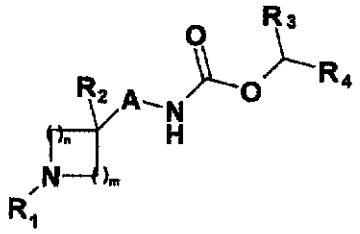
Alkylthiazol carbamate derivatives, preparation thereof and therapeutic use thereof

The invention relates to alkylthiazole carbamate derivatives, their preparation and their application in therapy.

There is still a need to find and to develop products which are inhibitors of the enzyme FAAH. The compounds of the invention meet this objective.

The compounds of the invention are of the general formula (I):



(I)

in which

R_2 represents a hydrogen or fluorine atom, a hydroxyl, cyano, trifluoromethyl, C_{1-6} alkyl or C_{1-6} alkoxy group or a group NR_8R_9;

n represents an integer 1, 2 or 3 and m represents an integer 1 or 2;

A represents a covalent bond or a C_{1-8} alkylene group;

R_1 represents a group R_5 which is optionally substituted by one or more groups R_6 and/or R_7;

R_5 represents a group selected from a phenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, naphthalenyl, quinolinyl, isoquinolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, cinnolinyl or naphthyridinyl;

R_6 represents a halogen atom, a cyano, $-CH_2CN$, nitro, hydroxyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} thioalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} halothioalkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-3} alkylene or C_{3-7} cycloalkyl-C_{1-3} alkylene-O- group, or a group NR_8R_9, NR_8COR_9, $NR_8CO_2R_9$, $NR_8SO_2R_9$, $NR_8SO_2NR_8R_9$, COR_8, CO_2R_8, $CONR_8R_9$, SO_2R_8, $SO_2NR_8R_9$ or –O-(C_{1-3}-alkylene)-O-;

R_7 represents a group selected from a furanyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazole, thiadiazole, phenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazine, naphthalenyl, quinolinyl, isoquinolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, imidazopyrimidinyl, thienopyrimidinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, indolyl, isoindolyl, indazolyl, pyrrolopyridinyl, furopyridinyl, thienopyridinyl, imidazopyridinyl, pyrazolopyridinyl, oxazolopyridinyl, isoxazolopyridinyl, thiazolopyridinyl, phenyloxy, benzyloxy or pyrimidinoxy, the group or groups R_7 being able to be substituted by one or more groups R_6 which are identical or different from one another;

R_3 represents a hydrogen or fluorine atom, a C_{1-6} alkyl group or a trifluoromethyl group;

R_4 represents a thiazole which is optionally substituted by one or more substituents selected from a halogen atom, a C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-3} alkylene, C_{1-6} haloalkoxy, cyano, NR_8R_9, NR_8COR_9, $NR_8CO_2R_9$, $NR_8SO_2R_9$, $NR_8SO_2NR_8R_9$, COR_8, CO_2R_8, $CONR_8R_9$, SO_2R_8, $SO_2NR_8R_9$, –O-(C_{1-3}-alkylene)-O-, phenyl, phenyloxy, benzyloxy, pyridinyl, pyrazinyl, pyridazinyl, triazinyl or pyrimidinyl group, it being possible for the phenyl, phenyloxy, pyridinyl, pyrazinyl, pyridazinyl, triazinyl and pyrimidinyl groups to be substituted by one or more substituents selected from a halogen atom and a cyano, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} thioalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} halothioalkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-3} alkylene group;

R_8 and R_9 represent independently of one another a hydrogen atom or a C_{1-6} alkyl group,
or form, with the atom or atoms bearing them,
in the case of NR_8R_9, a ring selected from azetidine, pyrrolidine, piperidine, morpholine, thiomorpholine, azepine, oxazepine or piperazine ring, this ring being optionally substituted by a C_{1-6} alkyl or benzyl group;

in the case of NR_8COR_9, a lactam ring; in the case of $NR_8CO_2R_9$, an oxazolidinone, oxazinone or oxazepinone ring; in the case of $NR_8SO_2R_9$, a sultam ring; in the case of $NR_8SO_2NR_8R_9$, a thiazolidine dioxide or

thiadiazinane dioxide ring.

The following compounds, described in document EP1780210, are excluded from the general formula (I):

- methyl 2-(3-{[2-(4-chlorophenyl)-4-methylthiazol-5-yl]methoxycarbonylamino}piperidin-1-yl)benzoate;
- 2-(3-{[2-(4-chlorophenyl)-4-methylthiazol-5-yl]methoxycarbonylamino}piperidin-1-yl)benzoic acid;
- methyl 3-(3-{[2-(4-chlorophenyl)-4-methylthiazol-5-yl]methoxycarbonylamino}piperidin-1-yl)benzoate;
- 3-(3-{[2-(4-chlorophenyl)-4-methylthiazol-5-yl]methoxycarbonylamino}piperidin-1-yl)benzoic acid.

Among the compounds of general formula (I) a first subgroup of compounds is composed of the compounds for which R_2 represents a hydrogen atom.

Among the compounds of general formula (I) a second subgroup of compounds is composed of the compounds for which n represents an integer 1 or 2 and m represents an integer 2.

Among the compounds of general formula (I) a third subgroup of compounds is composed of the compounds for which A represents a C_{1-8} alkylene group, more particularly a methylene or ethylene group.

Among the compounds of general formula (I), a fourth subgroup of compounds is composed of the compounds for which R_1 represents a group R_5 which is optionally substituted by one or more groups R_6 and/or R_7;

R_5 represents a pyridinyl or quinolinyl group;

R_6 represents a halogen atom, more particularly a chlorine or fluorine atom, a cyano, $-CH_2CN$, C_{1-6} alkyl, more particularly methyl, isopropyl or isobutyl, C_{1-6} alkoxy, more particularly methoxy or ethoxy, C_{1-6} haloalkyl, more particularly trifluoromethyl, C_{3-7} cycloalkyl, more particularly cyclohexyl, or C_{3-7} cycloalkyl-C_{1-3} alkylene-O-, more particularly cyclopropyl-CH_2-O- group, or a group NR_8R_9, NR_8COR_9, $NR_8CO_2R_9$, $NR_8SO_2R_9$, $CONR_8R_9$, SO_2R_8 or $SO_2NR_8R_9$;

R_7 represents a group selected from a thienyl, isoxazolyl, pyrazolyl, phenyl, pyridinyl, pyrimidinyl, naphthalenyl, quinolinyl or isoquinolinyl, it being possible for the group or groups R_7 to be substituted by one or more groups R_6 which are identical or different from one another;

R_8 and R_9 represent independently of one another a hydrogen atom or a C_{1-6} alkyl, more particularly methyl, ethyl, propyl or *tert*-butyl group, or form with the atom or atoms bearing them a ring selected from pyrrolidine, piperidine and morpholine rings.

Among the compounds of general formula (I) a fifth subgroup of compounds is composed of the compounds for which R_3 represents a hydrogen atom, a C_{1-6} alkyl group, more particularly methyl, or a trifluoromethyl group.

Among the compounds of general formula (I) a sixth subgroup of compounds is composed of the compounds for which R_4 represents a thiazole which is optionally substituted by one or more substituents selected from a halogen atom, more particularly chlorine, a C_{1-6} alkyl group, more particularly methyl, a C_{1-6} haloalkyl group, more particularly trifluoromethyl, a pyridinyl group or a group $CONR_8R_9$;
R_8 and R_9 represent independently of one another a hydrogen atom or a C_{1-6} alkyl group, more particularly a methyl.

Among the compounds of general formula (I) a seventh subgroup of compounds is composed of the compounds of general formula (I) in which at one and the same time R_1 and/or R_2 and/or R_3 and/or R_4 and/or n and/or m and/or A are as defined in the groups above.

The compounds of general formula (I) include the following compounds (IUPAC nomenclature generated by the AutoNom software):

1. thiazol-4-ylmethyl 6'-[thiophen-3-yl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]methylcarbamate

2. thiazol-4-ylmethyl 2-[(6'-thiophen-3-yl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate

3. thiazol-4-ylmethyl 6'-[(4-methylthiophen-3-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]methylcarbamate

4. thiazol-4-ylmethyl 2-[6'-(4-methylthiophen-3-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate

5. thiazol-4-ylmethyl 2-[6'-(5-cyanothiophen-2-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate

6. thiazol-2-ylmethyl 2-[6'-(2-methyl-2H-pyrazol-3-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate

7. thiazol-4-ylmethyl 6'-[2-methyl-2H-pyrazol-3-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]methylcarbamate

8. thiazol-4-ylmethyl 2-[6'-(2-methyl-2H-pyrazol-3-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate

9. thiazol-2-ylmethyl 2-[6'-(1-methyl-1H-pyrazol-4-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate

10. thiazol-4-ylmethyl 2-[6'-(1-methyl-1H-pyrazol-4-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate

11. thiazol-4-ylmethyl 2-[5'-(1-methyl-1H-pyrazol-4-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate

12. thiazol-4-ylmethyl 2-[5'-(2-methyl-2H-pyrazol-3-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate

13. thiazol-2-ylmethyl 2-[6'-(1-isobutyl-1H-pyrazol-4-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate

14. thiazol-4-ylmethyl 6'-[(1-isobutyl-1H-pyrazol-4-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]methylcarbamate

15. thiazol-4-ylmethyl 2-[6'-(1-isobutyl-1H-pyrazol-4-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate

16. thiazol-4-ylmethyl 2-[5'-(1-isobutyl-1H-pyrazol-4-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate

17. thiazol-4-ylmethyl 6'-[(3,5-dimethylisoxazol-4-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]methylcarbamate

18. thiazol-4-ylmethyl 2-[6'-(3,5-dimethylisoxazol-4-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate

19. thiazol-4-ylmethyl (4''-methoxy-3,4,5,6-tetrahydro-2H-[1,2';6',3'']terpyridin-4-yl)methylcarbamate

20. thiazol-4-ylmethyl 2-(4''-methoxy-3,4,5,6-tetrahydro-2H-[1,2';6',3'']terpyridin-4-yl)ethylcarbamate

21. thiazol-2-ylmethyl 2-(5''-fluoro-3,4,5,6- tetrahydro-2H-[1,2';6',3'']terpyridin-4-yl)ethylcarbamate

22. thiazol-4-ylmethyl 2-(5''-fluoro-3,4,5,6- tetrahydro-2H-[1,2';6',3'']terpyridin-4-yl)ethylcarbamate

23. thiazol-4-ylmethyl 2-(5''-fluoro-3,4,5,6- tetrahydro-2H-[1,2';5',3'']terpyridin-4-yl)ethylcarbamate

24. thiazol-4-ylmethyl 2-(6''-ethoxy-3,4,5,6-tetrahydro-2H-[1,2';6',3'']terpyridin-4-yl)ethylcarbamate

25. thiazol-4-ylmethyl (6'-pyrimidin-5-yl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)methylcarbamate

26. thiazol-2-ylmethyl {1-[5-(4-fluorophenyl)pyridin-2-yl]pyrrolidin-3-yl)}methylcarbamate

27. thiazol-4-ylmethyl {1-[5-(4-fluorophenyl)pyridin-2-yl]pyrrolidin-3-yl}methylcarbamate

28. thiazol-2-ylmethyl {2-[5'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl])ethylcarbamate

29. 2,2,2-trifluoro-1-thiazol-2-ylethyl (+/-)-{2-[5'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

30. thiazol-4-ylmethyl {2-[5'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

31. 2,2,2-trifluoro-1-thiazol-4-ylethyl (+/-)-{2-[5'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

32. 2-methylthiazol-4-ylmethyl {2-[5'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

33. thiazol-5-ylmethyl {2-[5'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

34. 2,2,2-trifluoro-1-thiazol-5-ylethyl (+/-)-{2-[5'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

35. thiazol-2-ylmethyl {2-[5'-(4-chlorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

36. thiazol-2-ylmethyl {2-[5'-(4-cyanophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

37. thiazol-5-ylmethyl {2-[5'-(4-cyanophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

38. thiazol-2-ylmethyl {2-[5'-(4-ethoxyphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

39. thiazol-4-ylmethyl {2-[5'-(4-ethoxyphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

40. thiazol-5-ylmethyl {2-[5'-(4-ethoxyphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

41. thiazol-2-ylmethyl {2-[5'-(3-cyanophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

42. thiazol-2-ylmethyl {2-[5'-(3-chlorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

43. thiazol-4-ylmethyl {2-[5'-(3-carbamoylphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

44. thiazol-2-ylmethyl {2-[5'-(3-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

45. thiazol-4-ylmethyl [6'-(3-trifluoromethylphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]methylcarbamate

46. thiazol-4-ylmethyl {2-[6'-(3-trifluoromethylphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

47. thiazol-4-ylmethyl [6'-(4-chlorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]methylcarbamate

48. thiazol-4-ylmethyl {2-[6'-(4-chlorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

49. thiazol-2-ylmethyl {2-[6'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

50. 2,2,2-trifluoro-1-thiazol-2-ylethyl (+/-)-{2-[6'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

51. thiazol-4-ylmethyl {2-[6'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

52. 2,2,2-trifluoro-1-thiazol-4-ylethyl (+/-)-{2-[6'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

53. 2-methylthiazol-4-ylmethyl {2-[6'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

54. thiazol-5-ylmethyl {2-[6'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

55. 2,2,2-trifluoro-1-thiazol-5-ylethyl (+/-)-{2-[6'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

56. thiazol-4-ylmethyl [6'-(4-methoxyphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]methylcarbamate

57. thiazol-4-ylmethyl {2-[6'-(4-methoxyphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

58. thiazol-4-ylmethyl [6'-(3-acetylaminophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]methylcarbamate

59. thiazol-4-ylmethyl {2-[6'-(3-acetylaminophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

60. thiazol-4-ylmethyl [6'-(3-chlorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]methylcarbamate

61. thiazol-4-ylmethyl {2-[6'-(3-chlorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

62. thiazol-4-ylmethyl (6'-m-tolyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]methylcarbamate

63. thiazol-4-ylmethyl [2-(6'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)]ethylcarbamate

64. thiazol-4-ylmethyl [6'-(2-chlorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]methylcarbamate

65. thiazol-4-ylmethyl [6'-(3,5-difluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]methylcarbamate

66. thiazol-4-ylmethyl {2-[6'-3,5-difluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

67. thiazol-4-ylmethyl [6'-(3,4,5-trimethoxyphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]methylcarbamate

68. thiazol-4-ylmethyl {2-[6'-(2,4-dimethoxyphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

69. thiazol-4-ylmethyl [6'-(4-isopropylphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]methylcarbamate

70. thiazol-4-ylmethyl {2-[6'-(4-isopropylphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

71. thiazol-4-ylmethyl [6'-(3-isopropylphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]methylcarbamate

72. thiazol-4-ylmethyl {2-[6'-(3-isopropylphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

73. thiazol-4-ylmethyl [6'-(4-cyclohexylphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]methylcarbamate

74. thiazol-4-ylmethyl {2-[6'-(4-cyclohexylphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

75. thiazol-4-ylmethyl [6'-(3-dimethylcarbamoylphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]methylcarbamate

76. thiazol-4-ylmethyl {2-[6'-(3-dimethylcarbamoylphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

77. thiazol-4-ylmethyl {2-[6'-(4-sulphamoylphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

78. thiazol-4-ylmethyl [6'-(4-carbamoylphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]methylcarbamate

79. thiazol-4-ylmethyl {2-[6'-(4-carbamoylphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

80. thiazol-4-ylmethyl [6'-(3-carbamoylphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]methylcarbamate

81. thiazol-4-ylmethyl {2-[6'-(3-carbamoylphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

82. thiazol-4-ylmethyl [6'-(3-ethylcarbamoylphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]methylcarbamate

83. thiazol-4-ylmethyl {2-[6'-(3-ethylcarbamoylphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

84. thiazol-4-ylmethyl [6'-(3-propylcarbamoylphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]methylcarbamate

85. thiazol-4-ylmethyl {2-[6'-(4-methanesulphonylaminophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

86. methyl 4-{4-[(thiazol-4-ylmethoxycarbonylamino)methyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-yl}phenylcarbamate

87. methyl 4-{4-[2-(thiazol-4-ylmethoxycarbonylamino)ethyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-yl}phenylcarbamate

88. thiazol-4-ylmethyl {2-[6'-(3-pyrrolidin-1-ylphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

89. thiazol-4-ylmethyl [6'-(2-morpholin-4-ylphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]methylcarbamate

90. thiazol-4-ylmethyl {2-[6'-(2-morpholin-4-ylphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

91. thiazol-4-ylmethyl {2-[6'-(3-ethoxyphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

92. thiazol-4-ylmethyl {2-[6'-(4-cyclopropylmethoxyphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

93. thiazol-4-ylmethyl [6'-(3-cyclopropylmethoxyphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]methylcarbamate

94. thiazol-4-ylmethyl {2-[6'-(3-cyclopropylmethoxyphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

95. thiazol-4-ylmethyl [6'-(4-cyanomethylphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]methylcarbamate

96. thiazol-4-ylmethyl [6'-(3-cyanomethylphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]methylcarbamate

97. thiazol-4-ylmethyl {6'-[4-(piperidine-1-sulphonyl)phenyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}methylcarbamate

98. thiazol-4-ylmethyl (2-{6'-[4-(piperidine-1-sulphonyl)phenyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl})ethylcarbamate

99. thiazol-4-ylmethyl [6'-(4-acetylaminophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]methylcarbamate

100. thiazol-4-ylmethyl {2-[6'-(4-acetylaminophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

101. thiazol-4-ylmethyl {2-[6'-(3-methanesulphonylphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

102. thiazol-4-ylmethyl [6'-(3-ethanesulphonylphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]methylcarbamate

103. thiazol-4-ylmethyl {2-[6'-(3-ethanesulphonylphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]}ethylcarbamate

104. thiazol-2-ylmethyl {2-[1-(6-chloroquinolin-2-yl)piperidin-4-yl]}ethylcarbamate

105. 4-trifluoromethylthiazol-2-ylmethyl {2-[1-(6-chloroquinolin-2-yl)piperidin-4-yl]}ethylcarbamate

106. 2,2,2-trifluoro-1-thiazol-2-ylethyl (+/-)-{2-[1-(6-chloroquinolin-2-yl)piperidin-4-yl]}ethylcarbamate

107. 1-thiazol-4-ylethyl (+/-)-{2-[1-(6-chloroquinolin-2-yl)piperidin-4-yl]}ethylcarbamate

108. 2,2,2-trifluoro-1-thiazol-4-ylethyl (+/-)-{2-[1-(6-chloroquinolin-2-yl)piperidin-4-yl]}ethylcarbamate

109. thiazol-4-ylmethyl {2-[1-(6-chloroquinolin-2-yl)piperidin-4-yl]}ethylcarbamate

110. 2-methylthiazol-4-ylmethyl {2-[1-(6-chloroquinolin-2-yl)piperidin-4-yl]}ethylcarbamate

111. 2-trifluoromethylthiazol-4-ylmethyl {2-[1-(6-chloroquinolin-2-yl)piperidin-4-yl]}ethylcarbamate

112. 2-chlorothiazol-4-ylmethyl {2-[1-(6-chloroquinolin-2-yl)piperidin-4-yl]}ethylcarbamate

113. 2-pyridin-3-ylthiazol-4-ylmethyl {2-[1-(6-chloroquinolin-2-yl)piperidin-4-yl]}ethylcarbamate

114. 2-pyridin-4-ylthiazol-5-ylmethyl {2-[1-(6-chloroquinolin-2-yl)piperidin-4-yl]}ethylcarbamate

115. thiazol-5-ylmethyl {2-[1-(6-chloroquinolin-2-yl)piperidin-4-yl]}ethylcarbamate

116. 2,2,2-trifluoro-1-thiazol-5-ylethyl (+/-)-{2-[1-(6-chloroquinolin-2-yl)piperidin-4-yl]}ethylcarbamate

117. thiazol-5-ylmethyl {2-[1-(6-fluoroquinolin-2-yl)piperidin-4-yl]}ethylcarbamate

118. thiazol-5-ylmethyl {2-[1-(7-fluoroquinolin-2-yl)piperidin-4-yl]}ethylcarbamate

119. thiazol-4-ylmethyl (6'-naphthalen-1-yl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)methylcarbamate

120. thiazol-4-ylmethyl [2-(6'-naphthalen-1-yl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)]ethylcarbamate

121. thiazol-4-ylmethyl (6'-naphthalen-2-yl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)methylcarbamate

122. thiazol-4-ylmethyl (6'-naphthalen-2-yl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)ethylcarbamate

123. thiazol-4-ylmethyl (6'-quinolin-4-yl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)methylcarbamate

124. thiazol-4-ylmethyl [2-(6'-quinolin-4-yl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)]ethylcarbamate

125. thiazol-4-ylmethyl (6'-quinolin-6-yl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)methylcarbamate

126. thiazol-4-ylmethyl [2-(6'-quinolin-6-yl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)]ethylcarbamate

127. thiazol-4-ylmethyl (6'-isoquinolin-4-yl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)methylcarbamate

128. thiazol-4-ylmethyl [2-(6'-isoquinolin-4-yl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)]ethylcarbamate

129. thiazol-4-ylmethyl (6'-isoquinolin-5-yl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)methylcarbamate

130. thiazol-4-ylmethyl (6'-isoquinolin-5-yl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)ethylcarbamate

131. 2-carbamoylthiazol-4-ylmethyl 2-[5'-(4-fluorophenyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate

132. 2-methylcarbamoylthiazol-4-ylmethyl 2-[5'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate

133. 4-carbamoylthiazol-2-ylmethyl 2-[5'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate

134. 4-methylcarbamoylthiazol-2-ylmethyl 2-[5'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate

in the form of the base or an addition salt with an acid.

The compounds of general formula (I) may include one or more asymmetric carbons. They may exist in the form of enantiomers or diastereoisomers. The compounds of general formula (I) may also exist in the form of *cis [Z]* or *trans [E]* stereoisomers. These stereoisomers, enantiomers and diastereoisomers, and also mixtures thereof, including the racemic mixtures, form part of the invention.

The compounds of formula (I) may exist in the form of bases or of addition salts with acids. Addition salts of this kind form part of the invention.

These salts are advantageously prepared with pharmaceutically acceptable acids, although the salts of other acids useful, for example, for purifying or isolating the compounds of formula (I) likewise form part of the invention.

In the context of the invention, the terms are understood as follows:

- C_{t-z}, where t and z may take the values from 1 to 8, is a carbon chain which may have from t to z carbon atoms; for example, C_{1-3} is a carbon chain which may have from 1 to 3 carbon atoms;
- alkyl is a saturated, linear or branched aliphatic group; for example, a C_{1-6} alkyl group represents a linear or branched carbon chain of 1 to 6 carbon atoms, more particularly a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *tert*-butyl, pentyl or hexyl;
- alkylene is a saturated, linear or branched divalent alkyl group; for example, a C_{1-3} alkylene group represents a linear or branched, divalent carbon chain of 1 to 3 carbon atoms, more particularly a methylene, ethylene, 1-methylethylene or propylene;
- cycloalkyl is a cyclic alkyl group; for example, a C_{3-7} cycloalkyl group represents a cyclic carbon group of 3 to 7 carbon atoms, more particularly a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl;

- alkoxy is an –O-alkyl group having a saturated, linear or branched aliphatic chain;
- thioalkyl is an –S-alkyl group having a saturated, linear or branched aliphatic chain;
- haloalkyl is an alkyl group in which one or more hydrogen atoms have been substituted by a halogen atom;
- haloalkoxy is an alkoxy group in which one or more hydrogen atoms have been substituted by a halogen atom;
- halothioalkyl is a thioalkyl group in which one or more hydrogen atoms have been substituted by a halogen atom;
- a halogen atom is a fluorine, chlorine, bromine or iodine;
- "(+/-)" denotes a compound in the form of the racemic mixture.

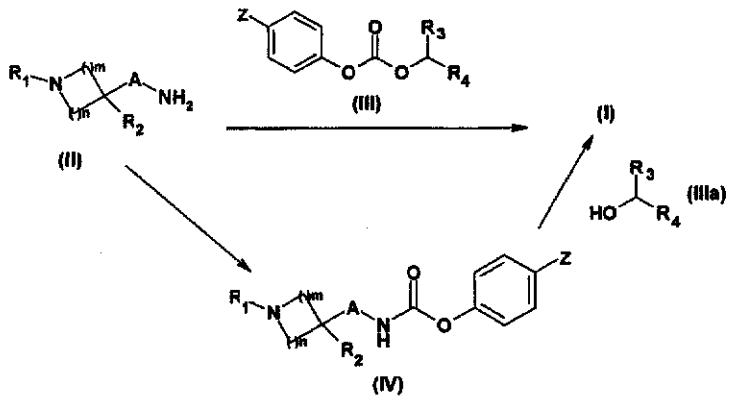
The compounds of the invention may be prepared by various methods, these methods being illustrated by the schemes below.

Thus a first method (scheme 1) comprises reacting an amine of general formula (II) in which A, R_1, R_2, m and n are as defined in the general formula (I) defined above with a carbonate of general formula (III) in which Z represents a hydrogen atom or a nitro group and R_3 and R_4 are as defined in the general formula (I) defined above, in the presence of a base such as triethylamine, pyridine, *N,N*-dimethylaminopyridine or diisopropylethylamine, in a solvent such as toluene or dichloroethane, at a temperature between the ambient temperature and the reflux temperature of the solvent.

One variant way of obtaining compounds of general formula (I) (scheme 1) comprises reacting an amine of general formula (II) as defined above with phenyl or 4-nitrophenyl chloroformate in the presence of a base such as triethylamine or diisopropylethylamine, in a solvent such as dichloromethane or tetrahydrofuran, at a temperature between 0°C and the ambient temperature, to give the carbamate derivative of general formula (IV) in which A, R_1, R_2, m and n are as defined in the general formula (I) defined above, and Z represents a hydrogen atom or a nitro group. The carbamate derivative of general formula (IV) thus obtained is then converted into a compound of general formula (I) by the action of an alcohol of general formula $HOCHR_3R_4$ (IIIa), in which R_3 and R_4 are as defined in the general formula (I) defined above, in the presence of a base such as triethylamine, pyridine, *N,N*-dimethylaminopyridine or

diisopropylethylamine, in a solvent such as toluene or dichloroethane, at a temperature between the ambient temperature and the reflux temperature of the solvent.

Scheme 1



A second method (scheme 2) comprises reacting, in a first stage, an amine of general formula (IIa) in which A, R_2, m and n are as defined in the general formula (I) defined above, and PG represents a protecting group such as a Boc (*tert*-butyloxycarbonyl), a Cbz (benzyloxycarbonyl), a benzyl or a benzhydryl, with a carbonate of general formula (III) as defined above, under the conditions described above for the reaction of the amine of general formula (II) with the carbonate of general formula (III), followed by a deprotecting reaction, for example in the presence of a solution of hydrochloric acid (5N) in isopropanol or dioxane, to give the intermediate of general formula (Ia) in which A, R_2, R_3, R_4, m and n are as defined in the general formula (I).

One variant way of obtaining intermediates of general formula (Ia) (scheme 2) comprises reacting an amine of general formula (IIa) as defined above with phenyl or 4-nitrophenyl chloroformate in the presence of a base such as triethylamine or diisopropylethylamine, in a solvent such as dichloromethane or tetrahydrofuran, at a temperature between 0°C and the ambient temperature, to give the carbamate derivative of general formula (IVa) in which A, R_2, m and n are as defined in the general formula (I) defined above, PG is as defined above and Z represents a hydrogen atom or a nitro group. The carbamate derivative of general formula (IVa) thus obtained is subsequently converted into a compound of general formula (Ia) by the action of an alcohol of general formula $HOCHR_3R_4$ (IIIa) as defined above, in the presence of a base such as triethylamine, pyridine,

N,N-dimethylaminopyridine or diisopropylethylamine, in a solvent such as toluene or dichloroethane, at a temperature between the ambient temperature and the reflux temperature of the solvent, followed by a deprotecting reaction, for example in the presence of a solution of hydrochloric acid (5N) in isopropanol or dioxane.

The compound of general formula (I) is then obtained by reacting the compound of general formula (Ia) with a derivative of general formula (V) in which R_1 is as defined in the general formula (I) and U_1 represents a halogen atom or an O-triflate group, utilizing the conditions of aromatic or heteroaromatic nucleophilic substitution reactions, by means for example of a base such as triethylamine, diisopropylamine, pyridine or *N,N*-dimethylaminopyridine in a solvent such as dichloromethane, dichloroethane, acetonitrile, *N,N*-dimethylformamide, dioxane or tetrahydrofuran, at a temperature between 0°C and the reflux temperature of the solvent. This conversion may also be performed using the Buchwald *N*-arylation or *N*-heteroarylation conditions, for example by means of a palladium or copper catalyst.

According to scheme 2 the compounds of general formula (I) in which R_1 represents a group R_5 which is substituted in particular by a group R_6 of C_{1-6} alkyl, C_{3-7} cycloalkyl or C_{3-7} cycloalkyl-C_{1-3} alkylene type, or by a group R_7 as defined in the general formula (I) defined above, may also be prepared by a coupling reaction, catalysed by means of a transition metal, for example palladium(0), performed on the compound of general formula (Ib) in which A, R_2, R_3, R_4, R_5, m and n are as defined in the general formula (I) and U_2 represents a chlorine, bromine or iodine atom or a triflate group, U_2 being in the position in which it is desired to introduce the group R_6 or R_7 (scheme 2):

alternatively by a Suzuki reaction, for example by means of an alkyl-, cycloalkyl-, aryl- or heteroaryl-boronic acid,

or by a Stille reaction, for example using an aryl or heteroaryl trialkyltin derivative

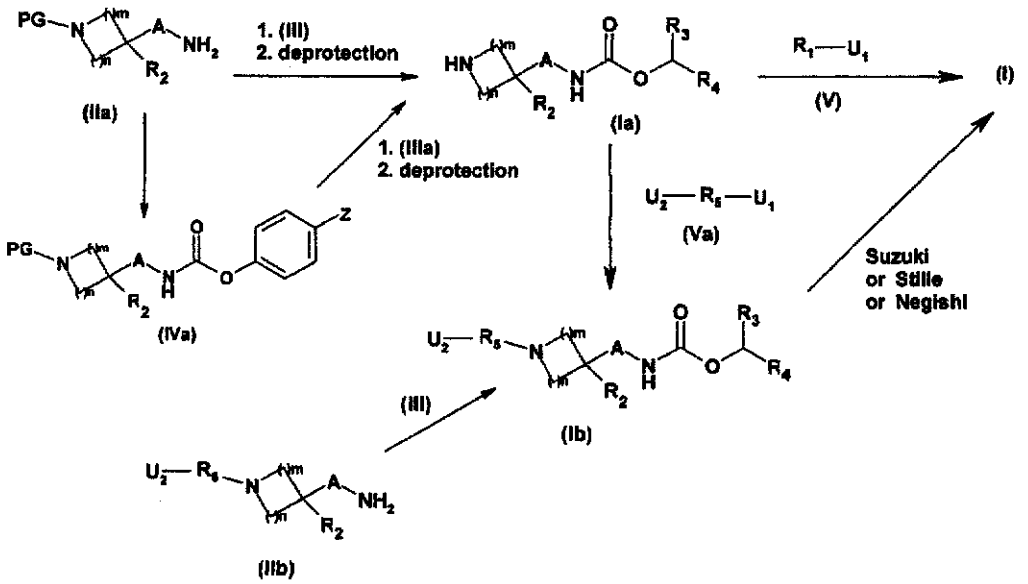
or by a Negishi reaction, for example using an alkyl, cycloalkyl, aryl or heteroaryl halide zincate derivative.

The intermediate of general formula (Ib) as defined above is obtained beforehand by reacting an amine of general formula (Ia) as defined above with a derivative of general formula (Va) in which R_5, U_1 and U_2 are as defined above, utilizing aromatic or heteroaromatic nucleophilic substitution reactions or Buchwald *N*-arylation or *N*-heteroarylation reactions, for

example by means of a palladium or copper catalyst.

One variant way of obtaining intermediates of general formula (Ib) (scheme 2) comprises reacting, in a first stage, an amine of general formula (IIb) in which A, R_5, R_2, m and n are as defined in the general formula (I) defined above, and U_2 is as defined above, with a carbonate of general formula (III) as defined above, under the conditions described above for the reaction of the amine of general formula (II) with the carbonate of general formula (III), to give the intermediate of general formula (Ib) in which A, R_5, R_2, R_3, R_4, m and n are as defined in the general formula (I), and U_2 is as defined above.

Scheme 2



The compounds of general formulae (II), (IIa), (IIb), (III), (IIIa), (V) and (Va) and also the other reactants are available commercially or are described in the literature, or else may be prepared by methods which are described therein or which are known to a person skilled in the art.

In particular the carbonate of general formula (III) may be prepared by any method described in the literature, for example by reaction of an alcohol of general formula $HOCHR_3R_4$ (IIIa), in which R_3 and R_4 are as defined in the general formula (I) as defined above, with phenyl or 4-nitrophenyl chloroformate, in the presence of a base such as triethylamine, *N*-methylmorpholine or diisopropylethylamine, in a solvent such as dichloromethane or tetrahydrofuran, at a temperature between 0°C and the ambient temperature.

The examples which follow illustrate the preparation of a number of compounds of the invention. These examples are not limiting and serve merely to illustrate the invention. The microanalyses, the IR and NMR spectra and/or the LC-MS (liquid chromatography coupled to mass spectroscopy) confirm the structures and the purities of the compounds obtained.

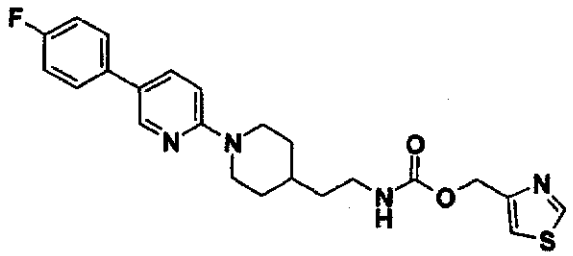
m.p. (°C) represents the melting point in degrees Celsius.

The numbers between brackets in the titles of the examples correspond to those in the 1st column of the subsequent table.

IUPAC (International Union of Pure and Applied Chemistry) nomenclature has been used for the naming of the compounds in the examples below.

Example 1 (compound 30)

Thiazol-4-ylmethyl 2-[5'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate



1.1. 2-(5'-Bromo-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)ethanol

An autoclave is charged with 11 g (46.43 mmol) of 2,5-dibromopyridine, 6 g (46.43 mmol) of piperidin-4-ylethanol and 6.74 g (48.76 mmol) of potassium carbonate in 8 ml of DMSO. This charge is subsequently heated at 160°C for 20 hours.

Following return to ambient temperature, the reaction mixture is taken up in ethyl acetate and water. The aqueous phase is separated off and extracted twice with ethyl acetate, the combined organic phases are washed with saturated aqueous sodium chloride solution and dried over sodium sulphate, and the filtrate is concentrated under reduced pressure.

This gives 11 g of product in the form of an oil, which is used as it is in the following step.

1.2. 2-[5'-(4-Fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethanol

Under an inert atmosphere, 3.6 g (12.62 mmol) of 2-(5'-bromo-3,4,5,6-

tetrahydro-2H-[1,2']bipyridinyl-4-yl)ethanol, prepared in step 1.1., 3.53 g (25.25 mmol) of 4-fluorophenylboronic acid, 5.23 g (37.87 mmol) of potassium carbonate and 4.88 g (15.15 mmol) of tetrabutylammonium bromide in suspension in 20 ml of water are introduced. Subsequently, 0.142 g (0.63 mmol) of $Pd(OAc)_2$ is added. The reaction mixture is subsequently heated at reflux for 24 hours.

Following return to ambient temperature, the salts are separated by filtration on Celite, and then the filtrate is taken up in ethyl acetate; the aqueous phase is separated off and extracted twice with ethyl acetate, and the combined organic phases are washed with saturated aqueous sodium chloride solution and dried over sodium sulphate. Following evaporation of the solvent, the residue obtained is purified by chromatography on silica gel, eluting with a 50/50 mixture of ethyl acetate and cyclohexane.

This gives 1.6 g of product in the form of a white powder.

m.p. (°C) = 118-120°C

1.3. 2-{2-[5'-(4-Fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethyl}isoindole-1,3-dione

A solution of 2 g (6.66 mmol) of 2-[5'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethanol, prepared in step 1.2., 2.096 g (7.99 mmol) of triphenylphosphine and 1.077 g (7.32 mmol) of phthalimide in 40 ml of tetrahydrofuran, cooled to approximately -2°C, is admixed dropwise under an inert atmosphere with a solution of 1.61 g (7.99 mmol) of diisopropyl azodicarboxylate (DIAD) in 4 ml of tetrahydrofuran, the temperature of the reaction mixture being maintained at between -2°C and 0°C. Stirring is continued at 0°C for 1 hour, and then at ambient temperature for 12 hours.

The reaction mixture is concentrated under reduced pressure and the residue is taken up in dichloromethane and water. The aqueous phase is separated off and then extracted twice with dichloromethane. The organic phases are combined and washed in succession with aqueous hydrochloric acid (1N), then with saturated aqueous sodium hydrogencarbonate solution and saturated aqueous sodium chloride solution. The organic phase is dried over sodium sulphate and the filtrate is concentrated under reduced pressure. The resulting residue is purified by chromatography on silica gel, eluting with a 20/80 mixture of ethyl acetate and cyclohexane.

This gives 2.1 g of the expected product in the form of a white powder.

m.p. (°C) = 180-182°C

1.4. 2-[5'-(4-Fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-

yl]ethylamine

A solution of 1.3 g (3.03 mmol) of 2-{2-[5'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethyl}isoindole-1,3-dione, prepared in step 1.3., in 30 ml of ethanol is admixed slowly at ambient temperature with 0.485 g (15.13 mmol) of hydrazine monohydrate. The reaction mixture is subsequently heated at reflux for three hours.

Following return to ambient temperature, the insoluble material is separated off by filtration and the filtrate is concentrated under reduced pressure. The residue is taken up in 20 ml of ether and is left with stirring at ambient temperature for an hour. The insoluble material is separated off again and the filtrate is concentrated under reduced pressure.

This gives 0.70 g of the expected product in the form of a white powder.

m.p. (°C) = 88-94°C

^{1}H NMR ($CDCl_3$) δ (ppm): 8.3 (d, 1H); 7.55 (dd, 1H); 7.35 (m, 2H); 7.05 (d, 1H); 7.1 (d, 1H); 6.65 (d, 1H); 4.25 (broad d, 2H); 3.0-2.8 (m, 4H); 1.8 (m, 2H); 1.6-1.1 (m, 5H).

1.5. Thiazol-4-ylmethyl 2-[5'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate

A solution of 0.3 g (1.07 mmol) of 2-[5'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylamine, prepared in step 1.4., 0.35 g (1.18 mmol) of thiazol-4-ylmethyl (4-nitrophenyl)carbonate (WO2008/013834) and 0.21 g (1.61 mmol) of N,N-diisopropylethylamine in 5 ml of 1,2-dichloroethane is heated at 70°C for 12 hours.

Following return to ambient temperature, the insoluble material is separated off by filtration and the filtrate is concentrated under reduced pressure. The residue is taken up in dichloromethane and water, the aqueous phase is separated off and extracted three times with dichloromethane, and the combined organic phases are washed with saturated aqueous sodium chloride solution and dried over sodium sulphate. Following evaporation of the solvent, the residue obtained is purified by chromatography on silica gel, eluting with a 95/5 mixture of dichloromethane and methanol.

This gives 0.3 g of pure product in the form of a white powder.

LC-MS: M+H = 441

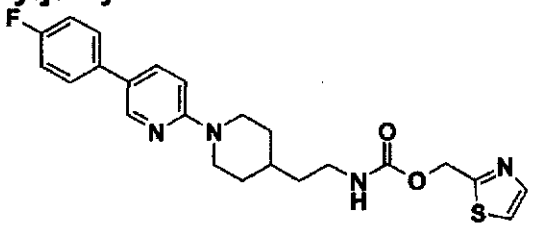
m.p. (°C): 130-132°C

^{1}H NMR (DMSO) δ (ppm): 9.1 (s, 1H); 8.45 (s, 1H); 7.85 (d, 1H); 7.7 (m,

4H); 7.3 (m, 2H); 6.95 (d, 1H); 5.15 (s, 2H); 4.30 (broad d, 2H); 3.1 (m, 2H); 2.8 (m, 2H); 1.8 (m, 2H); 1.6 (m, 1H); 1.4 (m, 2H); 1.1 (m, 2H).

Example 2 (compound 28)

Thiazol-2-ylmethyl 2-[5'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate



The procedure described in Example 1 (step 1.4.) is followed. Starting from 0.3 g (1.07 mmol) of 2-[5'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylamine, described in Example 1 (step 1.3.) and 0.35 g (1.18 mmol) of thiazol-2-ylmethyl (4-nitrophenyl)carbonate (EP486948A2), and after chromatography on silica gel, eluting with a 98/2 mixture of dichloromethane and methanol, gives 0.25 g of pure product in the form of a white powder.

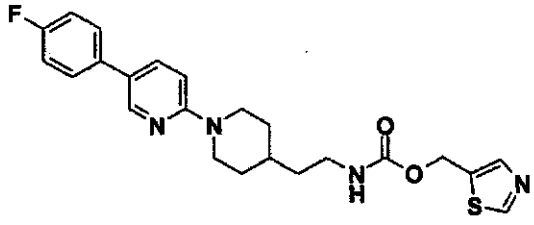
LC-MS: M+H = 441

m.p. (°C): 131-133°C

^{1}H NMR (DMSO) δ (ppm): 8.45 (s, 1H); 7.80 (m, 3H); 7.65 (dd, 2H); 7.45 (m, 1H); 7.25 (dd, 2H); 6.9 (d, 1H); 5.30 (s, 2H); 4.30 (broad d, 2H); 3.1 (m, 2H); 2.8 (m, 2H); 1.75 (m, 2H); 1.6 (m, 1H); 1.4 (m, 2H); 1.1 (m, 2H).

Example 3 (compound 33)

Thiazol-5-ylmethyl 2-[5'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate



The procedure described in Example 1 (step 1.4.) is followed. Starting from 0.16 g (0.53 mmol) of 2-[5'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylamine, described in Example 1 (step 1.3.) and

0.22 g (0.8 mmol) of thiazol-5-ylmethyl (4-nitrophenyl)carbonate, and after chromatography on silica gel, eluting with a 40/60 mixture of ethyl acetate and cyclohexane, gives 0.180 g of pure product in the form of a white powder.

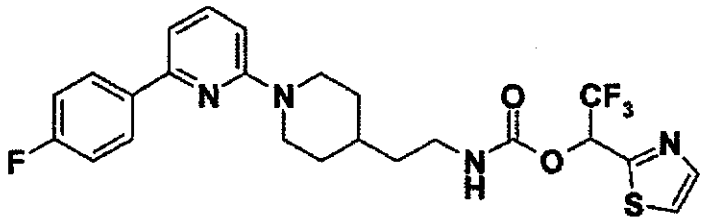
LC-MS: M+H = 441

m.p. (°C): 100-102°C

^{1}H NMR (DMSO) δ (ppm): 9.1 (s, 1H); 8.4 (broad s, 1H); 7.9 (s, 1H); 7.8 (dd, 1H); 7.60 (dd, 2H); 7.20 (m, 3H); 6.90 (d, 1H); 5.2 (s, 2H); 4.30 (broad d, 2H); 3 (m, 2H); 2.75 (m, 2H); 1.8-1.1 (m, 7H).

Example 4 (compound 50)

2,2,2-Trifluoro-1-thiazol-2-ylethyl (+/-)-2-[6'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate



4.1. 2-[6'-(4-Fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethanol

Under an inert atmosphere, 3.6 g (12.62 mmol) of 2-(6'-bromo-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl) ethanol (WO2004/099176), 3.53 g (25.25 mmol) of 4-fluorophenylboronic acid, 5.23 g (37.87 mmol) of potassium carbonate and 4.88 g (15.15 mmol) of tetrabutylammonium bromide in suspension in 20 ml of water are introduced. Subsequently 0.142 g (0.63 mmol) of $Pd(OAc)_2$ is added. The reaction mixture is subsequently heated at reflux for 24 hours.

Following return to ambient temperature, the salts are separated off by filtration on Celite, and then the filtrate is taken up in ethyl acetate; the aqueous phase is separated off and extracted twice with ethyl acetate, and the combined organic phases are washed with saturated aqueous sodium chloride solution and dried over sodium sulphate. Following evaporation of the solvent, the residue obtained is purified by chromatography on silica gel, eluting with a 99/1 mixture of dichloromethane and methanol.

This gives 3.6 g of product in the form of a white powder.

m.p. (°C) = 96-100°C

4.2. 2-{2-[6'-(4-Fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethyl}isoindole-1,3-dione

The procedure described in Example 1 (step 1.2.) is followed. Starting from 2 g (6.66 mmol) of 2-[6'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethanol, prepared in step 4.1., 2.096 g (7.99 mmol) of triphenylphosphine, 1.077 g (7.32 mmol) of phthalimide and 1.61 g (7.99 mmol) of diisopropyl azodicarboxylate (DIAD), and after chromatography on silica gel, eluting with a 15/85 mixture of ethyl acetate and cyclohexane, gives 1.4 g of pure product in the form of a white powder.

m.p. (°C) = 112-114°C

4.3. 2-[6'-(4-Fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylamine

The procedure described in Example 1 (step 1.3.) is followed. Starting from 1.3 g (3.03 mmol) of 2-{2-[6'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethyl}isoindole-1,3-dione, prepared in step 4.2., and 0.485 g (15.13 mmol) of hydrazine monohydrate gives 0.8 g of product in the form of a colourless liquid, which is used as it is in the following step.

^{1}H NMR ($CDCl_3$) δ (ppm): 8.2 (d, 1H); 8.15 (d, 1H); 7.75 (dd, 1H); 7.35 (broad t, 2H); 7.2 (d, 1H); 6.75 (d, 1H); 4.75 (broad d, 2H); 3.2-3.0 (m, 4H); 2.15 (m, 2H); 1.8-1.3 (m, 5H).

4.4. 4-Nitrophenyl 2-[6'-(4-fluorophenyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate

A solution of 5 g (16.7 mmol) of 2-[6'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylamine, prepared in step 4.3., 4.32 g (33.40 mmol) of *N,N*-diisopropylethylamine and 0.10 g (0.84 mmol) of *N,N*-dimethylaminopyridine in 80 ml of dichloromethane, cooled to approximately 0°C, is admixed in small portions with 3.7 g (18.37 mmol) of 4-nitrophenyl chloroformate. Stirring is continued at 0°C for 1 hour and then at ambient temperature for 2 hours.

Water is added to the reaction mixture, the aqueous phase is separated off and extracted a number of times with dichloromethane, the combined organic phases are washed with saturated aqueous sodium chloride solution and dried over sodium sulphate, and the filtrate is concentrated under reduced pressure.

Chromatography on silica gel, eluting with a 98/2 mixture of dichloromethane and methanol, gives 4.6 g of pure product in the form of a white powder.

m.p. (°C): 138-142°C

4.5. 2,2,2-Trifluoro-1-thiazol-2-ylethanol

A solution of 2 g (17.68 mmol) of thiazole-2-carboxaldehyde and 0.88 ml (0.88 mmol) of a 1M solution of tetrabutylammonium fluoride in THF, in 88 ml of THF, is admixed slowly at approximately 0° (ice bath) with 2.7 g (19.44 mmol) of trifluoromethyltrimethylsilane (TMS-CF_3). Stirring is continued at ambient temperature for 2 hours. The reaction mixture is admixed with 25 ml of 1N aqueous hydrochloric acid and ethyl acetate. The aqueous phase is separated off and extracted twice with ethyl acetate, and the combined organic phases are washed successively with saturated aqueous sodium bicarbonate solution and then with saturated aqueous sodium chloride solution and are dried over sodium sulphate. Following evaporation of the solvent, the residue obtained is purified by chromatography on silica gel, eluting with a 98/2 mixture of dichloromethane and methanol.

This gives 2.33 g of product in the form of a beige solid.

m.p. (°C): 90-92°C

4.6. 2,2,2-Trifluoro-1-thiazol-2-ylethyl (+/-)-2-[6'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate

A solution of 0.465 g (1 mmol) of 4-nitrophenyl 2-[6'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate, prepared in step 4.4., 0.19 g (1.5 mmol) of *N,N*-diisopropylethylamine, 0.006 g (0.05 mmol) of *N,N*-dimethylaminopyridine and 0.20 g (1.1 mmol) of 2,2,2-trifluoro-1-thiazol-2-ylethanol, obtained in step 4.5., in 5 ml of 1,2-dichloroethane is heated at 80°C for 12 hours.

Following return to ambient temperature, the insoluble material is separated off by filtration and the filtrate is concentrated under reduced pressure. The residue is taken up in dichloromethane and water, the aqueous phase is separated off and extracted twice with dichloromethane, the combined organic phases are washed successively with 1N aqueous sodium hydroxide and then with saturated aqueous sodium chloride solution and are dried over sodium sulphate. Following evaporation of the solvent, the residue obtained is purified by chromatography on silica gel, eluting with a 98/2 mixture of dichloromethane and methanol.

This gives 0.23 g of pure product in the form of a white powder.

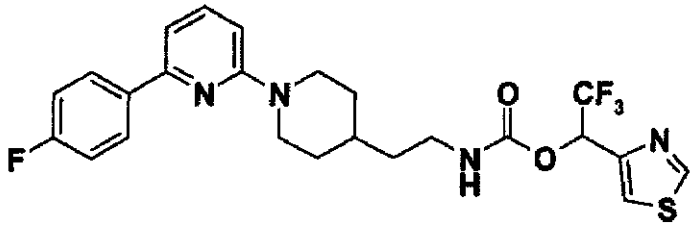
LC-MS: M+H = 509

m.p. (°C): 121-123°C

^{1}H NMR (DMSO) δ (ppm): 8.1 (m, 3H); 7.95 (m, 2H); 7.6 (t, 1H); 7.3 (t, 2H); 7.20 (d, 1H); 6.80 (d, 1H); 6.60 (m, 1H); 4.40 (broad d, 2H); 3.1 (m, 2H); 2.8 (m, 2H); 1.75 (broad d, 2H); 1.55 (m, 1H); 1.4 (m, 2H); 1.1 (m, 2H).

Example 5 (compound 52)

2,2,2-Trifluoro-1-thiazol-4-ylethyl (+/-)-2-[6'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate



5.1. 2,2,2-Trifluoro-1-thiazol-4-ylethanol

The method described in Example 4 (step 4.5.) is followed. Starting from 1 g (8.84 mmol) of thiazole-4-carboxaldehyde, 0.10 ml (0.10 mmol) of a 1M solution of tetrabutylammonium fluoride in THF and 1.38 g (9.72 mmol) of trifluoromethyltrimethylsilane (TMS-CF_3), and after chromatography on silica gel, eluting with a 98/2 mixture of dichloromethane and methanol, gives 0.54 g of pure product in the form of a colourless oil.

5.2. 2,2,2-Trifluoro-1-thiazol-4-ylethyl (+/-)-2-[6'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate

The procedure described in Example 4 (step 4.6.) is followed. Starting from 0.183 g (1 mmol) of 4-nitrophenyl 2-[6'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate, described in Example 4 (step 4.4.), 0.19 g (1.5 mmol) of *N,N*-diisopropylethylamine, 0.006 g (0.05 mmol) of *N,N*-dimethylaminopyridine and 0.51 g (1.1 mmol) of 2,2,2-trifluoro-1-thiazol-4-ylethanol, obtained in step 5.1., and after chromatography on silica gel, eluting with a 40/60 mixture of ethyl acetate and cyclohexane, followed by recrystallization from a mixture of diethyl ether and hexane, gives 0.240 g of pure product in the form of a white powder.

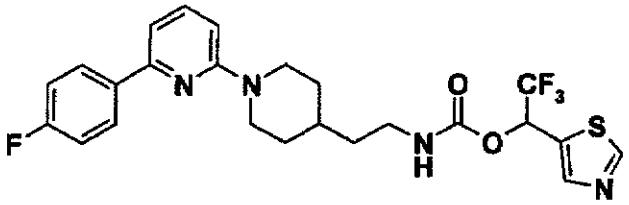
LC-MS: M+H = 509

m.p. (°C): 79-83°C

^{1}H NMR (DMSO) δ (ppm): 9.2 (s, 1H); 8.1 (dd, 2H); 8 (s, 1H); 7.85 (broad t, 1H); 7.6 (dd, 1H); 7.35 (t, 2H); 7.15 (d, 1H); 6.80 (d, 1H); 6.45 (m, 1H); 4.40 (broad d, 2H); 3.15 (m, 2H); 2.8 (m, 2H); 1.75 (broad d, 2H); 1.55 (m, 1H); 1.4 (m, 2H); 1.1 (m, 2H).

Example 6 (compound 55)

2,2,2-Trifluoro-1-thiazol-5-ylethyl (+/-)-2-[6'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate



6.1. 2,2,2-Trifluoro-1-thiazol-5-ylethanol

The method described in Example 4 (step 4.5.) is followed. Starting from 2 g (17.68 mmol) of thiazole-5-carboxaldehyde, 0.88 ml (0.88 mmol) of a 1M solution of tetrabutylammonium fluoride in THF and 2.765 g (19.44 mmol) of trifluoromethyltrimethylsilane (TMS-CF_3), and after chromatography on silica gel, eluting with a 98/2 mixture of dichloromethane and methanol, gives 2.23 g of pure product in the form of a colourless oil.

6.2. 2,2,2-Trifluoro-1-thiazol-5-ylethyl (+/-)-2-[6'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate

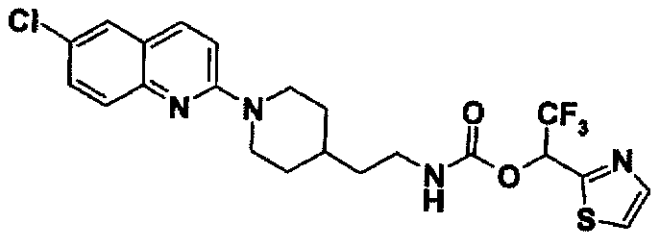
The procedure described in Example 4 (step 4.6.) is followed. Starting from 0.464 g (1 mmol) of 4-nitrophenyl 2-[6'-(4-fluorophenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate, described in Example 4 (step 4.4.), 0.19 g (1.5 mmol) of *N,N*-diisopropylethylamine, 0.006 g (0.05 mmol) of *N,N*-dimethylaminopyridine and 0.201 g (1.1 mmol) of 2,2,2-trifluoro-1-thiazol-5-ylethanol, obtained in step 6.1., and after chromatography on silica gel, eluting with a 98/2 mixture of dichloromethane and methanol, gives 0.240 g of pure product in the form of a gum.

LC-MS: M+H = 509

^{1}H NMR (DMSO) δ (ppm): 9.3 (s, 1H); 8.2 (s, 1H); 8.1 (dd, 2H); 7.85 (broad t, 1H); 7.6 (dd, 1H); 7.25 (dd, 2H); 7.15 (d, 1H); 6.90 (m, 1H); 6.80 (d, 1H); 4.40 (broad d, 2H); 3.15 (m, 2H); 2.8 (m, 2H); 1.75 (broad d, 2H); 1.55 (m, 1H); 1.4 (m, 2H); 1.1 (m, 2H).

Example 7 (compound 106)

2,2,2-Trifluoro-1-thiazol-2-ylethyl (+/-)-2-[1-(6-chloroquinolin-2-yl)piperidin-4-yl]ethylcarbamate



7.1. 2-[1-(6-Chloroquinolin-2-yl)piperidin-4-yl]ethyl methanesulphonate

A solution of 4 g (13.76 mmol) of 2-[1-(6-chloroquinolin-2-yl)piperidin-4-yl]ethanol (WO2004/099176), 3.55 g (27.51 mmol) of diisopropylethylamine and 0.84 g (6.88 mmol) of N,N-dimethylaminopyridine in 30 ml of dichloromethane, cooled to approximately 0°C, is admixed dropwise under an inert atmosphere with a solution of 2.36 g (20.63 mmol) of mesyl chloride in 3 ml of dichloromethane. Stirring is continued at 0°C for two hours and then at ambient temperature for one hour.

Water is added to the reaction mixture, the aqueous phase is separated off and extracted a number of times with dichloromethane, the combined organic phases are washed with saturated aqueous sodium chloride solution and dried over sodium sulphate, and the filtrate is concentrated under reduced pressure.

This gives 5.1 g of product in the form of an oil, which is used as it is in the following step.

7.2. 2-[4-(2-Azidoethyl)piperidin-1-yl]-6-chloroquinoline

A solution of 5 g (13.55 mmol) of 2-[1-(6-chloroquinolin-2-yl)piperidin-4-yl]ethyl methanesulphonate, prepared in step 7.1., and 1.76 g (27.11 mmol) of sodium azide in 30 ml of N,N-dimethylformamide is heated at reflux for 4 hours under an inert atmosphere.

Following return to ambient temperature, the reaction mixture is concentrated under reduced pressure. The residue is taken up in dichloromethane and water and the aqueous phase is separated off and extracted twice with dichloromethane, the combined organic phases are washed with saturated aqueous sodium chloride solution, and dried over sodium sulphate. Evaporation of the solvent gives 3.8 g of product in the form of an oil, which is used as it is in the following step.

7.3. 2-[1-(6-Chloroquinolin-2-yl)piperidin-4-yl]ethylamine

A solution of 3.5 g (11.08 mmol) of 2-[4-(2-azidoethyl)piperidin-1-yl]-6-chloroquinoline, obtained in step 7.2., in 100 ml of THF/water (1/1), is

admixed in small portions at ambient temperature with 4.36 g (16.62 mmol) of triphenylphosphine. Stirring is continued at ambient temperature for ten hours.

The reaction mixture is concentrated under reduced pressure. Ethyl acetate is added, the aqueous phase is separated off and extracted three times with ethyl acetate, the combined organic phases are washed with saturated aqueous sodium chloride solution and dried over sodium sulphate, and the filtrate is concentrated under reduced pressure. Chromatography on silica gel, eluting with a 90/10/1 mixture of dichloromethane, methanol and 28% aqueous ammonia, gives 1.77 g of pure product in the form of an oil which crystallizes at ambient temperature.

m.p. (°C): 68-70°C

^{1}H NMR ($CDCl_3$) δ (ppm): 7.7 (d, 1H); 7.5 (m, 2H); 7.35 (m, 1H); 6.95 (d, 1H); 4.45 (broad d, 2H); 2.9 (broad td, 2H); 2.7 (t, 2H); 1.7 (m, 2H); 1.6-1.1 (m, 5H).

7.4 4-Nitrophenyl 2-[1-(6-chloroquinolin-2-yl)piperidin-4-yl]ethyl}carbamate

The method described in Example 4 (step 4.4.) is followed. Starting from 5 g (17.25 mmol) of 2-[1-(6-chloroquinolin-2-yl)piperidin-4-yl]ethylamine, prepared in step 7.3., 3.825 g (18.98 mmol) of 4-nitrophenyl chloroformate, 4.46 g (34.51 mmol) of N,N-diisopropylethylamine and 0.105 g (0.86 mmol) of N,N-dimethylaminopyridine, and after trituration in a mixture of diisopropyl ether and hexane, gives 7.8 g of pure product in the form of a white powder.

m.p. (°C): 80-84°C

7.5. 2,2,2-Trifluoro-1-thiazol-2-ylethyl (+/-)-2-[1-(6-chloroquinolin-2-yl)piperidin-4-yl]ethylcarbamate

The procedure described in Example 4 (step 4.6.) is followed. Starting from 0.455 g (1 mmol) of 4-nitrophenyl 2-[1-(6-chloroquinolin-2-yl)piperidin-4-yl]ethyl}carbamate obtained in step 7.4., 0.19 g (1.5 mmol) of N,N-diisopropylethylamine, 0.006 g (0.05 mmol) of N,N-dimethylaminopyridine and 0.201 g (1.1 mmol) of 2,2,2-trifluoro-1-thiazol-2-ylethanol, described in Example 5 (step 5.5.), and after chromatography on silica gel, eluting with a 98/2 mixture of dichloromethane and methanol, followed by recrystallization from a mixture of diethyl ether and hexane, gives 0.3 g of pure product in the form of a white powder.

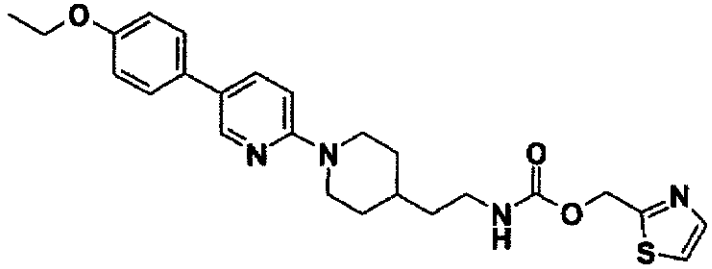
LC-MS: M+H = 499

m.p. (°C): 114-116°C

^{1}H NMR (DMSO) δ (ppm): 8.1 (t, 1H); 8 (m, 2H); 7.8 (s, 1H); 7.5 (m, 3H); 7.30 (d, 1H); 6.60 (m, 1H); 4.55 (broad d, 2H); 3.15 (m, 2H); 2.9 (m, 2H); 1.8 (broad d, 2H); 1.55 (m, 1H); 1.4 (m, 2H); 1.1 (m, 2H).

Example 8 (compound 38)

Thiazol-2-ylmethyl 2-[5'-(4-ethoxyphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate



8.1. tert-Butyl 2-(5'-bromo-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)ethylcarbamate

An autoclave is charged with 10.37 g (43.80 mmol) of 2,5-dibromopyridine, 10 g (43.80 mmol) of tert-butyl 2-piperidin-4-ylethylcarbamate and 6.05 g (43.8 mmol) of potassium carbonate. This initial charge is subsequently heated at 130°C for 12 hours.

Following return to ambient temperature, the reaction mixture is taken up in chloroform and saturated aqueous sodium hydrogencarbonate solution. The aqueous phase is separated off and extracted twice with chloroform, the combined organic phases are washed with saturated aqueous sodium chloride solution and dried over sodium sulphate, and the filtrate is concentrated under reduced pressure.

Chromatography on silica gel, eluting with a 95/5 mixture of dichloromethane and methanol, gives 6.9 g of pure product in the form of a white powder.

m.p. (°C): 108-110°C

8.2. 2-(5'-Bromo-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)ethylamine

A solution of 6.9 g (17.95 mmol) of tert-butyl 2-(5'-bromo-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)ethylcarbamate obtained in step 8.1., in 100 ml of dichloromethane, cooled by an ice/water bath, is admixed slowly with 20.47 g (179.54 mmol) of trifluoroacetic acid. Stirring is continued at ambient temperature for 2 hours. The reaction mixture is poured into a mixture of ice-water and 28% aqueous ammonia. The mixture is decanted,

the aqueous phase is extracted twice with dichloromethane, and the combined organic phases are washed with saturated aqueous sodium chloride solution, dried over sodium sulphate and concentrated under reduced pressure.

This gives 4.9 g of product in the form of an oil, which is used as it is in the following step.

8.3. Thiazol-2-ylmethyl 2-(5'-bromo-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)ethylcarbamate

The procedure described in Example 1 (step 1.4.) is followed. Starting from 4.3 g (15.13 mmol) of 2-(5'-bromo-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)ethylamine, obtained in step 8.2., 4.66 g (16.64 mmol) of thiazol-2-ylmethyl (4-nitrophenyl)carbonate (EP486948A2), 2.93 g (22.70 mmol) of N,N-diisopropylethylamine and 0.09 g (0.76 mmol) of N,N-dimethylaminopyridine, and after chromatography on silica gel, eluting with a 20/80 mixture of ethyl acetate and cyclohexane, gives 2.6 g of pure product in the form of a white powder.

8.4. Thiazol-2-ylmethyl 2-[5'-(4-ethoxyphenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]ethylcarbamate

Under an inert atmosphere, 0.425 g (1 mmol) of thiazol-2-ylmethyl 2-(5'-bromo-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)ethylcarbamate, obtained in step 8.3., 0.2 g (1.2 mmol) of 4-ethoxyphenylboronic acid and 0.977 g (3 mmol) of caesium carbonate in suspension in 5 ml of a 9/1 mixture of tetrahydrofuran and water are introduced. Subsequently 0.082 g (0.1 mmol) of $PdCl_2dppf.CH_2Cl_2$ is added. The mixture is subsequently heated at approximately 75°C for 12 hours.

Following return to ambient temperature, the salts are separated off by filtration on Celite, and then the filtrate is taken up in ethyl acetate and water; the aqueous phase is separated off and extracted twice with ethyl acetate and the combined organic phases are washed with saturated aqueous sodium chloride solution and dried over sodium sulphate. Following evaporation of the solvent, the residue obtained is purified by chromatography on silica gel, eluting with a 98/2 mixture of dichloromethane and methanol. The solid obtained is subsequently recrystallized from isopropanol.

This gives 0.39 g of product in the form of a white powder.

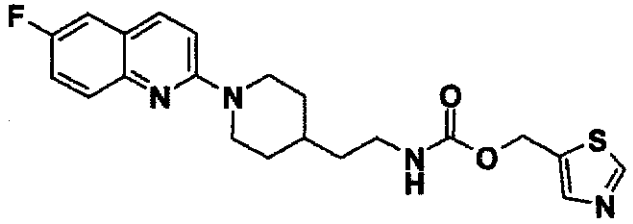
LC-MS: M+H = 467

m.p. (°C): 157-159°C

^{1}H NMR (DMSO) δ (ppm): 8.40 (s, 1H); 7.85 (d, 1H); 7.75 (m, 2H); 7.55 (d, 2H); 7.45 (t, 1H); 7 (d, 2H); 6.9 (d, 1H); 5.30 (s, 2H); 4.30 (broad d, 2H); 4.1 (q, 2H); 3.1 (m, 2H); 2.8 (t, 2H); 1.8 (d, 2H); 1.7 (m, 1H); 1.4 (m, 2H); 1.3 (t, 3H); 1.1 (m, 2H).

Example 9 (compound 117)

Thiazol-5-ylmethyl 2-[1-(6-fluoroquinolin-2-yl)piperidin-4-yl]ethylcarbamate



9.1. tert-Butyl 4-[2-(4-nitrophenoxycarbonylamino)ethyl]piperidine-1-carboxylate

The procedure described in Example 1 (step 1.4.) is followed. Starting from 5 g (21.90 mmol) of tert-butyl 4-(2-aminoethyl)piperidine-1-carboxylate, 4.63 g (23 mmol) of 4-nitrophenyl chloroformate, 5.66 g (43.80 mmol) of diisopropylethylamine and 0.134 g (1.09 mmol) of N,N-dimethylaminopyridine gives 8.6 g of product in the form of an oil which is used as it is in the following step.

9.2. tert-Butyl 4-[2-(thiazol-5-ylmethoxycarbonylamino)ethyl]piperidine-1-carboxylate

The procedure described in Example 4 (step 4.6.) is followed. Starting from 8.6 g (21.86 mmol) of tert-butyl 4-[2-(4-nitrophenoxycarbonylamino)ethyl]-piperidine-1-carboxylate, obtained in step 9.1., 2.77 g (24.04 mmol) of thiazol-2-ylmethanol, 5.65 g (43.72 mmol) of N,N-diisopropylethylamine and 0.134 g (1.09 mmol) of N,N-dimethylaminopyridine gives 3.6 g of product in the form of an oil, which is used as it is in the following step.

9.3. Thiazol-5-ylmethyl 2-piperidin-4-ylethylcarbamate hydrochloride

A solution of 3.6 g (9.74 mmol) of tert-butyl 4-[2-(thiazol-5-ylmethoxycarbonylamino)ethyl]piperidine-1-carboxylate, obtained in step 9.2., in 97 ml of diethyl ether, cooled by an ice/water bath, is admixed slowly with 40 ml (160 mmol) of a 4N solution of hydrochloric acid in dioxane. Stirring is continued at ambient temperature for 12 hours.

Evaporation under reduced pressure gives 2.4 g of product in the form of the hydrochloride, which is used as it is in the following step.

9.4. Thiazol-5-ylmethyl 2-[1-(6-fluoroquinolin-2-yl)piperidin-4-yl]ethylcarbamate

A sealed tube is charged with 0.09 g (0.39 mmol) of 2-bromo-6-fluoroquinoline, 0.1 g (0.33 mmol) of thiazol-5-ylmethyl 2-piperidin-4-ylethylcarbamate hydrochloride, obtained in step 9.3., and 0.2 ml (1.14 mol) of N,N-diisopropylethylamine. The system is subsequently heated at 100°C for 12 hours.

Following return to ambient temperature, the reaction mixture is taken up in dichloromethane and saturated aqueous ammonium chloride solution. The aqueous phase is separated off and extracted twice with dichloromethane, the combined organic phases are washed with saturated aqueous sodium chloride solution and dried over sodium sulphate, and the filtrate is concentrated under reduced pressure.

Chromatography on silica gel, eluting with a 95/5 mixture of dichloromethane and methanol, gives 0.039 g of pure product in the form of a white powder.

LC-MS: M+H = 415

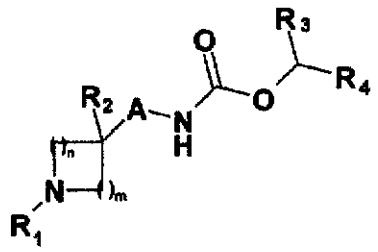
m.p. (°C): 100-102°C

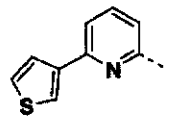
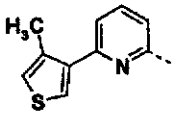
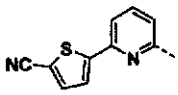
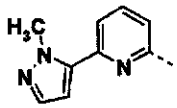
^{1}H NMR (DMSO) δ (ppm): 9.1 (s, 1H); 8 (d, 1H); 7.9 (s, 1H); 7.7 (m, 1H); 7.60 (dd, 1H); 7.5 (m, 1H); 7.30 (m, 2H); 5.3 (s, 2H); 4.50 (broad d, 2H); 3.10 (m, 2H); 2.85 (t, 2H); 1.9 (broad d, 2H); 1.60 (m, 1H); 1.4 (m, 2H); 1.1 (m, 2H).

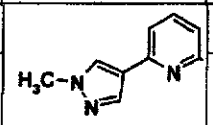
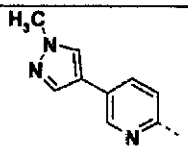
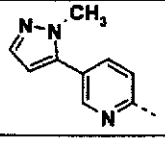
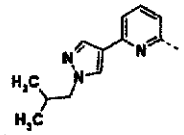
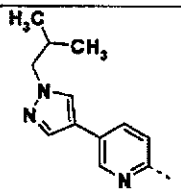
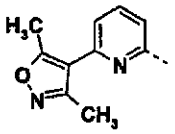
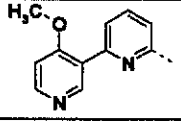
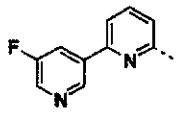
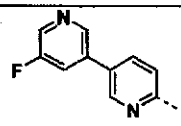
Table 1 below illustrates the chemical structures and the physical properties of a number of compounds according to the invention. In this table:

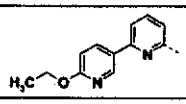
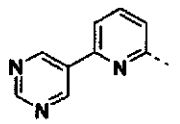
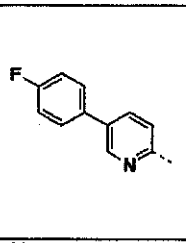
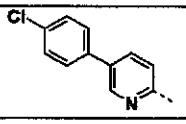
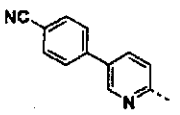
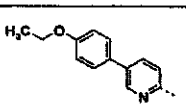
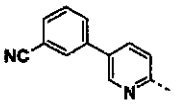
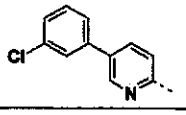
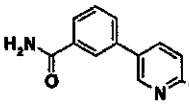
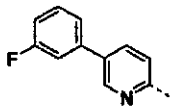
- in the column "base or salt", "base" represents a compound in free base form, "CF_3COOH" represents a compound in trifluoroacetate form and "HCl" represents a compound in hydrochloride form;
- in the column "A", "1" corresponds to a $-CH_2-$, "2" corresponds to a $-CH_2-CH_2-$;
- all the compounds containing an asymmetric carbon are in racemic mixture form.

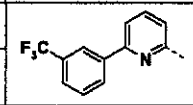
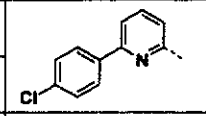
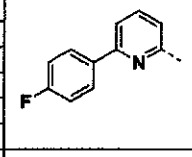
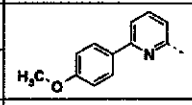
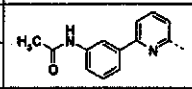
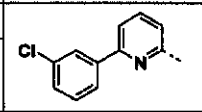
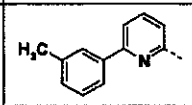
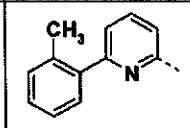
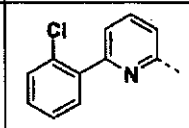
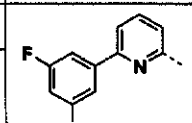
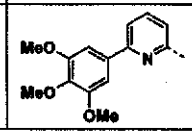
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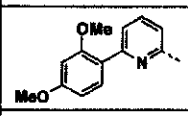
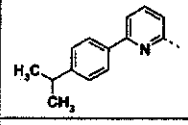
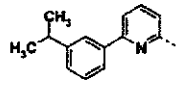
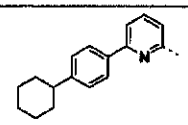
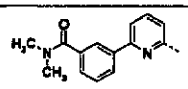
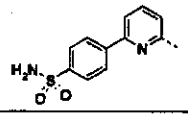
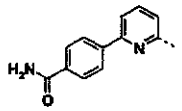
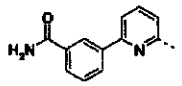
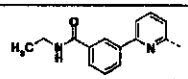
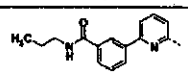
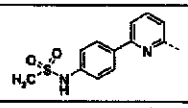
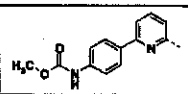
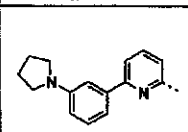


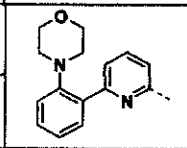
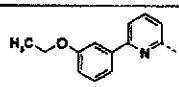
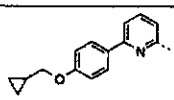
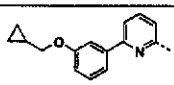
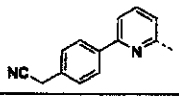
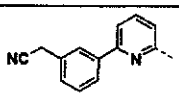
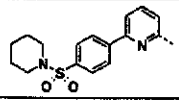
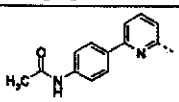
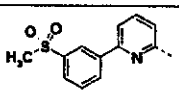
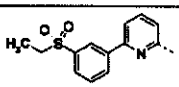
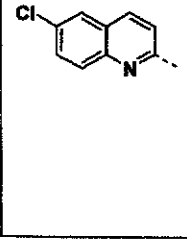
No.	R_1	m	n	A	R_2	R_3	R_4	base or salt	m.p. (°C) or M+H
1.		2	2	1	H	H	thiazol-4-yl	CF_3COOH	415
2.		2	2	2	H	H	thiazol-4-yl	CF_3COOH	429
3.		2	2	1	H	H	thiazol-4-yl	CF_3COOH	429
4.		2	2	2	H	H	thiazol-4-yl	CF_3COOH	443
5.		2	2	2	H	H	thiazol-4-yl	CF_3COOH	454
6.		2	2	2	H	H	thiazol-2-yl	HCl	125-127°C
7.		2	2	1	H	H	thiazol-4-yl	CF_3COOH	413
8.		2	2	2	H	H	thiazol-4-yl	base	94-95°C

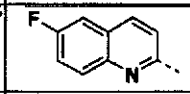
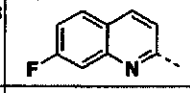
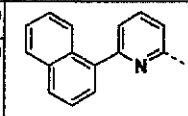
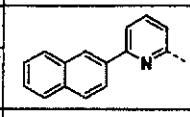
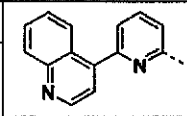
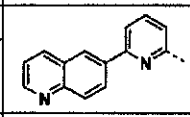
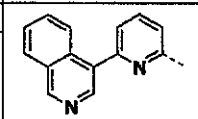
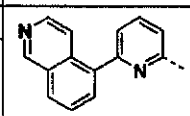
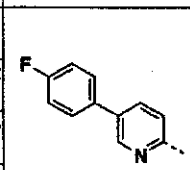
No.	R_1	m	n	A	R_2	R_3	R_4	base or salt	m.p. (°C) or M+H
9.		2	2	2	H	H	thiazol-2-yl	base	90°C (déc.)
10.		2	2	2	H	H	thiazol-4-yl	base	117-119°C
11.		2	2	2	H	H	thiazol-4-yl	base	153-155°C
12.		2	2	2	H	H	thiazol-4-yl	base	107-109°C
13.		2	2	2	H	H	thiazol-2-yl	base	132-134°C
14.		2	2	1	H	H	thiazol-4-yl	CF_3COOH	455
15.		2	2	2	H	H	thiazol-4-yl	CF_3COOH	469
16.		2	2	2	H	H	thiazol-4-yl	base	132-134°C
17.		2	2	1	H	H	thiazol-4-yl	CF_3COOH	428
18.		2	2	2	H	H	thiazol-4-yl	CF_3COOH	442
19.		2	2	1	H	H	thiazol-4-yl	CF_3COOH	413
20.		2	2	2	H	H	thiazol-4-yl	CF_3COOH	454
21.		2	2	2	H	H	thiazol-2-yl	base	124-126°C
22.		2	2	2	H	H	thiazol-4-yl	base	123-125°C
23.		2	2	2	H	H	thiazol-4-yl	base	133-135°C

No.	R_1	m	n	A	R_2	R_3	R_4	base or salt	m.p. (°C) or M+H
24.		2	2	2	H	H	thiazol-4-yl	CF_3COOH	468
25.		2	2	1	H	H	thiazol-4-yl	CF_3COOH	411
26.		2	1	1	H	H	thiazol-2-yl	base	96-98°C
27.		2	1	1	H	H	thiazol-4-yl	base	106-108°C
28.		2	2	2	H	H	thiazol-2-yl	base	131-133°C
29.		2	2	2	H	CF_3	thiazol-2-yl	base	132-134°C
30.		2	2	2	H	H	thiazol-4-yl	base	130-132°C
31.		2	2	2	H	CF_3	thiazol-4-yl	base	120-122°C
32.		2	2	2	H	H	2-CH_3-thiazol-4-yl	base	149-151°C
33.		2	2	2	H	H	thiazol-5-yl	base	100-102°C
34.		2	2	2	H	CF_3	thiazol-5-yl	base	165-167°C
35.		2	2	2	H	H	thiazol-2-yl	base	145-149°C
36.		2	2	2	H	H	thiazol-2-yl	base	189-191°C
37.		2	2	2	H	H	thiazol-5-yl	base	147-149°C
38.		2	2	2	H	H	thiazol-2yl	base	157-159°C
39.		2	2	2	H	H	thiazol-4-yl	base	160-162°C
40.		2	2	2	H	H	thiazol-5-yl	base	170-172°C
41.		2	2	2	H	H	thiazol-2-yl	base	114-116°C
42.		2	2	2	H	H	thiazol-2-yl	base	101-103°C
43.		2	2	2	H	H	thiazol-4-yl	base	195-197°C
44.		2	2	2	H	H	thiazol-2-yl	base	101-103°C

No.	R_1	m	n	A	R_2	R_3	R_4	base or salt	m.p. (°C) or M+H
45.		2	2	1	H	H	thiazol-4-yl	CF_3COOH	477
46.		2	2	2	H	H	thiazol-4-yl	CF_3COOH	491
47.		2	2	1	H	H	thiazol-4-yl	CF_3COOH	443
48.		2	2	2	H	H	thiazol-4-yl	CF_3COOH	457
49.		2	2	2	H	H	thiazol-2-yl	base	95-97 °C
50.		2	2	2	H	CF_3	thiazol-2-yl	base	121-123°C
51.		2	2	2	H	H	thiazol-4-yl	base	118-120°C
52.		2	2	2	H	CF_3	thiazol-4-yl	base	79-83°C
53.		2	2	2	H	H	2-CH_3-thiazol-4-yl	base	127-129°C
54.		2	2	2	H	H	thiazol-5-yl	base	78-82°C
55.		2	2	2	H	CF_3	thiazol-5-yl	base	509
56.		2	2	1	H	H	thiazol-4-yl	CF_3COOH	439
57.		2	2	2	H	H	thiazol-4-yl	CF_3COOH	453
58.		2	2	1	H	H	thiazol-4-yl	CF_3COOH	466
59.		2	2	2	H	H	thiazol-4-yl	CF_3COOH	480
60.		2	2	1	H	H	thiazol-4-yl	CF_3COOH	443
61.		2	2	2	H	H	thiazol-4-yl	CF_3COOH	457
62.		2	2	1	H	H	thiazol-4-yl	CF_3COOH	423
63.		2	2	2	H	H	thiazol-4-yl	CF_3COOH	437
64.		2	2	1	H	H	thiazol-4-yl	CF_3COOH	443
65.		2	2	1	H	H	thiazol-4-yl	CF_3COOH	445
66.		2	2	2	H	H	thiazol-4-yl	CF_3COOH	459
67.		2	2	1	H	H	thiazol-4-yl	CF_3COOH	499

No.	R_1	m	n	A	R_2	R_3	R_4	base or salt	m.p. (°C) or M+H
68.		2	2	2	H	H	thiazol-4-yl	CF_3COOH	483
69.		2	2	1	H	H	thiazol-4-yl	CF_3COOH	451
70.		2	2	2	H	H	thiazol-4-yl	CF_3COOH	465
71.		2	2	1	H	H	thiazol-4-yl	CF_3COOH	451
72.		2	2	2	H	H	thiazol-4-yl	CF_3COOH	465
73.		2	2	1	H	H	thiazol-4-yl	CF_3COOH	491
74.		2	2	2	H	H	thiazol-4-yl	CF_3COOH	505
75.		2	2	1	H	H	thiazol-4-yl	CF_3COOH	480
76.		2	2	2	H	H	thiazol-4-yl	CF_3COOH	494
77.		2	2	2	H	H	thiazol-4-yl	CF_3COOH	502
78.		2	2	1	H	H	thiazol-4-yl	CF_3COOH	452
79.		2	2	2	H	H	thiazol-4-yl	CF_3COOH	466
80.		2	2	1	H	H	thiazol-4-yl	CF_3COOH	452
81.		2	2	2	H	H	thiazol-4-yl	CF_3COOH	466
82.		2	2	1	H	H	thiazol-4-yl	CF_3COOH	480
83.		2	2	2	H	H	thiazol-4-yl	CF_3COOH	494
84.		2	2	1	H	H	thiazol-4-yl	CF_3COOH	494
85.		2	2	2	H	H	thiazol-4-yl	CF_3COOH	516
86.		2	2	1	H	H	thiazol-4-yl	CF_3COOH	482
87.		2	2	2	H	H	thiazol-4-yl	CF_3COOH	496
88.		2	2	2	H	H	thiazol-4-yl	CF_3COOH	492

No.	R_1	m	n	A	R_2	R_3	R_4	base or salt	m.p. (°C) or M+H
89.		2	2	1	H	H	thiazol-4-yl	CF_3COOH	494
90.		2	2	2	H	H	thiazol-4-yl	CF_3COOH	508
91.		2	2	2	H	H	thiazol-4-yl	CF_3COOH	467
92.		2	2	2	H	H	thiazol-4-yl	CF_3COOH	493
93.		2	2	1	H	H	thiazol-4-yl	CF_3COOH	479
94.		2	2	2	H	H	thiazol-4-yl	CF_3COOH	493
95.		2	2	1	H	H	thiazol-4-yl	CF_3COOH	448
96.		2	2	1	H	H	thiazol-4-yl	CF_3COOH	448
97.		2	2	1	H	H	thiazol-4-yl	CF_3COOH	556
98.		2	2	2	H	H	thiazol-4-yl	CF_3COOH	570
99.		2	2	1	H	H	thiazol-4-yl	CF_3COOH	466
100		2	2	2	H	H	thiazol-4-yl	CF_3COOH	479
101		2	2	2	H	H	thiazol-4-yl	CF_3COOH	501
102		2	2	1	H	H	thiazol-4-yl	CF_3COOH	501
103		2	2	2	H	H	thiazol-4-yl	CF_3COOH	515
104		2	2	2	H	H	thiazol-2-yl	base	121-123°C
105		2	2	2	H	H	4-CF_3-thiazol-2-yl	base	128-129°C
106		2	2	2	H	CF_3	thiazol-2-yl	base	114-116°C
107		2	2	2	H	CH_3	thiazol-4-yl	base	142-144°C
108		2	2	2	H	CF_3	thiazol-4-yl	base	111-113°C
109		2	2	2	H	H	thiazol-4-yl	base	126-128°C
110		2	2	2	H	H	2-CH_3-thiazol-4-yl	base	142-144°C
111		2	2	2	H	H	2-CF_3-thiazol-4-yl	base	148-150°C
112		2	2	2	H	H	2-Cl-thiazol-4-yl	base	130-132°C
113		2	2	2	H	H	2-(pyridin-3-yl)-thiazol-4-yl	base	152-154°C
114		2	2	2	H	H	2-(pyridin-4-yl)-thiazol-5-yl	base	155-157°C
115		2	2	2	H	H	thiazol-5-yl	base	132-134°C
116		2	2	2	H	CF_3	thiazol-5-yl	base	131-133°C

No.	R_1	m	n	A	R_2	R_3	R_4	base or salt	m.p. (°C) or M+H
117		2	2	2	H	H	thiazol-5-yl	base	100-102°C
118		2	2	2	H	H	thiazol-5-yl	base	115-117°C
119		2	2	1	H	H	thiazol-4-yl	CF_3COOH	459
120		2	2	2	H	H	thiazol-4-yl	CF_3COOH	473
121		2	2	1	H	H	thiazol-4-yl	CF_3COOH	459
122		2	2	2	H	H	thiazol-4-yl	CF_3COOH	473
123		2	2	1	H	H	thiazol-4-yl	CF_3COOH	460
124		2	2	2	H	H	thiazol-4-yl	CF_3COOH	474
125		2	2	1	H	H	thiazol-4-yl	CF_3COOH	460
126		2	2	2	H	H	thiazol-4-yl	CF_3COOH	474
127		2	2	1	H	H	thiazol-4-yl	CF_3COOH	460
128		2	2	2	H	H	thiazol-4-yl	CF_3COOH	474
129		2	2	1	H	H	thiazol-4-yl	CF_3COOH	460
130		2	2	2	H	H	thiazol-4-yl	CF_3COOH	474
131		2	2	2	H	H	2-$CONH_2$-thiazol-4-yl	base	230-232°C
132		2	2	2	H	H	2-$CONHCH_3$-thiazol-4-yl	base	184-186°C
133		2	2	2	H	H	4-$CONH_2$-thiazol-2-yl	base	199-201°C
134		2	2	2	H	H	4-$CONHCH_3$-thiazol-2-yl	base	177-178°C

LC-MS methods (M+H):
Acetonitrile + 0.5% trifluoroacetic acid/H_2O + 0.05% trifluoroacetic acid
Columns: Waters Xbridge C18 4 or YMC Jsphere 33*2
Flow rate: 1 ml/min

The compounds of the invention were subjected to pharmacological tests allowing determination of their inhibitory effect on the enzyme FAAH (Fatty Acid Amide Hydrolase).

The inhibitory activity was demonstrated in a radioenzymatic assay based on measuring the product of hydrolysis of anandamide [1-^{3}H ethanolamine] by FAAH (*Life Sciences (1995), 56, 1999-2005* and *Journal of Biochemical and Biophysical Methods (2004)*, 60(2), 171-177). Accordingly, mouse brains (minus the cerebellum) are removed and stored at -80°C. Membrane

homogenates are prepared at the time of use by homogenizing the tissues using a Precellys® apparatus in the reaction buffer (10 mM Tris-HCl pH=8, 150 mM NaCl and 1 mM ethylenediaminetetraacetic acid (EDTA)). The enzymatic reaction is conducted in 96-well Multiscreen filter plates, in a final volume of 70 µl. Reaction buffer supplemented with bovine serum albumin without fatty acids (BSA, 1 mg/ml) is used for the enzymatic reaction, the dilution of the compounds and of anandamide [1-^{3}H ethanolamine]. Added in succession to the wells are the reaction buffer containing the BSA (43 µl/well), the diluted test compounds at different concentrations (7 µl/well containing 1% DMSO) and the membrane preparation (10 µl/well or 200 µg of tissue per assay). After the compounds have been pre-incubated with the enzyme at 25°C for 20 minutes, the reaction is initiated by the addition of anandamide [1-^{3}H ethanolamine] (specific activity of 15-20 Ci/mmol) diluted with cold anandamide (10 µl/well, final concentration of 10 µM, 0.01 µCi per assay). After 20 minutes of incubation at 25°C, the enzymatic reaction is halted by addition of a 5M active carbon solution prepared in a 1.5M NaCl and 0.5M HCl buffer (50 µl/well). The mixture is stirred for 10 minutes and then the aqueous phase containing the ethanolamine [1-^{3}H] is recovered by filtration under vacuum and counted by liquid scintillation.

Under these conditions the most active compounds of the invention exhibit IC_{50} values (concentration inhibiting by 50% the control enzymatic activity of FAAH) of between 0.001 and 1 µM; for example compounds 28 and 30 have IC_{50} values of 0.003 and 0.007 µM respectively.

It is therefore apparent that the compounds according to the invention have an inhibitory activity on the FAAH enzyme.

The *in vivo* activity of the compounds of the invention was evaluated in an analgesia test.

Accordingly, intraperitoneal (i.p.) administration of PBQ (phenylbenzoquinone, 2 mg/kg in a 0.9% sodium chloride solution containing 5% of ethanol) to male OF1 mice weighing 25 to 30 g causes abdominal stretches, on average 30 twists or contractions during the period from 5 to 15 minutes after injection. The test compounds are administered orally (p.o.) or intraperitoneally (i.p.) in suspension in Tween 80 at 0.5%, 60 minutes or 120 minutes before the administration of PBQ. Under these conditions the most potent compounds of the invention reduce by 35% to 80% the number of stretches induced by PBQ, within a dose range of

between 1 and 30 mg/kg.

For example, compounds 28 and 30 of the table reduce by 33% and 80%, respectively, the number of stretches induced by PBQ, at a dose of 30 mg/kg p.o. at 120 minutes.

The enzyme FAAH (*Chemistry and Physics of Lipids*, (2000), 108, 107-121) catalyses the hydrolysis of endogenous derivatives of amides and of esters of various fatty acids such as *N*-arachidonoylethanolamine (anandamide), *N*-palmitoylethanolamine, *N*-oleoylethanolamine, oleamide or 2-arachidonoylglycerol. These derivatives exert various pharmacological activities by interacting, inter alia, with cannabinoid and vanilloid receptors.

The compounds of the invention block this degradation pathway and increase the tissue level of these endogenous substances. They can be used in this respect in the prevention and treatment of pathologies involving endogenous cannabinoids and/or any other substrates metabolized by the FAAH enzyme. Mention may be made, for example, of the following diseases and conditions:

pain, especially acute or chronic pain of neurogenic type: migraine, neuropathic pain, including forms associated with the herpes virus and with diabetes and with chemotherapy, acute or chronic pain associated with inflammatory diseases: arthritis, rheumatoid arthritis, osteoarthritis, spondylitis, gout, vasculitis, Crohn's disease, irritable bowel syndrome, acute or chronic peripheral pain, dizziness, vomiting, nausea, especially subsequent to chemotherapy, eating disorders, especially anorexia and cachexia of various kinds, neurological and psychiatric pathologies: shaking, dyskinesia, dystonia, spasticity, obsessive-compulsive behaviours, Tourette's syndrome, all forms of depression and anxiety of any kind and cause, mood disorders, psychoses, acute and chronic neurodegenerative diseases: Parkinson's disease, Alzheimer's disease, senile dementia, Huntington's chorea, lesions associated with cerebral ischaemia and with cranial and medullary trauma, epilepsy, sleep disorders, including sleep apnoea, cardiovascular diseases, especially hypertension, cardiac arrhythmias, arteriosclerosis, heart attack, cardiac ischaemia, renal ischaemia, cancers: benign skin tumours, papillomas and brain tumours, prostate tumours, brain tumours (glioblastomas, medulloepitheliomas, medulloblastomas, neuroblastomas, tumours of embryonic origin, astrocytomas, astroblastomas, ependyomas, oligodendrogliomas, plexus tumour, neuroepitheliomas, epiphysial tumour, ependymoblastomas, malignant meningiomas, sarcomatoses, malignant melanomas,

schwannomas), disorders of the immune system, especially autoimmune diseases: psoriasis, lupus erythematosis, diseases of the connective tissue or collagen diseases, Sjögren's syndrome, ankylosing spondylarthritis, undifferentiated spondylarthritis, Behcet's disease, haemolytic autoimmune anaemias, multiple sclerosis, amyotrophic lateral sclerosis, amyloses, transplant rejection, diseases affecting the plasmocytic line, allergic diseases: immediate or delayed-onset hypersensitivity, allergic rhinitis or conjunctivitis, contact dermatitis, infectious parasitic, viral or bacterial diseases: AIDS, meningitis, inflammatory diseases, especially diseases of the joints: arthritis, rheumatoid arthritis, osteoarthritis, spondylitis, gout, vasculitis, Crohn's disease, irritable bowel syndrome, osteoporosis, ocular conditions: ocular hypertension, glaucoma, pulmonary conditions: diseases of the respiratory tract, bronchospasms, coughing, asthma, chronic bronchitis, chronic obstruction of the respiratory tract, emphysema, gastrointestinal diseases: irritable bowel syndrome, intestinal inflammatory disorders, ulcers, diarrhoea, urinary incontinence and bladder inflammation.

The use of the compounds according to the invention, in the form of the base, an addition salt with an acid, a hydrate or pharmaceutically acceptable solvate, for preparing a medicinal product intended for treating the abovementioned pathologies forms an integral part of the invention.

The invention also provides medicinal products which comprise a compound of formula (I), or an addition salt with an acid, or else a hydrate or a pharmaceutically acceptable solvate of the compound of formula (I). These medicinal products are employed in therapy, especially in the treatment of the abovementioned pathologies.

According to another of its aspects the present invention provides pharmaceutical compositions comprising as active principle at least one compound according to the invention. These pharmaceutical compositions include an effective dose of a compound according to the invention, or an addition salt with an acid, or a hydrate, or a pharmaceutically acceptable solvate of said compound, and, optionally, one or more pharmaceutically acceptable excipients.

The said excipients are selected, according to the pharmaceutical form and the desired mode of administration, from the customary excipients which are known to a person skilled in the art.

In the pharmaceutical compositions of the present invention for oral, sublingual, subcutaneous, intramuscular, intravenous, topical, local, intrathecal, intranasal, transdermal, pulmonary, ocular or rectal administration, the active principle of formula (I) above, or its addition salt with an acid, solvate or hydrate, where appropriate, may be administered in a unit-dose administration form, in a mixture with conventional pharmaceutical excipients, to animals and to humans for the prophylaxis or treatment of the above disorders or diseases.

The unit-dose administration forms which are appropriate include oral forms such as tablets, soft or hard gelatin capsules, powders, granules, chewing gums and oral solutions or suspensions, forms for sublingual, buccal, intratracheal, intraocular and intranasal administration, and for administration by inhalation, forms for subcutaneous, intramuscular or intravenous administration, and forms for rectal or vaginal administration. For topical application the compounds according to the invention may be used in creams, ointments or lotions.

By way of example, a unit-dose administration form of a compound according to the invention in tablet form may comprise the following components:

Compound according to the invention	50.0 mg
Mannitol	223.75 mg
Sodium croscaramellose	6.0 mg
Corn starch	15.0 mg
Hydroxypropyl-methylcellulose	2.25 mg
Magnesium stearate	3.0 mg

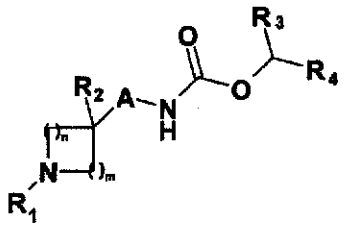
The said unit-dose forms contain a dose permitting daily administration of 0.01 to 20 mg of active principle per kg of body weight, depending on the pharmaceutical form.

There may be particular cases in which higher or lower doses are appropriate; such doses also belong to the invention. In accordance with customary practice, the dosage appropriate for each patient is determined by the doctor according to the mode of administration, the weight and the response of the said patient.

According to another of its aspects the invention likewise provides a method of treating the pathologies indicated above, which comprises administering an effective dose of a compound according to the invention, one of its addition salts with a pharmaceutically acceptable acid, a solvate or a hydrate of the said compound.

Claims

1. Compound of the formula (I)



(I)

in which

R_2 represents a hydrogen or fluorine atom, a hydroxyl, cyano, trifluoromethyl, C_{1-6} alkyl or C_{1-6} alkoxy group or a group NR_8R_9;

n represents an integer 1, 2 or 3 and m represents an integer 1 or 2;

A represents a covalent bond or a C_{1-8} alkylene group;

R_1 represents a group R_5 which is optionally substituted by one or more groups R_6 and/or R_7;

R_5 represents a group selected from a phenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, naphthalenyl, quinolinyl, isoquinolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, cinnolinyl or naphthyridinyl;

R_6 represents a halogen atom, a cyano, $-CH_2CN$, nitro, hydroxyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} thioalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} halothioalkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-3} alkylene or C_{3-7} cycloalkyl-C_{1-3} alkylene-O- group, or a group NR_8R_9, NR_8COR_9, $NR_8CO_2R_9$, $NR_8SO_2R_9$, $NR_8SO_2NR_8R_9$, COR_8, CO_2R_8, $CONR_8R_9$, SO_2R_8, $SO_2NR_8R_9$ or $-O-(C_{1-3}$-alkylene)-O-;

R_7 represents a group selected from a furanyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazole, thiadiazole, phenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazine, naphthalenyl, quinolinyl, isoquinolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, imidazopyrimidinyl, thienopyrimidinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, indolyl, isoindolyl, indazolyl, pyrrolopyridinyl, furopyridinyl, thienopyridinyl, imidazopyridinyl, pyrazolopyridinyl, oxazolopyridinyl, isoxazolopyridinyl, thiazolopyridinyl, phenyloxy, benzyloxy or pyrimidinoxy, the group or groups R_7 being able to be substituted by one or more groups R_6 which are identical or different from one another;

R_3 represents a hydrogen or fluorine atom, a C_{1-6} alkyl group or a trifluoromethyl group;

R_4 represents a thiazole which is optionally substituted by one or more substituents selected from a halogen atom, a C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-3} alkylene, C_{1-6} haloalkoxy, cyano, NR_8R_9, NR_8COR_9, $NR_8CO_2R_9$, $NR_8SO_2R_9$, $NR_8SO_2NR_8R_9$, COR_8, CO_2R_8, $CONR_8R_9$, SO_2R_8, $SO_2NR_8R_9$, –O-(C_{1-3}-alkylene)-O-, phenyl, phenyloxy, benzyloxy, pyridinyl, pyrazinyl, pyridazinyl, triazinyl or pyrimidinyl group, it being possible for the phenyl, phenyloxy, pyridinyl, pyrazinyl, pyridazinyl, triazinyl and pyrimidinyl groups to be substituted by one or more substituents selected from a halogen atom and a cyano, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} thioalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} halothioalkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-3} alkylene group;

R_8 and R_9 represent independently of one another a hydrogen atom or a C_{1-6} alkyl group,

or form, with the atom or atoms bearing them,

in the case of NR_8R_9, a ring selected from azetidine, pyrrolidine, piperidine, morpholine, thiomorpholine, azepine, oxazepine or piperazine ring, this ring being optionally substituted by a C_{1-6} alkyl or benzyl group;

in the case of NR_8COR_9, a lactam ring; in the case of $NR_8CO_2R_9$, an oxazolidinone, oxazinone or oxazepinone ring; in the case of $NR_8SO_2R_9$, a sultam ring; in the case of $NR_8SO_2NR_8R_9$, a thiazolidine dioxide or thiadiazinane dioxide ring;

in the form of the base or an addition salt with an acid;

the following compounds being excluded:

- methyl 2-(3-{[2-(4-chlorophenyl)-4-methylthiazol-5-yl]methoxycarbonylamino}piperidin-1-yl)benzoate;
- 2-(3-{[2-(4-chlorophenyl)-4-methylthiazol-5-yl]methoxycarbonylamino}piperidin-1-yl)benzoic acid;
- methyl 3-(3-{[2-(4-chlorophenyl)-4-methylthiazol-5-yl]methoxycarbonylamino}piperidin-1-yl)benzoate;
- 3-(3-{[2-(4-chlorophenyl)-4-methylthiazol-5-yl]methoxycarbonylamino}piperidin-1-yl)benzoic acid.

2. Compound of formula (I) according to Claim 1, characterized in that R_2 represents a hydrogen atom;

in the form of the base or an addition salt with an acid.

3. Compound of formula (I) according to Claim 1 or 2, characterized in that

n represents an integer 1 or 2 and m represents an integer 2;
in the form of the base or an addition salt with an acid.

4. Compound of formula (I) according to any of Claims 1 to 3, characterized in that A represents a C_{1-8} alkylene group; in the form of the base or an addition salt with an acid.

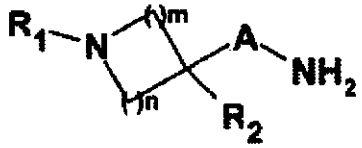
5. Compound of formula (I) according to any of Claims 1 to 4, characterized in that R_1 represents a group R_5 which is optionally substituted by one or more groups R_6 and/or R_7;
R_5 represents a pyridinyl or quinolinyl group;
R_6 represents a halogen atom, a cyano, $-CH_2CN$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{3-7} cycloalkyl or C_{3-7} cycloalkyl-C_{1-3} alkylene-O- group, or a group NR_8R_9, NR_8COR_9, $NR_8CO_2R_9$, $NR_8SO_2R_9$, $CONR_8R_9$, SO_2R_8 or $SO_2NR_8R_9$;
R_7 represents a group selected from a thienyl, isoxazolyl, pyrazolyl, phenyl, pyridinyl, pyrimidinyl, naphthalenyl, quinolinyl or isoquinolinyl, it being possible for the group or groups R_7 to be substituted by one or more groups R_6 which are identical or different from one another;
R_8 and R_9 represent independently of one another a hydrogen atom or a C_{1-6} alkyl group, or form with the atom or atoms bearing them a ring selected from pyrrolidine, piperidine and morpholine rings; in the form of the base or an addition salt with an acid.

6. Compound of formula (I) according to any of Claims 1 to 5, characterized in that R_3 represents a hydrogen atom, a C_{1-6} alkyl group or a trifluoromethyl group; in the form of the base or an addition salt with an acid.

7. Compound of formula (I) according to any of Claims 1 to 6, characterized in that
R_4 represents a thiazole which is optionally substituted by one or more substituents selected from a halogen atom and a C_{1-6} alkyl, C_{1-6} haloalkyl, pyridinyl and $CONR_8R_9$ group; R_8 and R_9 represent independently of one another a hydrogen atom or a C_{1-6} alkyl group;
in the form of the base or an addition salt with an acid.

8. Process for preparing a compound of formula (I) according to any of Claims 1 to 7, comprising the step of

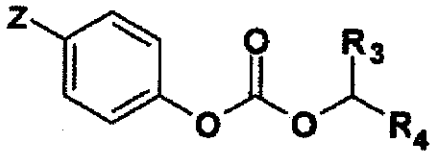
reacting an amine of general formula (II)



(II)

in which A, R_1, R_2, m and n are as defined in the general formula (I) according to Claim 1,

with a carbonate of general formula (III)



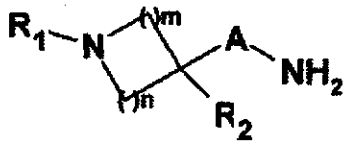
(III)

in which Z represents a hydrogen atom or a nitro group and R_3 and R_4 are as defined in the general formula (I) according to Claim 1,

in the presence of a base, in a solvent at a temperature between the ambient temperature and the reflux temperature of the solvent.

9. Process for preparing a compound of formula (I) according to any of Claims 1 to 7, comprising the step of

reacting an amine of general formula (II)



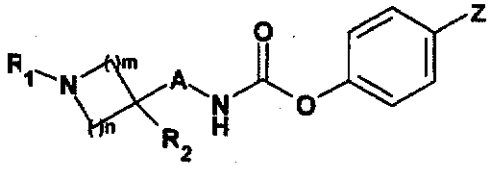
(II)

in which A, R_1, R_2, m and n are as defined in the general formula (I) according to Claim 1,

with phenyl or 4-nitrophenyl chloroformate,

in the presence of a base, in a solvent at a temperature between 0°C and the ambient temperature,

to give the carbamate derivative of general formula (IV)



(IV)

in which A, R_1, R_2, m and n are as defined in the general formula (I)

according to Claim 1, and Z represents a hydrogen atom or a nitro group; then converting the carbamate derivative of general formula (IV) thus obtained into a compound of general formula (I), by the action of an alcohol of general formula $HOCHR_3R_4$ (IIIa), in which R_3 and R_4 are as defined in general formula (I) according to Claim 1,
in the presence of a base, in a solvent at a temperature between the ambient temperature and the reflux temperature of the solvent.

10. Compound of formula (I) according to any of Claims 1 to 7, in the form of the base or an addition salt with a pharmaceutically acceptable acid, for use thereof as a medicinal product.

11. Pharmaceutical composition comprising at least one compound of formula (I) according to any of Claims 1 to 7, in the form of the base or an addition salt with a pharmaceutically acceptable acid, and, optionally, one or more pharmaceutically acceptable excipients.

12. Use of a compound of formula (I) according to any of Claims 1 to 7, in the form of the base or an addition salt with a pharmaceutically acceptable acid, for preparing a medicinal product intended for preventing or treating a pathology involving endogenous cannabinoids and/or any other substances metabolized by the enzyme FAAH.

13. Use of a compound of formula (I) according to any of Claims 1 to 7, in the form of the base or an addition salt with a pharmaceutically acceptable acid, for preparing a medicinal product intended for preventing or treating acute or chronic pain, dizziness, vomiting, nausea, eating disorders, neurological and psychiatric pathologies, acute or chronic neurodegenerative diseases, epilepsy, sleep disorders, cardiovascular diseases, renal ischaemia, cancers, disorders of the immune system, allergic diseases, infectious parasitic, viral or bacterial diseases, inflammatory diseases, osteoporosis, ocular conditions, pulmonary conditions, gastrointestinal diseases or urinary incontinence.