Exploring the Chemical Space of Neuroactive Small Molecules: Synthesis and Biological Activity of Novel Rivastigmine and Vincamine Analogs

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ASDRP
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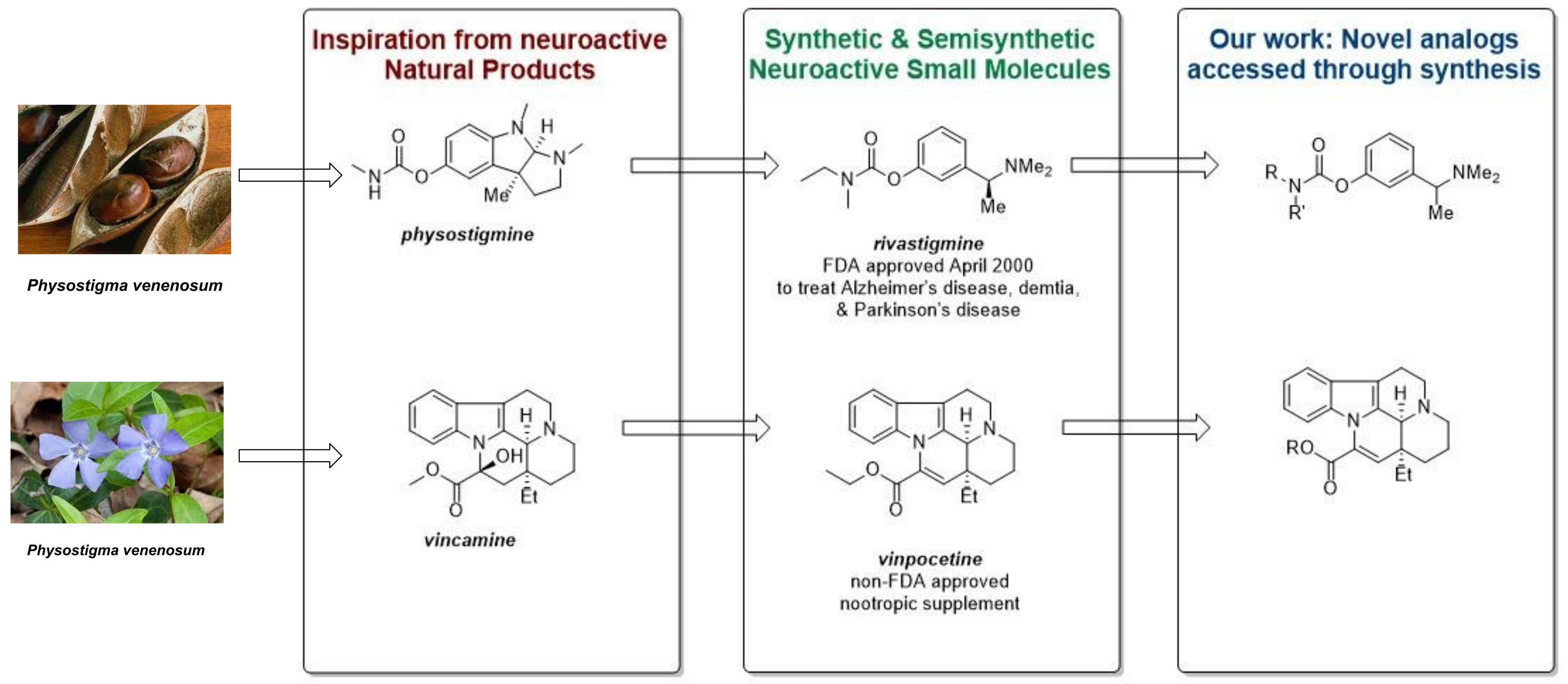
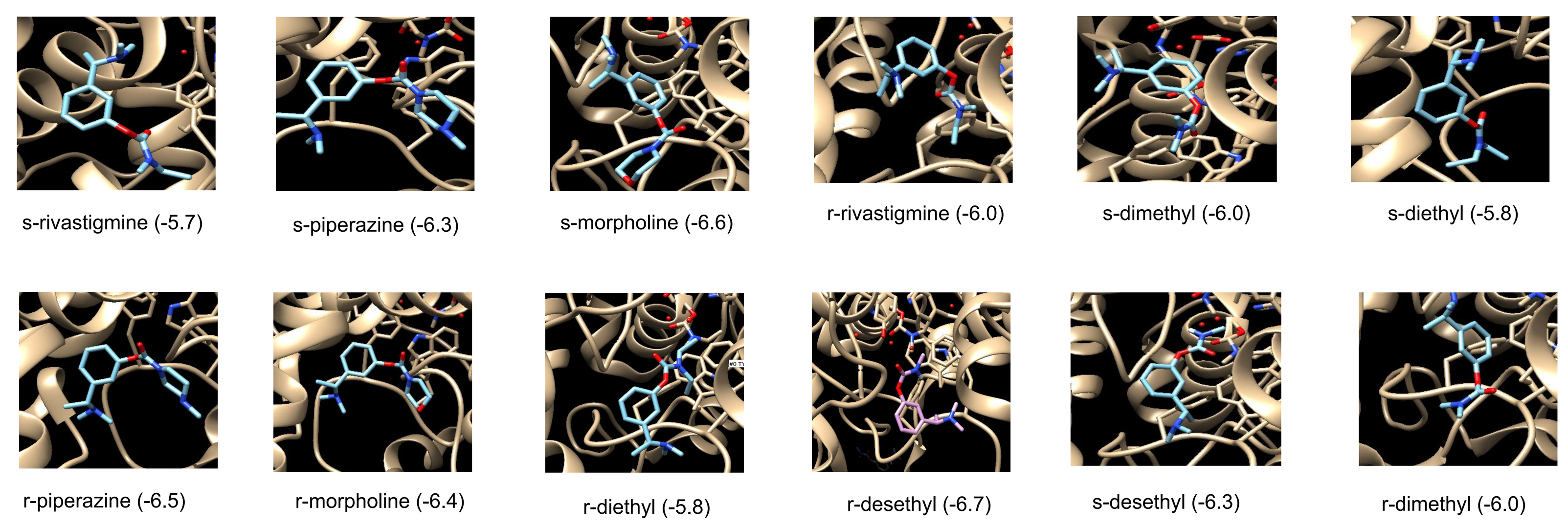
Abstract

Neuro-active natural product alkaloids have long served as the inspiration for small molecule chemical entities that have the potential to treat neurodegenerative and neurological disorders. Rivastigmine, a synthetic analog of the naturally occurring alkaloid, physostigmine, has been found to be a potent cholinesterase inhibitor and has shown great efficacy in treating neurodegenerative diseases such as Alzheimer's and Parkinson's. Likewise, vinpocetine, a semi-synthetic derivative of vincamine, has also shown improved biological activity over its natural product counterpart. Here we present efforts towards the chemical synthesis of novel analogs of rivastigmine and vincamine. Experimental results are coupled with computational modeling, including molecular docking experiments, to rationalize observed structure activity relationships.



In Silico Studies



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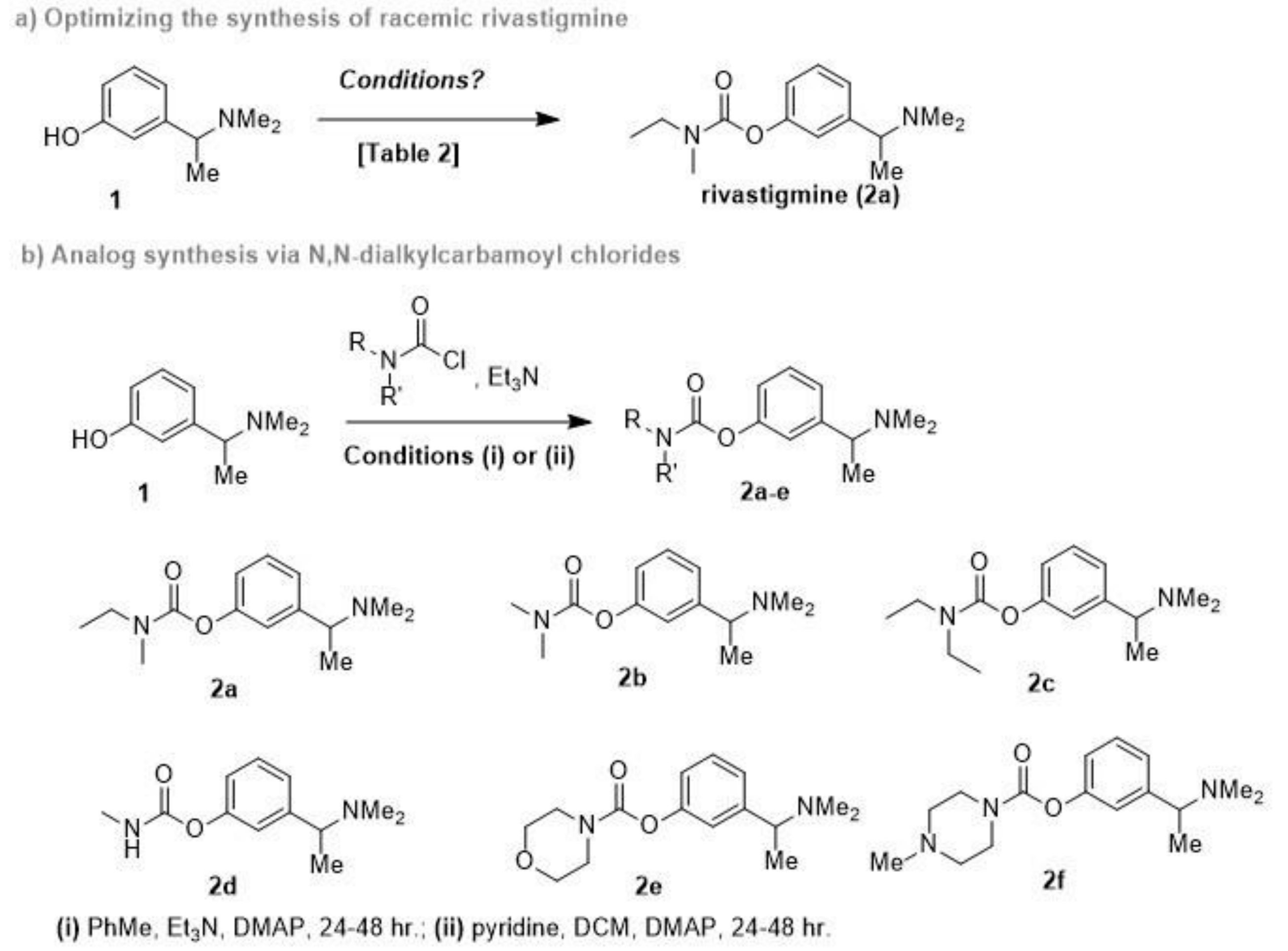
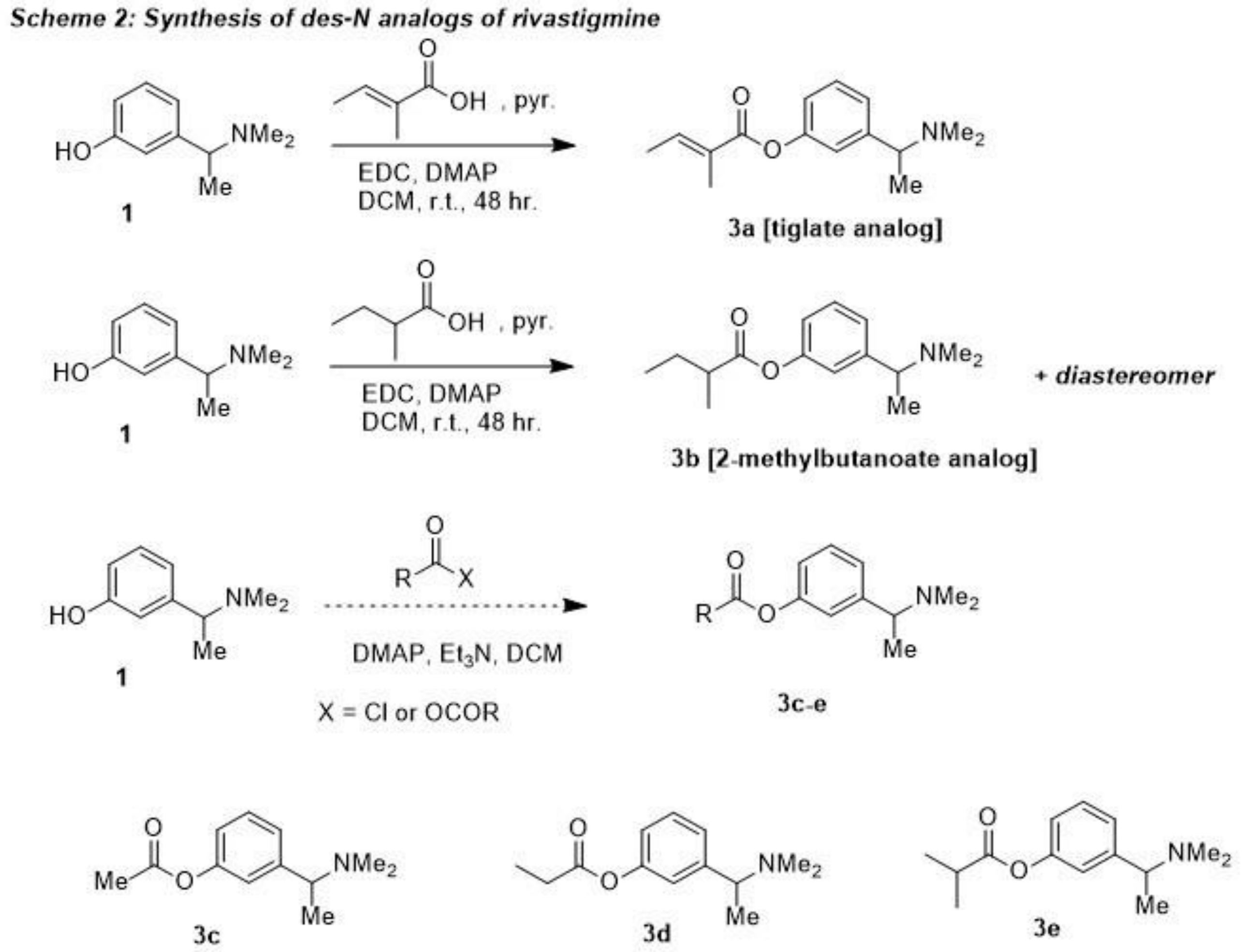
Methodology

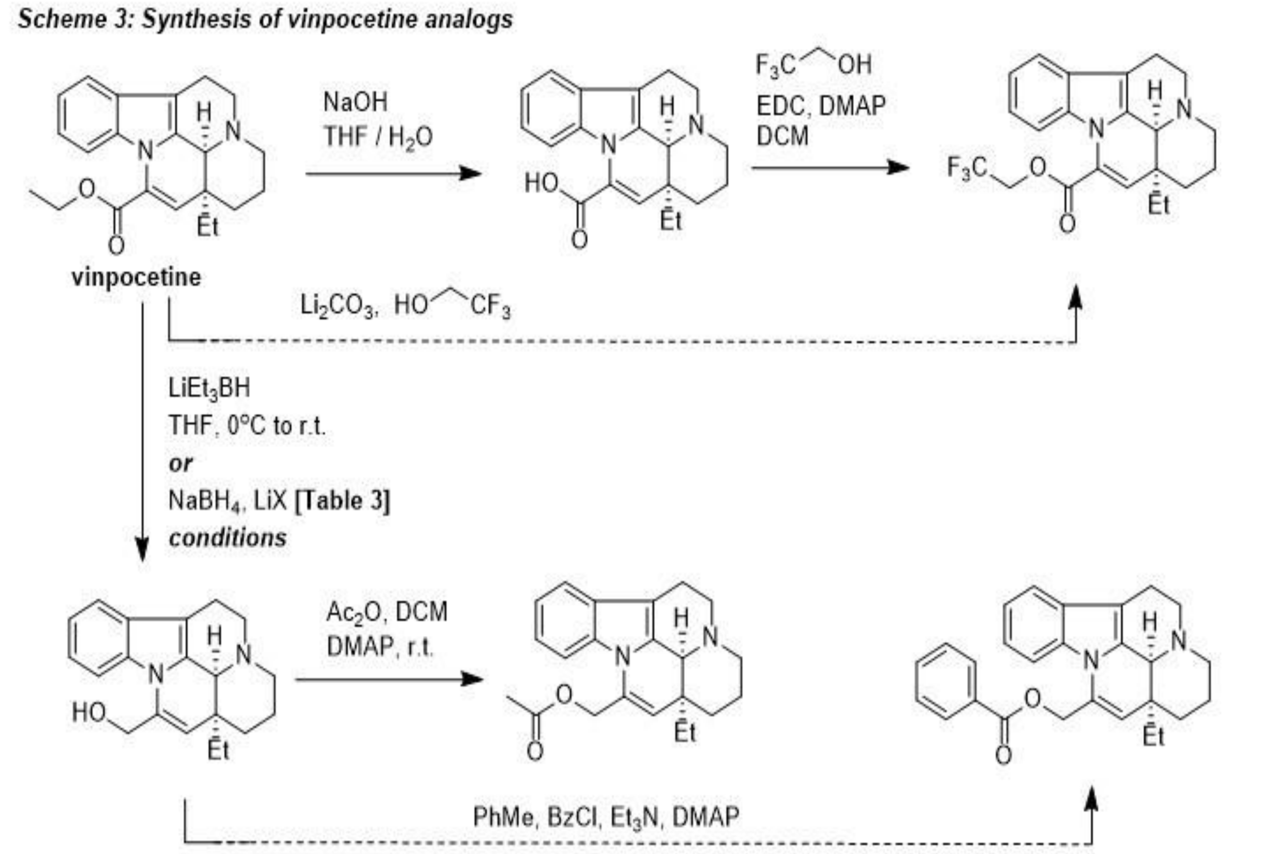
Scheme 1: Synthesis of carbamate anlaogs of rivastigmine



Scheme 2: Synthesis of des-N analogs of rivastigmine

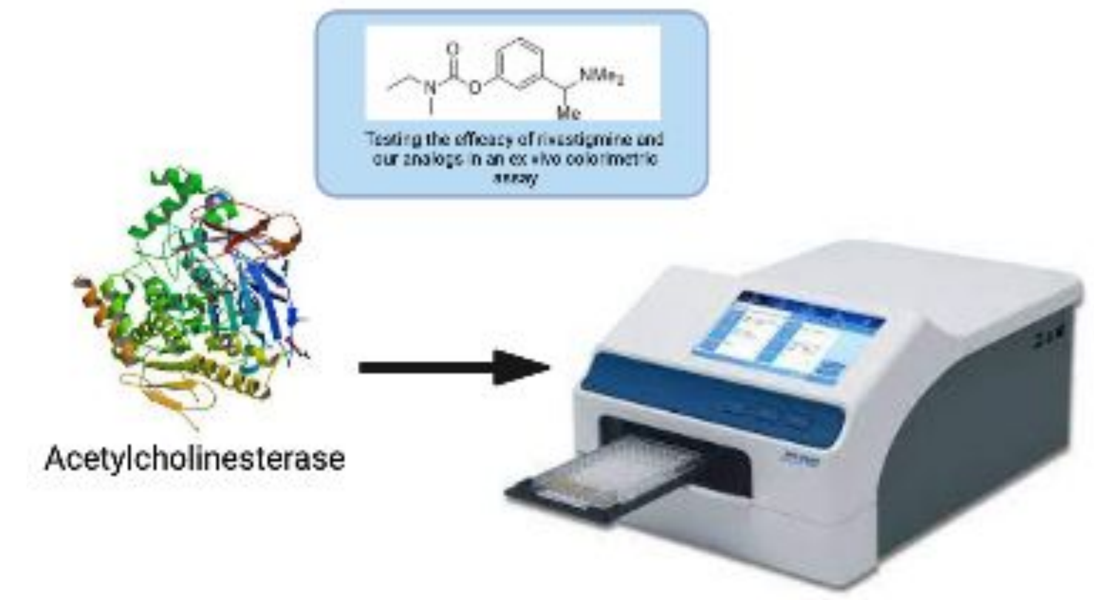


Scheme 3: Synthesis of vinpocetine analogs



Results

Entry	Solvent	Base/catalyst	Result
1	DCM	Pyridine	Slow conversion
2	PhMe	Et3N, DMAP	No conversion
3	PhMe (reflux)	Et3N	No conversion
4	DCM	DMAP, Et3N	Slow conversion
5	DCM	DMAP, pyridine	>30% yield



For our library of analogs, we focused on changing the ester of rivastigmine, and with this we synthesized the piperazine, morpholine, and diethyl compounds. Through rigorous monitoring of piperazine, we observed the presence of moisture, which interfered with the reaction mechanism causing the formation of side product, n-methyl piperazine. With further experimentation using different solvent systems, as well as catalysts, we were able to yield our desired product, while noticing that it was likely replaced with n-methyl piperazine as it is more electronegative than piperazine. Our next efforts were central to nitrogen substitutions and with this we synthesized the Methyl Butanoate and tiglate compounds. Here, with the tiglate, we faced the issue of achieving complete separation between excess tiglic acid and the formed product.

References

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