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RATIONAL DESIGN AND SYNTHESIS OF SOME SUBSTITUTED AMINOETHANONES AND ACETAMIDES AS NOVEL ACETYL CHOLINESTERASE INHIBITORS

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ABSTRACT:
Rivastigmine is one of the important drug presently used to treat Alzheimer's disease and it has short half life and limited usage. That was the main reason for the synthesis of Rivastigmine related amino ethanones and acetamide derivatives. 2-Chloro cycloamino ethanones and 2-chloro N-substituted acetamides were synthesized by adding chloroacetylchloride dropwise to a mixture of cycloamine, dichloromethane and triethylamine and stirring for 1 hour at 0^0c. These compounds were stirred at 60^0c for 5 hours with a solution of m-hydroxy acetophenone in DMSO in presence of potassium hydroxide to obtain 2-(3-acetyl)-phenoxy derivatives of 1-(cycloamino) ethanones and N-substituted acetamides. The synthesized compounds were characeterized on the basis of physical and spectroscopic data. Anticholinesterase inhibitory activity of these compounds was carried out by Ellman's esterase assay and was found to be active in 435 µM to 776 µM range. All the compounds were found to be drugable under Lipinski's rule.

Keywords: Anticholinesterase inhibition, Acetyl phenoxy aminoethanones, Acetyl phenoxy acetamides, Rivastigmine.

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INTRODUCTION

Alzheimer's disease (AD) is a complex neurological disorder that is clinically characterized by loss of memory and progressive deficits in different cognitive domains, particularly affecting cholinergic neurons in the basal forebrain. Primary cause of AD may be due to the massive deposition of amyloid plaques[1]. Acetyl cholinesterase (AChE) plays the crucial role in the pathogenesis of AD by mediating the hydrolysis of acetylcholine. Moreover, the neurotoxicity of amyloid components is increased by the presence of AChE[2]. So AChE inhibition has been broadly explored in AD treatment. Rivastigmine and other presently used drugs have short half life and limited usage[3-4]. In the present study we prepared some novel 2-(3-acetyl phenoxy) ethanones and N-substituted acetamides, which are structurally related to rivastigmine for better safety, efficacy and long half life.

MATERIALS AND METHODS

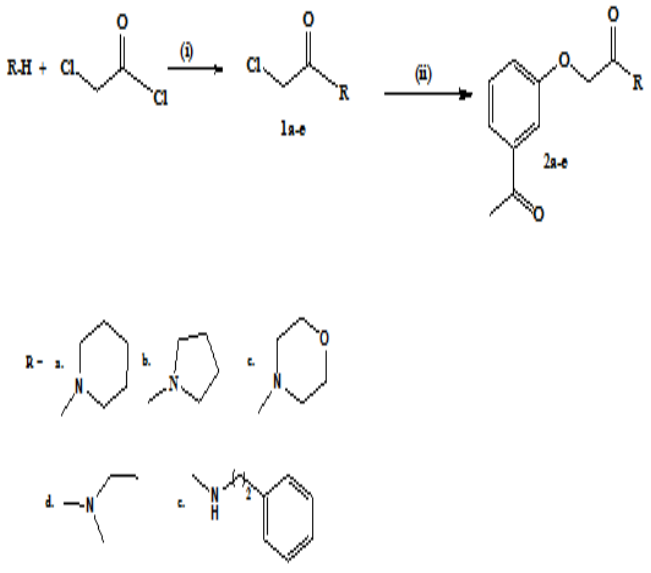
Preparation of 2-chlorocycloamino ethanones and 2-chloro N-substituted acetamides (1a-e): To a mixture of cycloamino/amine (1 equivalent), dichloromethane (20 ml) and triethylamine (2 equivalents), chloroacetylchloride (2 equivalents) was added dropwise and was stirred for 1 hour at 0^0c. Water was added to the reaction mixture and extracted further to collect dichloromethane fraction. Extract was dried over anhydrous sodium sulphate and concentrated in vacuo to afford the titled compounds as yellow coloured oily substances[5].

Preparation of 2-(3-acetyl phenoxy)-1-(cycloamino-1-yl)-ethanones and 2-(3-acetyl phenoxy)-N-substituted acetamides (2a-e): Potassium hydroxide (2 equivalents) was added to a solution of m-hydroxy acetophenone in DMSO and stirred at room temperature for 1 hour. Compounds (1a-e) (2

equivalents) were added to this reaction mixture and were stirred at 60^0c for 5 hours. Reaction mixture was then poured into ice cold water and neutralized with dilute hydrochloric acid. Mixture was further extracted with ethyl acetate and then evaporated in vacuo. Residual fraction of compounds was collected and then purified by column chromatography to obtain white amorphous powders[6]. Physical data of synthesized compound is shown in table 1.

Ellman Esterase Assay

The assay is based on the measurement of changes in absorbance at 412 nm. The assay uses thiol ester of acetylcholine instead of oxy ester acetylcholine. AChE hydrolyses the acetylcholine to produce thiolcholine and acetate. Thiocholine produced in the reaction reacts with 5, 5'-dithiobis-(2-nitrobenzoic acid) (DTNB) and releases 5-thio-2-nitrobenzoic acid (yellow colour complex) which absorbs light in the range of 400-420 nm with maximal absorption at 412 nm. The anticholinesterase activities were determined according to Ellman's Esterase assay method against freshly prepared AChE from rat plasma using rivastigmine as reference compound.



[a]Reagents and conditions:(i) CH_2Cl_2, Et_3N, 0 °C,1h.; (ii) $C_3H_4O_2$, DMSO, KOH, 60 °C, 5h.

Scheme : Synthetic Protocol of the titled compounds

RESULTS AND DISCUSSION

Structures of the synthesized compounds were confirmed by IR, H^1 NMR and mass spectra and were supported by physical data such as melting point differences and different Rf values. According to Ellman Esterase assay[7] compounds were found to be active in 435 µm to 776 µm range as given in the table 2. Among the synthesized compounds 2d was found to be more potent.

1H NMR spectra of compound 2a [300 MHz, d-DMSO]

1H NMR [300 MHz, d-DMSO]:δ 7.56(d, J=6Hz, 1H); 7.15-7.40 (m,2H); 7.20-7.17 (dd, J=9Hz and 3Hz, 1H); 4.89 (s, 2H); 3.44-3.39 (q, 4H), 2.57 (s, 3H); 1.62-1.52 (m,4H); 1.47-1.40 (m,2H)

GC-MS spectra of compound 2a

GC-MS (1M): m/z 261 $(M1)^+$, M1-15(246,-CH_3)$^+$; M1-43(218,-$COCH_3$)$^+$; M1-135(126,-$C_8H_7O_2$)$^+$;M1-149(112,-$C_9H_9O_2$)$^+$; M1-163(84,-$C_{10}H_9O_3$)$^+$; M6-15(69,-$C_{10}H_8NO_3$)$^+$

IR spectra of compound 2a

IR (KBr, cm^{-1}): 2933 cm^{-1} (-CH_3 Str); 2856 cm^{-1} (-CH_2 Str); 1649 (-CO- Str); 1479-1438 (ar C=C Str); 1224 (Assym C-O-C Str); 1132 (Sym C-O-C Str).

1H NMR spectra of compound **2b** [300 MHz, d-DMSO]

1H NMR (300 MHz, DMSO-d_6): δ7.56 (d, J=6Hz,1H); 7.45-7.41 (m, 2H); 7.21-7.17 (dd, J=9Hz and 3Hz, 1H); 4.81 (s, 2H); 3.48(t, J=4.31 Hz, 2H), 3.30 (s,2H); 2.50 (s, 3H); 1.95-1.85, (m, 2H); 1.82-1.73 (m, 2H).

GC-MS Spectra of compound 2b

GC-MS (1M): m/z 247$(M1)^+$, M1-15(232, -CH_3)$^+$; M1-43(204, -$COCH_3$)$^+$; M1-135(112, -$C_8H_7O_2$)$^+$; M1-149(98,-$C_9H_9O_2$)$^+$; M1-177(70,-$C_{10}H_9O_3$)$^+$.

IR Spectra of compound 2b

IR (KBr, cm^{-1}): 2937 cm^{-1} (-CH_3 Str); 2872 cm^{-1} (-CH_2 Str); 1683 (-CO- Str); 1485-1431 (Ar C=C Str); 1222 (Assym (C-O-C Str); 1085 (sym C-O-C Str).

Table 1: Physical data of synthesized compounds (2a-e):

Compound	Molecular Formula	Mol. Wt	Melting point	Yield %	Rf	λmax	Log P
2a	$C_{15}H_{19}O_3N$	261.32	66	78	0.54	216	1.04
2b	$C_{14}H_{17}O_3N$	247.29	72	88	0.39	216	0.62
2c	$C_{14}H_{17}O_4N$	263.29	62	39	0.49	216	0.09
2d	$C_{13}H_{17}O_3N$	297.35	64	60	0.70	214	0.64
2e	$C_{18}H_{19}O_3N$	235.12	Liquid	23	0.58	217	2.08

Table 2: Activity of compound in 435 µm to 776 µm range.

Compound code	IC_{50} (µm)
2a	556
2b	660
2c	776
2d	435
2e	549

CONCLUSION

The synthesised compounds were found to have interaction with the acetyl cholinesterase receptor as determined by Ellman's Assay. It was found that the synthesised compounds inhibited the enzyme at a range of 435.25 to 776.4μM. All of the compounds were found to be drugable under the Lipinski's rule.

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REFERENCES

1. G. Sinha. Peering inside Alzheimer's brains, Nature biotechnology 29: 384-387 (2011).
2. V. N. Talesa. Acetylcholinesterase in Alzheimer's disease, Mechanisms of Ageing and Development 122: 1961-1969 (2001).
3. K. Arumugam, M. R. Chamallamudi, R. R. Gibilli, R. Mullangi, S. Ganesan, R. Averineni, G. Shavia and N. Udupa. Development and validation of a HPLC method for quantification of rivastigmine in rat urine and identification of a novel metabolite in urine by LC-MS/MS, Biomed. Chromatogr. 25: 353-361 (2011).
4. H. Wen, Y. Zhou, C. Lin, H. Ge, L. Ma, Z. Wang, W. Peng and H. Song. Methyl 2-(2-(4-formylphenoxy) acetamido)-2-substituted acetate derivatives, A new class of acetylcholinesterase inhibitors, Bioorg. Med. Chem. Lett. 17: 2123-2125 (2007).
5. Qian-sheng Yu, H. W. Halloway, J. L. Flippen-Anderson, B. Hoffman, A. Brossi and N. H. Grieg. Methyl analogues of thee expiremental Alzheimer drug phenserine: Synthesis and structure activity relationships for acetyl and butyrylcholinesterase inhibitory action, J. Med. Chem. 44: 4062-4071 (2001).
6. A. Ohta, Y. Tonomura. Stereoselective synthesis of spicy components in peppers, Heterocycles 32: 965-974 (1991).
7. G. L. Ellman, K.D. Courtney, B. Andres, R. M. Featherstone. A new and rapid colorimetric determination of acetylcholinesterase activity, Biochem. Pharmacol. 7: 88-95 (1961).