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Novel synthesis of physovenine and physostigmine analogs

C. H. Wang [a], S. Alluri [a], G. Nikogosyan [a], C. DeCarlo [a], C. Monteiro [a], G. Mabagos [a], H. H. Feng [a], A. R. White [a], M. Bartolini [b], V. Andrisano [c], L. K. Zhang [d], A. K. Ganguly [a,*]

[a] Department of Biomedical Engineering, Chemistry and Biological Sciences Stevens Institute of Technology, Hoboken, NJ 07030, USA
[b] Department of Pharmacy and Biotechnology, University of Bologna, via Belmeloro 6, 40126 Bologna, Italy
[c] Department for Life Quality Studies, University of Bologna, Corso d'Augusto, 237, 47921 Rimini, Italy
[d] Merck Research Laboratories, 2015 Galloping Hill Road, Kenilworth, NJ 07033-1300, USA

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ABSTRACT

This Letter describes a versatile synthetic approach to prepare physovenine and physostigmine analogs. A series of analogs were synthesized and evaluated for cholinesterase inhibition activities, including human acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) from human serum.

Introduction

(−)-Physovenine and (−)-physostigmine (Fig. 1) are known to be acetylcholinesterase (AChE) inhibitors.[1a–c] These alkaloids have been used in the past for the treatment of *myasthenia gravis* and glaucoma and more recently AChE inhibitors such as Donepezil[2] and Rivastigmine[3] have found use for the treatment of Alzheimer's patients.

The main challenge for the synthesis of physovenine and physostigmine analogs is the construction of quaternary carbon center. There are reported syntheses in the literature[4a–e] toward achieving this goal. Our approach for the synthesis of physovenine and physostigmine analogs is different and novel. The present synthesis allows us to make structurally diverse compounds for establishing structure activity relationship. The key step in our synthesis is the formation of the spiro-oxindiole ring using radical cyclization process followed by further elaboration yielding the crucial alcohol intermediate (**A**).

In a previous publication[5] we have reported the synthesis of a novel class of progesterone receptor antagonists using the intermediate (**A**) and in this publication we have used the same intermediate (**A**) to synthesize novel physostigmine and physovenine analogs represented by structure (**D**, wherein X = N and X = O respectively). These novel analogs were synthesized through the intermediacy of aryl radicals (**B**) and (**C**).

Present study

Substituted γ-butyrolactones required for the synthesis of physostigmine and physovenine analogs were prepared as follows. Treatment[6] of γ-butyrolactone **1a** with sodium methoxide and aromatic aldehydes gave substituted butyrolactones **2a–d** (Scheme 1). However, the reaction of **1a** with acetaldehyde yielded an unexpected product **2e** involving the consumption of two equivalents of acetaldehyde. For the synthesis[7] of **2f** and **2g** we treated the corresponding ketone and aldehyde with NaH and diethyl(2-oxotetrahydrofuran-3-yl)phosphonate **1c**, which in turn was derived from α-bromo-γ-butyrolactone **1b**. Compound **1a** when treated with benzyl bromide yielded **2i**. It should be noted that the reaction of **1a** with 2-bromopropane yielded **2h**, as a result of self-condensation of γ-butyrolactone **1a**.

Treatment of compounds **2a–h** with 2-bromo-4-methoxyaniline and trimethylaluminum in toluene gave amides **3a–3h** (Scheme 2), respectively. These derivatives were acetylated using acetyl chloride and pyridine in DCM to protect the hydroxyl group and then *N*-alkylated using Cs_2CO_3 and alkyl halides in DMF yielding the desired precursors **5a–5h** for reductive radical cyclization. Following the above procedure radical precursors **8a–c** used for oxidative cyclization were prepared from **2i–j**. Compounds **5a–5g** upon treatment with AIBN and TBTH in toluene solution yielded both the *exo* and *endo* cyclization derived products through the intermediacy of **9** yielding compounds **10a–g** and **11a–e**, respectively (Scheme 3). Surprisingly, two atropisomers (**10h** and **10i**) were isolated from the radical reaction of **5h**. High resolution mass

* Corresponding author. Tel.: +1 617 4843806.
E-mail address: akganguly1@aol.com (A.K. Ganguly).

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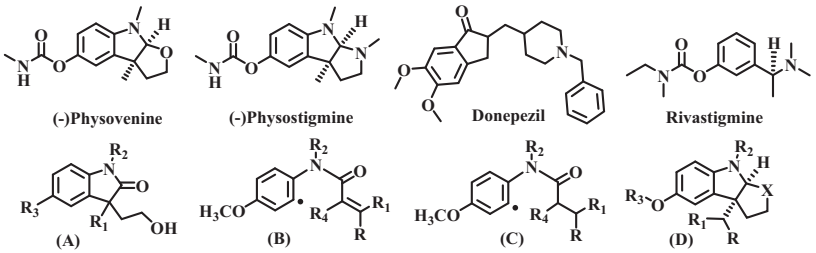
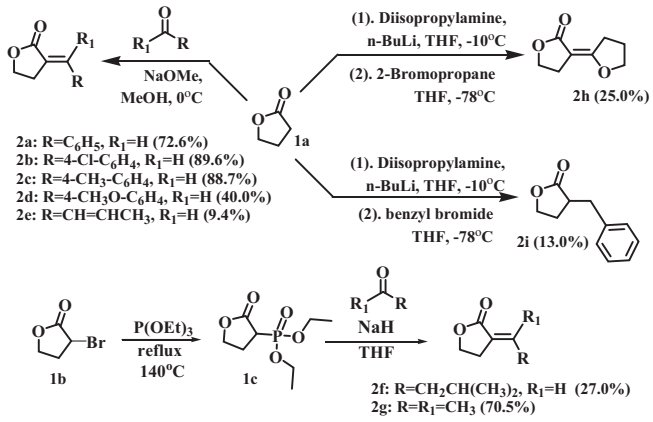


Figure 1. Examples of AChE inhibitors.



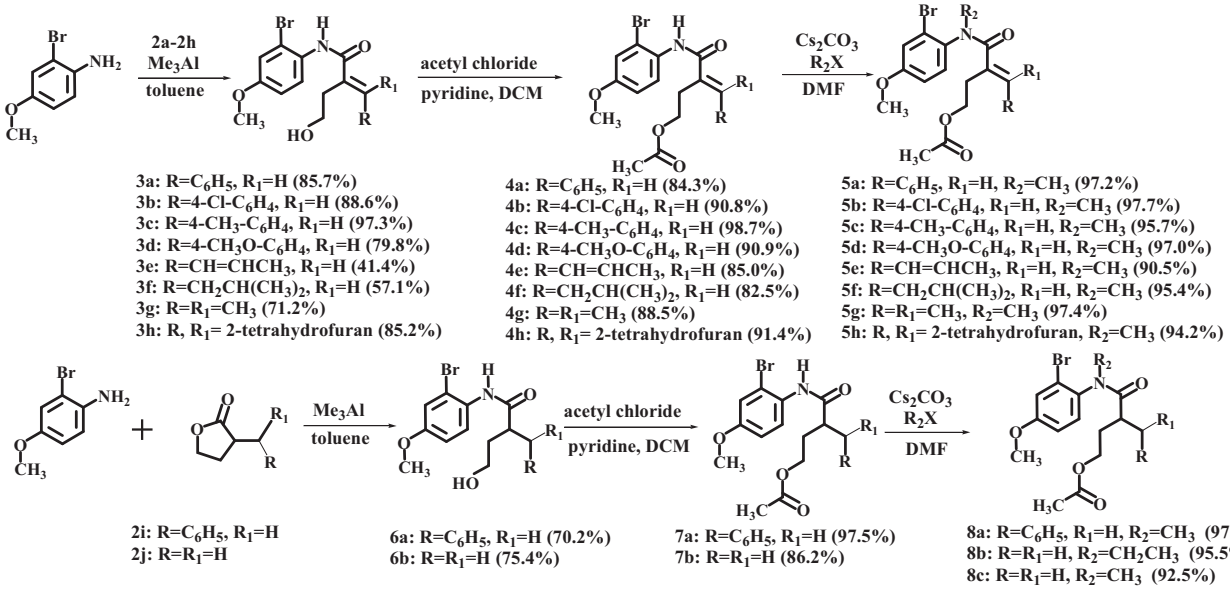
Scheme 1. Synthesis of substituted γ-butyrolactones.

spectroscopy established identical molecular compositions of both the above compounds. NMR spectra of **10h** and **10i** indicated that H_{10} in these compounds appear at δ 4.14 and δ 4.03 respectively. The quaternary carbon C_9 in **10h** appeared at δ 54.55, whereas C_9 in **10i** appeared at δ 54.22. Both spiro-oxindoles show identical correlations in COSY and HMBC. For example in HMBC, C_9 shows correlations with H_7, H_{15}, and H_{11}, whereas C_1 with H_{10}, H_{14}, and H_{17}. In addition, **10h** showed long range NOE between H_7 and H_{10}, whereas **10i** showed the correlations of H_7 with both H_{10} and H_{11} (Fig. 2). Treatment of **8a–c** with TBTH and AIBN produced the desired spirooxindoles (**10a**, **10j–k**), involving the rearrangement of **12** to the more stable radical **13**.

Hydrolysis of **10a–b** with 2 N NaOH in methanol yielded the corresponding alcohols **14a** and **14b**, which were then converted to aldehydes **15a** and **15b**, respectively using the Dess–Martin oxidation (Scheme 4). Condensation of methyl amine with **15a** followed by reduction with $LiAlH_4$ afforded **16a**. O-demethylation of **16a** using BBr_3 yielded the phenol **17a**. Similarly, **17b** was obtained from **14b.** Treatment of the phenols **17a–b** with NaH and substituted isocyanates yielded the desired physostigmine analogs **18a–c**.

Treatment of compounds **10a–k** and **14a–d** with $LiAlH_4$ in THF under reflux yielded the compounds with physovenine core structures **19a–j**. O-demethylation of compounds **19a–j** followed by reaction with substituted isocyanates furnished the desired physovenine analogs **21a–g**. The biological activities of the physostigmines (**18a–c**) and physovenines (**21a–g**) analogs are summarized in Table 1.

It is evident from the IC_{50} values reported in Table 1 that in the physostigmine series the benzyl substituted analogs **18a**, **18b**, and **18c** were inactive against hAChE but active against hBuChE. In the physovenine series benzyl substituted compounds **21a**, **21b**, and **21c** were selective hBuChE inhibitors with inhibitory potencies in the submicromolar range. The most active against hBuChE being **21a** with an IC_{50} value of 70 nM and selectivity around 58 folds. In the alkyl substituted derivatives, **21d**, **21e**, **21f**, and **21g** were slightly selective toward hAChE. Comparing compounds **21f** and



Scheme 2. Preparation of radical precursors.