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Bioorganic & Medicinal Chemistry Letters 15 (2005) 2711–2715
Bioorganic & Medicinal Chemistry Letters

Synthesis of tricyclic analogs of stephaoxocanidine and their evaluation as acetylcholinesterase inhibitors

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Received 10 March 2005; revised 31 March 2005; accepted 4 April 2005
Available online 4 May 2005

Abstract—The synthesis of simplified analogs of the novel isoquinoline alkaloid stephaoxocanidine, carrying the oxazaphenalene ABC-ring system of the natural product, and their activity as inhibitors of the enzyme acetylcholinesterase, are reported. 5,6-Dimethoxy-7*H* -8-oxa-1-aza-phenalen-9-one (**5**) was as active as a *Narcissus* extract enriched in galantamine.

The critical role of acetylcholine in cognitive function and the fact that cholinergic stimulation enhances performance of cognitive tasks in man and animals,[1] suggested that therapy with cholinomimetic agents may improve cognitive and memory deficits observed in Alzheimer's disease. Accordingly, to date cholinesterase inhibitors are the only class of compounds with proven efficacy in the treatment of the cognitive and functional symptoms of this disease, and became the cornerstone of its therapy.[2]

Galantamine (**1**), a natural benzazepine alkaloid,[3] and tacrine (**2**), a synthetic quinoline derivative, are among the first four medications approved by the FDA for the symptomatic treatment of mild to moderate Alzheimer's disease.

The stephaoxocanes (Fig. 1) are a small family of isoquinoline alkaloids recently uncovered by Japanese,[4] Chinese[5] and Brazilian [6] scientists, which share the tetracyclic skeleton **4a**. To date, only five members are known: stephaoxocanidine (**4b**) and stephaoxocanine (**4f**) isolated from *Stephania cepharantha* Hayata,[4] excentricine (**4d**) and *N*-methylexcentricine (**4e**), from

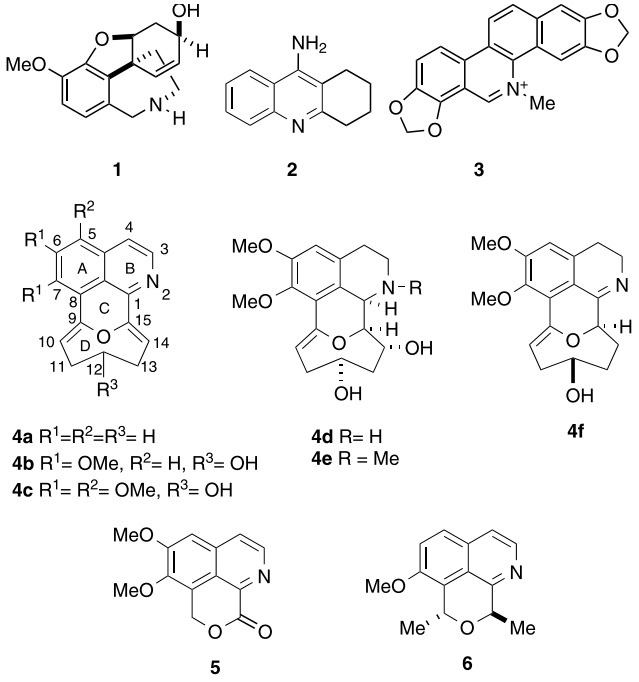

Figure 1.

Keywords: Acetylcholinesterase inhibitors; Oxazaphenalenes; Stephaoxocanes; Isoquinoline alkaloids.
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doi:10.1016/j.bmcl.2005.04.005

S. excentrica[5] and eletefine (**4c**) isolated from *Cissampelos pareira*.[6] These are Menispermaceae which have long found use in folk medicine.

The roots of *Cissampelos* species are widely used in indigenous and popular medical systems to cure heart, genital and urinary illnesses as well as respiratory diseases such as cold and asthma,[7] while *S. cepharantha* Hayata has been used in Chinese medicine for the treatment of diseases such as parotiditis, gastric ulcer and leukopenia.[8]

The genus *Stephania* is prolific in bioactive compounds. *S. cepharantha* has been recorded to produce cepharanthine and cycleanine, with activity on acetylcholine receptors.[9] Recently, interesting acetylcholinesterase inhibitory activity was found in *S. suberosa* Forman extracts, employed in Thai traditional neurotonic and rejuvenating medicine,[10] while *Stephania rotunda* has been used in Oriental medicine as treatment for dysautonomia (abnormal functioning of the autonomic nervous system). Furthermore, root extracts of *S. venosa*, a Thailand prescription for memory improvement in elderly, strongly inhibited acetylcholinesterase (90% inhibition with a 0.1 mg/ml extract)[11] and bisbenzyl-isoquinolines from *Stephania tetrandra* have also shown acetylcholinesterase inhibitory properties.[12]

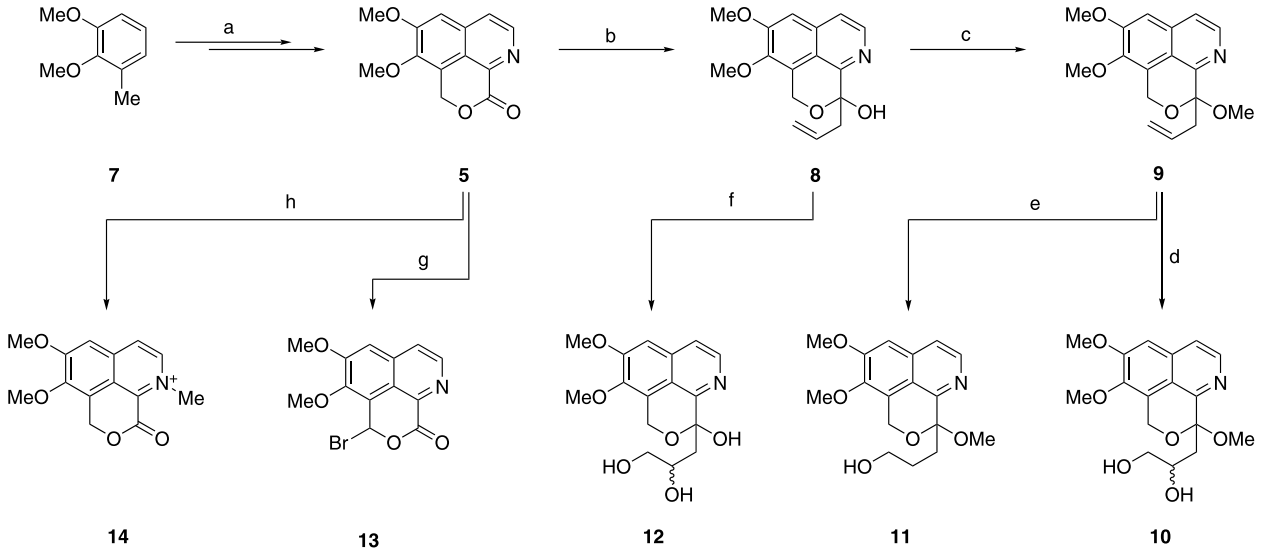
Interestingly, besides galantamine other alkaloids such as isoquinoline derivatives from Amarillidaceae[13] as well as protoberberines,[14c] and quaternary benzophenanthridine and isoquinoline alkaloids[14] including sanguinarine (**2**)[14b–d] and *N*-alkyl carneginium salts, have been shown to display acetylcholinesterase inhibitory activity.[15]

In retrospect, the use of natural products as templates has been the single most successful strategy in the discovery of novel medicines and in recent years the use of traditional medicine information on drug development has received considerable interest.[16] The chemistry and biological activity of the stephaoxocanes is an unexplored area; thus, we have developed two different approaches for the elaboration of the ABC ring system of stephaoxocanidine[17] and prepared compounds **5** and **6**.

Herein, we report the synthesis of tricyclic simplified analogs of stephaoxocanidine, some of which bear functionalized alkyl chains in place of its oxocane ring D, and their in vitro activity as inhibitors of the enzyme acetylcholinesterase. The synthesis was straightforward starting from the known oxazaphenalene lactone **5**, easily available from 2,3-dimethoxy toluene (**7**). Addition of allylmagnesium bromide at −20 °C furnished 85% of hemiacetal **8**, which was treated with trimethyl orthoformate under tosic acid catalysis, furnishing the corresponding methyl acetal **9** in 83% yield (see Scheme 1).

The use of CH_2Cl_2 at −20 °C as reaction condition for Grignard addition to **5** is remarkably unusual; nevertheless, this is a result of the poor solubility of lactone **5** in THF and Et_2O as well as in aromatics such as toluene, which prevented their use as solvents in this transformation. The lactone was only sparingly soluble in CH_2Cl_2 at −20 °C and the reaction did not proceed at temperatures below −35 °C due to its insolubility. Interestingly, however, yields of addition product were high in spite of the use of more than one equivalent of Grignard reagent, probably due to the insolubility of the resulting alkoxide in the reaction medium, while running the reaction at temperatures above −10 °C drastically reduced product yields.

Catalytic dihydroxylation of **8** and **9** furnished highly polar diols **10** and **12** in moderate to good yields, without spiroketalized products,[18] while exposure of **8** to an



Scheme 1. Reagents and conditions: (a) See Refs. 17b,c; (b) $CH_2{=}CHCH_2MgBr$, CH_2Cl_2, −20 °C (85%); (c) $HC(OMe)_3$, TsOH (cat.), MeOH–$CHCl_3$, rt, overnight (83%); (d) OsO_4 (cat.), NMO (1.25 equiv), acetone–H_2O (1:2, v/v), 0 °C → rt, overnight (74%); (e) (1) BH_3·THF, THF, 0 °C, (2) PCC/Al_2O_3, CH_2Cl_2, rt, (3) $NaBH_4$, MeOH, 0 °C (25%) or $AlCl_3$, $NaBH_4$ (27%); (f) OsO_4 (cat.), NMO (1.25 equiv), acetone–H_2O (1:2, v/v), 0 °C → rt, overnight (53%); (g) MeI, MeCN, reflux, 3 h (100%); (h) NBS, AIBN (cat.), CCl_4, reflux, 2 h (47%).