

**Orally active CCR5 antagonists as anti-HIV-1 agents. Part 3: Synthesis and biological activities of 1-benzazepine derivatives containing a sulfoxide moiety.**

*Bioorg Med Chem* 2005 Jan; **13** : 363-86

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**Abstract**

In order to develop orally active CCR5 antagonists, 1-propyl- or 1-isobutyl-1-benzazepine derivatives containing a sulfoxide moiety have been designed, synthesized, and evaluated for their biological activities. Sulfoxide compounds containing a 2-pyridyl group were first investigated, which led to discovering that the presence of a methylene group between the sulfoxide moiety and 2-pyridyl group was necessary for increased inhibitory activity in a binding assay. After further chemical modification, it was found that replacement of the pyridyl group with an imidazolyl or 1,2,4-triazolyl group enhanced activity in the binding assay and that S-sulfoxide compounds were more active than R-isomers. Particularly, compounds (S)-4r, (S)-4s, and (S)-4w exhibited highly potent CCR5 antagonistic activities ( $IC_{50}$ =1.9, 1.7, 1.6nM, respectively) and inhibitory effects ( $IC_{50}$ =1.0, 2.8, 7.7nM, respectively) in the HIV-1 envelope mediated membrane fusion assay, together with good pharmacokinetic properties in rats. In addition, we established the synthesis of (S)-4r and (S)-4w by asymmetric oxidation with titanium-(S)-(-)-1,1'-bi-2-naphthol complex.

**Other Details**

ISSN 0968-0896

Language eng

Date of Entry 2004 12 15

Pub Med Identifier 15598559