Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters 16 (2006) 2170–2172
Bioorganic & Medicinal Chemistry Letters

Isoquinoline derivatives as potential acetylcholinesterase inhibitors

Sutthatip Markmee,[a] Somsak Ruchirawat,[b] Vilailak Prachyawarakorn,[b] Kornkanok Ingkaninan[a] and Nantaka Khorana[a,*]

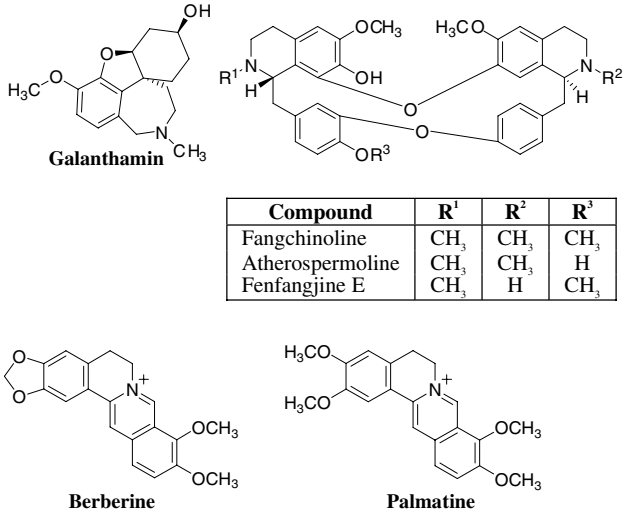
[a]*Department of Pharmaceutical Chemistry and Pharmacognosy, Faculty of Pharmaceutical Sciences, Naresuan University, Phitsanulok 65000, Thailand*
[b]*Chulabhorn Research Institute, Bangkok 10210, Thailand*

Received 21 December 2005; revised 10 January 2006; accepted 12 January 2006
Available online 17 February 2006

Abstract—Several bisbenzylisoquinoline alkaloid derivatives showed the inhibitory activity at acetylcholinesterase enzyme (AChE) in micromolar range. It is possible that monomeric moiety of bisbenzylisoquinoline alkaloid might be required for acetylcholinesterase enzyme inhibition. AChE inhibitory activity of related monomeric 1-benzylisoquinolines was examined by using Ellman colorimetric assay with galanthamine as a reference standard.

Alzheimer's disease (AD), a neurodegenerative disorder, is one of the severe health problems of aged population.[1,2] The deficiency in cholinergic neurotransmission is believed to be one of the major causes of the memory impairments in AD patients. The rational therapeutic approach to treat AD is to increase the amount of acetylcholine (ACh) in the brain. Inhibition of acetylcholinesterase (AChE), an enzyme responsible for the metabolic breakdown of ACh, is the main target to improve AD.[3–6] Currently, there are four AChE inhibitors available in the market. However, they can treat only mild to moderate levels of disease.[7] There is still a need to develop more efficient drugs for AD.

A number of bisbenzylisoquinoline (BBIQ) alkaloids; such as fangchinoline, atherospermoline, and fenfangjine E (Fig. 1), isolated from root of *Stephania tetrandra* S. Moore, Menispermaceae family, were found to inhibit acetylcholinesterase enzyme in micromolar range.[8] Moreover, the promising AChE inhibitory activity of simple rigid isoquinoline structures from plants, such as protoberberine alkaloids; berberine and palmatine (Fig. 1), has been reported.[9] It is likely that the simple substituted isoquinoline might display similar pharmacological activity as BBIQ. More examples of dimeric



Compound	R^1	R^2	R^3
Fangchinoline	CH_3	CH_3	CH_3
Atherospermoline	CH_3	CH_3	H
Fenfangjine E	CH_3	H	CH_3

Figure 1. Chemical structures of some AChE inhibitors from plants.

structures were found in tacrine analogs which showed good activity to acetylcholinesterase enzyme.[10] In order to prove the hypothesis, the simple substituted monomeric structures of BBIQ (Fig. 2) were taken to screen for their AChE inhibitory activity.

Isoquinoline derivatives studied in the present investigation were synthesized as intermediate compounds of anticancer drugs (Fig. 2)[11] and were obtained from Chulabhorn Research Institute. The assay for AChE

Keywords: Isoquinoline; Acetylcholinesterase inhibitors; Alzheimer's disease.
* Corresponding author. Tel.: +66 55 261000x3618; fax: +66 55 261057; e-mail: nantaka@hotmail.com

0960-894X/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2006.01.067

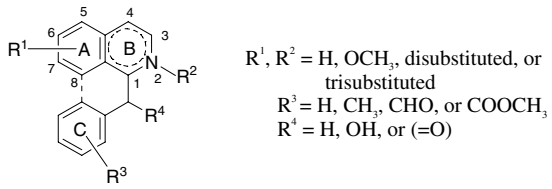


Figure 2. Chemical structures of 1-benzylisoquinoline derivatives.

inhibitory activity was performed according to the methods developed by Ellman et al.[12] and Ingkaninan et al.[13] using commercially available galanthamine as a reference standard. Various rigid analogs of 1-benzylisoquinolines; that is, aporphine structures **8** and **9**, and flexible forms of simple 1-benzylisoquinolines; that is, 1-benzyl-1,2,3,4-tetrahydroisoquinoline structures **1**–**7**, 1-benzyl-3,4-dihydroisoquinoline structures **10**, and 1-benzylisoquinoline structures **11**–**17** were chosen to examine for acetylcholinesterase inhibitory activity. All the compounds were tested for acetylcholinesterase inhibitory activity at the concentrations of 10^{-4} and 10^{-5} M (in methanol), except compound **9** which was tested at the concentration of 3×10^{-4} and 3×10^{-5} M due to the solubility problem. The results are shown in Table 1.

Interestingly, there were four compounds (**10**, **13**, **14**, and **17**) which showed more than 50% inhibition at concentration 10^{-4} M, but only compounds **10** and **13** displayed more than 50% inhibition at concentration 10^{-5} M. Compounds **1** and **2** gave percent inhibition in the range of 40–50% and the rest of the compounds showed less than 30% inhibition at 10^{-4} M. Hence, compounds **10**, **13**, **14**, and **17** were determined for concentration that gave 50% inhibition of AChE activity

Table 1. AChE inhibitory activity of isoquinoline derivatives

Structures	Compound	R^1	R^2	R^3	R^4	R^5	R^6	R^7	% Inhibition	
									10^{-4} M	10^{-5} M
Tetrahydroisoquinoline derivatives	**1**	H	H	OCH_3	OCH_3	OCH_3	OCH_3	OH	45.9 ± 7.1	11.4 ± 2.2
	2	CH_3	H	OCH_3	OCH_3	OCH_3	OCH_3	H	46.6 ± 1.9	9.2 ± 4.9
	3	CH_3	H	OCH_3	OCH_3	–OCH_2O–		H	38.4 ± 3.3	9.6 ± 6.4
	4	CHO	H	OCH_3	OCH_3	–OCH_2O–		H	13.2 ± 6.0	2.5 ± 7.7
	5	CHO	OCH_3	OCH_3	OCH_3	–OCH_2O–		H	14.5 ± 2.2	4.5 ± 3.9
	6	CHO	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	H	17.7 ± 1.4	2.4 ± 4.9
	7	$COOCH_3$	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	H	13.4 ± 0.9	4.2 ± 10.4
Aporphine derivatives	**8**	CH_3	H	OCH_3	OCH_3	OCH_3	OCH_3	H	34.5 ± 1.7	9.3 ± 6.9
	9	$COOCH_3$	OCH_3	OCH_3	OCH_3	H	OCH_3	OCH_3	15.9 ± 13.5	7.3 ± 1.0
Dihydroisoquinoline derivatives	**10**	CH_3	OCH_3	OCH_3	OCH_3	OCH_3			90.2 ± 1.4	52.4 ± 1.8
Isoquinoline derivatives	**11**	H	H	OCH_3	H	H	OH		11.4 ± 7.7	3.5 ± 9.2
	12	H	H	H	H	OCH_3	OH		14.7 ± 4.0	−4.0 ± 13.8
	13	OCH_3	OCH_3	H	H	OCH_3	OH		67.8 ± 6.3	53.5 ± 7.1
	14	OCH_3	OCH_3	OCH_3	OCH_3	H	OH		88.7 ± 2.4	45.5 ± 1.7
	15	OCH_3	OCH_3	H	H	H	=O		8.4 ± 4.9	4.6 ± 5.2
	16	OCH_3	OCH_3	OCH_3	OCH_3	H	=O		38.6 ± 7.8	2.3 ± 8.4
	17	OCH_3	OCH_3	OCH_3	OCH_3	H	H		88.2 ± 1.0	46.4 ± 3.0

Table 2. Determination of IC_{50} of some isoquinoline derivatives

Compound	IC_{50} (μM)
10	5.50 ± 1.05
13	6.94 ± 1.49[a]
14	10.73 ± 1.04
17	24.33 ± 12.68
Galanthamine	0.59 ± 0.10

[a] Range of inhibition 0–70%.

(IC_{50}) and IC_{50} values of 5.50 ± 1.05, 6.94 ± 1.49, 10.73 ± 1.04, and 24.33 ± 12.68 μM were obtained for **10**, **13**, **14**, and **17**, respectively (Table 2). In this experiment, galanthamine was used as reference standard with an IC_{50} value of 0.59 ± 0.10 μM. 1-Benzylisoquinolines **10** and **13** showed the highest acetylcholinesterase inhibitory activity in micromolar range; however, they are about ten times less potent than galanthamine.

Compound **2**, 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, showed mild activity for AChE (Table 1). When the unsaturation was added to the piperidine ring or quaternarized at basic nitrogen of piperidine, the activity improved by about 10- to 100-fold as shown by compounds **10** and **17**. Similar result was also found for compound **1** and its aromatic analog (**14**). Substituents on the benzene ring had quite an influence on the activity as seen by compounds **12** and **13**. The type of substituents and the position of the substitution also affected inhibition of acetylcholinesterase enzyme. The N-substitution might play an important role in inhibition as well. The amine derivative (**3**) lost activity when changed to its corresponding amide analog (**4**). Rigid molecule as in aporphine structures (**8** and **9**) displayed slightly reduced activity at concentration 10^{-4} M. Hybridization at benzyl part seemed to play an important role in inhibition as shown by hydroxyl derivative of compound **14** and the activity decrease when the molecule was oxidized to its ketone derivatives (**16**).

The aim of this study was more to determine if a monomeric moiety of BBIQ was enough to display the AChE activity than to develop novel template for AChE. From this study, it is determined that simple substituted monomeric 1-benzylisoquinoline derivatives display acetylcholinesterase inhibitory activity. 1-Benzylisoquinoline structure is a novel template to develop highly active acetylcholinesterase inhibitors and this is shown by good activity displayed by compounds **10** and **13**. This study has provided some insights into the SAR of 1-benzylisoquinoline derivatives on aromatization, unsaturation of the ring, quaternarization of the ring nitrogen atom, substitution at the nitrogen, substitutions on the aromatic portion, and conformation or rigidity at benzyl moiety for acetylcholinesterase enzyme inhibition. Additional studies are underway to determine additional structural requirements of this class of compounds.

Acknowledgment

We gratefully acknowledge the funding from the National Research Council of Thailand 2004.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2006.01.067.

References and notes

1. Perry, E. K. *Br. Med. Bull.* **1986**, *42*, 63.
2. Scapini, E.; Scheltens, P.; Feldman, H. *Lancet Neurol.* **2003**, *2*, 539.
3. Giacobini, E. *Pharmacol. Res.* **2004**, *50*, 433.
4. Benzi, G.; Moretti, A. *Eur. J. Pharmacol.* **1998**, *346*, 1.
5. Grutzendler, J.; Morris, J. C. *Drugs* **2001**, *61*, 41.
6. Johnson, C. N.; Roland, A.; Upton, N. *Drug Discov. Today: Therapeutic strategies* **2004**, *1*, 13.
7. Grossberg, G. T. *Curr. Ther. Res.* **2003**, *64*, 216.
8. Ogino, T.; Yamaguchi, T.; Sato, T.; Sasaki, H.; Sugama, K.; Okada, M.; Maruno, M. *Heterocycles* **1997**, *45*, 2253.
9. Shigeta, K.; Ootaki, K.; Tatemoto, H.; Nakanishi, T.; Inada, A.; Muto, N. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 2491.
10. Hu, M.-K.; Wu, L.-J.; Hsiao, G.; Yen, M.-H. *J. Med. Chem.* **2002**, *45*, 2277.
11. Ploypradith, P.; Mahidol, C.; Sahakitpichan, P.; Wangbundit, S.; Ruchirawat, S. *Angew. Chem. Int. Ed.* **2004**, *43*, 866.
12. Ellman, L. G.; Courtney, K. D.; Andres, V., Jr.; Featherstone, M. R. *Biochem. Pharmacol.* **1961**, *2*, 88.
13. Ingkaninan, K.; Temkitthawon, P.; Chuenchom, K.; Yuyaem, T.; Thongnoi, W. *J. Ethanopharmacol.* **2003**, *89*, 261.