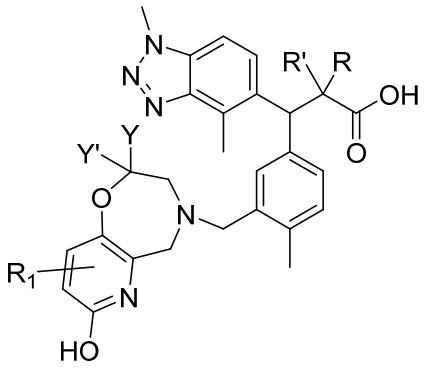
Claims

What is claimed is:

1. A compound of Formula (I):



(I)

wherein:

R is hydrogen or methyl;

R' is hydrogen or methyl;

R_1 is hydrogen, -OH, -C_{1-3}alkyl, -CF_3, difluoromethyl, or halo;

Y is hydrogen, -C_{1-5}alkyl, -C_{3-7}cycloalkyl, -CF_3, -CHF_2, -CH_2CF_3; and

Y' is hydrogen, -C_{1-5}alkyl, -C_{3-7}cycloalkyl, -CF_3, -CHF_2, -CH_2CF_3; or Y and Y' form -C_{3-7}cycloalkyl;

or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a tautomer thereof, or a hydrate thereof.

2. The compound according to claim 1, wherein

R is hydrogen or methyl;

R' is hydrogen or methyl;

R_1 is hydrogen, -C_{1-3}alkyl or halo;

Y is independently -C_{1-5}alkyl, -C_{3-5}cycloalkyl or -CF_3; and

Y' is hydrogen;

or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a tautomer thereof, or a hydrate thereof.

3. The compound according to claim 1, wherein

R is hydrogen or methyl;

R' is hydrogen or methyl;

R_1 is hydrogen, -C_{1-3}alkyl or halo;
Y is -C_{1-5}alkyl, -C_{3-5}cycloalkyl or -CF_3; and
Y' is methyl;
or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a tautomer thereof, or a hydrate thereof.

4. The compound according to claim 1, wherein
R is methyl;
R' is methyl
R_1 is hydrogen;
Y is methyl, ethyl or isopropyl; and
Y' is hydrogen;
or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a tautomer thereof, or a hydrate thereof.

5. The compound according to claim 1, wherein
R is hydrogen;
R' is hydrogen;
R_1 is hydrogen;
Y is methyl, ethyl or isopropyl; and
Y' is hydrogen;
or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a tautomer thereof, or a hydrate thereof.

6. A compound which is:
(*R*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*R*)-2-ethyl-7-hydroxy-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)propanoic acid;

(*R*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*S*)-7-hydroxy-2-isopropyl-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)propanoic acid;

(*R*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*R*)-7-hydroxy-2-isopropyl-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)propanoic acid;

(*R*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*R*)-7-hydroxy-2-methyl-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)propanoic acid;

(*R*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-((7-hydroxy-2,2-dimethyl-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)propanoic acid;

(*R*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*S*)-7-hydroxy-2-(trifluoromethyl)-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)propanoic acid;

(*R*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*S*)-2-ethyl-7-hydroxy-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)propanoic acid;

(*S*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*R*)-7-hydroxy-2-isopropyl-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)propanoic acid;

(*S*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*S*)-7-hydroxy-2-isopropyl-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)propanoic acid;

(*S*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*R*)-2-ethyl-7-hydroxy-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)propanoic acid;

(*S*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-((7-hydroxy-2,2-dimethyl-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)propanoic acid;

(*S*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*S*)-2-ethyl-7-hydroxy-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)propanoic acid;

(*S*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*R*)-2-ethyl-7-hydroxy-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)-2,2-dimethyl propanoic acid;

(*S*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*R*)-7-hydroxy-2-methyl-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)-2,2-dimethylpropanoic acid;

(*S*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*R*)-7-hydroxy-2-isopropyl-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)-2,2-dimethylpropanoic acid;

(*S*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*S*)-7-hydroxy-2-isopropyl-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)-2,2-dimethylpropanoic acid;

(*S*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-((7-hydroxy-2,2-dimethyl-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)-2,2-dimethylpropanoic acid;

(*S*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*S*)-2-ethyl-7-hydroxy-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)-2,2-dimethylpropanoic acid;

(*S*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*S*)-7-hydroxy-2-(trifluoromethyl)-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)-2,2-dimethylpropanoic acid;

(*R*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*R*)-7-hydroxy-2-(trifluoromethyl)-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)propanoic acid;

(*S*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*R*)-7-hydroxy-2-(trifluoromethyl)-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)-2,2-dimethylpropanoic acid;

(*R*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*R*)-2-ethyl-8-fluoro-7-hydroxy-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)propanoic acid;

(*S*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*S*)-7-hydroxy-2-methyl-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)-2,2-dimethylpropanoic acid;

(*S*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-((7-hydroxy-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)-2,2-dimethylpropanoic acid;

(*S*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((S)-7-hydroxy-2-(trifluoromethyl)-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)propanoic acid;

(*R*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*R*)-2-ethyl-7-hydroxy-2-methyl-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)propanonic acid;

(*R*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*S*)-2-ethyl-7-hydroxy-2-methyl-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)propanonic acid;

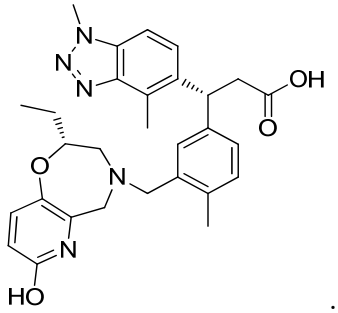
(*S*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*R*)-7-hydroxy-2-(trifluoromethyl)-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)propanoic acid;

(*R*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-((7'-hydroxy-3'H-spiro[cyclobutane-1,2'-pyrido[2,3-*f*][1,4]oxazepin-4'(5'*H*)-yl)methyl)-4-methylphenyl)propanonic acid; and

(*R*)-3-(3-(((*R*)-2-(*tert*-butyl)-7-hydroxy-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)propanoic acid;

or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a tautomer thereof, or a hydrate thereof.

7. A compound, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a tautomer thereof, or a hydrate thereof, which is



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8. A crystalline form of (*R*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*R*)-2-ethyl-7-hydroxy-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)propanoic acid hydrate, or a tautomer thereof, having an x-ray powder diffraction pattern comprising peaks at 15.76°, 7.86°, 9.58°, and 19.07° ±0.2° 2θ as measured by x-ray powder diffraction using an x-ray wavelength of 1.5406 Å.

9. The compound according to claim 1 which is (*R*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*R*)-2-ethyl-7-hydroxy-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)propanoic acid besylate salt, or a tautomer thereof.

10. A crystalline form of (*R*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*R*)-2-ethyl-7-hydroxy-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)propanoic acid besylate salt, or a tautomer thereof, having an x-ray powder diffraction pattern comprising peaks at 25.18°, 22.53°, 16.66°, and 7.82° ±0.2° 2θ as measured by x-ray powder diffraction using an x-ray wavelength of 1.5406 Å.

11. The compound according to claim 1 which is (*R*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*R*)-2-ethyl-7-hydroxy-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)propanoic acid mesylate salt hydrate, or a tautomer thereof.

12. A crystalline form of (*R*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*R*)-2-ethyl-7-hydroxy-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)propanoic acid mesylate salt hydrate, or a tautomer thereof, having an x-ray powder diffraction pattern comprising peaks at 19.84°, 17.25°, 21.06°, and 13.45° ±0.2° 2θ as measured by x-ray powder diffraction using an x-ray wavelength of 1.5406 Å.

13. A crystalline compound of (*R*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*R*)-2-ethyl-7-hydroxy-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)propanoic acid (free form), or a tautomer thereof.

14. A crystalline compound of (*R*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*R*)-2-ethyl-7-hydroxy-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)propanoic acid (free form), or a tautomer thereof, which is characterized by an x-ray powder diffraction pattern substantially in accordance with that shown in FIG. 1.

15. A crystalline form of (*R*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*R*)-2-ethyl-7-hydroxy-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)propanoic acid (free form), or a tautomer thereof, having an x-ray powder diffraction pattern comprising peaks at 12.38°, 25.90°, 19.35°, and 7.54° ±0.2° 2θ as measured by x-ray powder diffraction using an x-ray wavelength of 1.5406 Å.

16. Isolated crystalline (*R*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*R*)-2-ethyl-7-hydroxy-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)propanoic acid (free form), or a tautomer thereof.

17. A substantially pure crystalline form of (*R*)-3-(1,4-dimethyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(3-(((*R*)-2-ethyl-7-hydroxy-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)propanoic acid (free form), or a tautomer thereof.

18. The crystalline compound according to claim 13, wherein the crystalline compound is characterized by having at least five peaks selected from the diffraction data substantially in accordance with the following:

Diffraction Angle (°2θ)	***d*-Spacing (Å)**
6.69	13.20
7.54	11.72
12.38	7.14
12.90	6.86
13.55	6.53
13.99	6.33
16.40	5.40
17.49	5.07
17.82	4.97
18.30	4.84
19.35	4.58
19.96	4.44
20.98	4.23
22.74	3.91
25.90	3.44
26.79	3.33
27.36	3.26

19. A pharmaceutical composition comprising a compound, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a tautomer thereof, or a hydrate thereof, according to any one of claims 1–18 and one or more pharmaceutically acceptable excipients.

20. Use of a therapeutically effective amount of a compound according to any one of claims 1-18, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a tautomer thereof, or a hydrate thereof, in the manufacture of a medicament for the treatment of an Nrf2-regulated disease or disorder selected from COPD, asthma, ALI, ARDS, fibrosis, chronic asthma and acute asthma, lung disease secondary to environmental exposures, acute lung infection, chronic lung infection, α1 antitrypsin disease, cystic fibrosis, autoimmune diseases, diabetic nephropathy, chronic kidney disease, sepsis-induced acute kidney injury, acute kidney injury (AKI), kidney disease or malfunction seen during kidney transplantation, Pulmonary Arterial Hypertension, atherosclerosis, hypertension, heart failure, acute coronary syndrome, myocardial infarction, myocardial repair, cardiac remodelling, cardiac arrhythmias, heart failure with preserved ejection fraction, heart failure with reduced ejection fraction, diabetic cardiomyopathy, SCD, Progeria and cardiorenal syndrome (CRS), Parkinson’s disease (PD), Alzheimer’s disease (AD), Friedreich’s Ataxia (FA), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Huntington’s disease (HD), spinal cord injury, traumatic brain injury, ischemic stroke, stroke, Creutzfeldt-Jakob Disease, fatal familial insomnia, Gerstmann-Sträussler-Scheinker syndrome, and related prion diseases, progressive supranuclear palsy, chronic traumatic encephalopathy (CTE), neurodegeneration, dementias, frontotemporal dementias, tauopathies, retinitis pigmentosa, Pick’s disease, Neimann-Pick’s disease, amyloidosis, cognitive impairment, inflammatory bowel disease, colon cancer, neovascular (dry) AMD and neovascular (wet) AMD, eye injury, Fuchs Endothelial Corneal Dystrophy (FECD), uveitis or other inflammatory eye conditions, Non-alcoholic Steatohepatitis (NASH), toxin-induced liver disease (e.g., acetaminophen-induced hepatic disease), viral hepatitis, cirrhosis, psoriasis, dermatitis/topical effects of radiation, immunosuppression due to radiation exposure, Preeclampsia, and high altitude sickness.

21. The use according to claim 20 wherein the said medicament is administered orally.

22 The use according to claim 20 wherein the said medicament is administered intravenously.

23. The use according to claim 20 wherein the said medicament is administered by inhalation.

24. The use according to claim 20 wherein the disease is COPD.

25. The use according to claim 20 wherein the disease is heart failure.

26. The use according to claim 20 wherein the disease is heart failure with reduced ejection fraction.

27. The use according to claim 20 wherein the disease is heart failure with preserved ejection fraction.

28. A compound, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a tautomer thereof, or a hydrate thereof, according to any one of claims 1-18, for use in treating an Nrf2-regulated disease or disorder selected from COPD, asthma, ALI, ARDS, fibrosis, chronic asthma and acute asthma, lung disease secondary to environmental exposures, acute lung infection, chronic lung infection, α1 antitrypsin disease, cystic fibrosis, autoimmune diseases, diabetic nephropathy, chronic kidney disease, sepsis-induced acute kidney injury, acute kidney injury (AKI), kidney disease or malfunction seen during kidney transplantation, Pulmonary Arterial Hypertension, atherosclerosis, hypertension, heart failure, acute coronary syndrome, myocardial infarction, myocardial repair, cardiac remodelling, cardiac arrhythmias, heart failure with preserved ejection fraction, heart failure with reduced ejection fraction, diabetic cardiomyopathy, SCD, Progeria and cardiorenal syndrome (CRS), Parkinson's disease (PD), Alzheimer's disease (AD), Friedreich's Ataxia (FA), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Huntington's disease (HD), spinal cord injury, traumatic brain injury, ischemic stroke, stroke, Creutzfeldt-Jakob Disease, fatal familial insomnia, Gerstmann-Sträussler-Scheinker syndrome, and related prion diseases, progressive supranuclear palsy, chronic traumatic encephalopathy (CTE), neurodegeneration, dementias, frontotemporal dementias, tauopathies, retinitis pigmentosa, Pick's disease, Neimann-Pick's disease, amyloidosis, cognitive impairment, inflammatory bowel disease, colon cancer, neovascular (dry) AMD and neovascular (wet) AMD, eye injury, Fuchs Endothelial Corneal Dystrophy (FECD), uveitis or other inflammatory eye conditions, Non-alcoholic Steatohepatitis (NASH), toxin-induced liver

disease (e.g., acetaminophen-induced hepatic disease), viral hepatitis, cirrhosis, psoriasis, dermatitis/topical effects of radiation, immunosuppression due to radiation exposure, Preeclampsia, and high altitude sickness.

29. The compound, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a tautomer thereof, or a hydrate thereof, according to claim 28, for use in treating heart failure.

30. The compound, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a tautomer thereof, or a hydrate thereof, according to claim 28, for use in treating heart failure with reduced ejection fraction.

31. The compound, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a tautomer thereof, or a hydrate thereof, according to claim 28, for use in treating heart failure with preserved ejection fraction.

32. A pharmaceutical composition comprising a compound, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a tautomer thereof, or a hydrate thereof, according to claim 7, and one or more pharmaceutically acceptable excipients.

33. Use of a therapeutically effective amount of a compound according to claim 7, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a tautomer thereof, or a hydrate thereof, in the manufacture of a medicament for the treatment of an Nrf2-regulated disease or disorder which is heart failure.

34. The use according to claim 33, wherein the disease or disorder is heart failure with reduced ejection fraction.

35. The use according to claim 33, wherein the disease or disorder is heart failure with preserved ejection fraction.