

P014 [³H]Org 43553, the first small molecule radioligand at the human luteinizing hormone (LH) receptor.

Laura H. Heitman^a, Julia Oosterom^b, Cornelis M. Timmers^c, Peter Wiegerinck^d, Adriaan P. IJzerman^a

^aMedicinal Chemistry, Leiden University, Leiden and

^bMolecular Pharmacology, ^cMedicinal and ^dProcess Chemistry, N.V. Organon, Oss, The Netherlands

The present study characterizes the binding of a new low-molecular-weight (LMW) radioligand, [³H]Org 43553, at the LH receptor, for which high-molecular-weight (HMW) hCG and LH are the endogenous ligands.

Equilibrium saturation and displacement assays were developed and optimized. Specific binding of [³H]Org 43553 to CHO-K1 cell membranes expressing the human LH receptor and a CRE-luciferase reporter gene was saturable with a K_D of 2.4 ± 0.4 nM and a B_{max} of 1.6 ± 0.2 pmol/mg protein. Affinities of five LMW derivatives of Org 43553 were determined. All displaced the radioligand competitively with K_i values ranging from 3.3 - 100 nM. Lastly, the potency of these compounds in a cAMP-induced luciferase assay was also determined. There was a high correlation between affinity and potency ($r = 0.99$; $P < 0.0001$) of these compounds.

In the search for LMW ligands at the LH receptor, a HMW radioligand is not suitable as it is not displaced by a LMW compound. Therefore, [³H]Org 43553 is a very interesting new radioligand with good binding properties, which allows screening for new LMW ligands at the LH receptor.