Bioorganic & Medicinal Chemistry Letters 19 (2009) 5075–5077

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Design, synthesis and evaluation of novel 5,6-dimethoxy-1-oxo-2,3-dihydro-1*H*-2-indenyl-3,4-substituted phenyl methanone analogues

Mohamed Ashraf Ali [a,*], Mohammad Shahar Yar [b], Mohamed Zaheen Hasan [a], Mohamed Jawed Ahsan [a], Suresh Pandian [a]

[a] *New Drug Discovery Research, Department of Medicinal Chemistry, Alwar Pharmacy College, Alwar, Rajasthan 301 030, India*
[b] *Faculty of Pharmacy, Jamia Hamdard University, Department of Pharmaceutical Chemistry, Hamdard Nagar, New Delhi 110 062, India*

ARTICLE INFO

Article history:
Received 6 April 2009
Revised 5 June 2009
Accepted 7 July 2009
Available online 10 July 2009

Keywords:
Diketone
AChE inhibitory activities
Alzheimer's disease (AD)

ABSTRACT

In present investigation, a series of substituted phenyl-5,6-dimethoxy-1-oxo-2,3-dihydro-1*H*-2-indenyl-methanone analogues were synthesized and were tested for their potential for treating AD disease. All the newly synthesized compounds were showing moderate to high AChE inhibitory activities, with compound 5,6-dimethoxy-1-oxo-2,3-dihydro-1*H*-2-indenyl-3,4,5-trimethoxyphenylmethanone (**5f**) produced significant activities with 2.7 ± 0.01 μmol/L.

The mechanism of Alzheimer's disease (AD) is till unknown, three pathological hallmarks have been identified, for example, amyloid-β plaque, neurofibrillary tagles (NFTs) and synaptic loss. The neuritic senile plaques consist of afibrillar amyloid core surrounded by dystrophic neuritis and reactive microglia. Acetylcholinesterase is present throughout the central and peripheral nervous systems of mammals, where it catalyses the hydrolysis of the endogenous ester neurotransmitter acetylcholine (ACh), allowing the termination of ACh receptor-mediated ion gating at nerve–nerve and neuromuscular junctions.[1]

Alzheimer's disease (AD) is associated with an early and profound loss of central cholinergic function. This is due, in part, to a reduction in the activity of choline acetyltransferase, the enzyme primarily responsible for the synthesis of the neurotransmitter acetylcholine (ACh). Indeed, this cholinergic deficiency correlates with disease severity.[2,3]

About 4 million Americans-90 percent of whom are age 65 and older-have Alzheimer's disease. The prevalence of Alzheimer's disease doubles every five years beyond age 65.[4] In the past 25 years scientists have made great progress in unravelling the mysteries of Alzheimer's disease; however, much is still unknown. Unless prevention or a cure is found, the number of Americans with Alzheimer's disease could reach 14.3 million 50 years from now.

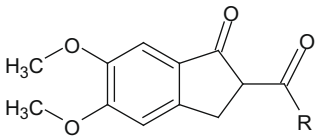
Alzheimer's disease (AD) is a devastating neurodegenerative disease with progressive loss in memory destruction of reasoning, imaginary power and ability to learn. The enzyme, acetylcholinesterase (AChE), is responsible for the termination of impulse signalling at cholinergic synapses by catalysing the hydrolysis of the neurotransmitter acetylcholine (ACh). Drugs that are currently prescribed for AD can have severe side-effects in patients with FTD.[5] Furthermore; FTD itself includes several clinical entities that require better biochemical characterization. Therefore, it is imperative to develop tools that enable an early, differential diagnosis. 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, indanone derivatives play a vital role in discovering novel candidates having the action of acetyl cholinesterase (AChEI) inhibitors. Also many literatures reveal that the indanone nucleus acts as protease inhibitors and acetyl cholinesterase (AChEI) inhibitors, it was considered to be worth to work on the above mentioned novel analogues.

5,6-Dimethoxy-1-oxo-2,3-dihydro-1*H*-2-indenyl-3,4-substituted phenyl methanone analogues **5a–5n** described in this study is shown in Table 1, and a reaction sequence for the preparation is outlined in Scheme 1. In the initial step, 5,6-dimethoxy-2-[(*E*)-1-phenylmethylidene]-1-indanone were synthesized condensing 5,6-dimethoxy-1-indanone with appropriate aromatic aldehydes in dilute methanolic sodium hydroxide solution at room temperature, then bromination of 5,6-dimethoxy-2-[(*E*)-1-phenylmethylidene]-1-indanone in minimum quantity of chloroform followed by hydrolysis with methanolic potassium hydroxide to get titled

* Corresponding author. Tel.: +91 9940531214; fax: +91 11 26059666.
E-mail address: asraf80med@rediffmail.com (M.A. Ali).

0960-894X/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2009.07.042

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



5_a-5_n

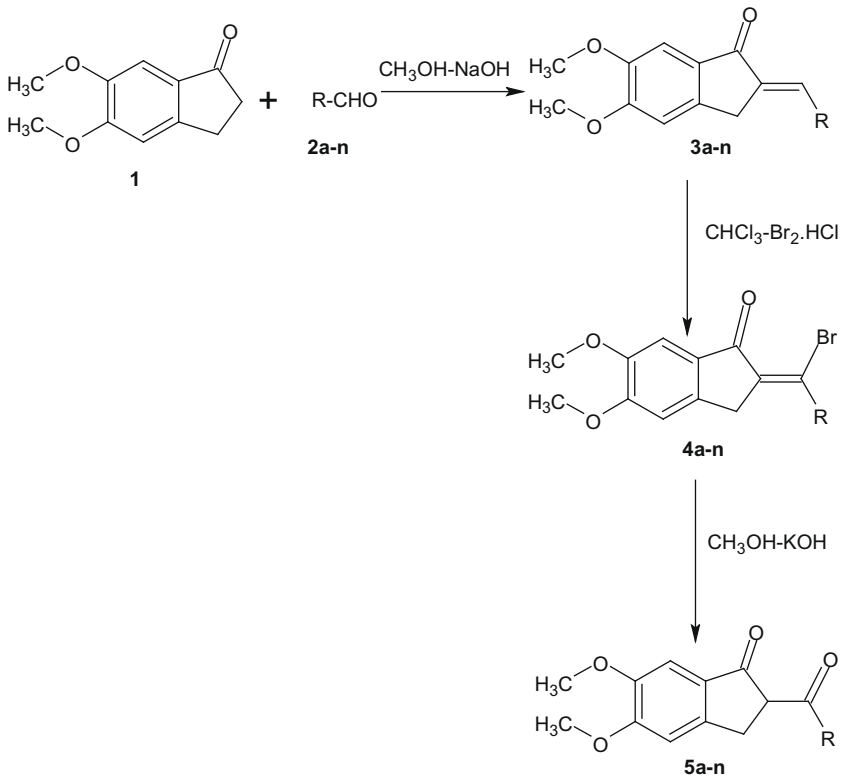
Compound	R	Yield (%)	MP (°C)	AChE inhibition (IC_{50} ± SD)[a] μmol/L)
5a	4-Methoxy phenyl-	74	164	6.2 ± 0.02
5b	4-Chloro phenyl-	70	142	41.2 ± 0.1
5c	4-Dimethylamino phenyl-	72	114	29.4 ± 0.1
5d	Phenyl-	80	131	21 ± 0.1
5e	3,4-Dimethoxy phenyl-	82	118	4.3 ± 0.01
5f	3,4,5-Trimethoxy phenyl-	85	133	2.7 ± 0.01
5g	4-Fluoro phenyl-	92	146	42 ± 0.1
5h	2-Chloro phenyl-	85	125	64 ± 0.1
5i	2,6-Dichloro phenyl-	77	154	102 ± 0.1
5j	3-Nitro Phenyl-	82	104	In active
5k	Furyl-	90	98	9.4 ± 0.1
5l	Thiophenyl	56	198	8.6 ± 0.1
5m	4-Bromo phenyl-	81	184	45 ± 0.1
5n	4-Cyano phenyl-	76	202	53 ± 0.1
Donepezil	—	—	—	0.12 ± 0.01

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

compounds in 56–92% yield after recrystallization with ethanol. 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, Infrared spectra (IR) revealed CH, C=O, and C–F peak at 1640, 1320 and 786 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 triple at δ 3.20–3.35 ppm corresponding to CH group; doublet at δ 3.41–3.44 ppm corresponding to CH_2 group; singlet at δ 3.82, 3.86 ppm corresponding to OCH_3 multiplet at δ 6.48–7.20 ppm corresponding to aromatic protons. The elemental analysis results were within ±0.4% of the theoretical values.

Among the novel substituted diketone derivatives for treating AD, their anticholinesterase activities (compounds **5a**–**n)** were assayed according to Ellmann's method[6] against freshly prepared AChE from electrophorus electricus using donepezil as reference compound. Inhibition of AChE activities of the synthesized compounds is shown in Table 1.The data listed in Table 1 clearly show that most of the designed compounds exhibited moderate inhibitory activities toward the cholinesterase. Among the fourteen newly synthesized compounds, compounds 5,6-dimethoxy-1-oxo-2,3-dihydro-1*H*-2-indenyl-3,4,5-trimethoxyphenylmethanone (**5f**) produced significant activities with 2.7 ± 0.01 μmol/L followed by (**5e**) 5,6-dimethoxy-1-oxo-2,3-dihydro-1*H*-2-indenyl-3,4-dimethoxyphenylmethanone and (**5a**) 5,6-dimethoxy-1-oxo-2,3-dihydro-1*H*-2-indenyl-4-methoxyphenylmethanone inhibitory activity with 4.3 ± 0.01 μmol/L and 6.2 ± 0.02 μmol/L, respectively. The electron stumpy group like methoxy substituted phenyl group 5,6-dimethoxy-1-oxo-2,3-dihydro-1*H*-2-indenyl-3,4,5-trimethoxyphenylmethanone (**5f**) showed higher inhibitory activity in general. However the furyl and thiophenyl substituted analogues produced moderate AChE inhibitory activity. On the other hand the electron rich group such as, 4-flurophenyl, 4-bromophenyl, 2-chlorophenyl, 2,6-dichlorophenyl and 4-nitrophenyl substituted analogue showed significant decrease in inhibitory activity.

Instead of electron withdrawing groups like 4-flurophenyl, 4-bromophenyl, 2-chlorophenyl, 2,6-dichlorophenyl and 4-nitrophenyl, electron donating group like 4-methoxy phenyl-,3,4-dimethoxy phenyl and 3,4,5-trimethoxy phenyl group substituted



Scheme 1. Protocol for synthesis.

diketone analogue to worse the AChE inhibitory activity. These reports clearly showed the increases the presence of OCH_3 group substituted phenyl ring at diketone derivatives causes remarkable improvement in AChE inhibitory.

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 diketone derivatives discovered in this study may provide valuable therapeutic intervention for the treatment of AD diseases.

Acknowledgment

Authors are thankful to the management people of Alwar Pharmacy College, Alwar, Rajasthan.

References and notes

1. Gilmer, J. F.; Lally, M. N.; Gardiner, P.; Dillon, G.; Gaynor, J. M.; Reidy, S. *Chem. Biol. Interact.* **2005**, *157–158*, 317.
2. Rossor, M. N. *Lancet* **1982**, *2*, 1200.
3. Bierer, L. M.; Haroutunian, V.; Gabriel, S.; Knott, P. J.; Carlin, L. S.; Purohit, D. P.; Perl, D. P.; Schmeidler, J.; Kanof, P.; Davis, K. L. *J. Neurochem.* **1995**, *64*, 749.
4. National Institute on Aging, 1999. Progress Report on Alzheimer's Disease, National Institutes of Health, Bethesda, MD, 1999.
5. Cummings, J. L.; Askin-Edgar, S. *CNS Drugs* **2000**, *13*, 385.
6. Ellman, G. L.; Courtney, K. D.; Andres, B.; Feartherstone, R. M. *Biochem. Pharmacol.* **1961**, *7*, 88 (**5f**): IR: (KBr) cm^{-1}: 3042 (CH), 1642 (C=O) ^{1}H NMR (DMSO-d_6) ppm: 3.20–3.35(1H, t, CH), 3.41–3.44 (2H, d, CH_2), 3.82, 3.86 (15H, s, OCH_3), 6.48–7.2 (4H, m, aromatic); mass (*m*/*z*) 386 (M^+); cal/ana [C (65.28) 65.27, H (5.74) 5.73, O (28.96) 28.97].