**BIOLOGICAL ACTIVITY**

**Description**
CP-105696 is a potent and selective Leukotriene B₄ Receptor antagonist, with an IC₅₀ of 8.42 nM.

<table>
<thead>
<tr>
<th>IC₅₀ &amp; Target</th>
<th>LTB₄</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC₅₀</td>
<td>8.42±0.26 nM (IC₅₀)</td>
</tr>
</tbody>
</table>

**In Vitro**
CP-105696 is a structurally novel, selective and potent LTB₄ receptor antagonist. In vitro, CP-105696 inhibits [³H]LTB₄ (0.3 nM) binding to high-affinity LTB₄ receptors on human neutrophils with an IC₅₀ value of 8.42±0.26 nM. Scatchard analyses of [³H]LTB₄ binding to these high-affinity receptors indicate that CP-105696 acts as a noncompetitive antagonist. CP-105696 inhibits human neutrophil chemotaxis mediated by LTB₄ (5 nM) in a noncompetitive manner with an IC₅₀ value of 5.0±2.0 nM. Scatchard analyses of [³H]LTB₄ binding to low-affinity receptors on neutrophils indicate that CP-105696 acts as a competitive antagonist at this receptor, and inhibition of LTB₄-mediated CD11b upregulation on human neutrophils is competitively inhibited by CP-105696 (pA₂=8.03±0.19). CP-105696 at 10 μM does not inhibit either human neutrophil chemotaxis or CD11b upregulation mediated through alternate (i.e., C5a, IL-8, PAF) G-protein coupled chemotactic factor receptors. In isolated human monocytes, LTB₄ (5 nM)-mediated Ca²⁺ mobilization is inhibited by CP-105696 with an IC₅₀ value of 940±70 nM.[1]

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

**In Vivo**
At a dose of 50 mg/kg/day (28 days), B10.BR (H2k) allografts transplanted into C57Bl/6 (H2b) recipients are significantly protected, as reflected by the mean survival time versus control grafts (27±20 days [n=10] vs. 12±6 days [n=14]; P=0.0146). Using an induction protocol (day -1 to day 3), CP-105696 at 100 mg/kg/day significantly prolongs allograft survival (33±23 days [n=9]; P=0.0026), but CP-105696 at 10 mg/kg/day does not (18±16 days [n=8]; P=0.1433). Syngeneic grafts survive indefinitely (n=11). Immunohistological evaluation of allografts at rejection reveals a mononuclear cell infiltrate composed primarily of CD3+ and CD11b+ (Mac-1+) cells, which are infrequent in syngeneic grafts. Allografts from mice treated with CP-105696 at 50 or 100 mg/kg/day demonstrate a selective reduction in β2-integrin (Mac-1) expression on monocytes/macrophages, as demonstrated by CD11b staining density compared with allograft controls[2].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

**PROTOCOL**

---

[1] MCE has not independently confirmed the accuracy of these methods. They are for reference only.

[2] MCE has not independently confirmed the accuracy of these methods. They are for reference only.
<table>
<thead>
<tr>
<th>Animal Administration [2]</th>
</tr>
</thead>
</table>
| Mice [2]  
Allogeneic donor hearts are harvested after intravenous heparinization of donor B10.BR mice (H2k) and are preserved via retrograde perfusion with cold cardioplegia solution into the left ventricle. Recipient C57Bl/6 mice (H2b) are prepared by ligating the lumbar vessels and isolating the abdominal aorta and vena cava; donor hearts are sutured in place by microvascular anastomoses of the donor aorta and pulmonary artery to the recipient aorta and inferior vena cava, respectively. CP-105696 is evaluated in a 28-day treatment protocol (50 mg/kg/day), a high-dose (100 mg/kg/day) induction protocol (day -1 to day 3), and a low-dose (10 mg/kg/day) induction protocol (day -1 to day 3). In all study groups, drug is administered orally in a 0.5% methylcellulose vehicle. In parallel studies, treatment of C57Bl/6 (H2b) recipients bearing B10.BR (H2k) cardiac allografts given FK506 (2 mg/kg/day for 28 days), our standard control immunosuppressant, significantly prolongs allograft survival (mean survival time [MST], 40±18 days [n=9]; P=0.0002) [2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES


Caution: Product has not been fully validated for medical applications. For research use only.

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com  
Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA