Picrotoxinin-derived NCEs as Allosteric $GABA_AR$ antagonists

Diverse NCEs boast higher efficacy and wider therapeutic window vs. natural compound

BD-2210

Background

- GABA type A (**$GABA_A$**) 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. As a tool compound, 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*.

Objective

- The Shenvi Lab is engaged in developing efficient synthetic routes to manufacture highly effective and potent psychoactive and psychedelic natural products against important receptors involved in neuropsychiatric diseases. Here, the group is targeting GABAAR with picrotoxane-derived NCAs and their derivatives (**new chemical entities** (**NCEs**)).

Target Product Profile

- defined **manufacturing route**; no reported total synthesis of PXN, yet;
- wider **therapeutic window;** *acute toxicity of PTX at LD_{50} of 2 mg/kg in rat, i.p.*,
- **selectivity** towards receptor; *no PXN analog has demonstrated selectivity*, and
- Improved **stability**; *at pH 7.4, PXN $t_{1/2}$ < 45 min.*

Milestones Achieved

- ✓ **NCE patent filed**
- ✓ Serum stability of PXN and analogs attested;
- ✓ Selectivity demonstrated towards GABAAR vs. GABABR (aka RDL)
- ✓ Candidate drug is orally bioavailable and is a brain penetrant

Next Steps

- Fundraising for a research funding/option agreement; use of proceeds to include
  - ❑ Manufacturing: diversify PXN analogs; stabilize the short-lived PXN scaffold;
  - ❑ PD: dial out GABAR-mediated toxicity;
  - ❑ Pipeline: expand pipeline to target additional ligand-gated ion channels (such as microbial pathogens or pests); other $GABA_A$ R subtypes.

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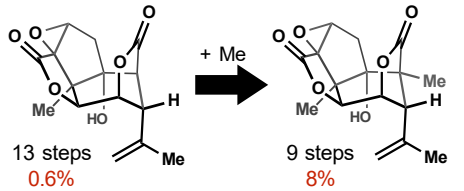
Target Structure

$GABA_A$ Receptor is a pentameric protein combinatorially formed from diverse subunits made of multiple subunits: α1–6, β1–3, γ1–3, δ, ε, θ, π, and ρ1–3

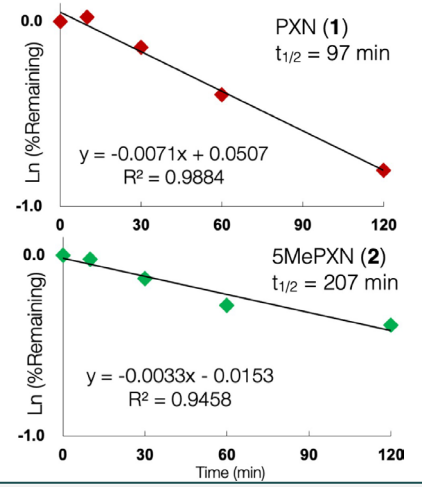
Barnard *J. Neurochem.* **1994**, 815

Synthetic Route

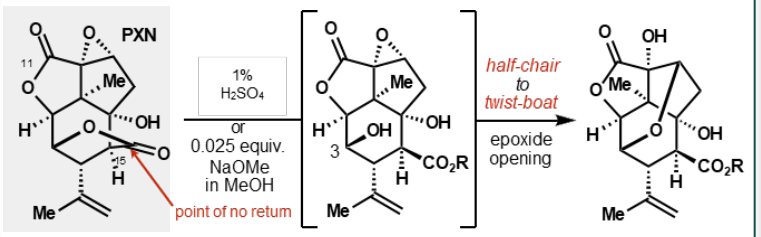


Easily accessible and diversifiable

Compound Stability in Serum (brain penetrant, orally bioavailable)



Compound Stability in Solution



NCEs' Selectivity towards $GABA_AR$ vs $GABA_BR$ (RDL)