SYNTHESIS OF 5-MEMBERED RING HETEROCYCLES FOR ALZHEIMER'S DISEASE

Andrews University
Office of Research & Creative Scholarship

Daniel Fajardo, Lisa Ahlberg, Ph.D.

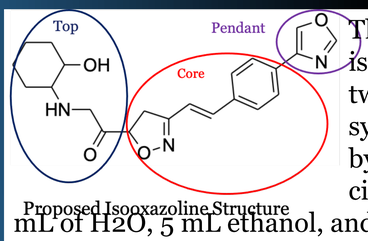
Department of Chemistry & Biochemistry
Andrews University

Department of Chemistry & Biochemistry
Andrews University

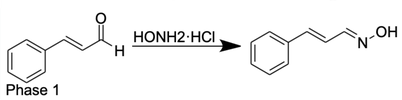
Abstract

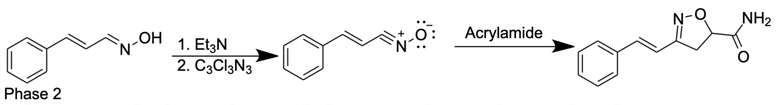
The progression of Alzheimer's disease (AD) is correlated to the degenerative activation of muscarinic acetylcholine receptors (mAChR) located in the brain. They are a family of five G-protein coupled receptors, (M1-M5), linked to have functions within the central and peripheral nervous system.[1] More specifically, activation of an M1 receptor with positive allosteric modulators (PAM), have shown to bind to the allosteric pocket and slow the degenerative process of AD with minimal intrinsic effects.[2] Structural motifs of potent PAM activity and weak agonism proposed a synthesis of an isooxazoline compound, incorporating a 1,3-dipolar cycloaddition. The core motif of the proposed isooxazoline structure has been created and further synthesis of the pendant and top is required.

Methodology



The creation of the proposed isooxazoline core motif occurs in two phases. The first phase synthesized cinnamaldehyde oxime by adding 20 mmol of cinnamaldehyde into a solution of 5 mL of H_2O, 5 mL ethanol, and 10 mL of ice. Added to this solution was 40 mmol of a 50% aqueous solution of NaOH and stirred for 18 hours at room temperature. The oxime was then extracted from the organic phase while the aqueous phase was acidified to pH 5 from HCl and was extracted once more.





The second phase formed the ring through 1,3-dipolar cycloaddition which is the core motif. This was synthesized by adding oxime with 2.79 mL of triethylamine and 1.864 g of cyanuric chloride in an ice bath for 15 minutes to create the nitrile. The oxide was then removed from the ice bath and left under constant agitation for 30 minutes with 20 mL of diethyl ether and extracted by gravity filtration. The oxide and 1.421 g of acrylamide was added and stirred for 24 hours. Mass spectrometer (MS) was used to analyze both phases while thin layer chromatography (TLC) and nuclear magnetic resonance (NMR) was used on the second phase.

Results

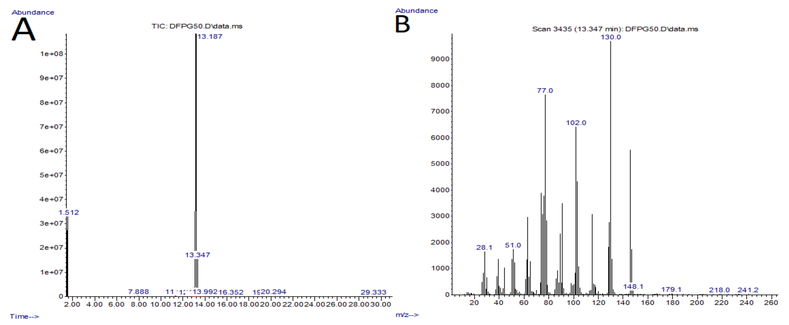


Figure A is the chromatogram of phase 1 in representative of the molecule of interest, cinnamaldehyde oxime, with the breakdown of the molecule on figure B. Figure B represents the shows multiple peaks at that 13.187 minutes, Figure A. There is a peak at 148.1 m/z and two large peaks at 130.0 m/z and 77.0 m/z.

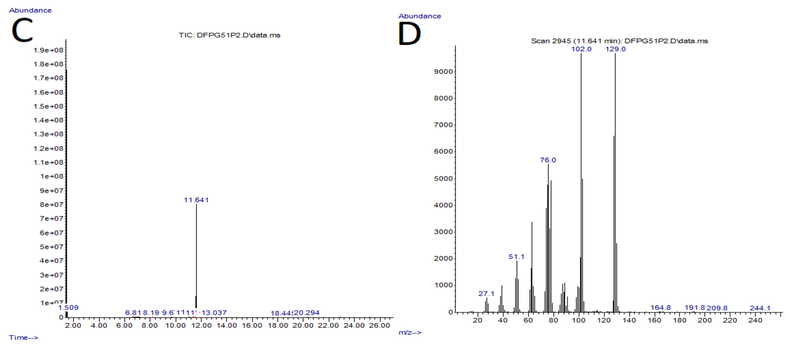


Figure C and E represents analysis for phase 2 for synthesizing the isooxazoline core motif. Figure D shows the mass spectroscopy data of the core motif breakdown at 11.641 minutes as seen on figure C. There are peaks at 129.0 m/z, 102.0 m/z, and 76.0 m/z that represents different parts of the molecule when being broken down.

Acknowledgements

AU Department of Chemistry & Biochemistry,
The Office of Research and Creative Scholarship

Discussion

We are interested in synthesizing a potential PAM-agonist with minimal intrinsic effects by using isooxazoline characteristic structure. The synthesis of isooxazoline through 1,3-dipolar cycloaddition with the purpose of being used as a potential PAM agonist with minimal intrinsic effects. The product from phase two is an electron rich dipole which allows its highest occupied molecular orbital (HOMO) to interact with the lowest unoccupied molecular orbital (LUMO) of a dipolarphile. This phase formed the ring which is characteristic of isooxazoline core motif. Analysis from figure A shows a peak at 148.1 m/z which shows the protonated version of the oxime of interest that has a molecular ion of 147.17. Correspondingly, 77.0 m/z is similar to that of a deprotonated benzene ring which has a molecular ion of 78.11

Analysis of MS from figure B showed that the compound of interest have been created. Phase two created the dipole, nitrile oxide, to be able to interact with the dipolarphile, acrylamide, through 1,3-dipolar cycloaddition. Analysis of TLC (not shown) showed unconvincing data that the core motif has been created. But, through the use of MS, there seems to be more convincing data. Figure D shows the benzene peak at 76.0 m/z. There is a styrene peak at 102.0 m/z which could be shown from the breakdown of the molecule. The peak at 129.0 m/z is the other half from the styrene which includes the carboxamide, isoxazole, and a methyl that has a total molecular ion of 128.13. Future research requires synthesizing the top and pendent motif for which it can be attached to the core to fully create the proposed isooxazoline structure. Looking further down the line, the proposed structure can be tested as a PAM-agonist compound hopefully with minimal intrinsic effects to test against Alzheimer's disease.

Bibliography

1) Discovery of the Potent and Selective M1 PAM-Agonist N-[(3R,4S)-3-Hydroxytetrahydro-2H-pyran-4-yl]-5-methyl-4-[4-(1,3-thiazol-4-yl)benzyl]pyridine-2-carboxamide (PF-06767832): Evaluation of Efficacy and Cholinergic Side Effects

2) Design and Synthesis of γ- and δ-Lactam M1 Positive Allosteric Modulators (PAMs): Convulsion and Cholinergic Toxicity of an M1-Selective PAM with Weak Agonist Activity