**BIOLOGICAL ACTIVITY**

**Description**

Ertiprotafib is an inhibitor of PTP1B, IkB kinase β (IKK-β), and a dual PPARα and PPARβ agonist, with an IC₅₀ of 1.6 μM for PTP1B, 400 nM for IKK-β, and an EC₅₀ of ~1 μM for PPARα/PPARβ.

<table>
<thead>
<tr>
<th>IC₅₀ &amp; Target</th>
<th>PTP1B 1.6 μM (IC₅₀)</th>
<th>IKK-β 400 nM (IC₅₀)</th>
<th>PPARα ~1 μM (EC₅₀)</th>
<th>PPARβ ~1 μM (EC₅₀)</th>
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**In Vitro**

Ertiprotafib is a potent inhibitor of IKK-β, with an IC₅₀ value of 400±40 nM, which is much lower than that required for the half-maximal inhibition of the p-nitrophenyl phosphatase activity of PTP1B. The reported IC₅₀ value of Ertiprotafib against PTP1B ranges from 1.6 to 29 μM depending on the assay conditions[^2]. Ertiprotafib is at least a dual PPARα and PPARβ agonist with EC₅₀ values for transactivation of 1 μM. Such activities readily explain the observations with suprapharmacologic doses of these.[^1]

**In Vivo**

As seen with treatment of ob/ob mice, both Ertiprotafib and compound 3 seem to significantly improve glucose metabolism in rats. At 25 mg/kg/day, these compounds decrease both fasting blood glucose and insulin levels compared with vehicle treated rats. Furthermore, both Ertiprotafib and compound 3 increase glucose disposal after an oral challenge. It is noteworthy that lipid levels are also reduced in treated animals. Both triglyceride and free fatty acid levels are substantially reduced in rats treated with 25 mg/kg/day of either compound. To summarize, both Ertiprotafib and compound 3 seem to be robust agents in improving glucose utilization in fa/fa rats while also decreasing lipid levels in these animals. Decreased lipid levels may be unexpected for a pure PTP1b inhibitor. It is more telling, as mentioned above, that rats treated with suprapharmacologic doses of Ertiprotafib show signs of PPAR family activation[^2].

**PROTOCOL**

**Animal Administration[^2]**

Mice, Rats[^2]

**Male Ob/ob mice** and **Zucker fa/fa rats** are used. They are kept on a 12-h/12-h light/dark cycle and fed Rodent Diet 5001 (for mice and rats) from Purina Mills. Compounds are dosed orally by gavage in an aqueous suspension of 2% Tween 80 and 0.5% methylcellulose. Whole blood (5 μL) is used for glucose readings via tail nick for measurement using the Ascensia Elite XL glucometer and glucose strips by preloading a strip into the meter and touching the end to a small drop of blood on each tail. Insulin levels are quantified by enzyme-linked immunosorbent assay[^2].
REFERENCES
