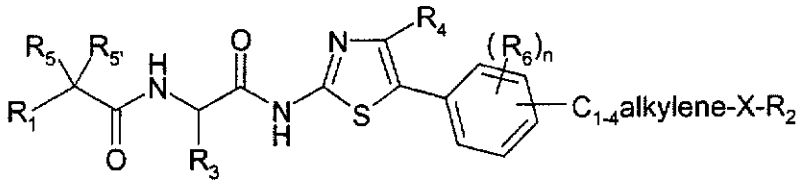
ACYLAMINOTHIAZOLE DERIVATIVES, PREPARATION METHOD THEREOF AND USE OF SAME AS BETA-AMYLOID PEPTIDE PRODUCTION INHIBITORS

The subject of the invention is acylaminothiazole derivatives, their preparation and their therapeutic use.

The first subject of the invention is compounds corresponding to the general formula (I):



(I)

in which,

X represents an oxygen or sulphur atom;

R_1 represents a C_{1-10} alkyl group optionally substituted with a C_{3-7} cycloalkyl, a phenyl, a thienyl; or R_1 represents a C_{3-7} cycloalkyl, thienyl, pyridinyl or pyrimidinyl group;

the thienyl groups being optionally substituted with one to 3 C_{1-3} alkyl groups; the phenyl group being optionally substituted with one to 5 halogen atoms or C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} fluoroalkyl or C_{1-3} fluoroalkoxy groups;

R_2 represents a C_{1-6} alkyl group optionally substituted with a C_{3-7} cycloalkyl, phenyl, C_{1-3} alkoxy, hydroxyl

group; or R_2 represents a C_{3-7} cycloalkyl, piperidinyl, phenyl or pyridinyl group;

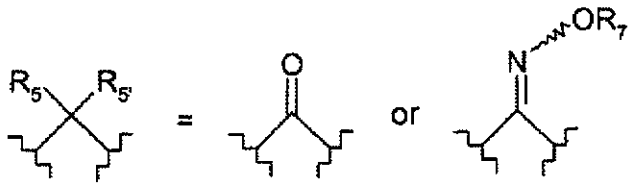
the C_{3-7} cycloalkyl and piperidinyl groups being optionally substituted with one or more C_{1-3} alkyl, C_{1-3} alkoxy, hydroxyl, C_{1-3} fluoroalkyl or C_{1-3} fluroalkoxy groups;

the phenyl and pyridinyl groups being optionally substituted with one or more halogen atoms or CN, C_{1-3} alkyl, C_{1-3} alkoxy, hydroxyl, C_{1-3} fluroalkyl or C_{1-3} fluoroalkoxy groups;

R_3 represents a hydrogen atom or a C_{1-6} alkyl group optionally substituted with a C_{3-7} cycloalkyl group;

R_4 represents a hydrogen atom or a C_{1-6} alkyl group;

R_5 and $R_{5'}$ represent, independently of each other, a hydrogen or halogen atom, a hydroxyl or C_{1-3} alkyl group; or R_5 and $R_{5'}$ form together an oxo or oxime group such as:



where R_7 represents a hydrogen atom or a C_{1-3} alkyl;

n represents an integer ranging from 0 to 3; and

R_6 represents independently of each other when n = 2 or 3, a hydrogen or halogen atom, a hydroxyl, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} fluoroalkyl or C_{1-3} fluoroalkoxy group.

Among the compounds of general formula (I), a sub-group of preferred compounds consists of the compounds for which:

- X represents an oxygen or sulphur atom; and/or
- R_1 represents a C_{1-5} alkyl group, preferably a methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl, propyl, 1-methylpropyl, 2-methylpropyl, 1-ethylpropyl, optionally substituted with a phenyl, a thienyl; or R_1 represents a C_{3-7} cycloalkyl group, preferably a cyclohexyl, a thienyl or pyridinyl group; the thienyl groups being optionally substituted with one or two C_{1-3} alkyl groups, preferably a methyl; the phenyl group being optionally substituted with one or two halogen atoms, preferably chlorine or fluorine; and/or
- R_2 represents a C_{1-6} alkyl group, preferably an ethyl, 1-methylethyl; or R_2 represents a C_{3-7} cycloalkyl group, preferably a cyclohexyl, phenyl or pyridinyl; the phenyl group being optionally substituted with one to three CN groups, C_{1-3} alkyl groups, preferably methyl or ethyl, C_{1-3} alkoxy groups, preferably methoxy, ethoxy or hydroxyl, fluoroalkoxy groups, preferably trifluoromethoxy, or halogen atoms, preferably chlorine or fluorine; and/or
- R_3 represents a C_{1-6} alkyl group, preferably a methyl, ethyl or propyl group; and/or
- R_4 represents a hydrogen atom or a C_{1-6} alkyl group,

preferably a methyl or a 4-methylpentyl; and/or

- R_5 and $R_{5'}$ represent, independently of each other, a hydrogen atom or a hydroxyl; or R_5 and $R_{5'}$ form together an oxo group; and/or
- R_6 represents a hydrogen or halogen atom, preferably chlorine or fluorine, a C_{1-3} alkyl, preferably a methyl, a C_{1-3} alkoxy, preferably a methoxy or an ethoxy; and/or
- n is equal to 0 or 1.

The compounds for which X, R_1, R_2, R_3, R_4, R_5, $R_{5'}$, R_6 and n are all as defined above in the subgroup of preferred compounds are particularly preferred and more specifically among these the compounds for which:
X represents an oxygen atom; and/or
the C_{1-4} alkylene group is a methylene; and/or
the carbon bearing the R_3 group is of (S) configuration.

By way of example of preferred compounds, the following compounds may be mentioned:

1. (2*S*)-2-{[(2*R*)-2-cyclohexyl-2-hydroxyacetyl]amino}-*N*-(5-{2-[(cyclohexyloxy)methyl]phenyl}-1,3-thiazol-2-yl)pentanamide
2. (2*S*)-2-{[(2*S*)-2-cyclohexyl-2-hydroxyacetyl]amino}-*N*-(5-{2-[(cyclohexyloxy)methyl]phenyl}-1,3-thiazol-2-yl)pentanamide
3. (2*S*)-*N*-(5-{2-[(cyclohexyloxy)methyl]phenyl}-1,3-thiazol-2-yl)-2-{[2-(3-pyridinyl)acetyl]-amino}pentanamide

4. *N*-((1*S*)-1-{[(5-{2-[(cyclohexyloxy)methyl]phenyl}-1,3-thiazol-2-yl)amino]carbonyl}butyl)-2-hydroxy-4-methylpentanamide

5. (2*S*)-*N*-{5-[2-(isopropoxymethyl)phenyl]-4-methyl-1,3-thiazol-2-yl}-2-{[2-(3-thienyl)acetyl]amino}-pentanamide

6. (2*S*)-*N*-{5-[2-(isopropoxymethyl)phenyl]-1,3-thiazol-2-yl}-2-{[2-(3-thienyl)acetyl]amino}-pentanamide

7. (2*S*)-*N*-{5-[2-(isopropoxymethyl)phenyl]-1,3-thiazol-2-yl}-2-{[3-(3-thienyl)propanoyl]amino}pentanamide

8. (2*S*)-*N*-{5-[2-(phenoxymethyl)phenyl]-1,3-thiazol-2-yl}-2-{[2-(3-thienyl)acetyl]amino}pentanamide

9. (2*S*)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]-amino}-*N*-{5-[2-(phenoxymethyl)phenyl]-1,3-thiazol-2-yl}pentanamide

10. (2*S*)-*N*-{5-[2-(phenoxymethyl)phenyl]-1,3-thiazol-2-yl}-2-{[2-(2-thienyl)acetyl]amino}butanamide

11. (2*S*)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]-amino}-*N*-{5-[2-(isopropoxymethyl)phenyl]-1,3-thiazol-2-yl}pentanamide

12. (2*S*)-*N*-{5-[2-(isopropoxymethyl)phenyl]-1,3-thiazol-2-yl}-2-{[2-(2-thienyl)acetyl]amino}-pentanamide

13. (2*S*)-2-[(3,3-dimethylbutanoyl)amino]-*N*-{5-[2-(isopropoxymethyl)phenyl]-1,3-thiazol-2-yl}-

pentanamide

14. *N*-{(1*S*)-1-[({5-[2-(isopropoxymethyl)phenyl]-1,3-thiazol-2-yl}amino)carbonyl]butyl}-3-methyl-2-oxopentanamide

15. (2*S*)-*N*-{5-[2-(ethoxymethyl)phenyl]-1,3-thiazol-2-yl}-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]-amino}pentanamide

16. (2*S*)-2-{[2-(2,5-dimethyl-3-thienyl)acetyl]amino}-*N*-{5-[2-(ethoxymethyl)phenyl]-1,3-thiazol-2-yl}pentanamide

17. (2*S*)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]-amino}-*N*-[5-(2-{[3-(trifluoromethoxy)phenoxy]-methyl}phenyl)-1,3-thiazol-2-yl]pentanamide

18. (2*S*)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]-amino}-*N*-{5-[4-methoxy-2-(phenoxymethyl)phenyl]-1,3-thiazol-2-yl}pentanamide

19. (2*S*)-*N*-(5-{2-[(2-fluorophenoxy)methyl]phenyl}-1,3-thiazol-2-yl)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]amino}pentanamide

20. (2*S*)-*N*-(5-{2-[(2-ethylphenoxy)methyl]phenyl}-1,3-thiazol-2-yl)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]amino}pentanamide

21. (2*S*)-2-{[3-(2,4-dichlorophenyl)propanoyl]amino}-*N*-{5-[2-(phenoxymethyl)phenyl]-1,3-thiazol-2-yl}pentanamide

22. (2*S*)-2-{[2-(5-methyl-2-thienyl)acetyl]amino}-*N*-{5-[2-(phenoxymethyl)phenyl]-1,3-thiazol-

2-yl}pentanamide

23. (2*S*)-*N*-(5-{2-[(2,3-dimethoxyphenoxy)methyl]-phenyl}-1,3-thiazol-2-yl)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]amino}pentanamide

24. (2*S*)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]-amino}-*N*-[5-(2-{[2-(trifluoromethoxy)phenoxy]-methyl}phenyl)-1,3-thiazol-2-yl]pentanamide

25. (2*S*)-*N*-(5-{2-[(3,5-dimethoxyphenoxy)methyl]-phenyl}-1,3-thiazol-2-yl)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]amino}pentanamide

26. (2*S*)-*N*-(5-{2-[(2,3-dimethylphenoxy)methyl]phenyl}-1,3-thiazol-2-yl)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]amino}pentanamide

27. (2*S*)-*N*-(5-{2-[(3,4-dimethylphenoxy)methyl]phenyl}-1,3-thiazol-2-yl)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]amino}pentanamide

28. (2*S*)-*N*-(5-{2-[(2,6-dimethylphenoxy)methyl]phenyl}-1,3-thiazol-2-yl)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]amino}pentanamide

29. (2*S*)-*N*-(5-{2-[(3-chlorophenoxy)methyl]phenyl}-1,3-thiazol-2-yl)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]amino}pentanamide

30. (2*S*)-*N*-(5-{2-[(3,4-dimethoxyphenoxy)methyl]-phenyl}-1,3-thiazol-2-yl)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]amino}pentanamide

31. (2*S*)-*N*-(5-{2-[(2,6-dimethoxyphenoxy)methyl]-phenyl}-1,3-thiazol-2-yl)-2-{[(2*S*)-2-hydroxy-

3,3-dimethylbutanoyl]amino}pentanamide

32. (2*S*)-*N*-(5-{2-[(2,4-dimethylphenoxy)methyl]phenyl}-1,3-thiazol-2-yl)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]amino}pentanamide

33. (2*S*)-*N*-(5-{2-[(2,5-dimethylphenoxy)methyl]phenyl}-1,3-thiazol-2-yl)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]amino}pentanamide

34. (2*S*)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]-amino}-*N*-{4-methyl-5-[2-(phenoxymethyl)phenyl]-1,3-thiazol-2-yl}pentanamide

35. (2*R*)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]-amino}-*N*-{5-[2-(phenoxymethyl)phenyl]-1,3-thiazol-2-yl}pentanamide

36. (2*S*)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]-amino}-*N*-(5-{2-[(2-methylphenoxy)methyl]phenyl}-1,3-thiazol-2-yl}pentanamide

37. (2*S*)-2-{[(2*S*)-2-hydroxy-3-methylbutanoyl]amino}-*N*-{5-[2-(phenoxymethyl)phenyl]-1,3-thiazol-2-yl}pentanamide

38. (2*S*)-2-[(2-hydroxy-3,3-dimethylbutanoyl)amino]-*N*-(5-{2-[(2-methoxyphenoxy)methyl]phenyl}-1,3-thiazol-2-yl}pentanamide

39. (2*S*)-*N*-(5-{2-[(2-ethoxyphenoxy)methyl]phenyl}-1,3-thiazol-2-yl)-2-[(2-hydroxy-3,3-dimethylbutanoyl)amino]pentanamide

40. (2*S*)-2-[(2-hydroxy-3-phenylpropanoyl)amino]-*N*-{5-[2-(phenoxymethyl)phenyl]-1,3-thiazol-

2-yl}pentanamide

41. (2*S*)-*N*-(5-{2-[(2,6-dichlorophenoxy)methyl]phenyl}-1,3-thiazol-2-yl)-2-[(2-hydroxy-3,3-dimethylbutanoyl)amino]pentanamide

42. (2*R*)-3-ethyl-2-hydroxy-*N*-{(1*S*)-1-[({5-[2-(phenoxymethyl)phenyl]-1,3-thiazol-2-yl}amino)-carbonyl]butyl}pentanamide

43. (2*S*)-3-ethyl-2-hydroxy-*N*-{(1*S*)-1-[({5-[2-(phenoxymethyl)phenyl]-1,3-thiazol-2-yl}amino)-carbonyl]butyl}pentanamide

44. (2*S*)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]-amino}-*N*-{5-[2-(isopropoxymethyl)-4-methoxyphenyl]-1,3-thiazol-2-yl}pentanamide

45. (2*S*)-*N*-(5-{2-[(2-(chloro-6-methylphenoxy)methyl]-phenyl}-1,3-thiazol-2-yl)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]amino}pentanamide

46. (2*S*)-*N*-(5-{2-[(2,6-difluorophenoxy)methyl]phenyl}-1,3-thiazol-2-yl)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]amino}pentanamide

47. (2*S*)-*N*-{5-[4-chloro-2-(phenoxymethyl)phenyl]-1,3-thiazol-2-yl}-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]amino}pentanamide

48. (2*S*)-*N*-{5-[4-fluoro-2-(phenoxymethyl)phenyl]-1,3-thiazol-2-yl}-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]amino}pentanamide

49. (2*S*)-2-{[(2*S*)-2-hydroxy-3-methylbutanoyl]amino}-*N*-{5-[4-methoxy-2-(phenoxymethyl)phenyl]-

1,3-thiazol-2-yl}pentanamide

50. (2*S*)-*N*-(5-{2-[(3,4-dichlorophenoxy)methyl]phenyl}-1,3-thiazol-2-yl)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]amino}pentanamide

51. (2*S*)-*N*-((1*S*)-1-{[(5-{2-[(cyclohexyloxy)methyl]-phenyl}-1,3-thiazol-2-yl)amino]carbonyl}butyl)-2-hydroxy-4-methylpentanamide

52. (2*S*)-*N*-{5-[4-ethoxy-2-(phenoxymethyl)phenyl]-1,3-thiazol-2-yl}-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]amino}pentanamide

53. (2*S*)-*N*-{5-[4-ethoxy-2-(phenoxymethyl)phenyl]-1,3-thiazol-2-yl}-2-{[(2*S*)-2-hydroxy-3-methylbutanoyl]amino}pentanamide

54. (2*S*)-*N*-{5-[5-fluoro-2-(phenoxymethyl)phenyl]-1,3-thiazol-2-yl}-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]amino}pentanamide

55. (2*S*)-*N*-{5-[5-chloro-2-(phenoxymethyl)phenyl]-1,3-thiazol-2-yl}-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]amino}pentanamide

56. (2*S*)-*N*-{5-[5-fluoro-2-(phenoxymethyl)phenyl]-1,3-thiazol-2-yl}-2-{[(2*S*)-2-hydroxy-3-methylbutanoyl]amino}pentanamide

57. (2*S*)-*N*-(5-{2-[(cyclohexyloxy)methyl]phenyl}-1,3-thiazol-2-yl)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]amino}pentanamide

58. (2*S*)-2-hydroxy-3,3-dimethyl-*N*-[(1*S*)-1-methyl-2-oxo-2-({5-[2-(phenoxymethyl)phenyl]-1,3-thiazol-

2-yl}amino)ethyl]butanamide

59. (2*S*)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]-amino}-*N*-{5-[4-methyl-2-(phenoxymethyl)phenyl]-1,3-thiazol-2-yl}pentanamide

60. (2*S*)-2-{[(2*S*)-2-hydroxy-3-methylbutanoyl]amino}-*N*-{5-[5-methyl-2-(phenoxymethyl)phenyl]-1,3-thiazol-2-yl}pentanamide

61. (2*S*)-*N*-(5-{2-[(3-cyanophenoxy)methyl]phenyl}-1,3-thiazol-2-yl)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]amino}pentanamide

62. (2*S*)-*N*-(5-{2-[(3-fluorophenoxy)methyl]phenyl}-1,3-thiazol-2-yl)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]amino}pentanamide

63. (2*S*)-*N*-(5-{2-[(3-fluorophenoxy)methyl]phenyl}-1,3-thiazol-2-yl)-2-{[(2*S*)-2-hydroxy-3-methylbutanoyl]amino}pentanamide

64. (2*S*)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]-amino}-*N*-{5-[5-methyl-2-(phenoxymethyl)phenyl]-1,3-thiazol-2-yl}pentanamide

65. (2*S*)-2-{[(2*S*)-2-hydroxy-3-methylbutanoyl]amino}-*N*-{5-[4-methyl-2-(phenoxymethyl)phenyl]-1,3-thiazol-2-yl}pentanamide

66. (2*S*)-*N*-{(1*S*)-2-[(5-{2-[(cyclohexyloxy)methyl]-phenyl}-1,3-thiazol-2-yl)amino]-1-methyl-2-oxoethyl}-2-hydroxy-3,3-dimethylbutanamide

67. (2*S*)-*N*-(5-{2-[(2-chloro-5-methylphenoxy)methyl]-phenyl}-1,3-thiazol-2-yl)-2-{[(2*S*)-2-hydroxy-

3,3-dimethylbutanoyl]amino}pentanamide

68. (2*S*)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]-amino}-*N*-(5-{2-[(3-methylphenoxy)methyl]phenyl}-1,3-thiazol-2-yl)pentanamide

69. (2*S*)-*N*-(5-{2-[(2-cyanophenoxy)methyl]phenyl}-1,3-thiazol-2-yl)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]amino}pentanamide

70. (2*S*)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]-amino}-*N*-(5-{2-[(4-pyridinyloxy)methyl]phenyl}-1,3-thiazol-2-yl)pentanamide

71. (2*S*)-*N*-(5-{2-[(2-chloro-4,5-dimethylphenoxy)-methyl]phenyl}-1,3-thiazol-2-yl)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]amino}pentanamide

72. (2*S*)-*N*-(5-{2-[(4-chloro-3-methylphenoxy)methyl]-phenyl}-1,3-thiazol-2-yl)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]amino}pentanamide

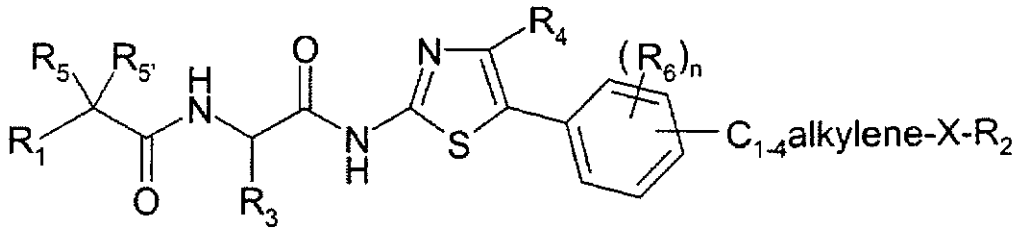
73. (2*S*)-*N*-(5-{2-[(2,3-dichlorophenoxy)methyl]phenyl}-1,3-thiazol-2-yl)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]amino}pentanamide

74. (2*S*)-*N*-(5-{2-[(2,3-difluorophenoxy)methyl]phenyl}-1,3-thiazol-2-yl)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]amino}pentanamide

75. (2*S*)-2-{[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]-amino}-*N*-{4-(4-methylpentyl)-5-[2-(phenoxymethyl)-phenyl]-1,3-thiazol-2-yl)pentanamide

The subject of the invention is also, among the compounds of general formula (I), compounds

corresponding to general formula (I'):



(I')

in which,

X represents an oxygen or sulphur atom;

R_1 represents a C_{1-10} alkyl group optionally substituted with a C_{3-7} cycloalkyl, a phenyl or a thienyl; or R_1 represents a C_{3-7} cycloalkyl, thienyl, pyridinyl or pyrimindinyl group;

the thienyl groups being optionally substituted with one to 3 C_{1-3} alkyl groups; the phenyl group being optionally substituted with one to 5 halogen atoms or C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} fluoroalkyl or C_{1-3} fluoroalkoxy groups;

R_2 represents a C_{1-6} alkyl group optionally substituted with a C_{3-7} cycloalkyl, phenyl, C_{1-3} alkoxy or hydroxyl group; or R_2 represents a C_{3-7} cycloalkyl, piperidinyl, phenyl or pyridinyl group;

the C_{3-7} cycloalkyl and piperidinyl groups being optionally substituted with one or more C_{1-3} alkyl, C_{1-3} alkoxy, hydroxyl, C_{1-3} fluoroalkyl or C_{1-3} fluoroalkoxy groups;

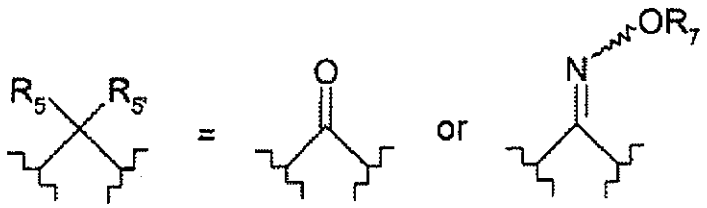
the phenyl and pyridinyl groups being optionally substituted with one or more halogen atoms or C_{1-3} alkyl, C_{1-3} alkoxy, hydroxyl, C_{1-3} fluoroalkyl or C_{1-3}

fluoroalkoxy groups;

R_3 represents a hydrogen atom or a C_{1-6} alkyl group optionally substituted with a C_{3-7} cycloalkyl group;

R_4 represents a hydrogen atom or a C_{1-4} alkyl group;

R_5 and $R_{5'}$ represent, independently of each other, a hydrogen or halogen atom, a hydroxyl or C_{1-3} alkyl group; or R_5 and $R_{5'}$ form together an oxo or oxime group such as:



where R_7 represents a hydrogen atom or a C_{1-3} alkyl;

n represents an integer ranging from 0 to 3; and

R_6 represents independently of each other when n = 2 or 3, a hydrogen or halogen atom, a hydroxyl, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} fluoroalkyl or C_{1-3} fluoroalkoxy group.

Among the compounds of general formula (I'), a sub-group of preferred compounds consists of the compounds for which:

- X represents an oxygen or sulphur atom; and/or
- R_1 represents a C_{1-5} alkyl group, preferably a methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl, propyl, 1-methylpropyl, 2-methylpropyl, 1-ethylpropyl, optionally substituted with a phenyl, a thienyl; or R_1 represents a C_{3-7} cycloalkyl group, preferably a cyclohexyl, a thienyl or pyridinyl group; the thienyl groups being optionally substituted with one or two

C_{1-3} alkyl groups, preferably a methyl; the phenyl group being optionally substituted with one or two halogen atoms, preferably chlorine or fluorine; and/or

- R_2 represents a C_{1-6} alkyl group, preferably an ethyl, 1-methylethyl; or R_2 represents a C_{3-7} cycloalkyl group, preferably a cyclohexyl or phenyl; the phenyl group being optionally substituted with 1 or 2 C_{1-3} alkyl groups, preferably methyl or ethyl, C_{1-3} alkoxy groups, preferably methoxy, ethoxy or hydroxyl, fluoroalkoxy groups, preferably trifluoromethoxy, or with one or two halogen atoms, preferably chlorine or fluorine; and/or
- R_3 represents a C_{1-6} alkyl group, preferably an ethyl or propyl; and/or
- R_4 represents a hydrogen atom or a C_{1-4} alkyl group, preferably a methyl; and/or
- R_5 and $R_{5'}$ represent, independently of each other, a hydrogen atom or a hydroxyl; or R_5 and $R_{5'}$ form together an oxo group; and/or
- R_6 represents a hydrogen or halogen atom, preferably a chlorine or a fluorine, a C_{1-3} alkoxy, preferably a methoxy; and/or
- n is equal to 0 or 1

In the context of the invention, the expression:

- C_{t-z} where t and z may take the values from 1 to 10,

is understood to mean a carbon chain which may have from t to z carbon atoms, for example C_{1-3} a carbon chain which may have from 1 to 3 carbon atoms, C_{3-6} a carbon chain which may have from 3 to 6 carbon atoms; and the like;

- alkyl is understood to mean a linear or branched saturated aliphatic group, for example a C_{1-6} alkyl group represents a linear or branched carbon chain of from 1 to 6 carbon atoms, more particularly a methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, and the like, preferably a methyl, ethyl, propyl or 1-methylethyl;
- alkylene is understood to mean a divalent alkyl group;
- cycloalkyl is understood to mean a cyclic alkyl group, for example a C_{3-7} cycloalkyl group represents a carbon cycle of from 3 to 7 carbon atoms, more particularly a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, preferably a cyclopentyl or cyclohexyl;
- alkoxy is understood to mean an -O-alkyl group where the alkyl group is as defined above;
- fluoroalkyl is understood to mean an alkyl group in which one or more hydrogen atoms have been substituted with a fluorine atom;
- fluoroalkoxy is understood to mean an alkoxy group in which one or more hydrogen atoms have been substituted

with a fluorine atom; and

- halogen atom is understood to mean a fluorine, a chlorine, a bromine or an iodine.

The compounds of general formula (I) may contain one or more asymmetric carbons. They may therefore exist in the form of enantiomers or of diastereoisomers. These enantiomers or diastereoisomers, and 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. Such addition salts form part of the invention. These salts are advantageously prepared with pharmaceutically acceptable acids, but the salts of other useful acids, for example, for the purification or the isolation of the compounds of formula (I), also form part of the invention.

The compounds of general formula (I) may exist in the form of hydrates or of solvates, namely in the form of associations or combinations with one or more molecules of water or with a solvent. Such hydrates and solvates also form part of the invention.

In the text which follows, the expression leaving group is understood to mean a group which can be easily cleaved from a molecule, with departure of an electron pair, by the breaking of a heterolytic bond. This group may thus be easily replaced by another group

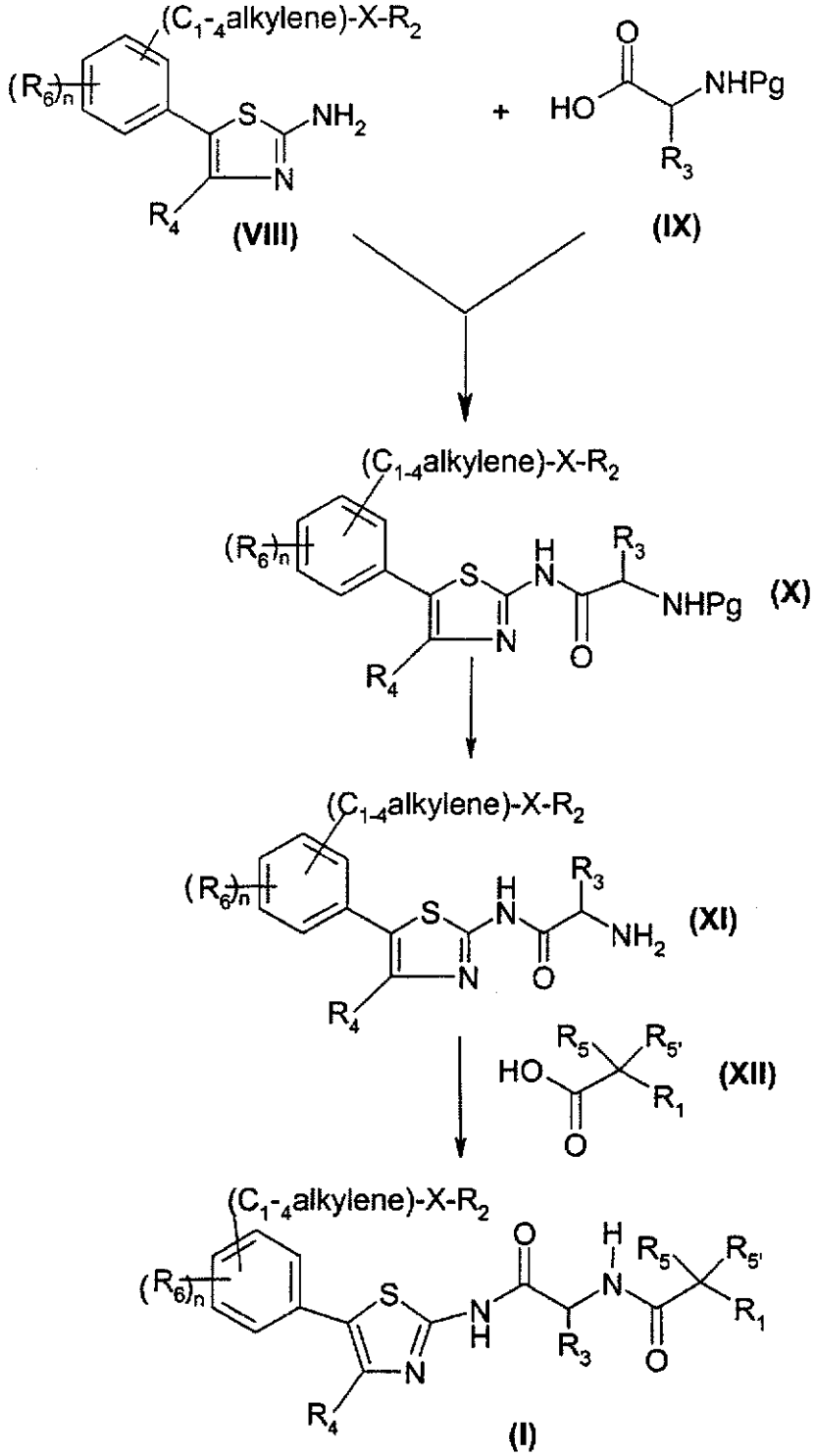
during a substitution reaction for example. Such leaving groups are, for example, halogens, or an activated hydroxyl group such as a mesylate, tosylate, triflate, acetyl and the like. Examples of leaving groups and references for their preparation are given in "Advanced Organic Chemistry", J. March, 3rd Edition, Wiley Interscience, p. 310-316.

The expression protecting group is understood to mean a group which makes it possible to prevent the reactivity of a functional group or a position, during a chemical reaction which may effect it, and which releases the molecule after cleavage according to methods known to persons skilled in the art. Examples of protecting groups and methods of protection and deprotection are given, inter alia, in *Protective groups in Organic Synthesis*, Greene et al., 2nd Ed. (John Wiley & Sons, Inc., New York).

The second subject of the invention is methods for preparing the compounds of formula (I).

Thus, these compounds may be prepared by methods, illustrated in the schemes which follow, whose operating conditions are conventional for persons skilled in the art.

Scheme 1

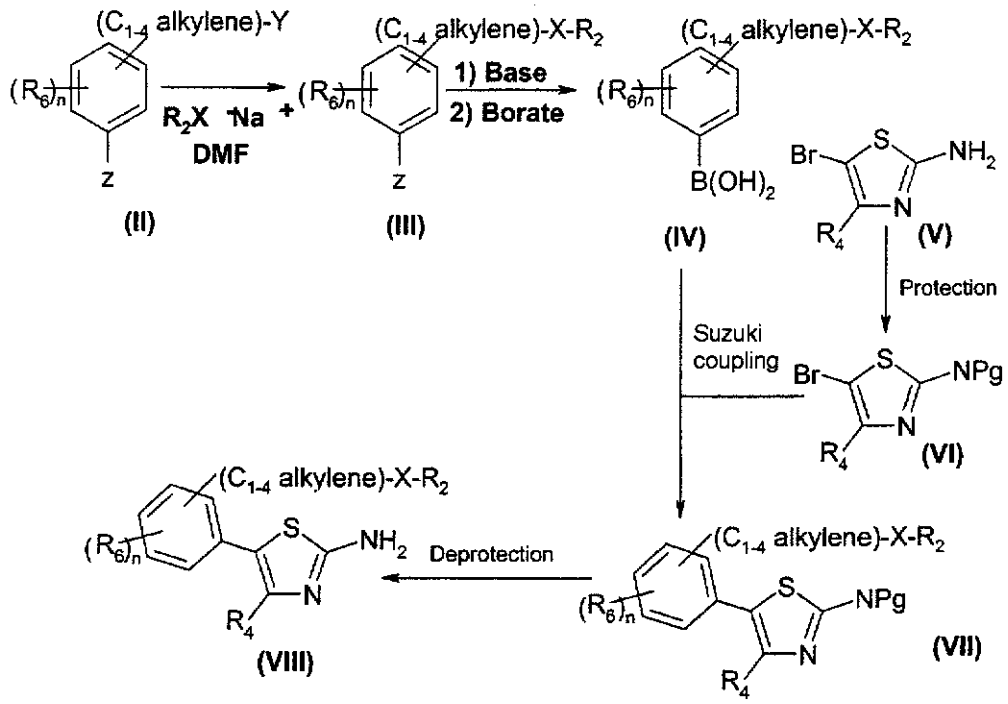

(C1-4alkylene)-X-R2
(R6)n
S
NH2
N
R4
(VIII)
+
HO
O
NHPg
R3
(IX)
(C1-4alkylene)-X-R2
H
N
R3
NHPg
(X)
(C1-4alkylene)-X-R2
NH2
(XI)
R5
R5'
R1
(XII)
(C1-4alkylene)-X-R2
(I)

According to Scheme 1, the compound of formula (I) may be obtained by peptide coupling of the amine of formula (XI) with the acid of formula (XII) according to conditions known to persons skilled in the art, for example in the presence of benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP) and *N*-ethylmorpholine or *N*-methylmorpholine in an inert solvent such as dimethylformamide, acetonitrile or dichloromethane at a temperature which may range from 0°C to room temperature.

The amine of formula (XI) is obtained by peptide coupling of the amine of formula (VIII) with the amino acid of formula (IX), in which Pg represents a protecting group, under conditions as described above, to give the compound of formula (X). The amino acid of formula (IX) is, for example, protected by means of an *N*-tert-butyloxycarbonyl (Boc). The compound (X) is then deprotected according to methods known to persons skilled in the art, to give the amine of formula (XI). For example, if the protecting group used is Boc, the latter may be deprotected by acid hydrolysis, in the presence of anhydrous gaseous hydrochloric acid.

The compound of formula (VIII) may be prepared according to Scheme 2.

Scheme 2



According to this scheme, the aralkyl of formula (II), in which Y represents a leaving group, preferably a halogen atom such as bromine and Z represents a halogen atom such as bromine, is condensed with an alkali metal thiolate or alcoholate, for example of formula $R_2X^- Na^+$ in which X represents an oxygen or sulphur atom. The reaction is carried out in an inert solvent such as dimethylformamide at a temperature which may range from 0°C to 50°C, to give the compound of formula (III). The aryl or formula (III) is converted to boronic acid of formula (IV) according to an adaptation of the method described by Schoevaars, J. Am. Chem. Soc., 1999, 121, 9550-9561. The conversion may, for example, be carried out by prior formation of the anion of the compound of

formula (III), for example by the action of a strong base such as butyllithium, in an ethereal solvent such as tetrahydrofuran, at temperatures which may range from -50°C to -80°C. This anion is then reacted with a borate such as trimethyl borate to give, after hydrolysis, the boronic acid of formula (IV).

The coupling of the boronic acid (IV) with the 5-bromothiazole of formula (VI) in which Pg represents a protecting group, such as an imino, for example a diphenyl ketone imine, may be carried out according to the Suzuki reaction, by adaptation of the method described by Wolfe, J. Org. Chem., 1997, 62, 4943-4948, to give the 5-phenylthiazole of formula (VII). The coupling is carried out, for example, in an ethereal solvent such as dioxane in the presence of tripotassium phosphate trihydrate and a catalyst such as tetrakis(triphenylphosphine)palladium (0) at a temperature which may range from room temperature to the reflux temperature of the solvent. The 5-phenylthiazole of formula (VII) thus prepared is then deprotected according to methods known to persons skilled in the art to generate the 5-phenyl-2-amino-thiazole of formula (VIII).

The 5-bromothiazole of formula (VI) is obtained by protecting the amino functional group of the corresponding compound of formula (V). Preferably, it is protected in the form of a diphenyl ketone imine

under conditions known to persons skilled in the art.

The starting compounds, in particular the compounds of formula (II), (V), (IX) and (XII) are commercially available or are described in the literature, or may be prepared by methods which are described therein or which are known to persons skilled in the art.

For example, 5-bromo-2-aminothiazole (V) may be obtained by bromination of the corresponding 2-amino-thiazole according to an adaptation of the method described by Kaye, J. Chem. Soc. Perkin I, 1981, 2335-2339.

For example, the compound of formula (XII) may be obtained by adaptation of the methods described by Middleton et al., J. Org. Chem., 45, 14, 1980, 2883-2887 and by Miyamoto et al., J. Amer. Chem. Soc., 114, 15, 1992, 6256-6257.

The meanings of X, R_1, R_2, R_3, R_4, R_5, $R_{5'}$, R_6 and n in the compounds of formula (II) to (XII) are as defined for the compounds of formula (I).

The following examples describe the preparation of some compounds in accordance with the invention. These examples are not limiting and only illustrate the invention. The exemplified compound numbers refer to those given in the Table below. The elemental microanalyses and the NMR, IR or mass spectra confirm the structure of the compounds obtained.

Example 1 (Compound No. 9)

(2S)-2-{[(2S)-2-hydroxy-3,3-dimethylbutanoyl]amino}-N-{5-[2-(phenoxymethyl)phenyl]-1,3-thiazol-2-yl}pentanamide

1.1 1-bromo-2-(phenoxymethyl)benzene

1.2 g of sodium hydride (at 50% in suspension in oil) are added at 5°C, in portions, to 20.2 g of phenol in solution in 150 ml of dimethylformamide. The mixture is stirred at room temperature and 37.2 g of 2-bromobenzyl bromide in solution in 15 ml of dimethylformamide are introduced at 5°C. After 2 hours at 20°C, the reaction medium is poured over ice-cold water and extracted with ethyl acetate. The organic phase is dried over anhydrous sodium sulphate and concentrated to give 36 g of oil.

^{1}H NMR: δ in ppm (DMSO d_6): 5.22 (s, 2H); 7.09-7.67 (unresolved complex, 9H).

1.2 2-(phenoxymethyl)phenylboronic acid

90 ml of n-butyllithium (1.6 M) in solution in hexane are added dropwise at -70°C to 36 g of 1-bromo-2-(phenoxymethyl)benzene, obtained in step 1.1, in solution in 150 ml of tetrahydrofuran. After 2 hours at -70°C, 16 ml of trimethyl borate are introduced dropwise. The temperature of the reaction medium is

allowed to rise to -30°C. The medium is hydrolysed with a saturated ammonium chloride solution, and then extracted with ethyl acetate and the organic phase is dried with anhydrous sodium sulphate. After evaporation, 33 g of a white solid are obtained.

^{1}H NMR: δ in ppm (DMSO d_6): 5.25 (s, 2H); 6.85-7.67 (unresolved complex, 11H).

1.3 5-bromo-N-(diphenylmethylene)-1,3-thiazol-2-amine

26 g of benzophenone imine are added to 34 g of 5-bromo-1,3-thiazol-2-amine hydrobromide, in suspension in 300 ml of 1,2-dichloroethane. The mixture is kept under reflux for 18 hours. The precipitate formed is filtered and the filtrate is concentrated to give 37.2 g of solid.

m.p. = 109°C

^{1}H NMR: δ in ppm (DMSO d_6): 7.34 (m, 2H); 7.50-7.76 (unresolved complex, 9H).

1.4 5-{2-[(phenoxy)methyl]phenyl}-N-(diphenylmethylene)-1,3-thiazol-2-amine

15 g of tripotassium phosphate dihydrate, 10.5 g of 5-bromo-N-(diphenylmethylene)-1,3-thiazol-2-amine, obtained in step 1.3, and 1.5 g of tetrakis(triphenylphosphine)palladium(0) are successively introduced into 14.8 g of 2-(phenoxymethyl)phenylboronic acid, obtained in step 1.2, in solution in 250 ml of 1,4-dioxane, and the

mixture is kept under reflux for 1 hour. The reaction medium is evaporated to dryness, the residue is taken up in ethyl acetate and washed with water. The organic phase is dried over anhydrous sodium sulphate and the solvates are concentrated. The residue is chromatographed on a silica gel column, eluting with dichloromethane to give 35 g of a yellow oil.

^{1}H NMR: δ in ppm: 4.81 (s, 2H); 7.17-7.83 (unresolved complex, 20H).

1.5 5-{2-[(phenoxy)methyl]phenyl}-1,3-thiazol-2-amine

150 ml of an aqueous hydrochloric acid solution (1 M) are added to 35 g of 5-{2-[(phenoxy)methyl]phenyl}-N-(diphenylmethylene)-1,3-thiazol-2-amine, obtained in step 1.4, in solution in 250 ml of methanol, and the mixture is stirred for 18 hours at 20°C. The mixture is evaporated to dryness, the residue is taken up in diethyl ether and washed with an aqueous sodium hydroxide solution (0.5 M). The organic phase is dried over anhydrous sodium sulphate and concentrated. The residue is chromatographed on a silica gel column, eluting with a dichloromethane/methanol 98/2 (v/v) mixture, to give 15 g of a beige solid.

m.p. = 154°C

^{1}H NMR: δ in ppm (DMSO d_6): 5.07 (s, 2H); 6.98-7.65 (unresolved complex, 10H).

1.6 *tert*-butyl (1S)-1-[({5-[2-(phenoxymethyl)phenyl]-1,3-thiazol-2-yl}amino)carbonyl]butylcarbamate

7.1 g of benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate are added at 0°C to 3.35 g of (2S)-2-[(*tert*-butyloxycarbonyl)amino]-pentanoic acid in solution in 35 ml of dimethylformamide, followed dropwise by 2.1 ml of N-methylmorpholine. After 15 minutes at 0°C, 4 g of 5-{2-[(phenoxy)methyl]phenyl}-1,3-thiazol-2-amine, obtained in step 1.5, are introduced and the mixture is stirred for 18 hours at room temperature. The medium is taken up in ethyl acetate and washed twice with water. The organic phase is dried over anhydrous sodium sulphate and concentrated. The residue is chromatographed on a silica gel column, eluting with a dichloromethane/methanol 98/2 (v/v) mixture to give 5.2 g of a colourless oil.

^{1}H NMR: δ in ppm (DMSO d_6): 0.88 (t, 3H); 1.22-1.65 (unresolved complex, 13H); 4.24 (q, 1H); 5.09 (s, 2H); 6.94-7.67 (unresolved complex, 10H); 12.23 (s, 1H).

1.7 (2S)-2-amino-N-(5-{2-[(phenoxy)methyl]phenyl}-1,3-thiazol-2-yl)pentanamide hydrochloride

25 ml of a solution of gaseous hydrochloric acid (4.5 M) in ethyl acetate are added dropwise at 0°C to 5 g of *tert*-butyl (1S)-2-[(5-{2-[(phenoxy)-

methyl]phenyl}-1,3-thiazol-2-yl)amino]-1-propyl-2-oxoethylcarbamate, obtained in step 1.6, in solution in 60 ml of ethyl acetate. The mixture is stirred for 18 hours at 20°C. The precipitate formed is filtered, rinsed twice with diethyl ether and dried to give 3 g of a white solid.

m.p. = 148°C

^{1}H NMR: δ in ppm (DMSO d_6): 0.90 (t, 3H); 1.39 (m, 2H); 1.85 (m, 2H); 4.18 (q, 1H); 5.08 (s, 2H); 6.94-7.68 (unresolved complex, 10H); 8.65 (s, 3H).

1.8 (2S)-2-{[(2S)-2-hydroxy-3,3-dimethylbutanoyl]amino}-N-{5-[2-phenoxymethyl)phenyl]-1,3-thiazol-2-yl}pentanamide

1.36 g of benzotriazol-1-yloxy-tripyrrolidinephosphonium hexafluorophosphate and 0.7 ml of N-ethylmorpholine are added successively at 0°C to 0.32 g of (2S)-2-hydroxy-3,3-dimethylbutanoic acid in solution in 25 ml of dimethylformamide. After 20 minutes at 0°C, 0.88 g of (2S)-2-amino-N-(5-{2-[(phenoxy)methyl]phenyl}-1,3-thiazol-2-yl)pentanamide hydrochloride, obtained in step 1.7, is introduced and the mixture is stirred for 18 hours at room temperature. The reaction medium is taken up in ethyl acetate and washed with water. The organic phase is dried over anhydrous sodium sulphate and concentrated. The residue is chromatographed on a silica gel column,

eluting with a dichloromethane/methanol 99/1 (v/v) mixture to give, after crystallization from isopropyl ether, 0.83 g of a white solid.

m.p. = 84°C

^{1}H NMR: δ in ppm (DMSO d_6): 0.89 (t, 3H); 0.93 (s, 9H); 1.33 (m, 2H); 1.71 (q, 21H); 3.57 (d, 1H); 4.61 (q, 1H); 5.09 (s, 2H); 5.61 (d, 1H); 6.97-7.02 (unresolved complex, 3H); 7.28-7.67 (unresolved complex, 7H); 7.81 (d, 1H); 12.28 (s, 1H).

$[\alpha]_D^{20}$ = -81.8 (c = 1/CH_3OH).

Example 2 (Compound No. 16)

(2S)-2-{[2-(2,5-dimethyl-3-thienyl)acetyl]amino}-*N*-{5-[2-(ethoxymethyl)phenyl]-1,3-thiazol-2-yl}pentanamide

2.1 2-(2,5-dimethyl-3-thienyl)-1-(4-morpholinyl)-1-ethanethione

1.68 g of sulphur and 6.5 ml of morpholine are added to 5 g of 2,5-dimethyl-3-acetylthiophene, and the mixture is heated under reflux for 10 hours. The mixture is brought to 20°C and poured over an aqueous hydrochloric acid solution (1N). The medium is extracted with ethyl acetate. The organic phase is dried over anhydrous sodium sulphate and it is concentrated. The residue is purified by chromatography on a silica gel column, eluting with a cyclohexane/-ethyl acetate 8/2 (v/v) mixture to give 6.8 g of an

orange-coloured oil.

^{1}H NMR: δ in ppm (DMSO d_6): 2.30 (2, 3H); 2.34 (s, 3H); 3.47 (t, 2H); 3.65 (m, 4H); 4.07 (s, 2H); 4.20 (t, 2H); 6.56 (s, 1H).

2.2 2-(2,5-Dimethyl-3-thienyl)acetic acid

2-(2,5-Dimethyl-3-thienyl)acetic acid is prepared according to a method described in Heterocycl. Chem; EN; 25; 1988; 1571-1581.

21 ml of an aqueous sodium hydroxide solution (50% by mass) are added to 6.7 g of 2-(2,5-dimethyl-3-thienyl)-1-(4-morpholinyl)-1-ethanethione obtained in step 2.1, in solution in 70 ml of methanol, and the mixture is heated for 6 hours under reflux. After evaporation of the methanol, the residue is diluted with water and acidified with an aqueous hydrochloric acid solution (6N). The precipitate formed is filtered and then it is chromatographed on a silica gel column, eluting with dichloromethane to give 3.6 g of beige crystals.

m.p. = 65°C

^{1}H NMR: δ in ppm (DMSO d_6): 2.26 (s, 3H); 2.34 (s, 3H); 3.39 (s, 2H); 6.56 (s, 1H).

2.3 (2S)-2-{[(2,5-Dimethyl-3-thienyl)acetyl]amino}-*N*-{5-[2-(ethoxymethyl)phenyl]-1,3-thiazol-2-yl}pentanamide

The procedure is carried out in the same manner as in step 1.8 of Example 1, replacing (2S)-2-hydroxy-3,3-dimethylbyutanoic acid with 2-(2,5-dimethyl-3-thienyl)acetic acid, obtained in step 2.2. 0.67 g of white crystals is obtained.

m.p. = 84°C

^{1}H NMR: δ in ppm (DMSO d_6): 0.89 (t, 3H); 1.16 (t, 3H); 1.29 (m, 2H); 1.65 (m, 2H); 2.25 (s, 3H); 2.30 (s, 3H); 3.33 (m, 2H); 3.47 (q, 2H); 4.44 (s, 2H); 4.49 (q, 1H); 4.55 (s, 1H); 7.35-7.55 (unresolved complex, 5H); 8.32 (d, 1H); 12.28 (s, 1H).

$[\alpha]_D^{20}$ = -103 (c = 1/CH_3OH).

Example 3 (Compound No. 22)

(2S)-2-{[2-(5-Methyl-2-thienyl)acetyl]amino}-*N*-{5-[2-(phenoxymethyl)phenyl]-1,3-thiazol-2-yl}pentanamide

3.1 2-(5-Methyl-2-thienyl)-1-(4-morpholinyl)-1-ethanethione

2-(5-Methyl-2-thienyl)-1-(4-morpholinyl)-4-ethanethione is prepared according to a method similar to that described in Example 2.1.

^{1}H NMR: δ in ppm (DMSO d_6): 2.40 (s, 3H); 3.49 (t, 2H); 3.64 (t, 2H); 3.81 (t, 2H); 4.19 (t, 2H); 4.40 (s, 2H);

6.49 (d, 1H); 6.77 (d, 1H).

3.2 2-(5-Methyl-2-thienyl)acetic acid

2-(5-Methyl-2-thienyl)acetic acid is prepared according to a method similar to that described in Example 2.2.

m.p. = 54°C

^{1}H NMR: δ in ppm (DMSO d_6): 2.38 (s, 3H); 3.72 (s, 3H); 6.61 (d, 1H); 6.69 (d, 1H).

3.3 (2S)-2-{[2-(5-Methyl-2-thienyl)acetyl]amino}-*N*-{5-[2-(phenoxymethyl)phenyl]-1,3-thiazol-2-yl}pentanamide

The procedure is carried out in the same manner as in step 1.8 of Example 1, replacing (2S)-2-hydroxy-3,3-dimethylbutanoic acid with 2-(5-methyl-2-thienyl)acetic acid, obtained in step 3.2. 0.73 g of beige crystals is obtained.

m.p. = 81°C

^{1}H NMR: δ in ppm (DMSO d_6): 0.87 (t, 3H); 1.32 (m, 2H); 1.64 (m, 2H); 2.36 (s, 3H); 3.62 (q, 2H); 4.48 (q, 1H); 5.07 (s, 2H); 6.59 (d, 1H); 6.67 (d, 1H); 6.95-7 (unresolved complex, 3H); 7.27-7.73 (unresolved complex, 7H); 8.41 (d, 1H); 12.30 (s, 1H).

$[\alpha]_D^{20}$ = -91.7 (c = 1/CH_3OH).

Example 4 (Compound No. 7)

(2S)-*N*-{5-[2-(Isopropoxymethyl)phenyl]-1,3-thiazol-2-yl}-2-{[3-(3-thienyl)propanoyl]amino}pentanamide

4.1 (*E*)-3-(3-Thienyl)-2-propenoic acid

46 g of malonic acid and 2 ml of piperidine are added to 25 g of 3-thienaldehyde in solution in 100 ml of pyridine, and the mixture is heated at 100°C for 4 hours. The reaction medium is cooled to 30°C and it is poured over an aqueous hydrochloric acid solution (2N). The precipitate formed is filtered and it is rinsed with isopropyl ether to give, after drying, 30 g of a white solid.

m.p. = 152°C

^{1}H NMR: δ in ppm (DMSO d_6): 6.36 (d, 1H); 7.51-7.62 (unresolved complex, 3H); 7.93 (d, 1H); 12.27 (s, 1H).

4.2 Ethyl (*E*)-3-(3-thienyl)-2-propenoate

11.5 g of potassium carbonate and 6.8 ml of iodoethane are added to 11 g of (*E*)-3-(3-thienyl)-2-propenoic acid, obtained in step 4.1, in solution in 50 ml of dimethylformamide, and the mixture is stirred for 48 hours at 20°C. The medium is taken up in ethyl acetate and it is washed with water. The organic phase is dried over anhydrous sodium sulphate and it is concentrated to give 12.5 g of oil.

^{1}H NMR: δ in ppm (DMSO d_6): 1.26 (t, 3H); 4.17 (q, 2H); 6.47 (d, 1H); 7.57-7.71 (unresolved complex, 3H); 8.01

(d, 1H).

4.3 Ethyl 3-(3-thienyl)-2-propanoate

4 g of 10% palladium on carbon are added to 12.5 g of ethyl (*E*)-3-(3-thienyl)-2-propenoate, obtained in step 4.2, in solution in 100 ml of ethanol, and the mixture is stirred for 24 hours at 60°C under 5 bar of hydrogen. The catalyst is filtered and the filtrate is concentrated to give 11 g of oil.

^{1}H NMR: δ in ppm (DMSO d_6): 1.20 (t, 3H); 2.62 (t, 2H); 2.88 (t, 2H); 4.07 (q, 2H); 7.02 (d, 1H); 7.18 (m, 1H); 7.45 (m, 1H).

4.4 3-(3-Thienyl)propanoic acid

75 ml of an aqueous sodium hydroxide solution (2N) are added to 11 g of ethyl 3-(3-thienyl)-2-propanoate, obtained in step 4.3, in solution in 100 ml of ethanol. The mixture is stirred for 18 hours at 20°C. After evaporation of the solvents, the residue is acidified. The precipitate formed is filtered and dried under vacuum to give 6.3 g of a beige solid.

m.p. = 59°C

^{1}H NMR: δ in ppm (DMSO d_6): 2.56 (t, 2H); 2.85 (t, 2H); 7.02 (t, 1H); 7.18 (s, 1H); 7.45 (m, 1H); 12.14 (s, 1H).

4.5 (2S)-*N*-{5-[2-Isopropoxymethyl)phenyl]-1,3-thiazol-

2-yl}-2-{[3-(3-thienyl)propanoyl]amino}pentanamide

The procedure is carried out in the same manner as in step 1.8 of Example 1, replacing (2S)-2-hydroxy-3,3-dimethylbutanoic acid with 3-(3-thienyl)-propanoic acid, obtained in step 4.4. 0.75 g of beige crystals is obtained.

m.p. = 101°C

^{1}H NMR: δ in ppm (DMSO d_6): 0.87 (t, 3H); 1.13 (d, 6H); 1.33 (m, 2H); 1.62 (m, 2H); 2.48 (t, 2H); 2.82 (t, 2H); 3.67 (m, 1H); 4.45 (s, 2H); 4.54 (q, 1H); 6.98 (d, 1H); 7.12 (d, 1H); 7.35-7.57 (unresolved complex, 6H); 8.21 (d, 1H); 12.26 (s, 1H).

$[\alpha]_D^{20}$ = -71 (c = 1/CH_3OH).

Example 5

(2*R*)-3-Ethyl-2-hydroxy-*N*-{(1S)-1-[({5-[2-(phenoxymethyl)phenyl]-1,3-thiazol-2-yl}amino)carbonyl]butyl}-pentanamide (Compound No. 42) and

(2S)-3-Ethyl-2-hydroxy-*N*-{(1S)-1-[({5-[2-(phenoxymethyl)phenyl]-1,3-thiazol-2-yl}amino)carbonyl]butyl}-pentanamide (Compound No. 43)

5.1 3-Ethyl-2-hydroxypentanoic acid

1.5 ml of trimethylsilyl cyanide are carefully added to a solution of 1.24 ml of 2-ethyl-butyraldehyde in 18 ml of anhydrous dichloromethane, followed by a catalytic quantity of zinc iodide. The

reaction medium is stirred for 2 hours at room temperature and then at 60°C for 3.5 hours. The reaction medium is cooled to 0°C and 3.5 ml of concentrated hydrochloric acid are added. The reaction medium is stirred for 18 hours at room temperature and then for 1 hour under reflux. After cooling, the reaction mixture is poured into water and extracted twice with 50 ml of ethyl acetate. The combined organic phases are extracted with 100 ml of sodium hydroxide (7.5N) at 4°C. After separation, the aqueous phase is washed with 3 times 50 ml of ethyl acetate. The aqueous phase is acidified with 70 ml of hydrochloric acid (12N) and extracted with 3 times 50 ml of ethyl acetate. The pooled organic phases are dried and the solvent is evaporated.

m.p. = 84°C

5.2 (2*R*)-3-Ethyl-2-hydroxy-*N*-{(1S)-1-[({5-[2-(phenoxymethyl)phenyl]-1,3-thiazol-2-yl}amino)carbonyl]butyl}pentanamide and (2S)-3-ethyl-2-hydroxy-*N*-{(1S)-1-[({5-[2-(phenoxymethyl)phenyl]-1,3-thiazol-2-yl}amino)carbonyl]butyl}pentanamide

The procedure is carried out in the same manner as in step 1.8 of Example 1, replacing (2S)-2-hydroxy-3,3-dimethylbutanoic acid with 3-ethyl-2-hydroxypentanoic acid, obtained in step 5.1. 0.78 g of white solid is obtained.

Compound No. 42 (SR):

m.p. = 67.4°C

^{1}H NMR: δ in ppm (DMSO d_6): 0.74 (t, 3H); 0.84-0.90 (unresolved complex, 6H); 1.26-1.71 (unresolved complex, 9H); 3.94 (m, 1H); 4.57 (q, 1H); 5.07 (s, 2H); 5.40 (s, 1H); 6.94-6.99 (unresolved complex, 3H); 7.26-7.93 (unresolved complex, 7H); 7.91 (d, 1H); 12.27 (s, 1H).

$[\alpha]_D^{20}$ = -41.5 (c = 1/CH_3OH).

Compound No. 43 (SS):

m.p. = 122.5°C

^{1}H NMR: δ in ppm (DMSO d_6): 0.78-0.89 (unresolved complex, 9H); 1.18-1.38 (unresolved complex, 6H); 1.55 (m, 1H); 1.68 (q, 2H); 3.92 (m, 1H); 4.60 (q, 1H); 5.07 (s, 2H); 5.49 (d, 1H); 6.95-7 (unresolved complex, 3H); 7.26-7.62 (unresolved complex, 7H); 7.87 (d, 1H); 12.27 (s, 1H).

$[\alpha]_D^{20}$ = -72.6 (c = 1/CH_3OH).

Example 6 (Compound No. 40)

(2S)-2-[(2-Hydroxy-3-phenylpropanoyl)amino]-*N*-{5-[2-(phenoxymethyl)phenyl]-1,3-thiazol-2-yl}pentanamide

6.1 3-Phenyl-2-hydroxypropionic acid

A solution of 0.829 g of sodium nitrite in 4.2 ml of water is added dropwise at 0°C to a

suspension of 1.6 g of phenylalanine in 5.3 ml of sulphuric acid (2.5N). The reaction mixture is stirred for 2 hours at 0°C and then for 17 hours at room temperature. The reaction mixture is extracted with twice 100 ml of ethyl acetate. The pooled organic phases are washed with 100 ml of a saturated sodium chloride solution in water. 1.2 g of yellow crystals are obtained after drying.

m.p. = 97°C

6.2 2-[(2-Hydroxy-3-phenylpropanoyl)amino]-*N*-{5-[2-(phenoxymethyl)phenyl]-1,3-thiazol-2-yl}pentanamide

The procedure is carried out in the same manner as in step 1.8 of Example 1, replacing (2S)-2-hydroxy-3,3-dimethylbutanoic acid with 3-phenyl-2-hydroxypropionic acid, obtained in step 6.1. 0.8 g of white solid is obtained.

m.p. = 86°C

^{1}H NMR: δ in ppm (DMSO d_6): 0.85 (t, 3H); 1.24 (m, 2H); 1.63 (m, 2H); 2.70 (m, 1H); 2.57 (m, 1H); 4.17 (m, 1H); 4.56 (q, 1H); 5.08 (s, 2H); 6.94-7.63 (unresolved complex, 15H); 8.02 (m, 1H); 12.25 (s, 1H).

$[\alpha]_D^{20}$ = -28 (c = 1/CH_3OH).

Example 7 (Compound No. 70)

(2S)-2-{[(2S)-2-Hydroxy-3,3-dimethylbutanoyl]amino}-N-(5-{2-[(4-pyridinyloxy)methyl]phenyl}-1,3-thiazol-2-

yl)pentanamide

7.1 2-(2-Amino-1,3-thiazol-5-yl)phenylmethanol

70 ml of a 3M aqueous hydrochloric acid solution are added to 29.86 g of 5-[2-(*tert*-butoxymethyl)phenyl]-*N*-diphenylmethylene)-1,3-thiazol-2-amine, prepared according to a method similar to that described in steps 1.1 to 1.4 of Example 1, in solution in 140 ml of methanol, and the mixture is kept at room temperature for 18 hours and then heated under reflux for 4 hours. The methanol is evaporated. The residue is taken up in a 6M aqueous hydrochloric acid solution and extracted with diethyl ether. The aqueous phase is brought to a basic pH while cooling it, and it is extracted with ethyl acetate. The ethyl acetate phase is dried over anhydrous sodium sulphate and concentrated. The residue is concreted with diisopropyl ether to give 6 g of a beige solid.

m.p. = 145°C

7.2 *tert*-Butyl 5-[2-(hydroxymethyl)phenyl]-1,3-thiazol-2-ylcarbamate

1.17 g of magnesium oxide and 29 ml of a 2M aqueous sodium hydroxide solution are added successively to 6 g of 2-(2-amino-1,3-thiazol-5-yl)-phenylmethanol, obtained in step 7.1, in solution in 80 ml of 1,4-dioxane, followed at 0°C, in portions, by

7.6 g of di-tert-butyl dicarbonate (BOC_2O). The mixture is left for 48 hours at room temperature, and then the medium is concentrated, it is taken up in water and it is extracted with ethyl acetate. The organic phase is washed with a 5% potassium hydrogen sulphate solution, it is dried over anhydrous sodium sulphate and it is concentrated. The residue is chromatographed on a silica gel column, eluting with a dichloromethane/methanol 99/1 (V/V) mixture to give 2.3 g of oil which is concreted with diisopropyl ether.

m.p. = 180.7°C

7.3 *tert*-Butyl 5-{2-[(4-pyridinyloxy)methyl]phenyl}-1,3-thiazol-2-ylcarbamate

4.15 g of diisopropyl azodicarboxylate (DIAD) are added, in portions at 0°C, to 5.24 g of triphenylphosphine in solution in 60 ml of tetrahydrofuran. After 30 minutes at about 10°C, 1.96 g of 4-hydroxypyridine are added in portions, the mixture is left for 30 minutes at about 10°C and 4.2 g of *tert*-butyl 5-[2-(hydroxymethyl)phenyl]-1,3-thiazol-2-ylcarbamate, obtained in step 7.2, are introduced. The mixture is left for 4 days at room temperature. The medium is concentrated, it is taken up in a saturated sodium carbonate solution and extracted with dichloromethane. The organic phase is dried over anhydrous sodium sulphate and it is concentrated. The residue is

chromatographed on a silica gel column, eluting with a mixture of increasing polarity dichloromethane/methanol 99/1 (V/V) up to dichloromethane/methanol 90/10 (V/V) to give 1 g of oil.

^{1}H NMR: δ in ppm (DMSO d6): 1.52 (s, 9H); 5.27 (s, 2H); 6.10 (q, 2H); 7.05 (m, 1H); 7.41-7.54 (unresolved complex, 6H); 11.60 (s, 1H).

7.4 5-{2-[(4-Pryidinyloxy)methyl]phenyl}-1,3-thiazolamine

20 ml of a 4M gaseous hydrochloric acid solution in ethyl acetate are added to 1 g of *tert*-butyl 5-{2-[(4-pyridinyloxy)methyl]phenyl}-1,3-thiazol-2-ylcarbamate, obtained in step 7.3, in 20 ml of dichloromethane. The mixture is left for 4 hours at room temperature. The reaction medium is concentrated and it is brought to a basic pH with a 5% sodium hydrogen sulphate solution. The precipitate formed is filtered and chromatographed on a silica gel column, eluting with a dichloromethane/methanol 95/5 (V/V) mixture to give 0.58 g of a beige foam.

^{1}H NMR: δ in ppm (DMSO d6): 5.25 (s, 2H); 6.10 (d, 2H); 6.98-7.55 (unresolved complex, 9H)

7.5 (2S)-2-{[(2S)-2-hydroxy-3,3-dimethylbutanoyl]-amino}-*N*-(5-{2-[(4-pyridinyloxy)methyl]phenyl}-1,3-thiazol-2-yl)pentanamide

The procedure is carried out in the same manner as in steps 1.6 to 1.8 of Example 1, replacing 5-{2-[(phenoxy)methyl]phenyl}-1,3-thiazol-2-amine with 5-{2-[(4-pyridinyloxy)methyl]phenyl}-1,3-thiazolamine, obtained in step 7.4.

0.4 g is obtained in the form of crystals.

m.p. = 112.7°C

^{1}H NMR: δ in ppm (DMSO d6): 0.89 (t, 3H); 0.92 (s, 9H); 1.34 (m, 2H); 1.68 (q, 2H); 3.58 (d, 1H); 4.61 (q, 1H); 5.24 (s, 2H); 5.61 (d, 1H); 6.09 (d, 2H); 7.04 (m, 1H); 7.41-7.53 (unresolved complex, 6H); 7.80 (d, 1H); 12.36 (s, 1H).

Compounds No. 61 ((2S)-*N*-(5-{2-[(3-cyanophenoxy)methyl]phenyl}-1,3-thiazol-2-yl)-2-{[(2S)-2-hydroxy-3,3-dimethylbutanoyl]amino}pentanamide) and No. 69 ((2S)-*N*-(5-{2-[(2-cyanophenoxy)methyl]phenyl}-1,3-thiazol-2-yl)-2-{[(2S)-2-hydroxy-3,3-dimethylbutanoyl]amino}pentanamide) may be prepared according to the method described in Example 7, replacing 4-hydroxypyridine with 3-cyanophenol or 2-cyanophenol, respectively.

The following table illustrates the chemical structures and the physical properties of a few of the compounds of the invention.

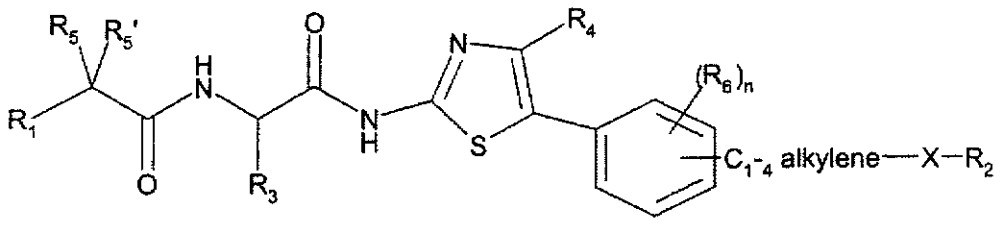
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- m.p. (°C) represents the melting point of the compound in degrees Celsius;

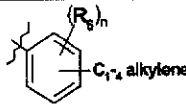
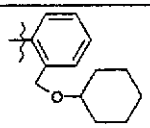
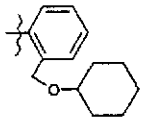
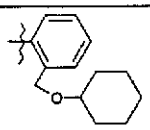
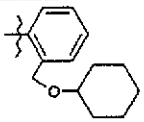
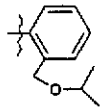
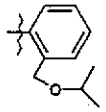
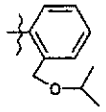
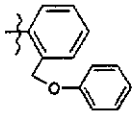
- $[\alpha_D]$ (c = 1, CH_3OH) represents the optical rotation of the compound at the concentration of 1 g/l in methanol;
- (S) or (R) in columns "R_3" and "R_5, $R_{5'}$" indicate the stereochemistry of the asymmetric carbons, carrying R_3 or R_5 respectively, in formula (I). For the carbon carrying R_5, the indication (S) or (R) does not relate to the case where R_5 and $R_{5'}$ form together an oxo or amine group.

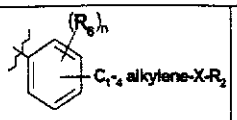
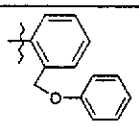
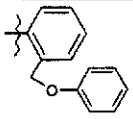
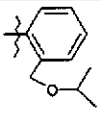
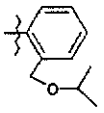
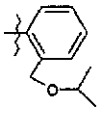
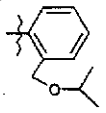
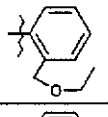
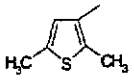
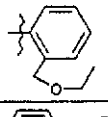
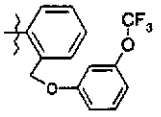
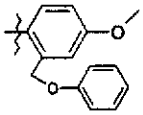
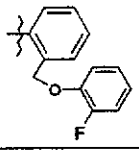
The compounds described in this table were prepared according to the methods described above.

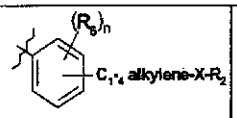
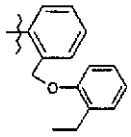
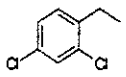
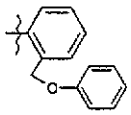
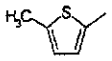
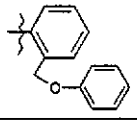
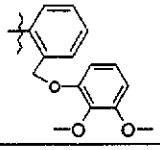
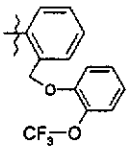
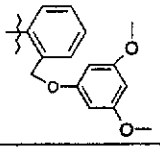
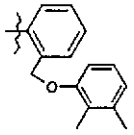
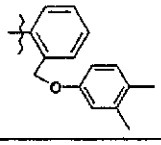
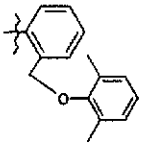
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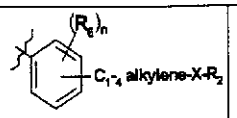
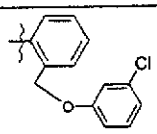
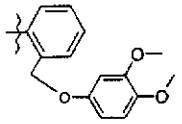
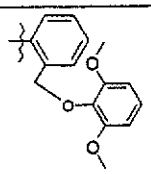
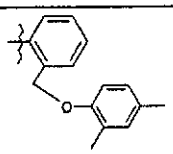
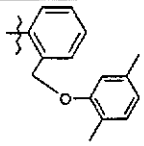
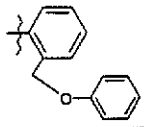
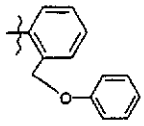
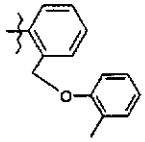
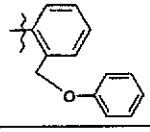


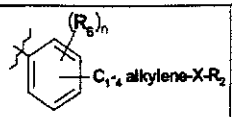
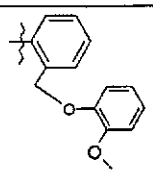
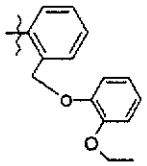
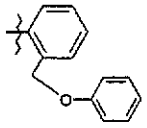
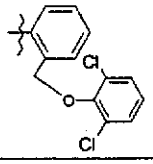
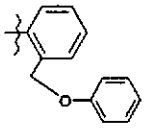
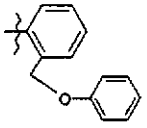
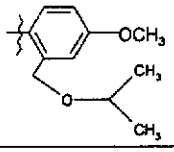
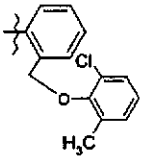
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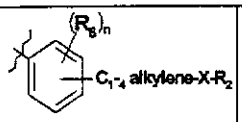
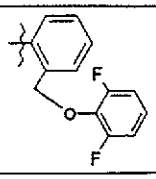
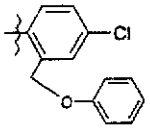
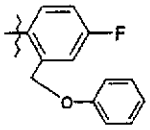
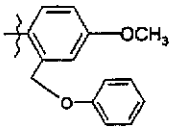
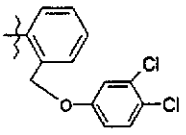
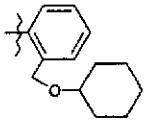
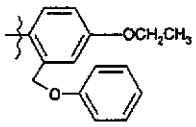
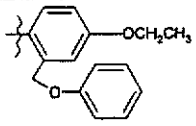
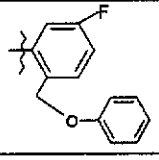
N°	R_1	R_3	R_4	R_5, $R_{5'}$		m.p. (°C)	$[\alpha_D]$ (c=1, CH_3OH)
1.		$CH_3(CH_2)_2$- (S)	H	OH, H (R)		120.5	-51
2.		$CH_3(CH_2)_2$- (S)	H	OH, H (S)		106	-81.8
3.		$CH_3(CH_2)_2$- (S)	H	H, H		110	-109.5
4.	$(CH_3)_2CHCH_2$-	$CH_3(CH_2)_2$- (S)	H	OH, H		85	-62.9
5.		$CH_3(CH_2)_2$- (S)	CH_3-	H, H		72	-65
6.		$CH_3(CH_2)_2$- (S)	H	H, H		51	-89
7.		$CH_3(CH_2)_2$- (S)	H	H, H		101	-71
8.		$CH_3(CH_2)_2$- (S)	H	H, H		74	-78.9

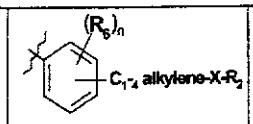
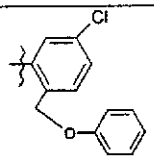
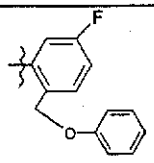
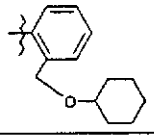
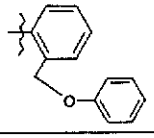
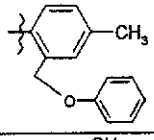
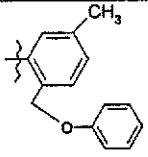
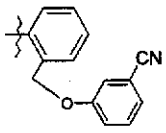
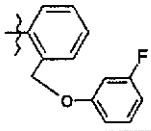
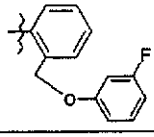
N°	R_1	R_3	R_4	R_5, $R_{5'}$		m.p. (°C)	$[\alpha_D]$ (c=1, CH_3OH)
9.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		84	-81.8
10.		CH_3CH_2- (S)	H	H, H		76.5	-100.2
11.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		63	-87
12.		$CH_3(CH_2)_2$- (S)	H	H, H		62	-88
13.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	H, H		77	-81
14.	$(CH_3CH_2)(CH_3)CH$-	$CH_3(CH_2)_2$- (S)	H	=O		112	-66
15.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		148	-87
16.		$CH_3(CH_2)_2$- (S)	H	H, H		84	-103
17.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		114	-75
18.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		117	-78.3
19.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		92	-77.7

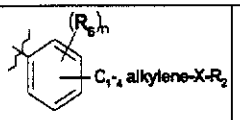
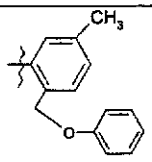
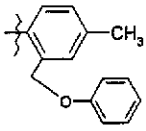
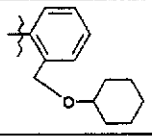
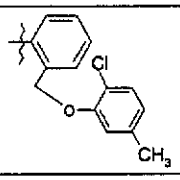
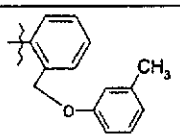
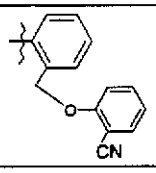
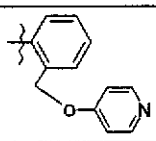
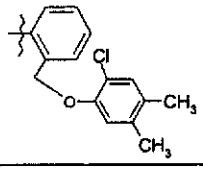
N°	R_1	R_3	R_4	R_5, $R_{5'}$		m.p. (°C)	$[\alpha_D]$ (c=1, CH_3OH)
20.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		107	-88.7
21.		$CH_3(CH_2)_2$- (S)	H	H, H		82	-31.3
22.		$CH_3(CH_2)_2$- (S)	H	H, H		81	-91.7
23.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		99	-71
24.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		66	-64.4
25.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		66.5	-65.4
26.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		88	-80.6
27.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		89	-74.6
28.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		87	-81.7

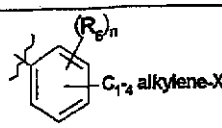
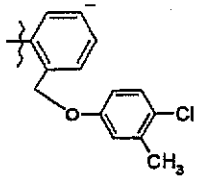
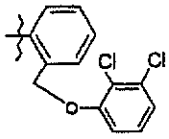
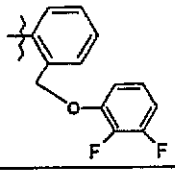
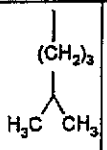
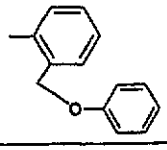
N°	R_1	R_3	R_4	R_5, $R_{5'}$		m.p. (°C)	$[\alpha_D]$ (c=1, CH_3OH)
29.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		169	-83.5
30.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		81.5	-63
31.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		69.5	-63.2
32.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		86	-70.5
33.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		87	-75.4
34.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	CH_3-	OH, H (S)		99	-74.4
35.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (R)	H	OH, H (S)		78.5	+46.7
36.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		96.5	-66.7
37.	$(CH_3)_2CH$-	$CH_3(CH_2)_2$- (S)	H	OH, H (R)		141	-59.6

N°	R_1	R_3	R_4	R_5, $R_{5'}$		m.p. (°C)	$[\alpha_D]$ (c=1, CH_3OH)
38.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		85	-78
39.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (R)		88	-74.4
40.		$CH_3(CH_2)_2$- (S)	H	OH, H		86	-28
41.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H		126	-62.5
42.	$(CH_3CH_2)_2CH$-	$CH_3(CH_2)_2$- (S)	H	OH, H (R)		67.5	-41.5
43.	$(CH_3CH_2)_2CH$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		122.5	-72.6
44.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		79	-77.9
45.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		96	-67.3

N°	R_1	R_3	R_4	R_5, $R_{5'}$		m.p. (°C)	$[\alpha_D]$ (c=1, CH_3OH)
46.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		63.5	-75
47.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		93.5	-80.5
48.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		75.5	-75.3
49.	$(CH_3)_2CH$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		159.5	-67.8
50.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		-	-72.1
51.	$(CH_3)_2CHCH_2$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		158	-70.2
52.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		81	-75.8
53.	$(CH_3)_2CH$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		107.8	-66.7
54.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		105.4	-78.4

N°	R_1	R_3	R_4	R_5, $R_{5'}$		m.p. (°C)	$[\alpha_D]$ (c=1, CH_3OH)
55.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		120.7	-77.2
56.	$(CH_3)_2CH$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		61.4	-48.6
57.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		88	-84.9
58.	$(CH_3)_3C$-	CH_3- (S)	H	OH, H (S)		118.6	-106.9
59.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		92.6	-88.5
60.	$(CH_3)_2CH$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		125.5	-85
61.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		162.6	-104.5
62.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		160.2	-71.5
63.	$(CH_3)_2CH$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		130.7	-71.6

N°	R_1	R_3	R_4	R_5, $R_{5'}$		m.p. (°C)	$[\alpha_D]$ (c=1, CH_3OH)
64.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		170	-78.4
65.	$(CH_3)_2CH$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		135.5	-72.2
66.	$(CH_3)_3C$-	CH_3- (S)	H	OH, H (S)		104.8	-108.6
67.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		82	-72
68.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		80.6	-64.7
69.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		99	-84.6
70.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		112.7	-63.3
71.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		85	-68

N°	R_1	R_3	R_4	R_5, $R_{5'}$		m.p. (°C)	$[\alpha_D]$ (c=1, CH_3OH)
72.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		83,4	-56,2
73.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		71,1	-69,81
74.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)	H	OH, H (S)		82	-76,1
75.	$(CH_3)_3C$-	$CH_3(CH_2)_2$- (S)		OH, H (S)		96,2	-56,3

The compounds of the invention have been the subject of pharmacological trials which have shown their value as active substances in therapy.

They have in particular been tested for their β-amyloid peptide (β-A4) production inhibiting effects.

β-Amyloid peptide (β-A4) is a fragment of a larger precursor protein called APP (amyloid precursor protein). The latter is produced and is present in various cells of animal or human tissue. At the cerebral level, its cleavage by protease-type enzymes leads to the formation of the β-A4 peptide which accumulates in the form of an amyloid plaque. The two proteases responsible for the production of the amyloid peptide are known by the name of beta- and gamma-

secretases (Wolfe MS, Secretase targets for Alzheimer's disease: identification and therapeutic potential, J. Med. Chem., 2001 June 21; 44(13), 2039-60).

However, it has been demonstrated that this gradual deposition of the β-A4 peptide is neurotoxic and could play an important role in Alzheimer's disease.

Thus, the compounds of the present invention, as inhibitor of the production of β-amyloid peptide (β-A4) by inhibition of gamma-protease, can be used in the treatment of pathologies such as senile dementia, Alzheimer's disease, Down's syndrome, Parkinson's disease, amyloid angiopathy, cerebrovascular disorders, frontotemporal dementia and Pick's disease, post-traumatic dementia, pathologies linked to neuroinflammatory processes, Huntington's disease and Korsakov's syndrome.

The tests were carried out according to the protocol described below.

For the β-amyloid cellular trial, the CHO-K1 line coexpressing the CT100 of APP and PS1 M146L clone 30-12 is used. The line targets the inhibition of gamma-secretase. Presenilin is linked to the gamma-secretase activity (Wolfe MS, Haass C., The Role of presenilins in gamma-secretase activity, J. Biol. Chem., 2001 Feb. 23, 276(8), 5413-6) and its coexpression with the amyloid protein or its N-terminal

fragment causes an increase in the secretion of the A1-42 peptide (β-A4) thus generating a pharmacological tool which makes it possible to evaluate inhibition by the compounds of formula (I) of the production of the β-A4 peptide. The inoculation of the 96-well culture plates is carried out at the rate of 1×10^5 cells per well in 150 µl of incubation medium. The presence of a minimum percentage (1.3% final) of serum allows cellular adhesion to the plastic after 2-3 hours of incubation at 37°C, in the presence of 5% CO_2. The products (15 µl) are tested at 10 µM DMSO 1% final and are incubated for 24-25 h at 37°C in the presence of 5% CO_2 and of 100% humidity. After this incubation of 24-25 h, the cellular supernatants (100 µl) are transferred to the ELISA plates, treated with the capture antibody 6E10 (6E10, epitope: aa1-17, INTERCHIM/SENETEK 320-10), to determine the amount of amyloid peptides secreted by the cells in the presence of compounds according to the invention. A series for a synthetic control peptide, "peptide 1-40", at 5 and 10 ng/ml is treated in parallel. The ELISA plates are incubated overnight at 4°C.

The quantity of bound peptide is detected in an indirect manner in the presence of a competitor corresponding to the truncated peptide, peptide 1-28 coupled to biotin which is then detected with streptavidin coupled to alkaline phosphatase. The

substrate, p-Nitrophenyl Phosphate (pNPP *FAST* p-Nitrophenyl Phosphate, Sigma N2770), gives a yellow soluble reaction product which can be read at 405 nm. The reaction is stopped with a 0.1M EDTA solution. For that, after attachment of the amyloid peptide in the ELISA plate, 50 µl of biotinylated peptide 1-28 are added to 100 µl of cell supernatant and incubated for 30 minutes at room temperature. The ELISA plates are then washed 3 times. After drying by inverting on absorbent paper, 100 µl of streptavidin-Alkaline Phosphatase (Interchim/Jackson ImmunoResearch Laboratories 016-050-084), are added per well and incubated for 1 hour at room temperature. The plates are again washed and then alkaline phosphatase substrate (pNPP 1 mg/ml) is added in an amount of 100 µl per well. After incubating for 30 minutes at room temperature, the reaction is stopped by the addition of 100 µl per well of 0.1M EDTA and the reading is carried out at 405 nm.

The compounds of formula (I) according to the invention showed an EC50 (50% effective concentration) of less than 500 nM. In particular, compound No. 50 in the Table showed an EC50 equal to 295 nM. The compounds for formula (I) according to the invention showed more particularly an EC50 of less than 100 nM.

The results of the biological tests show that the compounds are inhibitors of the formation of the β-

amyloid peptide (β-A4).

Thus, these compounds may be used in the treatment of pathologies in which an inhibitor of the formation of the β-amyloid peptide (β-A4) provides a therapeutic benefit. In particular, such pathologies are senile dementia, Alzheimer's disease, Down's syndrome, Parkinson's disease, amyloid angiopathy, cerebrovascular disorders, frontotemporal dementia and Pick's disease, post-traumatic dementia, pathologies linked to neuroinflammatory processes, Huntington's disease and Korsakov's syndrome.

The use of the compounds according to the invention, in the form of base, salt, hydrate or pharmaceutically acceptable solvate, for the preparation of a medicament for treating the abovementioned pathologies forms an integral part of the invention.

The subject of the invention is also medicaments which comprise a compound of formula (I), or an addition salt thereof with a pharmaceutically acceptable acid or alternatively a hydrate or a solvate of the compound of formula (I). These medicaments find their use in therapy, in particular in the treatment of the abovementioned pathologies.

According to another of its aspects, the present invention relates to pharmaceutical compositions containing, as active ingredient, at least

one compound according to the invention. These pharmaceutical compositions contain an effective dose of a compound according to the invention, or a pharmaceutically acceptable salt, a hydrate or a solvate of the said compound, and optionally one or more pharmaceutically acceptable excipients.

The said excipients are chosen, according to the pharmaceutical dosage form and the desired mode of administration, from the usual excipients which are known to persons skilled in the art.

In the pharmaceutical compositions of the present invention for oral, sublingual, subcutaneous, intramuscular, intravenous, topical, local, intratracheal, intranasal, transdermal or rectal administration, the active ingredient of formula (I) above, or its optional salt, solvate or hydrate, may be administered in unit form for administration, as a mixture with conventional pharmaceutical excipients, to animals and to human beings for the prophylaxis or the treatment of the above disorders or diseases.

The appropriate unit forms for administration comprise the forms for oral administration such as tablets, soft or hard gelatine capsules, powders, granules, chewing gums and oral solutions or suspensions, the forms for sublingual, buccal, intratracheal, intraocular or intranasal administration or for administration by inhalation, the forms for

subcutaneous, intramuscular or intravenous administration and the 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 form for administration of a compound according to the invention in the form of a tablet can comprise the following components:

Compound according to the invention	50.0 mg
Mannitol	223.75 mg
Sodium croscarmellose	6.0 mg
Maize starch	15.0 mg
Hydroxypropylmethylcellulose	2.25 mg
Magnesium stearate	3.0 mg

To obtain the desired prophylactic or therapeutic effect, the dose of active ingredient may vary between 0.1 mg and 200 mg per kg of bodyweight and per day. Although these dosages are examples of an average situation, there may be specific cases where higher or lower dosages are appropriate, such dosages also belong to the invention. According to the usual 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.

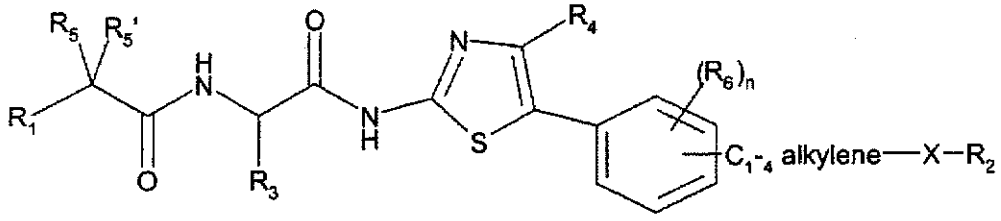
Each unit dose may contain from 0.1 to

1000 mg, preferably from 0.1 to 500 mg, of active ingredient in combination with one or more pharmaceutical excipients. This unit dose may be administered 1 to 5 times per day so as to administer a daily dosage of 0.5 to 5000 mg, preferably of 0.5 to 2500 mg.

The present invention according to another of its aspects also relates to a method for treating the pathologies indicated above which comprises the administration of a compound according to the invention, of a pharmaceutically acceptable salt, of a solvate or of a hydrate of the said compound.

Claims

1. Compound corresponding to the general formula (I):



(I)

in which,

X represents an oxygen or sulphur atom;

R_1 represents a C_{1-10} alkyl group optionally substituted with a C_{3-7} cycloalkyl, a phenyl or a thienyl; or R_1 represents a C_{3-7} cycloalkyl, thienyl, pyridinyl or pyrimindinyl group;

the thienyl groups being optionally substituted with one to 3 C_{1-3} alkyl groups; the phenyl group being optionally substituted with one to 5 halogen atoms or C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} fluoroalkyl or C_{1-3} fluoroalkoxy groups;

R_2 represents a C_{1-6} alkyl group optionally substituted with a C_{3-7} cycloalkyl, phenyl, C_{1-3} alkoxy or hydroxyl group; or R_2 represents a C_{3-7} cycloalkyl, piperidinyl, phenyl or pyridinyl group;

the C_{3-7} cycloalkyl and piperidinyl groups being optionally substituted with one or more C_{1-3} alkyl, C_{1-3}

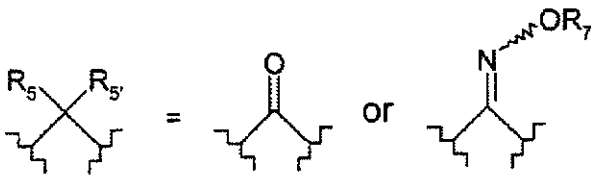
alkoxy, hydroxyl, C_{1-3} fluoroalkyl or C_{1-3} fluoroalkoxy groups;

the phenyl and pyridinyl groups being optionally substituted with one or more halogen atoms or CN, C_{1-3} alkyl, C_{1-3} alkoxy, hydroxyl, C_{1-3} fluoroalkyl or C_{1-3} fluoroalkoxy groups;

R_3 represents a hydrogen atom or a C_{1-6} alkyl group optionally substituted with a C_{3-7} cycloalkyl group;

R_4 represents a hydrogen atom or a C_{1-6} alkyl group;

R_5 and $R_{5'}$ represent, independently of each other, a hydrogen or halogen atom, a hydroxyl or C_{1-3} alkyl group; or R_5 and $R_{5'}$ form together an oxo or oxime group such as:



where R_7 represents a hydrogen atom or a C_{1-3} alkyl;

n represents an integer ranging from 0 to 3; and

R_6 represents independently of each other when n = 2 or 3, a hydrogen or halogen atom, a hydroxyl, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} fluoroalkyl or C_{1-3} fluoroalkoxy group;

in the form of a base, of an addition salt with an acid, of a hydrate or of a solvate.

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

X represents an oxygen or sulphur atom;

R_1 represents a C_{1-5} alkyl group, optionally substituted with a phenyl or a thienyl; or R_1 represents a C_{3-7} cycloalkyl group, a thienyl or pyridinyl group; the thienyl groups being optionally substituted with one or two C_{1-3} alkyl groups; the phenyl group being optionally substituted with one or two halogen atoms;

R_2 represents a C_{1-6} alkyl, C_{3-7} cycloalkyl, phenyl or pyridinyl group; the phenyl group being optionally substituted with one to three CN, C_{1-3} alkyl, C_{1-3} alkoxy, hydroxyl or fluoroalkoxy groups, or halogen atoms;

R_3 represents a C_{1-6} alkyl group;

R_4 represents a hydrogen atom or a C_{1-6} alkyl group;

R_5 and $R_{5'}$ represent, independently of each other, a hydrogen atom or a hydroxyl; or R_5 and $R_{5'}$ form together an oxo group;

R_6 represents a hydrogen or halogen atom, a C_{1-3} alkyl, a C_{1-3} alkoxy; and

n is 0 or 1;

in the form of a base, of an addition salt with an acid, of a hydrate or of a solvate.

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

X represents an oxygen atom;

R_1 represents a methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl, propyl, 1-methylpropyl, 2-methylpropyl or 1-ethylpropyl, optionally substituted with a phenyl

or with a thienyl; or R_1 represents a cyclohexyl, thienyl or pyridinyl; the thienyl groups being optionally substituted with one or two methyl groups; the phenyl group being optionally substituted with one or two chlorine or fluorine atoms;

R_2 represents an ethyl, 1-methylethyl, cyclohexyl, phenyl or pyridinyl group;

the phenyl group being optionally substituted with one to three CN, methyl, ethyl, methoxy, ethoxy, hydroxyl or trifluoromethoxy groups, or chlorine or fluorine atoms;

R_3 represents a methyl, ethyl or propyl group;

R_4 represents a hydrogen atom or a methyl or 4-methylpentyl group;

R_5 and $R_{5'}$ represent, independently of each other, a hydrogen atom, a hydroxyl; or R_5 and $R_{5'}$ form together an oxo group;

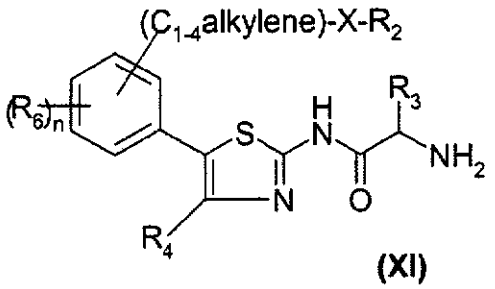
R_6 represents a hydrogen, chlorine or fluorine atom, a methyl, a methoxy or an ethoxy;

n is 0 or 1; and

the C_{1-4} alkylene group is a methylene;

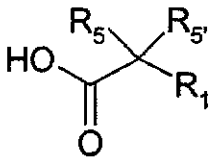
in the form of a base, of an addition salt with an acid, of a hydrate or of a solvate.

4. Method for preparing a compound of formula (I) according to any one of Claims 1 to 3, by peptide coupling of an amine of formula (XI)



(XI)

with an acid of formula (XII)



(XII)

in which X, R_1, R_2, R_3, R_4, R_5, $R_{5'}$, R_6 and n are as defined in formula (I) according to Claim 1.

5. Pharmaceutical composition containing at least one compound of formula (I) according to any one of Claims 1 to 3, in the form of a pharmaceutically acceptable base, salt, hydrate or solvate and optionally one or more pharmaceutically acceptable excipients.

6. Compound of formula (I) according to any one of Claims 1 to 3, in the form of a pharmaceutically acceptable base, salt, hydrate or solvate, for its use as a medicament.

7. Use of a compound of formula (I) according to any one of Claims 1 to 3, in the form of a pharmaceutically acceptable base, salt, hydrate or

solvate, for the preparation of a medicament for treating a pathology in which an inhibitor of the formation of β-amyloid peptide β-A4 offers a therapeutic benefit.

8. Use of a compound of formula (I) according to any one of Claims 1 to 3, in the form of a pharmaceutically acceptable base, salt, hydrate or solvate, for the preparation of a medicament for treating senile dementia, Alzheimer's disease, Down's syndrome, Parkinson's disease, amyloid angiopathy, cerebrovascular disorders, frontotemporal dementia and Pick's disease, post-traumatic dementia, pathologies linked to neuroinflammatory processes, Huntington's disease and/or Korsakov's syndrome.