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Review

Keynote review: Medicinal chemistry strategies to CB_1 cannabinoid receptor antagonists

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The proven clinical efficacy of the CB_1 cannabinoid receptor antagonist rimonabant in both obesity and smoking cessation and its therapeutic potential in other disorders has given a tremendous impetus to the discovery of novel CB_1 antagonists. The number of disclosed patents wherein novel chemical entities having CB_1 antagonistic or inverse agonistic properties have been claimed has exploded. Besides novel compound classes that were identified in screening, rational medicinal chemistry approaches such as conformational constraint and scaffold hopping have been successfully applied. CB_1 receptor modelling has provided insight into crucial receptor-ligand interaction points thereby leading to a general CB_1 inverse agonist pharmacophore model.

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rimonabant; therapeutic applications; scaffold hopping; bioisosterism; pharmacophore; conformational constraint; CB1 receptor modeling

The proven clinical efficacy of the CB_1 cannabinoid receptor antagonist rimonabant in obesity and its further therapeutic potential has given a tremendous impetus to the discovery of novel CB_1 antagonists

1

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Jos H.M. Lange Jos Lange was born in Sint Hubert, the Netherlands and studied chemistry at the University of Nijmegen, where he specialized in organic chemistry and chemometrics. In 1989 he obtained his PhD in synthetic organic chemistry at the same university under the supervision of Binne Zwanenburg. He joined the Medicinal Chemistry department at Solvay Pharmaceuticals in 1988. Lange made significant contributions to several research programs, including anti-ischaemics (Ca-overload blockers) and dopamine, cholecystokinin, neurokinin and neurotensin

modulators. Since 1997 he has primarily been involved as a senior scientist in cannabinoid research which resulted in the discovery of several selective CB1 receptor antagonists from different chemical classes.

2

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Chris G. Kruse Chris Kruse (1952) studied organic and medicinal chemistry at Leiden University, the Netherlands. He received his PhD in 1978. He joined Philips Forschungslabor in Aachen, Germany and moved to Solvay Pharmaceuticals in 1981. He has maintained several positions, including departmental head of medicinal chemistry. Since 1995 he has been responsible for all psychiatry drug discovery activities up to Phase II. He has been responsible for the discovery of more than 10 clinical candidates. He has also been appointed as professor of drug discovery sciences at the University of Amsterdam in 1997. Kruse is member of several research advisory committees and editorial boards. He is (co)author of more than 100 publications.

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