Bioorganic & Medicinal Chemistry Letters 23 (2013) 2984–2989

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Design, synthesis and evaluation of some new 4-aminopyridine derivatives in learning and memory

Saurabh K. Sinha, Sushant K. Shrivastava *

Pharmaceutical Chemistry Research Laboratory, Department of Pharmaceutics, Indian Institute of Technology, Banaras Hindu University, Varanasi, UP 221005, India

ARTICLE INFO

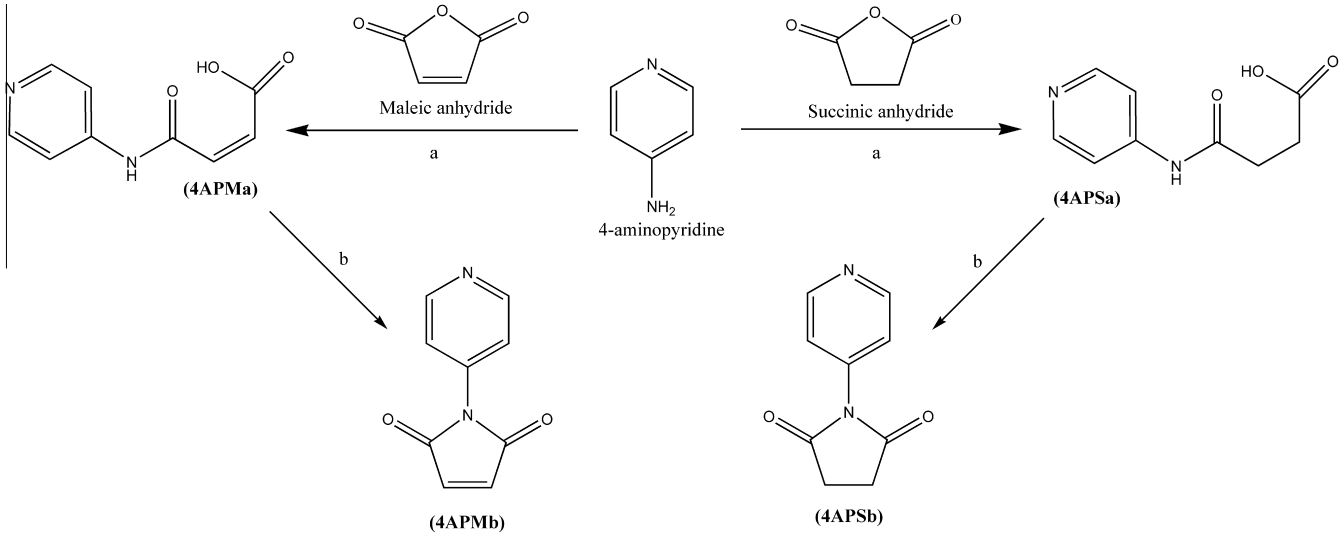
Article history:
Received 1 October 2012
Revised 21 February 2013
Accepted 8 March 2013
Available online 16 March 2013

Keywords:
4-Aminopyridine
Nootropic
Antiamnesic
Anticholinesterase
Elevated plus maze

ABSTRACT

Some new anilide and imide derivatives of 4-aminopyridine (4AP) were synthesized and evaluated against antiamnesic, cognition enhancing and anticholinesterase activity through their respective in vitro and in vivo models. These newly synthesized derivatives have illustrated an enhanced cognition effect on elevated plus maze model and also demonstrated a significant reversal in scopolamine-induced amnesia in same model. The IC_{50} value of synthesized compounds showed maximum activity of **4APMb** compared to standard drug donepezil and other derivatives, whereas its enzyme kinetic study revealed a non-competitive inhibition of acetycholinesterase (AChE) and a competetive inhibition of butyrylcholinesterase (BChE). Significant inhibitions in AChE activity by all the synthesized compounds were found in specific brain regions that is prefrontal cortex, hippocampus and hypothalamus. The docking study confirmed their consensual interaction with AChE, showed an affinity and binding with the key peripheral anionic site residues Trp-286, Tyr-124 and Tyr-341 of AChE.

Progressive impairment in memory, cognitive functions and behavioral disturbance has always been a major area of concern for complex neurodegenerative disorders of the central nervous system such as Alzheimer's disease (AD).[1] Patients suffering with AD have low level of acetylcholine (ACh) and biosynthetic enzyme choline acetyltransferase (ChAT) in the cortex and hippocampus.[2,3]



Scheme 1. The synthetic pathway of the compounds here presented. Reagents and conditions: (a) THF, 25 °C, 3 h; (b) Ac_2O, AcONa, 80 °C 5 h.

* Corresponding author. Tel.: +91 9452156527; fax: +91 5422368428.
E-mail addresses: sksinha.rs.phe@itbhu.ac.in, skshrivastava.phe@itbhu.ac.in (S.K. Shrivastava).

0960-894X/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmcl.2013.03.026

Table 1
Concentration of synthesized derivatives and donepezil required for 50% inhibition of AChE and BChE

Compound	IC_{50}(μM) ± SEM		Selectivity for AChE[a]
	AChE	BChE	
4APSa	40.33 ± 0.88	56.45 ± 0.60	1.39
4APSb	0.49 ± 0.02	3.82 ± 0.83	7.79
4APMa	48.67 ± 1.20	656.85 ± 1.60	13.49
4APMb	0.03 ± 0.014	11.02 ± 0.76	367
Donepezil	0.04 ± 0.012	15.24 ± 0.88	381

[a] Selectivity for AChE is defined as IC_{50} (BChE)/IC_{50} (AChE).

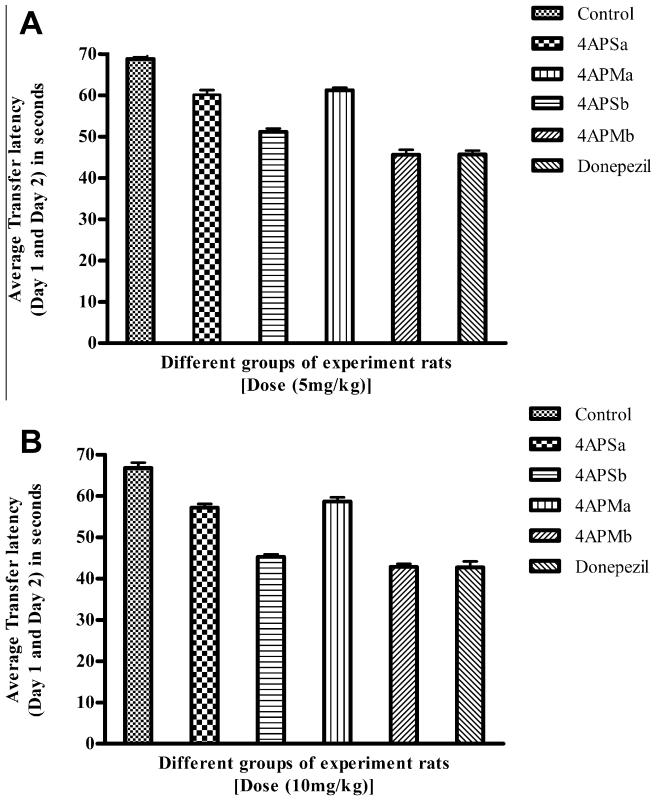


Figure 1. Effect of synthesized derivatives and Donepezil on learning impairment on elevated plus maze in wistar rats [A] at dose (5 mg/kg), [B] at dose (10 mg/kg).

Table 2
Reverse effect of synthesized derivative on scopolamine-induced amnesia on elevated plus maze in rats

Treatment [dose (mg/kg)]	Transfer latency (s)	
	Day 1	Day 2
VEHICLE	67.67 ± 0.88	62.50 ± 0.76
SCP (1.0)	86.83 ± 0.90	81.50 ± 0.76[a]
4APSa (5.0) + SCP (1.0)	77.67 ± 0.76	71.67 ± 0.66[b]
4APSa (10.0) + SCP	74.83 ± 0.60	70.00 ± 0.57[b]
4APSb (5.0) + SCP	66.83 ± 0.60	60.67 ± 0.66[b]
4APSb (10.0) + SCP	65.50 ± 0.76	58.33 ± 0.88[b]
4APMa (5.0) + SCP	80.50 ± 0.76	75.33 ± 0.80[b]
4APMa (10.0) + SCP	77.67 ± 0.66	72.50 ± 0.76[b]
4APMb (5.0) + SCP	64.67 ± 0.84	56.33 ± 0.88[b]
4APMb (10.0) + SCP	61.33 ± 0.61	53.83 ± 0.60[b]
Donepezil (5.0) + SCP	65.33 ± 0.66	56.67 ± 0.66[b]
Donepezil (10.0) + SCP	62.50 ± 0.76	54.50 ± 0.76[b]

Data are expressed as mean ± SEM ($n = 6$). Data were statistically analyzed by one way ANOVA.
[a] Significantly different from control (vehicle treated) group $p < 0.001$.
[b] Significantly different from scopolamine treated group $p < 0.001$.

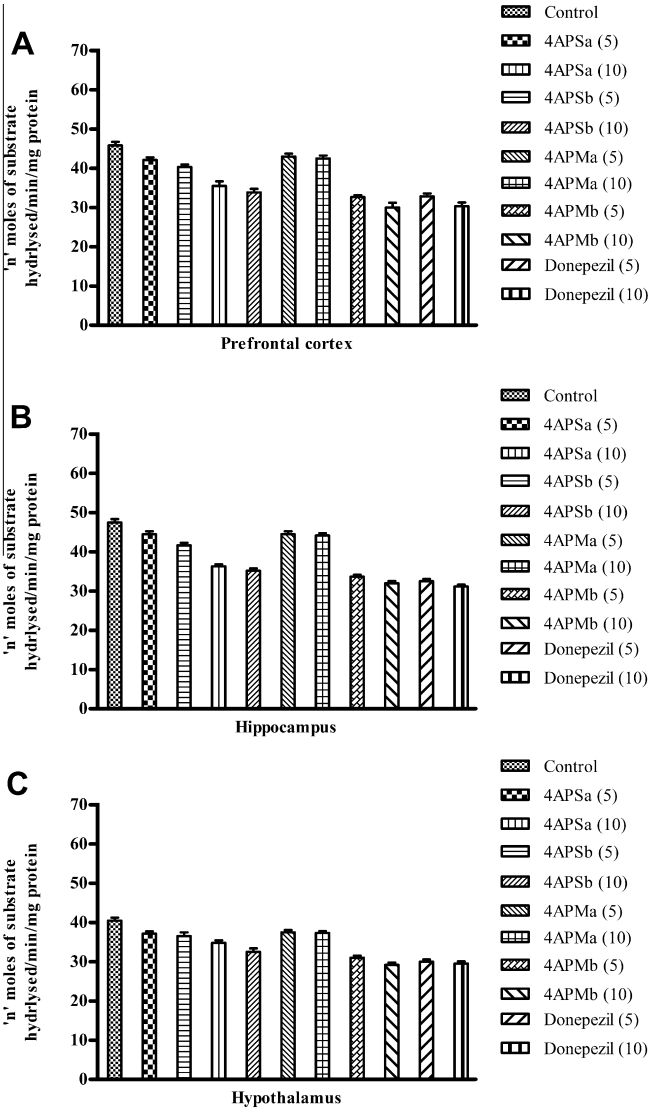


Figure 2. Effect of synthesized derivatives and donepezil (5 and 10 mg/kg) on acetylcholinesterase (AchE) activity on different region of rat brain [A] prefrontal cortex [B] hippocampus [C] hypothalamus. Results are expressed as mean ± SEM ($n = 6$).

These parameters have a vital role in learning and memory therefore, in order to treat this specific disease it is necessary to improve cholinergic neurotransmission which may be achieved by preventing the biotransformation of acetylcholine into the inactive metabolites choline and acetate at the specific sites of brain.[4] Based on this approach some drugs have been established and used to treat the AD.[5,6] The utility of 4AP derivatives in treating various neuromuscular disorders such as multiple sclerosis, botulism, spinal cord injury, Alzheimer's disease and myasthenia gravis have already been reported in previous investigations[7,8]which may be attributed to its capacity to penetrate the blood–brain barrier[9] but the therapeutic applications of the most common 4AP derivatives such as tacrine[10] and velnacrine[11] have been restricted due to their high toxicity. Another tacrine derivative amiridine is now under Phase III study in Japan.[12]