Research Article

7Synthesis, Characterisation and Biological Evaluation of 1,5-benzothiazepine Derivatives Containing Phenothiazine Ring

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ABSTRACT
In search of new potential anti-inflammatory agents, the aim of the present study was synthesize the series of 1, 5-Benzothiazepine analogs by a simple and accessible approach and evaluate for their anti-inflammatory activity. Synthetic methodology involves the reaction of an α, β-unsaturated ketones (5 a-g) with 2-aminothiophenol(6) and 3-4 drops of glacial acetic acid in methanol at 80^{0}C, which afforded a series of novel 1,5-Benzo thiazepine derivatives (7 a-g) in good yields. The structures of the synthesized compounds were provided by spectral and elemental analysis . Novel 1, 5-benzothiazepine derivatives were synthesized and characterized by spectral studies. The newly synthesized compounds (8 a–g) were screened for in vivo anti-inflammatory activity at a dose of 10 mg/kg BW. Among those tested, compounds **8d** and **8e** exhibited significant anti-inflammatory activity in models of acute inflammation such as rat paw edema, while compounds 8dand 8e showed considerable activity compared with diclofenac as a standard drug.

Keywords: Benzo thiazepine, Chalcones, phenothiazine, Synthesis, Anti-inflammatory activity.

INTRODUCTION

Chalcones constitute an important class of natural products and some of them possess a wide range of pharmacological activities such as anticancer, anti-tubercular, antiviral[1]. Recent studies on biological evaluation of Chalcones revealed some to be antibacterial, antifungal, Anti-inflammatory, anti hyperglycaemic[2], and antimalarial agents[3].The chalcones are **α, β** unsaturated ketones containing the reactive keto ethylene group. These compounds are also known as benzylidene acetophenones or benzalacetophenones, which are documented as Chalcones by Kostanecki and Tambor.

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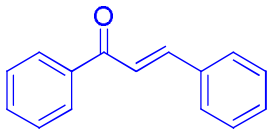
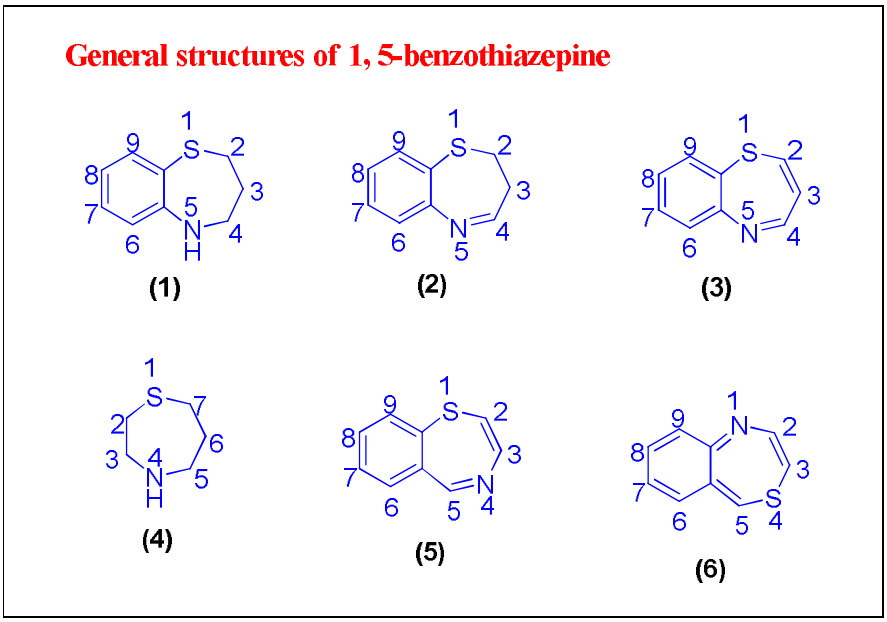


Organic synthetic chemistry is now a fast growing research field in chemistry. Among the various organic compounds, heterocyclic compounds have been associated with various biologically activities. Due to bioactivity connected with heterocycle and ease of preparation, a number of researchers are takings more interested into the study of this. N- and S- containing heterocycle,

such as thiazepine and its derivatives, exhibit a broad spectrum of biological activity[4,5]. Thiazepine fused with a benzene ring is known as benzothiazepine, and it is associated with antibacterial, antifungal[6], antimicrobial[7], anticonvulsant[8], and anti-breast cancer activity[9], acting as a central nervous system depressant[10].

The 1,5-benzothiazepines[11] (1, 2,3) are Important nitrogen- and sulfur-containing seven membered heterocyclic compounds in drug research since they possess diverse bioactivities[12-19]. 1,5-Benzothiazepines are the most well-known representatives of benzologs of 1,4-thiazepine (4) and one of the three possible benzo condensed derivatives, viz. 1,4-(5), 4,1- (6) and 1,5- benzothiazepines[20-23].



The importance of the l,5-benzothiazepine nucleus has been well established as illustrated by a large number of compounds which have been patented as chemotherapeutic agents[24]. A number of biological activities have been associated with it, such as antifeedant[25], coronary vasodilatory[26], tranquilizer[27] antidepressant[28], CNS stimulant[29], antihypertensive[30], calcium channel blocker[31], antiulcer[32], calcium antagonist[33], antimicrobial[34] and anticonvulsant agents[35]. l,5-Benzothiazepine molecules have been found to be useful in mucosal blood flow, as antiulcer and gastric secretion inhibitor. Recently, anticancer activities[36], hemodynamic effects[37], and spasmolytic activities[38] have also been reported[39]. Diltiazem has been used in the treatment of hypertension, angina pectoris, arrhythmias and other cardiac disorders. It also increases the supply of blood and oxygen to heart[40-41]. Thiazesim act as psychotopic agent, clentiazem have antiatherogenic effect[42], and clothiapine shows antimuscarinic potential[43].

As 1,5-benzothiazepine plays an important role in the pharmacological and medicinal field, various researchers are interested in its synthesis[44] and characteristics[45,46]. Recently, synthesis and a biological evaluation of thiazepine from chalcone and 2-amino thio phenol has been investigated[47] and a written survey revealed that different synthetic routes of thiazepine had been reported[48,49].

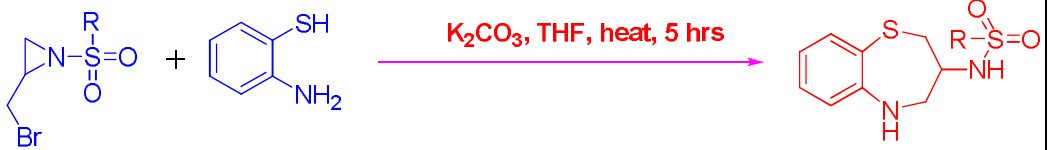
Encouraged by the significance of benzo thiazepine cited in literature and the movement of our work in the bioorganic field[50-52], we have studied its anti-inflammatory activity. In this current investigation, we report the synthesis, characterisation,biological evaluation and of benzothiazepine derivatives.

General methods of synthesis

A number of Established protocols are there for the synthesis of 1,5-benzothiazepine moiety, which can be well modified to prepare a number of differently substituted 1,5-benzothiazepines. Some of the conventional methods are given below.

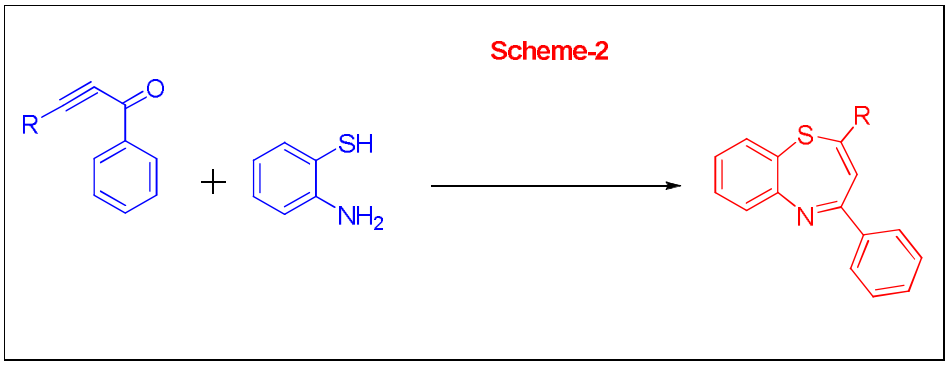
(1) Treatment of 2-(bromo methyl)aziridines with 1.2 equiv of 2-aminothiophenol in THF in the presence of potassium carbonate provide an easy access to 3-sulfonamido-2,3,4,5-tetrahydro-1,5-benzothiazepines after reflux for 5 h[53]. (Scheme-1).

Scheme-1



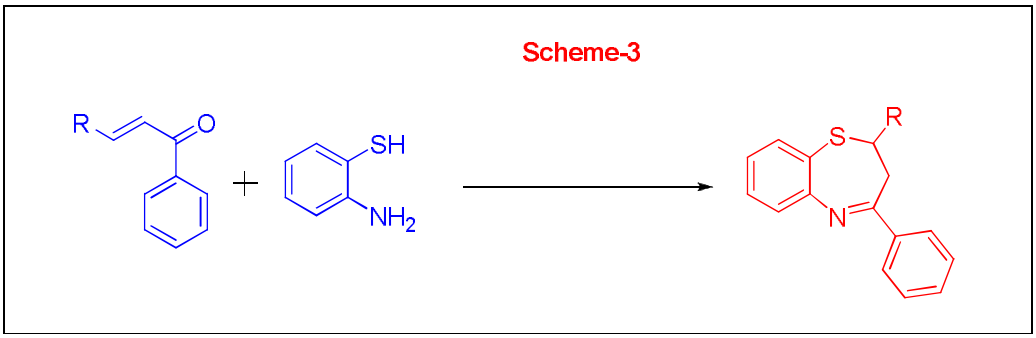
(2) The preparation of 2,4-disubstituted 1,5- benzothiazepines occurs by the reaction of 2- amino thiophenol with acetylinic ketones[54] (**Scheme-2**).

Scheme-2



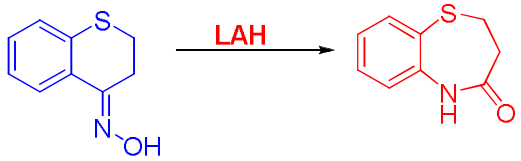
(3) The reaction of chalcone with o-aminothiophenol in presence of 1-2 drop of piperidine in alcoholic solution of ethanol gives the corresponding 1,5- benzo thiazepines[55] (**Scheme-3**).

Scheme-3



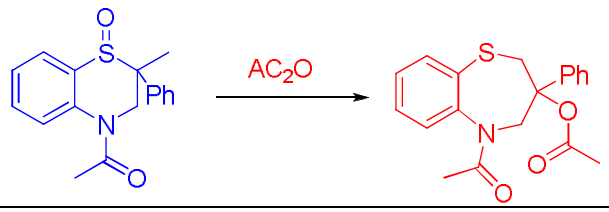
(**4**) 2, 3, 4, 5-Tetrahydro-1,5-benzothiazepine has been obtained by reductive expansion of the ring of 1-thio chromanone oxime with lithium aluminum hydride[56] (Scheme-4).

Scheme 4



(**5**) It has been observed that benzothiazoline-S-oxide is capable of undergoing ring expansion, 2,3,4,5-tetrahydro3-phenyl-3-acetoxy-5-acetyl-1,5-benzothiazepine is formed as one of the products when 4-acetyl-2-methyl-2phenyl-2,3-dihydro-4H-1,4-benzothiazin-1-one is refluxed in acetic anhydride[56] (Scheme-5).

Scheme 5



The literature study reveals that l, 5-benzo thiazepine nucleus containing derivatives are a significant pharmacophore and exhibits outstanding biological activities. Encourage by these observation, we synthesized a new series of l,5-benzothiazepine nucleus derivatives by incorporating the phenothiazine moiety with the hope of obtaining better Anti inflammatory activity agent. All the synthesized compounds have been screened for their Anti-inflammatory activities.

MATERIALS AND METHODS

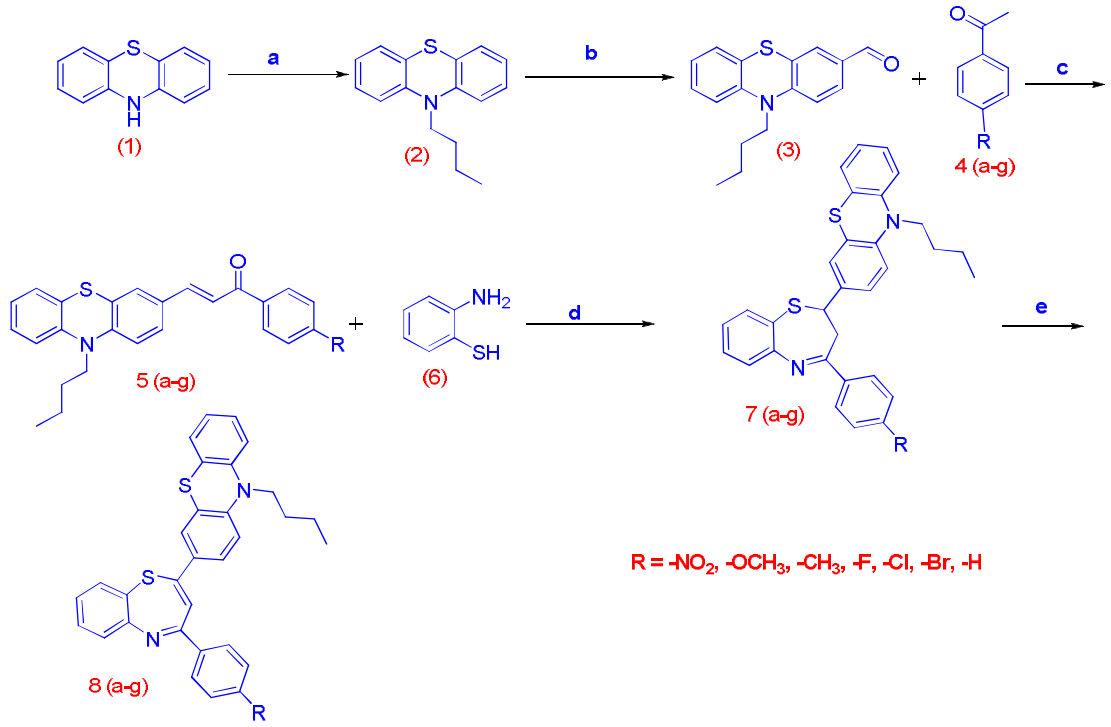
Laboratory chemicals were provided by Rankem India Ltd. and Ficher Scientific Ltd. Melting points were determined by the open tube capillary method and are not correct. The purity of the compounds was determined by thin layer chromatography (TLC) plates (silica gel G) in the solvent system toluene:ethyl acetate (8:2). The spots were observed by exposure to iodine Vapours or by UV light. The IR spectra were received by PerkineElmer 1720 FT-IR spectrometer (KBr pellets). The ^{1}H NMR &^{13} C NMR spectra were obtained by Bruker Advance II 400 spectrometer using TMS because the internal standard in $CDCl_3$. Elemental analysis of the new synthesized compounds were obtained by Carlo Erba 1108 analyzer. The synthesis of the compounds as per the following **Scheme I** given below.

Scheme I

The synthetic route was depicted in scheme **I**

The title compounds 8(a-g) were synthesised in FIVE sequential steps using different reagents and reaction conditions, the 8(a-g) were obtained in moderate yields. The structure were established by spectral (IR, ^{1}H-NMR, ^{13}C-NMR and mass) and analytical data.

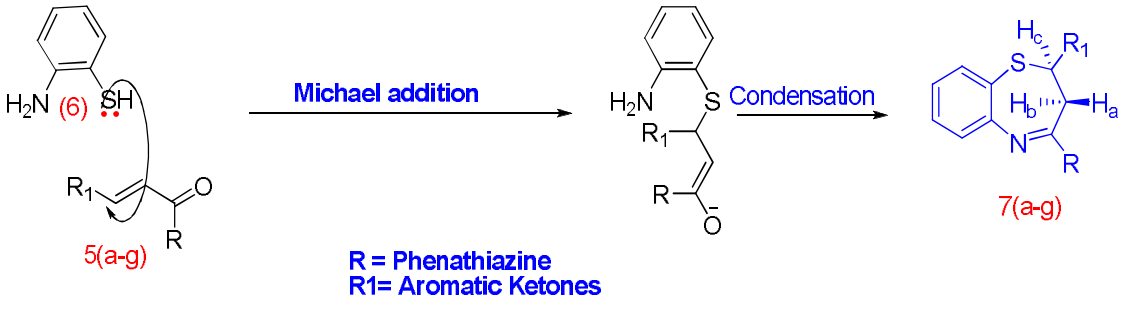
SYNTHETIC SCHEME : I



Reagents and Reaction conditions

(a) Butyl bromide, Aceto Nitrile, $NaHCO_3$,100^{0}C **(b)** DMF,$POCl_3$,1,2 DCE,Reflux (**c**)KOH,Ethanol, RT (**d**) Methanol, HCl, Reflux (**e**)DDQ(2,3-dicyano-5,6-dichloro-p-benzoquinone) $CHCl_3$, RT,24 hrs

Possible Mechanism for 1,5-benzothiazepines 6(a-g) formation



Designed series of molecules 7 (a-g) were characterized by spectral and elemental analysis before being evaluated for their Anti- inflammatory activity. The structural assignments were made by NMR

analysis by considering compound (7a) as the representative compound. In its ^{1}H NMR spectra, **Ha, Hb** and **Hc** protons of the benzothiazepine ring appeared as a doublet of doublet. The doublet of **Ha** appeared at δ 1.822 ppm; doublet of **Hb** appeared at δ 2.112 ppm; and that of **Hc** appeared at δ 3.665 ppm. Doublets of **Ha** and **Hb** are due to diastereotopic nature of methylene protons. Among **Ha**, **Hb** and **Hc** protons, **Hc** is the most deshielded due to its close proximity to benzene ring. **Hc** couples not only with **Ha** but also with **Hb** and appears as doublet of doublet instead of a triplet i.e., the methylene protons of benzothizepine ring (**Ha and Hb**) exhibited a typical **ABX** spin system with **Hc** as a doublet of doublets as shown in diagram-7(a-g). Further it showed signals due to substituent and aromatic protons at the expected region. All compounds displayed the signals in the similar pattern.

Experimental Section

All reactions were carried out under argon in oven-dried glassware with magnetic stirring. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. All solvents were reagent grade. THF was distilled from sodium benzophenone ketyl and degassed thoroughly with dry argon directly before use. Unless otherwise noted, organic extracts were dried with anhydrous Na_2SO_4, filtered through a fitted glass funnel, and concentrated with a rotary evaporator (20–30 Torr). Flash chromatography was performed with silica gel (200–300 mesh) by using the mobile phase indicated. The NMR spectra were measured with a 400 MHz Bruker Avance spectrometer at 400.1 and 100.6 MHz, for ^{1}H for ^{13}C, respectively, in $CDCl_3$ solution with tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ) and are referenced to the residual proton resonances of the solvents. Proton and carbon magnetic resonance spectra (1H NMR and ^{13}C NMR) were recorded using tetramethylsilane (TMS) in the solvent of $CDCl_3$-d or DMSO-d_6 as the internal standard (^{1}H NMR: TMS at 0.00 ppm, $CDCl_3$ at 7.26 ppm ,DMSO at 2.50 ppm; ^{13}C NMR: $CDCl_3$ at 77.16 ppm, DMSO at 40.00 ppm).

General procedure for the preparation of 10-butyl-10H-phenothiazine Compound (2)[57]

To a solution of 1 (**0.1 m.mol**) in dry acetonitrile (5 ml) was added 1-bromobutane (**0.15 m.mol**) and $NaHCO_3$ (**1 m.mol**). The solution was refluxed under stirring during 8 h , neutralised with HCl (2N, 7 ml) and methylene chloride (20 ml) was added. The organic phase was separated, washed twice with water (40 ml) and evaporated. to give a yellow oil (3)

Yield :58%.

^{1}H-NMR (400 M.HZ, DMSO-d_6)

δ 0.90 (t, J = 7.3 Hz, 3H), 1.40 (m, 2H), 1.49 (m, 2H), 3.90 (t, J = 7.0 Hz, 2H), 7-7.3(8H,m,Ar-H)

IR(KBr,cm^{-1})

3110 cm^{-1} (Ar C-H stret), 1550 cm^{-1} (C=C Stret), 2900 (SP^3 C-H Stretch) Wave numbers respectively.

General procedure for the preparation of 10-butyl-10H-phenothiazine-3-carbaldehyde (Compound 3)[58]

Introduce 8.5 ml (**110 m.mol**) of dry Dimethyl formamide, Cool the dimethylformamide (**DMF**) and add over 30 minutes 2.61 ml (**28 m,mol**) of phosphoryl chloride(**$POCl_3$**),Then add, over 40 minutes, the solution of 3 g (**25.5 m.mol**) of compound(2) in 5 ml of anhydrous 1,2 Di chloro Ethane, making sure that the temperature does not rise above 10^0 C. Stir the mixture for 45 minutes at 10^0 C. then for 40 minutes at 85^0 C. Add 10 g of crushed ice, stir the compact mixture vigorously and add a further 10 g of crushed ice. Continue the stirring and add progressively, by a dropping funnel, a solution of 11.3 g (**282 m.mol**) of sodium hydroxide in 30 ml of water, slowly at first, then more rapidly, maintaining a good level of stirring. Then bring the solution to the boil for 15 minutes, recover by filtration and wash the isolated semi solid several times with water.

Yield: 70 %

^{1}H-NMR (400 M.HZ, DMSO-d_6)

δ 0.90 (t, J = 7.3 Hz, 3H), 1.40 (m, 2H), 1.49 (m, 2H), 3.90 (t, J = 7.0 Hz, 2H), 7-7.3(7H,m,Ar-H), 9.2 (1H,S, **H**-C=O)

IR(KBr,cm^{-1})

3110 cm^{-1} (Ar C-H stret), 1550 cm^{-1} (C=C Stret), 2900 (SP^3 C-H Stretch), 1725 cm^{-1} (C=O Stretch) Wave numbers respectively.

General procedure for the preparation of (E)-3-(10-butyl-10H-phenothiazin-3-yl)-1-(4-nitro/Methoxy/Methyl/Fluoro/Chloro/Bromo phenyl)prop-2-en-1-one (5 a-f), (E)-3-(10-butyl-10H-phenothiazin-3-yl)-1-phenylprop-2-en-1-one (5g)[59]

10-butyl-10H-phenothiazine-3-carbaldehyde (Compound 3) (**5 m.mol**) and Acetophenone derivatives 4(a-g) (**5 m.mol**) were dissolved in Ethanol (**10 ml**) with stirring. Potassium hydroxide (70%) (**15 m.mol**) was added in portions to give a blood-red solution. Resulting solution was stirred for 8–28h, during which Corres[onding chalcone precipitated as the potassium salt. The solution/suspension was poured into cold 2 N HCl (10 ml), and further concentrated HCl was added until the solution was acidic. The resulting yellow solid was filtered, washed with water (20 ml), and re crystallized from corresponding solvent (MeOH or MeOH/CH_2Cl_2) to give the products 5(a-g).

Table 1: Yields & Melting Points of Corresponding Compounds (5 a-g)

S.NO	Yield (%)	Melting Point (^{0}C)
5a	75	111-112
5b	72	183-184
5c	70	126-127
5d	76	143-144
5e	73	115-116
5f	71	124-126
5g	78	90-91

Table 2: IR(KBr,cm-^{1}) data of Compounds 5 (a-g)

Compound	ν_{max}, cm^{-1}
5a	3110 cm^{-1} (Ar C-H stret), 1610 cm^{-1} (C=C Stret), 2900 (SP^3 C-H Stretch), 1525 & 1350 cm^{-1} (two bands,N-O Stretch in –NO_2 Group) Wave numbers respectively.
5b	3100 cm^{-1} (Ar C-H stret), 2910 cm^{-1} (SP^3 C-H Stretching), 1550 cm^{-1} (C=C Stret), 1150 (C-O-C Stretch), Wave numbers respectively.
5c	3110 cm^{-1} (Ar C-H stret), 290 cm^{-1} (SP^3 C-H Stretching), 1550 cm^{-1} (C=C Stret), Wave numbers respectively.
5d	3110 cm^{-1} (Ar C-H stret), 2900 cm^{-1} (SP^3 C-H Stretching), 1550 cm^{-1} (C=C Stret), 1368 cm^{-1} (C-F Stretch) Wave numbers respectively.
5e	3110 cm^{-1} (Ar C-H stret), 2940 cm^{-1} (SP^3 C-H Stretching), 1550 cm^{-1} (C=C Stret), 768 cm^{-1} (C-Cl Stretch), 770 cm^{-1} (C-Cl Stretch) Wave numbers respectively.
5f	3110 cm^{-1} (Ar C-H stret), 2920 cm^{-1} (SP^3 C-H Stretching), 1580 cm^{-1} (C=C Stret), 568 cm^{-1} (C-Br Stretch) Wave numbers respectively.
5g	3120 cm^{-1} (Ar C-H stret), 2940 cm^{-1} (SP^3 C-H Stretching), 1550 cm^{-1} (C=C Stret), Wave numbers respectively.

Table 3: ^{1}H –NMR data of Synthesised compounds 5(a-g)

Compound	^{1}H-NMR ($CDCl_3$-d_1) (δ ppm)
5a	δ 0.90 (t, J = 7.3 Hz, 3H), 1.40 (m, 2H), 1.49 (m, 2H), 3.90 (t, J = 7.0 Hz, 2H), 7-7.3(7H,m,Ar-H), 8(1H,d,J=14HZ,Beta alkene Proton from carbonyl group), 7.5(1H, d, J=14Hz,alpha alkene proton from carbonyl group), 8.1(2H,d,J=8HZ, meta to nitro group), 8.5(2H,d,J=8HZ, ortho to nitro group).
5b	δ 0.90 (t, J = 7.3 Hz, 3H), 1.40 (m, 2H), 1.49 (m, 2H), 3.90 (t, J = 7.0 Hz, 2H), 7-7.2(7H,m,Ar-H), 8(1H,d,J=14HZ,Beta alkene Proton from carbonyl group), 7.5(1H, d, J=14Hz,alpha alkene proton from carbonyl group), 8.2(2H,d,J=8HZ, meta to Methoxy group), 7.2(2H,d,J=8HZ,ortho to Methoxy group), 3.9(3H,S, -OC**H**$_3$)
5c	δ 0.90 (t, J = 7.3 Hz, 3H), 1.40 (m, 2H), 1.49 (m, 2H), 3.90 (t, J = 7.0 Hz, 2H), 7-7.2(7H,m,Ar-H), 8(1H,d,J=14HZ,Beta alkene Proton from carbonyl group), 7.5(1H, d, J=14Hz,alpha alkene proton from carbonyl group), 8(2H,d,J=8HZ, meta to Methyl group), 7.5(2H,d,J=8HZ,ortho to Methyl group), 2.3(3H, S, -CH_3)
5d	δ 0.90 (t, J = 7.3 Hz, 3H), 1.40 (m, 2H), 1.49 (m, 2H), 3.90 (t, J = 7.0 Hz, 2H), 7-7.2(7H,m,Ar-H), 8(1H,d,J=14HZ,Beta alkene Proton from carbonyl group), 7.5(1H, d, J=14Hz,alpha alkene proton from carbonyl group), 7.9(2H,d,J=8HZ, meta to Fluoro group), 7.5(2H,d,J=8HZ,ortho to Fluoro group)
5e	δ 0.90 (t, J = 7.3 Hz, 3H), 1.40 (m, 2H), 1.49 (m, 2H), 3.90 (t, J = 7.0 Hz, 2H), 7-7.2(7H,m,Ar-H), 8(1H,d,J=14HZ,Beta alkene Proton from carbonyl group), 7.5(1H, d, J=14Hz,alpha alkene proton from carbonyl group), 7.9(2H,d,J=8HZ, meta to chloro group), 7.7(2H,d,J=8HZ,ortho to Chloro group)
5f	δ 0.90 (t, J = 7.3 Hz, 3H), 1.40 (m, 2H), 1.49 (m, 2H), 3.90 (t, J = 7.0 Hz, 2H), 7-7.2(7H,m,Ar-H), 8(1H,d,J=14HZ,Beta alkene Proton from carbonyl group), 7.5(1H, d, J=14Hz,alpha alkene proton from carbonyl group), 7.9(2H,d,J=8HZ, meta to Bromo group), 7.8(2H,d,J=8HZ,ortho to Bromo group)
5g	δ 0.90 (t, J = 7.3 Hz, 3H), 1.40 (m, 2H), 1.49 (m, 2H), 3.90 (t, J = 7.0 Hz, 2H), 7-7.7(12H,m,Ar-H)

General procedure for the preparation of 10-butyl-3-(4-(4-nitro/Methoxy/Methyl/Fluoro/Chloro/Bromo phenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-2-yl)-10H-phenothiazine (7a–f), 10-butyl-3-(4-phenyl-2,3-dihydrobenzo[b][1,4]thiazepin-2-yl)-10H-phenothiazine (7g)[60]

To a solution of chalcone derivatives (**5 a-g**) (**0. 1 m.mol**in 10 ml of Ethanol, **0.1 m.mol** of O-amino thio phenol and 2–3 drops of glacial acetic acid were added. The reaction mixture was refluxed by heating for 6 hours, and the progress of the reaction was monitored by TLC. After completion of the reaction, the resulting solution was cooled and transferred into crushed ice. The solid product was filtered and recrystallized from EtOH to enable benzo thiazepine derivatives 7a–g.

Table 4: Yields & Melting Points of Corresponding Compounds (7 a-g)

S.NO	Yield (%)	Melting Point (^{0}C)
7a	65	141-142
7b	72	123-124
7c	70	166-167
7d	73	173-174
7e	75	125-126
7f	70	144-146
7g	72	80-81

Table 5: IR(KBr,cm-^{1}) data of Compounds 7(a-g)

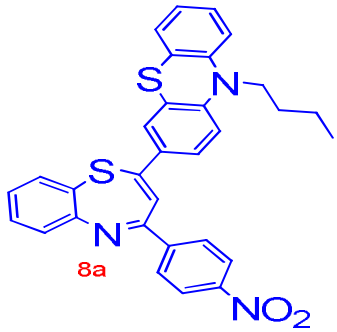
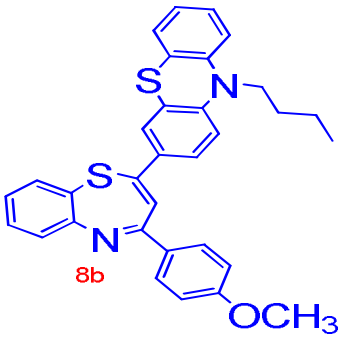
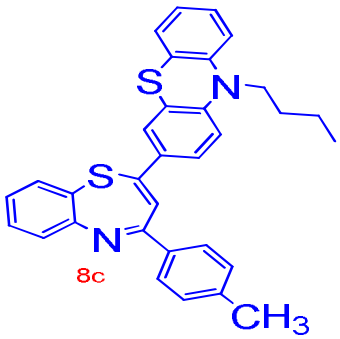
Compound	ν_{max}, cm^{-1}
7a	3110 cm^{-1} (Ar C-H stret), 1610 cm^{-1} (C=C Stret), 2900 (SP^3 C-H Stretch), 1525 & 1350 cm^{-1} (two bands,N-O Stretch in –NO_2 Group) Wave numbers respectively.
7b	3100 cm^{-1} (Ar C-H stret), 2910 cm^{-1} (SP^3 C-H Stretching), 1550 cm^{-1} (C=C Stret), 1150 (C-O-C Stretch), Wave numbers respectively.
7c	3110 cm^{-1} (Ar C-H stret), 290 cm^{-1} (SP^3 C-H Stretching), 1550 cm^{-1} (C=C Stret), Wave numbers respectively.
7d	3110 cm^{-1} (Ar C-H stret), 2900 cm^{-1} (SP^3 C-H Stretching), 1550 cm^{-1} (C=C Stret), 1368 cm^{-1} (C-F Stretch) Wave numbers respectively.
7e	3110 cm^{-1} (Ar C-H stret), 2940 cm^{-1} (SP^3 C-H Stretching), 1550 cm^{-1} (C=C Stret), 768 cm^{-1} (C-Cl Stretch), 770 cm^{-1} (C-Cl Stretch) Wave numbers respectively.
7f	3110 cm^{-1} (Ar C-H stret), 2920 cm^{-1} (SP^3 C-H Stretching), 1580 cm^{-1} (C=C Stret), 568 cm^{-1} (C-Br Stretch) Wave numbers respectively.
7g	3120 cm^{-1} (Ar C-H stret), 2940 cm^{-1} (SP^3 C-H Stretching), 1550 cm^{-1} (C=C Stret), Wave numbers respectively.

Table 6: ^{1}H –NMR data of Synthesised compounds 7(a-g)

Compound	^{1}H-NMR ($CDCl_3$-d_1) (δ ppm)
7a	δ 0.90 (t, J = 7.3 Hz, 3H), 1.40 (m, 2H), 1.49 (m, 2H), 3.90 (t, J = 7.0 Hz, 2H), 7-7.3(11H,m,Ar-H), 4(1H,dd,J=14HZ, 7HZ proton which is attached to carbon atom adjacent to Sulphur atom), 2.1(1H,dd), 1.9(1H,dd), 8.1(2H,d,J=8HZ, meta to nitro group), 8.5(2H,d,J=8HZ, ortho to nitro group).
7b	δ 0.90 (t, J = 7.3 Hz, 3H), 1.40 (m, 2H), 1.49 (m, 2H), 3.90 (t, J = 7.0 Hz, 2H), 7-7.3(11H,m,Ar-H), 4(1H,dd,J=14HZ, 7HZ proton which is attached to carbon atom adjacent to Sulphur atom), 2.1(1H,dd), 1.9(1H,dd), 8(2H,d,J=8HZ, meta to Methoxy group), 7(2H,d,J=8HZ, ortho to Methoxy group), 3.9(3H,S, -OC**H**$_3$)
7c	δ 0.90 (t, J = 7.3 Hz, 3H), 1.40 (m, 2H), 1.49 (m, 2H), 3.90 (t, J = 7.0 Hz, 2H), 7-7.3(11H,m,Ar-H), 3.8(1H,dd,J=14HZ, 7HZ proton which is attached to carbon atom adjacent to Sulphur atom), 2.1(1H,dd), 1.9(1H,dd), 7.8(2H,d,J=8HZ, meta to Methyl group), 7.3(2H,d,J=8HZ, ortho to Methyl group), 2.4(3H, S, -CH_3)
7d	δ 0.90 (t, J = 7.3 Hz, 3H), 1.40 (m, 2H), 1.49 (m, 2H), 3.90 (t, J = 7.0 Hz, 2H), 7-7.3(11H,m,Ar-H), 3.8(1H,dd,J=14HZ, 7HZ proton which is attached to carbon atom adjacent to Sulphur atom), 2.1(1H,dd), 1.9(1H,dd), 7.8(2H,d,J=8HZ, meta to Fluorine atom), 7.4(2H,d,J=8HZ, ortho to Fluorine atom).
7e	δ 0.90 (t, J = 7.3 Hz, 3H), 1.40 (m, 2H), 1.49 (m, 2H), 3.90 (t, J = 7.0 Hz, 2H), 7-7.4(11H,m,Ar-H), 3.8(1H,dd,J=14HZ, 7HZ proton which is attached to carbon atom adjacent to Sulphur atom), 2.1(1H,dd), 1.9(1H,dd), 7.9(2H,d,J=8HZ, meta to -Cl atom), 7.5(2H,d,J=8HZ, ortho to -Cl atom).
7f	δ 0.90 (t, J = 7.3 Hz, 3H), 1.40 (m, 2H), 1.49 (m, 2H), 3.90 (t, J = 7.0 Hz, 2H), 7-7.4(11H,m,Ar-H), 3.8(1H,dd,J=14HZ, 7HZ proton which is attached to carbon atom adjacent to Sulphur atom), 2.1(1H,dd), 1.9(1H,dd), 7.8(2H,d,J=8HZ, meta to –Br atom), 7.6(2H,d,J=8HZ, ortho to –Br atom).
7g	δ 0.90 (t, J = 7.3 Hz, 3H), 1.40 (m, 2H), 1.49 (m, 2H), 3.90 (t, J = 7.0 Hz, 2H), 7-7.4(11H,m,Ar-H), 3.8(1H,dd,J=14HZ, 7HZ proton which is attached to carbon atom adjacent to Sulphur atom), 2.1(1H,dd), 1.8(1H,dd)

General procedure for the preparation of 10-butyl-3-(4-(4-nitro/Methoxy/methyl/Fluoro/Chloro/Bromo phenyl)benzo[b][1,4]thiazepin-2-yl)-10H-phenothiazine (8a-f), 10-butyl-3-(4-phenylbenzo[b][1,4]thiazepin-2-yl)-10H-phenothiazine (8g)[61]
To a solution of DDQ (**0.5 m.mol**) was added a solution of the di hydro benzo thiazepine derivatives 7 (a-g) (**0.1 m.mol**) in $CHCl_3$. The reaction is stirred at RT for 24 hrs, Upon completion of the reaction, the solution is filtered and diluted with CH_2Cl_2 and washed with water (80 ml), The organic Solution is then washed with Saturated aqueous NaCl, dried over sodium sulphate and concentrated.
Yield : 75-80%.

Table 7: Structures of final Compounds and Its corresponding Names

Chemical Structure	Chemical Name
	10-butyl-3-(4-(4-nitrophenyl)benzo[b][1,4]thiazepin-2-yl)-10H-phenothiazine
	10-butyl-3-(4-(4-methoxyphenyl)benzo[b][1,4]thiazepin-2-yl)-10H-phenothiazine
	10-butyl-3-(4-p-tolylbenzo[b][1,4]thiazepin-2-yl)-10H-phenothiazine

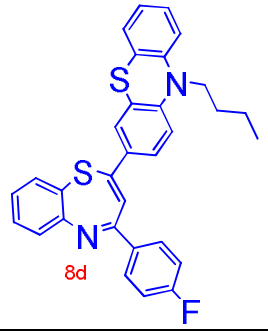
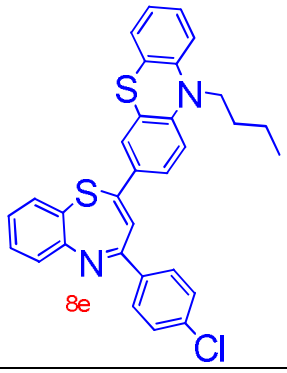
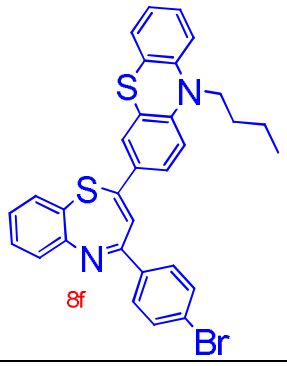
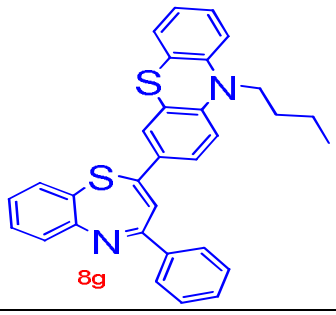
 8d	10-butyl-3-(4-(4-fluorophenyl)benzo[b][1,4]thiazepin-2-yl)-10H-phenothiazine
 8e	10-butyl-3-(4-(4-chlorophenyl)benzo[b][1,4]thiazepin-2-yl)-10H-phenothiazine
 8f	3-(4-(4-bromophenyl)benzo[b][1,4]thiazepin-2-yl)-10-butyl-10H-phenothiazine
 8g	10-butyl-3-(4-phenylbenzo[b][1,4]thiazepin-2-yl)-10H-phenothiazine

Table 8: Characterisation data of Novel Benzo Thazepine derivatives 8 (a-g)

Comp	M.P. /^{0}C	Molecular Weight (m/z)	YIELD (%)	Molecular Formula	Found % (Calculated %)		
					C	H	N
8a	120-122^{0}C	558[**M+Na**]	75	$C_{31}H_{25}N_3O_2S_2$	69.5 (69.51)	4.74 (4.70)	7.81 (7.84)
8b	163-165^{0}C	521[**M+H**]	80	$C_{32}H_{28}N_2OS_2$	73.80 (73.81)	5.40 (5.42)	5.36 (5.38)
8c	140-142^{0}C	505[**M+H**]	76	$C_{32}H_{28}N_2S_2$	76.13 (76.15)	5.56 (5.59)	5.53 (5.55)
8d	137-138^{0}C	509[**M+H**]	74	$C_{31}H_{25}FN_2S_2$	73.2 (73.20)	4.92 (4.92)	5.48 (5.51)
8e	160-162^{0}C	526[**M+H**]	76	$C_{31}H_{25}ClN_2S_2$	70.9 (70.9)	4.7 (4.8)	5.34 (5.33)
8f	174-176^{0}C	570[**M+H**]	76	$C_{31}H_{25}BrN_2S_2$	65.35 (65.37)	4.40 (4.42)	4.8 (4.92)
8g	110-111^{0}C	491[**M+H**]	80	$C_{31}H_{26}N_2S_2$	75.86 (75.88)	5.34 (5.39)	5.73 (5.71)

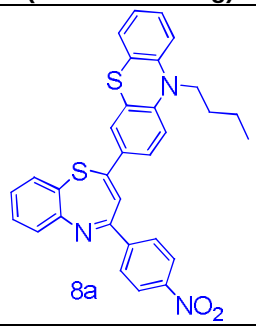
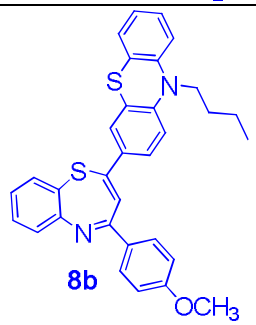
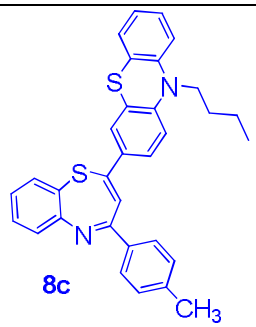
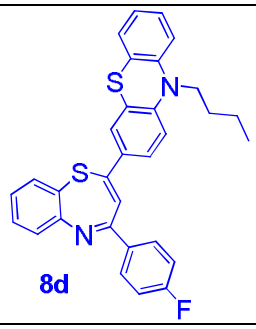
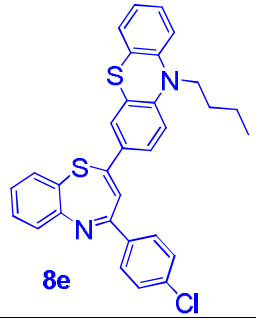
Table 9: IR data of Compounds 8 (a-g)

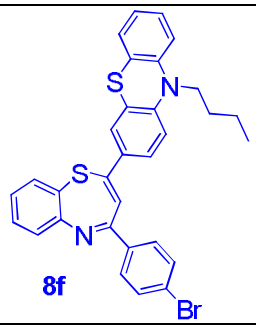
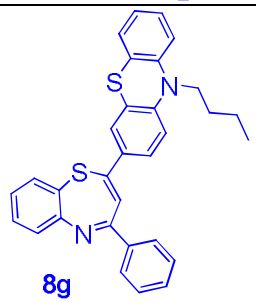
Compound	ν_{max}, cm^{-1}
8a	3120 cm^{-1} (Ar C-H stret), 1610 cm^{-1} (C=C Stret), 2900 (SP^3 C-H Stretch), 1535 & 1340 cm^{-1} (two bands , N-O Stretch in –NO_2 Group) Wave numbers respectively.
8b	3130 cm^{-1} (Ar C-H stret), 2910 cm^{-1} (SP^3 C-H Stretching), 1550 cm^{-1} (C=C Stret), 1160 (C-O Stretch), Wave numbers respectively.
8c	3120 cm^{-1} (Ar C-H stret), 290 cm^{-1} (SP^3 C-H Stretching), 1550 cm^{-1} (C=C Stret), Wave numbers respectively.
8d	3110 cm^{-1} (Ar C-H stret), 2900 cm^{-1} (SP^3 C-H Stretching), 1550 cm^{-1} (C=C Stret), 1358 cm^{-1} (C-F Stretch) Wave numbers respectively.
8e	3110 cm^{-1} (Ar C-H stret), 2940 cm^{-1} (SP^3 C-H Stretching), 1550 cm^{-1} (C=C Stret), 758 cm^{-1} (C-Cl Stretch), 770 cm^{-1} (C-Cl Stretch) Wave numbers respectively.
8f	3110 cm^{-1} (Ar C-H stret), 2920 cm^{-1} (SP^3 C-H Stretching), 1580 cm^{-1} (C=C Stret), 558 cm^{-1} (C-Br Stretch) Wave numbers respectively.
8g	3120 cm^{-1} (Ar C-H stret), 2920 cm^{-1} (SP^3 C-H Stretching), 1550 cm^{-1} (C=C Stret), Wave numbers respectively.

Table 10: ^{1}H –NMR data of Synthesised compounds 8(a-g)

Compound	^{1}H-NMR (DMSO-d_6) (δ ppm)
8a	δ 0.90 (t, J = 7.3 Hz, 3H), 1.40 (m, 2H), 1.49 (m, 2H), 3.90 (t, J = 7.0 Hz, 2H), 7-7.4(11H,m,Ar-H), 6.5(1H,S), 8.1(2H,d,J=8HZ, meta to nitro group), 8.5(2H,d,J=8HZ, ortho to nitro group).
8b	δ 0.90 (t, J = 7.3 Hz, 3H), 1.40 (m, 2H), 1.49 (m, 2H), 3.90 (t, J = 7.0 Hz, 2H), 7-7.3(11H,m,Ar-H), 6.3(1H,S), 8(2H,d,J=8HZ, meta to Methoxy group), 7(2H,d,J=8HZ, ortho to Methoxy group), 3.9(3H,S, -OC**H**$_3$)
8c	δ 0.90 (t, J = 7.3 Hz, 3H), 1.40 (m, 2H), 1.49 (m, 2H), 3.90 (t, J = 7.0 Hz, 2H), 7-7.3(11H,m,Ar-H), 6.2(1H, S), 7.8(2H,d,J=8HZ, meta to Methyl group), 7.3(2H,d,J=8HZ, ortho to Methyl group), 2.4(3H, S, -CH_3)
8d	δ 0.90 (t, J = 7.3 Hz, 3H), 1.40 (m, 2H), 1.49 (m, 2H), 3.90 (t, J = 7.0 Hz, 2H), 7-7.3(11H,m,Ar-H), 6.2(1H,S), 7.8(2H,d,J=8HZ, meta to Fluorine atom), 7.4(2H,d,J=8HZ, ortho to Fluorine atom).
8e	δ 0.90 (t, J = 7.3 Hz, 3H), 1.40 (m, 2H), 1.49 (m, 2H), 3.90 (t, J = 7.0 Hz, 2H), 7-7.4(11H,m,Ar-H), 6.2(1H,S), 7.9(2H,d,J=8HZ, meta to -Cl atom), 7.5(2H,d,J=8HZ, ortho to -Cl atom).
8f	δ 0.90 (t, J = 7.3 Hz, 3H), 1.40 (m, 2H), 1.49 (m, 2H), 3.90 (t, J = 7.0 Hz, 2H), 7-7.4(11H,m,Ar-H), 6.6(1H,S), 7.8(2H,d,J=8HZ, meta to –Br atom), 7.6(2H,d,J=8HZ, ortho to –Br atom).
8g	δ 0.90 (t, J = 7.3 Hz, 3H), 1.40 (m, 2H), 1.49 (m, 2H), 3.90 (t, J = 7.0 Hz, 2H), 7-7.4(11H,m,Ar-H), 6.48(1H,S)

Table 11: ^{13}C –NMR data of of Novel Synthesised compounds 8(a-g)

Structure of the compound (With numbering)	^{13}CNMR (100 M.HZ, DMSO-d_6, δ ppm)
 8a	120-150 (25 Aromatic carbons), 50(N-**C**H_2), 13-25(3 aliphatic carbons) respectively.
 8b	110-165 (25 Aromatic carbons), 52(N-**C**H_2), 13-35(3 aliphatic carbons), 55 (-O-**C**H_3) respectively.
 8c	110-165 (25 Aromatic carbons), 51.3(N-**C**H_2), 13-35(4 aliphatic carbons) respectively.
 8d	110-165 (25 Aromatic carbons), 52.3(N-**C**H_2), 13-30(3 aliphatic carbons) respectively.
 8e	110-155 (25 Aromatic carbons), 52.3(N-**C**H_2), 13-30 (3 aliphatic carbons) respectively.

 8f	110-150(25 Aromatic carbons), 50(N-**C**H_2), 13-30(3 aliphatic carbons) respectively.
 8g	110-140(25 Aromatic carbons), 50(N-**C**H_2), 13-32(3 aliphatic carbons) respectively.

BIOLOGICAL EVALUATION

In vivo anti-inflammatory activity

All the newly synthesized benzothiazepines (8 a–g) were screened for their in vivo anti-inflammatory activity by paw edema method. Wister rats were used in the study were fed in house diet and water adlibitum and maintained at 10-12h dark light cycle, 25^0 C. Animals were administered Diclofenac 10 mg/kg, or test compound 10 mg/kg p.o., (n=3) two hours prior to injection of 0.1% formaldehyde in the paw. The anti-inflammatory was then calculated 120 minutes after induction and presented in **Table–12** as the mean paw dimension in addition to the percentage inhibition. Paw dimension was measured by digital vernier calliper (Mitutoya, Japan.)

The order of activity was **8d>8e>8f>8a>8g>8c>8b**

Table 12: **Anti-inflammatory activity of the compounds 8 a–g**

Compound	Animal	Paw volume (mm)		% Inhibition
		Un induced	Induced	
8a	1	6.3	8.2	3.80
	2	6.2	8.1	
	3	6.1	8.6	
8b	1	6.1	8,2	0.51
	2	6.4	8.1	
	3	6.2	8.3	
8c	1	6.2	7.7	1.52
	2	6.2	8.3	
	3	6.1	8.1	
8d	**1**	**6.3**	**8.0**	**10.89**
	2	**6.4**	**8.6**	
	3	**6.1**	**7.9**	
8e	1	6.4	8.2	6.52
	2	6.2	8.1	
	3	6.1	8.5	
8f	1	6.3	8.2	6.14
	2	6.2	8.0	
	3	6.2	7.6	
8g	1	6.1	8.2	2.21
	2	6.4	8.1	
	3	6.2	8.3	
Untreated	1	6.2	8.1	0.00
	2	6.1	8.3	
	3	6.3	8.2	
Diclofenac	1	6.3	7.2	14.21
	2	6.2	7.1	
	3	6.0	6.7	

Out of the seven compounds tested, three compounds (**8d, 8e and 8f**) showed significant anti-inflammatory activity. Among these compounds, the compound 8d (**R= -F**) was found to be highly active with 10.89 % inhibition activity, while **8e** and **8f** with **–Cl** and **–Br** groups were also found have a respective inhibition rate of 6.52 % and 6.14 %. However, the compounds **8c** and **8b** with methyl, methoxy groups were found to be less active with 1.52 and 0.51 % inhibition respectively. The 8d with Fluoro group displayed considerable potent anti-inflammatory activity (10.89 % inhibition) comparable with diclofenac (14.21 % inhibition). However, none was found to be superior to the reference drug.

The present investigation reports the synthesis of 1, 5 benzo thiazepine derivatives and the evaluation of their anti-inflammatory activity (**Figure 1**).

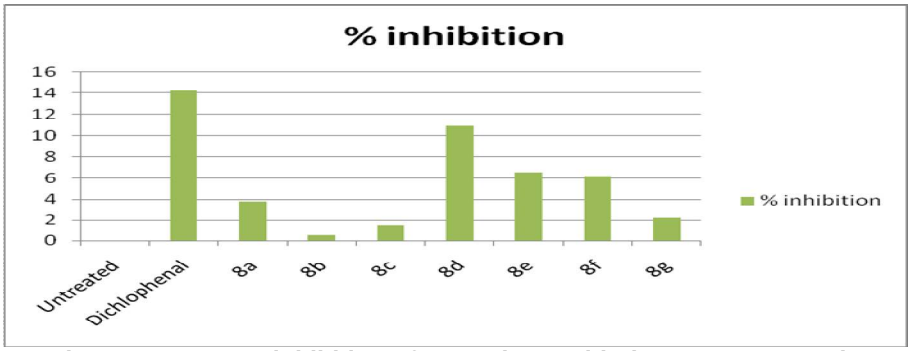


Fig. 1: Percentage inhibition of paw edema with the test compounds

Table 13: Information about X-Axis & Y-Axis Values

Compound (X-Axis)	% inhibition (Y-Axis)
Untreated	0
Dichlophenal	14.21
8a	3.8
8b	0.51
8c	1.52
8d	**10.89**
8e	6.52
8f	6.14
8g	2.21

RESULTS AND DISCUSSIONS

Characterization

The IR spectrum of the title Compounds 8(a-g) has given stretching vibration at 3100cm^{-1}, due to the stretching vibration corresponding to Ar-H Stretching vibrations. The absorption peak at 2935 cm^{-1} is due to The stretching vibration corresponding to the SP^3 C-H (methyl gp).The strong Intensity absorption at 1350 & 1530 cm^{-1} is due to The stretching vibration of -N-O Stretching in Nitro group, 1360 cm^{-1} is due to The stretching vibration of C-F bond. 760 cm^{-1} is due to The stretching vibration of C-Cl bond. 560 cm^{-1} is due to The stretching vibration of C-Br bond. The weak Intensity absorption at 1620 cm^{-1} corresponds to a C=N Stretching vibration.1150cm^{-1} corresponding to C-O Stretching.

It has been observed from chemical structure of compound 8(a-g) that different pair of protons. The protons of Methyl group which is attached to benzene ring appeared as a singlet at δ =2.3 ppm, The protons of Methoxy group appeared as a Singlet at δ =3.8 ppm, . The protons attached benzene ring appeared between δ =7.2-8.3 ppm respectively.

The chemical shifts of the final compound carbon vary from δ = 165 to 23 ppm. The carbon nucleus under the influence of a strong electronegative environment appeared down field, The carbon chemical shift of the methyl group at δ= 23 ppm. The carbon chemical shift of the Methoxy group at δ= 55 ppm.

Readily available starting materials and simple synthesizing procedures make this method very attractive and convenient for the synthesis of 1,5 Benzo di azepine derivatives. Formation of products was confirmed by recording their Elemental analysis, ^{1}H NMR, ^{13}C,FT-IR,mass spectra. The Elemental analysis data showed good agreement between the experimentally determined values and the theoretically calculated values with in ±0.4% .

Anti inflammatory screening

The results of Anti-inflammatory studies of newly synthesized compounds reveal that the compounds possess significant Anti inflammatory activities. The results of these studies are given in **Table 12**. From Anti inflammatory screening results, it has been observed that compounds 8d possess good activity.

CONCLUSION

We have synthesized a series of new 1, 5-benzothiazepines 8(a-g) containing bioactive heteryl pharmacophores such as phenothiazine ring using convenient method.

In conclusion, the present investigation reports the synthesis of 1, 5 benzothiazepine derivatives and the evaluation of their anti-inflammatory activity (**Figure 1**).

The submission pattern of the 1, 5 benzothiazepine was rationalized to be correlated to the aryl heterocyclic template. Among all tested compounds, Fluoro -substituted benzo thiazepine derivative 8d showed the highest anti inflammatory activity (10.89 % inhibition) that was comparable to diclofenac (14.21 % inhibition), while compounds 8e and 8f displayed good anti-inflammatory activity (6.52% and 6.14 % inhibition), respectively. However, none of the newly synthesized compounds were found to be superior to the reference drug.

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