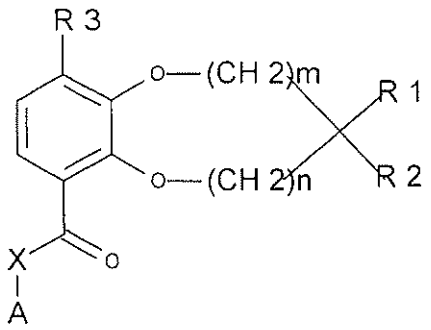
CLAIMS

1. A compound of general formula I



I

wherein

each of m and n is independently 0 or 1;

R_1 and R_2, together with the carbon atom to which they are attached, form a heterocyclic ring comprising one or two heteroatoms selected from oxygen, sulfur, -S(O)- and –$S(O)_2$-;

R_3 is $-CHF_2$, $-CF_3$, $-OCHF_2$, $-OCF_3$, $-SCHF_2$ or $-SCF_3$;

X is a bond, $-CH_2$-, or –NH-;

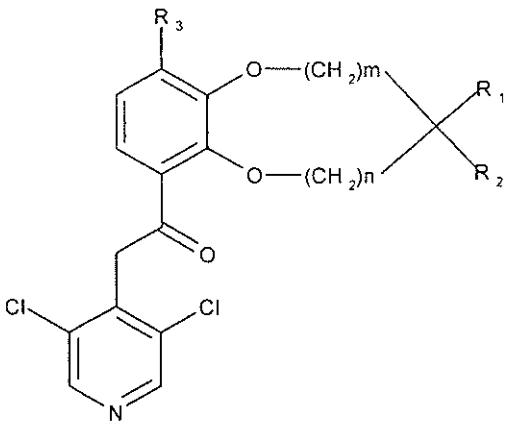
A is aryl, cycloalkyl, cycloalkenyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkenyl, optionally substituted with one or more, same or different substituents selected from R_4; and

R_4 is hydrogen, amino, thioxo, alkyl, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, halogen, oxo, thia, or hydroxy;

or a pharmaceutically acceptable salt, hydrate or solvate thereof.

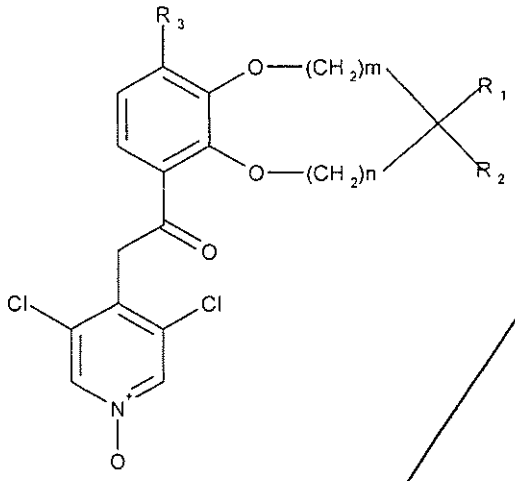
2. A compound according to claim 1 wherein X is $-CH_2$- or –NH-;

3. A compound according to claim 1 or 2 of general formula IIa



IIa

or IIb



IIb

wherein m, n, R_1, R_2 and R_3 are as defined in claim 1.

4. A compound according to claim 1,2 or 3, wherein m and n are both 0.

5. A compound according to claim 1, 2 or 3, wherein m and n are both 1.

6. A compound according to any one of claims 1-5, wherein R_3 is $-OCHF_2$ or $-OCF_3$.

7. A compound according to claim 6, wherein R_3 is $-OCHF_2$.

8. A compound according to any one of claims 1-5, wherein R_3 is $-SCHF_2$ or $-SCF_3$.

9. A compound according to any one of claims 1-8, wherein R_1 and R_2, together with the carbon atom to which they are attached, form a 4-, 5- or 6-membered heterocyclic ring.

10. A compound according to claim 9, wherein the heterocyclic ring is tetrahydropyran, oxetane, [1,3]dioxolane, [1,3]dioxane, tetrahydrothiopyran, tetrahydrothiopyran-1,1-dioxide, tetrahydrothiopyran-1-oxide, tetrahydrothiophene, [1,3]-dithiane, thietane, [1,3]-dithiane-1,3-dioxide, thietane-1-oxide, or thiethane-1,1-dioxide.

11. A compound according to claim 9, wherein the heterocyclic ring comprises one heteroatom.

12. A compound according to claim 11, wherein the heteroatom is oxygen or $-S(O)_2$.

13. A compound according to claim 1, 2 or 3 selected from the group consisting of
2-(3,5-Dichloropyridin-4-yl)-1-{9-difluoromethoxy-spiro[2H-1,5-benzodioxepin-3(4H),3'-oxetane]-6-yl}ethanone (compound 101)
2-(3,5-Dichloro-1-oxido-pyridin-4-yl)-1-{9-difluoromethoxy-spiro[2H-1,5-benzodioxepin-3(4H),3'-oxetane]-6-yl}ethanone (compound 102)
2-(3,5-Dichloropyridin-4-yl)-1-{9-diflouromethoxy-spiro[2H-1,5-benzodioxepin-3(4H),4'-tetrahydropyran]-6-yl}ethanone (compound 103)
2-(3,5-Dichloro-1-oxido-pyridin-4-yl)-1-{9-difluoromethoxy-spiro[2H-1,5-benzodioxepin-3(4H),4'-tetrahydropyran]-6-yl}ethanone (compound 104)
2-(3,5-Dichloropyridine-4-yl)-1-(7-difluoromethoxy-2´,3´,5´,6´-tetrahydro-spiro[1,3-benzodioxole-2,4´-(4H)-pyran]-4-yl)ethanone (compound 105)
2-(3,5-Dichloro-1-oxido-pyridine-4-yl)-1-(7-difluoromethoxy-2´,3´,5´,6´-tetrahydro-spiro[1,3-benzodioxole-2,4´-(4H)-pyran]-4-yl)ethanone (compound 106)
2-(3,5-Dichloropyridine-4-yl)-1-(7-difluoromethoxy-2´,3´,5´,6´-tetrahydro-spiro[1,3-benzodioxole-2, 4´-(4H)-thiopyran]-4-yl)ethanone (compound 107)
2-(3,5-Dichloro-1-oxido-pyridine-4-yl)-1-(7-difluoromethoxy-2´,3´,5´,6´-tetrahydro-spiro[1,3-benzodioxole-2, 4´-(4H)-thiopyran-1´,1´-dioxide]-4-yl)ethanone (compound 108)
2-(3,5-Dichloropyridine-4-yl)-1-(7-difluoromethoxy-2´,3´,5´,6´-tetrahydro-spiro[1,3-benzodioxole-2, 4´-(4H)-thiopyran-1´,1´-dioxide]-4-yl)ethanone (compound 109)
N-(3,5-Dichloro-4-pyridyl)-7-Difluoromethoxy-2',3',5',6'-tetrahydro-spiro[1,3-benzodioxole-2,4'-(4H)-thiopyran]-4-carbamide (compound 110)
N-(3,5-dichloro-1-oxo-4-pyridyl)-7-(difluoromethoxy)-1',1'-dioxo-spiro[1,3-benzodioxole-2,4'-thiane]-4-carboxamide (compound 111)

14. A compound according to any one of claims 1-13 for use in therapy.

15. A compound according to any one of claims 1-13 for use in the treatment of inflammatory diseases such as bronchial asthma, COPD, allergic rhinitis, and nephritis; autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, Crohn's disease, and systemic lupus erythematosus; diseases of the central nervous system such as depression, amnesia, and dementia; organopathy associated with ischemic reflux caused by cardiac failure, shock, and cerebrovascular diseases, and the like; insulin-resistant diabetes; wounds; cancer; proliferative and inflammatory skin disorders such as psoriasis, epidermal inflammation, acne, dermatitis, atopic dermatitis, seborrheic dermatitis, contact dermatitis, urticaria, pruritis and eczema; and other skin conditions such as alopecia, skin atrophy, steroid induced skin atrophy, skin ageing and photo skin ageing.

16. A pharmaceutical composition comprising, as a therapeutically active ingredient, a compound according to any one of claims 1-13 and a pharmaceutically acceptable carrier or vehicle.

17. A composition according to claim 16, wherein the pharmaceutically acceptable carrier or vehicle is one that is suitable for oral administration.

18. A composition according to claim 16 or 17 further comprising one or more additional therapeutically active ingredients.

19. A method of preventing, treating or ameliorating an inflammatory disease or condition, the method comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to any one of claims 1-13.

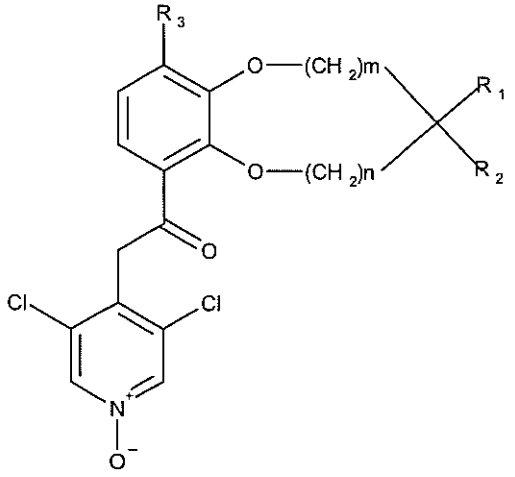
20. The method of claim 19, wherein the disease or condition is selected from the group consisting of inflammatory diseases such as bronchial asthma, COPD, allergic rhinitis, and nephritis; autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, Crohn's disease, and systemic lupus erythematosus; diseases of the central nervous system such as depression, amnesia, and dementia; organopathy associated with ischemic reflux caused by cardiac failure, shock, and cerebrovascular diseases, and the like; insulin-resistant diabetes; wounds; cancer; proliferative and inflammatory skin disorders such as psoriasis, epidermal inflammation, acne, dermatitis, atopic dermatitis,

seborrheic dermatitis, contact dermatitis, urticaria, pruritis and eczema; and other skin conditions such as alopecia, skin atrophy, steroid induced skin atrophy, skin ageing and photo skin ageing.

21. The method of claim 19 or 20, wherein the compound is administered by the oral route.

CLAIMS

1. A compound of general formula IIb



IIb

wherein

each of m and n is independently 0 or 1;

R_1 and R_2, together with the carbon atom to which they are attached, form a heterocyclic ring comprising one or two heteroatoms selected from oxygen, sulfur, -S(O)- and $-S(O)_2-$; and

R_3 is $-OCHF_2$, or $-OCF_3$;

or a pharmaceutically acceptable salt, hydrate or solvate thereof.

2. A compound according to claim 1, wherein m and n are both 0.

3. A compound according to claim 1, wherein m and n are both 1.

4. A compound according to claim 1, wherein R_3 is $-OCHF_2$.

5. A compound according to claim 1, wherein R_1 and R_2, together with the carbon atom to which they are attached, form a 4-, 5- or 6-membered heterocyclic ring.

6. A compound according to claim 5, wherein the heterocyclic ring is tetrahydropyran, oxetane, [1,3]dioxolane, [1,3]dioxane, tetrahydrothiopyran, tetrahydrothiopyran-1,1-dioxide, tetrahydrothiopyran-1-oxide, tetrahydrothiophene, [1,3]-dithiane, thietane, [1,3]-dithiane-1,3-dioxide, thietane-1-oxide, or thiethane-1,1-dioxide.

7. A compound according to claim 5, wherein the heterocyclic ring comprises one heteroatom.

8. A compound according to claim 7, wherein the heteroatom is oxygen or $-S(O)_2$.

9. A compound according to claim 1, selected from the group consisting of 2-(3,5-Dichloro-1-oxido-pyridin-4-yl)-1-{9-difluoromethoxy-spiro[2H-1,5-benzodioxepin-3(4H),3'-oxetane]-6-yl}ethanone (compound 102);
2-(3,5-Dichloro-1-oxido-pyridin-4-yl)-1-{9-difluoromethoxy-spiro[2H-1,5-benzodioxepin-3(4H),4'-tetrahydropyran]-6-yl}ethanone (compound 104);
2-(3,5-Dichloro-1-oxido-pyridine-4-yl)-1-(7-difluoromethoxy-2´,3´,5´,6´-tetrahydrospiro[1,3-benzodioxole-2,4´-(4H)-pyran]-4-yl)ethanone (compound 106); and
2-(3,5-Dichloro-1-oxido-pyridine-4-yl)-1-(7-difluoromethoxy-2´,3´,5´,6´-tetrahydrospiro[1,3-benzodioxole-2, 4´-(4H)-thiopyran-1´,1´-dioxide]-4-yl)ethanone (compound 108), or a pharmaceutically acceptable salt, hydrate or solvate thereof.

10. A pharmaceutical composition comprising, as a therapeutically active ingredient, a compound according to claim 1 and a pharmaceutically acceptable carrier or vehicle.

11. A composition according to claim 10, wherein the pharmaceutically acceptable carrier or vehicle is one that is suitable for oral administration.

12. A compound according to claim 1 which is 2-(3,5-Dichloro-1-oxido-pyridin-4-yl)-1-{9-difluoromethoxy-spiro[2H-1,5-benzodioxepin-3(4H),3'-oxetane]-6-yl}ethanone (compound 102), or a pharmaceutically acceptable hydrate or solvate thereof.

13. A compound according to claim 1 which is 2-(3,5-Dichloro-1-oxido-pyridin-4-yl)-1-{9-difluoromethoxy-spiro[2H-1,5-benzodioxepin-3(4H),4'-tetrahydropyran]-6-yl}ethanone (compound 104), or a pharmaceutically acceptable hydrate or solvate thereof.

14. A compound according to claim 1 which is 2-(3,5-Dichloro-1-oxido-pyridine-4-yl)-1-(7-difluoromethoxy-2´,3´,5´,6´-tetrahydro-spiro[1,3-benzodioxole-2,4´-(4H)-pyran]-4-yl)ethanone (compound 106), or a pharmaceutically acceptable hydrate or solvate thereof.

15. A compound according to claim 1 which is 2-(3,5-Dichloro-1-oxido-pyridine-4-yl)-1-(7-difluoromethoxy-2´,3´,5´,6´-tetrahydro-spiro[1,3-benzodioxole-2, 4´-(4H)-thiopyran-1´,1´-dioxide]-4-yl)ethanone (compound 108), or a pharmaceutically acceptable hydrate or solvate thereof.

16. A compound according to claim 1 which is 2-(3,5-Dichloro-1-oxido-pyridin-4-yl)-1-{9-difluoromethoxy-spiro[2H-1,5-benzodioxepin-3(4H),3'-oxetane]-6-yl}ethanone (compound 102).

17. A compound according to claim 1 which is 2-(3,5-Dichloro-1-oxido-pyridin-4-yl)-1-{9-difluoromethoxy-spiro[2H-1,5-benzodioxepin-3(4H),4'-tetrahydropyran]-6-yl}ethanone (compound 104).

18. A compound according to claim 1 which is 2-(3,5-Dichloro-1-oxido-pyridine-4-yl)-1-(7-difluoromethoxy-2´,3´,5´,6´-tetrahydro-spiro[1,3-benzodioxole-2,4´-(4H)-pyran]-4-yl)ethanone (compound 106).

19. A compound according to claim 1 which is 2-(3,5-Dichloro-1-oxido-pyridine-4-yl)-1-(7-difluoromethoxy-2´,3´,5´,6´-tetrahydro-spiro[1,3-benzodioxole-2, 4´-(4H)-thiopyran-1´,1´-dioxide]-4-yl)ethanone (compound 108).

20. A compound according to claim 1 which is 2-(3,5-Dichloro-1-oxido-pyridin-4-yl)-1-{9-difluoromethoxy-spiro[2H-1,5-benzodioxepin-3(4H),3'-oxetane]-6-yl}ethanone (compound 102), or a pharmaceutically acceptable hydrate thereof.

21. A compound according to claim 1 which is 2-(3,5-Dichloro-1-oxido-pyridin-4-yl)-1-{9-difluoromethoxy-spiro[2H-1,5-benzodioxepin-3(4H),4'-tetrahydropyran]-6-yl}ethanone (compound 104), or a pharmaceutically acceptable hydrate thereof.

22. A compound according to claim 1 which is 2-(3,5-Dichloro-1-oxido-pyridine-4-yl)-1-(7-difluoromethoxy-2´,3´,5´,6´-tetrahydro-spiro[1,3-benzodioxole-2,4´-(4H)-pyran]-4-yl)ethanone (compound 106), or a pharmaceutically acceptable hydrate thereof.

23. A compound according to claim 1 which is 2-(3,5-Dichloro-1-oxido-pyridine-4-yl)-1-(7-difluoromethoxy-2´,3´,5´,6´-tetrahydro-spiro[1,3-benzodioxole-2, 4´-(4H)-thiopyran-1´,1´-dioxide]-4-yl)ethanone (compound 108), or a pharmaceutically acceptable hydrate thereof.

24. A compound according to claim 1 which is 2-(3,5-Dichloro-1-oxido-pyridin-4-yl)-1-{9-difluoromethoxy-spiro[2H-1,5-benzodioxepin-3(4H),3'-oxetane]-6-yl}ethanone (compound 102), or a pharmaceutically acceptable solvate thereof.

25. A compound according to claim 1 which is 2-(3,5-Dichloro-1-oxido-pyridin-4-yl)-1-{9-difluoromethoxy-spiro[2H-1,5-benzodioxepin-3(4H),4'-tetrahydropyran]-6-yl}ethanone (compound 104), or a pharmaceutically acceptable solvate thereof.

26. A compound according to claim 1 which is 2-(3,5-Dichloro-1-oxido-pyridine-4-yl)-1-(7-difluoromethoxy-2′,3′,5′,6′-tetrahydro-spiro[1,3-benzodioxole-2,4′-(4H)-pyran]-4-yl)ethanone (compound 106), or a pharmaceutically acceptable solvate thereof.

27. A compound according to claim 1 which is 2-(3,5-Dichloro-1-oxido-pyridine-4-yl)-1-(7-difluoromethoxy-2′,3′,5′,6′-tetrahydro-spiro[1,3-benzodioxole-2, 4′-(4H)-thiopyran-1′,1′-dioxide]-4-yl)ethanone (compound 108), or a pharmaceutically acceptable solvate thereof.

28. A pharmaceutical composition comprising, as a therapeutically active ingredient, a compound according to claim 12 and a pharmaceutically acceptable carrier or vehicle.

29. A pharmaceutical composition comprising, as a therapeutically active ingredient, a compound according to claim 13 and a pharmaceutically acceptable carrier or vehicle.

30. A pharmaceutical composition comprising, as a therapeutically active ingredient, a compound according to claim 14 and a pharmaceutically acceptable carrier or vehicle.

31. A pharmaceutical composition comprising, as a therapeutically active ingredient, a compound according to claim 15 and a pharmaceutically acceptable carrier or vehicle.

32. A composition according to claim 28, wherein the pharmaceutically acceptable carrier or vehicle is one that is suitable for oral administration.

33. A composition according to claim 29, wherein the pharmaceutically acceptable carrier or vehicle is one that is suitable for oral administration.

34. A composition according to claim 30, wherein the pharmaceutically acceptable carrier or vehicle is one that is suitable for oral administration.

35. A composition according to claim 31, wherein the pharmaceutically acceptable carrier or vehicle is one that is suitable for oral administration.