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SYNTHESIS AND BIOLOGICAL EVALUATION OF BENZOFUSED THIAZINE DERIVATIVES

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ABSTRACT:

New series of benzofused thiazine derivatives has been synthesized and characterized by using IR, ^{1}H NMR and ^{13}C NMR. Among the synthesized compounds, compound P1 was evaluated for their antioxidant and anti-inflammatory activity. Compound P1 was found to be shown good reducing power activity with excellent nitric oxide scavenger as compared to standard ascorbic acid. Compound P1 was also shown remarkable anti-inflammatory activity as compared with standard diclofenac sodium.

KEYWORDS: *Benzofused thiazine derivatives, Antioxidant activity.*

INTRODUCTION:

Heterocycles containing nitrogen and sulphur as hetero atoms undoubtedly constitute an important class of highly applicable bioactive molecules because of their interesting biological activities and uses as key structural moiety for the synthesis of various natural products of pharmaceutical interest [1]. Amongst them a large number of thiazine ring containing drugs with versatile type of applications are being used clinically. These compounds have immense chemotherapeutic importance as vasodilator[2], antidiabetic[3,4], antioemetic[5], antimicrobial[7], anti-vitro[8], anti-tumar[9], anti-inflammatory anti-oxidant[10], antibacterial[11] activities, etc. These compounds are also reported as calcium channel blockers anticancer, analgesic[12,13], phosphodiesterase inhibitors antifungal[14], 5-HT3 antagonists[15], anti-HIV agents[16], cytostatic agents[17], anti-inflammatory[18], antithrombotic[19] and lipoxygenase inhibitors [20]. The basic unit present in mammalian red hair and feather is 1,4- benzofused thiazine nucleus[21]. Benzofused thiazine also find uses as steel corrosion inhibitors [22], KATP-Channel Openers[23], antioxidants[24], dyes[25] and photosensitizers[26]. A recent review by Brown et al.[27] provides an excellent account of the chemistry of benzofused thiazine and their related compounds.

The importance and utility of benzofused thiazine derivatives have led to the development of various synthetic routes. The most convenient method for the synthesis of these compounds involves the treatment of dinucleophiles with suitable carbon fragments under appropriate reaction conditions, e.g., reaction of α-halo ketones with 2-aminothiophenol and its derivatives. A relatively unexplored heterocyclic ring system, with respect to both synthesis and biological activity is benzofusedthiazine derivatives[28]. Quantitative structure activity relationship (QSAR) is one of the most important areas in chemometrics, and is a valuable tool that is used extensively in drug design and medicinal chemistry. Once a reliable QSAR model is established, we can predict the activities of molecules, and know which structural features play an important role in biological processes [29].

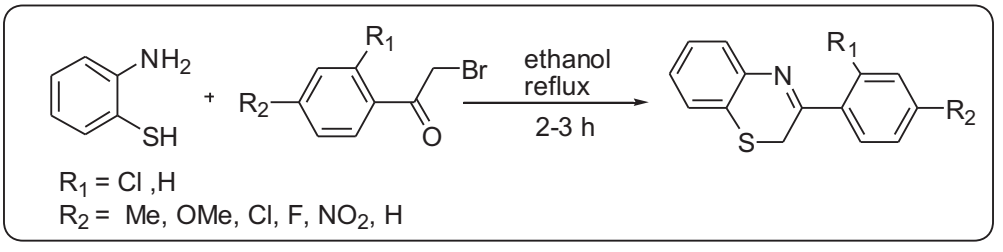
With our recent success on the development of new selective environment-friendly methodologies using polyethylene glycol (PEG-400)[30, 31] as a solvent for the preparation of biologically active compounds,

herein we report the synthesis and biological activities of benzothiazine derivative (P1).

2. EXPERIMENTAL

The title compounds were synthesized by reacting 2-aminobenzenethiol with various substituted α-haloketones in ethanol as reaction medium. Melting points (°C) were determined with a MELTEMP II capillary apparatus (LAB Devices, Holliston, MA, USA) without correction. IR spectra were recorded on FT-IR spectrometer (Perkin Elmer) using KBr disc method. ^{1}H NMR spectra were recorded on 400 MHz spectrometer in $CDCl_3$ as a solvent. 13C NMR spectra were recorded on Brucker 400 MHz spectrometer in DMSO as a solvent. TLC was performed on silica gel coated plates for monitoring the reactions.

Scheme 1.



2.1. The general procedure for the synthesis of substituted benzofused thiazine derivatives

A mixture of 2-aminobenzenethiol (3mmol) and various substituted α-haloketones (3 mmol) were dissolved in 30 mL of dry ethanol and refluxed on a water bath for about 2-3 hrs. After completion of the reaction (monitored by TLC), the solid so obtained was filtered washed, and recrystallised from ethanol solvent to afford pure title compounds in high yields.

2.2. Spectral data of 3-(-4methoxyphenyl)-2H-benzo(b)(1,4)thiazine (P1)

Molecular formula: $C_{15}H_{12}ONS$; Yield: 85%; M.P. 260°C;

IR: 3073.93, 2936.48, 2834.67, 1603.78cm, 1462.21, 1217.28, 1019.54, 782.35, 751.08cm^{-1}

^{1}HNMR ($CDCl_3$, 400MHz): 3.62d (s, 3H), 3.90d (s, 2H), 7.05d (d, 2H), 8.03d (d, 2H), 7.13d (t,1H), 7.28d (t, 1H), 7.36d (d, 1H), 7.52d (d, 1H); ^{13}C NMR (400 MHz, DMSO-d_6, d in ppm):162, 156, 129, 127, 126, 121, 63, 55, 33, 23.

3. ANTIOXIDANT ACTIVITY:

3.1. DPPH• radical scavenging activity

The ability of compunds to scavenge DPPH radical was assessed using Kumar et al.[24] method with modification. Briefly, 1 ml of synthesized compounds as 1 mM, was mixed with 3.0 mL DPPH (0.5 mmol/L in methanol), the resultant absorbance was recorded at 517 nm after 30 min. incubation at 37°C. The percentage of scavenging activity was derived using the following formula,

Percentage of inhibition (%) =[(A control − A sample) / A control] x 100

Where A control - absorbance of DPPH

A sample - absorbance reaction mixture (DPPH with Sample).

3.2. Nitric oxide radical scavenging activity

Nitric oxide radical scavenging was carried out as per the method of Kumar et al[24]. Nitric oxide radicals were generated from sodium nitroprusside solution. One mL of 10 mM sodium nitroprusside was mixed with 1 mL of 1 mM synthetic compounds in phosphate buffer (0.2 M pH 7.4). The mixture was incubated at 25°C for 150 min. After incubation the reaction mixture mixed with 1.0 mL of pre-prepared Griess reagent (1% sulphanilamide, 0.1% napthylethylenediamine dichloride and 2% phosphoric acid). The absorbance was measured at 546 nm and percentage of inhibition was calculated using the same formula as above. The decreasing absorbance indicates a high nitric oxide scavenging activity.

3.3. Superoxide radical scavenging assay

The reaction mixture consisting of 1ml of nitro blue tetrazolium (NBT) solution (156 mM NBT in phosphate buffer, pH 7.4), 1 ml NADH solution (468 mM NADH in phosphate buffer, pH 7.4), and 1ml of synthetic compound (1mM) solution was mixed. The reaction was started by adding 1 ml of phenazinemethosulfate (PMS) solution (60 mM PMS in phosphate buffer, pH 7.4) to the mixture. The reaction mixture was incubated at 25°C for 5 min and the absorbance was measured at 560 nm against blank sample and compared with standards and percentage of inhibition was calculated using the same formula as above. Decreased absorbance of reaction mixture indicated increased superoxide anion scavenging activity.

3.4. Reducing power assay

The reducing power of synthesized compound P1 was determined as per the reported method [Oyaizu 1986]. Concentrations of compound (1mM) in 1ml of DMSO were mixed with phosphate buffer (2.5 ml, 0.2 M, pH 6.6) and potassium ferrocyanide (2.5 ml, 1%). The mixture was incubated at 50oC for 20 min. A portion (2.5 ml) of trichloroacetic acid (10%) was added to the mixture, which was then centrifuged at 3000 rpm for 10 min. The upper layer of the solution (2.5 ml) was mixed with distilled water (2.5 ml) and FeCl3 (0.5 ml, 0.1%) and the absorbance was measured at 700 nm and compared with standards. Increased absorbance of the reaction mixture indicated increased reducing power.

3.5. In vitro anti-inflammatory activity by Protein denaturation method [25]

The reaction mixture (10 mL) consisted of 0.4 mL of egg albumin (from fresh hen's egg), 5.6 mL of phosphate buffered saline (PBS, pH 6.4) and 4 mL of synthetic derivatives (1 mM). Similar volume of double-distilled water served as control. Then the mixtures were incubated at (37°C ±2) in a incubator for 15 min and then heated at 70°C for 5 min. After cooling, their absorbance was measured at 660 nm by using vehicle as blank. Diclofenac sodium at the 1 mM) was used as reference drug and treated similarly for determination of absorbance. The percentage inhibition of protein denaturation was calculated by using the following formula,

$$\% \text{ inhibition} = 100 \times (Vt / Vc - 1)$$

Where, Vt = absorbance of test sample,
Vc = absorbance of control.

4. RESULTS AND DISCUSSION:

4.1. General chemistry

In the present investigation the Benzofusedthiazine derivatives (4a-g) have been prepared by reacting 2-amino thiophenol with various substituted a-haloketones (Scheme 1). All the compounds were obtained in good to excellent yields. The completion of the reaction was monitored by TLC. IR, ^{1}H NMR and ^{13}C NMR spectroscopic data are in good agreement with their proposed structure.

4.2. Anti-inflammatory activity

The denaturation of protein is one of the cause of rheumatoid arthritis was documented. Production of auto antigen in certain arthritis disease may due to denaturation of protein. Among the series one compound is evaluated for anti-inflammatory activity by protein denaturation method and results are presented in Table 1. The result revealed that compound P1 (87.15%), showed significant inhibition as compared with standard diclofenac sodium (90.21%) From the result, it can be stated that the tested compound is capable of controlling the production of auto antigen and thereby they inhibit the denaturation of protein and their effect was compared with standard drug diclofenac sodium.

4.3. Antioxidant activity

Among the series the synthesized compound P1 is also evaluated for antioxidant activity against reactive oxygen species like DPPH, Nitric oxide scavenging activity, superoxide radical scavenging activity and ferrous reducing power and results are presented in Table 1. In case of DPPH and superoxide radical scavenging activity the tested compound showed moderate activity (22.36% and 37.27% respectively) as compared to standard

ascorbic acid (44.18% and 74.07% respectively).

The nitric oxide scavenging activity and ferrous reducing power activity result revealed that compound P1 was found to be shown excellent activity in both the assays as compared to standard ascorbic acid and results are presented in Table 1.

5. CONCLUSION:

In conclusion, various substituted benzofused thiazine derivatives have been synthesized with excellent yields. Among the series, the compound P1 was evaluated for their anti-inflammatory and antioxidant activity and showed good reducing power activity with excellent nitric oxide scavenger as compared to standard ascorbic acid. Compound P1 was also showed remarkable anti-inflammatory activity as compared with standard diclofenac sodium. Overall compound P1 can be considered as lead molecule for novel antioxidant agent in addition to having good anti-inflammatory activity.

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Conflict of Interest

Authors have no conflict of interest

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Table 1. Anti-inflammatory and antioxidant activity of Benzothiazine derivative P1

Compound	Anti-inflammatory activity	Antioxidant activity			
	% inhibition	DPPH	Nitric oxide scavenging activity	Superoxide radical scavenging activity	Reducing power activity (absorbance)
P1	**87.15**	22.36	**80.83**	37.27	**0.58**
Ascorbic acid	--	44.18	42.63	74.07	0.40
Diclofenac sodium	90.21	--	--	--	--

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