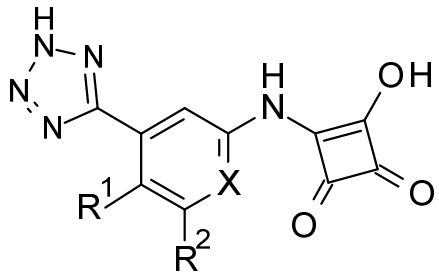
~~What is claimed is:~~Claims

1. A compound of formula (1):



(1)

or a salt or tautomer thereof, wherein~~;~~:

X is N or CH;

R^1 is H or halo;

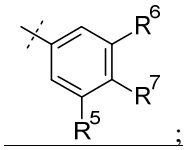
R^2 is H, halo, or

i) ~~optionally substituted~~ C_{1-6} alkyl, ~~optionally substituted~~ C_{3-6} cycloalkyl, or ~~optionally substituted~~ C_{1-6} alkoxy, each of which is optionally substituted with 1 to 6 fluorine atoms; or

~~optionally substituted~~ ii) aryl, ~~optionally substituted~~ heteroaryl or ~~optionally substituted~~ *O*-aryl, each of which is optionally substituted with R^3~~.~~;

R^3 is H, halo, C_{1-6} alkyl optionally substituted with 1 to 6 fluorine atoms, C_{3-6} cycloalkyl optionally substituted with 1 to 6 fluorine atoms, C_{1-6} alkoxy optionally substituted with 1 to 6 fluorine atoms, $-CO_2R^4$, $-CONHCH_2R^4$, $-CONHCH_2CH_2OR^4$, $-OR^4$, $-OCH_2R^4$, $-CH_2R^4$, $-OCH_2R^4$, $-CH_2CH_2OR^4$, $-OCH_2CH_2OR^4$, $-CONHR^4$ or $-CON(CH_3)R^4$;

wherein R^4 is H, C_{1-6} alkyl optionally substituted with 1 to 6 fluorine atoms, or a group:



;

Wherein R^5, R^6 and R^7 are independently H, halo, CO_2R^8, $CONR^8R^9$ or C_{1-6} alkyl optionally substituted with 1 to 6 fluorine atoms, and wherein one or two carbon atoms of the C_{1-6} alkyl group may be optionally replaced by O;

R^8 and R^9 are independently H or C_{1-6} alkyl optionally substituted with 1 to 6 fluorine atoms.

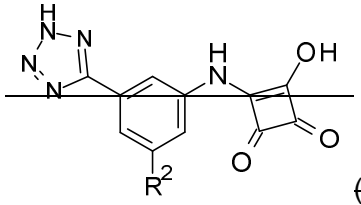
2. The compound according to claim 1, or a salt or tautomer thereof, wherein X is CH.

~~3. The compound according to claim 1, or a salt or tautomer thereof, wherein X is N.~~

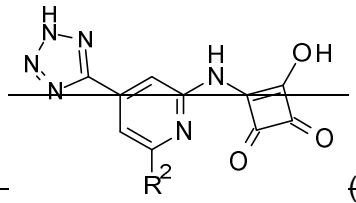
~~4.~~3. The compound according to ~~any one of~~ claim~~s~~ 1 ~~to~~ or claim ~~3~~2, or a salt or tautomer thereof, wherein R^1 is H.

~~5.~~4. The compound according to ~~any one of~~ claims 1 ~~to~~ or claim ~~3~~2, or a salt or tautomer thereof, wherein R^1 is Cl or F.

~~6. The compound according to claim 1, which is a compound of formula (2a) or (2b):~~



~~(2a);~~



~~(2b);~~

~~or a salt or tautomer thereof.~~

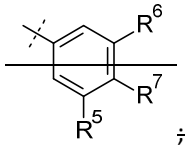
~~7.~~5. The compound according to any one of claims 1 to 4 ~~6~~, or a salt or tautomer thereof, wherein R^2 is H, $C_{1\text{-}6}$ alkyl optionally substituted with 1 to 6 fluorine atoms, $C_{3\text{-}6}$ cycloalkyl optionally substituted with 1 to 6 fluorine atoms or $C_{1\text{-}6}$ alkoxy optionally substituted with 1 to 6 fluorine atoms.

~~8. The compound according to claim 7, or a salt or tautomer thereof, wherein R^2 is H, trifluoromethyl, ethyl, cyclopropyl, cyclohexyl or methoxy.~~

6. The compound according to any one of claims 1 to ~~6~~4, or a salt or tautomer thereof, wherein R^2 is phenyl optionally substituted with R^3, pyridyl optionally substituted with R^3, *O*-phenyl optionally substituted with R^3, indazolyl optionally substituted with R^3 or pyridazinyl optionally substituted with R^3.~~,~~

~~9. wherein R^3 is H, halo, $C_{1\text{-}6}$ alkyl optionally substituted with 1 to 6 fluorine atoms, $C_{3\text{-}6}$ cycloalkyl optionally substituted with 1 to 6 fluorine atoms, $C_{1\text{-}6}$ alkoxy optionally substituted with 1 to 6 fluorine atoms, $-CO_2R^4$, $-CONHCH_2R^4$, $-CONHCH_2CH_2OR^4$, $-OR^4$, $-OCH_2R^4$, $-CH_2R^4$, $-OCH_2R^4$, $-CH_2CH_2OR^4$, $-OCH_2CH_2OR^4$, $-CONHR^4$ or $-CON(CH_3)R^4$;~~

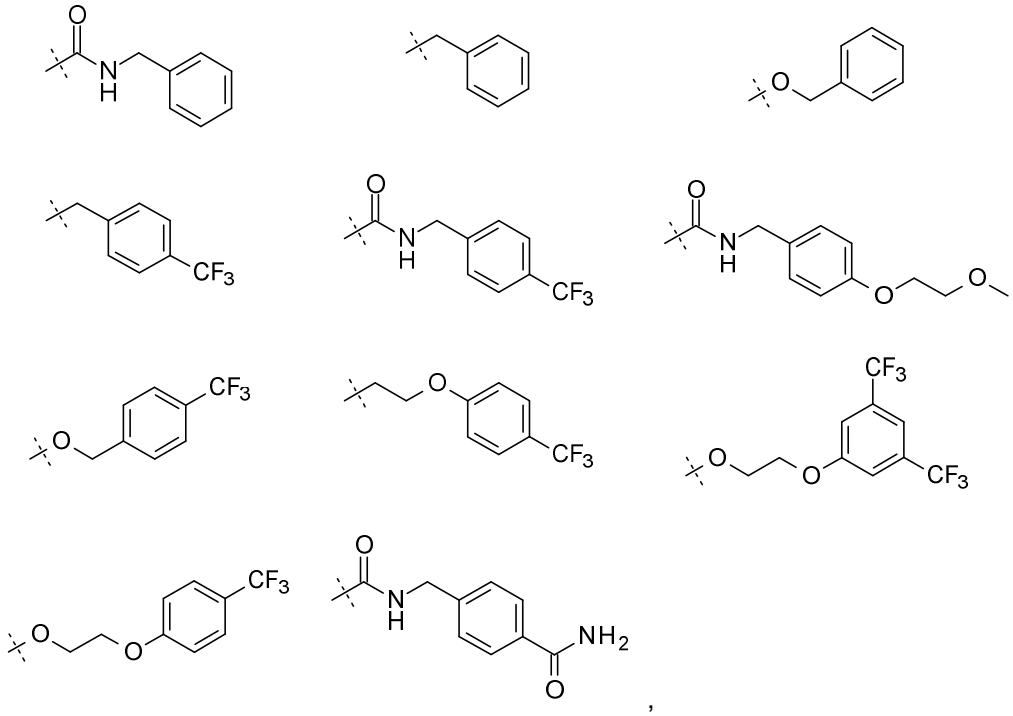
~~where R^4 is H, $C_{1\text{-}6}$ alkyl optionally substituted with 1 to 6 fluorine atoms, or a group:~~



~~R^5, R^6 and R^7 are independently H, halo, CO$_2$R^8, CONR^{8}R^9 or C$_{1-6}$ alkyl optionally substituted with 1 to 6 fluorine atoms, wherein one or two carbon atoms of the C$_{1-6}$ alkyl group may be optionally replaced by O;~~

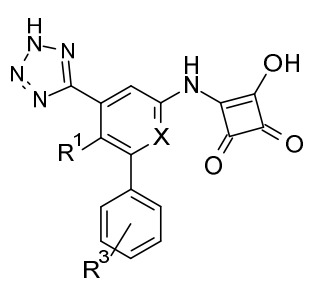
~~R^8 and R^9 are independently H or C$_{1-6}$ alkyl optionally substituted with 1 to 6 fluorine atoms~~

~~10.~~7. The compound according to claim ~~9~~6, wherein R^3 is OMe, CO_2H, CO_2Et, $CON(CH_3)_2$, $CONHCH_2CH_2OCH_3$, or is selected from the group consisting of:

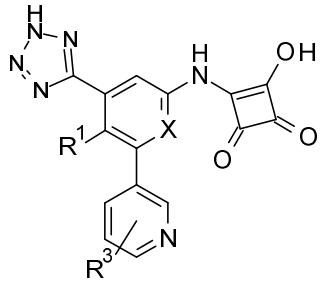


or a salt or tautomer thereof.

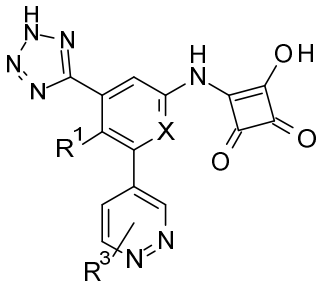
~~11.~~8. The compound according to claim ~~9~~6 or claim ~~10~~7, which is a compound of formula (3a), (3b), (3c), (3d) or (3e):



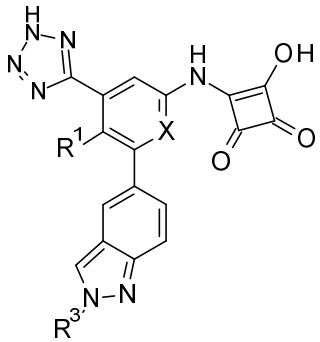
(3a);



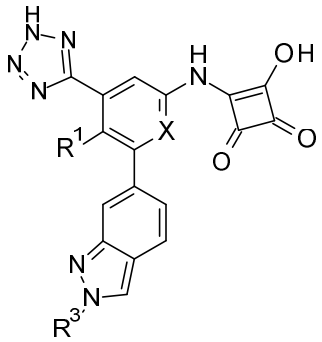
(3b);



(3c);



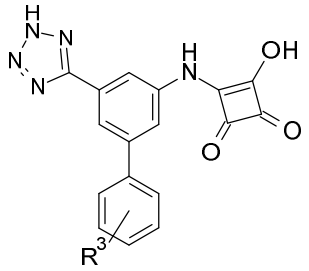
(3d);



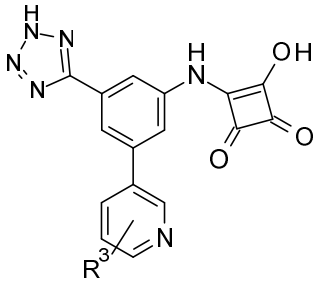
(3e);

or a salt or tautomer thereof.

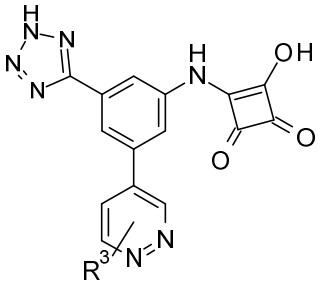
12.9. The compound according to claim 9 6 or claim 107, which is a compound of formula (4a), (4b), (4c), (4d) or (4e):



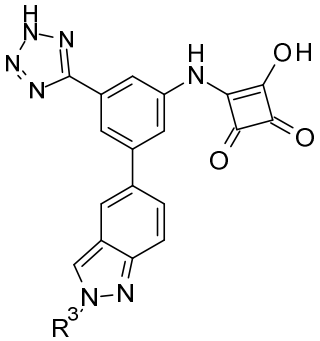
(4a);



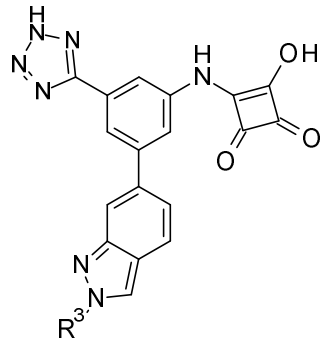
(4b);



(4c);



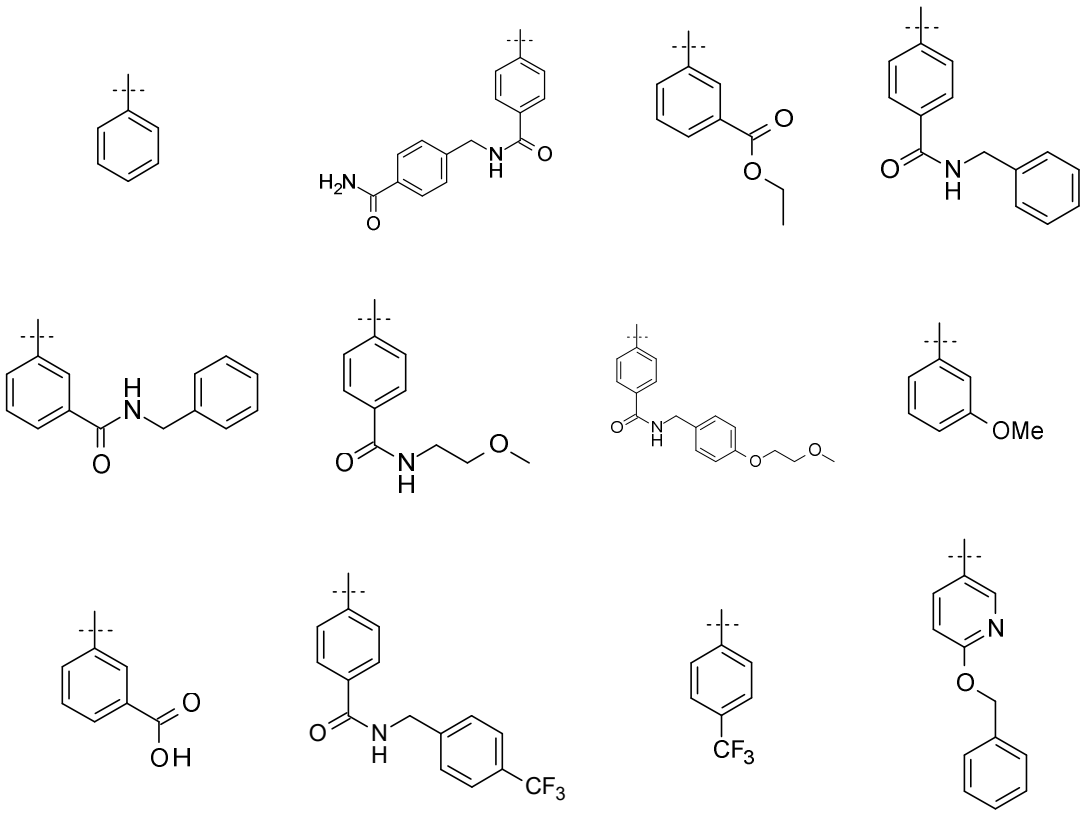
(4d);

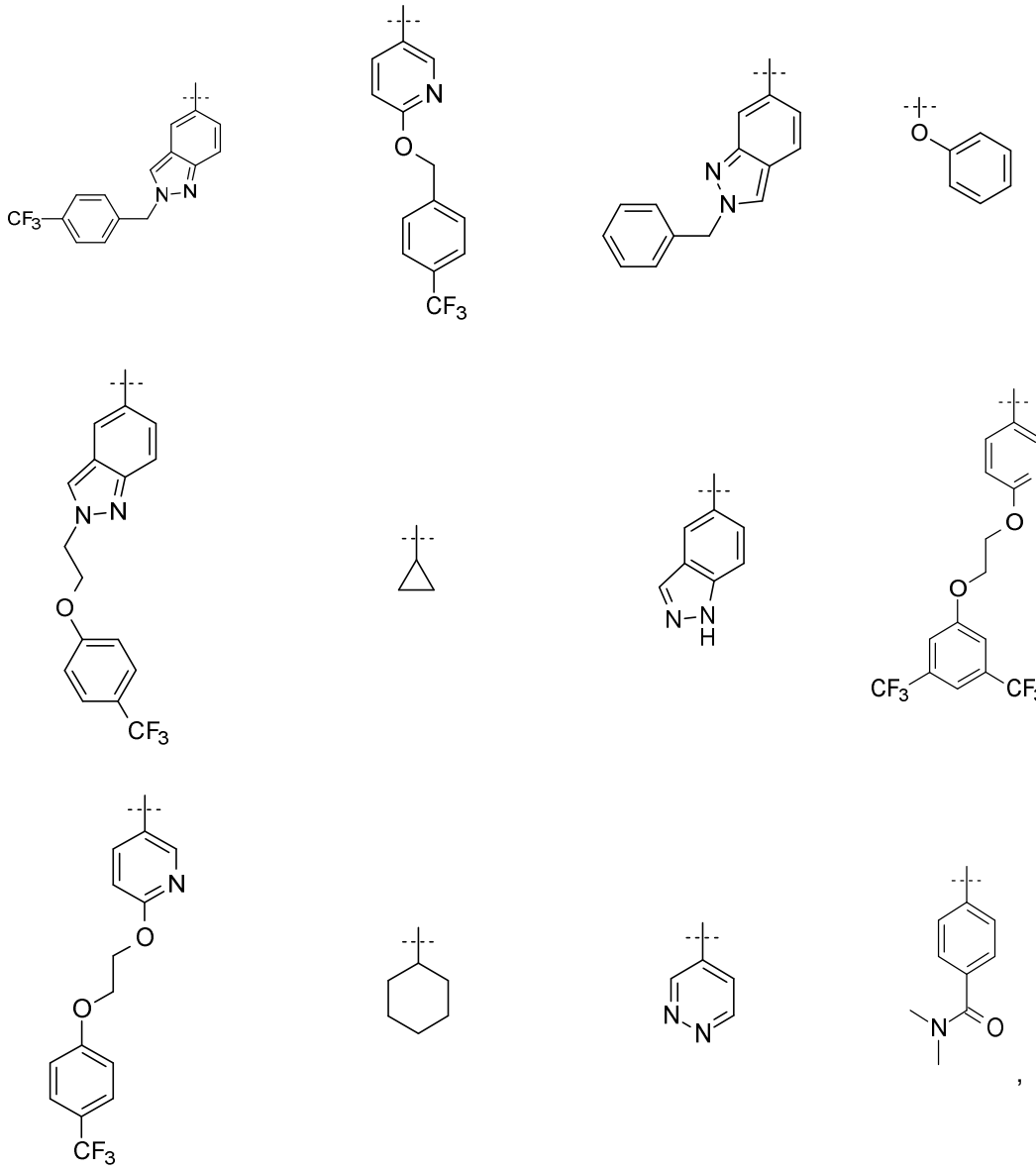


(4e);

or a salt or tautomer thereof.

~~13.~~10. The compound according to any one of claims 1 to 6, wherein R^2 is selected from the group consisting of:





or a salt or tautomer thereof.

~~14.~~11. The compound according to claim 1, which is selected from the group consisting of:

3-((3-(1H-tetrazol-5-yl)phenyl)amino)-4-hydroxycyclobut-3-ene-1,2-dione;

3-((3-(1H-tetrazol-5-yl)-5-(trifluoromethyl)phenyl)amino)-4-hydroxycyclobut-3-ene-1,2-dione;

3-((5-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-3-yl)amino)-4-hydroxycyclobut-3-ene-1,2-dione;

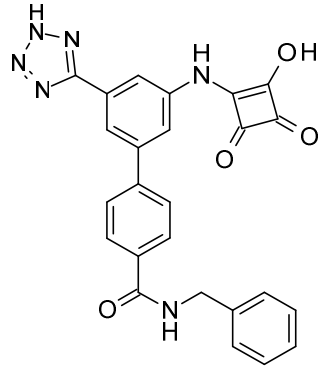
ethyl 3'-((2-hydroxy-3,4-dioxocyclobut-1-en-1-yl)amino)-5'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-3-carboxylate;

N-benzyl-3'-((2-hydroxy-3,4-dioxocyclobut-1-en-1-yl)amino)-5'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-carboxamide;
N-benzyl-3'-((2-hydroxy-3,4-dioxocyclobut-1-en-1-yl)amino)-5'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-3-carboxamide;
3'-((2-hydroxy-3,4-dioxocyclobut-1-en-1-yl)amino)-N-(2-methoxyethyl)-5'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-carboxamide;
3'-((2-hydroxy-3,4-dioxocyclobut-1-en-1-yl)amino)-N-(4-(2-methoxyethoxy)benzyl)-5'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-carboxamide;
3-hydroxy-4-((3'-methoxy-5-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-3-yl)amino)cyclobut-3-ene-1,2-dione;
3-((3-ethyl-5-(1H-tetrazol-5-yl)phenyl)amino)-4-hydroxycyclobut-3-ene-1,2-dione;
3'-((2-hydroxy-3,4-dioxocyclobut-1-en-1-yl)amino)-5'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-3-carboxylic acid;
3'-((2-hydroxy-3,4-dioxocyclobut-1-en-1-yl)amino)-5'-(1H-tetrazol-5-yl)-N-(4-(trifluoromethyl)benzyl)-[1,1'-biphenyl]-4-carboxamide;
3-((4-fluoro-3-(1H-tetrazol-5-yl)phenyl)amino)-4-hydroxycyclobut-3-ene-1,2-dione;
3-((4-chloro-3-(1H-tetrazol-5-yl)phenyl)amino)-4-hydroxycyclobut-3-ene-1,2-dione;
3-((5-(1H-tetrazol-5-yl)-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)amino)-4-hydroxycyclobut-3-ene-1,2-dione;
3-((3-(6-(benzyloxy)pyridin-3-yl)-5-(1H-tetrazol-5-yl)phenyl)amino)-4-hydroxycyclobut-3-ene-1,2-dione;
3-hydroxy-4-((6-methoxy-4-(1H-tetrazol-5-yl)pyridin-2-yl)amino)cyclobut-3-ene-1,2-dione;
3-hydroxy-4-((6-phenyl-4-(1H-tetrazol-5-yl)pyridin-2-yl)amino)cyclobut-3-ene-1,2-dione;
3-((3-(1H-tetrazol-5-yl)-5-(2-(4-(trifluoromethyl)benzyl)-2H-indazol-5-yl)phenyl)amino)-4-hydroxycyclobut-3-ene-1,2-dione;
3-((3-(1H-tetrazol-5-yl)-5-(6-((4-(trifluoromethyl)benzyl)oxy)pyridin-3-yl)phenyl)amino)-4-hydroxycyclobut-3-ene-1,2-dione;
3-((3-(2-benzyl-2H-indazol-5-yl)-5-(1H-tetrazol-5-yl)phenyl)amino)-4-hydroxycyclobut-3-ene-1,2-dione;
3-hydroxy-4-((6-phenoxy-4-(1H-tetrazol-5-yl)pyridin-2-yl)amino)cyclobut-3-ene-1,2-dione;
3-((3-(1H-tetrazol-5-yl)-5-(2-(2-(4-(trifluoromethyl)phenoxy)ethyl)-2H-indazol-6-yl)phenyl)amino)-4-hydroxycyclobut-3-ene-1,2-dione;
3-((3-cyclopropyl-5-(1H-tetrazol-5-yl)phenyl)amino)-4-hydroxycyclobut-3-ene-1,2-dione;

3-((3-(1H-indazol-5-yl)-5-(1H-tetrazol-5-yl)phenyl)amino)-4-hydroxycyclobut-3-ene-1,2-dione;
3-((3-(6-(2-(3,5-bis(trifluoromethyl)phenoxy)ethoxy)pyridin-3-yl)-5-(1H-tetrazol-5-yl)phenyl)amino)-4-hydroxycyclobut-3-ene-1,2-dione;
3-((3-(1H-tetrazol-5-yl)-5-(6-(2-(4-(trifluoromethyl)phenoxy)ethoxy)pyridin-3-yl)phenyl)amino)-4-hydroxycyclobut-3-ene-1,2-dione;
3-((3-cyclohexyl-5-(1H-tetrazol-5-yl)phenyl)amino)-4-hydroxycyclobut-3-ene-1,2-dione;
3-hydroxy-4-((3-(pyridazin-4-yl)-5-(1H-tetrazol-5-yl)phenyl)amino)cyclobut-3-ene-1,2-dione;
3'-((2-hydroxy-3,4-dioxocyclobut-1-en-1-yl)amino)-N,N-dimethyl-5'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-carboxamide;
N-(4-carbamoylbenzyl)-3'-((2-hydroxy-3,4-dioxocyclobut-1-en-1-yl)amino)-5'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-carboxamide;
or a salt or tautomer thereof.

~~15.~~12. The salt according to any one of claims 1 to ~~14~~11, which is a pharmaceutically acceptable salt.

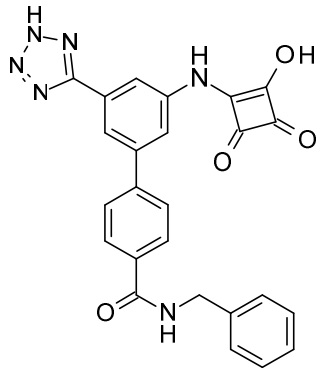
~~16.~~13. The compound or salt according to claim 1, wherein the compound is



,

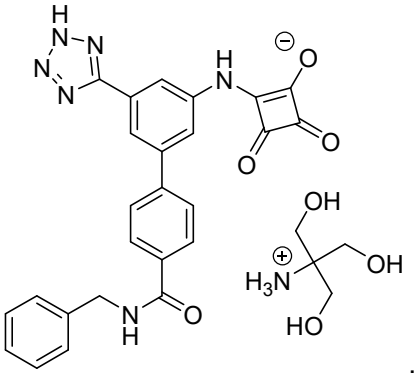
or a pharmaceutically acceptable salt thereof.

~~17.~~14. The compound according to claim 1, wherein the compound is



.

~~18.~~15. The pharmaceutically acceptable salt according to claim ~~16~~13, which is a tromethamine salt having the structure:



.

~~19.~~16. The compound or salt according to any one of claims 1 to ~~18~~ 15 for use in therapy.

~~20.~~17. A pharmaceutical composition comprising the compound or salt according to any one of claims 1 to ~~19~~ 15 and a pharmaceutically acceptable excipient.

18. ~~(21) The~~Use of the compound, salt, or composition according to any one of claims 1 to ~~20~~ 17 in the manufacture of a medicament for the treatment of~~for use in~~:

i) ~~the treatment of~~ mast cell disorders, acute and chronic pain conditions or diseases associated with allergic or inflammatory diseases in both the gastrointestinal system and the lung; or ~~.~~

~~(22)~~

ii) ~~The compound, salt, or composition according to any one of claims 1 to 20 for use in the treatment of~~ gastrointestinal disorders or conditions, symptoms of pain associated with gastrointestinal disease or other visceral conditions, or pulmonary diseases or conditions.

19. ~~(23) The compound, salt, or composition for u~~Use according to claim ~~20~~18, wherein:

i) ~~-~~the gastrointestinal disorder or condition is selected from the group consisting of: food allergy, food intolerance and allergic disorders, celiac disease, gastrointestinal symptoms associated with systemic mastocytosis and other mast cell related disorders (mast cell activation syndrome, clonal mast cell disorder, monoclonal mast cell activation syndrome, idiopathic urticaria, idiopathic anaphylaxis), mastocytic colitis, irritable bowel syndrome (IBS), gastrointestinal motility disorders, functional gastrointestinal disorders, gastroesophageal reflux disease (GERD), duodenogastric reflux, diarrhoeal diseases, eosinophilic gastroenteritis, eosinophilic esophagitis, infectious diarrhea (such as Clostridium difficile, Salmonella, Shigella toxin), microscopic colitis, immune mediated gastrointestinal diseases, Crohn's disease, ulcerative colitis, inflammatory bowel disease, and visceral abdominal pain; or~~.~~

~~i)~~ ~~(24)~~ the symptoms of pain are associated with a gastrointestinal disease or other visceral condition selected from the group consisting of: Crohn's disease, ulcerative colitis, inflammatory bowel disease, radiation colitis, radiation cystitis, celiac disease, gluten enteropathy, radiation cystitis, interstitial cystitis, painful bladder syndrome, cancer, gastroesophageal reflux disease, chemotherapy and radiotherapy mucositis, pancreatitis, prostatitis, pelvic pain, endometriosis, hepatitis, hepatic fibrosis, and cirrhosis

~~ii)~~

~~iii)~~ii) .

~~21. (25) The compound, salt, or composition for use according to claim 20, wherein the pulmonary disease or condition is selected from the group consisting of: chronic obstructive pulmonary diseases, asthma, chronic bronchitis, cystic fibrosis, emphysema, chronic idiopathic cough, hyperactive airway disorder, and idiopathic pulmonary fibrosis.~~

~~22.~~20. Use according to claim 18 or 19, ~~(26)A method of treating diseases, conditions, or disorders in a subject in need thereof according to any one of claims 18~~21 to ~~or 19~~25, ~~comprising administering to the subject~~ wherein a therapeutically effective amount of the compound, salt, or composition is to be administered to a subject in need thereof ~~according to any one of claims 1 to 20~~17.

~~23.~~21. ~~(27)The method~~ Use according to claim ~~26~~20, wherein the subject is a human.

~~24.~~22. ~~(28)~~The pharmaceutically acceptable salt according to claim ~~18~~15, wherein the salt is in a crystalline form.

~~25.~~23. ~~(29)~~The crystalline form according to claim ~~28~~22, which is a hydrate.

24. ~~(30)~~The crystalline form according to claim ~~29~~23, which has:

i) an XRPD pattern substantially in accordance with Figure 1; or .

ii) ~~(31)The crystalline form according to claim 29, which has~~ an XRPD pattern comprising diffraction angles at 3.9±0.2, 7.7±0.2, 10.0±0.2, and 15.8±0.2 °2θ, when measured using Cu K_α radiation.

25. ~~(32)~~The crystalline form according to claim ~~29~~23, which has:

i) an XRPD pattern substantially in accordance with Figure 4; or

ii) ~~.~~

~~(33)The crystalline form according to claim 29, which has~~ an XRPD pattern comprising diffraction angles at 4.4±0.2, 14.4±0.2, and 23.9±0.2 °2θ, when measured using Cu K_α radiation.