

Identification of CCR5 non-peptide agonists

using structure-based virtual screening

Esther Kellenberger,¹ Jean-Yves Springael,² Marc Parmentier,² Muriel Hachet-Haas,³ Jean-Luc Galzi³ and Didier Rognan¹

¹ Bioinformatics of the Drug, CNRS UMR7175-LC1, F-67400 Illkirch

² Institut de Recherche Interdisciplinaire en Biologie Humaine et Moléculaire (IRIBHM), Université Libre de Bruxelles, B-1070 Brussels, Belgium.

³ Dynamics of G protein-coupled receptors, CNRS UMR7175-LC1, F-67400 Illkirch

A three-dimensional model of the chemokine receptor CCR5 has been built to fulfill structural peculiarities of its α -helix bundle and to distinguish known CCR5 antagonists from randomly-chosen drug-like decoys. In silico screening of a library of 1.6 million commercially-available compounds against the CCR5 model by sequential filters (drug-likeness, 2-D pharmacophore, 3-D docking, scaffold clustering) yielded a hit list of 77 compounds, out of which 10 exhibited a detectable binding affinity to the CCR5 receptor. Unexpectedly, all binders tested in a functional assay were shown to be agonists of the CCR5 receptor. Moreover, one of these non-peptide agonists of CCR5 was shown to promote efficient receptor internalization, which is a process therapeutically favorable for protection against HIV-1 infection.

Keywords: HIV, CCR5, GPCR, agonist, docking, virtual screening