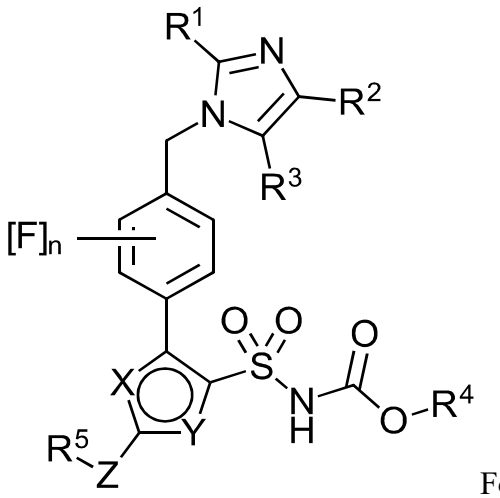
CLAIMS

1. A compound of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof,

in which

R^1 represents

H,

C_2-C_6 alkyl substituted with 0, 1 or 2 substituents selected from the group consisting of OR^6, SR^7, NR^8R^9, halogen, thiazole, oxazole and pyrazole,

C_3-C_6 cycloalkyl substituted with 0, 1 or 2 substituents selected from the group consisting of OR^6, SR^7 and NR^8R^9,

thiazole,

benzyl in which the phenyl moiety is substituted with 0, 1 or 2 substituents selected from the group consisting of OR^6, SR^7 and NR^8R^9, or

$(CH_2)_m$-R^{10},

R^2 represents

H,

F,

Cl,

C_2-C_6 alkyl substituted with 0, 1 or 2 substituents selected from the group consisting of OR^6, SR^7, NR^8R^9, halogen, thiazole, oxazole and pyrazole,

C_3-C_6 cycloalkyl substituted with 0, 1 or 2 substituents selected from the group consisting of OR^6, SR^7 and NR^8R^9,

benzyl in which the phenyl moiety is substituted with 0, 1 or 2 substituents selected from the group consisting of OR^6, SR^7 and NR^8R^9, or

$(CH_2)_m$-R^{10},

provided that R^1 and R^2 are not both H,

R^3 represents

H,

halogen, or

C_1-C_3 alkyl substituted with 0, 1, 2 or 3 halogens selected from the group consisting of F and Cl,

R^4 and R^5 independently represent C_1-C_6alkyl substituted with 0, 1, 2 or 3 F,

X represents CH=CH, CH, N, NH, O or S;

Y represents CH=CH, CH, N, NH, O or S,

provided that:

(a) X and Y are not the same,

(b) when X represents CH=CH then Y may only represent CH, and

(c) when Y represents CH=CH then X may only represent CH,

Z represents a single bond, O or S,

R^6, R^7, R^8 and R^9 independently represent

H, or

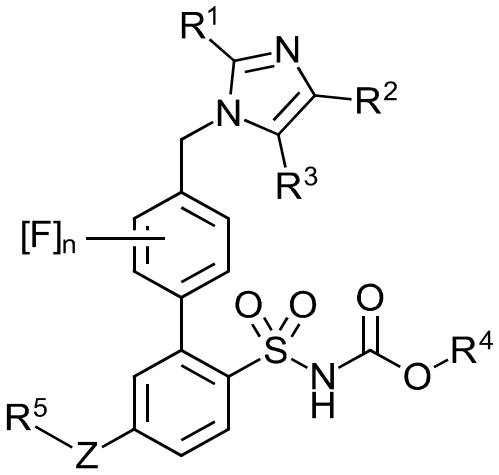
C_1-C_3 alkyl substituted with 0,1, 2 or 3 F,

R^{10} is selected from the group consisting of phenyl, thiazole, oxazole and pyrazole,

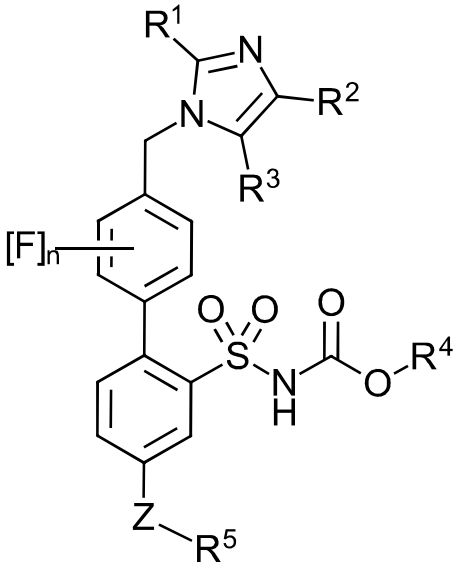
n is 0, 1, 2, 3 or 4, and

m is 0 or 1.

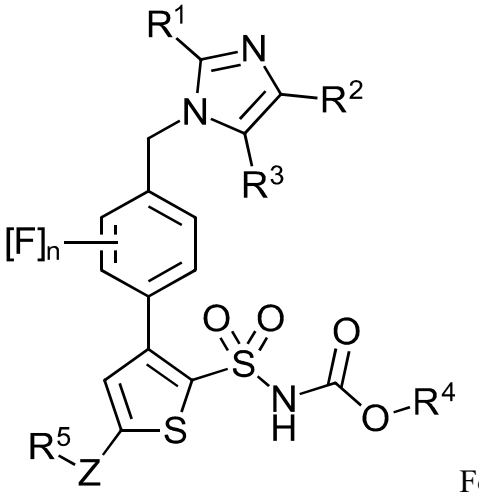
2. A compound according to Claim 1, or a pharmaceutically acceptable salt thereof, which is a compound of Formula Ia, Formula Ib, Formula Ic or Formula Id:



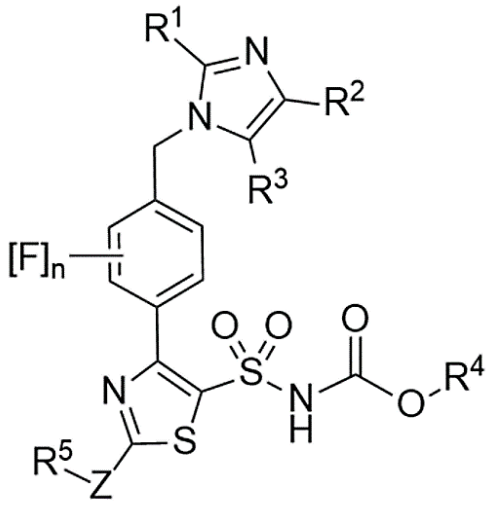
Formula Ia,



Formula Ib,



Formula Ic,



Formula Id.

3. A compound according to Claim 1 or 2, in which R^1 represents C_2-C_6 alkyl substituted with 0, 1 or 2 substituents selected from the group consisting of OR^6, SR^7, NR^8R^9, halogen, thiazole, oxazole and pyrazole.

4. A compound according to Claim 1, 2 or 3, in which R^2 and R^3 independently represent H.

5. A compound according to Claim 3 or 4, in which R^1 is *tert*-butyl, isopropyl or cyclopropyl.

6. A compound as according to Claim 3 or 4, in which R^1 is C_2-C_6 alkyl substituted by an -OH group or a F atom.

7. A compound according to Claim 6, in which R^1 is 2-hydroxyprop-2-yl, 1-ethanol or 2-fluoroprop-2-yl.

8. A compound according to any preceding claim, in which R^4 is selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, and *tert*-butyl.

9. A compound according to Claim 8, in which R^4 is methyl or *n*-butyl.

10. A compound according to any preceding claim, in which R^5 is selected from the group consisting of ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl and *tert*-butyl.

11. A compound according to Claim 10, in which R^5 is isopropyl or isobutyl.

12. A compound according to any preceding claim, in which n is 0.

13. A compound according to any preceding claim, in which Z is a single bond.

14. A compound according to any preceding claim, which is one or more of the following:

methyl ((4'-((2-*(tert*-butyl)-1*H*-imidazol-1-yl)methyl)-5-isobutyl-[1,1'-biphenyl]-2-yl)sulfonyl)carbamate,

butyl ((4'-((2-*(tert*-butyl)-1*H*-imidazol-1-yl)methyl)-5-isobutyl-[1,1'-biphenyl]-2-yl)sulfonyl)carbamate,

methyl ((4-(4-((2-*(tert*-butyl)-1H-imidazol-1-yl)methyl)phenyl)-2-isobutylthiazol-5-yl)sulfonyl) carbamate,

butyl ((4-(4-((2-*(tert*-butyl)-1H-imidazol-1-yl)methyl)phenyl)-2-isobutylthiazol-5-yl)sulfonyl) carbamate,

methyl ((4-(4-((2-*(tert*-butyl)-1H-imidazol-1-yl)methyl)phenyl)-2-propylthiazol-5-yl)sulfonyl)carbamate,

butyl ((4-(4-((2-*(tert*-butyl)-1H-imidazol-1-yl)methyl)phenyl)-2-propylthiazol-5-yl)sulfonyl) carbamate,

butyl ((4'-((2-(2-hydroxypropan-2-yl)-1H-imidazol-1-yl)methyl)-5-isobutyl-[1,1'-biphenyl]-2-yl)sulfonyl)carbamate,

methyl ((4'-((2-(2-hydroxypropan-2-yl)-1H-imidazol-1-yl)methyl)-5-isobutyl-[1,1'-biphenyl]-2-yl)sulfonyl)carbamate,

butyl ((4'-((2-*(tert*-butyl)-1H-imidazol-1-yl)methyl)-5-propyl-[1,1'-biphenyl]-2-yl)sulfonyl)carbamate,

methyl ((4'-((2-*(tert*-butyl)-1H-imidazol-1-yl)methyl)-5-propyl-[1,1'-biphenyl]-2-yl)sulfonyl)carbamate,

butyl ((3-(4-((2-*(tert*-butyl)-1H-imidazol-1-yl)methyl)phenyl)-5-isobutylthiophen-2-yl)sulfonyl)carbamate,

methyl ((3-(4-((2-*(tert*-butyl)-1H-imidazol-1-yl)methyl)phenyl)-5-isobutylthiophen-2-yl)sulfonyl)carbamate,

butyl ((4-(4-((2-(2-hydroxypropan-2-yl)-1H-imidazol-1-yl)methyl)phenyl)-2-propyl thiazol-5-yl)sulfonyl)carbamate,

butyl ((4-(4-((2-isopropyl-1H-imidazol-1-yl)methyl)phenyl)-2-propylthiazol-5-yl) sulfonyl)carbamate,

butyl ((2-isobutyl-4-(4-((2-(thiazol-2-yl)-1H-imidazol-1-yl)methyl)phenyl)thiazol-5-yl) sulfonyl)carbamate,

butyl ((4-(4-((2-(2-hydroxypropan-2-yl)-1H-imidazol-1-yl)methyl)phenyl)-2-isobutyl thiazol-5-yl)sulfonyl)carbamate,

butyl ((2-isobutyl-4-(4-((2-isopropyl-1H-imidazol-1-yl)methyl)phenyl)thiazol-5-yl) sulfonyl)carbamate,

methyl ((4-(4-((2-(2-hydroxypropan-2-yl)-1H-imidazol-1-yl)methyl)phenyl)-2-isobutylthiazol-5-yl)sulfonyl)carbamate,

methyl ((2-isobutyl-4-(4-((2-isopropyl-1H-imidazol-1-yl)methyl)phenyl)thiazol-5-yl) sulfonyl)carbamate,

butyl ((2-propyl-4-(4-((2-(thiazol-2-yl)-1H-imidazol-1-yl)methyl)phenyl)thiazol-5-yl) sulfonyl)carbamate,

butyl ((4-(4-((2-(1-hydroxyethyl)-1H-imidazol-1-yl)methyl)phenyl)-2-isobutylthiazol-5-yl)sulfonyl)carbamate,

methyl ((4-(4-((2-(1-hydroxyethyl)-1H-imidazol-1-yl)methyl)phenyl)-2-isobutylthiazol-5-yl)sulfonyl)carbamate,

butyl ((4-(4-((2-(1-hydroxyethyl)-1H-imidazol-1-yl)methyl)phenyl)-2-propylthiazol-5-yl)sulfonyl)carbamate,

methyl ((4-(4-((2-(1-hydroxyethyl)-1H-imidazol-1-yl)methyl)phenyl)-2-propylthiazol-5-yl)sulfonyl)carbamate,

methyl ((4-(4-((2-cyclopropyl-1H-imidazol-1-yl)methyl)phenyl)-2-isobutylthiazol-5-yl)sulfonyl)carbamate,

butyl ((4-(4-((2-cyclopropyl-1H-imidazol-1-yl)methyl)phenyl)-2-isobutylthiazol-5-yl)sulfonyl)carbamate,

methyl ((4-(4-((2-cyclopropyl-1H-imidazol-1-yl)methyl)phenyl)-2-propylthiazol-5-yl)sulfonyl)carbamate,

butyl ((4-(4-((2-cyclopropyl-1H-imidazol-1-yl)methyl)phenyl)-2-propylthiazol-5-yl)sulfonyl)carbamate,

methyl ((4'-((2-(2-hydroxypropan-2-yl)-1H-imidazol-1-yl)methyl)-5-propyl-[1,1'-biphenyl]-2-yl)sulfonyl)carbamate,

butyl ((4'-((2-(2-hydroxypropan-2-yl)-1*H*-imidazol-1-yl)methyl)-5-propyl-[1,1'-biphenyl]-2-yl)sulfonyl)carbamate,

butyl ((4'-((2-(2-fluoropropan-2-yl)-1*H*-imidazol-1-yl)methyl)-5-isobutyl-[1,1'-biphenyl]-2-yl)sulfonyl)carbamate,

methyl ((5-isobutyl-4'-((2-(thiazol-2-yl)-1*H*-imidazol-1-yl)methyl)-[1,1'-biphenyl]-2-yl)sulfonyl)carbamate,

methyl ((4'-((2-(2-fluoropropan-2-yl)-1*H*-imidazol-1-yl)methyl)-5-isobutyl-[1,1'-biphenyl]-2-yl)sulfonyl)carbamate,

butyl ((5-isobutyl-4'-((2-(thiazol-2-yl)-1*H*-imidazol-1-yl)methyl)-[1,1'-biphenyl]-2-yl)sulfonyl)carbamate,

methyl ((5-isobutyl-4'-((2-(isopropan-2-yl)-1*H*-imidazol-1-yl)methyl)-[1,1'-biphenyl]-2-yl)sulfonyl)carbamate,

butyl ((5-isobutyl-4'-((2-(isopropan-2-yl)-1*H*-imidazol-1-yl)methyl)-[1,1'-biphenyl]-2-yl)sulfonyl)carbamate,

butyl ((5-isobutyl-4'-((2-(cyclopropan-2-yl)-1*H*-imidazol-1-yl)methyl)-[1,1'-biphenyl]-2-yl)sulfonyl)carbamate,

methyl ((5-isobutyl-4'-((2-(cyclopropan-2-yl)-1*H*-imidazol-1-yl)methyl)-[1,1'-biphenyl]-2-yl)sulfonyl)carbamate,

butyl ((5-isobutyl-3-(4-(2-(2-hydroxypropan-2-yl)-1*H*-imidazol-1-yl)methyl)phenyl)-2-yl)sulfonyl)carbamate,

methyl ((5-isobutyl-3-(4-(2-(2-hydroxypropan-2-yl)-1*H*-imidazol-1-yl)methyl)phenyl)-2-yl)sulfonyl)carbamate,

butyl ((5-isobutyl-3-(4-(2-(2-fluoropropan-2-yl)-1*H*-imidazol-1-yl)methyl)phenyl)-2-yl)sulfonyl)carbamate,

methyl ((5-isobutyl-3-(4-(2-(2-fluoropropan-2-yl)-1*H*-imidazol-1-yl)methyl)phenyl)-2-yl)sulfonyl)carbamate,

2-methoxyethyl ((5-isobutyl-3-(4-(2-(2-tertbutyl)-1*H*-imidazol-1-yl)methyl)phenyl)-2-yl)sulfonyl)carbamate,

butyl ((4-(4-((2-(2-fluoropropan-2-yl)-1H-imidazol-1-yl)methyl)phenyl)-2-propyl thiazol-5-yl)sulfonyl)carbamate,

methyl ((4-(4-((2-(2-fluoropropan-2-yl)-1H-imidazol-1-yl)methyl)phenyl)-2-propyl thiazol-5-yl)sulfonyl)carbamate,

butyl ((4-(4-((2-(2-fluoropropan-2-yl)-1H-imidazol-1-yl)methyl)phenyl)-2-isobutylthiazol-5-yl)sulfonyl)carbamate,

methyl ((4-(4-((2-(2-fluoropropan-2-yl)-1H-imidazol-1-yl)methyl)phenyl)-2-isobutylthiazol-5-yl)sulfonyl)carbamate,

butyl ((4'-((2-(tert-butyl)-1H-imidazol-1-yl)methyl)-3'-fluoro-5-isobutyl-[1,1'-biphenyl]-2-yl)sulfonyl)carbamate, or

methyl (4'-((2-(tert-butyl)-1H-imidazol-1-yl)methyl)-3'-fluoro-5-isobutyl-[1,1'-biphenyl]-2-yl)sulfonylcarbamate.

15. A compound according to Claim 14, which is:

methyl ((4'-((2-(tert-butyl)-1H-imidazol-1-yl)methyl)-5-isobutyl-[1,1'-biphenyl]-2-yl)sulfonyl)carbamate,

methyl ((4-(4-((2-*(tert*-butyl)-1H-imidazol-1-yl)methyl)phenyl)-2-isobutylthiazol-5-yl)sulfonyl) carbamate,

methyl ((3-(4-((2-*(tert*-butyl)-1H-imidazol-1-yl)methyl)phenyl)-5-isobutylthiophen-2-yl)sulfonyl)carbamate,

methyl (4'-((2-(tert-butyl)-1H-imidazol-1-yl)methyl)-3'-fluoro-5-isobutyl-[1,1'-biphenyl]-2-yl)sulfonylcarbamate,

or a pharmaceutically acceptable salt thereof.

16. A compound according to any preceding claim, for use as a medicament.

17. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any of Claims 1 to 15, together with at least one pharmaceutically acceptable carrier, excipient and/or diluent.

18. A compound according to any preceding claim for treating and/or preventing a disease, disorder or condition associated with angiotensin II, in which the compound exhibits an acceptable level of CYP inhibition of one or more CYPs.

19. A compound according Claim 18, for use in the treatment and/or prevention of a disease, disorder and/or condition selected from the group consisting of hypertension, heart failure, stroke, chronic kidney disease, nephropathy, pulmonary fibrosis such as idiopathic pulmonary fibrosis, sclerosis such as systemic sclerosis, sarcoidosis such as pulmonary sarcoidosis, obstructive lung diseases, such as chronic obstructive lung disease, autoimmune diseases, such as rheumatoid arthritis, viral respiratory tract infections and pneumonia as a consequence thereof, and any combination thereof.

20. Use of a compound according to Claim 18 in the manufacture of a medicament for the treatment of a disease, disorder and/or condition selected from the group consisting of hypertension, heart failure, stroke, chronic kidney disease, nephropathy, pulmonary fibrosis such as idiopathic pulmonary fibrosis, sclerosis such as systemic sclerosis, sarcoidosis such as pulmonary sarcoidosis, obstructive lung diseases, such as chronic obstructive lung disease, autoimmune diseases, such as rheumatoid arthritis, viral respiratory tract infections and pneumonia as a consequence thereof, and any combination thereof.

21. A compound for use according to Claim 19 or use according to Claim 20, in which the disease is an interstitial lung disease.

22. A compound for use or use according to Claim 21, in which the interstitial lung disease is idiopathic pulmonary fibrosis or sarcoidosis.

23. A compound for use according to Claim 19 or use according to Claim 20, in which the diseases are heart failure, chronic kidney disease, rheumatoid arthritis and virally-induced pneumonia.

24. A pharmaceutical formulation comprising a compound according to any of Claims 1 to 15, a therapeutic agent that is known to be metabolized by a CYP enzyme; and a pharmaceutically-acceptable adjuvant, diluent or carrier.

25. A kit of parts comprising:

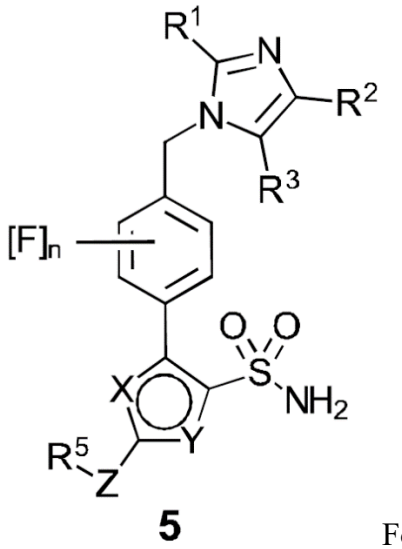
(a) a pharmaceutical formulation including a compound according to any of Claims 1 to 15 in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation including a therapeutic agent that is known to be metabolized by a CYP enzyme, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,

which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

26. A formulation according to Claim 24, or a kit of parts according to Claim 25, in which the therapeutic agent is selected from the group consisting of pirfenidone, naproxen, propranolol, riluzole, tizanidine, warfarin, celecoxib, clopidogrel, irbesartan, meloxicam, piroxicam, torsemide, cyclophosphamide, indomethacin, atorvastatin, cilostazol, cyclosporine, deflazacort, hydrocortisone, lidocaine, selexipag, sildenafil and/or simvastatin.

27. A process for the preparation of a compound of Formula I as defined in any preceding claim, by reaction of a compound of Formula 5,

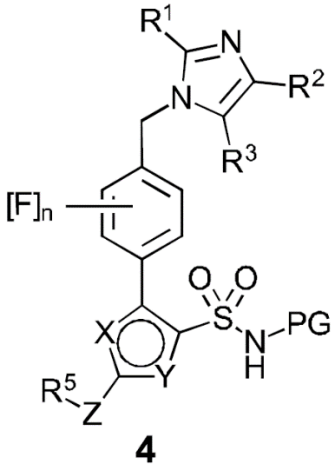


5 Formula 5

in which R^1, R^2, R^3, R^5, X, Y, Z and n are as defined in Claim 1 with a compound of Formula 6,

$R^4OC(O)X$ (Formula 6)

in which X represents a suitable leaving group, such as halo (e.g. chloro), and R^4 is as defined in Claim 1, optionally following deprotection of a compound of Formula 4,



Formula 4

in which PG represents a protecting group and R^1, R^2, R^3, R^5, X, Y, Z and n are as defined above to yield a compound of Formula 5 as an intermediate.