New Product Highlights

(Z)-Guggulsterone: Farnesoid X receptor (FXR) antagonist

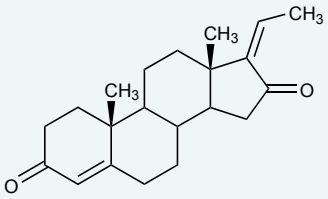
The farnesoid X receptor (FXR) is a nuclear hormone receptor that controls expression of critical genes involved in bile acid and **cholesterol** (Prod. No. C 8667) homeostasis. According to recent studies, activation of FXR inhibits expression of cholesterol 17α-hydroxylase, sterol 12α-hydroxylase, the Na^+/taurocholate co-transporting polypeptide and **apolipoprotein A-I** (Prod. No. A 0722). In addition, it activates expression of intestinal bile acid-binding protein (I-BABP), phospholipid transfer protein, bile salt export pump (BSEP), dehydroepiandrosterone sulfotransferase and **apolipoprotein C-II** (Prod. No. A 7910) [1-4].

The resin of the guggul tree *Commiphora mukul* has been widely used to treat a variety of ailments, including obesity and lipid disorders. The active ingredients of the resin extract are the stereoisomers (E)-and **(Z)-guggulsterone** (Prod. No. G 5168), which activate FXR and directly decrease hepatic cholesterol levels. In transient transfections of mouse hepatocyte cells with a synthetic FXR responsive reporter plasmid, (Z)-guggulsterone alone had no effect on FXR activity, but it strongly inhibited FXR activation by **chenodeoxycholic acid** (CDCA; Prod. No. C 9377), the most potent of the bile acid agonists [5]. In the presence of 100 µM CDCA, 10 µM (Z)-guggulsterone decreased FXR transactivation by nearly 50% while 100 µM (Z)-guggulsterone resulted in 90% inhibition [5].

Very similar results were observed with the promoter of the orphan receptor SHP, which contains an FXR-retinoid X receptor (FXR-RXR) heterodimer binding site and is induced by bile acids [6]. Guggulsterone does not activate or inhibit transactivation by several other receptors associated with lipid metabolism, including liver X receptor α (LXRα), peroxisome proliferator activated receptor α (PPARα) and retinoid X receptor α (RXRα) [5].

Guggulsterone, although acting as an FXR antagonist in coactivator association assays, enhances FXR agonist-induced transcription of the bile salt export pump (BSEP), a major hepatic bile acid transporter. In the presence of an FXR agonist such as CDCA or GW4064, guggulsterone enhanced endogenous BSEP expression in HepG2 cells with a maximum induction of 400-500% higher than that induced by an FXR agonist alone [4]. Expression of SHP was also significantly increased, whereas expression of other FXR targets remained unchanged.

Sigma-RBI is pleased to offer (Z)-guggulsterone and FXR antagonist and a selective bile acid receptor modulator (SBARM). (Z)-Guggulsterone represents a new class of FXR ligands that antagonize FXR agonist-induced coactivator recruitment in coactivator association assays, but that selectively enhance FXR target expression in cells and animals [4]. It will be a useful tool for studying lipid metabolism and cholesterol research.



(Z)-Guggulsterone
Prod. No. G 5168

References

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2. Sinal, C.J., et al., *Cell*, **102**, 731-744 (2000).
3. Singh, R.B., et al., *Cardiovasc. Drugs Ther.*, **8**, 659-664 (1994).
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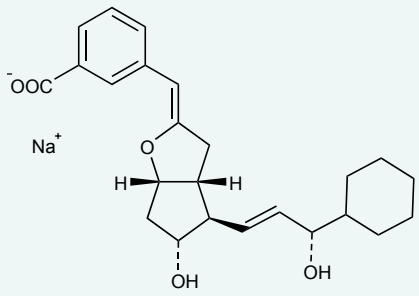
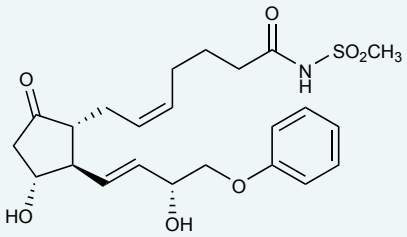
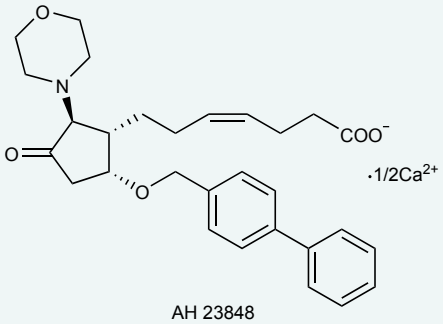


Taprostene
Prod. No. T 4949



Sulprostone
Prod. No. S 8692



AH 23848
Prod. No. A 8227

Taprostene

Highly selective IP_1 prostanoid receptor agonist.
Br. J. Pharmacol., **134**, 313-324 (2001).

Sulprostone

EP_1/EP_3 prostanoid receptor agonist.
Biochem. Biophys. Res. Commun., **290**, 162-168 (2002).

AH 23848

EP_4 prostanoid receptor antagonist with TP blocking activity.
Br. J. Pharmacol., **130**, 1919-1926 (2000).