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Newer α-acyl β-phenylpropanoic acid derivative as PPAR-α based hypolipidemic agent

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A comparative QSAR study through Hansch analysis on PPAR α and γ agonists was carried out on following three series:

1) 2-Alkoxydihydrocinnamates.

$-\log EC_{50}=2.053(\pm0.899)R_1Vw-1.921(\pm0.625)R_2Vw+6.476(\pm0.375)$

$n=12$, $r=0.95$, $s=0.18$, $F=41.37$, $R^2=0.90$, $R^2_{adj}=0.88$, RMSE=0.38, $Q^2=0.81$

2) Azaindole-α-alkyloxyphenylpropionic acids.

$-\log EC_{50}= -0.96(\pm0.472)RVw+0.847(\pm0.344)I_1+0.495(\pm0.249)I_2+6.476$

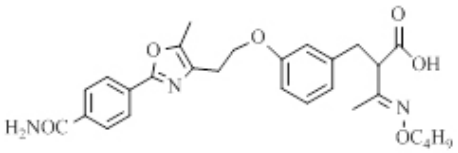
$n=18$, $r=0.94$, $s=0.19$, $F=32.58$, $R^2=0.88$, $R^2_{adj}=0.85$, RMSE=0.20, $Q^2=0.78$

3) Oxime ethers of α-acyl-β-phenylpropanoic acids.

$-\log EC_{50}=11.344(\pm6.549)CMR-0.415(\pm0.255)CMR^2-68.072(\pm42.133)$

$n=15$, $r=0.90$, $s=0.26$, $F=24.84$, $R^2=0.82$, $R^2_{adj}=0.80$,RMSE=0.41, $Q^2=0.73$

On the basis of internally and laterally validated QSAR models and results of QSAR equation on oxime ethers of α-acyl-β-phenylpropanoic acids, scaled calculated optimum molar refractivity (CMR_o) value of 14.3 for molecules was required for maximum agonistic activity. Using this clue, some oxime ethers of α-acyl-β-phenylpropanoic acids were proposed which were within the probability density derived applicability domain. The structural effects of ligand binding were examined on the basis of hydrogen bond interactions and binding energies in the final complexes obtained from molecular docking simulations. Compound RM-KT-01 was found to possess optimum calculated activity, passed Lipinski's "rule of five" for oral absorption and lacked toxicity (mutagenicity, carcinogenicity, teratogenicity and embryotoxicity predicted by *PASS*). The derivative was synthesized and characterized by their physicochemical data and spectral analysis (F.T.I.R, ^{1}H N.M.R., Elemental analysis and Mass spectroscopy). The synthesized compound RM-KT-01 (1) was screened for human PPAR (hPPAR) α agonistic activity on full length PPARα receptor transfected in HepG2 cells. The *in vitro* PPAR α agonistic activity (EC_{50}) of synthesized compound was reported to be 78 nM. The *in vitro* activity suggests relevancy of presence of phenyl carboxamide group at one end and *n*-butyl group attached with phenylpropanoic acid chain of oxime ether of α-acyl-β phenylpropanoic acid. The result of transactivation assay also suggests that RM-KT-01 (1) is PPAR α selective and shows no activity on PPAR γ and PPAR δ.



RM-KT-01

Biography

Manish Sharma completed his BPharm from Rajasthan University and Post-graduation from BITS-Pilani. He conducted his Pre-doctoral research from University of Montana and PhD from JNU, Rajasthan. He is Dean of School of Pharmaceutical Sciences, Bahra University, Solan-HP, India. He has published more than 10 papers in reputed journals and has been serving as reviewer of repute. His area of research interest is QSAR and molecular modeling studies of biologically active small molecules.

Notes:

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