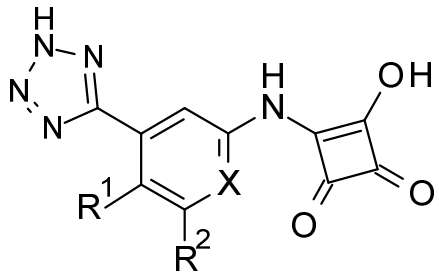
Claims

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;

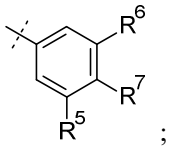
R^2 is H, halo, or

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

ii) aryl, heteroaryl or *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.

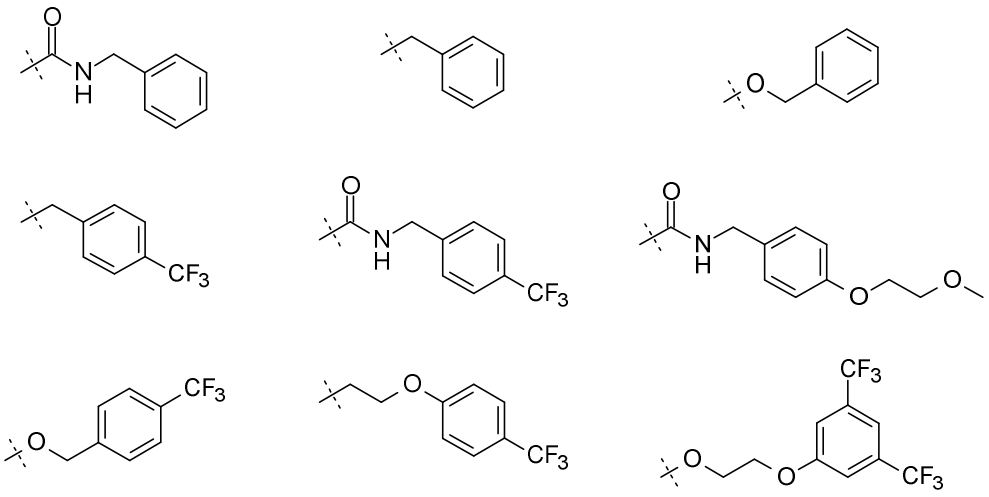
3. The compound according to claim 1 or claim 2, or a salt or tautomer thereof, wherein R^1 is H.

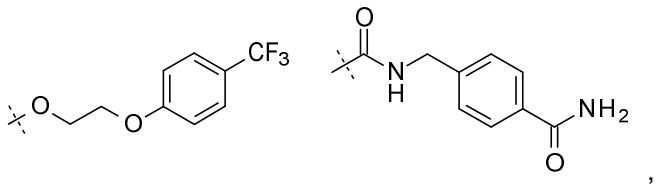
4. The compound according to claims 1 or claim 2, or a salt or tautomer thereof, wherein R^1 is Cl or F.

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

6. The compound according to any one of claims 1 to 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.

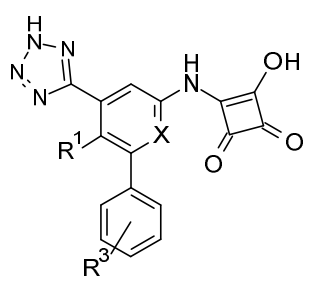
7. The compound according to claim 6, wherein R^3 is OMe, CO_2H, CO_2Et, $CON(CH_3)_2$, $CONHCH_2CH_2OCH_3$, or is selected from the group consisting of:



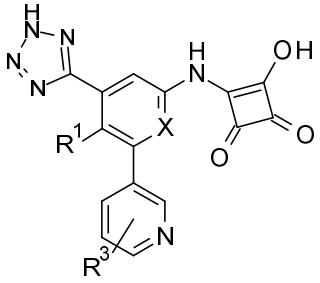


or a salt or tautomer thereof.

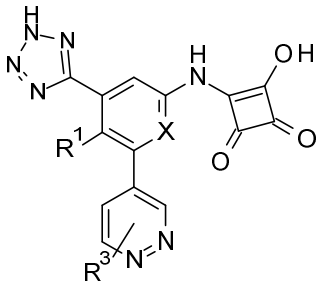
8. The compound according to claim 6 or claim 7, which is a compound of formula (3a), (3b), (3c), (3d) or (3e):



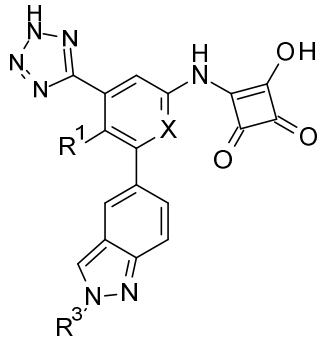
(3a);



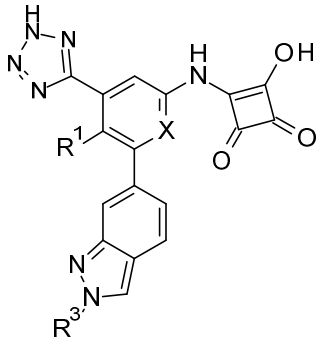
(3b);



(3c);



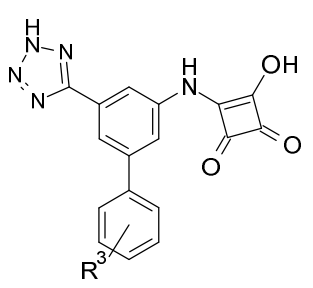
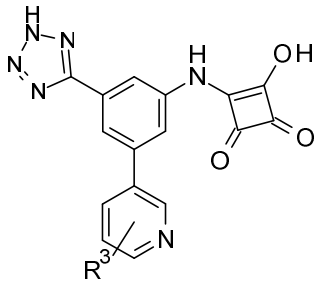
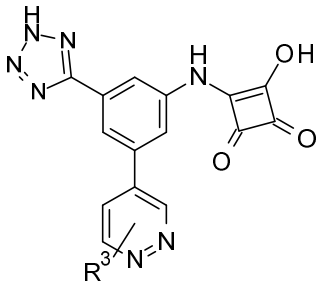
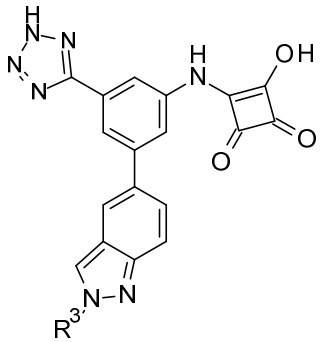
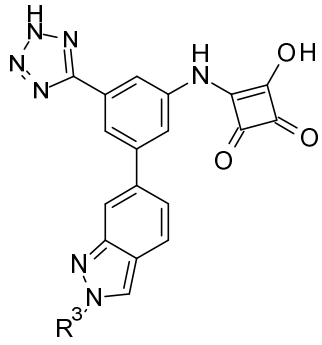
(3d);



(3e);

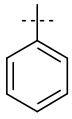
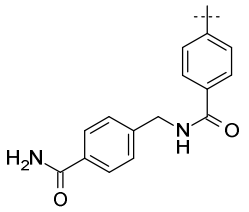
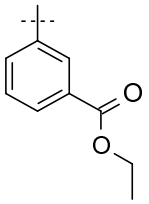
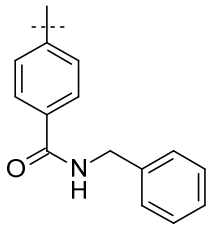
or a salt or tautomer thereof.

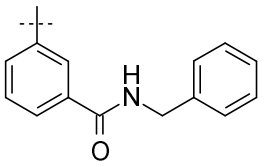
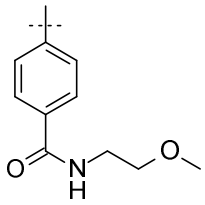
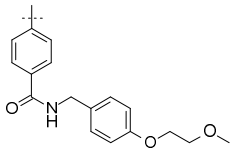
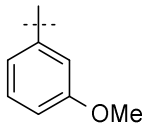
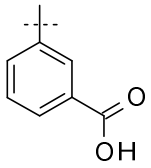
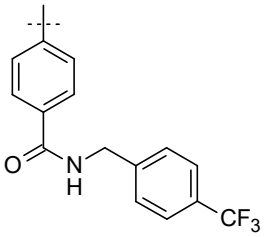
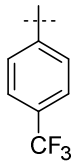
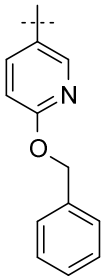
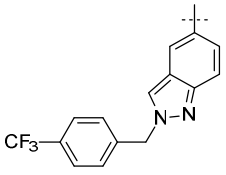
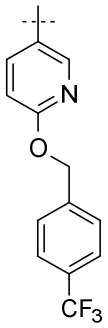
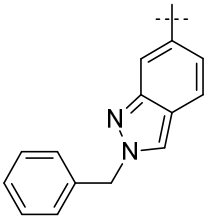
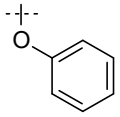
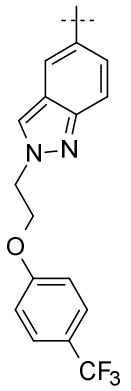
9. The compound according to claim 6 or claim 7, which is a compound of formula (4a), (4b), (4c), (4d) or (4e):

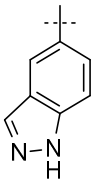
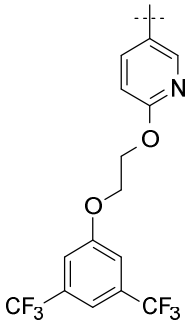

(4a);

(4b);

(4c);

(4d);

(4e);

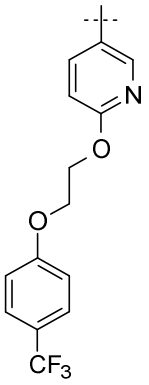
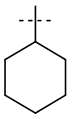
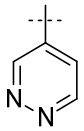
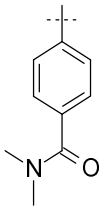
or a salt or tautomer thereof.

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.

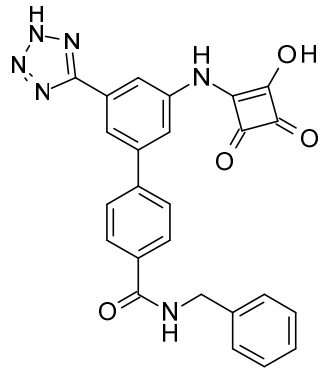
11. The compound according to claim 1, which is selected from the group consisting of:

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.

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

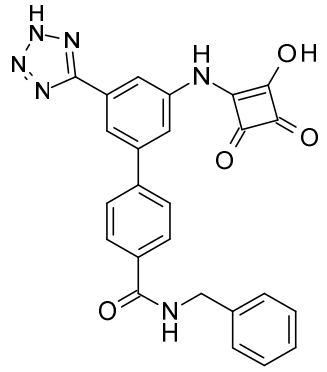
13. The compound or salt according to claim 1, wherein the compound is



,

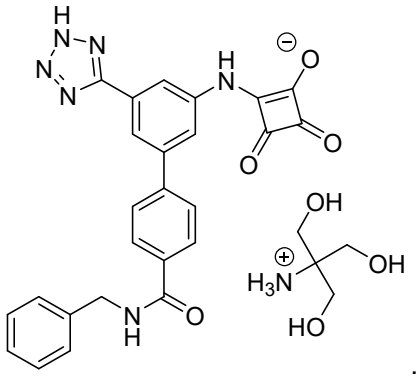
or a pharmaceutically acceptable salt thereof.

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



.

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



.

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

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

18. Use of the compound, salt, or composition according to any one of claims 1 to 17 in the manufacture of a medicament for the treatment of:

i) 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

ii) gastrointestinal disorders or conditions, symptoms of pain associated with gastrointestinal disease or other visceral conditions, or pulmonary diseases or conditions.

19. Use according to claim 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

ii) 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.

20. Use according to claim 18 or 19, wherein a therapeutically effective amount of the compound, salt, or composition is to be administered to a subject in need thereof.

21. Use according to claim 20, wherein the subject is a human.

22. The pharmaceutically acceptable salt according to claim 15, wherein the salt is in a crystalline form.

23. The crystalline form according to claim 22, which is a hydrate.

24. The crystalline form according to claim 23, which has:
i) an XRPD pattern substantially in accordance with Figure 1; or .
ii) 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. The crystalline form according to claim 23, which has:
i) an XRPD pattern substantially in accordance with Figure 4; or
ii) 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.