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Design, Synthesis, Structural Characterization and Antimicrobial Screening of Several Novel Benzothiophene Linked Thiazolidines

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A novel sequence of (19*E*)-(3-(benzo[*b*]thiophen-3-yl)-*N*′-((*Z*)-5-benzyliden-4-oxo-3-phenyl thiazolidin-2-ylidene)propanehydrazides **(6a-f)** was synthesized in moderate to good yields from the final intermediate, (*E*)-(3-(benzo[*b*]thiophen-3-yl)-*N*′-(4-oxo-3-phenylthiazolidin-2-ylidene)propane hydrazide **(5)**. In present work, 3-(benzo[*b*]thiophen-3-yl)propanoic acid (**1**) was selected as raw material and compounds such as 1-(benzo[*b*]thiophen-3-yl)pentan-3-one (**2**), 3-(benzo[*b*]thiophen-3-yl)propanehydrazide (**3**) and 1-(3-(benzo[*b*]-thiophen-3-yl)-propanoyl)-4-phenylsemicarbazide (**4**) were materialized as intermediates. All the isolated intermediates and target compounds have been characterized with the data obtained from different spectroscopic methods. The products were also examined against few microorganisms. According to the screening results, the tested targets performed satisfactory growth of inhibition.

Keywords: Benzothiophene, Thiazolidines, Hybrid molecules, Antimicrobial activity.

INTRODUCTION

Heteroaromatic compounds have an immensely prime part in the realization and expansion of novel drugs owing to their biological and medicinal properties namely antioxidant [1], anti-inflammatory [2], antibacterial [3], anti-parasitic [4], anti-cancer [5] and antifungal [6]. Furthermore, they are also working as strong L1210 cell selectors [7], topoisomerase inhibitors [8], potassium channel openers [9] and inhibitors of lipid peroxidation [10]. Benzothiophene was growingly acknowledged as a pharmacophore that provides superiority together with chemical and pharmacological stability, low intrinsic toxicity [11,12] and most predominantly rich chemistry which permitted medicinal chemists to prospected molecular heterogeneity in a speedy vogue. Benzothiophenes are familiar candidates belonging to the class of heteroaromatic and are employed as pharmaceuticals such as sertaconazole [13], zileuton [14] and raloxifene [15].

In recent years, benzothiophenes have typically been synthesized from the cyclization and Claisen rearrangement [16]. Thiazolidine is a class of analogue that has an abnormal interest because of various vital medical applications like antiparasite, antifungal, anticancer, antiviral, antibacterial and anti-tuberculosis activities [17-20]. The heterocyclic like thiazolidine has engrossed the peculiarity of researchers with their pharmacological activities [21-25]. Hence, keeping in mind above mentioned facts, the authors are interested to design, synthesize and explore the antimicrobial screening of some novel benzothiophene linked thiazolidines.

EXPERIMENTAL

All the chemicals and solvents were utilized as obtained from the different reputed commercial sources and were of highest purity. The melting points were measured with a Fisher-Johns meter in the open glass capillary technique and are uncorrected. The progress of the reaction and purity of analogues have been tracked from the TLC employing Merck precoated $60F_{254}$ sheets. IR spectra were recorded on a FTIR 5000 spectrometer. The PMR spectra were collected at ambient temperature using a Varian spectrometer at 300 MHz operating frequency using tetramethylsilane (TMS) as reference. The molecular weight of the compounds was identified with a VG-Micromass 7070H spectrometer with a 70 eV operating voltage.

Synthesis of 1-(benzo[*b*]thiophen-3-yl)pentan-3-one (2): A mixture of 3-(benzo[*b*]thiophen-3-yl)propanoic acid (**1**) (0.01 mol), ethyl alcohol (15 mL) and conc. H_2SO_4 (1 mL) was maintained under reflux temperature for 2 h. The crude obtained was filtered, washed in cold water, dried and recrystallized from ethanol to obtain 1-(benzo[*b*]thiophene-3-yl)pentan-3-one (**2**). Yield: 72%. m.p.: 102-104 ºC. IR (KBr, ν_{max}, cm^{-1}): 3042, 2962, 1741, 1560, 1127. PMR ($CDCl_3$, δ ppm, 300 MHz): 7.57-7.84 (4H, m, Ar-H), 5.25 (1H, s, CH), 3.24 (2H, q, *J* = 5.6 Hz, OCH_2), 2.89 (2H, t, *J* = 4.8 Hz, $COCH_2$), 2.17 (2H, t, *J* = 4.8 Hz, CH_2), 1.10 (3H, t, *J* = 5.6 Hz, CH_3). MS (*m/z*, M^++1) 235. Elemental analysis calcd. (found) % of $C_{13}H_{14}O_2S$: C, 66.64 (66.42); H, 6.02 (6.01); O, 13.66 (13.61); S, 13.68 (13.62).

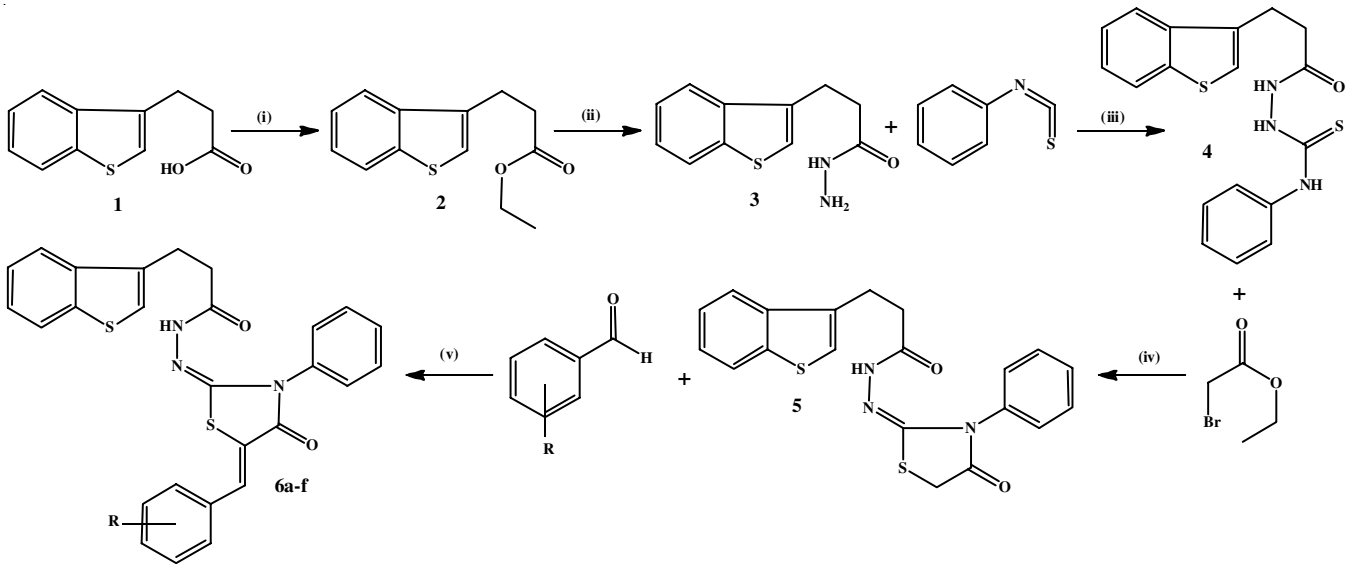
Synthesis of 3-(benzo[*b*]thiophen-3-yl)propane hydrazide (3): A liquid mxiture of compound **2** (0.01 mol), hydrazine hydrate (15 mL) in ethyl alcohol (20 mL) was refluxed for 3 h. The reaction solution was cooled and then poured into a cool water (20 mL) to get solid crude, filtered, dried and then recrystallized by using ethyl alcohol to obtain 3-(benzo[*b*]thiophen-3-yl)propanehydrazide (**3**) in pure form. Yield: 68%. m.p.: 107-109 ºC. IR (KBr, ν_{max}, cm^{-1}): 3325, 3125, 3042, 2971, 1632, 1574. PMR ($CDCl_3$, δ ppm, 300 MHz): 7.68 (1H, s, NH), 7.52-7.79 (4H, m, Ar-H), 5.31 (1H, s, CH), 4.24 (2H, s, NH_2), 3.70 (2H, t, *J* = 5.4 Hz, $COCH_2$), 2.45 (2H, t, *J* = 5.4 Hz, CH_2,). MS (*m/z*, M^++1) 221. Elemental analysis calcd. (found) % of $C_{11}H_{12}N_2OS$: C, 59.97 (58.87); H, 5.49 (5.48); N, 12.72 (12.69); O, 7.26 (7.25); S, 14.56 (14.53).

Synthesis of 1-(3-(benzo[*b*]thiophen-3-yl)propanoyl)-4-phenylsemicarbazide (4): A solution of compound **3** (0.01 mol), phenyl isothiocyanate (0.01 mol) and ethyl alcohol (15 mL) was maintained under reflux for 3 h. The resulting blend was dropped into ice-cold water and washed with water, filtered, dried and then recrystallized from ethyl alcohol to obtain 1-(3-(benzo[*b*]thiophen-3-yl)propanoyl)-4-phenylsemicarbazide (**4**) in pure form. Yield: 74%. m.p.: 120-122 ºC. IR (KBr, ν_{max}, cm^{-1}): 3325, 3275, 3069, 2960, 1647, 1593. PMR ($CDCl_3$, δ ppm, 300 MHz): 8.65 (1H, s, NH), 8.45 (1H, s, NH), 7.67 (1H, s, NH), 7.42-7.58 (9H, m, Ar-H), 5.12 (1H, s, CH), 3.22 (2H, t, *J* = 4.5 Hz, $COCH_2$), 2.86 (2H, t, *J* = 4.5 Hz, CH_2). MS (*m/z*, M^++1) 356. Elemental analysis calcd. (found) % of $C_{18}H_{17}N_3OS_2$: C, 60.82 (60.54); H, 4.82 (4.81); N, 11.82 (11.80); O, 4.50 (4.49); S, 18.04 (18.02).

Synthesis of (*E*)-(3-(benzo[*b*]thiophen-3-yl)-*N*′-(4-oxo-3-phenylthiazolidin-2-ylidene)propanehydrazide (5): A mixture of compound **4** (0.01 mol), sodium acetate (0.05 mol), ethyl bromoacetate (0.01 mol) and ethyl alcohol (15 mL) was maintained at reflux temperature for 6 h. The reaction mixture was filtered and the crude solid was recrystallized using ethyl alcohol to obtain pure (*E*)-(3-(benzo[*b*]thiophen-3-yl)-*N*′-(4-oxo-3-phenylthiazolidin-2-ylidene)propanehydrazide (**5**). Yield: 78%. m.p.: 132-134 ºC. IR (KBr, ν_{max}, cm^{-1}): 3321, 3047, 2968, 1672, 1655, 1523. PMR ($CDCl_3$, δ ppm, 300 MHz): 7.65 (1H, s, NH), 7.57-7.25 (9H, m, Ar-H), 5.15 (1H, s, CH), 3.47 (2H, t, *J* = 5.2 Hz, $COCH_2$), 3.14 (2H, s, CH_2), 2.82 (2H, t, *J* = 5.2 Hz, CH_2). MS (*m/z*, M^++1) 396. Elemental analysis calcd. (found) % of $C_{20}H_{17}N_3O_2S_2$: C, 60.74 (60.58); H, 4.33 (4.32); N, 10.62 (10.60); O, 8.09 (8.08); S, 16.22 (16.20).

Synthesis of (19*E*)-(3-(Benzo[*b*]thiophen-3-yl)-*N*′-((*Z*)-5-benzyliden-4-oxo-3-phenylthiazolidin-2-ylidene)propane hydrazides (6a-f): A homogeneous solution of compound **5** (0.01 mol), aryl aldehyde (0.01 mol), sodium ethoxide (0.02 mol) and ethyl alcohol (20 mL) was maintained at reflux temperature for 3-4 h. The resultant solution was poured into a ice-cool water, neutralized with HCl solution to get solid crude product and then recrystallized by using ethyl alcohol to yield (19*E*)-(3-(benzo[*b*]thiophen-3-yl)-*N*′-((*Z*)-5-benzyliden-4-oxo-3-phenylthiazolidin-2-ylidene)propane hydrazides (**6a-f**) (**Scheme-I**).

(19*E*)-(3-(Benzo[*b*]thiophen-3-yl)-*N*′-((*Z*)-5-benzyliden-4-oxo-3-phenylthiazolidin-2-ylidene) propane hydrazides



(i) C_2H_5OH, H_2SO_4, reflux, 2 h; (ii) $NH_2NH_2.H_2O$, C_2H_5OH, reflux, 3 h; (iii) C_2H_5OH, reflux, 3 h; (iv) NaOAc, C_2H_5OH, reflux, 3 h; (v) NaOEt, C_2H_5OH, reflux, 3-4 h; 6 (a) H, (b) 2-CH_3, (c) 2-Cl, (d) 2-Br, (e) 2-OH, (f) 2-NO_2

Scheme-I

(6a): Yield: 78%. m.p.: 105-107 ºC. IR (KBr, ν_{max}, cm^{-1}): 3340, 3028, 2932, 1656, 1548, 1438. PMR ($CDCl_3$, δ ppm, 300 MHz): 7.75 (1H, s, NH), 7.70-7.25 (14H, m, Ar-H), 5.12 (1H, s, CH), 4.89 (1H, s, CH), 3.12 (2H, t, *J* = 4.5 Hz, CH_2), 2.86 (2H, t, *J* = 4.5 Hz, CH_2). MS (*m/z*, M^++1) 484. Elemental analysis calcd. (found) % of $C_{27}H_{21}N_3O_2S_2$: C, 66.89 (67.06); H, 4.37 (4.38); N, 8.68 (8.69); O, 6.61 (6.62); S, 13.24 (13.26).

(19*E*)-(3-(Benzo[*b*]thiophen-3-yl)-*N*′-((*Z*)-5-benzyliden-4-oxo-3-(2-methylphenyl)thiazolidin-2-ylidene)propane hydrazides (6b): Yield: 70%. m.p.: 140-142 ºC. IR (KBr, ν_{max}, cm^{-1}): 3321, 3047, 2968, 1655, 1558, 1448. PMR ($CDCl_3$, δ ppm, 300 MHz): 7.85 (1H, s, NH), 7.68-7.36 (13H, m, Ar-H), 4.95 (1H, s, =CH), 4.85 (1H, s, CH), 3.10 (2H, t, *J* = 4.8 Hz, CH_2), 2.85 (2H, t, *J* = 4.8 Hz, CH_2), 2.23 (3H, s, CH_3). MS (*m/z*, M^++1) 498. Elemental analysis calcd. (found) % of $C_{28}H_{23}N_3O_2S_2$: C, 67.58 (67.39); H, 4.66 (4.65); N, 8.44 (8.43); O, 6.43 (6.42); S, 12.89 (12.87).

(19*E*)-(3-(Benzo[*b*]thiophen-3-yl)-*N*′-((*Z*)-5-benzyliden-4-oxo-3-(2-chlorophenyl)thiazolidin-2-ylidene)propane hydrazides (6c): Yield: 66%. m.p.: 118-120 ºC. IR (KBr, ν_{max}, cm^{-1}): 3318, 3038, 2940, 1665, 1562, 1448. PMR ($CDCl_3$, δ ppm, 300 MHz): 7.78 (1H, s, NH), 7.72-7.18 (13H, m, Ar-H), 5.08 (1H, s, CH), 4.81 (1H, s, CH), 3.20 (2H, t, *J* = 5.0 Hz, CH_2), 2.78 (2H, t, *J* = 5.0 Hz, CH_2). MS (*m/z*, M^++1) 518. Elemental analysis calcd. (found) % of $C_{27}H_{20}ClN_3O_2S_2$: C, 62.60 (62.54); H, 3.89 (3.88); Cl, 6.84 (6.83); N, 8.11 (8.10); O, 6.18 (6.17); S, 12.38 (12.36).

(19*E*)-(3-(Benzo[*b*]thiophen-3-yl)-*N*′-((*Z*)-5-benzyliden-4-oxo-3-(2-bromophenyl)thiazolidin-2-ylidene)propane hydrazides (6d): Yield: 72%. m.p.: 132-134 ºC. IR (KBr, ν_{max}, cm^{-1}): 3352, 3035, 2928, 1662, 1560, 1442. PMR ($CDCl_3$, δ ppm, 300 MHz): 7.72 (1H, s, NH), 7.68-7.30 (13H, m, Ar-H), 5.09 (1H, s, CH), 4.85 (1H, s, CH), 3.19 (2H, t, *J* = 5.2 Hz, CH_2), 2.82 (2H, t, *J* = 5.2 Hz, CH_2). MS (*m/z*, M^++1) 562. Elemental analysis calcd. (found) % of $C_{27}H_{20}BrN_3O_2S_2$: C, 57.65 (57.60); H, 3.58 (3.57); Br, 14.21 (14.19); N, 7.47 (7.46); O, 5.69 (5.68); S, 11.40 (11.38).

(19*E*)-(3-(Benzo[*b*]thiophen-3-yl)-*N*′-((*Z*)-5-benzyliden-4-oxo-3-(2-hydroxyphenyl)thiazolidin-2-ylidene)propane hydrazides (6e): Yield: 66%. m.p.: 142-144 ºC. IR (KBr, ν_{max}, cm^{-1}): 3352, 3036, 2942, 1662, 1536, 1448. PMR ($CDCl_3$, δ ppm, 300 MHz): 10.28 (1H, s, OH), 7.71 (1H, s, NH), 7.65-7.30 (13H, m, Ar-H), 5.21 (1H, s, CH), 4.75 (1H, s, CH), 3.25 (2H, t, *J* = 5.4 Hz, CH_2), 2.75 (2H, t, *J* = 5.4 Hz, CH_2). MS (*m/z*, M^++1) 500. Elemental analysis calcd. (found) % of $C_{27}H_{21}N_3O_3S_2$: C, 64.91 (64.81); H, 4.24 (4.23); N, 8.41 (8.40); O, 9.61 (9.60); S, 12.84 (12.82).

(19*E*)-(3-(Benzo[*b*]thiophen-3-yl)-*N*′-((*Z*)-5-benzyliden-4-oxo-3-(2-nitrophenyl)thiazolidin-2-ylidene)propane hydrazides (6f): Yield: 70%. m.p.: 132-134 ºC. IR (KBr, ν_{max}, cm^{-1}): 3320, 3036, 2935, 1652, 1539, 1442. PMR ($CDCl_3$, δ ppm, 300 MHz): 7.74-7.32 (13H, m, Ar-H), 7.68 (1H, s, NH), 5.06 (1H, s, CH), 4.78 (1H, s, CH), 3.25 (2H, t, *J* = 5.6 Hz, CH_2), 2.92 (2H, t, *J* = 5.6 Hz, CH_2). MS (*m/z*, M^++1) 529. Elemental analysis calcd. (found) % of $C_{27}H_{20}N_4O_4S_2$: C, 61.35 (61.20); H, 3.81 (3.80); N, 10.60 (10.59); O, 12.11 (12.10); S, 12.13 (12.11).

RESULTS AND DISCUSSION

In anticipation of the fascinating pharmacological properties in medicinal chemistry demonstrated by benzothiophene and thiazolidines, structural alteration of thiazolidines has attempted as part of our continuing research on the magnification of novel methodologies in heterocyclic synthesis. In the present work, the design and synthesis of some novel (19*E*)-(3-(benzo[*b*]thiophen-3-yl)-*N*′-((*Z*)-5-benzyliden-4-oxo-3-phenylthiazolidin-2-ylidene)propane hydrazides (**6a-f**) are reported. During the course of synthesis, the formation of some new intermediates was also observed. Additionally, the product molecules have been employed to evaluate their ability against some fungal organisms after established their chemical structures by various spectroscopic approaches like mass, NMR and IR.

The intermediate as shown in **Scheme-I**, 1-(benzo[*b*]thiophen-3-yl)pentan-3-one (**2**) through esterification was obtained by treating the starting material, 3-(benzo[*b*]thiophen-3-yl)-propanoic acid (**1**) with ethanol in existence of small proportion of sulphuric acid under reflux on water bath with constant stirring for 2 h. Compound **2** had the expected structure based on the spectral and elemental analysis data. The newly emerged groups like CH_3CH_2 and CO of ester in its IR spectrum was recognized at predicted absorption bands. The PMR spectrum disclosed related signals of CH_3-CH_2 group as triplet and quartet with equal coupling constant (*J* = 4.8 Hz) at absorption frequencies δ 3.36 ppm and δ 2.48 ppm. The mass spectrum showed the molecular ion peak at *m/z* 234, which was precisely equal to its molecular weight to conform to the chemical structure.

Subsequently, compound **2** was treated with hydrazine hydrate in ethyl alcohol under reflux temperature and stirred for 3 h to offer the next intermediate, 3-(benzo[*b*]thiophen-3-yl)propanehydrazide (**3**) in good yield. The authentication for the origination of intermediate **3** was acquired from its IR, NMR, mass spectra. The IR spectrum exhibited a band at 3335 cm^{-1}, while a sharp band at 3227 cm^{-1} validated presence of the NH_2NH group. Its PMR spectrum revealed a broad singlet at δ 4.45 ppm on account of NH_2 group and the NH proton resonated as singlet at δ 7.70 ppm. The molecular ion peak in its mass spectrum, is recorded at *m/z* 220 that was equal to molecular weight of compound **3**. Thus, it is concluded that ester group of compound **2** successfully transformed into acyl hydrazine of compound **3**.

Moreover, third intermediate, 1-(3-(benzo[*b*]thiophen-3-yl)propanoyl)-4-phenylsemicarbazide (**4**) was acquired by treating moiety **3** with phenyl isothiocyanate at reflux temperature for 3 h with steady stirring. The chemical structure of intermediate **4** has been confirmed from mass, NMR and IR spectroscopy techniques. The IR spectrum displayed broad stretching bands at 3318 and 3226 cm^{-1} due to N-H absorptions. The amide C=O vibrational band was observed at 1656 cm^{-1} that was not appear in precursor **3**. In the PMR spectrum, three signals of three NH groups are appeared as singlet at δ 8.65 ppm, 8.45 ppm and 7.62 ppm. A signal in δ 7.65-7.37 ppm multiplet for nine protons can be attributed to two aromatic rings. The C-H signal was found to be δ 5.12 ppm. Finally, the peak that was associated with its molecular weight is observed

TABLE-1
SCREENING (ANTIMICROBIAL) RESULTS PRODUCTS **6a-f**

Compound	Antibacterial activity				Antifungal activity	
	B. subtilis	*S. aureus*	*E. coli*	*P. aeuroginosa*	*C. albicans*	*A. niger*
6a	13	10	09	15	17	11
6b	11	12	12	12	10	10
6c	12	11	11	10	13	13
6d	20	24	23	17	18	20
6e	25	21	18	16	21	22
6f	19	20	18	22	15	19

at *m/z* 355 in the corresponding mass spectrum confirmed this conversion.

The final intermediate, (*E*)-(3-(benzo[*b*]thiophen-3-yl)-*N*′-(4-oxo-3-phenylthiazolidin-2-ylidene) propanehydrazide **(5)** was achieved from the cyclization of intermediate **4** with ethyl bromoacetate with sodium acetate in the presence of ethyl alcohol on reflux for 3 h. This compound's chemical structure was determined through MS, IR and PMR spectroscopic data. The vibrational band at 3328 cm^{-1} is given by N-H group. A couple of bands of both amide CO groups were identified at 1662 cm^{-1} and 1645 cm^{-1}. On the other hand, in the PMR spectrum, the NH group signal is located at δ 7.68 ppm as singlet and a new signal regarding δ 3.14 ppm for two protons as singlet corresponding to $COCH_2$, which is part of five membered ring as expected for the formation of compound **5**. The molecular weight of this compound is consistent with its molecular formula, which shows a molecular ion peak at *m/z* 395 in the mass spectrum.

Furthermore, title compounds, (19*E*)-(3-(benzo[*b*]thiophen-3-yl)-*N*′-((*Z*)-5-benzyliden-4-oxo-3-phenylthiazolidin-2-ylidene)propanehydrazides **(6a-f)**, have been achieved at satisfactory yields through condensation between compound **5** and various aromatic aldehydes in presence of sodium ethoxide in reflux ethanol for 3-4 h. The spectroscopic evidences of this series of compounds were in granting with expected structures. For instance, the PMR spectrum of product **6a**, exhibited a signal as singlet at δ 4.89 ppm, which is associate with CH group which is generated from the condensation. The fragment ion peak of same compound is located at 483 *m/z* related to its molecular weight. The rest of compounds of this class have been emerged with expected chemical structures. Finally, the entire products were utilized to judge the ability against some microorganisms.

Biological activities: All the newly synthesized compounds, (19*E*)-(3-(benzo-[*b*]thiophen-3-yl)-*N*′-((*Z*)-5-benzyliden-4-oxo-3-phenylthiazolidin-2-ylidene)propane hydrazides (**6a-f**) were employed to evaluate their *in vitro* antibacterial efficiency. The agar diffusion method was employed for this study towards both Gram-positive bacteria like *Staphylococcus aureus* and *Bacillus subtilis* and two Gram-negative bacteria namely *Pseudomonas aeuroginosa* and *Escherichia coli* utilizing DMSO solvent [26]. The antifungal study for the same targets was also examined with fungal organisms like *Aspergillus niger* and *Candida albicans* by employing Sabouraud dextrose agar channel. The efficiency of these molecules is measured in terms of diameters of zone of inhibition in millimetre. The results of the present study is compared with standard drugs like ciprofloxacin (antibacterial) and fluoconazole (antifungal) results.

The title compounds examined showed remarkable zone of inhibition, though the effectiveness of the compounds against different bacteria varied (Table-1). Thus, compound **6e** against *B. subtilis*, analogue **6d** against *E. coli* and *S. aureus*, while compound **6f** in case of *P. aeuroginosa* revealed the maximum antibacterial efficiency. Additionally, target molecule **6d** towards *B. subtilis*, title compounds **6f**, **6e** in the direction of *S. aureus* and final analogue **6e** in case of *E. coli* displayed increased antibacterial activity. The lowest activity was outlined from the derivatives **6b** in case of *P. aeuroginosa and B. subtilis* and **6c** with regard to *E. coli* and *S. aureus*. The remaining compounds performed medium to adequate activity. Compound **6e**, on the other hand, reveals strong efficacy against the studied fungal organisms. The minimum efficiency has been exhibited by compounds **6c** & **6b** towards *C. albicans* the same has been observed for compound **6c** too towards *A. niger*.

Conclusion

In conclusion, a new series of benzothiophene linked thiazolidines derivatives as a novel class of antimicrobial agents was synthesized and characterized. Among the synthesized (19*E*)-(3-(benzo[*b*]thiophen-3-yl)-N′-((*Z*)-5-benzyliden-4-oxo-3-phenylthiazolidin-2-ylidene)propane hydrazides (**6a-f**), Compound **6e** exhibited a good antibacterial activity against *B. subtilis*, while counterpart **6d** had shown a good antibacterial activity against *E. coli* and *S. aureus*. Additionally, compound **6f** had the highest antibacterial efficacy against *P. aeuroginosa*. In contrast, compound **6e** demonstrates the maximum significant activity against the studied fungal species.

CONFLICT OF INTEREST

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

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