WEB2086: A Chemical Probe for PTAFR

Version 1.0 (10th January 2024)

Web link for more details: https://www.sgc-ffm.uni-frankfurt.de/#!specificprobeoverview/WEB2086

Overview

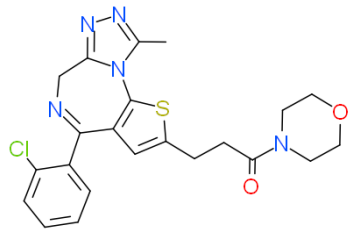
PTAFR is a G-protein-coupled seven-transmembrane receptor which is activated by platelet-activating-factor (PAF), a family of structurally related agonistic phospholipids that bind with high affinity to the receptor. PTAFR stimulation mediates numerous cellular responses such as activation of the mitogen-activated protein kinase (MAPK) pathway, phosphoinositol turnover, platelet and granulocyte aggregation, and chemotaxis of leukocytes.

Summary

Chemical Probe Name	WEB2086 (Apafant, WEB 2086BS)
Negative control compound	WEB2387
Target(s) (synonyms)	PTAFR (Platelet activating factor receptor)
Recommended *in vitro* assay concentration	Use at concentration of 300 nM for WEB2086 and WEB2387; use with negative control for best interpretation of data
Suitability for *in* vivo use and recommended dose	Tested in guinea pigs with 0.1 - 2 mg/kg po and 0.01 -0.1 mg/kg iv dose.
Publications	PMID: 3598913, PMID: 3342883, PMID: 15286429
In vitro assay(s) used to characterise	Competition with [3H]PAF binding to human platelets
Cellular assay(s) for target-engagement	Inhibition of PAF-induced human platelet aggregation; Inhibition of PAF-induced human neutrophil aggregation

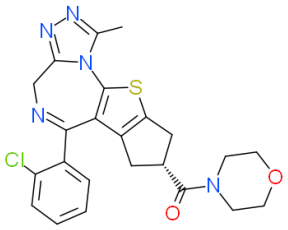
Chemical Probe & Negative Control Structures and Use

WEB2086 Chemical Probe



SMILES: Cc1nnc2CN=C(c3ccccc3[Cl])c3cc(CCC(N4CCOCC4)=O)sc3n12
InChiKey: JGPJQFOROWSRRS-UHFFFAOYSA-N
Molecular weight: 455.12 g/mol
Storage: As a dry powder or as DMSO stock solutions (10 mM) at -20 °C. DMSO stocks beyond 3-6 months or 2 freeze/thaw cycles should be tested for activity before use
Dissolution: Soluble in DMSO up to 10 mM; use only 1 freeze/thaw cycle per aliquot

WEB2387 Negative Control



SMILES: Cc1nnc2CN=C(c3ccccc3[Cl])c3c4C[C@H](Cc4sc3n12)C(N1CCOCC1)=O
InChiKey: FWYVRZOREBYLCY-CQSZACIVSA-N
Molecular weight: 467.12 g/mol
Storage: As a dry powder or as DMSO stock solutions (10 mM) at -20 °C. DMSO stocks beyond 3-6 months or 2 freeze/thaw cycles should be tested for activity before use
Dissolution: Soluble in DMSO up to 10 mM; use only 1 freeze/thaw cycle per aliquot

Chemical Probe Profile

In vitro Potency & Selectivity:

WEB2086 is a potent PTAFR inhibitor with Ki = 9.9 nM in a competition assay with [3H]PAF binding to human platelets. There are no close target analogues. Closest off-targets in the Eurofins SafteyScreen (44 targets) at 10 µM [% Ctrl] are BZD/CENTR (rat) (12) and PTGS2 (47). However, Ki = 388 nM for rat Benzodiazepine receptor inhibition.

Potency in Cells and Cellular Target Engagement:

IC_{50} = 170 nM for inhibition of PAF-induced human platelet aggregation and IC_{50} = 360 nM for inhibition of PAF-induced human neutrophil aggregation.