**SYNTHESIS OF NEW ISOXAZOLE DERIVATIVES AS FXR AGONISTS WITH IMPROVED PHARMACOKINETIC PROPERTIES**

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FXR is one of the most investigated targets, expressed by entero-hepatic tissues including liver, gallbladder, intestine, and by the kidney, for its involvement in several psychopathological aspect of the organism. FXR is a bile acid sensor, with primary bile acids, chenodeoxycholic acid in humans, and cholic acid (CA) in mouse, and the corresponding taurine or glycine amide conjugates, serving as natural ligands.1 FXR activation governs bile acid homeostasis by repressing bile acid synthesis and uptake while increases their urinary excretion, as protective mechanism in conditions of impaired biliary excretion (cholestasis).2 In addition, FXR plays functional roles in regulating glucose and lipid metabolism, exerting robust anti-inflammatory activity in intestine and in the liver, and it is considered a validated target for the treatment of liver diseases, such as cholestasis, liver fibrosis, steatohepatitis (NASH), diabetes, as well as obesity and metabolic syndrome. Considering the growing interest toward this receptor, several small molecules ranging from bile acid derivatives to non-steroidal ligands have been synthesized. The first in class non-steroidal FXR ligand is GW4064,3 whose use was limited by reduced bioavailability as well as a stilbene-mediated photo-instability. Thus, recent, intense medicinal chemistry protocols have been performed in order to identify new isoxazole derivatives, modified mainly on the stilbene moiety, while the trisubstituted isoxazole, the isopropyl group at C-5 and the 2,6-dicloro-substituted phenyl moiety at C-3 were conserved.

In this contribution, we report the design and the synthesis of modified GW4064 derivatives, identifying novel isoxazoles endowed with FXR agonistic activity and improved ADME properties. The pharmacological characterization and molecular docking studies allowed the identification of several FXR agonists with nanomolar potency in transactivation and SRC-1 recruitment assays. This characterization resulted in the identification of a potent FXR agonist, that prevent acute liver failure in mice caused by acetaminophen overdose in an FXR-dependent manner.

**References**

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