New Product Highlights

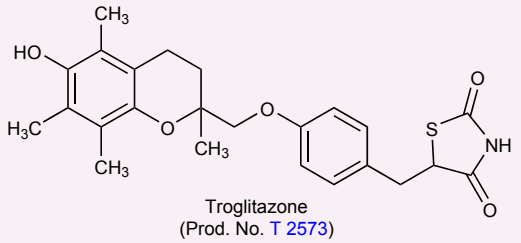
Troglitazone: A potent and selective PPARγ agonist

Peroxisome proliferator-activated receptors (PPARs) are ligand-dependent transcription factors that belong to the nuclear hormone receptor superfamily. These receptors play an important role in many cellular functions including lipid metabolism, cell proliferation, cell differentiation, adipogenesis and inflammatory signaling [1,2]. Currently, three PPAR subtypes have been identified and are referred to as PPARα, PPARβ (also known as PPARδ) and PPARγ. PPARγ is the most studied of the three subtypes on account of its role in adipocyte differentiation as well as its involvement in glucose and lipid metabolism [2]. Thus, this receptor has become an important drug target for the treatment of various diseases including diabetes, cancer, atherosclerosis and hypertension [2-6].

Sigma-RBI is pleased to offer **Troglitazone** (Prod. No. **T 2573**) a member of the thiazolidinedione (TZD) class of anti-diabetic agents commonly referred to as "glitazones". These compounds were the first agents to be identified as high affinity PPARγ agonists and include **ciglitizone** (Prod No. **C 3974**), rosiglitazone and pioglitzone. Using a cell-based PPAR-GAL4 transactivation assay, troglitazone was shown to be a selective PPARγ agonist displaying EC_{50} values of 780 nM and 550 nM for murine and human receptors, respectively [2]. In this same assay, troglitazone was inactive against both mouse and human PPARα and PPARδ receptors at concentrations up to 10 µM [2]. In a separate study, troglitazone exhibited a dose-dependent effect on cell cycle arrest as well as apoptosis in several hepatocarcinoma cell lines with an EC_{50} value of 10 µM [6].

Troglitazone was approved for the treatment of insulin resistance and hyperglycemia in Type II diabetes, but was removed from the market due to its liver toxicity. However, the preclinical data suggest that troglitazone should serve as an important research tool for elucidating the role of PPARγ in various metabolic diseases.

In addition to troglitazone, Sigma-RBI is pleased to provide several other PPAR research tools, specifically **GW9662** (Prod. No. **M 6191**), a selective PPARγ antagonist, **GW1929** (Prod. No. **G 5668**), a PPARγ agonist and **GW7647** (Prod. No. **G 6793**), a PPARα agonist. These products are sold for research purposes only, pursuant to an agreement from GlaxoSmithKline.



Troglitazone
(Prod. No. T 2573)

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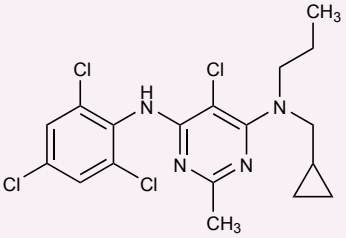
NBI 27914: A potent, selective, non-peptide CRF_1 corticotropin-releasing factor receptor antagonist

Corticotropin-releasing factor (CRF) plays an important role in the regulation of the hypothalamic-pituitary-adrenal axis. In response to a variety of stressors, CRF causes the release of hormones such as **adrenocorticotropic hormone** (ACTH, Prod. No. **O 2275**) and **hydrocortisone** (Cortisol, Prod. No. **H 5885**). In addition, clinical findings support the hypothesis that dysfunction of the CRF system is implicated in certain stress-related neuropsychiatric disorders such as anxiety and depression [1]. The effects of CRF are mediated through two receptor types referred to as CRF_1 and CRF_2 ($CRF_{2\alpha}$, $CRF_{2\beta}$ and $CRF_{2\gamma}$). CRF_1 receptors, unlike CRF_2 receptors, are widely distributed throughout the central nervous system [2]. Recently, emphasis has been placed on developing non-peptide CRF_1 receptor antagonists as potential therapeutic agents.

Sigma-RBI is pleased to introduce **NBI 27914** (Prod. No. **N 3911**), a potent and selective non-peptide CRF_1 receptor antagonist [3]. NBI 27914 binds to the CRF_1 receptor with high affinity with a K_i value of 1.7 nM and appears to be devoid of activity at the human $CRF_{2\alpha}$ receptor [4]. It inhibits CRF-mediated increases in adenylyl cyclase activity and ACTH release from rat anterior pituitary cells with EC_{50} values of 150 nM and 70 nM, respectively [5]. In addition, when administered centrally in rats, NBI 27914 increases the latency and decreases the duration of CRF-induced seizures [6].

NBI 27914 is therefore a selective tool with which to study the function of CRF_1 receptors and should prove useful in elucidating the contribution of CRF to the genesis of neuropsychiatric disorders.



NBI 27914
(Prod. No. N 3911)

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