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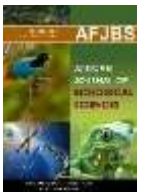

Microwave Accelerated Sustainable Approach for Synthesis of Novel Indolizine Derivatives of Antifungal and Anti-Alzheimer's Agents

Tairabi Khanadal[1], Pramod N. Patil[2], M.V. Chethana[3] and Basavaraj Padmashali[1*]

[1]Department of Chemistry, Rani Channamma University, Belagavi, Karnataka, India- 591156.

[1*]Department of Chemistry, Rani Channamma University, Belagavi, Karnataka, India- 591156.

Corresponding Author:

Basavaraj Padmashali Department of Chemistry, Rani Channamma University,Belagavi, Karnataka, India

E-mail: basavarajpadmashali@yahoo.com

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Abstract: The newly synthesised N-fused derivatives **(2a-e)** and **(3a-e)** are synthesised in eco-friendly method with trim in time, yielding good product results. These eco-friendly indolizine derivatives are essential in pharmacological activities. Alzheimer's disease, affects the elderly and is chronic condition with no cure, and treatment is provided only for temporary relief. The disease possesses in two different forms of molecular series that target the multi-factorial aspects of the disease cells. The framework of designed molecule inhibits oxidative damage, acetylcholinesterase (AChE), and aggregation of Aβ fibrils that are the main aspect of disease and also exhibits good radical scavenging capacity. Certainly, these synthesised molecules show potential effective for Alzheimer's disease. In addition, the derivatives were also screened for antifungal activities.

Key words: AChE, Alzheimer's, antifungal, indolizine, 1,3-cycloaddition.

Introduction

In the field of organic chemistry, heterocyclic compound plays a pivotal role due to their various biological potential in medicine and pharmaceuticals, especially for anti-inflammatory, antibacterial, and anti-cancer potential. Heterocyclic compounds containing aromatic ring with combined with a pyrrole ring possess significant biological activity, indolizine motifs being noteworthy, amid Indolizine being N-bridged aromatic compound, isolated from fauna, flora, pests, and microorganism. The derivatives of indolizine also play important role and, hold prominence in medicinal chemistry, and drug design. In this study, we are focused on the neurodegenerative diseases such as Alzheimer's, amyotrophic lateral

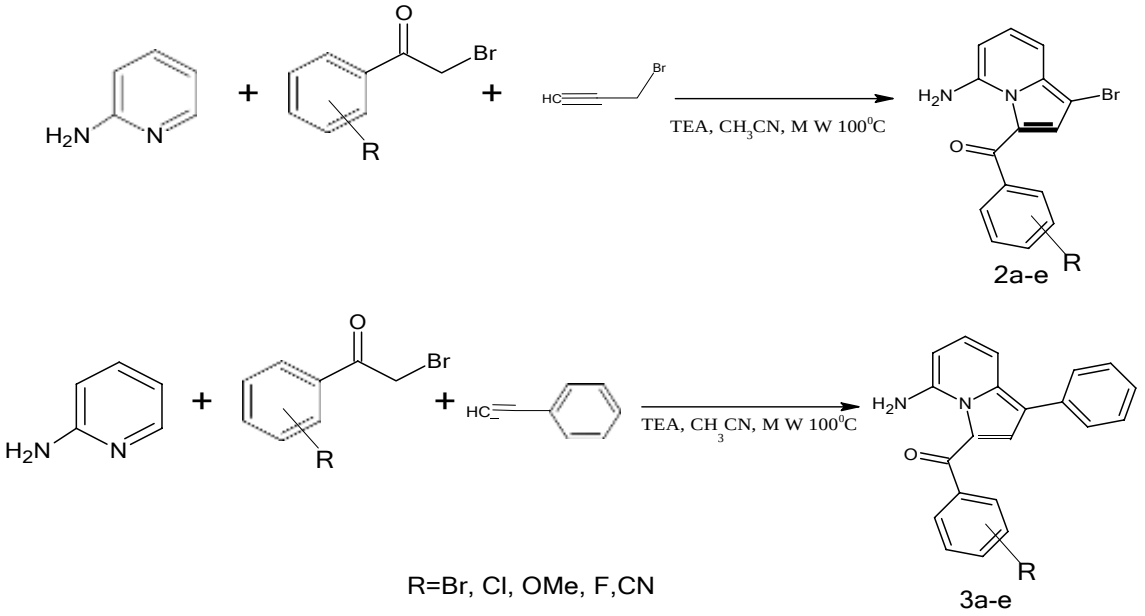
sclerosis (ALS), chronic diseases, the potential cause of this diseases which is nearly affected to 13. 2 million people for which there is no cure, if so, it might cost amounting $ 259 billion. Most of the available drug are acetylcholinesterase (AChE) inhibitors that typically provide short-time relief. Therefore, in this article we have mainly focused on treatment of Alzheimer's disease (AD). Amid to synthesis the anti-Alzheimer's, we choose to synthesis the molecule by green chemistry, that has become an essential realm of study, encouraging the development of approach to minimise the environmental damage and significantly producing targeted derivatives. Amid many principles of green chemistry, two key ones stand out, the use of **"Safer Solvents"** and **"energy efficiency"** in synthetic process. By adhering these guidelines, scientist and industry experts are contributing in the development of more sustainable and eco-friendly chemical process. Certainly, in current studies we have developed a significant method using microwave irradiation, which is shown to be 100 times faster than that of conventional methods and simplifies chemical reaction. The advantage of this method over conventional method is trim in time, reduced by-product, increased yield all of which contribute to a minimal environmental and health impact.

MATERIALS AND METHODS:

CHEMISTRY:

Melting points were determined using in Buchi melting point B-545 apparatus and are uncorrected. The IR spectra was recorded on a Thermo Fisher Scientific Fourier Transform spectrometer. NMR spectra. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker AV 800 spectrometer, with chemical shifts reported in δ ppm with Tetra methyl silane as an internal standard and $CDCl_3$. The antibacterial activity of indolizine derivatives were carried using disc diffusion method with *C. albicans* as reference standard and brain heart infusion as growth medium, following the protocol outlined in clinical microbiology procedures handbook. The enzymatic of TcAChE was carried as described by Asha Mathad et. al.

Scheme-1



Experimental Section

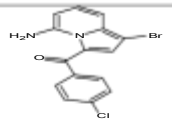
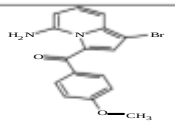
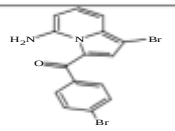
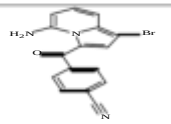
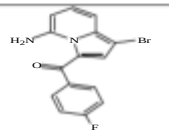
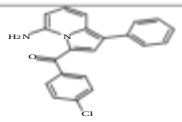
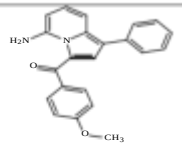
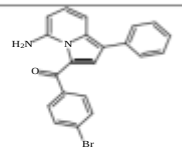
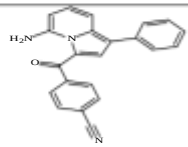
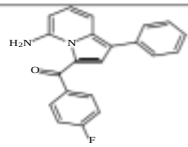
General procedure for the synthesis of (5-amino-1-bromoindolizin-3-yl)(4-bromophenyl)methanone 2c (2a-e)

It is a single pot reaction, in which three components namely 2-amino pyridine, substituent phenacyl bromide, prograyl bromide and triethyl amine as a base were taken in round bottom flask provided with reflux condenser at top and was irradiated under micro-Owen @ 100^0C for 5 minutes. The progress of reaction was monitored by TLC using ethyl acetate and hexane as mobile phase. After the completion of reaction, the crude product was poured in crushed ice, and was extracted with ethyl acetate and was washed with brine solution. The organic layer obtained was dried over anhydrous Na_2SO_4 and the solvent was evaporated to dryness to yield **2a.** The remaining substituent derivatives were synthesised with same protocol **(2a-e)** The compound **2c** is characterised by spectroscopical data including Ir, ^{1}HNMR, and ^{13}C NMR. The IR spectrum shows an aromatic peak at 3420.31 cm^{-1}, a carbonyl peak at 1633.55 cm^{-1} and peak at 825 cm^{-1} indicates carbon-bromine bon. The ^{1}H proton NMR (δ in ppm) displays signal at 8.08-8.06 (1H, m), 7.90-7.87 (1H, m), 7.76 (1H, m), 7.61-7.58 (1H, m), 7.24 (1H, m), 7.17 (2H, m), 7.12-7.06 (2H, m); 6.76-6.73 (1H, m), showcasing multiple complex aromatic protons. Additionally, the ^{13}C-NMR spectrum ($CDCl_3$ –d. 150MHz) with signals at 131.94, 127.64, 125.38, 121.98, 117.67, 112.74, 108.30 indicates various signals of a bromo substituted aromatic ring. This data confirms the structure of molecule of **2c**.

General procedure for the synthesis of (5-amino-1-phenylindolizin-3-yl)(4-chlorophenyl)methanone **3a (3a-e).**

It is a single pot reaction, in which three components namely 2-amino pyridine, substituent phenacyl bromide, phenyl acetylene and triethyl amine as a base were taken in round bottom flask provided with reflux condenser at top and was irradiated under micro-Owen @ 100^0C for 5 minutes. The progress of reaction was monitored by TLC using ethyl acetate and hexane as mobile phase. After the completion of reaction, the crude product was poured in crushed ice, and was extracted with ethyl acetate and was washed with brine solution. The organic layer obtained was dried over anhydrous Na_2SO_4 and the solvent was evaporated to dryness to yield **3a.** The remaining substituent derivatives were synthesised with same protocol **(3a-e)**. The compound **3a** is characterised by spectroscopical data including Ir, ^{1}HNMR, and ^{13}C NMR. The IR spectrum shows an aromatic peak at 3445.28 cm^{-1}, a carbonyl peak at 1634 $cm^{-1,}$ peak at 935.93 cm^{-1} indicates carbon-chlorine bond and peak at 1404 cm^{-1} indicating aromatic ring. The ^{1}H proton NMR (δ in ppm) displays signal at 8.09-8.07 (1H, m), 7.87-7.80 (1H, m), 7.62-7.59 (1H, m), 7.38-7.36 (1H, m), 7.24 (1H, s), 7.18-7.14 (1H, m), 6.78-6.75 (1H, m). showcasing multiple complex aromatic protons. Additionally, the ^{13}C-NMR spectrum ($CDCl_3$ –d. 150MHz) with signals at 145.27, 133.73, 132.39, 128.98, 127.32, 125.35, 117.63, 112.69, 108.28, indicates various signals of a bromo substituted aromatic ring. This data confirms the structure of molecule of **3a**.

Table:1 Physiochemical Characteristics of Indolizine derivatives **(2a-3e)**

Code	Structure	Molecular. Weight	Melting Point in ^{0}C	Yield
2a		$C_{15}H_{10}BrClN_2O$ **349.6**;	164-166.	80%
2b		$C_{16}H_{13}BrN_2O_2$ **345.2**	170-172	86%
2c		$C_{15}H_{10}Br_2N_2O$ **394.1**	150-151	78%
2d		$C_{16}H_{10}BrN_3O$ **340.2**	168-170.	90%
2e		$C_{15}H_{10}BrN_2O$ **333.2**	154-156.	76%
3a		$C_{21}H_{15}ClN_2O$ **346.8**	140-141	86%
3b		$C_{22}H_{18}N_2O_2$ **342.4**	177-178.	87%;
3c		$C_{21}H_{15}BrN_2O_2$ **391.3**	159-161	90%;
3d		$C_{22}H_{15}N_3O$ **337.4**	162-164	90%;
3e		$C_{21}H_{15}FN_2O$ **330.4**	156-158	86%

- All the synthetic compounds were characterized by physical and spectral data
- Yield was calculated after column chromatography purification and confirmation.

Characterization of compounds

(5-amino-1-bromoindolizin-3-yl)(4-chlorophenyl)methanone **2a**

IR (KBr, cm $^{-1}$); 3445.28 (Ar-NH_2), 1633 (C=O), 935.93 (Ar-C-Cl), 707.15 (C-Br). **^{1}H NMR** ($CDCl_3$-d. 400 MHz); δin ppm: 8.043 (1H, S), 7.84-7.77 (1H, m), 7.59-7.57 (1H, m), 7.37-7.35 (1H, m), 7.24 (2H, m), 7.16-7.12 (2H, m), 6.75-6.72 (1H, m). **^{13}C-NMR** ($CDCl_3$ –d. 150MHz); 145.60, 133.76, 132.39, 128.99, 127.34, 125.69, 125.01, 117.66, 112.70, 108.26, 77. 10. **Molecular Formula**: $C_{15}H_{10}BrClN_2O$; wt: 349.6; yield:80%; mp:164-166.

(5-amino-1-bromoindolizin-3-yl)(4-methoxyphenyl)methanone **2b.**

IR (KBr, cm $^{-1}$); 3425.56 (Ar-NH_2), 1633.34 (C=O), 3075.94 (Ar-C-OCH_3), 709 (C-Br). **^{1}H NMR** ($CDCl_3$-d. 400 MHz); δin ppm: 8.05-8.03 (1H, S), 7.85-7.81 (1H, m), 7.72 (1H, m), 7.57-7.55 (1H, m), 7.44-7.42 (2H, m), 7.22 (2H, s), 7.11-7.09 (1H, m); 6.97-6.90 (1H, m), 6.70-6.77 (1H, m), 5.10 (3H, s). **^{13}C-NMR** ($CDCl_3$ –d. 150MHz); 159.65, 145.69, 132.85, 126.96, 125.11, 117.57, 115.26, 114.21, 113.37, 110.91, 107.35, 76.84, 55.57, 35.56. **Molecular Formulae**:$C_{16}H_{13}BrN_2O_2$; wt: 345.2; yield:86%; mp:170-172.

(5-amino-1-bromoindolizin-3-yl)(4-bromophenyl)methanone **2c.**

IR (KBr, cm $^{-1}$); 3420.31 (Ar-NH_2), 1633.55 (C=O), 3074.09 (Ar-C-Br), 825 (C-Br). **^{1}H NMR** ($CDCl_3$-d. 400 MHz); δin ppm: 8.08-8.06 (1H, m), 7.90-7.87 (1H, m), 7.76 (1H, m), 7.61-7.58 (1H, m), 7.24 (1H, m), 7.17 (2H, m), 7.12-7.06 (2H, m); 6.76-6.73 (1H, m). **^{13}C-NMR** ($CDCl_3$ –d. 150MHz); 131.94, 127.64, 125.38, 121.98, 117.67, 112.74, 108.30, 77.10. **Molecular Formulae**: **$C_{15}H_{10}Br_2N_2O$**; wt: 394.1; yield:78%; mp: 150-151.

4-(5-amino-1-bromoindolizine-3-carbonyl)benzonitrile **2d.**

IR (KBr, cm $^{-1}$); 3038.77 (Ar-NH2), 1606.13 (C=O), 2220.35 (Ar-C-CN), 709.81 (C-Br). **^{1}H NMR** ($CDCl_3$-d. 400 MHz); δin ppm: 8.11-8.05 (1H, m), 7.90-7.71 (1H, m), 7.76 7.59(1H, m), 7.24-7.21 (2H, m), 7.20-7.17 (2H, m), 6.80-6.78 (1H, s). **^{13}C-NMR** ($CDCl_3$ –d. 150MHz); 146.04, 143.77, 138.35, 132.68, 126.44, 125.74, 119.17, 117.93, 113.15, 111.15, 109.61, 77.12. **Molecular Formulae**: $C_{16}H_{10}BrN_3O$; wt: 340.2; yield:90%; mp: 168-170.

(5-amino-1-bromoindolizin-3-yl)(4-fluorophenyl)methanone **2e.**

IR (KBr, cm $^{-1}$); 3439.61 (Ar-NH2), 1633.51 (C=O), 1371 (Ar-C-F), 743 (C-Br). **^{1}H NMR** ($CDCl_3$-d. 400 MHz); δin ppm: 8.08-8.06 (1H, m), 7.90-7.87 (1H, m), 7.69-7.58 (1H, m),

7.24-7.17 (1H, m), 7.12-7.06 (1H, m), 6.76-6.73 (1H, s). **^{13}C-NMR** ($CDCl_3$ –d. 150MHz); 145.34, 130.04, 127.76, 125.66, 124.89, 117.56, 115.74, 112.60, 107.87, 77.12.

Molecular Formula: $C_{15}H_{10}BrN_2O$; wt: 333.2; yield: 76%; mp: 154-156.

(5-amino-1-phenylindolizin-3-yl)(4-chlorophenyl)methanone **3a.**

IR (KBr, cm $^{-1)}$; 3445.28 (Ar-NH2), 1634 (C=O), 935.93 (Ar-C-Cl), 1404 (C6H6). **^{1}H NMR** ($CDCl_3$-d. 400 MHz); δin ppm: 8.09-8.07 (1H, m), 7.87-7.80 (1H, m), 7.62-7.59 (1H, m), 7.38-7.36 (1H, m), 7.24 (1H, s), 7.18-7.14 (1H, m), 6.78-6.75 (1H, m). **^{13}C-NMR** ($CDCl_3$ – d. 150MHz); 145.27, 133.73, 132.39, 128.98, 127.32, 125.35, 117.63, 112.69, 108.28, 77.13.

Molecular Formula: $C_{21}H_{15}ClN_2O$; wt: 346.8; yield: 86%; mp: 140-141.

(5-amino-1-phenylindolizin-3-yl)(4-methoxyphenyl)methanone **3b.**

IR (KBr, cm −1); 3464.02 (Ar-NH2), 1634 (C=O), 3021.21 (Ar-C-OCH_3), 1404 (C6H6).**^{1}H NMR** ($CDCl_3$-d. 400 MHz); δin ppm: 8.07-8.03 (1H, m), 7.87-7.85 (1H, m), 7.24 (1H, s), 7.14-7.10 (1H, m), 6.95-6.93 (1H, m), 6.75-6.70 (1H, m), 4.00 (1H, s). **^{13}C-NMR** ($CDCl_3$ – d. 150MHz); 159.64, 145.25, 127.36, 126.57, 125.55, 125.51, 117.36, 114.20, 112.31, 107.32, 77.14, 55.39 **Molecular Formula**: $C_{22}H_{18}N_2O_2$; wt: 342.4; yield: 87%; mp: 177-178.

5-amino-1-phenylindolizin-3-yl)(4-bromophenyl)methanone **3c.**

IR (KBr, cm −1); 3420.01 (Ar-NH2), 1633.82 (C=O), 706 (Ar-C-Br), 1467 (C6H6). **^{1}H NMR** ($CDCl_3$-d. 400 MHz); δin ppm: 8.12-8.07 (1H, m), 7.81-7.99 (1H, m), 7.61-7.59 (1H, m), 7.24-7.14 (1H, m), 6.77-6.75 (1H, m). **^{13}C-NMR** ($CDCl_3$ –d. 150MHz); 132.84, 131.993, 127.64, 125.37, 121.96, 117.68, 112.73, 108.30, 77.44.

Molecular Formulae: $C_{21}H_{15}BrN_2O_2$; wt: 391.3; yield: 90%; mp: 159-161.

4-(5-amino-1-phenylindolizine-3-carbonyl)benzonitrile **3d**

IR (KBr, cm −1); 3427.44 (Ar-NH2), 1634 (C=O), 2220 (Ar-C-CN), 1451 (C6H6).**^{1}H NMR** ($CDCl_3$-d. 400 MHz); δin ppm: 8.12-8.03 (1H, m), 8.00-7.99 (1H, m), 7.68-7.66 (1H, m), 7.61-7.59 (1H, m), 7.20-7.19 (1H, m), 6.81-6.78 (1H, m). **^{13}C-NMR** ($CDCl_3$ –d. 150MHz); 146.01, 143.70, 138.36, 132.63, 126.40, 125.75, 119.17, 117.87, 113.14, 111.07, 109.63, 77.75. **Molecular Formula**:$C_{22}H_{15}N_3O$; wt: 337.4; yield: 90%; mp: 162-164.

(5-amino-1-phenylindolizin-3-yl)(4-fluorophenyl)methanone **3e.**

IR (KBr, cm $^{-1}$); 3137.65 (Ar-NH2), 1633 (C=O), 1126 (Ar-C-F), 1484 (C6H6).**^{1}H NMR** ($CDCl_3$-d. 400 MHz); δin ppm: 8.09 (1H, s), 7.93-7.88 (1H, m), 7.79 (1H, s), 7.63-7.60 (1H, m), 7.24 (1H, s), 7.17-7.07 (1H, m), 6.77-6.75 (1H, m). **^{13}C-NMR** ($CDCl_3$ –d. 150MHz); 163.97, 161.52, 145.74, 144.93, 130.07, 127.74, 125.66, 129.87, 117.48, 115.71, 112.55, 107.88, 77.76**. Molecular Formula;** $C_{21}H_{15}FN_2O$; wt: 330.4; yield: 86%; mp 156-158.

Biological Studies

Antifungal Activity:

Hydro alcohols were extracted from *In-vitro* antifungal activities. The part of plant body which antifungal activities that were extracts against pathogenic bacteria that are two Gram-positive and negative. Quantitative micro spectrophotometric helps to measure antifungal activities. Growth of inhibition measured at 595nm. Typically, process was carried out with 75ul/ml, 50ul/ml, 25ul/ml and 10ul/ml respectively. The plates were kept at room temperature for 30 min. This helps to know the growth of fungal activity**.**

Anti-Alzheimer's Agents:

The enzymatic activity TcAChE was measured using an adaptation of the method previously described with modification [1,2] The assay solution contained 374 μL of HEPES buffer (50 mM and pH 8.0), a variable volume (10–50 μL) of the stock solution of each compound in methanol (1 mg/mL), 25 μL of AChE stock solution, and the necessary amount of methanol to attain 0.925 mL of the sample mixture in a 1 mL cuvette. The samples were left to incubate for 15 min, and then, 75 μL of acetylthiocholine iodide (AChI) solution (16 mM) and 476 μL of DTNB (3 mM) were added. The reaction was monitored for 5 min at 40 nm. Assays were run with a blank containing all the components except AChE, which was replaced by HEPES buffer. The velocities of the reaction were calculated as well as the enzyme activity. A control reaction was carried out using the sample solvent (methanol) in the absence of any tested compound, and it was considered as 100% activity. The percentage inhibition of the enzyme activity due to the presence of increasing test compound concentration was calculated by the following Eqn. 3.

$$\%I = 100 - (\frac{V_i}{V_0} \times 100) \qquad (3)$$

where vi is the initial reaction rate in the presence of inhibitor and v0 is the initial rate of the control reaction. The inhibition curves were obtained by plotting the percentage of enzymatic inhibition versus inhibitor concentration, and a calibration curve was obtained from which the linear regression parameters were obtained.

$$IC_{50} = \left(\frac{50-b}{m}\right) \qquad (4)$$

Where b is the interception in the y axis and m is the slope. The statistical analysis was performed in Microsoft Office Excel®.

***In vitro* activities towards AChE inhibition**

Code	AChE Inhib[a] IC_{50}(µM)±SD
2a	**0.34±0.05**
2b	**0.53±0.04**
2c	**0. 26±0.02**
2d	**0. 44±0.04**
2e	**0. 28±0.05**
3a	**0. 34±0.02**
3b	**0. 56±0.06**
3c	**0. 36±0.02**
3d	**0. 72±0.06**
3e	**0. 54±0.05**
Tacrine (std)	**0.32±0.04**

[a]. The values are mean of five independent experiments ± SD.
(2c and 2e –good activity 2a,3a and 3c -comparable activity)

RESULTS AND DISCUSSION:

In following the current scenario, of adapting eco-friendly technique we have successfully achieved targeted motifs utilising microwave irradiation techniques. Certainly, this method resulted in minimal solvent usage, higher yields and trim in time, in one-pot reaction

followed by 1,3- dipolar cycloaddition reaction. Spectral characterisation such as Ir, ^{1}HNMR, and ^{13}C NMR confirmed the purity of the derivates obtained. In addition, the synthesised (5-amino-1-bromoindolizin-3-yl)(4-bromophenyl)methanone **(2a-e)** and (5-amino-1-phenylindolizin-3-yl)(4-chlorophenyl)methanone **3a (2a-e).** were evaluated for anti-Alzheimer's activity against tacrine as reference standard. Amid all hybrid compounds **2a, 2c, 2e 3a, and 3c** have shown the highest inhibitory capacity with IC_{50} values **0.34±0.05, 0. 26±0.02, 0. 28±0.05, 0. 34±0.02,** and **0. 36±0.02** respectively with parent drug **tacrine (**IC_{50}(µM) =0.32±0.04). The remaining compound **2b, 2d, 3b, 3d and 3e** have shown good to moderate AChE inhibition. The SAR study reveals that the substituents with chlorine and bromine at the benzene ring **2a, 2e** and **3a, 3e** have shown respectively excellent AChE inhibition compared to the parent drug. In certain, the synthesized derivatives are found to be promising anti- Alzheimer's potential.

CONFLICT OF INTERESTS:

Author declared no conflict of interests.

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