LXRα/β: FRET-based compound-CoF peptide profiling

In the upper two pix (A) and (B), recruitment of a NCoA3 cofactor peptide in dependency on increasing concentrations of ligands are shown. Whereas the known reference agonists Ref Cpd 1 and Ref Cpd 2 show about the same efficacy level in NCoA3 peptide recruitment with slightly differing potency, the natural ligand 22(R)-Hydroxycholesterol as well as the Phenex proprietary compound Px Cpd 2 demonstrate partial agonism in that their curves do not reach the same top as Ref Cpd 1 or Ref Cpd 2. However, the level of efficacy (should correlate with degree of agonism) of NCoA3 recruitment is different for the two LXR alpha and beta subtypes.

In the lower two pix (C) and (D), recruitment of a NCoR corepressor peptide in dependency on increasing concentrations of ligands are shown. Here the degree of “agonistic” corepressor displacement is different between the four ligands tested. Whereas the full agonist Ref Cpd 1 shows strong NCoR peptide displacement for both LXR subtypes, Ref Cpd 2 and Px Cpd 2 show even NCoR recruitment to LXRalpha. Ref Cpd 2 also displaces NCoR with LXRbeta but not Px Cpd 2. 22(R)-Hydroxycholesterol seems to be NCoR recruiting with both LXR subtypes. Hence, a detailed molecular profile of ligands can be compiled.