Molecular modelling of the rat peroxisome proliferator-activated receptor - (rPPAR) by homology with the human retinoic acid X receptor (hRXR) and investigation of ligand binding interactions I: QSARs

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„...generally possessing an acidic function (or one unmasked by **metabolism**) or its bioisostere (Ahmad and Caldwell, 1994 Esbenshade et...logD74 and pKa, were calculated using the Pallas system (**CompuDrug** Ltd, Budapest, Hungary), which includes the evaluation of...”

Abstract

The construction of a homology model of the ligand binding domain of the rat peroxisome proliferator-activated receptor- (rPPAR) based on the crystal structure of the human retinoic acid X receptor- (hRXR) is reported. It is demonstrated that many known peroxisome proliferators are able to occupy the putative ligand binding site of the rPPAR, including clofibric acid, ciprofibrate, nafenopin and related compounds. The log. relative potency of several peroxisome proliferators can be quantitatively related (R=0.99) to their binding affinity and lipophilicity as measured by their distribution coefficients ($logD_{7.4}$ values) and other QSARs are discussed in the light of receptor–ligand interactions. The molecular modelling of a representative number of peroxisome proliferators within the putative ligand binding site is consistent with experimental information on relative potency and enantioselectivity.

Author Keywords: peroxisome proliferator-activated receptor; molecular modelling; quantitative structure–activity relationships

Abbreviations: hER=human estrogen receptor; LBD=ligand-binding domain; LTB_4=leukotriene B_4; MO=molecular orbit; PPAR=peroxisome proliferator-activated receptor; QSAR=quantitative structure–activity relationship

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