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In-vitro Acetylcholine Esterase Inhibition activity of Chalcones with Phenothiazine Moiety

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Abstract

A series of chalcones (3a-g) were synthesized by Claisen-Schmidt condensation between 2-acetyl phenothizine (1) and aromatic aldehydes (2a-g). All the synthesized chalcones were characterized by their spectral data (UV, IR, ^{1}H-NMR, ^{13}C-NMR, MS and elemental analyses). Acetylcholine esterase inhibition activity was carried out for all the synthesized chalcones which showed an IC_{50} value between 1.0 to 6.4µg/ml and indicated a comparable inhibitory potency, when compared to the control neostigmine with IC_{50} value of 8.3µg/ml.

Keywords: Chalcones, IR, NMR, MS technique, acetylcholine esterase inhibition, alzheimer's disease.

Introduction

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 is based on cholinergic system abnormalities with intellectual impairment[1]. The cholinergic dysfunction, a role for β-amyloid deposition, oxidative stress and inflammation has been investigated in the aetiology of AD and currently trials are underway to test modifying agents. Nevertheless, attempts to treat acetylcholine deficiency in the brain of affected individuals were first carried in form of acetylcholine esterase inhibitors (AChEIs) and however three agents' donepezil, rivastigmine and galantamine are licensed in UK. The main use of AChEIs resulted in stabilization of cognitive decline, improvement in behavioural and psychological symptoms of dementia[2]. The development of acetylcholine esterase (AChEI) inhibitor drugs has followed the finding that cholinergic pathways in cerebral cortex and basal forebrain are compromised in Alzheimer's disease [3] and the resultant cholinergic deficit contributes to the cognitive impairment of these patients [4]. An unfortunate result of rapid rise in geriatric populations worldwide is the increasing prevalence of age related cognitive disorders[5,6].

Chalcones, one of the major classes of natural products with widespread occurrence in fruits, vegetables, spices, tea and soy-based food stuffs, have been recently the subject of extensive investigations due to their interesting pharmacological activities. Chemically they consist of open chain flavonoids in which the two aromatic rings are joined by three carbons α, β-unsaturated carbonyl system[7]. The compounds with the backbone of chalcones have been reported to possess various biological activities such as antimicrobial, anti-inflammatory, analgesic, antiplatelet, antiulcerative, antimalarial, anticancer, antiviral, antileishmanial, antioxidant, antitubercular, antihyperglycemic, immunomodulator, inhibition of chemical mediators release, inhibition of leukotriene B_4, inhibition of tyrosine, inhibition of aldose reductase activities[8]. From a chemical point of view an important feature of chalcones and their heteroanalogs is the ability to act as activated unsaturated systems in conjugate addition reactions of carbanions in presence of base catalysts[9]. 1, 3-diarylpropenones (Chalocnes) have been popular substrates for the generation of variety of heterocyclic, carbocyclic and flavonoids[10].

In the present work we report the reaction of 2-acetyl phenothiazine with different aromatic aldehydes to form chalcones (3a-g). Many reports were available for the preparation of chalcones[11-14] but acetylcholine esterase activity was not reported for chalcones in literature. Molecules that possess sulfur atoms are universal and crucial in living organisms[15]. Phenothiazines were important kind compounds containing one sulfur and one nitrogen atom. This prompted us to synthesize chalcones containing phenothiazine moiety and to carry out the acetylcholine esterase inhibitor activity.

Material and Methods

Chemistry: Melting points (uncorrected) were determined using a Guna melting point apparatus. UV spectra were obtained UV 2460 shimadzu spectrophotometer. IR spectra were carried out on a Perkin-Elmer 1650 spectrophotometer. NMR spectra were recorded in $CDCl_3$ on a Bruker AM 400 MHz spectrometer, using residual $CHCl_3$ and TMS as an internal standard. Mass spectra were recorded on a VG-70-S instrument. Elemental analysis was carried out in a Perkin Elmer 240C model instrument. Column chromatography and TLC were carried out on silica gel 60 -120 mesh and silicagel 'G' respectively. All the chemicals are of AR grade.

General procedure for the preparartion of compounds 3a-g: 2-acetyl phenothiazine **1** (0.01 mol) was dissolved in 25 ml methanol and different benzaldehyde derivatives(**2a-g**) (0. 01

mol) were added, heated for 6 hrs with constant stirring in a magnetic stirrer and a catalytic amount of NaOH was added in drops. The reaction was poured into ice-cold water, neutralized with con.HCl and left over night in a refrigerator. The precipitate was filtered, dried and purity of the compound was checked by TLC using chloroform as the solvent. The compound was purified by column chromatography using silica gel (60-120 mesh).

(E)-3-(4-methoxyphenyl)-1-(10H-phenothiazin-2-yl)prop-2-en-1-one 3a: Yield 66%; m.p.: 202^{o}C; UV λ max: 399.50, 263.50; IR (KBr) cm^{-1}: 3344, 1666, 1590; ^{1}H-NMR (400MHz $CDCl_3$) δ: 7.11 (d, 1H, J=1.6Hz, H-1'), 7.38 (dd, 1H, J=8Hz, 1.6Hz, H-3'), 6.88 (d, 1H, J=8Hz, H-4'), 6.98 (d, 1H, J=8Hz, H-5'), 6.76 (td, 1H, J=8, 1.6Hz, H-6'), 6.93 (dd, 1H, J=8, 1.6Hz, H-7'), 6.48 (dd, 1H, J=8, 1.6Hz, H-8'), 7.68 (d, 1H, J=16Hz, H-2), 7.23 (d, 1H, J=16Hz, H-3), 7.51 (d, 2H, J=8Hz, H-2", 6"), 6.85 (m, 2H, H-3", 5"), 3.79 (s, 3H, $0CH_3$), 8.79 (s, 1H, NH); ^{13}C-NMR: 119.32, 137.69, 126.34), 127.64, 126.73, 114.64, 128.20, 114.46 , 140.80, 113.46, 144.62, 124.20, 189.50, 122.81, 144.23, 127.78, 130.24, 114.46, 161.00, 114.46, 130.24, 55.42; MS $[M+1]^+$ = 361; Anal. Calcd. for $C_{22}H_{12}O_2NS$: C, 77.64%; H, 3.52%; N, 4.11%; Found: C, 77.58%; H, 3.67%; N, 4.23%.

(E)-3-(4-methoxyphenyl)-1-(10H-phenothiazin-2-yl)prop-2-en-1-one 3b: Yield 64%; m.p.: 168^{o}C; UV λ max: 438.00, 312.00, 247.00; IR (KBr) cm^{-1}: 3350, 1650, 1590; ^{1}H-NMR (400MHz $CDCl_3$) δ: 7.31 (d, 1H, J=1.6Hz, H-1'), 7.46 (m, 1H, H-3'), 7.09 (d, 1H, J=7.8Hz, H-4'), 6.91 (d, 1H, J=7.8Hz, H-5'), 6.77 (t, 1H, J=7.8Hz, H-6'), 6.99 (td, 1H, J=7.8Hz, H-7'), 6.67 (d, 1H, J=7.8Hz, H-8'), 7.46 (m, 2H, H-3",5"), 7.87 (m, 2H, H-2", 6"), 7.63 (d, 1H, H-4"), 7.77 (d, 2H, J=16Hz, H-2,3), 8.89 (s, 1H, NH). ^{13}C-NMR: 121.90, 141.10, 126.24, 127.94, 126.11, 114.57, 128.75, 112.92, 142.82, 115.19, 143.72, 123.58, 188.02, 122.52, 143.72, 136.85, 122.08, 128.90, 130.57, 134.66, 126.40. MS $[M+1]^+$ = 329; Anal. Calcd. for $C_{21}H_{15}ONS$: C, 76.59%; H, 4.55%; N, 4.25%; Found: C, 76.67%; H, 4.44%; N, 4.34%.

(E)-3-(4-chlorophenyl)-1-(10H-phenothiazin-2-yl)prop-2-en-1-one 3c: Yield 65%; m.p.: 212^{o}C. UV λ max: 342.00, 282.00; IR (KBr) cm^{-1}: 3380, 1650, 1590; ^{1}H-NMR (400MHz $CDCl_3$) δ: 7.30 (d, 1H, J=1.6Hz H-2'), 7.63 (dd, 1H, J=8,1.6Hz, H-3'), 7.09 (d, 1H, J=8Hz, H-4'), 6.93 (dd, 1H, J=8Hz, H-5'), 6.78 (dt, 1H, J=8, 1.6Hz, H-6'), 7.00 (td, 1H, J=8, 1.6Hz, H-7'), 6.52 (dd, 1H, J=8, 1.6Hz, H-8'), 7.71 (d, 1H, J=16Hz, H-2), 7.83 (d, 1H, J=16Hz, H-2), 7.91 (d, 2H, J=8Hz, H-2",6"), 7.53 (d, 2H, H-3",5"), 8.79 (s, 1H, NH); ^{13}C-NMR: 115.16, 141.07, 126.34, 127.98, 126.10, 114.58, 128.94, 112.86, 136.75, 113.75, 142.13, 122.09, 187.92, 122.09, 142.24, 135.04, 127.98, 128.94, 133.65. MS $[M+1]^+$ = 362; Anal. Calcd. for $C_{21}H_{14}ONSCl$: C, 69.34%; H, 3.85%; N, 3.85%; Found: C, 69.29%; H, 3.80%; N, 3.91%.

(E)-1-(10H-phenothiazin-2-yl)-3-p-tolylprop-2-en-1-one 3d: Yield 62%; m.p.: 170^{o}C. UV λ max: 432.50, 315.50, 248.50; IR (KBr) cm^{-1}: 3380, 1620, 1590; ^{1}H-NMR (400MHz $CDCl_3$) δ: 7.30 (d, 1H, J=1.6Hz, H-1'), 7.61 (dd,1H, J=8, 1.6Hz, H-3'), 7.08 (d, 1H, J=8Hz, H-4'), 6.91 (dd, 1H, J=8, 1.6Hz, H-5'), 6.76 (td, 1H, J=8, 1.6Hz, H-6'), 6.92 (td, 1H, J=8, 1.6Hz, H-7'), 6.65 (dd, 1H, J=8, 1.6Hz, H-8'), 7.71 (d, 1H, J=16Hz, H-2), 7.75 (d, 1H, J=16Hz, H-3), 7.71 (d, 2H, H-2",6"), 7.28 (d, 1H, J=8Hz, H-3",5"), 2.35 (s, 3H, CH_3), 8.77 (s, 1H, NH); ^{13}C-NMR: 115.23, 141.12, 126.23, 127.98, 126.08, 114.57, 128.76, 112.93, 136.97, 123.44, 143.81, 122.41, 187.98, 122.07, 142.11, 131.93, 129.53, 131.93, 140.66, 21.05. MS $[M+1]^+$ = 345; Anal. Calcd. for $C_{22}H_{17}ONS$: C, 76.96%; H, 4.95%; N, 4.07%; Found: C, 76.93%; H, 4.84%; N, 4.23%.

(E)-3-(3-nitrophenyl)-1-(10H-phenothiazin-2-yl)prop-2-en-1-one 3e: Yield 61%; m.p.: 198^{o}C.; UV λ max: 432.50, 315.50, 248.50; IR (KBr) cm^{-1}: 3336, 1658, 1593; ^{1}H-NMR (400MHz $CDCl_3$) δ: 7.31 (d, 1H, J=1.6Hz, H-1'), 7.68 (dd, 1H, J=8, 1.6Hz, H-3'), 7.08 (d, 1H, J=8Hz, H-4'), 6.93 (dd, 1H, J=8, 1.6Hz, H-5'), 6.79 (td, 1H, J=8, 1.6Hz, H-6'), 6.99 (td, 1H, J=8, 1.6Hz, H-7'), 6.67 (d, J=8, 1.6Hz, 1H, H-8'), 7.80 (d, 1H, J=16Hz, H-2), 8.02 (d, 1H, J=16Hz, H-3), 8.74 (m, 1H, H-2"), 8.26 (dd, 1H, J=8, 1.6Hz, H-4"), 7.74 (t, 1H, J=8Hz, H-5"), 8.28 (m, 1H, H-6"), 8.75 (s, 1H, NH); ^{13}C-NMR: 112.93, 141.03, 126.21, 122.82, 126.07, 114.58, 127.97, 112.86, 136.57, 124.62, 141.11, 124.57, 187.85, 124.04, 142.12, 136.53, 148.39, 130.31, 134.92, 122.08, 122.82; MS $[M+1]^+$ = 374; Anal. Calcd. for $C_{21}H_{14}O_3N_2S$: C, 67.38%; H, 3.74%; N, 7.48%; Found: C, 67.48%; H, 3.65%; N, 7.54%.

(E)-3-(4-bromophenyl)-1-(10H-phenothiazin-2-yl)prop-2-en-1-one 3f: Yield 65%; m.p.: 208^{o}C. UV λ max: 448.50, 319.50, 247.50; IR (KBr) cm^{-1}: 3348, 1651, 1581; ^{1}H-NMR (400MHz $CDCl_3$) δ: 7.30 (d, 1H, J=8Hz, H-1'), 7.61 (dd, 1H, J=8Hz, H-3'), 7.09 (d, 1H, J=8Hz, H-4'), 6.91(dd, 1H, J=8, 1.6Hz, H-5'), 6.77 (td, 1H, J=8, 1.6Hz, H-6'), 7.00 (td, 1H, J=8, 1.6Hz, H-7'), 6.68 (dd, 1H, J=8, 1.6Hz, H-8'), 7.67 (m, 1H, J=16Hz, H-2), 7.83 (m, 1H, J=16Hz, H-3), 7.80 (m, 2H, H-2",6"), 7.67 (m, 2H, H-3",5"), 8.78 (s, 1H, NH); ^{13}C-NMR: 115.17, 141.06, 126.23, 127.97, 126.10, 114.58, 123.90, 112.87, 136.75, 123.76, 142.13, 122.70, 187.94, 122.09, 142.32, 133.97, 130.64, 131.87, 122.59; MS $[M+1]^+$ = 407; Anal. Calcd. for $C_{21}H_{14}ONSBr$: C, 61.78%; H, 3.43%; N, 3.43%; Found: C, 61.84%; H, 3.51%; N, 3.45%.

(E)-4-(3-oxo-3-(10H-phenothiazin-2-yl)prop-1-enyl)benzaldehyde 3g: Yield 64%; m.p.: 191^{o}C; UV λ max: 455.00, 304.50, 249.50; IR (KBr) cm^{-1}: 3344, 1666, 1590; ^{1}H-NMR(400MHz $CDCl_3$) δ: 7.31 (d, 1H, J=1.6Hz, H-1'), 7.61 (dd, 1H, J=8, 1.6Hz, H-3'), 7.09 (d, 1H, J=8Hz, H-4'), 6.91 (dd, 1H, J=8, 1.6Hz, H-5'), 6.78 (td,1H, J=8, 1.6Hz, H-6'), 7.00 (td, 1H, J=8, 1.6Hz, H-7'), 6.67 (d, 1H, J=8, 1.6Hz, H-8'), 7.90 (m, 2H, H-2",6"), 8.09 (m, 2H, H-3",5"), 7.78 (d, 1H, J=16Hz, H-2), 7.91 (d, 2H, J=16Hz, H-3), 8.79 (s, 1H, NH), 10.05 (s, 1H, CHO); ^{13}C-NMR: 115.14, 141.03, 126.23, 127.99, 126.12, 114.59, 124.02, 112.87 , 136.99, 124.82, 142.16, 122.70, 187.94, 124.02, 142.00, 136.60, 129.85, 129.26, 140.30, 192.59; MS $[M+1]^+$ = 357; Anal. Calcd. for $C_{22}H_{15}O_2NS$: C, 73.39%; H, 4.20%; N, 3.91%; Found: C, 73.47%; H, 4.25%; N, 4.31%.

***In- vitro* acetylcholine esterase inhibition activity:** Acetylcholine esterase activity[16] was carried out for all the synthesized compounds 3a-g as shown in table 1. Spectrophotometric assay was used to determine the inhibitory potential of the compounds against acetylcholine esterase enzyme isolated from red blood cells. Acetyl thiocholine iodide was used as a substrate. 2.81ml of phosphate buffer of pH 8 was taken in each test tube. The test sample solutions of different concentrations of 2µg, 4µg, 6µg, 8µg, 10µg were added and 30µl of enzyme were added. The mixture was allowed standing for 10min. The colouring reagent DTNB (dithiobisnitro benzoic acid) was added which produces the yellow anion of 5-thio-2-nitro benzoic acid and then substrate 30µl followed by incubation for 20 min. The absorbance was measured at 412nm. The percentage inhibition in enzyme activity can be calculated as follows:

% inhibition = Absorbance (control) – Absorbance (test) / Absobance (control) × 100

Table-1
AChEI assay with IC_{50} value of the compounds 3a-g

S.No	Compound	IC_{50} value in (µg/ml)
1	3a	4.0
2	3b	6.4
3	3c	1.0
4	3d	2.9
5	3e	2.8
6	3f	3.3
7	3g	4.0
8	Neostigmine	8.3

Results and Discussion

Spectral values of chalcones 3a-g: Compounds (**3a-g**) were synthesized by the reaction between 2-acetyl phenothiazine with different aromatic aldehydes by Claisen- Schmidt condensation reaction as shown in scheme 1. For the compounds **3a-g**, IR spectra showed characteristic absorption bands to show the presence of carbonyl group at 1651cm^{-1}, C=C at 1600cm^{-1}, NH stretching at 3336.85 cm^{-1}. For all the synthesized compounds, the signals for the aromatic carbons and protons were assigned using known effects of substituents, position, multiplicities and integral values. In ^{1}H-NMR spectra for the compound (**3a-g**) H-2 and H-3 are found to be trans protons where δ value appears between δ 7.30 and 7.77 and the coupling constant J value is 16Hz. NH proton appeared as a singlet at δ 8.79. In compound **3a**, OCH_3 proton appeared as a singlet in the range δ 1.18 showing the presence of three protons, similarly in **3d**, CH_3 appeared at δ 2.35. In **3g**, the singlet at δ 10.05 is due to CHO group and all the aromatic protons appeared between δ 6.50-8.28. The ^{13}C –NMR signals were assigned based on their positions and intensities. The ^{13}C-NMR spectrum of chalcone were recorded in $CDCl_3$ and spectral signals were in good agreement with the proposed structures; C-1 (i.e) C=O group shows the presence at δ 187.92. In compound **3a**, the methoxy carbon appeared at δ 55.42 and in compound **3d**, CH_3 carbon appeared at δ 21.05. For **3g**, the aldehyde carbon appeared at δ 192.59 and all the aromatic carbon or unsaturated C=C appeared between 100-160. Characteristic molecular ion peaks were observed in the mass spectra of the chalcone and shown in experimental section.

***In-vitro* acetylcholine esterase inhibition activity:** In the literature, the structure activity relation (SAR) of many nitrogen containing AChE inhibitors such as tacrine, physostigmine, benylamines, benzyl piperidine, benziooxazoles and huperzine A has been reported. All of them gave an overall conclusion that these drugs bind to acetylcholine esterase through the nitrogen containing heterocyclic part of the molecule. It was also reported that quarternary ammonium salts act as strong acetylcholine esterase inhibitors. In previous reports regarding the SAR of AChE inhibitors, it was concluded that the substitution in the benzene ring enhanced the activity of the molecule[16].

In present study, *in-vitro* acetylcholine esterase inhibition activity was carried out for all the synthesized chalcones from 3a-g as shown in table 1. However, the synthesized chalcone contains phenothiazine moiety with one nitrogen and sulphur are present in a heterocyclic moiety. The substitution on aromatic ring was found to markedly improve AChE activity. All the derivatives showed greater affinity and potency when compared to the control neostigmine. The potency of the molecules follows the order 3c > 3e > 3d > 3f > 3g, 3a > 3b which was based on IC_{50} value from 1.0 to 6.4µg/ml whereas for the control neostigmine IC_{50} value was found to be 8.3µg/ml. The most potent compound was 3c where the aromatic ring having the substituent Cl yielded excellent activity. However other electronegative groups like NO_2, Cl, Br, and CHO substituted in aromatic ring enhanced the activity than the control. Compound 3a and 3d having methoxy and methyl substituent in aromatic and the unsubstituted benzene ring 3b also showed good activity but it was less when compared to the other molecule.

Conclusion

In conclusion, a series of chalcones (**3a-g**) were synthesized by Claisen-Schmidt condensation reaction. The *in vitro* acetylcholine esterase inhibition activity was evaluated for all synthesized compounds showed a good inhibitory potency with an IC_{50} value between 1.0 to 6.4µg/ml, when compared to the control neostigmine with IC_{50} value of 8.3µg/ml.

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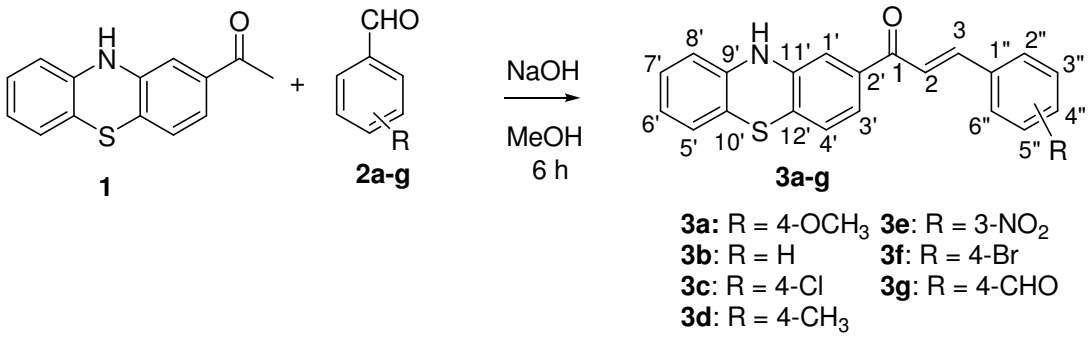

Scheme-1
Synthesis of Chalcones 3a-g

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