COLLEGE OF ARTS AND SCIENCES | DEPARTMENT OF CHEMISTRY AND BIOCHEMISTRY

Synthetic Approach to Realkylation of Aged Acetylcholinesterase Using Quinone Methide Precursors

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Introduction

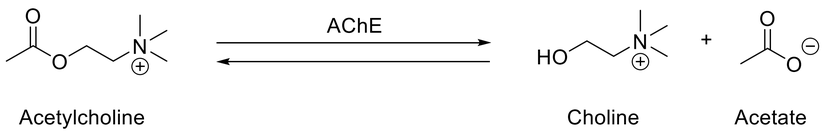
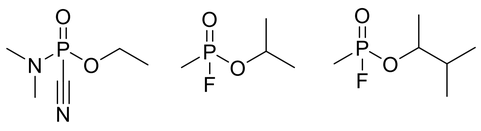
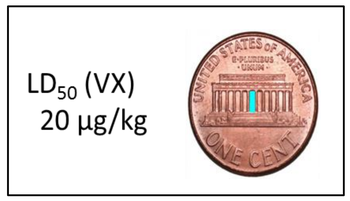


Figure 1. Hydrolysis of Acetylcholine (ACh) to Choline by AChE





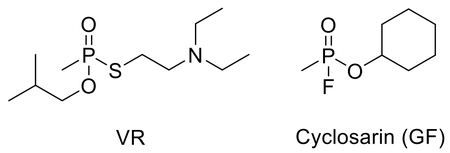


Figure 2. Library of Organophosphorus (OP) Nerve Agents

OP nerve agents are substrate analogues of ACh that irreversibly inhibit AChE by reacting in the enzyme's active site.

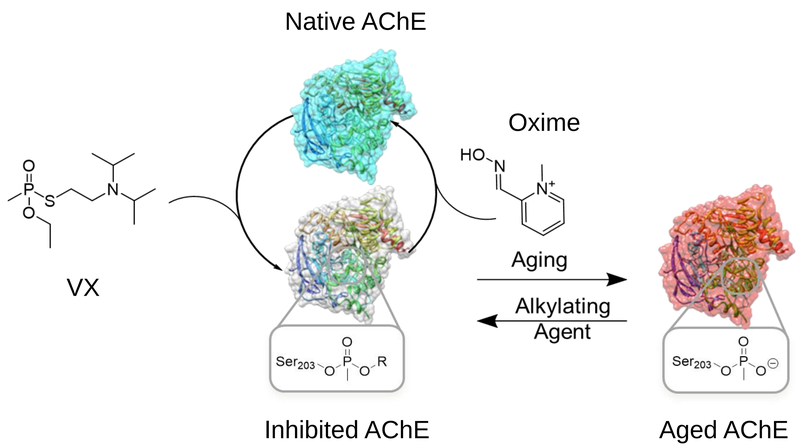


Figure 3. Inhibition and Aging of AChE

- Inhibited AChE can be reactivated by oximes to yield native AChE
- Aging occurs when the OP-AChE adduct is dealkylated
- Oxime treatment is ineffective on the aged form of AChE
- Quinone methides (QM) can potentially realkylate aged AChE

QMs as Alkylating Agents

- Synthesize a library of quinone methide precursors (QMPs) that will generate active electrophilic quinone methides (QMs) *in situ*
- Investigate their ability to realkylate model phosphonates and the aged form of AChE
- If alkylated, reactivation of inhibited AChE is possible (treatment with oximes)

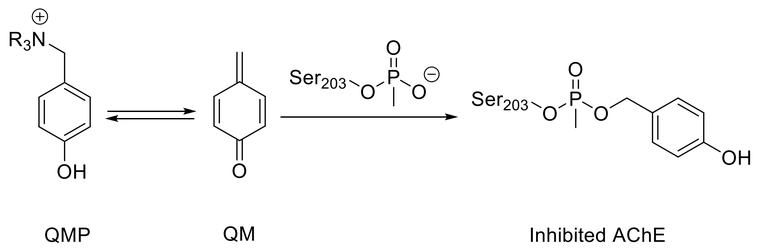


Figure 4. Alkylation of Aged AChE by QM *in situ*

Design and Synthesis of QMP Library

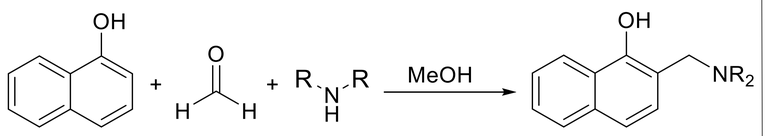


Figure 5. Synthesis of QMPs by Mannich Reaction

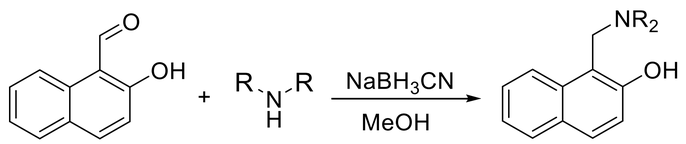


Figure 6. Synthesis of QMPs by Reductive Amination

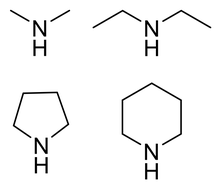
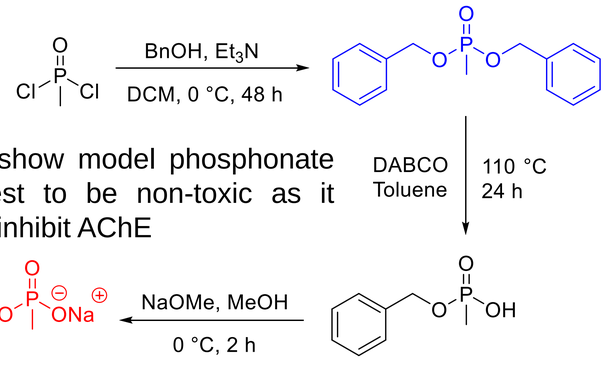


Figure 7. Selection of Amine Leaving Groups

Final QMPs will have protonated and methylated amine leaving groups

Synthesis of Model Phosphonate



Studies show model phosphonate of interest to be non-toxic as it failed to inhibit AChE

Figure 8. Synthesis of Model Phosphonate from Methyl Phosphonic Dichloride

Nucleophilicity of Model Phosphonate

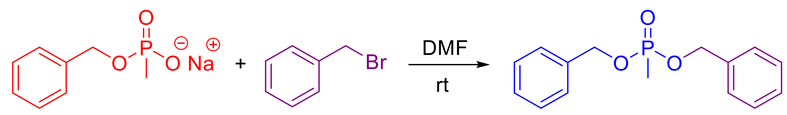


Figure 9. Model Phosphonate Reaction with Benzyl Bromide

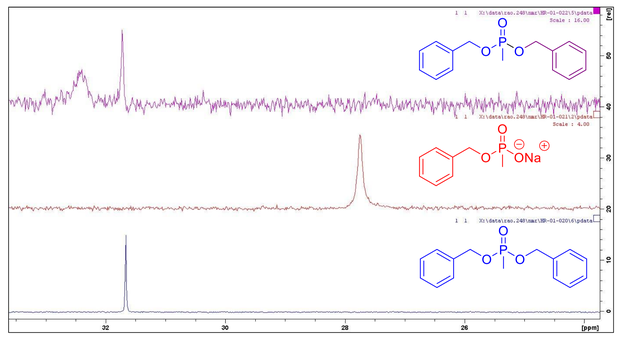


Figure 10. ^{31}P-NMR Data

Future Directions

Screen QMP library for reaction with model phosphonate and monitor it by ^{31}P-NMR spectroscopy

References

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Acknowledgements

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