INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Research Article

Development Of 1,5-Benzothiazepine-Based Molecules with Potential Antimicrobial Activity

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ARTICLE INFO

Published: 06 Oct 2025
Keywords:
Potential Antimicrobial Activity, epidermidis, Fluconazole a reference drug
DOI:
10.5281/zenodo.17277591

ABSTRACT

One of the most common methods for the synthesis of 1,5-¬ benzothiazepines is based on condensation reaction of o-aminothiophenol with chalcones under acidic or basic media [1]. The synthesis of compounds 1a–1g (Scheme 1) was performed in three steps. compound 3 P-Hydroxy aromatic aldehydes were condensed with 2,4- pentandione in dry benzene using piperidine as a catalyst to yield compound 3. And then the Michael addition of o-aminothiophenol to compound 3, gave 4-substituted pentandione derivatives 4. The intramolecular cyclisation of 4 followed by dehydration in acetic acid/methanol finally gave compounds 1, which were purified by crystallization from dry methanol. The synthesized new compounds were identified on the basis of their elemental analysis, IR and 1HNMR and Mass etc. The synthesized compounds were evaluated for their in-vitro antimicrobial activities against the three bacterial strains C. albicans, S. aureus, S. epidermidis by using disk diffusion method. Some of the title compounds exhibited significant activity as compared to Fluconazole a reference drug.

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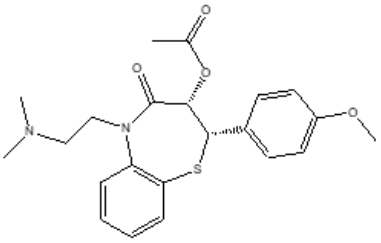
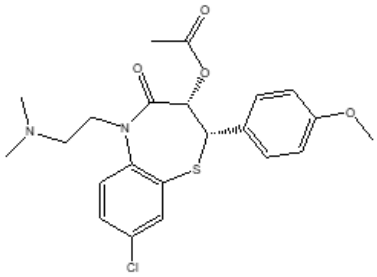
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

INTRODUCTION

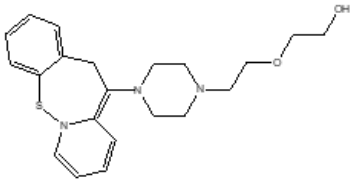
Prompt action through the use of antimicrobial drugs is essential to treat microorganisms caused disease. Available antimicrobial agents currently do not cope with the effect of microbes [1-3]. Resistance to the number of antimicrobial agents for clinically significant microbial species arose as a global problem [4]. This condition of concerns is because of the issues such as antimicrobial resistance, restricted antimicrobial spectrum and hypersensitivities and systemic toxicities. Therefore,
the growing clinical significance of drug-resistant microbial pathogens
had necessitated development
of new antimicrobial agents as an immediate need for the humanity [5]. Therefore, there is an increased demand for the design and synthesis of newer antimicrobial agents to fight the microbial diseases with improved characteristics such as selectivity, efficacy, reduced duration of treatments and lower toxicity [6-7]. Benzothiazepine is a unique scaffold which is present in a number of drugs used nowadays. Diltiazem FIG (1) and Clentiazem FIG (2) are used for their cardiovascular properties for their cardiovascular properties8-10. Other benzothiazepine derivatives quetiapine FIG (3), thiazesim FIG (4), and clothiapine FIG (5) respectively are employed clinically for the treatment of central nervous system disorders [8-13].



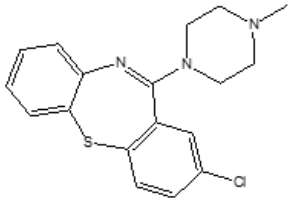
Diltiazem FIG (1)



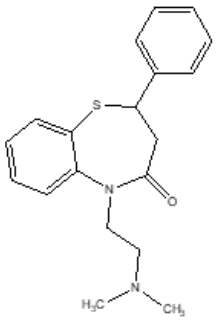
Clentiazem FIG (2)



Quetiapine FIG (3)



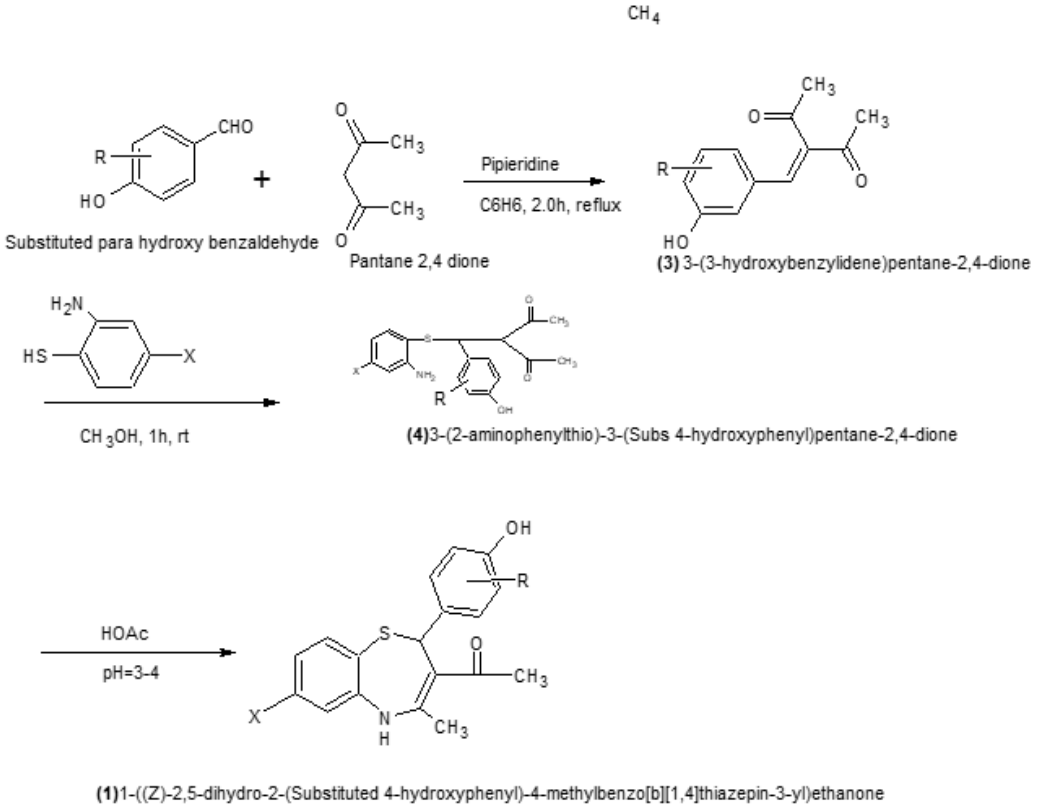
Clothiapine FIG (4)



Thiazesim FIG (5)

Experimental

All melting points were measured in open capillaries and are not corrected. The extent of reaction progress and purity of the compounds were monitored by TLC on percolated silica gel plate with chloroform-ethyl acetate mixture (7:3). Compounds were detected by iodine vapours. IR spectra were taken on FTIR 4100 type A spectrophotometer while 1 H NMR (DMSO) was taken on Bruker FTAC spectrometer with TMS as internal standard.



SCHEME 1

Compd	X	R
1a	H	p-NO2
1b	H	o-NO2
1c	H	p-Cl
1d	H	o-Cl
1e	H	p-CH3
1f	H	p-OH
1g	H	H

CHEMISTRY

The compounds 1a–g were synthesized by three step process as outlined in Scheme 1. Compound 3 Piperidine catalyzed Knoevenagel condensation of Para hrdroxy aromatic aldehydes with 2,4-pentandione in dry benzene to afford compound 3. Subsequently, was added to compound 3 **(3)**3-(3-hydroxybenzylidene) pentane-2,4-dionevia Michael addition to give the pentandione derivatives 4 **(4)**3-(2-aminophenylthio)-3-(Subs 4-hydroxyphenyl) pentane-2,4-dione.Warming the resulting intermediate 4 to room temperature followed by dehydration in acetic acid/methanol yielded compounds **(1)**1-((Z)-2,5-dihydro-2-(Substituted 4-hydroxyphenyl)-4-methylbenzo[b][1,4] thiazepin-3-yl) ethenone, which were purified through crystallization from anhydrous methanol.[14]

Synthesis of (3)3-(3-hydroxybenzylidene) pentane-2,4-dione

15.3 mL (0.5 mol) of 2,4-pentanedione and 150 mL dry benzene were dissolved in piperidine (0.9 mL). Then 0.15 mol of benzaldehyde (substituted) was added dropwise at room temperature over 20 min. The mixture was slowly heated to reflux, and stirred for 6 h (monitored by TLC). The organic layer was washed after cooling with cold aqueous 10% sodium carbonate, water and aqueous 5% acetic acid. Organic layer was then dried and evaporated under reduced pressure and crude product was recrystallized from ether.

Synthesis of (4)3-(2-aminophenylthio)-3-(Subs 4-hydroxyphenyl) pentane-2,4-dione A mixture of 3-benzylidene-2,4-pentandione (3) (25 mmol) and o-aminothiophenol (3.1 g, 25 mmol) in dry methanol (50 mL) was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure, cooled, and the solid was collected by filtration, washed with water and cold methanol. The crude products were purified by crystallization from the appropriate solvent.

(1)1-((Z)-2,5-dihydro-2-(Substituted 4-hydroxyphenyl)-4-methylbenzo[b][1,4] thiazepin-3-yl) ethanone(1a–1g) A solution of 3-(1-aryl-1-o-aminophenylthio methyl)-2,4-pentandione (4) (20 mmol) in dry methanol (40 ml) was brought to pH 4 with acetic acid and stirred at room temperature for 13 h. The precipitate was filtered off, well washed with cold methanol and recrystallized from methanol.

1-((Z)-2,5-dihydro-2-(Para nitro Phenyl 4-hydroxyphenyl)-4-methylbenzo[b][1,4] thiazepin-3-yl) ethanone (1a). Yield 32%; mp 161 0C; MS [M + H+]: 433.50; C18H16N2O3S, found: C, 63.40; H, 4.87; N, 8.10; Calcd: C, 63.51; H, 4.74; N, 8.23; IR KBr (ν cm-1) OH (phenolic): broad peak around 3200–3600 cm^{-1},1665–1695 — C=O (acetyl ketone), 1340–1370 (medium/strong) — NO_2 asymmetric and symmetric stretches ,Aromatic C–H stretch: 3050–3100 cm^{-1}, 3050 (medium) — aromatic C–H stretches. , 2950–2850 (weak) — aliphatic C–H (methyl), 1600–1470 (medium) — aromatic C=C stretches. 700–600 (weak–medium) — C–S / ring deformation bands (thiazepine sulfur contributes absorptions in fingerprint).

1 H NMR (400 MHz, CDCl3), δ 9.5–10.5 (s, 1H) — phenolic OH, δ 8.2–8.4 (2H) p-nitrophenyl H ortho to NO_2, δ 7.5–7.8 (d, J ≈ 8–9 Hz, 2H) — p-nitrophenyl H meta to NO_2, δ 7.0–7.6 (multiplets, total 3–4H) — aromatic protons of the fused benzo ring and remaining aryl signals , δ 6.7–7.2 (two doublets, J ≈ 8–9 Hz, 2H + 2H) — 4-hydroxyphenyl ring

1-((Z)-2,5-dihydro-2-(Ortho nitro Phenyl 4-hydroxyphenyl)-4-methylbenzo[b][1,4] thiazepin-3-yl) ethanone(1b).

Yield 31%; mp 127 0C MS [M + H+]: 433.50; C18H16N2O3S: found: C, 63.40; H, 4.87; N, 8.10; Calcd: C, 63.51; H, 4.74; N, 8.23; IR KBr (ν cm-1) 3200–3600 (broad) — phenolic O–H stretch, 1660–1695 — C=O (acetyl ketone) , 1520–1560 (strong) and 1340–1370 (medium/strong) — NO_2 asymmetric and symmetric stretches , 3050–3000 — aromatic C–H stretches, 2950–2850 — aliphatic C–H (methyls) , 1600–1470 — aromatic C=C stretches.

1 H NMR (400 MHz, CDCl3), δ 9.5–10.5 (br s, 1H) — phenolic OH, δ 8.2–8.8 (multiple signals, total 3–4H) — ortho-nitrophenyl protons, δ 7.0–7.8 (multiplets, 3–5H) — fused benzo ring protons, δ 6.7–7.2 (two d, J ≈ 8–9 Hz, total 4H) — 4-hydroxyphenyl ring.

1-((Z)-2,5-dihydro-2-(Para chloro Phenyl 4-hydroxyphenyl)-4-methylbenzo[b][1,4] thiazepin-3-yl) ethanone(1c).

Yield 42%; mp 117 0C; MS [M + H+]: 422.95 g·mol⁻¹; C18H16ClNOS: found: C, 65.42; H, 5.01; N, 4.14; Calcd: C, 65.54; H, 4.89; N, 4.25; IR KBr (ν cm-1) 1708 (C]O), 1635 (C]C), OH (phenolic): broad peak around 3200–3600 cm⁻¹, Aromatic C–H stretch: 3050–3100 cm⁻¹, C=N (thiazepine ring): around 1600–1650 cm⁻¹, C–S stretch: 600–700 cm⁻¹, Aromatic C=C: 1500–1600 cm⁻¹, 750–710 and ~690–670 — C–Cl,

1 H NMR (400 MHz, CDCl3), d (ppm): 6.74–7.07 (8H, m, –C6H4), 6.29 (1H, s,NH), 5.63 (1H, s, SCH), 2.56 (3H, s, –CO–CH3), 2.18 (3H, s, –CH3), δ 7.25–7.40 (d, J ≈ 8.5 Hz, 2H) — p-chloro-phenyl protons ortho to Cl (

1-((Z)-2,5-dihydro-2-(ortho chloro Phenyl 4-hydroxyphenyl)-4-methylbenzo[b][1,4] thiazepin-3-yl) ethanone(1d).

Yield 40%; mp 1490C; MS [M + H+]: 422.95 g·mol⁻¹; C18H16ClNOS: found: C, 65.42; H, 5.01; N, 4.14; Calcd: C, 65.54; H, 4.89; N, 4.25; IR KBr (ν cm-1) 1) 1701 (C]O), 1637 (C]C) OH (phenolic): broad peak around 3200–3600 cm⁻¹, Aromatic C–H stretch: 3050–3100 cm⁻¹, C=N (thiazepine ring): around 1600–1650 cm⁻¹, C–S stretch: 600–700 cm⁻¹, Aromatic C=C: 1500–1600 cm⁻¹,750–710 and ~690–670 — aromatic C–Cl;

1 H NMR (400 MHz, CDCl3), d (ppm): 6.51–7.30 (8H, m, –C6H4), 6.39 (1H, s, NH), 5.86 (1H, s, SCH), 2.57 (3H, s, –CO–CH3), 2.14 (3H, s, –CH3), δ 7.80–8.30 (multiple dd/d, total ~2–3H) — ortho-chloro-phenyl protons

1-((Z)-2,5-dihydro-2-(Para methyl Phenyl 4-hydroxyphenyl)-4-methylbenzo[b][1,4] thiazepin-3-yl) ethanone(1e).

Yield 47%; mp 139 C; MS [M + H+]: 402.57 g·mol⁻¹; C19H19NOS: found: C, 73.62; H, 6.31; N, 4.39; Calcd: C, 73.75; H, 6.19; N, 4.4.53; IR KBr (ν cm-1) 1724 (C]O), 1635 (C]C) OH (phenolic): broad peak around 3200–3600 cm⁻¹, Aromatic C–H stretch: 3050–3100 cm⁻¹, C=N (thiazepine ring): around 1600–1650 cm⁻¹, C–S stretch: 600–700 cm⁻¹, Aromatic C=C: 1500–1600 cm⁻¹, 2950–2850 — aliphatic C–H (methyl groups, including the p-methyl and ring methyl).

; 1 H NMR (400 MHz, CDCl3), d (ppm): 6.69–7.49 (8H, m, –C6H4), 6.51 (1H, s, NH), 5.62 (1H, s, SCH), 2.55 (3H, s, –CO–CH3), 2.17 (3H, s, –CH3), 2.01 (3H, s, PhCH3–),δ 2.30–2.45 (s, 3H) — para-methyl on the p-methylphenyl ring (singlet ~2.3 ppm)

1-((Z)-2,5-dihydro-2-(Para hydroxy Phenyl 4-hydroxyphenyl)-4-methylbenzo[b][1,4] thiazepin-3-yl) ethanone(1f).

Yield 31%; mp 177 C; MS [M + H+]: 403; C18H17NO2S: found: C, 69.31; H, 5.62; N, 4.36; Calcd: C, 69.43; H, 5.50; N, 4.50 IR KBr (ν cm-1) 1697 (C]O), 1635 (C]C), OH (phenolic): broad peak around 3200–3600 cm⁻¹, Aromatic C–H stretch: 3050–3100 cm⁻¹, C=N (thiazepine ring): around 1600–1650 cm⁻¹, C–S stretch: 600–700 cm⁻¹, Aromatic C=C: 1500–1600 cm⁻¹,3200–3600 cm⁻¹ (broad) — phenolic O–H stretches (two phenols → broad, possibly multiple bands/H-bonding)

; 1 H NMR (400 MHz, CDCl3), d (ppm): 6.64–7.53 (8H, m, –C6H4), 6.39 (1H, s, NH), 5.69 (1H, s, SCH), 5.36 (1H, s, OH), 2.29 (3H, s, –COCH3), 1.87 (3H, s, –CH3). δ 6.7–7.2 (two d, J ≈ 8–9 Hz, 4H) — one p-hydroxyphenyl

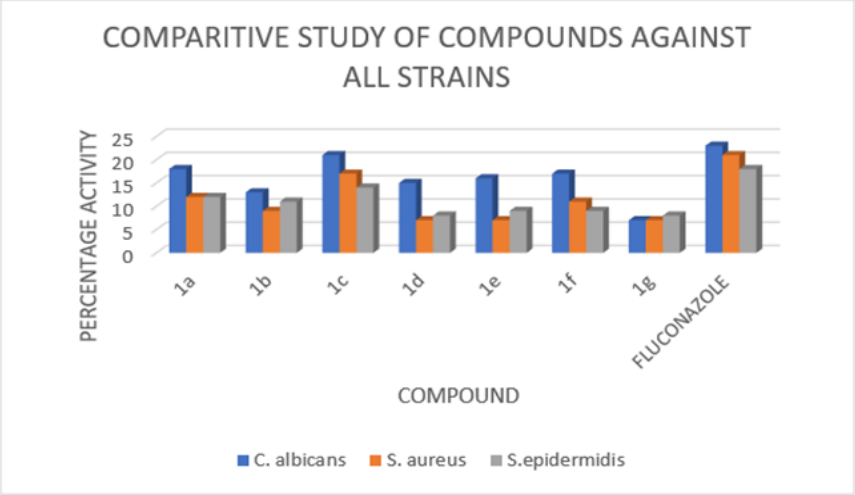
1-((Z)-2,5-dihydro-2-(Phenyl 4-hydroxyphenyl)-4-methylbenzo[b][1,4] thiazepin-3-yl) ethanone(1g). Yield 49%; mp 167

0C; MS MS [M + H+]: 387.49 g·mol⁻¹; C18H17NOS: found: C, 73.31; H, 5.70; N, 4.82; Calcd: C, 73.22; H, 5.76; N, 4.75; IR KBr (ν cm-1) 1708 (C]O), 1636 (C]C), OH (phenolic): broad peak around 3200–3600 cm⁻¹, Aromatic C–H stretch: 3050–3100 cm⁻¹, C=N (thiazepine ring): around 1600–1650 cm⁻¹, C–S stretch: 600–700 cm⁻¹, Aromatic C=C: 1500–1600 cm⁻¹; 1 H NMR (400 MHz, CDCl3), d (ppm): 6.70–7.28 (9H, m, –C6H4,–C6H5), 6.41 (1H, s, NH), 5.69 (1H, s, SCH), 2.59 (3H, s, –COCH3), 2.20 (3H, s, –CH3).

BIOLOGICAL ACTIVITY

New 1,5-Benzothiazepine Derivatives derivatives(D1-D4) were evaluated in-vitro for antimicrobial activity against C. albicans, S. aureus, S. epidermidis, using DMF as solvent by cup-plate method. Preparation of nutrient broth, subcultures, base layer medium, agar medium and peptone water was done as per the standard procedure. 5 mg of each test compound was dissolved in 5 ml of dimethylformamide (1000 µg/ml), which was used as sample solution. The cups were made by scooping out agar medium in a Petri dish, which were previously inoculated with the microorganisms. The solution of each test compound (0.1 ml) was added in the cups and petri dishes were incubated at 370C for 24 hrs. Fluconazole was used as reference drug and DMF as control. Zone of inhibition was measured in mm. The comparable zone of inhibition and antimicrobial activities with known chosen drug are reported in table no. 2. The graph of comparative study of the compounds against all strains is shown in fig.no.1.

Compd	X	R	Dose (µg/disc)		
			100	100	100
			Zone of inhibition (mm)		
			C. albicans	S. aureus	S. epidermidis
1a	H	p-NO2	18	12	12
1b	H	o-NO2	13	9	11
1c	H	p-Cl	21	17	14
1d	H	o-Cl	15	7	8
1e	H	p-CH3	16	7	9
1f	H	p-OH	17	11	9
1g	H	H	7	7	8
Fluconazole			23	21	18



RESULT AND DISCUSSION

A variety of Benzothiazepine derivatives have proved the efficiency and efficacy in combating various diseases and found to have good antibacterial. It has been observed that Benzothiazepine analogues incorporated with different nuclei have shown variety of pharmacological profiles. The Benzothiazepine moiety has been independently reported to hold potent antimicrobial activity. The outcomes of antimicrobial screening were encouraging. Further investigations with appropriate structural amendment of title compounds may result in therapeutically valuable conclusions for future researchers. The above results established the fact that synthesized Benzothiazepine derivatives could be a wealthy source of prospective entities in hunt of new generation for biologically active compounds and be worthwhile to explore the opportunity in this area by fusing differently substituted moieties which may result in better pharmacological activities.

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HOW TO CITE: Priyanka*, Neha Sahay, Deepak Kumar, Vineeta Rawat, Deval Harswrup, Priyanshu, Monika, Development Of 1,5-Benzothiazepine-Based Molecules with Potential Antimicrobial Activity, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 10, 475-482 https://doi.org/10.5281/zenodo.17277591