KDDF
Korea Drug Development Fund

Asset #47
The Scripps Research Institute

Picrotoxinin-derived NCEs as Allosteric $GABA_AR$ antagonists

Therapeutic Area	Neurology	**Indications**	GABA Related Diseases
Modality	Small Molecule	**Development Stage**	Hit to Lead/Lead Optimization

Overview

Background

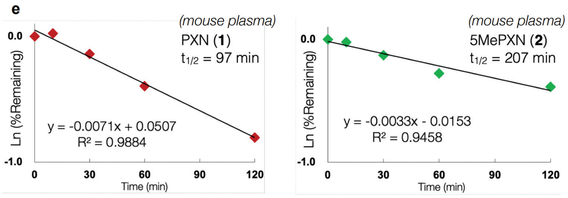
- GABA type A (GABAA) receptor (GABAAR) is a ligand-gated chloride ion channel that interacts with its namesake inhibitory neurotransmitter, GABA, and a variety of functional (though not structural) analogs, known collectively as sedatives, barbiturates or depressants.
- Picrotoxane is a family of botanicals that act as non-competitive agonists (NCA)/allosteric modulators of GABAAR. Picrotoxinin (PXN) can be dosed alone or in a 1:1 mixture with its less active C12 hydrate (Picrotin, PTN) – together known as picrotoxin (PTX). To date, known picrotoxane NCAs are associated with lethal convulsions – a feature absent in the sesquiterpenoids bilobalide & jiadifenolide

Technology Advantages

- Defined manufacturing route; no reported total synthesis of PXN, yet
- Wider therapeutic window; acute toxicity of PTX at LD50 of 2 mg/kg in rat, i.p.
- Selectivity towards receptor; no PXN analog has demonstrated such selectivity
- Improvedstability;atpH7.4,PXNt1/2 < 45 min
- Candidate drug is orally bioavailable and is a brain penetrant

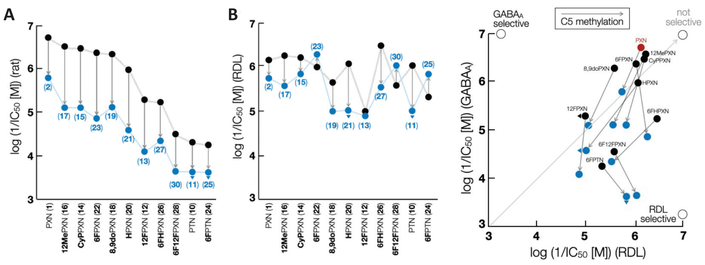
Key Data

Compound Stability in Serum (brain penetrant, orally bioavailable)



The relative rates of hydrolysis observed in mouse plasma was investigated. C5 methylation led to a doubling of the extrapolated half-life in plasma.

Experimental and computational analysis of LGIC binding and selectivity



(A), Relative potencies of PXN (•) and 5MePXN (•) analogs at GABAAR ([3H]-TBOB). (B), Relative potencies of PXN (•) and 5MePXN (•) analogs at RDL receptors measured by electrophysiology; (C), Selectivity between vertebrate (GABAA) and invertebrate (RDL) receptors by PXN analogs: C5-methylated analogs are selective for invertebrate receptors.

IP Status & Publication(s)

Intellectual Property

Patent Number
PCT-US2020-070376 (2020.08.06)

Patent Family
PCT

Publication(s)

- Crossley, S. W. M. et al. (2020). Synthesis of (−)-Picrotoxinin by Late-Stage strong bond activation. Journal of the American Chemical Society, 142(26), 11376–11381.
- Tong, G., & Shenvi, R. A. (2021). Revision of the unstable picrotoxinin hydrolysis product. Angewandte Chemie, 60(35), 19113–19116.
- Tong G, et al. (2022) Methylation Confers Accessibility, Stability and Selectivity to Picrotoxinin. ChemRxiv. Cambridge: Cambridge Open Engage