Neolignan analogs lead to a selective RXR modulator

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Nuclear receptors are interesting molecular targets since they act as ligand-regulated transcription factors. In humans 48 nuclear receptors are known, of which the type II nuclear receptors bind as heterodimers to DNA. Their heterodimer partner is the retinoid X receptor (RXR) and ligands for this receptor (rexinoids) may influence the transactivation activity of permissive heterodimers. Endogenous ligands of these permissive heterodimers are lipids and xenobiotics indicating that these receptors play a key role in the regulation of energy metabolism and detoxification. Currently available rexinoids that act as full agonist, like Bexarotene, suffer from side effects, like hypertriglyceridemia. Thus selective RXR modulators (SRXRMs) might be a promising strategy for modulating the lipid metabolism in a favorable way.

Neolignans of Magnolia bark have been identified as interesting peroxisome proliferator-activated receptor (PPAR)γ and RXRα agonists, but also as ligands for the GABA and cannabinoid receptors [1-6]. We, therefore screened a library of 53 (semi)synthetic neoligan analogs [5,6] that led to the identification of LRK071 (EC_{50}: 165.5 nM) that shows a different co-regulator recruitment profile compared to Bexarotene, and an interesting profile in functional cell models: LRK071 does not induce adipogenicity in 3T3–L1 preadipocytes, promotes cholesterol efflux from THP-1 macrophages, but does not induce lipid accumulation in HepG2 cells. RXR heterodimer co-transfection models show that LRK071 transactivates PPARγ, but not liver X receptor (LXRs) heterodimers, and thus acts as true SRXRM.

[1] Fakhrudin N, *et al*. *Mol Pharmacol*. 77(4):559-66, 2010.

[2] Kotani H, *et al*. *J Nat Prod*. 73:1332, 2010.

[3] Zhang H, *et al*. *Plos One* 6(11): e28253, 2011.

[4] Atanasov AG, *et al*. *Biochim Biophys Acta*. 1830:4813, 2013.

[5] Rycek L, *et al*. *Bioorg Med Chem Lett*. 25:400, 2015.

[6] Schuehly W, *et al*. *Chem Biol*. 18:1053-64, 2011.