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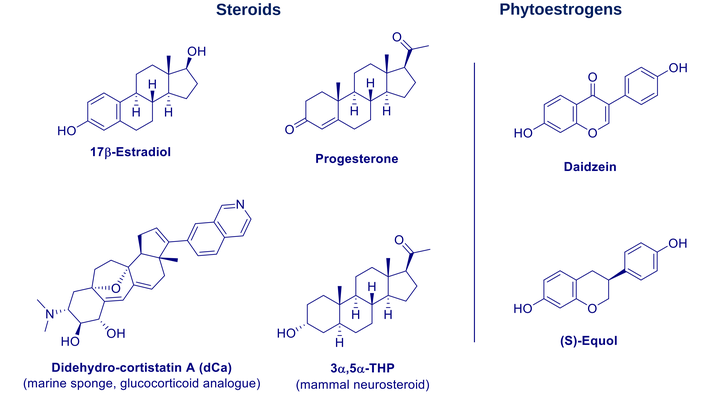
HIV Neurotoxicity

- Currently, about 1.2 million people are suffering from HIV in the U.S.
- Combined antiretroviral therapeutics (cART) can eradicate circulatory viral load of HIV and have extended the lives of HIV-1 infected individuals.
- About half of HIV-1 patients suffer from affective and cognitive neurological symptoms (called “neuroHIV”).

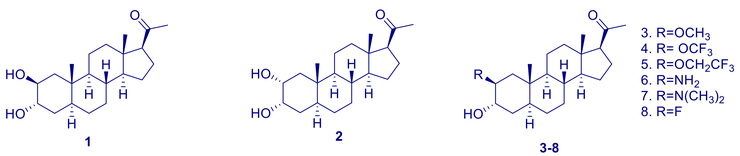
Neurotoxic Viral Proteins

- Neurotoxic viral proteins such as the trans-activator of transcription (Tat), and glycoprotein 120 (gp120), are thought to be present in the central nervous system and contribute to neuroHIV which cannot be eradicated by cART.
- Tat can disrupt ion homeostasis through activation of NMDA receptors and Ca^{2+} channels.
- Ion dysregulation and mitochondrial stress result in translocation of pro-apoptotic Bax, *cyt* c and cause neuronal damage or death.
- As a result, Tat promotes cognitive and affective dysfunction in mice.

Neuroprotective Agents against HIV-Tat Protein



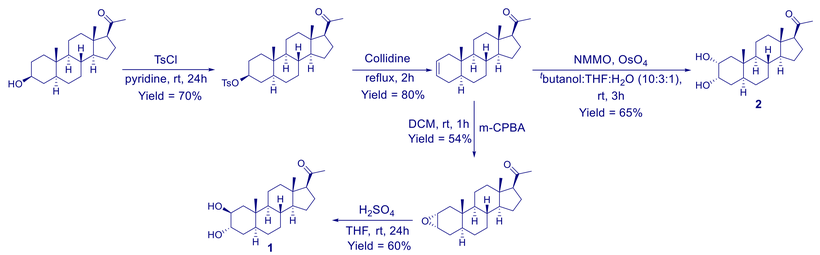
3α,5α-THP Analogues

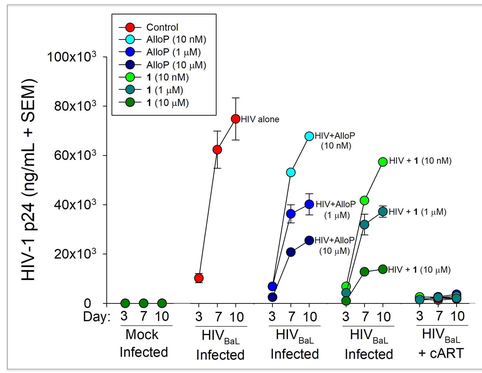


Our Goal

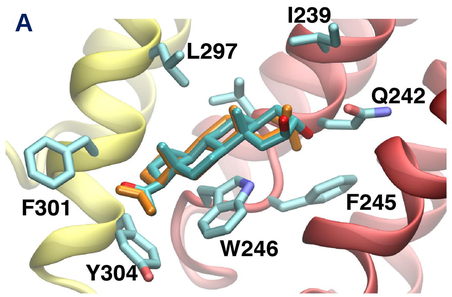
- Using structure based drug discovery approach, we designed analogues through stereospecific functionalization at C2 position of 3α,5α-THP (allopregnanolone).
- Our hypothesis is our designed compounds will ameliorate the viremia, inflammation, and neurotoxicity caused by infectious HIV-1 both in vitro and in vivo animal model.
- Preliminary results of in vitro showed that stereospecific modification at C2 position of 3α,5α-THP is crucial for activity.
- Currently we are working on a library of potential compounds having good PK profile, complement cART, and potent against neuroHIV symptomatology.

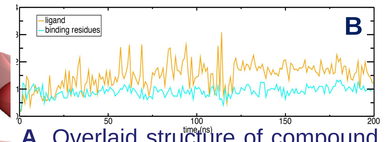
Synthetic Scheme





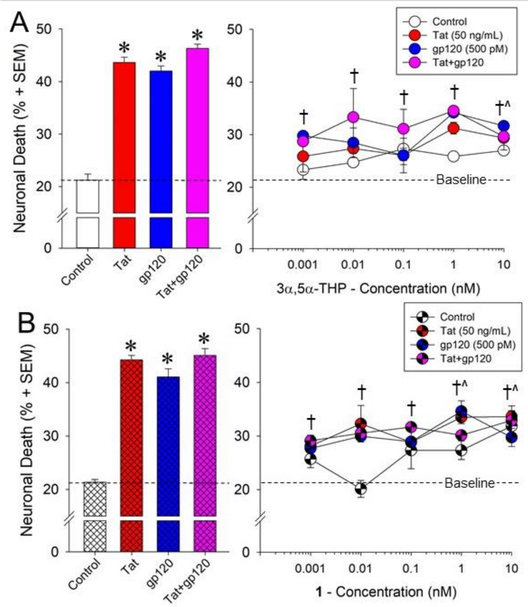
Allopregnanolone or compound **1** attenuates HIV-1BaL (1 ng/mL p24) replication over 10 days as indicated by the accumulation of p24 HIV capsid protein. Neither allopregnanolone nor compound **1** impair the efficacy of cART when co-administered.





A. Overlaid structure of compound **1** and α1-β3 intersubunit site of $GABA_A$ R (PDB ID **6I53**). **B**. RMSD of compound **1** and side chains of the binding residues in MD simulation

Results



HIV-1 Tat and/or gp120 produced necrosis of mouse primary medium spiny neurons in mixed glial co-culture following 20 h (see *). Pretreatment with 3α,5α-THP (panel A) or compound **1** (panel B) significantly attenuated necrosis at every dose assessed (see †). The highest concentrations of either compound increased baseline cell death modestly (see ^), but were still protective, $p < 0.05$.

Discussion

- As a proof-of-concept, compound **1** showed protection against HIV neurotoxicity and viremia.
- Both allopregnanolone and compound **1** showed inhibition of Cav1.1 channel and modulation of $GABA_A$ receptor.
- Compound **2** did not show good activity suggested the importance of stereospecific functionalization of 3α,5α-THP.
- Further computational investigation showed that unlike compound 2, compound **1** has good binding interaction in α1-β3 intersubunit site of $GABA_A$ receptor. MD simulation also confirmed the stability of the binding interaction.
- Currently, we are investigating PK profile and *in vivo* efficacy of compound **1** in anxiety-like behavior, depression-like behavior, cognition and motor function of HIV-1 Tat expressing transgenic mice model.

Conclusion & Future Plan

- Compound **1** showed protection against neuroHIV.
- We will assess compounds **3**-**8** in *in vitro* model.
- Pharmacokinetics, cART interaction, and neuroHIV symptomatology studies of **1** are being carried out in *in vivo* model.

References: **1)** https://www.hiv.gov/hiv-basics/overview/data-and-trends/statistics **2)** Gendelman, H. E.; Meltzer, M. S. Mononuclear Phagocytes and the Human Immunodeficiency *Virus*. *Curr*. *Opin*. *Immunol*. 1990, 2, 414–419. **3)** Hong, S.; Banks, W. A. Role of the Immune System in HIV-Associated Neuroinflammation and Neurocognitive Implications. *Brain*. *Behav*. *Immun*. 2015, 45, 1–12. **4**) Paris, J. J.; Zou, S. P.; Hahn, Y. K.; Knapp, P. E.; Hauser, K. F. 5α-Reduced Progestogens Ameliorate Mood-Related Behavioral Pathology, Neurotoxicity, and Microgliosis Associated with Exposure to HIV-1 Tat. *Brain*. *Behav*. *Immun*. 2016, 55, 202–214.