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Novel Pharmacotherapy for Treating Cognitive Dysfunction and Chronic Pain in Alzheimer's Disease

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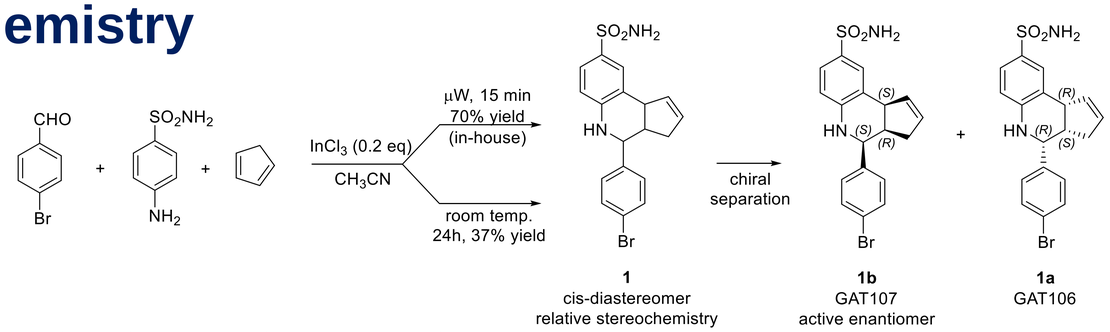
Abstract and Background:

Alzheimer's disease (AD) is an irreversible neurodegenerative disorder which leads to dementia and chronic pain; a combination difficult to manage, and worsens over time, completely incapacitating the individual. Current therapies modestly manage only one of these medical conditions at a time and a pharmacotherapy that addresses all the above issues without significant side effects is an unmet medical need. In the past couple of decades, α7 nicotinic acetylcholine receptor (nAChR) has emerged as a target that holds such a promise. The activation of α7 nAChRs through potent orthosteric agonists has met with limited clinical success due to lack of efficacy, off target activity and hERG inhibition. An alternative strategy is to target the allosteric site(s) on the α7 nAChRs. As allosteric sites are less conserved as compared to orthosteric sites, they significantly lack off-target activity. 4BP-TQS, an allosteric agonist-positive allosteric modulator (ago-PAM) was found to be one such ligand that activated the receptor on its own and enhanced the activity of the endogenous ligands (e.g. Acetylcholine). In-house microwave-accelerated synthesis of 4BP-TQS and its enantioseparation yielded GAT107 [(+) enantiomer], which was found to be the active enantiomer in electrophysiology studies in *Xenopus* oocytes. GAT107 was furthered into in vivo studies with various animal models of memory and chronic pain models to evaluate its efficacy.
Our preliminary data strongly supports that this novel class of compounds acting through a unique mechanism (ago-PAM) provides a better approach for improving cognitive deficiencies and associated chronic pain. GAT107 will help develop novel, potent and safe α7 nAChR ago-PAMs as an effective and unique pharmacotherapy for Alzheimer's disease.

Hypothesis

The allosteric agonism and modulation of α7 nAChR is a novel approach which helps in improving cognitive and memory impairments and alleviating chronic/neuropathic pain in Alzheimer's disease.

Chemistry



1
cis-diastereomer
relative stereochemistry

1b
GAT107
active enantiomer

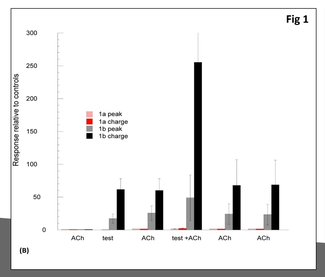
1a
GAT106

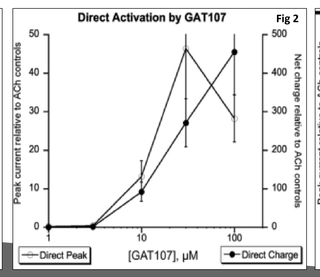
Using our in-house developed synthetic approach with a microwave synthesizer, we were able to synthesize the racemate 4BP-TQS using the three-component Povarov reaction, in 15 minutes at double (70%) the yield as compared to the conventional method which required 24 hrs. It was then separated into its enantiomers GAT106 (**1a**) and GAT107 (**1b**) using chiral chromatography.

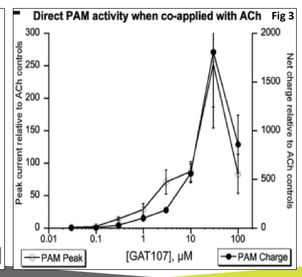
Results and Methods

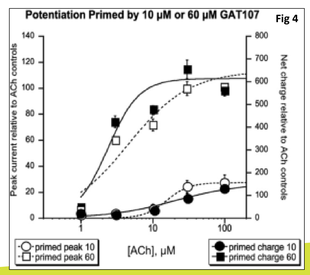
In vitro model:

Data shows the effectiveness of the (+) enantiomer **1b**, but not **1a**, as an allosteric agonist and a PAM (10µM). These effects were not affected when **1a** was co-applied, suggesting that **1a** is not a competitive antagonist of the active isomer. GAT107 displayed 3 types of activities – direct activation, direct potentiation and primed potentiation.

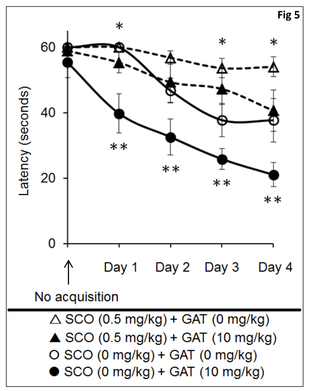




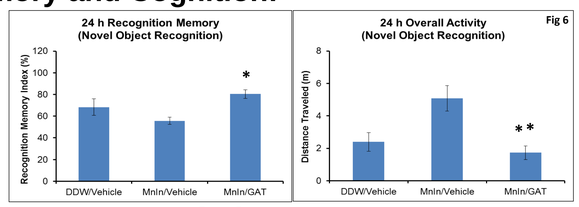




In vivo models of Memory and Cognition:

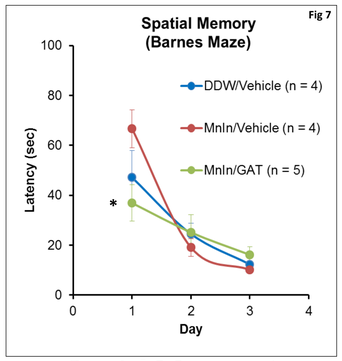


Morris Water Maze



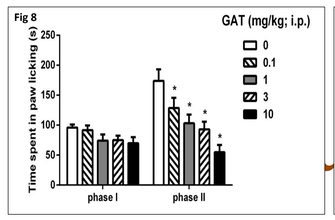
Novel Object Recognition

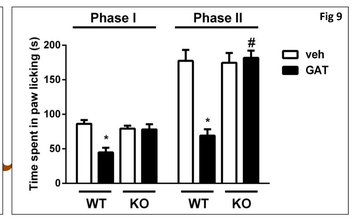
As seen from the data, GAT107 reversed the scopolamine induced memory impairment in the **Morris water Maze**. It also was effective in reversing the metal toxicity induced memory impairment in the **Novel Object Recognition** test and the **Barnes Maze**.



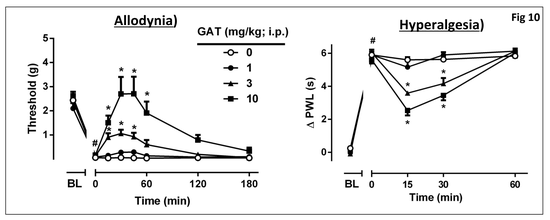
Spatial Memory / Barnes Maze

In vivo models of Pain:

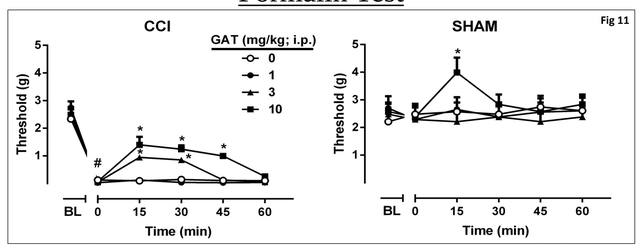




Formalin Test



Complete Freund's Adjuvant (CFA) Model



Chronic Constructive injury (CCI) Model

The formalin test is the test of inflammation; the CFA test is the test for chronic pain and the CCI mouse model is used to evaluate the ability of GAT107 to reverse neuropathic pain induced by injuring the sciatic nerve. In the all these mouse models, GAT107 was able to dose dependently exhibit statistically significant anti-inflammatory, anti-allodynic and anti-hyperalgesic effects. These effects were not seen in α7 knock out mice and the a7 inverse agonist MLA blocked these effects in all three models.

Summary

- Electrophysiological revealed that all the activity resided in the (+) enantiomer (**GAT107**) with 3a*R*,4*S*,9b*S* as the absolute stereochemistry. The inactive (-) enantiomer did not affect its activity when co-applied. **GAT107** has three different activities: direct activation, direct potentiation and primed potentiation.
- **GAT107** was found to be effective in all the animal models of cognition and memory as well as inflammation, chronic and neuropathic pain and did not have any locomotor or hypothermic side effects.
- Our preliminary data strongly supports that this novel class of compounds acting through a unique mechanism (ago-PAM) provides a better therapeutic avenue. **GAT107** is currently being optimized for the development of novel, potent and safer ago-PAMs of α7 nAChR as effective pharmacotherapy for dementia and chronic pain in Alzheimer's disease.

References

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