NOVEL OBETICHOLIC ACID KETODERIVATIVES AND ISOMERS AS POTENTIAL LIGANDS OF BILE ACID RECEPTORS

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Metabolic diseases with altered cholesterol and triglyceride levels are serious healthcare problem, emerging in western population, and are tightly linked to inflammation. Recently, obeticholic acid (OCA), a potent farnesoid X receptor (FXR) agonist, has been shown to be a promising treatment against inflammatory hepatic disorders. Therefore, we aimed to synthesize new derivatives and isomers of OCA (named A-I) and assess their capacity to activate nuclear receptors involved in metabolic regulation including FXR, vitamin D receptor (VDR), pregnane x receptor (PXR) and constitutive androstane receptor (CAR).[1, 2] Gene reporter assays were performed to determine their capacity to activate nuclear receptors of interest and changes on expression of target genes were analysed by real time qPCR. Furthermore, these isomers were subjected to LC/MS analysis to determine their stability and possible conversion to OCA in HepG2 cell line and primary human hepatocytes. Our results showed that all derivatives could significantly activate FXR and PXR in therapeutic doses. Compound G is an equally strong ligand of FXR as OCA itself. We have also found that compound H is an activator of VDR. None of the tested compounds was able to activate CAR. Here, we have presented novel ligands of bile acid nuclear receptors derived from OCA. Moreover, we have found a new dual FXR/VDR agonist, compound H, which may have a promising use in the therapy of inflammatory metabolic disorder including steatohepatitis or atherosclerosis.[3]

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