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ARTICLE

Eco-Friendly Approach for the Synthesis of Thiophene Linked Benzothiazepines as Biocompatible Free Radical Scavengers

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ABSTRACT

A series of new thiophene tethered benzothiazepines (**5a-h**) were synthesized through citrus juice mediated (4+3) annulations of thienyl chalcones with 2-aminobenzenethiol in the presence of tetrabutylammonium bromide as phase transfer catalyst under reflux conditions. The synthesized compounds were characterized by spectroscopic and CHN analysis. To check the antioxidant potentials of the synthesized compounds, *in vitro* DPPH and hydroxyl radical scavenging assays were conducted. The results shows that amongst the series, compounds **5b** with (21.44-49.72%) and (16.88-42.60%); **5c** with (24.88-56.00%) and (22.33-53.12%); and **5h** with (22.80-47.10%) and (15.33-44.12%) excellent DPPH and hydroxyl radical potencies comparable with the respective standards used in the experiments.

KEYWORDS

Annulation, Antioxidant, Citrus, Chalcone, Phase transfer catalyst.

INTRODUCTION

Benzothiazepines constitute valuable structural units in the field of pharmaceutical research [1]. 1,4-Benzothiazepine derivatives are of considerable interest from both synthetic and pharmacological points of view. The chemistry of this family of compounds has been developed by several research groups with a number of attractive approaches [2]. Amongst the methods in the literature for the synthesis of benzothiazepines, a few to mention being; benzothiazepines were synthesized by the reaction of chalcones with 2-aminothiophenol in the presence of potassium dodecatungstocobaltate trihydrate (PDTC) as reusable heterogeneous catalyst [3]. The polysubstituted benzothiazepines by one pot synthesis involving intramolecular C-2 ring expansion reaction under ultrasonic conditions [4], the reaction of cyclic sulfenamides with methylpropiolate catalyzed by pyridine, *via* a postulated allenolate intermediate [5] by the reactions of α,β-unsaturated keto esters and 2-aminobenzenethiol [6], an acid catalyzed (4+3) annulation reaction of chalcone with 2-aminobenzenethiol [7-9]. Wang resin as solid supported [4+3] annulation of α,β-unsaturated ketones with aminothiophenol results with a potential crown gall tumor and butyrylcholinesterase inhibiting benzothiazepines [10].

Interestingly, a base catalyzed ring-enlargement reactions of monochloro-β-lactam-fused 2-aryl-1,3-benzothiazines in

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methyl alcohol with 2 equiv. of sodium methoxide yields 1,4-benzothiazepines *via* ring expansion, also led to form indolo-1,4-benzothiazepines *via* rearrangement [11]. H-Ferrierite zeolite an acidic catalyst mediated (4+3) annulations of chalcones with 2-aminothiophenol under solvent free conditions [12], A multicomponent reaction involving coumarin-3-carboxylic acid, 2-aminothiophenol and an isocyanate at room temperature [13], a one-pot reaction between 2-aminobenzo[*d*]isothiazol-3-one and alkyl propiolates in presence of triphenylphosphine [14] leads to benzothiazepines.

Reports on bio-potentiality of benzothiazepine shows that, these classes of compounds exhibit enormous applications. For instance, benzothiazepine display a selective inhibition for butyrylcholinesterase (BChE) [15], antipsychotic [16], anti-convulsant [17], MAP kinase protein inhibitor [18], antifungal and antibacterial [19,20], antimicrobial [21,22], antioxidant [23], anticonvulsant and acute toxicity [24] activities. Benzothiazepines also known to exhibit VRV-PL-8a and H^+/K^+ ATPase inhibitor [25], benzodiazepine receptor affinity [26], prevention of cardiac cell damage [27] properties. TIBO structural analogues of benzothiazepines show anti-HIV activity [28]. In this context, this study demonstrates an efficient greener protocol for the synthesis of novel benzothiazepines through (4+3) annulations of thienyl chalcones with 2-aminothiophenol in citrus juice medium and the results of their *in vitro* free radical scavenging activities.

EXPERIMENTAL

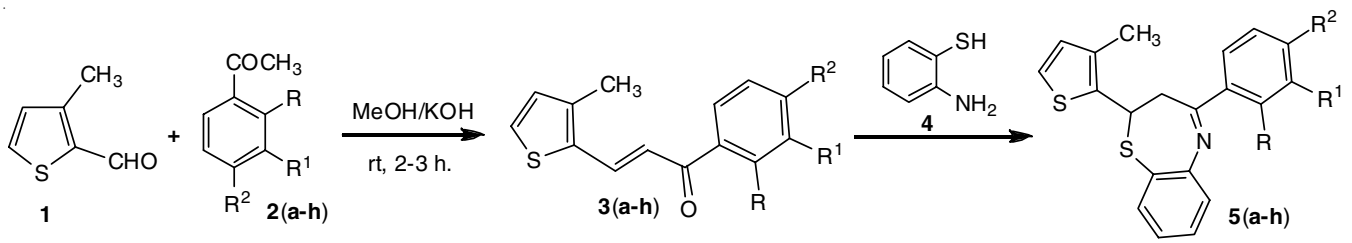
In search of new potent antioxidant small molecules, herein, we report, citrus juice mediated eco-friendly approach for the synthesis of thienyl-benzothiazepines and the results of their *in vitro* screening of their antioxidant activities. The demonstrated synthesis opens the gate for future efforts at synthesizing benzothiazepines. Initially, an intermediate 1-aryl-3-(3-methylthiophen-2-yl)prop-2-en-1-ones (**3a-h**) synthesized *via* Claisen-Schmidt reaction of 3-methylthiophene-2-carbaldehyde (**1**) with acetophenones (**2a-h**) in methyl alcohol according to previous report [29]. Then the reaction of chalcones (**3a-h**) and 2-aminobenzenethiol (**4**), in citrus extract medium in the presence of tetrabutylammonium bromide (TBAB) as phase transfer catalyst (PTC) under reflux conditions produced thienyl-benzothiazepines (**5a-h**). Alternatively, the target compounds were synthesized by conventional heating in acetic acid (40%) medium (**Scheme-I**).

Extraction of juice (**citrus extract**): Orange lemons bought from the locally grown lemon trees. Lemons were squeezed to urge the pulp juice (100 mL) into a beaker, diluted with water (50 mL) and then well agitated to a fine solution with the help of mechanical stirrer. The solution warmed for 30 min at 45-50 ºC and filtered to urge fine juice and diluted to 30% with water [30].

General procedure for synthesis of thiophene conjugated benzothiazepines (5a-h): To a solution of chalcones (**3a-h**) (5 mmol) and 2-aminobenzenethiol (**4**, 5 mmol) in freshly prepared lemon juice (30 mL, aq. 40%), tetrabutylammonium bromide (TBAB) (0.001 mmol) was added and then the mixture refluxed on a water bath for 2-3 h. After the completion, the reaction mixture was filtered and the filtrate quenched into crushed ice. The separated solids were filtered and washed successively with 5% $NaHCO_3$ and water; the crude solids crystallized from ethyl alcohol to get target molecules **5a-h** in moderate yields. Alternatively, the reaction was conducted with a solution mixture of chalcones (**3a-h**) (5 mmol) and 2-aminobenzenethiol (**4**, 5 mmol) in acetic acid (40%) under reflux conditions on a water bath for 2-3 h.

2-(3-Methylthiophen-2-yl)-4-phenyl-2,3-dihydrobenzo[*b*][1,4]thiazepine (5a): Obtained from 3-(3-methylthiophen-2-yl)-1-phenylprop-2-en-1-one (**3a**, 1.14g, 5 mmol) and 2-aminobenzenethiol (**4**, 0.68 g, 5 mmol) in 70% yield, m.p. 131-133 ºC; IR (KBr disc, cm^{-1}): 2905, 1644; ^{1}H NMR ($CDCl_3$, δ ppm): 2.296 (s, 3H, CH_3), 2.623 (dd, 1H, *J* = 6.5, 17.0 Hz, C_3-H_a), 2.818 (dd, 1H, *J* = 7.3, 13.2 Hz, C_3-H_b), 4.433 (dd, 1H, *J* = 7.6, 13.3 Hz, C_2-H), 6.990-7.202 (m, 4H, Ar-H), 7.242-7.710 (m, 7H, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 13.2 (CH_3), 40.7 (1C, C-3), 46.6 (1C, C-2), 116.5 (1C), 120.1 (1C), 123.0 (1C), 124.3 (1C), 126.2 (1C), 127.9 (2C), 128.6 (2C), 131.3 (1C), 132.0 (1C), 132.5 (1C), 135.2 (1C), 135.7 (1C), 137.5 (1C), 154.4 (1C), 161.5 (1C, C-4). MS (ES+) *m/z*: 335.04 (M+, 100); Anal. calcd. (found) % for $C_{20}H_{17}NS_2$ (%): C, 71.60 (71.48); H, 5.11 (5.09); N, 4.18 (4.15).

4-(4-Fluorophenyl)-2-(3-methylthiophen-2-yl)-2,3-dihydrobenzo[*b*][1,4]thiazepine (5b): Obtained from 1-(4-fluorophenyl)-3-(3-methylthiophen-2-yl)prop-2-en-1-one (**3b**, 1.23 g, 5 mmol) and 2-aminobenzenethiol (**4**, 0.68 g, 5 mmol) in 69% yield, m.p. 107-108 ºC; IR (KBr disc, cm^{-1}): 2866, 1627, 1218; ^{1}H NMR ($CDCl_3$, δ ppm): 2.305 (s, 3H, CH_3), 2.612 (dd, 1H, *J* = 6.7, 16.9 Hz, C_3-H_a), 2.816 (dd, 1H, *J* = 6.9, 13.6 Hz, C_3-H_b), 4.366 (dd, 1H, *J* = 7.7, 13.6 Hz, C_2-H), 7.062-7.185 (m, 4H, Ar-H), 7.378-7.740 (m, 6H, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 13.0 (CH_3), 40.2 (1C, C-3), 45.2 (1C, C-2), 114.9 (2C), 116.3 (1C), 120.5 (1C), 123.6 (1C), 124.6 (1C), 126.5 (1C), 128.8 (2C), 131.8 (1C), 132.9 (1C), 133.4 (1C),



5a) R=H, R^1=H, R^2=H; **5b**) R=H, R^1=H, R^2=F; **5c**) R=H, R^1=H, R^2=Cl; **5d**) R=H, R^1=H, R^2=CH_3;
5e) R=H, R^1=H, R^2=OCH_3; **5f**) R=OCH_3, R^1=H, R^2=H; **5g**) R=H, R^1=OCH_3, R^2=OCH_3; **5h**) R=H, R^1=-OCH_2O-= R^2

Reagents and conditions: (i) Citrus extract, TBAB, reflux, 2-3 h; (ii) CH_3COOH (40%), reflux, 2-3 h.

Scheme-I: Synthetic route of thiophene tethered benzothiazepines **5**(**a-h**)

135.4 (1C), 136.3 (1C), 154.2 (1C), 160.0 (1C), 161.4 (1C, C-4). MS (ES+) *m/z*: 353.08 (M+, 100); Anal. calcd. (found) % for $C_{20}H_{16}NS_2F$ (%): C, 67.96 (67.83); H, 4.56 (4.53); N, 3.96 (3.94).

4-(4-Chlorophenyl)-2-(3-methylthiophen-2-yl)-2,3-dihydrobenzo[*b*][1,4]thiazepine (5c): Obtained from 1-(4-chlorophenyl)-3-(3-methylthiophen-2-yl)prop-2-en-1-one (**3c**, 1.31 g, 5 mmol) and 2-aminobenzenethiol (**4**, 0.68 g, 5 mmol) in 71% yield, m.p. 148-150 °C; IR (KBr disc, cm^{-1}): 2891, 1650, 717; ^{1}H NMR ($CDCl_3$, δ ppm): 2.312 (s, 3H, CH_3), 2.646 (dd, 1H, *J* = 6.9, 17.1 Hz, C_3-H_a), 2.834 (dd, 1H, *J* = 7.6, 13.8 Hz, C_3-H_b), 4.456 (dd, 1H, *J* = 7.8, 13.8 Hz, C_2-H), 6.992-7.123 (m, 4H, Ar-H), 7.320-7.676 (m, 6H, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 13.1 (CH_3), 42.5 (1C, C-3), 47.1 (1C, C-2), 116.7 (1C), 120.5 (1C), 123.0 (1C), 124.4 (1C), 126.3 (1C), 128.1 (2C), 128.8 (2C), 132.0 (1C), 132.7 (1C), 135.1 (1C), 135.6 (1C), 136.2 (1C), 136.7 (1C), 154.9 (1C), 163.7 (1C, C-4). MS (ES+) *m/z*: 369.05 (M+, 100), 371.03 (M+2, 34); Anal. calcd. (found) % for $C_{20}H_{16}NS_2Cl$ (%): C, 64.94 (64.80); H, 4.36 (4.35); N, 3.79 (3.77).

2-(3-Methylthiophen-2-yl)-4-(*p*-tolyl)-2,3-dihydrobenzo[*b*][1,4]thiazepine (5d): Obtained from 3-(3-methylthiophen-2-yl)-1-(*p*-tolyl)prop-2-en-1-one (**3d**, 1.21g, 5 mmol) and 2-aminobenzenethiol (**4**, 0.68 g, 5 mmol) in 70% yield, m.p. 114-115 ºC; IR (KBr disc, cm^{-1}): 2885, 1643; ^{1}H NMR ($CDCl_3$, δ ppm): 2.267 (s, 3H, CH_3), 2.422 (s, 3H, CH_3), 2.597 (dd, 1H, *J* = 6.4, 16.9 Hz, C_3-H_a), 2.821 (dd, 1H, *J* = 7.0, 13.5 Hz, C_3-H_b), 4.433 (dd, 1H, *J* = 7.6, 13.3 Hz, C_2-H), 7.130-7.214 (m, 3H, Ar-H), 7.294-7.725 (m, 7H, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 13.8 (CH_3), 20.7 (CH_3), 40.5 (1C, C-3), 45.8 (1C, C-2), 117.5 (1C), 120.3 (1C), 123.4 (1C), 124.4 (1C), 126.5 (1C), 126.9 (2C), 128.9 (1C), 132.0 (1C), 132.4 (1C), 133.5 (1C), 135.7 (1C), 136.8 (1C), 139.1 (1C), 155.2 (1C), 161.9 (1C, C-4). MS (ES+) *m/z*: 349.07 (M+, 100); Anal. calcd. (found) % for $C_{21}H_{19}NS_2$ (%): C, 72.17 (72.04); H, 5.48 (5.45); N, 4.01 (4.00).

4-(4-Methoxyphenyl)-2-(3-methylthiophen-2-yl)-2,3-dihydrobenzo[*b*][1,4]thiazepine (5e): Obtained from 1-(4-methoxyphenyl)-3-(3-methylthiophen-2-yl)prop-2-en-1-one (**3e**, 1.29 g, 5 mmol) and 2-aminobenzenethiol (**4**, 0.68 g, 5 mmol) in 67% yield, m.p.: 135-136 ºC; IR (KBr disc, cm^{-1}): 2901, 1621; ^{1}H NMR ($CDCl_3$, δ ppm): 2.245 (s, 3H, CH_3), 2.585 (dd, 1H, *J* = 6.1, 16.0 Hz, C_3-H_a), 2.762 (dd, 1H, *J* = 6.5, 12.7 Hz, C_3-H_b), 3.850 (s, 3H, OCH_3), 4.322 (dd, 1H, *J* = 7.1, 13.0 Hz, C_2-H), 7.008-7.116 (m, 4H, Ar-H), 7.195-7.681 (m, 6H, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 13.7 (CH_3), 41.4 (1C, C-3), 47.0 (1C, C-2), 55.1 (OCH_3), 114.5 (2C), 117.5 (1C), 120.0 (1C), 123.3 (1C), 124.0 (1C), 126.2 (1C), 128.6 (2C), 129.3 (1C), 132.1 (1C), 132.6 (1C), 135.5 (1C), 136.7 (1C), 153.6 (1C), 160.2 (1C), 161.9 (1C, C-4). MS (ES+) *m/z*: 365.06 (M+, 100); Anal. calcd. (found) % for $C_{21}H_{19}NOS_2$ (%): C, 69.01 (68.89); H, 5.24 (5.21); N, 3.83 (3.82).

4-(2-Methoxyphenyl)-2-(3-methylthiophen-2-yl)-2,3-dihydrobenzo[*b*][1,4]thiazepine (5f): Obtained from 1-(2-methoxyphenyl)-3-(3-methylthiophen-2-yl)prop-2-en-1-one (**3f**, 1.29 g, 5 mmol) and 2-aminobenzenethiol (**4**, 0.68 g, 5 mmol) in 63% yield (gummy mass); IR (KBr disc, cm^{-1}): 2912, 1633; ^{1}H NMR ($CDCl_3$, δ ppm): 2.304 (s, 3H, CH_3), 2.610 (dd, 1H, *J* = 6.49, 16.7 Hz, C_3-H_a), 2.796 (dd, 1H, *J* = 7.2, 12.8 Hz, C_3-H_b), 3.844 (s, 3H, OCH_3), 4.390 (dd, 1H, *J* = 7.6, 13.7 Hz, C_2-H), 7.122-7.186 (m, 3H, Ar-H), 7.318-7.897 (m, 7H, Ar-H); Anal. calcd. (found) % for $C_{21}H_{19}NOS_2$ (*m.w.* 365) (%): C, 69.01 (68.92); H, 5.24 (5.22); N, 3.83 (3.83).

4-(3,4-Dimethoxyphenyl)-2-(3-methylthiophen-2-yl)-2,3-dihydrobenzo[*b*][1,4]thiazepine (5g): Obtained from 1-(3,4-dimethoxyphenyl)-3-(3-methylthiophen-2-yl)prop-2-en-1-one (**3g**, 1.44 g, 5 mmol) and 2-aminobenzenethiol (**4**, 0.68g, 5 mmol) in 58% yield, m.p.: 143-144 ºC; IR (KBr disc, cm^{-1}): 2854, 1642; ^{1}H NMR ($CDCl_3$, δ ppm): 2.290 (s, 3H, CH_3), 2.599 (dd, 1H, *J* = 6.6, 16.6 Hz, C_3-H_a), 2.784 (dd, 1H, *J* = 7.3, 13.4 Hz, C_3-H_b), 3.842 (s, 6H, OCH_3), 4.389 (dd, 1H, *J* = 7.4, 13.3 Hz, C_2-H), 6.984-7.133 (m, 4H, Ar-H), 7.214-7.693 (m, 5H, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 13.1 (CH_3), 41.5 (1C, C-3), 46.6 (1C, C-2), 55.4 (2C, OCH_3), 112.4 (2C), 115.8 (1C), 121.4 (1C), 122.1 (2C), 123.9 (1C), 124.0 (1C), 126.4 (1C), 127.5 (1C), 132.0 (1C), 133.2 (1C), 136.2 (1C), 136.7 (1C), 153.0 (1C), 155.2 (1C), 161.9 (1C, C-4). MS (ES+) *m/z*: 395.03 (M+, 100); Anal. calcd. (found) % for $C_{22}H_{21}NO_2S_2$ (%): C, 66.81 (66.70); H, 5.35 (5.32); N, 3.54 (3.52).

4-(Benzo[*d*][1,3]dioxol-5-yl)-2-(3-methylthiophen-2-yl)-2,3-dihydrobenzo[*b*][1,4]thiazepine (5h): Obtained from 1-(benzo[*d*][1,3]dioxol-5-yl)-3-(3-methylthiophen-2-yl)prop-2-en-1-one (**3h**, 1.36 g, 5 mmol) and 2-aminobenzenethiol (**4**, 0.68g, 5 mmol) in 65% yield, (gummy mass); IR (KBr disc, cm^{-1}): 2910, 1655; ^{1}H NMR ($CDCl_3$, δ ppm): 2.286 (s, 3H, CH_3), 2.597 (dd, 1H, *J* = 6.4, 16.2 Hz, C_3-H_a), 2.788 (dd, 1H, *J* = 6.9, 12.8 Hz, C_3-H_b), 4.355 (dd, 1H, *J* = 7.5, 13.7 Hz, C_2-H), 6.028 (s, 2H, OCH_2O), 6.986-7.110 (m, 4H, Ar-H), 7.206-7.553 (m, 5H, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 13.4 (CH_3), 40.8 (1C, C-3), 45.7 (1C, C-2), 101.6 (OCH_2O), 114.2 (1C), 116.6 (1C), 118.8 (1C), 120.8 (1C), 121.3 (1C), 123.1 (1C), 124.8 (1C), 126.7 (1C), 127.0 (1C), 132.3 (1C), 132.8 (1C), 135.1 (1C), 136.0 (1C), 147.9 (1C), 150.4 (1C), 154.8 (1C), 161.9 (1C, C-4). MS (ES+) *m/z*: 379.05 (M+, 100); Anal. calcd. (found) % for $C_{21}H_{17}NO_2S_2$ (%):C, 66.47 (66.33); H, 4.52 (4.50); N, 3.69 (3.66).

DPPH radical scavenging activity: The DPPH radical scavenging ability of the synthesized compounds **5a-h** was performed by Blois method [31]. The experiments were performed with different aliquots of test samples (25, 50, 75 and 100 μg mL^{-1}) in methanol and therefore, the absorbance was read against blank at 517 nm in an Elico SL 159 UV visible spectrophotometer. Experiments were conducted in triplicate, and the results are expressed as I% ± standard deviations.

Hydroxyl radical scavenging activity: Hydroxyl radical scavenging assay was performed by a known procedure [32]. Mixture of 0.1 mL of phosphate buffer; 0.2 mL of 2-deoxyribose, test compounds (25, 50, 75 and 100 μg/mL in methanol), 0.1 mL of H_2O_2 (10 mM), 0.1 mL of ascorbic acid (1 mM), 0.1 mL of EDTA and 0.01 mL of $FeCl_3$ (100 mM) was incubated at 37 ºC for 60 min. Thereafter, the reaction was terminated by adding 1mL of cold 2.8% trichloroacetic acid and the reaction product was measured by adding 1 mL of 1% thiobarbituric acid (1 g in 100 mL of 0.05 N NaOH) in boiling water for 15 min. The absorbance was measured at 535 nm. Butylated hydroxyanisole (BHA) was used as a positive control. The experiment was carried out in triplicate, results were expressed as I% ± standard deviations.

RESULTS AND DISCUSSION

The reaction of chalcones with hydrazines to yield pyrazole derivatives in good yields was achieved in the presence of protic solvents and/or Lewis acids. The acidic citrus extract facilitates the cyclocondensation reaction of chalcone and phenylhydrazine to substituted pyrazoles in good yields [30]. Here, we were successful in extending the utility of the citrus extract as protic medium for the cyclocondensation reaction involving chalcones and 2-aminothiophenol in the synthesis of benzothiazepines (**5a-h**), instead of the more conventional acid catalyzed (CH_3COOH or MeOH/HCl) conditions. Interestingly, the citrus extract mediated synthesis and traditional acid-catalyzed methods require almost the identical response time and resulted yields with ±3% deviation. IR spectra of compounds **5a-j** recorded on FTIR Agilent spectrophotometer using KBr pellet method show stretching frequencies; weak bands at 1655-1621 cm^{-1} for C=N, medium bands at 2912-2854 cm^{-1} for C-H functions. Other than these, compound **5b** show absorption band at 1218 cm^{-1} (C-F, *str.*), and **5c** at 717 cm^{-1} (C-Cl, *str.*). The ^1H NMR spectra of the compounds **5a-h** recorded on Agilent-NMR 400 MHz spectrometer confirms that the C-3 position of the newly benzothiazepines ring are diastereotopic. Spectra shows a doublet of doublets at δ 2.585-2.646 (J = 6.1-6.9 Hz and J = 16.0-17.1 Hz) ppm for C_3-H_a; at δ 2.762-2.834 (J = 6.5-7.6 Hz and J = 12.7-13.8 Hz) ppm for C_3-H_b; and δ 4.322-4.456 (J = 7.1-7.8 Hz and J = 13.0-13.8 Hz) ppm for C_2-H protons, respectively. The methyl protons of thiophene substitution show singlets in the region δ 2.245-2.312 ppm.

The ^{13}C NMR spectra of the compounds recorded on Agilent-NMR 100 MHz spectrometer shows the signals for C-3, C-2 and C-4 carbons of benzothiazepines ring at δ 40.2-42.5, 45.2-47.1 and 161.4-163.7 ppm, respectively. The aromatic and substituent protons and carbons show the signals in the respective region in their spectra. Mass spectra of the compounds recorded on ESI/APCI-Hybrid Quadrupole, Synapt G2 HDMS ACQUITY UPLC model spectrometer shows the base peaks comparable to their molecular masses, and CHN analysis obtained on a Thermo Finnigan Flash EA 1112 CHN analyzer show comparable data with the theoretical values.

DPPH radical scavenging activity: The DPPH radical scavenging activity of the synthesized compounds **5a-h** was performed according to reported procedure [31]. The absorbance was read against blank at 517 nm in an ELICO SL 159 UV-visible spectrophotometer. Experiments were carried out in triplicate and the results are expressed as I% ± standard deviations (Table-1).

Preliminary assessment result shows that off the series **5a-h**; compounds 4-(4-fluorophenyl)-2-(3-methylthiophen-2-yl)-2,3-dihydrobenzo[*b*][1,4]thiazepine (**5b** with DPPH radical scavenging abilities of (21.44-49.72%), 4-(4-chlorophenyl)-2-(3-methylthiophen-2-yl)-2,3-dihydrobenzo[*b*][1,4]thiazepine (**5c** with (24.88-56.00%) and 4-(benzo[*d*][1,3]dioxol-5-yl)-2-(3-methylthiophen-2-yl)-2,3-dihydrobenzo[*b*][1,4]-thiazepine (**5h** with (22.80-47.10%) exhibit excellent activities comparable to ascorbic acid. Compound 2-(3-methylthiophen-2-yl)-4-phenyl-2,3-dihydrobenzo[*b*][1,4]thiazepine (**5a** with a ability of (15.02-24.10%) show good activity. Compounds 2-(3-methylthiophen-2-yl)-4-(*p*-tolyl)-2,3-dihydrobenzo[*b*]-[1,4]thiazepine (**5d** with (13.99-19.80%), 4-(4-methoxyphenyl)-2-(3-methylthiophen-2-yl)-2,3-dihydrobenzo[*b*][1,4]thiazepine (**5e** with (11.24-17.47%) and 4-(2-methoxyphenyl)-2-(3-methylthiophen-2-yl)-2,3-dihydrobenzo[*b*][1,4]thiazepine (**5f** with (12.30-18.22%) shows moderate activities. However, 4-(3,4-dimethoxyphenyl)-2-(3-methylthiophen-2-yl)-2,3-dihydrobenzo[*b*][1,4]thiazepine (**5g** (7.02-13.08%) having two methoxy substitutions in the phenyl ring found less or inactive at the tested concentrations.

TABLE-1
DPPH RADICAL POTENTIAL OF COMPOUNDS **5(a-h)** AT DIFFERENT CONCENTRATIONS

Compd.	Radical scavenging activity (%)*			
	25 µg/mL	50 µg/mL	75 µg/mL	100 µg/mL
5a	15.02 ± 0.52	18.00 ± 0.71	22.06 ± 0.87	24.10 ± 0.97
5b	21.44 ± 0.65	31.83 ± 0.65	40.52 ± 1.22	49.72 ± 0.83
5c	24.88 ± 1.24	36.60 ± 1.50	45.20 ± 0.76	56.00 ± 1.13
5d	13.99 ± 1.05	15.55 ± 1.10	17.04 ± 0.92	19.80 ± 1.00
5e	11.24 ± 0.67	13.87 ± 0.53	15.18 ± 1.06	17.47 ± 1.00
5f	12.30 ± 0.85	14.12 ± 0.75	15.96 ± 0.48	18.22 ± 0.70
5g	7.02 ± 0.65	9.55 ± 0.90	11.78 ± 0.86	13.08 ± 0.66
5h	22.80 ± 1.30	31.98 ± 1.50	40.04 ± 0.94	47.10 ± 1.10
AA	15.10 ± 0.84	17.85 ± 0.84	21.90 ± 0.55	24.50 ± 0.30

*Values are mean (I%) (n = 3) ± SD; AA = Ascorbic acid (standard antioxidant)

Hydroxyl radical scavenging activity: The hydroxyl radical scavenging assay of the synthesized compounds **5a-h** was performed by a known procedure. The absorbance was read against blank at 535 nm in an ELICO SL 159 UV-Visible spectrophotometer. Experiments were carried out in triplicate and the results are expressed as I% ± standard deviations. Preliminary result reveals that compounds **5b** with hydroxyl radical trapping potencies of (16.88-42.60%), **5c** with (22.33-53.12%), and **5h** with (15.33-44.12%) shows excellent activities comparable to BHA. Compound **5a** shows good hydroxyl radical scavenging susceptibility with values of (12.20-31.10%). Moderate activities were observed with compound **5d** with (8.05-18.00%), **5e** with (8.01-18.05%), and **5f** with (8.00-17.66%); while compound **5g** with (5.75-12.00%) found inactive at the tested concentrations (Table-2). It was observed from the results that the DPPH and hydroxyl radical scavenging abilities were influenced by the presence of nature, position and number of substitutions, in the phenyl rings of the compounds of compounds **5a-h**.

TABLE-2
HYDROXYL RADICAL POTENTIALS OF COMPOUNDS **5(a-h)** AT DIFFERENT CONCENTRATIONS

Compd.	Radical scavenging activity (%)*			
	25 µg/mL	50 µg/mL	75 µg/mL	100 µg/mL
5a	12.20 ± 0.70	16.95 ± 0.85	24.88 ± 0.65	31.10 ± 1.00
5b	16.88 ± 1.00	23.42 ± 0.66	32.75 ± 0.81	42.60 ± 1.05
5c	22.33 ± 1.10	31.85 ± 1.22	40.55 ± 0.96	53.12 ± 0.85
5d	8.05 ± 0.55	13.20 ± 0.76	16.12 ± 1.00	18.00 ± 1.10
5e	8.01 ± 0.85	13.07 ± 0.90	16.10 ± 1.20	18.05 ± 0.75
5f	8.00 ± 0.93	12.52 ± 0.55	15.90 ± 1.05	17.66 ± 1.15
5g	5.75 ± 0.62	7.82 ± 0.82	10.22 ± 1.10	12.00 ± 0.96
5h	15.33 ± 1.00	24.56 ± 1.24	35.90 ± 0.95	44.12 ± 0.75
BHA	12.02 ± 0.05	17.95 ± 0.12	25.58 ± 0.20	32.03 ± 0.32

*Values are mean (I%) (n = 3) ± SD; BHA = Butylated hydroxy anisole (standard antioxidant).

Conclusion

A new greener protocol was developed for the synthesis of benzothiazepines *via* cycloaddition reaction of chalcones with 2-aminobenzenethiol in citrus juice medium. Results of *in vitro* antioxidant studies shows that the compounds **5b** with flurophenyl, **5c** with chlorophenyl and **5h** with 2,3-methylenedioxyphenyl substitutions on the benzothiazepine rings have excellent DPPH and hydroxyl radical scavenging potencies, and therefore these compounds might acts as lead molecules as antioxidant agents.

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