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Targeted Testing of FXR Tox21 Active Compounds

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Abstract

The farnesoid-X-receptor (FXR), a nuclear hormone receptor, plays an integral role in bile acid homeostasis. Once considered an orphan receptor with no known endogenous ligand, it was discovered that endogenous bile acids effectively induce FXR activity at physiological concentrations, thus establishing the role of FXR as a bile acid receptor. FXR also regulates lipid and glucose metabolism. To characterize FXR activity, a mammalian one-hybrid assay using a beta-lactamase reporter gene was used to screen the Tox21 10K chemical library. Approximately 1.5% of the chemicals displayed FXR agonist activity, while 2.7% showed some level of antagonism. Twenty-one of these potential FXR-active chemicals, representing the range of agonist and antagonist responses and including established actives and novel compounds, were tested in confirmatory *in vitro* assays using human or Medaka FXR constructs transfected into CV-1 African green monkey-derived kidney cells. Chemicals were tested at concentrations from 10 nM to 100 μM and 24 hr post-exposure luciferase activity was determined. These *in vitro* results will be confirmed by monitoring alterations in gene expression and liver histopathology in a Medaka, *Oryzias latipes*, elutheroembryo model.

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