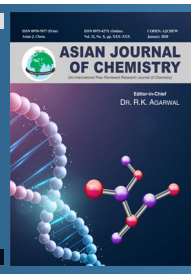
Asian Journal of Chemistry; Vol. 32, No. 10 (2020), 2601-2605

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2020.22861



An Efficient Synthesis of Thiophene Conjugated Benzothiazepines: *in vitro* Screening for their Antimicrobial Activity

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Received: 17 June 2020; *Accepted*: 15 July 2020; *Published online*: 25 September 2020; AJC-20076

A series of novel thiophene conjugated benzothiazepines were synthesized by the reaction of chalcones with 2-aminobenzenethiol in citrus juice medium. The new compounds were characterized by spectroscopic studies. Results of *in vitro* antimicrobial evaluation of newly synthesized compounds **5a-j** shows that the compounds **5a** and **5c** have excellent antimicrobial inhibition in the range of 12.5-25.0 µg/mL against bacteria *S. aureus, E. coli*, *P. aeruginosa* and fungi *A. niger*, *A. flavus* organisms comparable to ciprofloxacin and nystatin and therefore these compounds might acts as lead molecules as antimicrobial agents.

Keywords: 2-Aminobenzenethiol, Thiophene, Benzothiazepines, Chalcone, Antibacterial activity, Antifungal activity.

INTRODUCTION

An interest in design and synthesis of novel small molecules with antimicrobial effects is propelling research in the wider research community. Benzothiazepines constitute valuable structural units in the field of pharmaceutical research [1]. In particular, 1,5-benzothiazepine entity in compounds result with attractive biological profiles [2]. Such a large number of biological activities has provided impetus for chemists to invent a number of synthetic strategies to access 1,5-benzothiazepine scaffold. Chalcones or α,β-unsaturated carbonyl compounds or alkenes are regarded as useful intermediates for the five membered heterocycles such as pyrazoles [3], pyrrolines [4,5], thiadiazoles [6], isoxazoles [7,8], six-membered heterocycles like pyrimidines [9], seven membered heterocycles benzothiazepines [10], *etc*. For example, synthesized 1,5-benzothiazepines show drug likeness property using Lipinski's rule of five, by binding to active site amino acid and specific inhibition with MAP kinase protein [11]. More commonly employed methods off the several protocols being; an efficient onepot synthesis of polysubstituted benzothiazepines by ring expansion reaction under ultrasonic conditions [12], the reaction of cyclic sulfenamides with methylpropiolate catalyzed by pyridine, *via* a postulated allenolate intermediate [13], by the reactions of α,β-unsaturated keto esters and 2-aminobenzenethiol [14], acid catalyzed annulation reaction of chalcone with 2-aminobenzenethiol [15-18], the reaction of chalcones with 2-aminothiophenol in the presence of potassium dodecatungstocobaltate trihydrate (PDTC) as reusable heterogeneous catalyst [19]. Interesting report is that a base catalyzed ring enlargement reactions of monochloro-β-lactam-fused 2-aryl-1,3-benzothiazines in methyl alcohol with 2 equiv. of sodium methoxide yields 1,4-benzothiazepines *via* ring expansion, also led to the form indolo-1,4-benzothiazepines *via* rearrangement [20].

Literature reveals that small molecules with benzothiazepine core wide range of biological applications. For instance, benzofuran conjugated 1,5-benzothiazepines display a selective inhibition for butyrylcholinesterase (BChE) [21], antimicrobial [22], antifungal and antibacterial [23], antioxidant [24] activities. A library of 32-hydroxy-2,3-dihydrobenzothiazepines prepared through Wang resin as solid support show potential crown gall tumor and butyrylcholinesterase inhibition properties [25]. Coumarin fused benzothiazepines shows *in vitro* antioxidant activity against free radical form of ABTS and cytotoxic activity against U87 human glioma cells [26], Mannich bases derived from 2,3-dihydro-1,5-benzothiazepines show anticonvulsant [27] activity. Benzothiazepines also known to exhibit VRV-PL-8a and H^+/K^+ ATPase inhibitor [28],

benzodiazepine receptor affinity [29] properties. In present study, an efficient protocol for the synthesis of novel benzothiazepines by greener approach using citrus juice medium and their *in vitro* antimicrobial evaluation results is reported.

EXPERIMENTAL

Melting points were determined in an open capillary tube and are uncorrected. Elemental analysis was obtained on a Thermo-Finnigan Flash EA 1112 CHN analyzer. ^{1}H & ^{13}C NMR spectra were recorded on Agilent-NMR 400 MHz and 100 MHz spectrometer, respectively. Mass spectra were obtained on ESI/APCI-Hybrid Quadrupole, Synapt G2 HDMS ACQUITY UPLC model spectrometer.

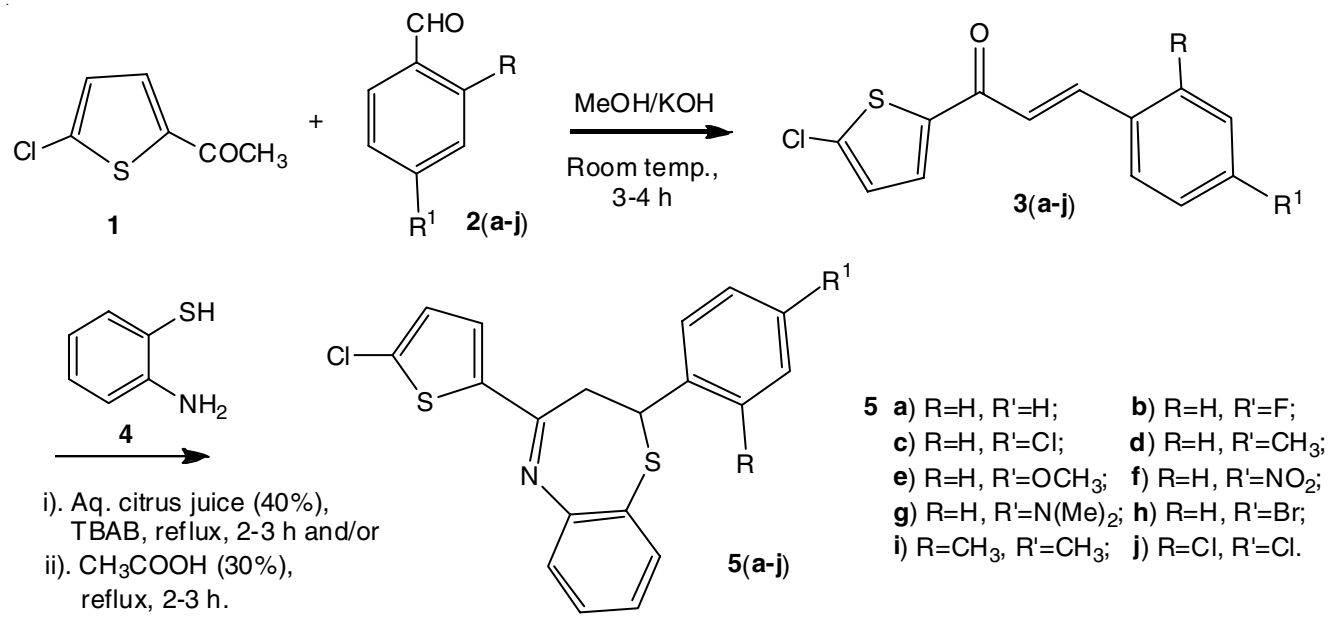
General procedure for the synthesis of thienyl-benzothizepines (5a-j): A series of new thienyl-benzothizepines (**5a-j**) was synthesized by the reaction of chalcones (**3a-j**) with 2-aminothiophenol (**4**) in citrus juice medium. Initially, the intermediate 3-aryl-1-(5-chlorothiophen-2-yl)prop-2-en-1-ones (**3a-j**) were synthesized *via* Claisen-Schmidt reaction of 5-chloro-2-acetylthiophene (**1**) with aromatic aldehydes **2a-j** in methyl alcohol [30-32]. The reaction of compounds **3a-j** with 2-aminothiophenol (**4**) in freshly prepared lemon juice [32] in the presence of tetrabutylammonium bromide (TBAB) under reflux conditions yielded benzothizepine analogues **5a-j** (**Scheme-I**). Alternatively, compounds were synthesized by conventional acetic acid medium of which produced 5-10% of higher yields comparable to citrus juice mediated method.

4-(5-Chlorothiophen-2-yl)-2-phenyl-2,3-dihydrobenzo-[*b*][1,4]thiazepine (5a): Yield: 78% yield, m.p. 136-137 ºC; IR (KBr disc, ν_{max}, cm^{-1}): 675, 1630, 2890; ^{1}H NMR ($CDCl_3$, δ ppm): 2.592 (dd, 1H, *J* = 5.8, 16.1 Hz, C_3-H_a), 2.926 (dd, 1H, *J* = 6.5, 12.0 Hz, C_3-H_b), 4.345 (dd, 1H, *J* = 6.3, 12.5 Hz, C_2-H), 6.904-6.946 (m, 2H, Ar-H), 7.180-7.355 (m, 9H, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 39.2 (1C, C-3), 51.4 (1C, C-2), 118.0 (1C), 125.0 (1C), 125.5 (1C), 125.9 (1C), 127.1 (1C), 127.5 (2C), 127.9 (2C), 128.5 (2C), 129.0 (1C), 130.4 (1C), 134.5 (1C), 136.1 (1C), 152.0 (1C), 164.8 (1C, C-4). MS (ES+) *m/z*: 355.02 (M+, ^{35}Cl, 100), 357.01 (M+2, ^{37}Cl, 32); Anal. calcd. (found) for $C_{19}H_{14}NS_2Cl$ (%): C, 64.12 (64.01); H, 3.97 (3.95); N, 3.94 (3.92).

4-(5-Chlorothiophen-2-yl)-2-(4-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]thiazepine (5b): Yield 75%, m.p. 108-110 ºC; IR (KBr disc, ν_{max}, cm^{-1}): 679, 1230, 1644, 2892; ^{1}H NMR ($CDCl_3$, δ ppm): 2.644 (dd, 1H, *J* = 6.8, 17.1 Hz, C_3-H_a), 2.980 (dd, 1H, *J* = 6.9, 13.0 Hz, C_3-H_b), 4.450 (dd, 1H, *J* = 7.3, 13.5 Hz, C_2-H), 6.966-6.995 (m, 2H, Ar-H), 7.165-7.392 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 39.7 (1C, C-3), 52.7 (1C, C-2), 116.2 (2C), 117.8 (1C), 125.0 (1C), 125.3 (1C), 125.8 (1C), 127.3 (1C), 128.1 (1C), 129.0 (2C), 130.2 (1C), 132.7 (1C), 136.3 (1C), 138.3 (1C), 160.6 (1C), 150.5 (1C), 165.5 (1C, C-4). MS (ES+) *m/z*: 373.01 (M+, ^{35}Cl, 100), 375.04 (M+2, ^{37}Cl, 31); Anal. calcd. (found) for $C_{19}H_{13}NS_2ClF$ (%): C, 61.04 (61.12); H, 3.50 (3.48); N, 3.75 (3.72).

2-(4-Chlorophenyl)-4-(5-chlorothiophen-2-yl)-2,3-dihydrobenzo[*b*][1,4]thiazepine (5c): Yield: 75%, m.p. 158-160 ºC; IR (KBr disc, ν_{max}, cm^{-1}): 685, 755, 1635, 2848; ^{1}H NMR ($CDCl_3$, δ ppm): 2.563 (dd, 1H, *J* = 6.3, 16.6 Hz, C_3-H_a), 2.955 (dd, 1H, *J* = 6.6, 12.8 Hz, C_3-H_b), 4.433 (dd, 1H, *J* = 6.7, 12.9 Hz, C_2-H), 6.947-6.973 (m, 2H, Ar-H), 7.172-7.450 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 40.7 (1C, C-3), 54.9 (1C, C-2), 117.3 (1C), 125.1 (1C), 125.4 (1C), 125.7 (1C), 127.6 (1C), 128.2 (2C), 128.6 (1C), 129.5 (2C), 130.4 (1C), 130.9 (1C), 134.1 (1C), 136.5 (1C), 142.4 (1C), 151.3 (1C), 165.3 (1C, C-4). MS (ES+) *m/z*: 389.04 (M+, 100), 391.05 (M+2, 63), 393.03 (M+4, 10); Anal. calcd. (found) for $C_{19}H_{13}NS_2Cl_2$ (%): C, 52.37 (58.32); H, 3.04 (3.34); N, 4.70 (4.57).

4-(5-Chlorothiophen-2-yl)-2-(*p*-tolyl)-2,3-dihydrobenzo[*b*][1,4]thiazepine (5d): Yield 73%, m.p. 113-114 ºC; IR (KBr disc, ν_{max}, cm^{-1}): 685, 1626, 2857; ^{1}H NMR ($CDCl_3$, δ ppm): 2.140 (s, 3H, CH_3), 2.601 (dd, 1H, *J* = 6.8, 16.7 Hz, C_3-H_a), 3.010 (dd, 1H, *J* = 6.3, 12.7 Hz, C_3-H_b), 4.336 (dd, 1H, *J* = 7.2, 13.6 Hz, C_2-H), 6.980-7.016 (m, 2H, Ar-H), 7.222-7.607



Scheme-I: Schematic diagram for the synthesis of thienyl-benzothiazepines, **5**(**a-j**)

(m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 21.2 (1C, CH_3), 42.9 (1C, C-3), 50.4 (1C, C-2), 116.8 (1C), 125.1 (1C), 125.4 (1C), 125.8 (1C), 126.6 (2C), 127.5 (1C), 128.3 (1C), 129.4 (2C), 130.9 (1C), 132.3 (1C), 136.7 (1C), 137.6 (1C), 141.0 (1C), 150.8 (1C), 161.0 (1C, C-4). MS (ES+) *m/z*: 369.06 (M+, ^{35}Cl, 100), 371.07 (M+2, ^{37}Cl, 31); Anal. calcd. (found) for $C_{20}H_{16}NS_2Cl$ (%): C, 64.94 (64.80); H, 4.36 (4.34); N, 3.79 (3.76).

4-(5-Chlorothiophen-2-yl)-2-(4-methoxyphenyl)-2,3-dihydrobenzo[*b*][1,4]thiazepine (5e): Yield 60%, m.p. 107-109 ºC; IR (KBr disc, ν_{max}, cm^{-1}): 690, 1623, 2877; ^{1}H NMR ($CDCl_3$, δ ppm): 2.612 (dd, 1H, *J* = 6.7, 16.5 Hz, C_3-H_a), 2.977 (dd, 1H, *J* = 6.8, 12.7 Hz, C_3-H_b), 3.840 (s, 3H, OCH_3), 4.303 (dd, 1H, *J* = 7.1, 12.4 Hz, C_2-H), 6.904-7.058 (m, 4H, Ar-H), 7.174-7.402 (m, 6H, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 43.0 (1C, C-3), 52.5 (1C, C-2), 55.4 (1C, OCH_3), 114.5 (2C), 116.4 (1C), 124.8 (1C), 125.2 (1C), 125.7 (1C), 126.6 (1C), 127.6 (1C), 128.3 (2C), 130.4 (1C), 134.0 (1C), 135.6 (1C), 137.7 (1C), 151.1 (1C), 154.8 (1C), 160.4 (1C, C-4). MS (ES+) *m/z*: 385.06 (M+, ^{35}Cl, 100), 387.05 (M+2, ^{37}Cl, 32); Anal. calcd. (found) for $C_{20}H_{16}NOS_2Cl$ (%):C, 62.25 (62.13); H, 4.18 (4.16); N, 3.63 (3.60).

4-(5-Chlorothiophen-2-yl)-2-(4-nitrophenyl)-2,3-dihydrobenzo[*b*][1,4]thiazepine (5f): Yield 61% (gummy mass); IR (KBr disc, ν_{max}, cm^{-1}): 688, 1546, 1640, 2862; ^{1}H NMR ($CDCl_3$, δ ppm): 2.561 (dd, 1H, *J* = 5.9, 17.4 Hz, C_3-H_a), 2.990 (dd, 1H, *J* = 6.9, 12.7 Hz, C_3-H_b), 4.380 (dd, 1H, *J* = 6.9, 13.0 Hz, C_2-H), 6.990-7.031 (m, 2H, Ar-H), 7.210-7.355 (m, 6H, Ar-H), 8.026-8.190 (m, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 38.0 (1C, C-3), 50.7 (1C, C-2), 118.5 (1C), 123.7 (2C), 125.3 (1C), 125.7 (1C), 126.1 (1C), 127.6 (1C), 127.9 (1C), 128.6 (2C), 130.9 (1C), 133.0 (1C), 136.8 (1C), 145.3 (1C), 147.1 (1C), 152.2 (1C), 163.6 (1C, C-4). MS (ES+) *m/z*: 400.08 (M+, ^{37}Cl, 100), 402.06 (M+2, ^{37}Cl, 34); Anal. calcd. (found) for $C_{19}H_{13}N_2O_2S_2Cl$ (%): C, 56.92 (56.80); H, 3.27 (3.25); N, 6.99 (6.96).

4-(4-(5-Chlorothiophen-2-yl)-2,3-dihydrobenzo[*b*]-[1,4]thiazepin-2-yl)-*N*,*N*-dimethyl aniline (5g): Yield 60%, m.p. 141-143 ºC; IR (KBr disc, ν_{max}, cm^{-1}): 700, 1112, 1652, 2899; ^{1}H NMR ($CDCl_3$, δ ppm): 2.698 (dd, 1H, *J* = 6.9, 17.7 Hz, C_3-H_a), 2.930 (dd, 1H, *J* = 7.8, 13.9 Hz, C_3-H_b), 3.012 (s, 6H, *N*-CH_3), 4.501 (dd, 1H, *J* = 7.5, 13.6 Hz, C_2-H), 6.720-6.912 (m, 4H, Ar-H), 7.144-7.420 (m, 6H, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 39.1 (1C, C-3), 40.6 (2C, *N*-CH_3), 52.9 (1C, C-2), 113.6 (2C), 117.6 (1C), 125.1 (1C), 125.4 (1C), 125.7 (1C), 127.1 (1C), 127.9 (2C), 128.4 (2C), 128.7 (1C), 133.1 (1C), 136.8 (1C), 140.3 (1C), 151.7 (1C), 163.5 (1C, C-4). MS (ES+) *m/z*: 398.02 (M+, ^{35}Cl, 100), 400.06 (M+2, ^{37}Cl, 34); Anal. calcd. (found) for $C_{21}H_{19}N_2S_2Cl$ (%): C, 63.22 (63.10); H, 4.80 (4.78); N, 7.02 (7.00).

2-(4-Bromophenyl)-4-(5-chlorothiophen-2-yl)-2,3-dihydrobenzo[*b*][1,4]thiazepine (5h): Yield 66% (gummy mass); IR (KBr disc, ν_{max}, cm^{-1}): 643, 712, 1666, 2890; ^{1}H NMR ($CDCl_3$, δ ppm): 2.575 (dd, 1H, *J* = 6.1, 16.3 Hz, C_3-H_a), 2.890 (dd, 1H, *J* = 6.9, 12.6 Hz, C_3-H_b), 4.501 (dd, 1H, *J* = 6.7, 12.1 Hz, C_2-H), 6.977-7.012 (m, 2H, Ar-H), 7.196-7.543 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 43.2 (1C, C-3), 52.7 (1C, C-2), 118.3 (1C), 120.2 (1C), 124.6 (1C), 125.1 (1C), 125.8 (1C), 126.8 (1C), 127.9 (1C), 129.0 (2C), 129.6 (1C), 130.9 (1C), 131.6 (2C), 134.5 (1C), 142.0 (1C), 150.1 (1C), 160.1 (1C, C-4). MS (ES+) *m/z*: 433.04 (M+, 100), 435.01 (98), 437.03 (32), 439.04 (2); Anal. calcd. (found) for $C_{19}H_{12}NS_2BrCl$ (%): C, 52.49; H, 3.01; N, 3.22; Found: C, 52.32; H, 3.00; N, 3.20.

4-(5-Chlorothiophen-2-yl)-2-(2,4-dimethylphenyl)-2,3-dihydrobenzo[*b*][1,4]thiazepine (5i): Yield 74%; m.p. 150-152 ºC; IR (KBr disc, ν_{max}, cm^{-1}): 708, 1633, 2875; ^{1}H NMR ($CDCl_3$, δ ppm): 2.282 (s, 6H, CH_3), 2.574 (dd, 1H, *J* = 6.1, 16.5 Hz, C_3-H_a), 2.950 (dd, 1H, *J* = 6.8, 12.3 Hz, C_3-H_b), 4.380 (dd, 1H, *J* = 6.9, 12.6 Hz, C_2-H), 6.971-7.106 (m, 4H, Ar-H), 7.166-7.388 (m, 6H, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 20.9 (2C, CH_3), 40.4 (1C, C-3), 51.9 (1C, C-2), 116.6 (1C), 125.0 (1C), 125.6 (1C), 125.9 (1C), 127.8 (1C), 128.1 (2C), 128.4 (2C), 128.8 (1C), 129.9 (1C), 132.9 (1C), 134.0 (1C), 136.2 (1C), 137.5 (1C), 150.5 (1C), 161.5 (1C, C-4). MS (ES+) *m/z*: 383.01 (M+,^{35}Cl, 100), 385.03 (M+2, ^{37}Cl, 34); Anal. calcd. (found) for $C_{21}H_{18}NS_2Cl$ (%): C, 65.69 (65.55); H, 4.73 (4.71); N, 3.65 (3.62).

4-(5-Chlorothiophen-2-yl)-2-(2,4-dichlorophenyl)-2,3-dihydrobenzo[*b*][1,4]thiazepine (5j): Yield 77%; m.p. 163-164 ºC; IR (KBr disc, ν_{max}, cm^{-1}): 686, 744, 1650, 2906; ^{1}H NMR ($CDCl_3$, δ ppm): 2.590 (dd, 1H, *J* = 5.7, 16.0 Hz, C_3-H_a), 2.998 (dd, 1H, *J=6.3, 11.8 Hz*, C_3-H_b), 4.311 (dd, 1H, *J=6.6, 12.2 Hz*, C_2-H), 6.914-6.952 (m, 2H, Ar-H), 7.100-7.467 (m, 7H, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 40.5 (1C, C-3), 53.7 (1C, C-2), 116.6 (1C), 124.7 (1C), 125.1 (1C), 125.6 (1C), 126.3 (1C), 127.0 (1C), 127.8 (1C), 128.1 (1C), 129.7 (1C), 130.1 (1C), 130.5 (1C), 133.0 (1C), 134.4 (1C), 136.0 (1C), 137.8 (1C), 151.1 (1C), 163.3 (1C, C-4). MS (ES+) *m/z*: 423.06 (M+, 100), 425.01 (95), 427.02 (30), 429.06 (3); Anal. calcd. (found) for $C_{19}H_{12}NS_2Cl_3$ (%): C, 53.72 (53.61); H, 2.85 (2.83); N, 3.30 (3.28).

Antimicrobial activity: The antimicrobial activities of compounds **5a-j** were determined as minimum inhibitory concentrations (MIC) by serial dilution method [33]. Bacterial pathogens *Escherichia coli* (MTCC 1687), *Bacillus subtilis* (MTCC 441) and *Staphylococcus aureus* (MTCC 737) and fungal stains *Aspergillus niger*, *Aspergillus flavus* and *Candida albicans* (MTCC 227) used for the study. Ciprofloxacin and nystatin were used as positive control against bacterial and fungal species, respectively. Dimethyl sulfoxide was used as solvent control. The experiments were carried out in triplicate; the results were taken as a mean ± standard deviation (SD).

RESULTS AND DISCUSSION

IR spectra of the synthesized compounds **5a-j** show stretching frequencies in the region; strong bands at 712-675 cm^{-1} for thienyl C-Cl, weak bands at 1666-1623 cm^{-1} for C=N, medium bands at 2906-2848 cm^{-1} for C-H functions. Other important stretching bands shown by compounds being; **5b** at 1230 cm^{-1} (C-F, *str.*), **5h** at 643 cm^{-1} (C-Br, *str.*), **5g** at 1112 cm^{-1} (C-N, *w*), **5f** at 1546 cm^{-1} (N-O, *str.*), **5c** and **5i** at 755 and 744 cm^{-1} (phenyl C-Cl, *str.*). The absorption bands at 1690-1660 cm^{-1} and 1640-1610 cm^{-1} due to α,β-unsaturated C=O and C=C of compounds **3a-j**; at 2600-2560, 1340-1270 and 3550-3410 cm^{-1} due to S-H, C-N and N-H groups of 2-aminobenezenethiol (**2**) were absent.

TABLE-1
ANTIMICROBIAL ACTIVITY OF SYNTHESIZED SERIES OF COMPOUNDS **5(a-j)**

Compound	Minimum inhibitory concentrations (MIC's, µg/mL)					
	S. aureus	*E. coli*	*P. aeruginosa*	*A. niger*	*A. flavus*	*C. albicans*
5a	12.5	12.5	12.5	25.0	25.0	50.0
5b	25.0	25.0	25.0	50.0	75.0	25.0
5c	12.5	12.5	12.5	25.0	25.0	50.0
5d	75.0	50.0	75.0	75.0	75.0	75.0
5e	100.0	75.0	62.5	100.0	75.0	125.0
5f	>200.0	>200.0	>200.0	>200.0	>200.0	>200.0
5g	50.0	50.0	25.0	>200.0	>200.0	>200.0
5h	>200.0	>200.0	>200.0	100.0	100.0	75.0
5i	50.0	100.0	50.0	75.0	75.0	100.0
5j	>200.0	>200.0	>200.0	100.0	100.0	75.0
Ciprofloxacin	25.0	25.0	12.5	–	–	–
Nystatin	–	–	–	50.0	50.0	25.0

*Values are the mean of three determinations (n = 3)

^{1}H NMR spectra shows a doublet of doublets at δ 2.561-2.698 (J = 5.7-6.9 Hz and 16.0-17.7 Hz) ppm for C_3-H_a; δ 2.890-3.010 (J = 6.3-7.8 Hz and 11.8-13.9 Hz) ppm for C_3-H_b; and δ 4.303-4.501 (J = 6.3-7.5 Hz and 12.1-13.6 Hz) ppm for C_2-H protons, respectively. These three doublets of doublets show that the C-3 atoms of benzothizepine ring are diastereotopic. ^{13}C NMR spectra shows the resonance signals for C-2, C-3 and C-4 carbons of benzothizepine rings at δ 50.4-54.9, 38.0-43.2 and 160.1-165.5 ppm, respectively. Besides these, all showed the signals for aromatic and substituent proton and carbons in the respective region. Further, the designed series of compounds shows base peak comparable to their molecular masses, and also halogen isotopic mass peaks in the mass spectra and comparable elemental analysis data.

Antimicrobial activity: The results show that amongst the synthesized compounds **5a-j**, compounds **5a** and **5c** exhibit excellent activities against *S. aureus* (12.5 µg/mL), *E. coli* (12.5 µg/mL), *P. aeruginosa* (12.5 µg/mL), *A. niger* (25.0 µg/mL), and *A. flavus* (25.0 µg/mL) species, but moderate activity against *C. albicans* (50.0 µg/mL) comparable to positive controls used. Compounds **5f**, **5g**, **5h** and **5j** were found to be inactive against the tested organisms having MIC's with (>200 µg/mL), which might be because of nitro, *N,N*-dimethylamino, bromo and trichloro substitutions. However, compound **5g** found moderately active against bacterium *S. aureus* (50.0 µg/mL), *E. coli* (50.0 µg/mL), *P. aeruginosa* (25.0 µg/mL); **5h** and **5j** against fungi *A. niger* (100.0 µg/mL) and *A. flavus* (100.0 µg/mL), *C. albicans* (75.0 µg/mL) species (Table-1).

Compound **5b** shows good activities against *S. aureus*, *E. coli*, *A. niger*, *C. albicans* and moderately active against *P. aeruginosa* and *A. flavus* concentrations. Compounds **5d**, **5e** and **5i** exhibited moderate activities with MIC's in the range against *S. aureus* and *E. coli*; *A. niger* and *A. flavus* show poor activities against *P. aeruginosa* and *C. albicans* comparable to respective positive controls (Table-1).

Conclusion

A series of novel thienyl-benzothiazepines were efficiently synthesized by the reaction of chalcones with 2-aminobenzenethiol in citrus juice medium and characterized. The results of *in vitro* antimicrobial evaluation of newly synthesized compounds **5a-j** shows that compounds **5a** and **5c** have excellent antimicrobial inhibition in the range of 12.5-25.0 µg/mL against bacteria *S. aureus, E. coli*, *P. aeruginosa*, and fungi *A. niger*, *A. flavus* organisms comparable to ciprofloxacin and nystatin and therefore, these compounds might acts as antimicrobial agents.

ACKNOWLEDGEMENTS

The authors are grateful to IOE Instrumentation facility, University of Mysore, Mysuru, India for providing the spectroscopic analysis.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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