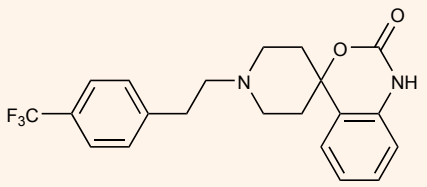
New Product Highlights

RS-102895: A CCR2b chemokine receptor antagonist

Chemokine receptors and their ligands play major roles in asthma, atherosclerosis, cancer, inflammation and infectious diseases such as AIDS. Chemokine receptors are seven-transmembrane G protein-coupled receptors and since their discovery ten years ago, they have become the targets of intense drug discovery and development research. Chemokine receptor classification is based on the spacing of the amino-terminal cysteine residues and are designated as CXC (α-subclass), CC (β-subclass) and CX_3C (minor subclass). CCR2 receptors belong to the β-subclass of chemokine receptors and are also known as **Monocyte Chemoattractant Protein-1** receptors after one of their natural ligands, **MCP-1** (Prod. Nos. **M-208**, rat recombinant and **M 6667**, human recombinant) **MCP-2** (Prod. No. **M 4292**, human recombinant), **MCP-3** (Prod. No. **M 8431**, human recombinant) and **MCP-4** (Prod. No. **M-246**, human recombinant). CCR2 receptors are among the inducible (inflammatory) chemokine receptors in contrast to the constitutive (developmentally regulated) chemokine receptors [1,2]. Two subtypes of CCR2 receptors exist and are referred to as CCR2a and CCR2b. In contrast to the CCR2a receptor, the CCR2b receptor isoform is five-fold more potent in inducing chemotaxis and also induces calcium influx [1,2].

RS-102895 (Prod. No. **R 1903**) is a novel spiropiperidine that is a potent and specific CCR2b chemokine receptor antagonist. The binding of RS-102895 to the CCR2b chemokine receptor has been carefully mapped through mutagenesis studies using the cloned receptor. In chinese hamster lung cells (CRL-1657) stably transfected and expressing the human CCR2b chemokine receptor, RS-102895 displayed IC_{50} values of 360 nM and 17.8 µM, respectively, for MCP-1 / CCR2 vs. macrophage inflammatory peptide -1α (MIP1-α) / CCR1 binding [3]. In chemotaxis studies using THP-1-5X cells, RS-102895 inhibited MCP-1 and displaying an IC_{50} value of 1.7 µM, inhibited RANTES, which acts through the CCR1 chemokine receptor, displaying an IC_{50} value of 37 µM [3]. In calcium influx studies using CRL-1657 cells, RS-102895 displayed IC_{50} values of 31 nM and 130 nM, respectively, for MCP-1 and MCP-3 [3].

Administration of CCR2 chemokine receptor antagonists or neutralizing antibodies for its ligand, MCP-1, reduces inflammation in animal models, including adjuvant-induced arthritis, lung granuloma and glomerulonephritis. Animals genetically deleted of CCR2 or MCP-1 are protected from inflammation and atherosclerosis induced by bacterial products and high fat diets. These findings suggest that potent and selective antagonists of the CCR2b receptor will help elucidate the post-receptor signaling events that mediate these pathological conditions. RS-102895 exhibits the requisite selectivity and affinity for the CCR2b chemokine receptor and should prove to be a valuable tool to further study these mechanisms.



RS-102895
(Prod. No. R 1903)

References

1. Proudfoot, A.E., *Nature Rev. Immunol.*, **2**, 106-115 (2002).
2. Proudfoot, A.E., et al., *Immunol. Rev.*, **177**, 246-256 (2000).
3. Mirzadegan, T. et al., *J. Biol. Chem.*, **275**, 25562-25571 (2000).

Related Products

M 2420	**Monoclonal Anti-MCP-1**
M-253	**Anti-MCP-1** (goat)
M 8413	**Monoclonal Anti-MCP-2**
M-254	**Anti-MCP-2** (goat)
M 8663	**Monoclonal Anti-MCP-3**
M-255	**Anti-MCP-3** (goat)