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Substituted spiro [2.3′] oxindolespiro [3.2″]-5,6-dimethoxy-indane-1″-one-pyrrolidine analogue as inhibitors of acetylcholinesterase

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ABSTRACT

Series of pyrolidine analogues were synthesized and examined as acetylcholinesterase (AChE) inhibitors. Among the compounds, compounds **4k** and **6k** were the most potent inhibitors of the series. Compound **4k**, showed potent inhibitory activity against acetyl cholinesterase enzyme with IC_{50} 0.10 μmol/L. Pyrolidine analogues might be potential acetyl cholinesterase agents for AD.

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Alzheimer's disease (AD) is a neurodegenerative disorder that is the most common cause of dementia among the elderly. In the last decade, treatment for AD has been based on the 'cholinergic hypothesis'.[1] This hypothesis suggested that patients with AD suffer from a deficit of cholinergic function in the brain such as decrease in hippocampal and cortical levels of acetylcholine (ACh) and associated enzyme choline transferase. Many AChE inhibitors used clinically for the treatment of AD are natural products or natural product analogues, such as rivastigmine (a physostigmine derivative), galantamine and huperzine A (available in China; in phase II trials in the USA).[2,3] The only approved natural agents for the treatment of AD are alkaloids, which along with many of the synthetic AChE inhibitors (e.g., donepezil and tacrine) possess side-effects including nausea, vomiting, diarrhoea and loss of appetite. In fact, tacrine was discontinued due to its significant side effect profile.[4] there is considerable interest therefore in the discovery of more centrally selective non-alkaloidal inhibitors which may avoid the side-effects that have been recorded with alkaloids. These natural products could also provide templates for the development of other compounds.[5]

For a quarter of a century, the pathogenesis of Alzheimer's disease (AD) has been linked to a deficiency in the brain neurotransmitter acetylcholine. This was based on observations that correlated cholinergic system abnormalities with intellectual impairment.[6] The pathogenesis of Alzheimer's disease (AD) has been linked to a deficiency in the brain neurotransmitter acetylcholine. Subsequently, acetylcholinesterase inhibitors (AChEIs) were introduced for the symptomatic treatment of AD. The prevailing view has been that the efficacy of AChEIs is attained through their augmentation of acetylcholine-medicated neuron to neuron transmission.[7]

In the search for new molecules with the potential effect of inhibiting the enzyme acetyl cholinesterase it is important to note that many heterocycles have shown significant inhibitory activity on this enzyme, including three of the four AD drugs currently on the market. In the recent past, medicinal plants with hetero atom containing molecules attracted attention due to their potential role in dementia. Also most heterocyclic systems have been used as a source to discover new compounds with varied biological potentials. Especially, pyrolidine derivatives play a vital role in discovering novel candidates having the action of acetyl cholinesterase (AChEI) inhibitors.

In the scope of a research program aiming at the design, synthesis and evaluation of new neuroactive lead-compound candidates

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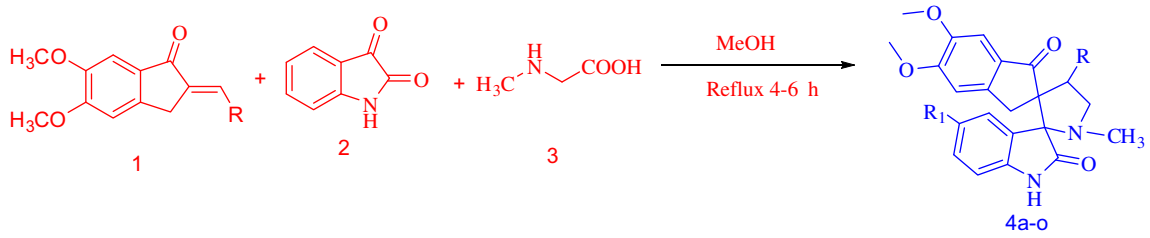
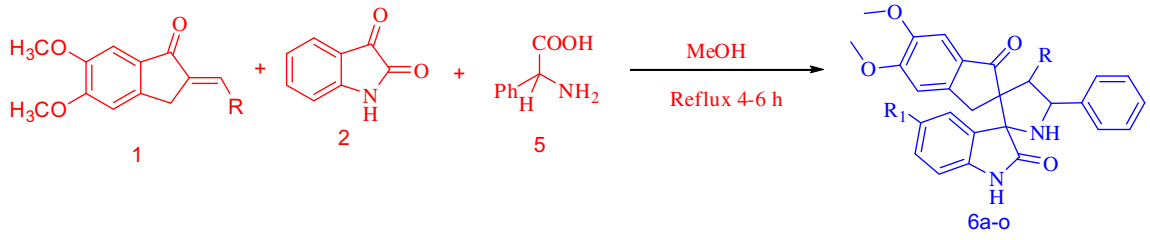


Scheme 1. Protocol for synthesis.

Table 1
Physical constants and inhibition of AchE activities of the synthesized compounds

Compound	R	R^1	R_f value	Yield (%)	Mp (°C)	AchE inhibition[a] (IC_{50} ± SD) μmol/L
4a	Pyridyl-	H	0.67	74	204	0.46 ± 0.02
4b	4-Flurophenyl-	H	0.64	65	183	2.12 ± 0.02
4c	3,4-Dimethoxy phenyl-	H	0.69	72	194	4.2 ± 0.02
4d	Phenyl-	H	0.62	80	161	3.12 ± 0.1
4e	2-Chloro phenyl-	H	0.78	82	138	4.3 ± 0.01
4f	Pyridyl-	Cl	0.73	85	113	0.37 ± 0.01
4g	4-Flurophenyl-	Cl	0.76	92	126	3.7 ± 0.1
4h	3,4-Dimethoxy phenyl-	Cl	0.74	85	105	4.2 ± 0.1
4i	Phenyl-	Cl	0.66	77	154	11.2 ± 0.1
4j	2-Chloro phenyl-	Cl	0.70	82	162	6.6 ± 0.1
4k	Pyridyl-	NO_2	0.78	90	126	0.10 ± 0.1
4l	4-Flurophenyl-	NO_2	0.82	56	178	8.6 ± 0.1
4m	3,4-Dimethoxy phenyl-	NO_2	0.85	81	194	6.10 ± 0.1
4n	Phenyl-	NO_2	0.59	76	172	13.2 ± 0.1
4o	2-Chloro phenyl-	NO_2	0.83	72	182	7.6 ± 0.1

[a] Data are means standard deviation of duplicate independent experiments.

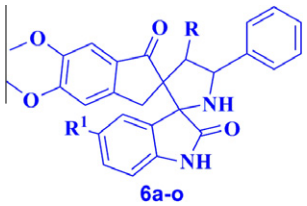


Scheme 2. Protocol for synthesis.

with beneficial effects in treatment of AD as AChE inhibitors, we became interested in developing new pyrolidine analogues. It was considered to be worth to work on the above mentioned novel analogues substituted spiro [2.3′] oxindolespiro [3.2″]-5, 6-dimethoxy-indane-1″-one-pyrrolidine analogue **4a–o** and **6a–o** described in this study is shown in Tables 1 and 2, and a reaction sequence for the preparation is outlined in Scheme 1.

In the present investigation, the 1,3-dipolar cycloaddition of azomethine ylides, generated in situ via decarboxylative condensation of sarcosine **3** and substituted isatins **2** (R = H, Cl, NO_2) to 2-(arylmethylene)-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-ones **1** in methanol afforded novel *N*-methyl-spiro[2.3′]oxindolespiro[3.2″]-5,6-dimethoxy-1″-indanone-4-(aryl substituted) pyrrolidine **4a–o** (Scheme 1, Table 1), **5** phenylglycine and substituted isatins **2** (R = H, Cl, NO2) to 2-(arylmethylene)-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-ones **1** in methanol afforded novel spiro[2.3′]oxindolespiro[3.2″]-5,6-dimethoxy-1″-indanone-4-(aryl substituted)-5-phenyl pyrrolidine **6a–o** (Scheme 2, Table 2). The reaction was performed by heating an equimolar mixture of 2-(arylmethylene)-5,6-dimethoxy2,3-dihydro-1*H*-inden-1-ones **1**, substituted isatins **2** and sarcosine or phenylglycine **3** or **5** in methanol under reflux for 4–6 h. After completion of the reaction (TLC), the reaction mixture was poured into ice-water, the resulting crude solid was filtered off and purified by column chromatography to obtain pure pyrrolidine derivatives **4a–o** and **6a–o** in 56–92% yields after recrystallization with pet ether/ethyl acetate (4:1). The purity of the compounds was checked by TLC and elemental analyses. Both analytical and spectral data (^{1}H NMR, IR) of all the synthesized compounds were in full agreement with the proposed structures. In general, Infra red spectra (IR) 1525,

Table 2
Physical constants and inhibition of AchE activities of the synthesized compounds



6a-o

Compound	R	R^1	R_f value	Yield (%)	Mp (°C)	AchE inhibition[a] (IC_{50} ± SD) μmol/L
6a	Pyridyl-	H	0.90	78	164	0.30 ± 0.02
6b	4-Flurophenyl-	H	0.71	82	175	6.86 ± 0.02
6c	3,4-Dimethoxy phenyl-	H	0.78	72	134	5.2 ± 0.02
6d	Phenyl-	H	0.89	80	171	5.12 ± 0.1
6e	2-Chloro phenyl-	H	0.85	82	148	7.3 ± 0.01
6f	Pyridyl-	Cl	0.83	85	183	0.42 ± 0.01
6g	4-Flurophenyl-	Cl	0.81	92	146	9.86 ± 0.02
6h	3,4-Dimethoxy phenyl-	Cl	0.83	85	125	8.26 ± 0.02
6i	Phenyl-	Cl	0.79	77	154	7.26 ± 0.02
6j	2-Chloro phenyl-	Cl	0.84	92	146	12.2 ± 0.02
6k	Pyridyl-	NO_2	0.88	85	145	0.24 ± 0.1
6l	4-Flurophenyl-	NO_2	0.75	77	184	14.3 ± 0.01
6m	3,4-Dimethoxy phenyl-	NO_2	0.63	82	204	15.37 ± 0.01
6n	Phenyl-	NO_2	0.82	90	118	3.7 ± 0.1
6o	2-Chloro phenyl-	NO_2	0.80	56	168	4.2 ± 0.1
Donepezil	—			—	—	0.12 ± 0.01

[a] Data are means standard deviation of duplicate independent experiments.

1690, 1724 and 3290 cm^{-1}, respectively. In the nuclear magnetic resonance spectra (^{1}H NMR) the signals of the respective protons of the prepared titled compounds were verified on the basis of their chemical shifts, multiplicities and coupling constants. The spectra showed a singlet at δ 2.32 ppm corresponding to CH_3 group; doublet at δ 2.43–2.60 ppm corresponding to CH_2 group; singlet at δ 3.82 ppm corresponding to OCH_3, triplet at δ 3.43–3.46 ppm to CH proton; multiplet at δ 6.84–7.20 ppm corresponding to aromatic protons, multiplet at δ 7.42–8.27 ppm corresponding to pyridine ring proton, singlet at δ 8.46 corresponding to NH proton. The elemental analysis results were within ±0.4% of the theoretical values.

All the newly synthesized (**4a–4o** and **6a–6o**) pyrolidine derivatives were tested for their inhibitory activities toward AChE in vitro according to Ellmann's method[8] against freshly prepared human AChE, in comparison to the donepezil as reference compound. Inhibition of AChE activities of the synthesized compounds is shown in Tables 1 and 2 the data listed in Table 1 and 2 clearly showed that most of the designed compounds exhibited good to moderate inhibitory activities toward the acetylcholinesterase. Among the thirty newly synthesized compounds, compounds spiro[2.3′]oxindolespiro[3.2″]-5,6-dimethoxy-1″-indanone-4-(pyridyl)-1-*N*-methyl pyrolidine (**4k**) produced significant activities with 0.10 ± 0.1 μmol/L followed by (**6k**), (**4f**), (**4a**),(**6f**) and (**6a**) 0.24 ± 0.1 μmol/L, 0.30 ± 0.02 μmol/L, 0.37 ± 0.01 μmol/L, 0.42 ± 0.02 μmol/L and 0.46 ± 0.02 μmol/L, respectively.

The compound containing group like nitro with pyridine substituted (**4k**) showed higher inhibitory activity in general. However the pyridine substituted (**4f**), (**4a**), (**6f**) and (**6a**) analogues also produced good AChE inhibitory activity. Among the two series of compounds, (**4a–4o** and **6a–6o**) the compounds belonging to both series (**4a–4o** and **6a–6o**) with nitro group on the isatin nucleus and pyridine ring at 4th position of pyrolidine ring display higher potency than other substitution on either series (**4a–4o** and **6a–6o**).

These reports clearly showed pyrolidine substituted derivatives causes' remarkable improvement in AChE inhibitory activity. Among the newer derivatives, it is conceivable that derivatives showing AChE inhibitory activity can be further modified to exhibit better potency than the standard drugs. Further studies to acquire more information about quantitative structure–activity relationships (QSAR) are in progress in our laboratory. The indanone containing pyrolidine derivatives discovered in this study may provide valuable therapeutic intervention for the treatment of AD diseases.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.09.108.

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