; R^{5a} is H, F, Me or Cl or Br; R^{5b} is H or F; R^{6a} and R^{6b} are each H; and R^7 is methyl or ethyl; or a pharmaceutically acceptable salt, solvate or hydrate, thereof.

19. A compound of claim 17, or any pharmaceutically acceptable salts, solvates, hydrates, N-oxides, tautomers or rotamers thereof, which compound is substantially free of other isomers at the carbon atom bearing R^3.

20. A compound of claim 17, or any pharmaceutically acceptable salts, solvates, hydrates, N-oxides, tautomers or rotamers thereof, wherein R^4 is Y.

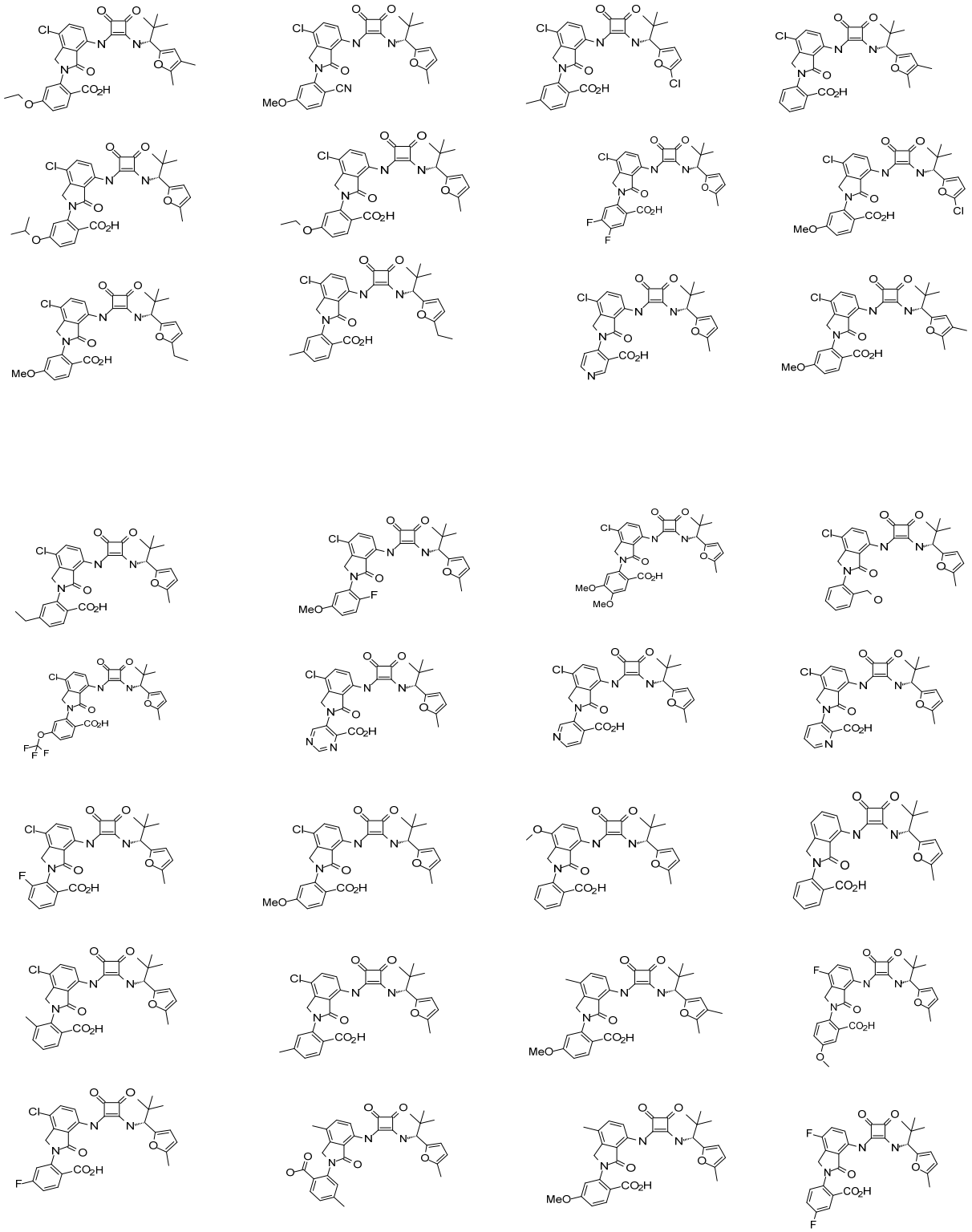
21. A compound of claim 1, having the formula (A2):

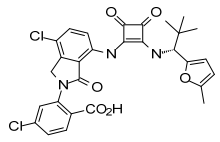
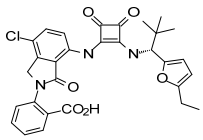
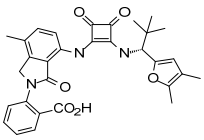
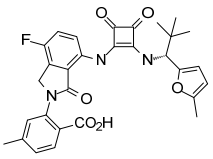
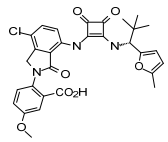
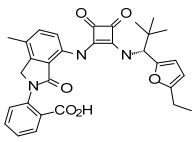
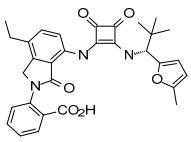
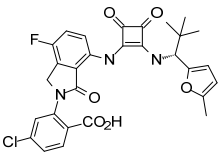
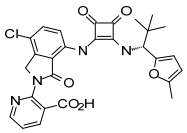
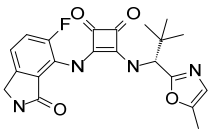
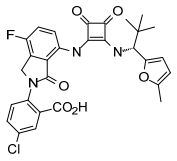
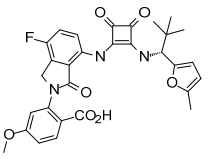
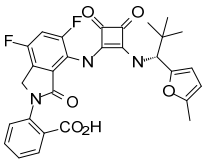
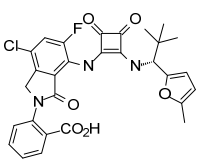
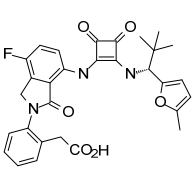
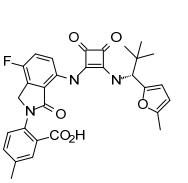
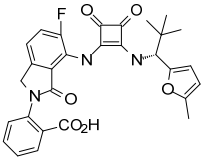
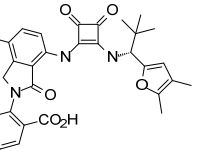
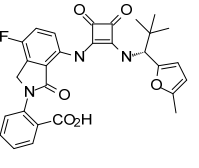
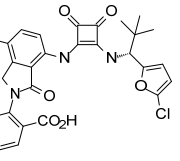
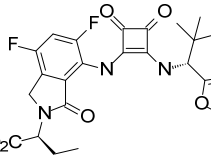
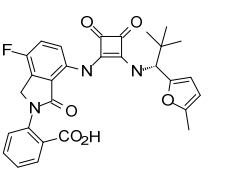
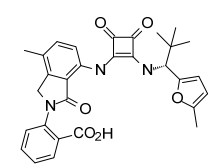
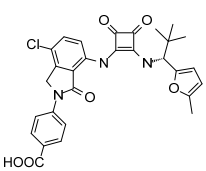
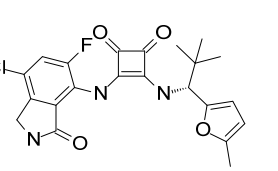
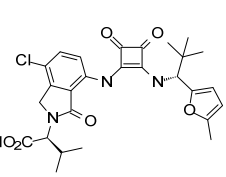
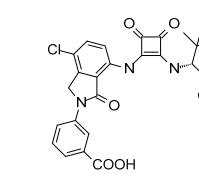
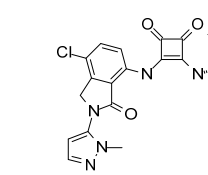


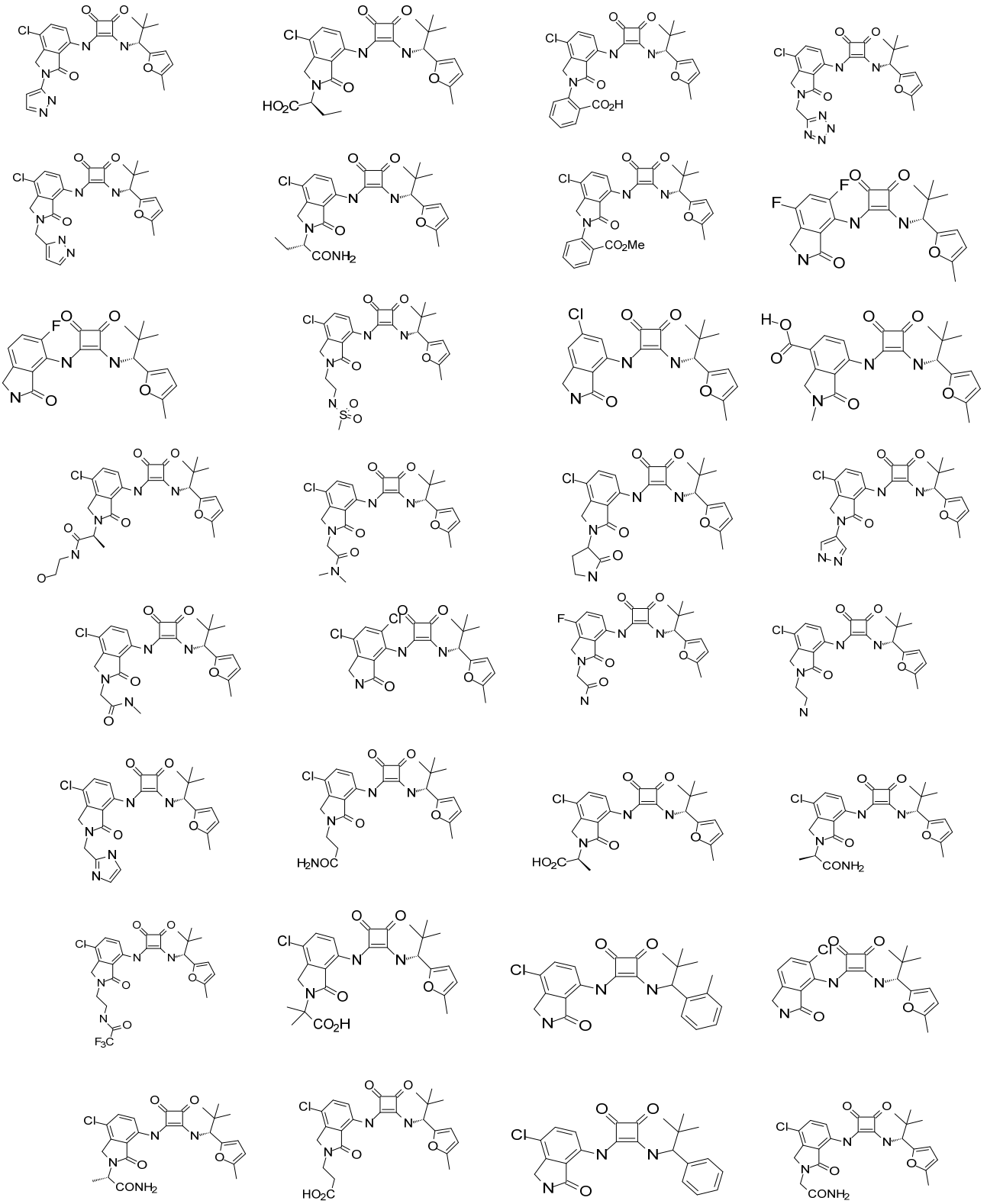
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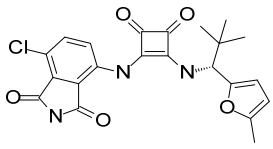
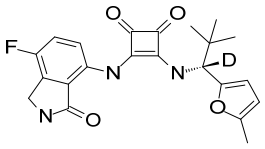
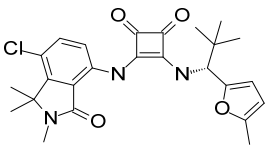
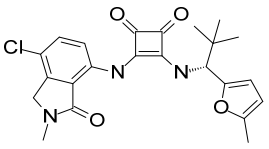
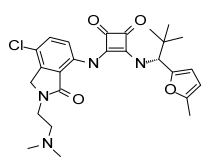
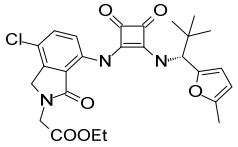
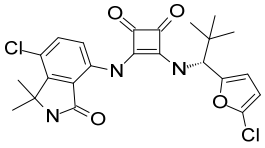
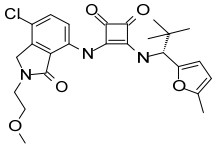
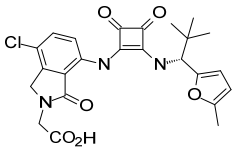
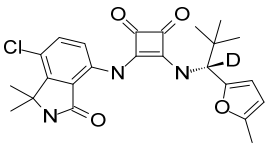
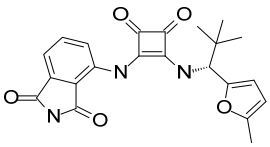
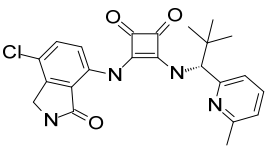
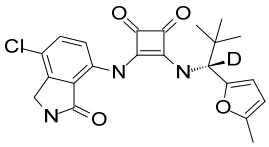
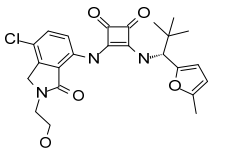
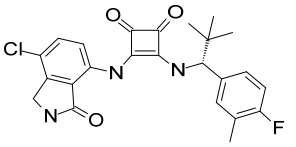
wherein R^{1a} is selected from CH_3 and Cl; R^{1b} is H or CH_3; R^3 is H or D; R^{4a} and R^{4b} are independently selected from halogen, -CN, -C_{1-4} alkyl, -C_{1-4} alkoxy, -C_{1-4} hydroxyalkyl, -C_{1-4} haloalkyl, OCF_3, -CO_2R^a, -$CONR^aR^b$, -$C(O)R^a$, -$OC(O)NR^aR^b$, -$NR^aC(O)R^b$, -$CH_2CO_2R^a$, and R^a and R^b are independently selected from hydrogen, C_{1-4} alkyl, C_{1-4} hydroxyalkyl and C_{1-4} haloalkyl; R^{5a} and R^{5b} are each independently selected from H, F, Cl, Br and CH_3; R^{6a} and R^{6b} are each independently selected from H and CH_3; and R^7 is selected from the group consisting of methyl, ethyl and C_{1-2} haloalkyl; or a pharmaceutically acceptable salt, solvate or hydrate, thereof.

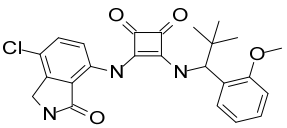
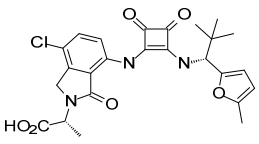
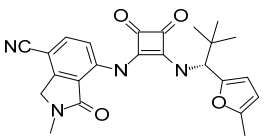
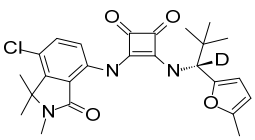
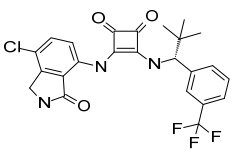
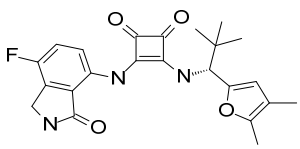
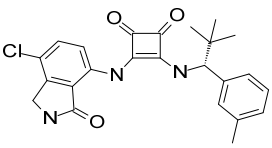
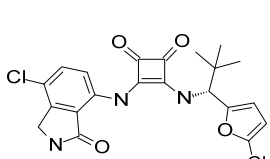
22. The compound of claim 1, or a pharmaceutically acceptable salt thereof, selected from the group consisting of:

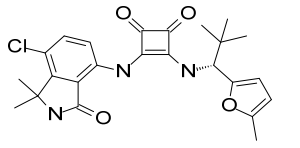
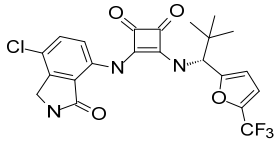
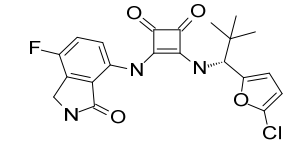
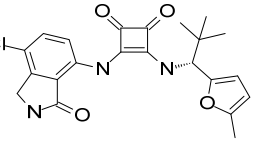
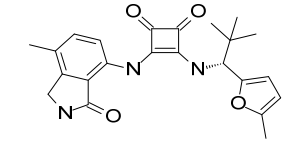
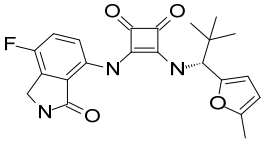
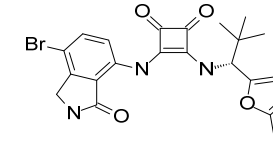
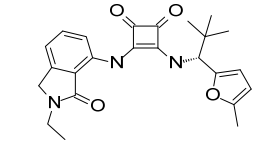


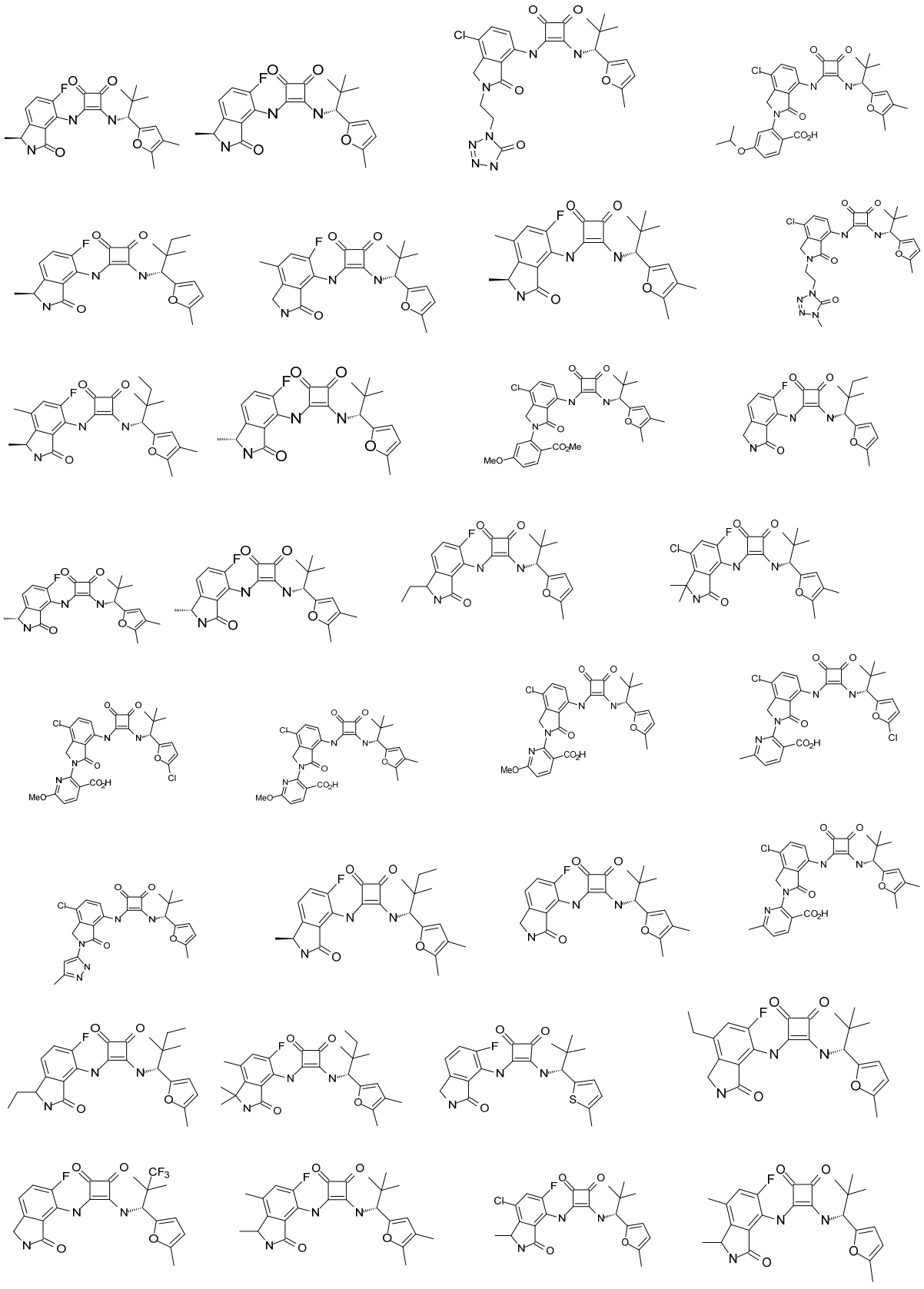





























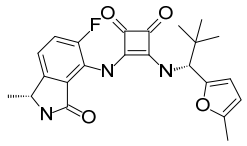
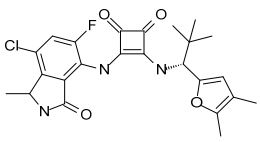
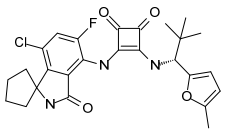
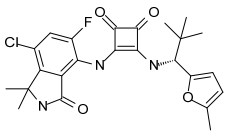
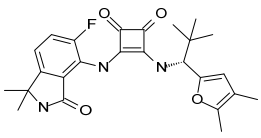
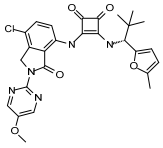
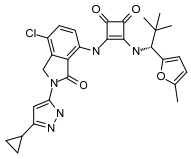
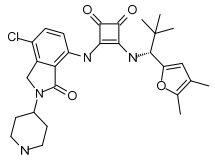
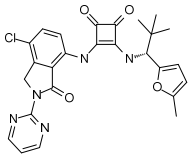
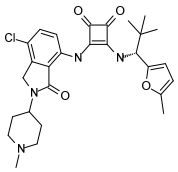
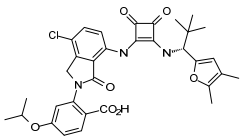
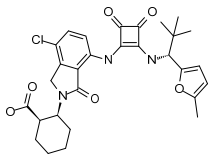
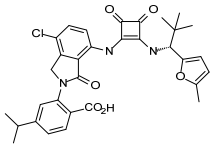
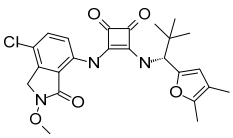
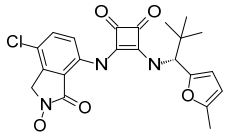
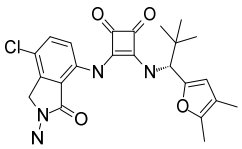
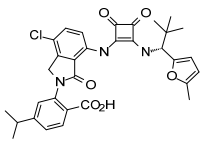
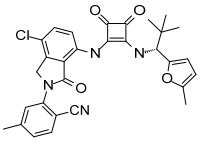
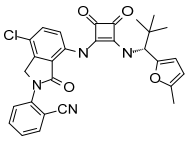
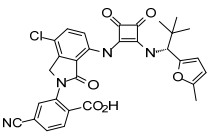
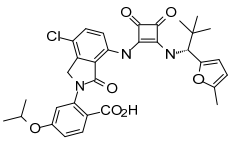
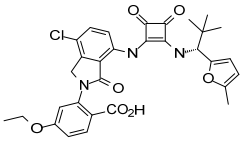
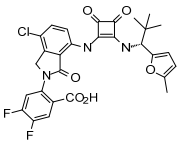
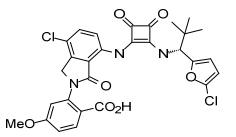
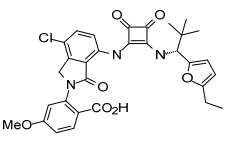
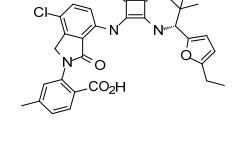
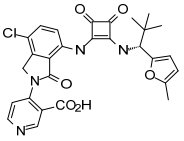
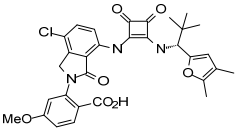
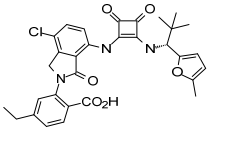
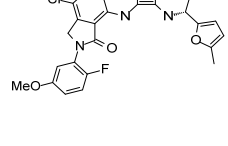
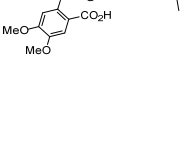
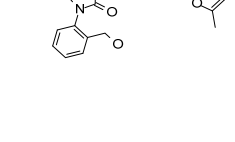
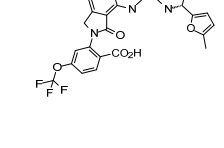
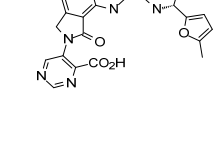
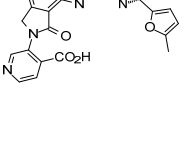
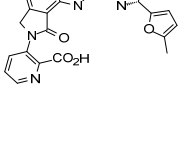


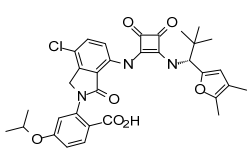
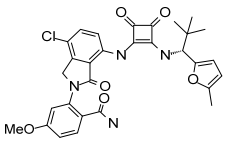
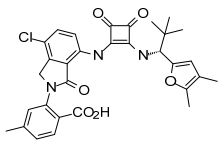
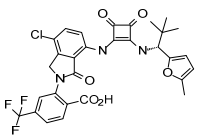
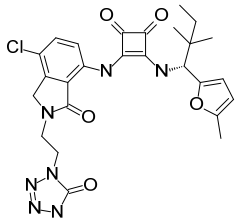
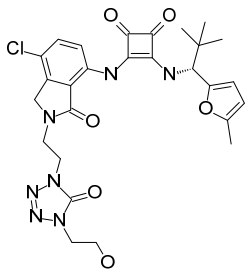
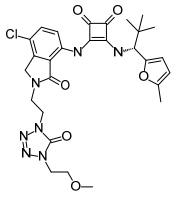
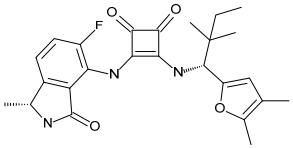
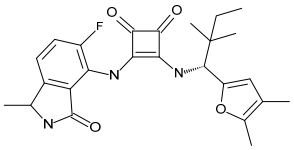
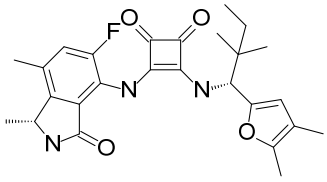
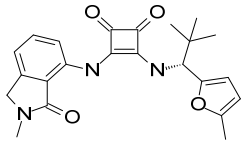
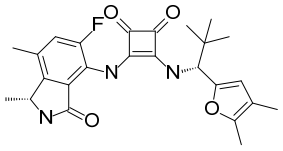
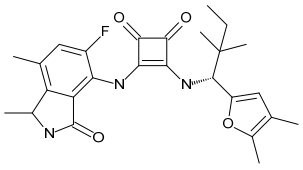
















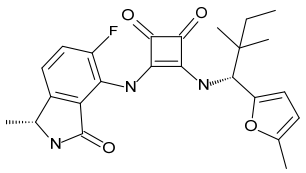
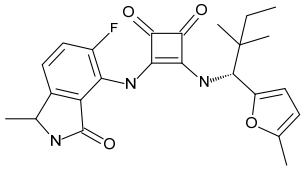
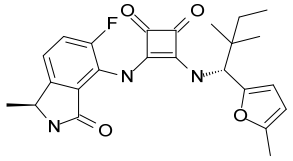
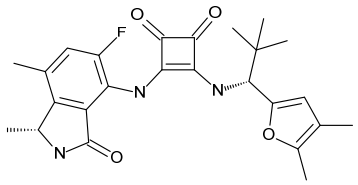
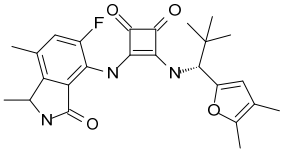
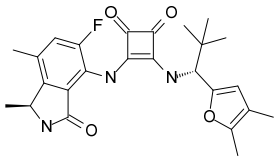


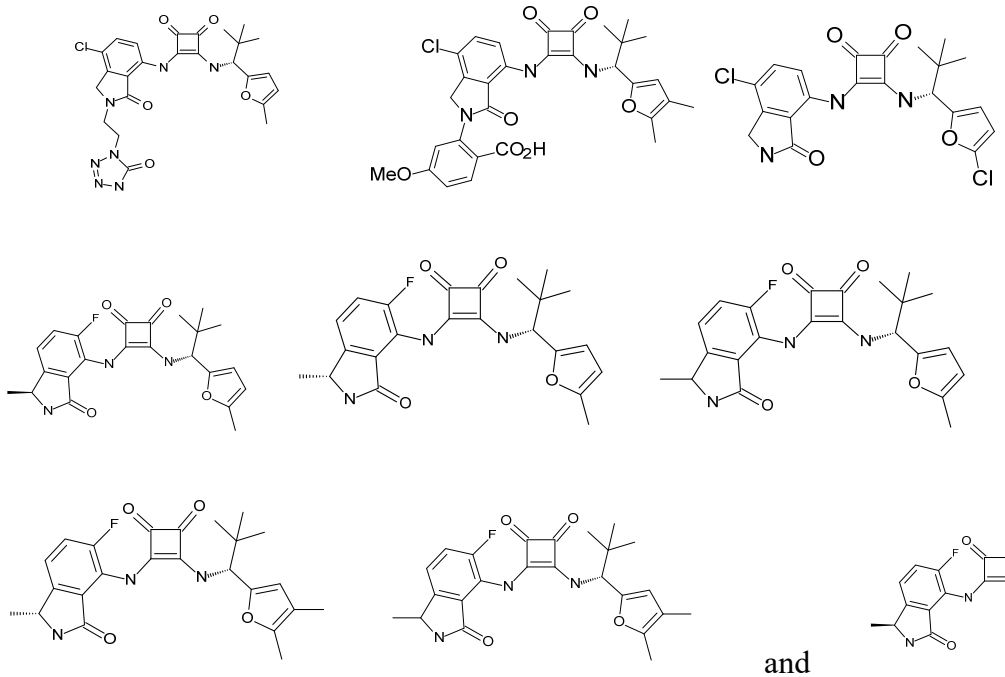





































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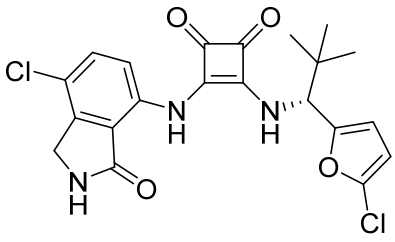
23. The compound of claim 1, or a pharmaceutically acceptable salt thereof, selected from the group consisting of:



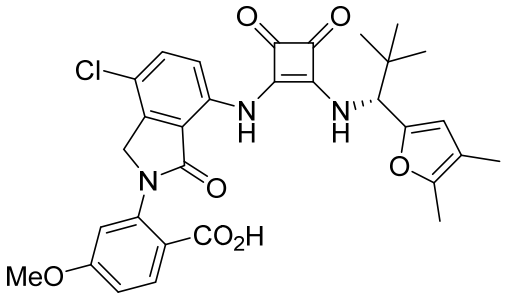
and .

24. A compound of claim 1, having the formula



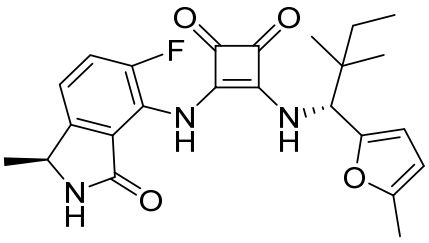
, or a pharmaceutically acceptable salt thereof.

25. A compound of claim 1, having the formula



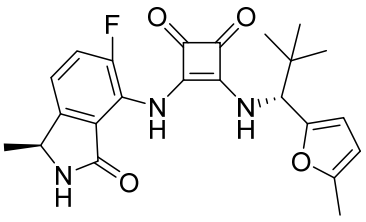
, or a pharmaceutically acceptable salt thereof.

26. A compound of claim 1, having the formula



, or a pharmaceutically acceptable salt thereof.

27. A compound of claim 1, having the formula



, or a pharmaceutically acceptable salt thereof.

28. A pharmaceutical composition comprising a compound of any one of claims 1 to 23.

29. The pharmaceutical composition of claim 28 further comprising one or more additional therapeutic agents.

30. The pharmaceutical composition of claim 29 wherein the one or more additional therapeutic agent is selected from the group consisting of cytotoxic chemotherapy, anti-cancer or anti-tumor vaccines, anti-immunocytokine therapies, immunocytokine therapies, chimeric antigen receptor (CAR) T cell receptors, gene transfer therapy, checkpoint inhibitors, corticosteroids, retinoid-like agents, antineoplastics, and interferons analogs.

31.. The pharmaceutical composition of claim 29 wherein the one or more additional therapeutic agent is selected from the group consisting of a TNF alpha ligand inhibitor, a TNF binding agent, an IL-1 ligand inhibitor; an IL-6 ligand inhibitor, an IL-8 ligand inhibitor; an IL-17 antagonist a TNF antagonist, a Retinoic acid receptor gamma antagonist, an IL-17A ligand inhibitor; an IL-17F ligand inhibitor, a sphingosine-1-phosphate receptor-1 antagonist, a sphingosine-1-phosphate receptor-1 modulator, , an IL-12 antagonist; an IL-23 antagonist, a type II TNF receptor modulator, an IL-23A inhibitor, a PDE 4 inhibitor, a JAK tyrosine kinase inhibitor, a Jak1 tyrosine kinase inhibitor; a Jak3 tyrosine kinase inhibitor, t, a Retinoic acid receptor agonist, a Sphingosine-1-phosphate receptor-1 modulator, or, a TLR-7

antagonist, a TLR-8 antagonist a TLR-9 antagonist an IL-8 antagonist, a drug that blocks the activity of CTLA-4 (CD152), PD-1 (CD279), PDL-1 (CD274), TIM-3, LAG-3 (CD223), VISTA, KIR, NKG2A, BTLA, PD-1H, TIGIT, CD96, 4-1BB (CD137), 4-1BBL (CD137L), GARP, CSF-1R, A2AR, CD73, CD47, tryptophan 2,3-dioxygenase (TDO) or indoleamine 2,3 dioxygenase (IDO), and agonists of OX40, GITR, 4-1BB, ICOS, STING or CD40.

32.. Use of a compound of any one of claims 1 to 27 or a pharmaceutically acceptable salt thereof in the preparation of a pharmaceutical composition for the treatment of a CXCR2- and/or CCR6-mediated disease or condition in a subject in need thereof, wherein the disease or condition is an acute or chronic inflammatory disorder or a cancer.

33.. A use of claim 32, wherein the acute or chronic inflammatory disorder is psoriasis, dry eye disease, atherosclerosis, discoid lupus erythematosus, rheumatoid arthritis, lupus, radiation induced fibrotic lung disease, autoimmune bullous dermatosis (AIBD), chronic obstructive pulmonary disease, or ozone-induced airway inflammation.

34.. A use of claim 32, wherein the disease is a cancer selected from the group consisting of cutaneous T-cell lymphoma, non-Hodgkin lymphoma, Mycosis fungoides, Pagetoid reticulosis, Sézary syndrome, Granulomatous slack skin, Lymphomatoid papulosis, Pityriasis lichenoides chronica, Pityriasis lichenoides et varioliformis acuta, CD30+ cutaneous T-cell lymphoma, Secondary cutaneous CD30+ large cell lymphoma, non-mycosis fungoides CD30 cutaneous large T-cell lymphoma, Pleomorphic T-cell lymphoma, Lennert lymphoma, subcutaneous T-cell lymphoma, angiocentric lymphoma, blastic NK-cell lymphoma, B-cell Lymphomas, hodgkins Lymphoma (HL), Head and neck tumor; Squamous cell carcinoma, rhabdomyocarcoma, Lewis lung carcinoma (LLC), non-small cell lung cancer, esophageal squamous cell carcinoma, esophageal adenocarcinoma, renal cell carcinoma (RCC), colorectal cancer (CRC), acute myeloid leukemia (AML), breast cancer, gastric cancer, prostatic small cell neuroendocrine carcinoma (SCNC), liver cancer, glioblastoma, liver cancer, oral squamous cell carcinoma, pancreatic cancer, thyroid papillary cancer, intrahepatic cholangiocellular carcinoma, hepatocellular carcinoma, bone cancer, metastasis, and nasopharyngeal carcinoma.

35. A use of claim 34, wherein the compound or pharmaceutical composition is to be used alone or in combination with one or more other anti-cancer therapies.

36. A use of claim 35, wherein the compound or pharmaceutical composition is to be used in combination with one or more of a cytotoxic chemotherapy, an anti-cancer vaccine, an anti-tumor vaccine, an anti-immunocytokine therapy, an immunocytokine therapy, a checkpoint inhibitor, and a chimeric antigen receptor (CAR) T cell receptors, gene transfer therapy.

37. A use of claim 35, wherein the one or more other anti-cancer therapy is selected from the group consisting of: drugs that block the activity of CTLA-4 (CD152), PD-1 (CD279), PDL-1 (CD274), TIM-3, LAG-3 (CD223), VISTA, KIR, NKG2A, BTLA, PD-1H, TIGIT, CD96, 4-1BB (CD137), 4-1BBL (CD137L), GARP, CSF-1R, A2AR, CD73, CD47, tryptophan 2,3-dioxygenase (TDO) or indoleamine 2,3 dioxygenase (IDO), and agonists of OX40, GITR, 4-1BB, ICOS, STING or CD40.

38. A use of claim 33 wherein the compound or pharmaceutical composition is to be used alone or in combination with one or more other therapeutic agents.

39. A use of claim 38, wherein the compound or pharmaceutical composition is to be used in combination with one or more of a corticosteroid, a retinoid-like agent, an antineoplastics, and interferons analogs, TNF alpha ligand inhibitor, a TNF binding agent, an IL-1 ligand inhibitor; an IL-6 ligand inhibitor, an IL-8 ligand inhibitor; an IL-17 antagonist, a TNF antagonist, a Retinoic acid receptor gamma antagonist, an IL-17A ligand inhibitor; an IL-17F ligand inhibitor, a sphingosine-1-phosphate receptor-1 antagonist, a sphingosine-1-phosphate receptor-1 modulator, an IL-12 antagonist; an IL-23 antagonist, a type II TNF receptor modulator, an IL-23A inhibitor, a PDE 4 inhibitor, a JAK tyrosine kinase inhibitor, a Jak1 tyrosine kinase inhibitor; a Jak3 tyrosine kinase inhibitor, a Retinoic acid receptor agonist, a Sphingosine-1-phosphate receptor-1 modulator, a TLR-7 antagonist, a TLR-8 antagonist a TLR-9 antagonist, or an IL-8 antagonist.

40. A compound of any one of claims 1 to 27 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of any one of claims 28 to 31 for use in the treatment of a CXCR2- and/or CCR6-mediated disease or condition in a subject in need

thereof, wherein the disease or condition is an acute or chronic inflammatory disorder or a cancer.