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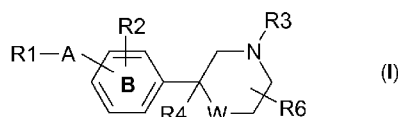
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[Continued on next page]

(54) Title: (THIO)MORPHOLINE DERIVATIVES AS SIP MODULATORS



(57) **Abstract:** The present invention relates to (thio)morpholine derivatives of the formula (I), wherein R1 is selected from cyano, (2-4C)alkynyl, (1-4C)alkyl, (3-6C)cycloalkyl, (4-6C)cycloalkenyl, (6-8C)bicycloalkyl, (8-10C)bicyclic group, each optionally substituted with (1-4C)alkyl, phenyl, biphenyl, naphthyl, each optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkyloptionally substituted with one or more fluoro atoms, (2-4C)alkynyl, (1-4C)alkoxy optionally substituted with one or more fluoro atoms, amino, di(1-4C)alkylamino, -SO₂-(1-4C)alkyl, -CO-(1-4C)alkyl, -CO-O-(1-4C)alkyl, -NH-CO-(1-4C)alkyl and (3-6C)cycloalkyl, phenyl substituted with phenoxy, benzyl, benzyloxy, phenylethyl or monocyclic heterocycle, each optionally substituted with (1-4C)alkyl, monocyclic heterocycle optionally substituted with halogen, (1-4C)alkyl or with phenyl optionally substituted with (1-4C)alkyl, and bicyclic heterocycle optionally substituted with (1-4C)alkyl; A is selected from -CO-O-, -O-CO-, -NH-CO-, -CO-NH-, -C=C-, -CCH₃-O- and the linking group -Y-(CH₂)_n-X- wherein Y is attached to R1 and selected from a bond, -O-, -S-, -SO-, -SO₂-, -CH₂-O-, -CO-, -O-CO-, -CO-O-, -CO-NH-, -NH-CO-, -C=C- and -C≡C-; n is an integer from 1 to 10; and X is attached to the phenylene / pyridyl group and selected from a bond, -O-, -S-, -SO-, -SO₂-, -NH-, -CO-, -C=C- and -C≡C-; ring structure B optionally contains one nitrogen atom; R2 is H, (1-4C)alkyl optionally substituted with one or more fluoro atoms, (1-4C)alkoxy optionally substituted with one or more fluoro atoms, or halogen; and R3 is (1-4C)alkylene-R5 wherein the alkylene group may be substituted with (CH₂)₂ to form a cyclopropyl moiety or one or two halogen atoms, or R3 is (3-6C)cycloalkylene-R5 or -CO-CH₂-R5, wherein R5 is -OH, -PO₃H₂, -OPO₃H₂, -COOH, -COO(1-4C)alkyl or tetrazol-5-yl; R4 is H or (1-4C)alkyl; R6 is one or more substituents independently selected from H, (1-4C)alkyl or oxo; W is -O-, -S-, -SO- or -SO₂-; or a pharmaceutically acceptable salt, a solvate or hydrate thereof; with the proviso that the derivative of formula (I) is not 2-(4-ethylphenyl)-4-morpholinoethanol or 4-[4-(2-hydroxyethyl)-2-morpholinyl]benzeneacetonitrile or a pharmaceutically acceptable salt, a solvate or hydrate thereof. The compounds of the invention have affinity to SIP receptors and may be used in the treatment, alleviation or prevention of SIP receptor mediated diseases and conditions.



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