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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antimicrobial activities of highly functionalised novel β-lactam and thiazolidine-grafted tetrahydrobenzothiophenes

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Abstract A series of biologically active *N*-(3-chloro-2-oxo-4-phenylazetidin-1-yl)/3-*N*-(4-oxo-2-arylthiazolidin-3-yl)-2-(methylsulfonamido)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamides derivatives have been synthesised in good yield. The structures of compounds have been established on the basis of IR, ^{1}H, ^{13}C NMR, and elemental analysis. The structure–activity relationships have been studied by screening of antimicrobial activity over a representative panel of bacterial and fungal strains using two-fold serial dilution method. All these synthesised compounds exhibited significant activities against all bacterial and fungal strains.

Keywords Azetidine · Thiazolidine · Antimicrobial screening · Tetrahydrobenzo[*b*]thiophene

Introduction

Azetiditine, the β-lactam, as a synthetic intermediate has been widely recognised in organic synthesis (Alcaide *et al.*, 2007; Alcaide and Almendros, 2004; Deshmukh *et al.*, 2004; Claudio *et al.*, 2001; Alcaide and Almentros, 2002) because it is an active moiety present in most widely used antibiotics such as penicillins (Brynaert and Brulé, 2008), cephalosporins (Alcaide *et al.*, 2008), carbapenems, nocardicins and monolactams, which are also used as chemotherapeutic agents for treating microbial diseases. (Halve *et al.*, 2007). Derivatives of β-lactam also act as antihyperglycemic (Jenny, 2006), antitumour (Veinberg *et al.*, 2004), anti-HIV (Sperka *et al.*, 2005), anti-inflammatory, analgesic agents (Saturnino *et al.*, 2000) and serine-dependent enzyme inhibitors (Clemente *et al.*, 2001). Hence, there has been renewed interest in the synthesis of such interesting β-lactam-based heterocycles with potential applications. Likewise, thiazolidinones also exhibit antimicrobial, anthelmintic, anti-HIV, antiviral, antiradiation, anticonvulsant and hypnotic activities (Rao *et al.*, 2004; Kucukguzel *et al.*, 2006).

Another heterocyclic system which has been the subject of extensive chemical and pharmacological investigations in recent times is the tetrahydrobenzothiophene (THBT). 2-Amino-3-ethoxycarbonyl-tetrahydrobenzothiophene core is a potent pharmacophore and compounds encompassing this structural core (e.g. tetrahydrothiophene pyrazine carboxylate analogues) are reported to be potent inhibitors of NS5B polymerase (Laporte *et al.*, 2006), an enzyme that is essential for the replication of hepatitis C (HCV) a positive single-stranded RNA virus which is responsible for high mortality due to chronic hepatitis, cirrosis and heptocellular carcinoma (Cohen, 1999). Further, structure–activity relationship (SAR) studies disclosed (Laporte *et al.*, 2006) that the presence of an acidic moiety such as acyl sulfonamide on 2-amino group of THBT increases the activity against HCV polymerase, while maintaining selectivity.

In view of antiviral properties associated with 2-amino-3-ethoxycarbonyl-tetrahydrobenzothiophene structural core and in continuation of our interest on antimicrobial properties of azetidin-2-ones and thiazolidin-4-ones incorporating coumarin core (Jeyachandran & Ramesh, 2009), we anticipated that THBT-grafted azetidinones and thiazolidinones

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might exhibit useful biological properties. With this objective, we have undertaken the synthesis of a series of hitherto unknown THBT-grafted azetidin-2-ones (**5a–j**) and thiazolidin-4-ones (**6a–j**) from 2-methanesulfonamido-2-ethoxycarbonyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene core. The attachment of methanesulfonyl moiety (mesyl) to 2-NH_2 function serves two purposes: (a) it acts as a versatile protecting group facilitating chemoselective reactions at the adjacent ethoxycarbonyl group for assembling azetidinone and thiazolidinone nuclei. (b) It also modulates the pharmacokinetic properties of synthesised compounds by altering their lipophilicity.

The synthetic plan for assembling THBT-grafted azetidinones and thiazolidinones is outlined in Scheme 1. As a preliminary study to assess the biological properties of THBT-grafted azetidinones/thiazolidinones, we have subjected **5a–j** and **6a–j** for antibacterial and antifungal screening (Table 1). The details pertaining to synthesis, characterisation, and antimicrobial evaluation of THBT-grafted azetidinones/thiazolidinones are presented in this paper.

Results and discussion

Reaction of ethyl 2-(methylsulfonamido)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (**2**), with hydrazine hydrate in boiling alcohol afforded *N*-(3-(hydrazinylcarbonyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)methanesulfonamide (**3**). Condensation of **3** with appropriate aromatic aldehydes yielded the corresponding Schiff bases **4a–j**, which on reaction with chloroacetyl chloride (TEA, DME) gave azetidinones **5a–j**, while similar reaction of **4a–j** with thioglycolic acid ($ZnCl_2$/DMF) afforded the thiazolidinones **6a–j** (Scheme 1). The intermediates and final products have been characterised by their spectroscopic data (IR, ^{1}H NMR and ^{13}C NMR.).

Compound **4a** (a representative example) was homogeneous on TLC and contained nitrogen and sulphur. The appearance of IR bands at 3410, 3271 and 1673 cm^{-1} suggested the presence of *NH*SO_2Me, –CO*NH* and amide (carbonyl) groups in it. In the ^{1}H NMR spectrum of **4a**, the upfield multiplet (4H) centred at δ 1.79–1.92 was assigned to the methylene protons of C-5 and C-6, while the downfield multiplet (4H) centred at δ 2.35 was ascribed to the methylene protons of C-4 and C-7. The three-proton singlet at δ 2.82 was due to methyl group of –$NHSO_2$Me, and the sharp low intensity signal at δ 4.19 integrating for one-proton was ascribed to the amino proton of –N*H*SO_2Me group. The sharp low intensity one-proton singlet in the aromatic region at δ 8.12 was assigned to *N*-benzylidene methine proton (N=C*H*Ph) and the far downfield sharp one-proton singlet that exchanged with D_2O was assigned to the proton of N*H*CO. The aromatic protons (5H) resonated as a complex multiplet in the region δ 7.38–7.72. The ^{13}C NMR spectrum of **4a** registered among other signals, a downfield carbon signal at δ 163.9 assignable to carbonyl carbon of CO–NH–N= unit. On the basis of comparitive spectroscopic data of **4a** with that of its precursor 3, **4a** has been formulated as *N*-(3-(2-benzylidenehydrazinylcarbonyl)-4,5,6,7-tetrahydrobenzo-[*b*]thiophen-2-yl)methanesulfonamide.

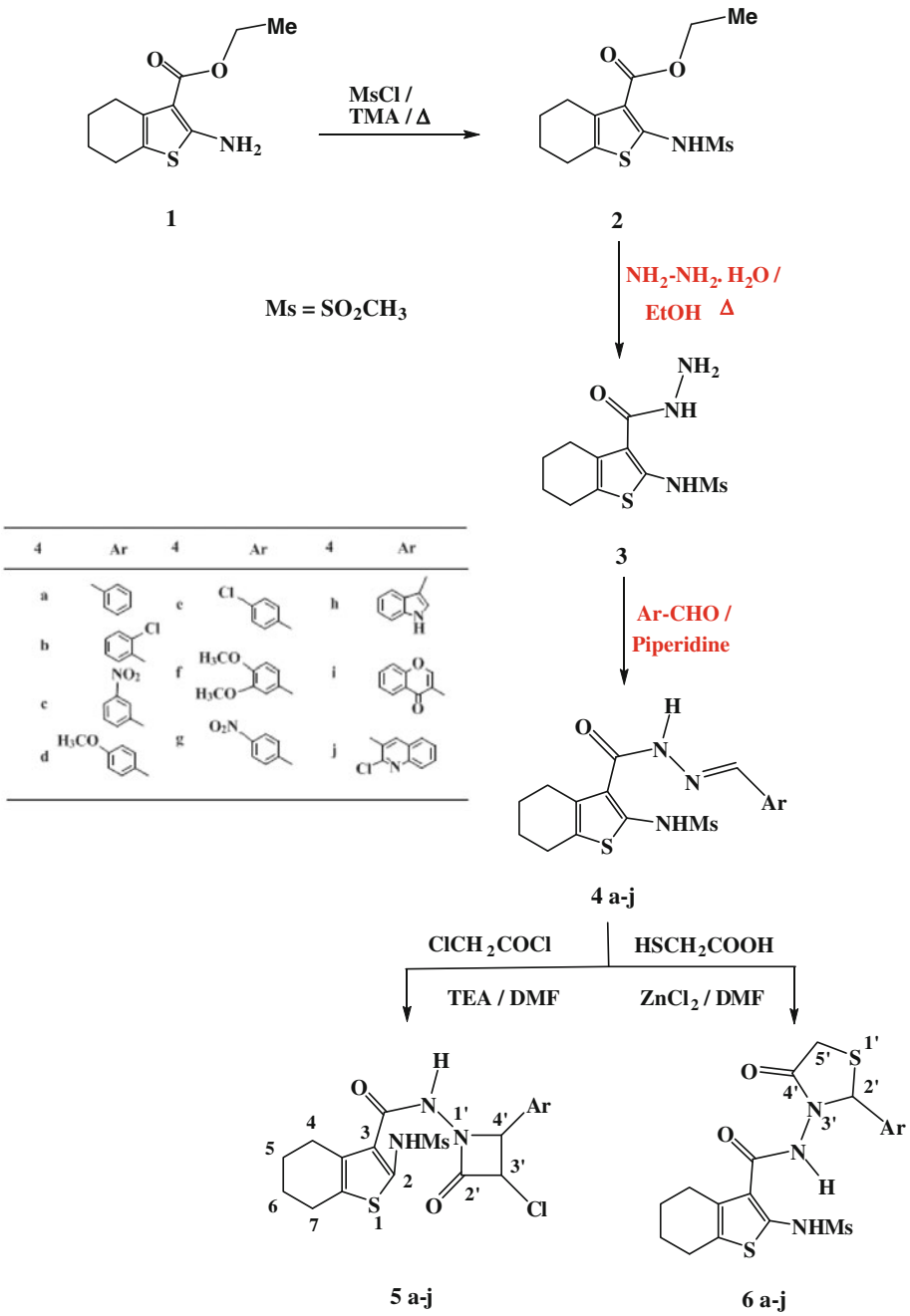
Compound **5a** was homogeneous on TLC and answered for nitrogen, sulphur and chlorine. In the IR spectrum of **5a**, a pair of bands of equal intensity at 3324 and 3262 cm^{-1} were ascribed to N–H stretching vibrations of CO–*NH* and *NH*SO_2Me groups. Of the pair of high intensity sharp bands, the one at 1745 cm^{-1} was assigned to CO

Table 1 Antibacterial activity of compounds **5(a–j)** and **6(a–j)**

Antibacterial activity of compounds
(zone of inhibition (diameter) mm at 10 μg/mL)

Compounds	**5a–j**		**6a–j**	
	B. subtilis ATCC 6631	*E. coli* ATCC 35218	*B. subtilis* ATCC 6631	*E. coli* ATCC 35218
a (Ph)	6	6	5	6
b (2-Cl)	7	7	6	11
c (3-NO_2)	7	10	7	7
d (4-OMe)	6	8	5	11
e (4-Cl)	8	9	8	8
f (3,4-diOMe)	7	8	6	7
g (4-NO_2)	8	10	8	10
h (3-indolyl)	7	9	6	10
i (3-chromonyl)	6	8	7	7
j (2-chloro-quinolin-3-yl)	6	6	6	8
Ciproflaxacin	9	12	9	12

Scheme 1 Synthetic route to title compounds **5a-j** and **6a-j**



group of the strained azetidine moiety, while the other band at 1685 cm^{-1} was ascribed to the C=O of carbamoyl unit. In the ^{1}H NMR spectrum of **5a**, the upfield three-proton singlet at δ 2.76 was due to methyl group of $–NHSO_2Me$ and the low intensity one-proton singlet at δ 4.11 was due to NH of SO_2Me. A pair of one-proton doublets ($J = 12.3$ Hz) at δ 4.73 and 5.16 were assigned to vicinal methine protons H-4 and H-3, respectively, of azetidinone moiety (Ar–*CH–CH–Cl*). The aromatic protons (5H) resonated as a complex multiplet in the region δ 6.98–7.65 and the downfield one-proton sharp singlet at δ 9.68 was ascribed to NH proton of –CONH–. The ^{13}C NMR spectrum of **5a** registered only two carbon signals at δ 163.1 and 168.4; the downfield signal δ 168.4 was assigned to the carbon of C=O of azetidinone, while the upfield signal δ 163.1 which was also present in the ^{13}C NMR spectrum of its precursor **4a**, was due to CO of –CONH.

The formation of THBT grafted intact azetidinone molecule was revealed from the molecular ion peak (*m/z* 453) and fragment ion peaks at *m/z* 376 ($M^{+\bullet}$–$C_6H_5^{\bullet}$, 65), *m/z* 321 ($M^{+\bullet}$–C_8H_4S, 100), 136 ($C_8H_8S^{+\bullet}$). The appearance of fragment ions at *m/z* 136 ($C_8H_8S^{+\bullet}$) and 165 ($C_9H_9S^{+}O$) confirmed the presence of THBT core in **5a** while the prominent fragment peaks at *m/z* 195 ($C_9H_8OClN_2^{+\bullet}$, 25), 181

($C_9H_8OClN^{+\bullet}$, 38) and 103 ($C_6H_5C{\equiv}N^{+\bullet}$) proved beyond doubt the formation of 3-chloro-4-phenylazetidin-2-one moiety in **5a**.

A comparison of spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR and DEPT-135) of **5a** with that of **4a** (Schiff base) proved the presence of azetidinone moiety in **5a** and established the structure of **5a** as *N*-(3-chloro-2-oxo-4-phenylazetidin-1-yl)-2-(methylsulfonamido)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide.

Compound **6a** was homogeneous on TLC and answered for nitrogen and sulphur. Its IR spectrum displayed a pair of sharp bands of equal intensity at 3320 and 3261 cm^{-1} due to N–H stretch (CO–*NH* and –*NH*SO_2Me) and a low intensity sharp band at 1740 cm^{-1} was assigned to CO of the thiazolidine ring and the strong band at 1672 cm^{-1} was ascribed to CO of –NHCO unit. The presence of SO_2 moiety of SO_2Me was revealed by the characteristic bands at 1345 (strong) and 1164 cm^{-1} (medium) (for antisymmetric and symmetric stretching vibrations of SO_2 group). The ^{1}H NMR spectrum of **6a** displayed in addition to signals due to protons of ring methylene (δ 1.52–1.79 and 2.62–2.78) and protons of methyl group of SO_2Me (δ 3.16), a pair of one-proton doublets ($J = 2.1$ Hz) at δ 4.81 and 5.08. From the magnitude of the coupling constant ($J = 2.1$ Hz), these signals were assigned to the geminal protons of C–5 of the thiazolidinone ring; such geminal coupling is generally observed only in rigid cyclopentanone ring system, where the geminal hydrogens are adjacent to CO group. (Williams and Fleming, 2001) The low intensity one-proton singlet at δ 6.28 was ascribed to *N*-benzylic methine proton (–NCHPh) of the thiazolidinone ring. The far downfield one-proton singlet at δ 9.64 was assigned to the proton of –NH–CO– unit and the aromatic protons appeared as a complex multiplet (5H) in the region δ 7.26–7.52. The ^{13}C NMR spectrum of **6a** registered six aliphatic carbon signals, which were grouped into four methylene, one methine and one methyl carbon based on DEPT experiment; of the two downfield carbon signals, the one at δ 168 was ascribed to carbon of CO of thiazolidinone ring, while the upfield signal at δ 164.8, which was also present in the ^{13}C NMR spectrum of its precursor **4a**, was assigned to the carbon of C=O of –NHCO– unit. A comparison of the spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR and DEPT) of **6a** with that of its precursor **4a** established the formation of the thiazolidinone ring in **6a**.

The formation of intact THBT grafted 4-oxo-2-phenylthiazolidine is evident by the appearance of parent ion peak of moderate intensity at *m/z* 451 (20) and fragment ion peaks at *m/z* 374 ($M^{+\bullet}$–$C_6H_5^{\bullet}$, 65) and 258 ($M^{+\bullet}$–193, 100). The presence of prominent fragmentation peak in the mass spectrum of 6a at *m/z* 178 ($C_9H_8NOS^{+\bullet}$, 50) and 193 ($C_9H_9N_2OS^+$, 45) proved beyond doubt the formation of 4-oxo-2-phenylthiazolidine moiety and the appearance of ion peaks at *m/z* 165 ($C_9H_9OS^+$) and 136 ($C_8H_8S^{+\bullet}$) are diagnostic of THBT core.

Thus based on the above evidence, **6a** has been formulated as 2-(methylsulfonamido)-*N*-(4-oxo-2-phenylthiazolidin-3-yl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide.

Antimicrobial activity

Antibacterial activity

The newly synthesised compounds **5a–j** and **6a–j** were evaluated for in vitro antibacterial activity against microorganisms, *Bacillus subtilis* ATCC 6631 *and Escherichia coli* ATCC 35218 which were obtained from Bose Clinical Laboratory, Madurai.

The agar diffusion method (Nogrady, 2004) was used for the determination of antibacterial activity of synthesised compounds **5a–j** and **6a–j** against microorganism listed above. The results of antibacterial activity of the synthesised β-lactam and thiazolidine compounds **5a–j** and **6a–j** against human bacterial pathogens with ciprofloxacin as reference control were presented in Table 1.

Antibacterial screening data (Table 1) revealed that all the tested compounds, **5a–j** and **6a–j** registered significant activity against both *Gram-positive* and *Gram-negative* bacteria at a concentration of 10 μg/mL. Compounds **5b** (2-Cl), **5c** (3-NO_2), **5e** (4-Cl), **5f** (3,4-diOMe), **5g** (4-NO_2) and **5h** (3-indolyl) showed significant activity in the order **5e** = **5g** > **5b** = **5c** = **5f** = **5h** against *B. subtilis*, whereas compounds **5b** (2-Cl), **5c** (3-NO_2), **5d** (4-OMe), **5e** (4-Cl), **5f** (3,4-diOMe), **5 g** (4-NO_2), **5 h** (3-indolyl), **5i** (3-chromonyl) registered significant inhibition in the order **5c** = **5g** > **5h** = **5e** > **5d** = **5f** = **5i** > **5b** > **5j** against *E. coli*.

Among compounds of **6a–j** series, **6e** (4-Cl), **6g** (4-NO_2), **6c** (3-NO_2), **6i** (3-chromonyl) showed high activity against *B. subtillis*, while **6b** (2-Cl), **6d** (4-OMe), **6g** (4-NO_2), **6h** (3-indolyl) and **6j** (2-chloroquinolin-2-yl) registered high activity against *E. coli*. Compounds **5/6e** and **5/6g** registered very high activity against both *Gram-positive* (*B. subtillis*) and *Gram-negative* (*E. coli*) organisms; the level of activity is almost comparable to that of the standard (ciprofloxacin) and they turn out to be the most potent antibacterial compounds of **5** and **6** series.

A scrutiny of results of antibacterial activity disclosed that *electron-withdrawing* groups of aryl moiety increased the antibacterial activity. The significant activity shown by compounds **5d** (4-OMe) and **6f** (3,4-diOMe) is understandable on the assumption that in the absence of direct conjugation between the aryl and β-lactam/thiazolidinone rings, the OMe group which has opposing −I and +M effects, can exert only −I effect and not +M effect.

Table 2 Antifungal activities of the compounds 5(**a**–**j**) and **6**(**a**–**j**)

Antifungal activities of the compounds zone of inhibition (diameter) mm at 10 μg/mL					
Compound **5**	*A. fumigatus* ATCC 28212	*A.niger* ATCC 16404	Compound **6**	*A. fumigatus* ATCC 28212	*A.niger* ATCC 16404
a (Ph)	4	13	**a** (Ph)	5	9
b (2-Cl)	6	15	**b** (2-Cl)	6	20
c (3-NO_2)	8	18	**c** (3-NO_2)	6	14
d (4-OMe)	6	12	**d** (4-OMe)	6	14
e (4-Cl)	5	13	**e** (4-Cl)	7	13
f (3,4-OMe)	9	21	**f** (3,4-OMe)	6	12
g (4-NO_2)	6	16	**g** (4-NO_2)	8	15
h (3-Indolyl)	7	12	**h** (3-Indolyl)	6	18
i (3-Chromonyl)	7	14	**i** (3-Chromonyl)	4	12
j (2-Chloro-quinolin-3-yl)	6	22	**j** (2-Chloro-quinolin-3-yl)	8	19
Ketoconazole (10 μg/mL)	10	25	Ketoconazole	10	25
Clotrimazole (10 μg/mL)	20 (2)	21	Clotrimazole (10 μg/mL)	20 (2)	21

Antifungal activity

Antifungal activity was assessed against fungal strains (*Aspergillus fumigatus* ATCC 28212 *and Aspergillus niger* ATCC 16404) by agar cup plate method in a modified manner (Kucukguzel *et al.*, 2006,). Ketoconazole (10 μg/mL) and Clotrimazole (10 μg/mL) were used as standard fungicides and the inhibitory activities were expressed as percentage inhibition (Table 2). All the tested compounds showed significant fungal inhibition at a concentration of 10 μg/mL.

Among tested compounds **5a–j**, **5c** (3-NO_2), and **5f** (3, 4-diOMe) exhibited high activity against fungal strains, *A. fumigatus* and *A. niger*, while compound **5j** (2-chloroquinolin-3-yl) registered very high activity; the level of activity was comparable to that of the standards (Ketoconazole and Clotrimazole).

Among 6 series of compounds, **6j** (2-chloroquinolin-3-yl) registered very high activity against both *A. fumigatus* and *A. niger*, while **6h** (3-indolyl) and **6b** (2-Cl) registered very high activity against *A. niger*; compounds **6g** (4-NO_2) and **6e** (4-Cl) showed high activity against *A. fumigatus*.

A close examination of the data generated on antifungal activity (Table 2) suggested that although *electron-withdrawing* groups of aryl moiety promoted the activity as in case of antibacterial activity, the trend is less clear-cut in case of antifungal activity exhibited by **5/6a–j**. It appears that the steric nature of the attached aryl/heterocyclic ring system controls the antifungal activity, although most *electron-withdrawing* groups are also sterically bulky.

SAR study of the substitution pattern of the aryl group towards antibacterial and antifungal activity has shown that *electron-withdrawing* groups have more impact on the activities.

Conclusions

This paper reports the synthesis and antimicrobial activity of novel and new THBT derivatives incorporating 2-azetidinone and 4-thiazolidinone moieties. All the synthesised compounds have been characterised beyond doubt by modern spectroscopic techniques. Most of the compounds registered excellent antimicrobial activity, and the level of activity of some of them is comparable to that of the standard. Our preliminary results on the antimicrobial properties of THBT grafted azetidinones and thiazolidinones are promising enough to explore their role as potential inhibitors of HCVB polymerase.

Experimental section

General

Melting points were determined on sulphuric acid bath in open capillaries and were uncorrected. Elemental analysis was carried out on Perkin-Elmer 2400 Series-II instrument. The IR spectra were recorded on 8400 S Shimadzu-FT IR Spectrophotometer and JASCO-410 IR Spectrophotometer using KBr pellets/chloroform. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 300 MHz instrument with TMS as internal standard.

In vitro antibacterial and antifungal activity

Discs measuring 6.25 mm in diameter were punched from Whatmann no. 1 filtre paper. Batches of 10 discs were dispensed to each screw-capped bottle and sterilised by dry

heat at 140 °C for an hour. The test compounds were prepared with a concentration of 0.5 % using methanol. The discs of each concentration were placed in triplicate in meat peptone agar medium and seeded with fresh bacterial culture separately and incubated at 37 °C for 24 h. The zone of inhibition was measured in millimetres using 10 μg/mL concentrations of synthesised compounds (**5a–j** and **6a–j**); methanol was used both as a solvent and as a control. No zone of inhibition was observed in control (i.e., in methanol).

Potato dextrose agar (PDA) was used as basal medium for test fungi. Glass Petri dishes were sterilised, and sterilised melted PDA medium (~45 °C) was poured at the rate of 15 mL into each petridish (90 mm). After solidification of the medium, small portions of the mycelium of each fungus were spread carefully over the centre of each PDA plate with the help of sterilised needles. Then, each fungus was transferred to a number of PDA plates, which were then incubated and ready for use after 5 days of incubation. Prepared discs of samples were placed gently on solidified agar plates, freshly seeded with the test organisms with sterile forceps.

A control disc was also placed on the test plates to compare the effect of the test samples and to nullify the effect of solvent, respectively. The plates were then kept in a refrigerator at 4 °C for 24 h, so that the materials had sufficient time to diffuse over a considerable area of the plates. After this process, the plates were incubated at 25 °C for 72 h. Methanol (0.5 %) was used as solvent to prepare desired solutions of the compounds initially and also to maintain proper control. The zone of inhibition was measured in millimetres at 10 μg/mL concentration of the synthesised compounds **5a–j** and **6a–j**; no zone of inhibition was observed in control (i.e. in methanol).

*Synthesis of ethyl 2-(methylsulfonamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**2**)*

To a mixture of cyclohexanone (0.01 mol), ethyl cyanoacetate (0.01 mol), and sulphur (0.01 mol) in ethanol (30 mL), diethylamine (0.01 mol) was added dropwise. The crystals of ethyl 2-amino-4,5,6,7-tetrahydrobenzo [*b*]thiophene-3-carboxylate **1** (Zeng *et al.*, 2010) that separated were filtered and crystallised from ethanol. A solution of **1** (0.01 mol) in triethylamine (10 mL) was treated with methanesulfonyl chloride (0.05 mol) and the reaction mixture was warmed on a water bath for 30 min and left overnight. The solid that separated on adding ice-water was filtered, dried and crystallised from aq. ethanol.

Mp 146–148 °C (aq. ethanol); yield: 72 %. IR (KBr, cm^{-1}): 3223 ($NHSO_2$ str.), 1730 (ester C=O), 1351 (SO_2Me unsym. str.), 1148 (SO_2Me sym. str.). ^{1}H NMR (300 MH_Z, $CDCl_3$): δ 1.36 (t, 3H, $-OCH_2CH_3$), 1.85–1.98 (m, 4H, H-5,6), 2.53–2.68 (m, 4H, H-4,7), 1.75–2.24 (m, 8H, 4× CH_2), 2.97 (s, 3H, SO_2Me), 4.16 (s, 1H, $NHSO_2Me$), 4.32 (q, 2H, $-OCH_2CH_3$). ^{13}C NMR (75 MH_Z, $CDCl_3$):14.72 (OCH_2CH_3), 23.5, 24.9, 39.8 (SO_2CH_3), 62.49 (OCH_2CH_3), 114.3, 128.3, 131.6, 139.0, 164.4 (C=O).

*Synthesis of N-[3-(hydrazinylcarbonyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl] methanesulfonamide, (**3**)*

To an alcoholic solution of **2** (0.01 mol), hydrazine hydrate (0.02 mol) was added and the reaction mixture was refluxed on a water bath for 3 h and the course of the reaction was monitored by TLC. The solid that separated on evaporation of the solvent was filtered, washed with water and dried; crystallisation from aq. ethanol gave *N*-[3-(hydrazinylcarbonyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl] methanesulfonamide **3**.

Mp 134–135 °C (aq. ethanol); yield: 76 %. IR (KBr,cm^{-1}): 3425 (CO*NH*NH_2 *str.*), 3394 (CONH*NH_2 str.*), 3218 (SO_2*NH str.*), 1683 (*CO*NH *str.*), 1357 (*SO_2*Me unsym. str.), 1154 (*SO_2*Me sym. str.). ^{1}H NMR (300 MH_Z, $CDCl_3$): δ 1.78–1.93 (m, 4H, *H-5,6*), 2.65–2.84 (m, 4H, *H-4,7*), 2.95 (s, 3H, SO_2CH_3), 4.14 (s, 1H, *NH*SO_2Me), 4.54 (s, 2H, NH*NH_2*), 9.68 (s, 1H, CO*NH*). ^{13}C NMR (75 MH_Z, $CDCl_3$): 22.4, 23.7, 24.9, 39.4 (SO_2CH_3), 115.3, 125.3, 134.6, 139.0, 164.4 (*CO*NH)

*General procedure for the synthesis of N-[3-(2-arylidenehydrazinyl-carbonyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl]methanesulfonamide (Schiff base), (**4a–j**)*

To an alcoholic solution of **3** (0.01 mol), appropriate aromatic aldehydes (0.01 mol) and 5 % NaOH (20 mL) were added and stirred at room temperature for about 3 h; then the reaction mixture was carefully neutralised with 1:1 HCl under ice cold condition, the solid **4a–j** that separated was filtered, washed with water, dried and crystallised from aq. alcohol.

4a: Mp 192–194 °C (aq. ethanol); yield: 71 %. IR (KBr, cm^{-1}): 3410 (CO*NH str.*), 3271 (*NH*SO_2Me *str.*), 1673 (*CO*NH *str.*), 1361 (*SO_2*Me unsym. str.), 1176 (*SO_2*Me sym. str.). ^{1}H NMR (300 MH_Z, $CDCl_3$): δ 1.79–1.92 (m, 4H, *CH_2-5,6*), 2.35–2.48 (m, 4H, *CH_2-4,7*), 2.82 (s, 3H, SO_2CH_3), 4.19 (s, 1H, *NH*SO_2Me), 7.32–7.72 (m, 5H, Ar*H*), 8.12 (s, 1H, N=*CH*Ph), 9.81 (s, 1H, CO*NH*). ^{13}C NMR (75 MH_Z, $CDCl_3$): 24.5, 25.1, 28.4, 40.7 (SO_2CH_3), 114.3, 124.6, 127.8, 132.3, 133.6, 136.2, 140.7, 147.8 (N=*CH*), 163.9 (*CO*NH). DEPT-135: δ 22.98 (↓), 24.49 (↓), 25.12 (↓), 39.55 (↑), 125.91 (↑), 127.28 (↑), 130.02 (↑), 146.12 (↑) (N=*CH*ϕ).

*General procedure for the synthesis of azetidinones (5**a**–**j**)*

To a solution of Schiff bases (0.01 mol) **4a**–**j** in DMF (10 mL), chloroacetyl chloride (0.01 mol) and triethylamine (0.05 mol) were added and the reaction mixture was stirred at room temperature for 24 h; after completion of the reaction (TLC) the reaction mixture was poured into cold water and the liberated compounds were extracted with chloroform. Evaporation of the solvent in vacuo afforded the corresponding azetidinones **5a**–**j**.

*N-(3-Chloro-2-oxo-4-phenylazetidin-1-yl)-2-(methylsulfonamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**5a**)* Mp 137 °C (aq. alcohol); Yield: 76 %. IR (KBr, cm^{-1}): 3324 (br. CO*NH*), 3262 (br. *NH*SO_2), 1745 (N*CO*CH), 1685 (*CO*NH), 1361 (*SO_2*Me unsym. str.), 1159 (*SO_2*Me sym. str.). ^{1}H NMR (300 MH_Z, $CDCl_3$): 1.76–1.93 (m, 4H, *CH*$_2$*-5,6*), 2.29–2.43 (m, 4H, *CH*$_2$*-4,7*), 2.76 (s, 3H, –SO_2CH_3), 4.11 (s, 1H, *NH*SO_2Me), 4.73 (d, 1H, $J = 12.3$ Hz, *CH*Ar), 5.16 (d, 1H, $J = 12.3$ Hz, *CH*Cl), 6.93–7.26 (m, 5H, Ph), 9.68 (s, 1H, *NH*). ^{13}C NMR (75 MH_Z, $CDCl_3$): 21.6, 25.5, 25.9, 40.7 (SO_2CH_3), 58.8, 62.9, 113.6, 123.1, 129.6, 131.9, 134.8, 142.3, 163.1 (–N*CO*CH), 168.4 (*CO*NH). DEPT-135: δ 21.44 (↓), 23.09 (↓), 30.49 (↓), 37.94 (↑) (SO_2CH_3), 52.90 (↑), 64.13 (↑), 126. 97 (↑), 128.91 (↑). Anal. Calcd for $C_{19}H_{20}ClN_3O_4S_2$: C, 50.27 %; H, 4.44 %. Found: C 50.28 %; H 4.40 %.

*N-[3-Chloro-2-(2-chlorophenyl)-4-oxoazetidin-1-yl]-2-(methylsulfonamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**5b**)* Mp 148 °C (aq. alcohol); Yield: 69 %. IR (KBr, cm^{-1}): 3320 (br. CO*NH*), 3265 (br. *NH*SO_2), 1749 (N*CO*CH), 1642 (*CO*NH), 1354 (*SO_2*Me unsym. str.), 1163 (*SO_2*Me sym. str.). ^{1}H NMR (300 MH_Z, $CDCl_3$): 1.62–1.79 (m, 4H, *CH*$_2$*-5,6*), 2.65–2.78 (m, 4H, *CH*$_2$*-4,7*), 2.79 (s, 3H, –SO_2CH_3), 4.08 (s, 1H, *NH*SO_2Me), 4.93 (d, 1H, $J =$ 9.6 Hz, *CH*Ar), 5.36 (d, 1H, $J = 9.6$ Hz, *CH*Cl), 7.20–7.80 (m, 4H, Ar*H*), 9.84 (s, 1H, CO*NH*). ^{13}C NMR (75 MH_Z, $CDCl_3$): 23.6, 25.4, 26.4, 40.7 (SO_2CH_3), 58.8, 62.9, 113.6, 124.1, 129.6, 131.9, 134.8, 142.3, 163.1 (–N*CO*CH), 168.4 (CO*NH*). DEPT-135: δ 23.41 (↓), 24.90 (↓), 28.05 (↓), 38.96 (↑) (SO_2CH_3), 59.65 (↑), 67.86 (↑), 124.92 (↑), 129.06 (↑). Anal. Calcd for $C_{19}H_{19}Cl_2N_3O_4S_2$: C, 46.72; H, 3.92. Found: C 46.70 %; H 3.95 %.

*N-[3-Chloro-2-(3-nitrophenyl)-4-oxoazetidin-1-yl]-2-(methylsulfonamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**5c**)* Mp 129 °C (methanol); Yield: 68 %.IR (KBr, cm^{-1}): 3346 (br. CO*NH*), 3268 (br. *NH*SO_2), 1741 (N*CO*CH), 1669 (*CO*NH), 1538 (*NO_2* asym. str.), 1324 (*NO_2* sym. str.,), 1345 (*SO_2*Me unsym. str.), 1159 (*SO_2*Me sym. str.). ^{1}H NMR (300 MH_Z, $CDCl_3$): 1.65–1.83 (m, 4H, *CH*$_2$*-5,6*), 2.71–2.82 (m, 4H, *CH*$_2$*-4,7*), 2.89 (s, 3H, –SO_2CH_3), 4.10 (s, 1H, *NH*SO_2Me), 4.88 (d, 1H, $J = 8.7$ Hz, *CH*Ar), 5.26 (d, 1H, $J = 8.7$ Hz, *CH*Cl), 7.16–7.45 (m, 4H, Ar*H*), 9.85 (s, 1H, CO*NH*). ^{13}C NMR (75 MH_Z, $CDCl_3$): 23.1, 23.8, 24.6, 39.4 (CO*CH*$_2$S), 62.3, 65.1, 114.9, 122.4, 125.2, 128.6, 133.8, 135.2, 139.6, 145.6, 163.8 (–N*CO*CH), 168.7 (CO*NH*). DEPT-135: δ 21.37 (↓), 25.32 (↓), 27.12 (↓), 40.38 (↑) (SO_2CH_3), 62.08 (↑), 67.48 (↑), 121.30 (↑), 127.32 (↑), 128.74 (↑). *Anal. Calcd for* $C_{19}H_{19}ClN_4O_6S_2$: C, 45.74; H, 3.84;. Found: C, 45.70; H, 3.85.

*N-[3-Chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]-2-(methylsulfonamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**5d**)* Viscous liquid; Yield: 65 %.IR (KBr, cm^{-1}): 3317 (br. CO*NH*), 3253 (br. *NH*SO_2), 1744 (N*CO*CH), 1672 (*CO*NH), 1350 (*SO_2*Me unsym. str.), 1154 (*SO_2*Me sym. str.).^{1}H NMR (300 MH_Z, $CDCl_3$): 1.58–1.72 (m, 4H, *CH*$_2$*-5,6*), 2.61–2.74 (m, 4H, *CH*$_2$*-4,7*), 2.77 (s, 3H, –SO_2CH_3), 3.96 (s, 3H, –O*CH*$_3$), 4.12 (s, 1H, *NH*SO_2Me), 5.06 (d, 1H, $J = 9.0$ Hz, *CH*Ar), 5.43 (d, 1H, $J = 9.0$ Hz, *CH*Cl), 6.94–7.27 (m, 4H, Ar*H*), 9.78 (s, 1H, *NH*). ^{13}C NMR (75 MH_Z, $CDCl_3$): 21.4, 24.6, 25.5, 39.8 (SO_2CH_3), 55.1 (*–OCH_3*), 62.4, 67.5, 112.9, 113.3, 122.7, 126.0, 135.6, 139.1, 157.3, 162.8 (–N*CO*CH), 164.7 (CO*NH*). DEPT-135: δ 21.24 (↓), 24.32 (↓), 25.71 (↓), 39.16 (↑) (SO_2CH_3), 55.74 (↑) (*–OCH_3*), 61.53 (↑), 66.38 (↑), 127.47 (↑), 129.38 (↑). Anal. Calcd for $C_{20}H_{22}ClN_3O_5S_2$: C, 49.63; H, 4.58. Found: C, 49.61; H, 4.60.

*N-[3-Chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl]-2-(methylsulfonamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**5e**)* Mp 122 °C (aq. alcohol); Yield: 69 %. IR (KBr, cm^{-1}): 3320 (br. CO*NH*), 3260 (br. *NH*SO_2Me), 1748 (N*CO*CH), 1684 (*CO*NH), 1353 (*SO_2*Me unsym. str.), 1159 (*SO_2*Me sym. str.). ^{1}H NMR (300 MH_Z, $CDCl_3$): 1.64–1.87 (m, 4H, *CH*$_2$*-5,6*), 2.64–2.86 (m, 4H, *CH*$_2$*-4,7*), 2.84 (s, 3H, –SO_2CH_3), 4.05 (s, 1H, *NH*SO_2Me), 4.90 (d, 1H, $J = 9.3$ Hz, *CH*Ar), 5.35 (d, 1H, $J = 9.3$ Hz, *CH*Cl), 7.42–7.76 (m, 4H, Ar*H*), 9.69 (s, 1H, *NH*). ^{13}C NMR (75 MH_Z, $CDCl_3$): 23.6, 25.5, 25.9, 40.2 (SO_2CH_3), 59.8, 62.9, 119.6, 121.1, 125.6, 131.9, 134.8, 142.3, 163.1 (–N*CO*CH), 168.4 (CO*NH*). DEPT-135: δ 23.44 (↓), 25.29 (↓), 26.49 (↓), 39.95 (↑) (SO_2CH_3), 59.40 (↑), 63.14 (↑), 118.97 (↑), 121.91 (↑). Anal. Calcd for $C_{19}H_{19}Cl_2N_3O_4S_2$: C, 46.72; H, 3.92. Found: C, 46.70; H, 3.94.

*N-[3-Chloro-2-(3,4-dimethoxyphenyl)-4-oxoazetidin-1-yl]-2-(methylsulfonamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**5f**)* Mp 126 °C (aq. alcohol); Yield: 72 %. IR (KBr, cm^{-1}): 3317 (br. CO*NH*), 3254 (br. *NH*SO_2Me), 1744 (N*CO*CH), 1667 (*CO*NH), 1343 (*SO_2*Me unsym. str.), 1146 (*SO_2*Me sym. str.). ^{1}H NMR (300 MH_Z, $CDCl_3$): 1.71–1.82 (m, 4H, *CH*$_2$*-5,6*), 2.69–2.78 (m, 4H,

CH$_2$-4,7), 2.93 (s, 3H, –SO$_2$*CH$_3$*), 3.97 (s, 6H, 2x*CH$_3$*), 4.10 (s, 1H, *NH*SO$_2$Me), 4.95 (d, 1H, $J = 9.0$ Hz, *CH*Ar), 5.26 (d, 1H, $J = 9.0$ Hz, *CH*Cl), 6.93–7.49 (m, 3H, Ar*H*), 9.87 (s, 1H, *NH*). ^{13}C NMR (75 MH$_Z$, CDCl$_3$): 22.4, 24.6, 25.5, 39.8 (SO$_2$*CH$_3$*), 55.1 (–*OCH$_3$*), 62.9, 65.5, 112.9, 119.3, 121.7, 126.0, 135.6, 139.1, 157.3, 162.8 (–N*CO*CH), 164.7 (CO*NH*). DEPT-135: δ 21.94 (↓), 24.19 (↓), 25.32 (↓), 39.58 (↑) (SO$_2$*CH$_3$*), 54.34 (↑) (–*OCH$_3$*), 63.17 (↑), 67.14 (↑), 118.63 (↑), 121.86 (↑). Anal. Calcd for $C_{21}H_{24}ClN_3O_6S_2$: C, 49.07; H, 4.71. Found: C, 49.04; H, 4.76.

*N-[3-Chloro-2-(4-nitrophenyl)-4-oxoazetidin-1-yl]-2-(methyl sulfonamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**5g**)* Mp 137–138 °C (aq. alcohol); Yield: 62 %. IR (KBr, cm^{-1}): 3322 br. CO*NH*), 3256 (br. *NH*SO$_2$Me), 1756 (N*CO*CH), 1680 (*CO*NH), 1359 (*SO$_2$* Me unsym. str.), 1159 (*SO$_2$*Me sym. str.). ^{1}H NMR (300 MH$_Z$, CDCl$_3$): 1.71–1.81 (m, 4H, *CH$_2$-5,6*), 2.67–2.85 (m, 4H, *CH$_2$-4,7*), 2.96 (s, 3H, -SO$_2$*CH$_3$*), 4.10 (s, 1H, *NH*SO$_2$Me), 4.95 (d, 1H, $J = 8.4$ Hz, *CH*Ar), 5.38 (d, 1H, $J = 8.4$ Hz, *CH*Cl), 7.41–8.28 (m, 4H, Ar*H*), 9.79 (s, 1H, CO*NH*). ^{13}C NMR (75 MH$_Z$, CDCl$_3$): 23.4, 25.9, 26.3, 40.2 (SO$_2$*CH$_3$*), 62.3, 65.9, 116.7, 117.3, 120.7, 124.3, 129.4, 134.2, 135.7, 139.7, 149.3, 160.1 (–N*CO*CH), 166.7 (CO*NH*).DEPT-135: δ 23.26 (↓), 23.45 (↓), 31.73 (↓), 36.49 (↑) (SO$_2$*CH$_3$*), 62.53 (↑), 66.31 (↑), 127.62 (↑), 128.53 (↑). Anal. Calcd for $C_{19}H_{19}ClN_4O_6S_2$: C, 45.74; H, 3.84;. Found: C, 45.76; H, 3.86.

*N-[3-Chloro-2-(indol-3-yl)-4-oxoazetidin-1-yl]-2-(methyl sulfonamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**5h**)* Mp 152 °C (aq. alcohol); Yield: 68 %. IR (KBr, cm^{-1}): 3317 (br. CO*NH*), 3253 (br. *NH*SO$_2$Me), 1744 (N*CO*CH), 1665 (*CO*NH), 3329 (–*NH* of *indol-3-yl*), 1350 (*SO$_2$*Me unsym. str.), 1159 (*SO$_2$*Me sym. str.). ^{1}H NMR (300 MH$_Z$, CDCl$_3$): 1.61–1.77 (m, 4H, *CH$_2$-5,6*), 2.64–2.82 (m, 4H, *CH$_2$-4,7*), 2.94 (s, 3H, –SO$_2$*CH$_3$*), 4.05 (s, 1H, *NH*SO$_2$Me), 5.14 (d, 1H, $J = 9.3$ Hz, *CH*Ar), 5.49 (d, 1H, $J = 9.3$ Hz, *CH*Cl), 7.10–7.73 (m, 5H, Ar*H*), 9.62 (s, 1H, *NH*), 10.45 (s, 1H, *–NH of indol-3-yl*). ^{13}C NMR (75 MH$_Z$, CDCl$_3$): 21.4, 25.6, 26.5, 39.8 (SO$_2$*CH$_3$*), 58.1, 67.5, 112.9, 113.3, 121.7, 123.0, 126.7, 130.3, 133.6, 139.1, 157.3, 162.8 (–N*CO*CH), 164.5 (CO*NH*). DEPT-135: 23.41 (↓), 24.90 (↓), 25.05 (↓), 39.68 (↑) (SO$_2$*CH$_3$*), 59.65 (↑), 67.86 (↑), 127.92 (↑), 129.06 (↑).

*N-[3-Chloro-2-(4-oxo-4H-chromen-2-yl)-4-oxoazetidin-1-yl] -2-(methylsulfonamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**5i**)* Mp 139 °C (aq. alcohol), Yield: 74 %. IR (KBr, cm^{-1}): 3321(br. CO*NH*), 3258 (br. *NH*SO$_2$Me), 1760 (N*CO*CH), 1742 (*CO* of chromone), 1662 (*CO*NH), 1352 (*SO$_2$*Me unsym. str.), 1159 (*SO$_2$*Me sym. str.). ^{1}H NMR (300 MH$_Z$, CDCl$_3$): 1.52–1.76 (m, 4H, *CH$_2$-5,6*), 2.67–2.80 (m, 4H, *CH$_2$-4,7*), 2.87 (s, 3H, –SO$_2$*CH$_3$*), 4.09 (s, 1H, *NH*SO$_2$Me), 4.91 (d, 1H, $J = 8.7$ Hz, *CH*Ar), 5.36 (d, 1H, $J = 8.7$ Hz, *CH*Cl), 7.14–8.25 (m, 5H, Ar*H*), 9.87 (s, 1H, *NH*). ^{13}C NMR (75 MH$_Z$, CDCl$_3$): 23.4, 25.9, 27.9, 41.8 (SO$_2$*CH$_3$*), 62.3, 65.9, 116.7, 117.3, 120.7, 124.2, 129.4, 134.2, 135.7, 139.7, 149.3, 160.1(–N*CO*CH), 161.7 (CO*NH*). Anal. Calcd for $C_{22}H_{20}ClN_3O_6S_2$: C, 50.62; H, 3.86. Found: C, 50.64; H, 3.87.

*N-[3-Chloro-2-(2-chloroquinolin-3-yl)-4-oxoazetidin-1-yl]-2-(methylsulfonamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**5j**)* Mp 154 °C (aq. alcohol); Yield: 77 %. IR (KBr, cm^{-1}): 3312 (br. CO*NH*), 3255 (br. *NH*SO$_2$Me), 1762 (N*CO*CH), 1672 (*CO*NH), 1340 (*SO$_2$*Me unsym. str.), 1159 (*SO$_2$*Me sym. str.). ^{1}H NMR (300 MH$_Z$, CDCl$_3$): 1.62–1.79 (m, 4H, *CH$_2$-5,6*), 2.72–2.84 (m, 4H, *CH$_2$-4,7*), 2.96 (s, 3H, –SO$_2$*CH$_3$*), 4.12 (s, 1H, *NH*SO$_2$Me), 5.10 (d, 1H, $J = 8.4$ Hz, *CH*Ar), 5.45 (d, 1H, $J = 8.4$ Hz, *CH*Cl), 7.35–8.30 (m, 5H, Ar*H*), 9.85 (s, 1H, CO*NH*).^{13}C NMR (75 MH$_Z$, CDCl$_3$): 23.5, 25.7, 26.4, 39.2 (SO$_2$*CH$_3$*), 52.0, 61.9, 112.7, 121.7, 123.6, 127.5, 129.6, 134.8, 137.1, 139.6, 142.8, 145.2, 155.3, 161.8 (–N*CO*CH), 167.7 (CO*NH*). DEPT-135: δ 23.38 (↓), 24.37 (↓), 25.89 (↓), 39.57 (↑) (SO$_2$*CH$_3$*), 56.20 (↑), 61.22 (↑), 126.10 (↑), 129.59 (↑), 143.5 (↑). *Anal. Calcd for* $C_{22}H_{23}Cl_2N_4O_4S_2$: C, 48.71; H, 4.27. Found: C, 48.70; H, 4.25.

*General procedure for the synthesis of thiazolidinones (**6a–j**)*

To a solution of Schiff bases (0.01 mol) **4a–j** in DMF (10 mL), thioglycolic acid (0.01 mol) and anhydrous zinc chloride (0.02 mol) were added and the contents were refluxed for 5 h. The reaction mixture was poured into cold water and the liberated compounds were extracted with chloroform. Evaporation of the solvent in vacuo afforded the corresponding thiazolidinones **6a–j**.

*N-(2-phenyl-4-oxo-thiazolidin-3-yl)-2-(methylsulfonamido)-4,5,6,7-tetrahydrobenzo[b]-thiophene-3-carboxamide, (**6a**)* Mp 144 °C (aq. alcohol); Yield: 74 %. IR (KBr, cm^{-1}): 3320 (br. CO*NH*), 3261 (br. *NH*SO$_2$), 1740 (N*CO*CH$_2$), 1672 (*CO*NH), 1345 (*SO$_2$*Me unsym. str.), 1164 (*SO$_2$*Me unsym. str.). ^{1}H NMR (300 MH$_Z$, CDCl$_3$): 1.52–1.79 (m, 4H, *CH$_2$-5,6*), 2.62–2.78 (m, 4H, *CH$_2$-4,7*), 3.16 (s, 3H, –SO$_2$*CH$_3$*), 4.10 (s, 1H, *NH*SO$_2$Me), 4.81 (d, 1H, $J = 2.1$ Hz, S*CH$_a$*), 5.08 (d, 1H, $J = 2.1$ Hz, S*CH$_b$*), 6.28 (s, 1H, N*CH*ϕ), 7.26–7.52(m, 5H, Ar*H*), 9.64 (s, 1H, CO*NH*). ^{13}C NMR (75 MH$_Z$, CDCl$_3$): 22.3, 23.4, 25.1, 37.0 (CO*CH$_2$*S), 39.8 (*SO$_2$*CH$_3$), 54.6, 112.5, 114.9, 126.3, 127.5, 128.6, 134.8, 139.6, 164.8 (*CO*CH$_2$S), 168.0 (*CO*NH). DEPT-135: δ 19.57 (↓), 23.71 (↓), 27.25 (↓),

36.41 (↓) (CO*CH*$_2$S), 39.82 (↑) (*SO*$_2$*CH*$_3$), 59.32 (↑) (SO$_2$*CH*$_3$), 63.06 (↑), 109.27 (↑), 112.20 (↑), 120.39 (↑), 124.17 (↑), 126.15 (↑). *Anal. Calcd for* $C_{19}H_{21}N_3O_4S_3$: C, 50.53; H, 4.69. Found: C, 50.52; H, 4.70.

*N-[2-(2-Chlorophenyl)-4-oxothiazolidin-3-yl]-2-(methylsulfonamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**6b**)* Mp 119–120 °C (aq. alcohol); Yield: 71 %. IR (KBr, cm^{-1}): 3345 (br. CO*NH*), 3264 (br. *NH*SO$_2$), 1724 (>N*CO*CH$_2$), 1656 (*CO*NH), 1354 (*SO*$_2$Me unsym. str.), 1158 (*SO*$_2$Me unsym. str.). ^{1}H NMR (300 MH$_Z$, CDCl$_3$): 1.77–1.94 (m, 4H, *CH*$_2$*-5,6*), 2.56–2.69 (m, 4H, *CH*$_2$*-4,7*), 2.97 (s, 3H, SO$_2$*CH*$_3$), 4.26 (s, 1H, *NH*SO$_2$Me), 4.88 (d, 1H, $J = 2.1$ Hz, S*CH*$_a$), 4.91 (d, 1H, $J = 2.1$ Hz, S*CH*$_b$), 6.13 (s, 1H, N*CHϕ*), 7.08–7.64 (m, 4H, Ar*H*), 9.76 (s, 1H, CO*NH*). ^{13}C NMR (75 MH$_Z$, CDCl$_3$): 22.3, 23.4, 25.1, 37.0 (CO*CH*$_2$S), 39.8 (SO$_2$*CH*$_3$), 54.6, 112.5, 114.7, 126.3, 127.5, 128.6, 134.8, 139.6, 164.8 (*CO*CH$_2$S), 167.8 (*CO*NH). DEPT-135: δ 23.41 (↓), 24.90 (↓), 28.05 (↓), 37.05 (↓) (CO*CH*$_2$*S*), 38.96 (↑) (SO$_2$*CH*$_3$), 59.65 (↑), 127.92 (↑), 128.92 (↑), 129.06 (↑). *Anal. Calcd for* $C_{19}H_{20}ClN_3O_4S_3$: C, 46.95; H, 4.15. Found: C, 46.93; H, 4.17.

*N-[2-(3-Nitrophenyl)-4-oxo-2-thiazolidin-3-yl]-2-(Methane sulfonamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide, (**6c**)* Viscous liquid; Yield: 70 %. IR (KBr, cm^{-1}): 3328 (br. CO*NH*), 3265 (br. *NH*SO$_2$), 1758 (N*CO*CH$_2$), 1667 (*CO*NH), 1530 (*N=O* unsym. str.), 1320 (*N=O* sym. str.), 1341 (*SO*$_2$Me unsym. str.), 1164 (*SO*$_2$Me unsym. str.). ^{1}H NMR (300 MH$_Z$, CDCl$_3$): 1.59–1.79 (m, 4H, *CH*$_2$*-5,6*), 2.53–2.69 (m, 4H, *CH*$_2$*-4,7*), 2.90 (s, 3H, –SO$_2$*CH*$_3$), 4.19 (s, 1H, *NH*SO$_2$Me), 4.66 (d, 1H, $J = 1.8$ Hz, S*CH*$_a$), 4.74 (d, 1H, $J = 1.8$ Hz, S*CH*$_b$), 6.23 (s, 1H, N*CHϕ*), 7.17–7.42 (m, 4H, Ar*H*), 9.69 (s, 1H, CO*NH*). ^{13}C NMR (75 MH$_Z$, CDCl$_3$): 23.4, 25.9, 27.9, 35.8 (CO*CH*$_2$S), 40.8 (SO$_2$*CH*$_3$), 62.3, 65.9, 116.7, 120.7, 124.3, 129.4, 134.2, 135.7, 139.7, 149.3, 160.1 (*CO*CH$_2$S), 161.7 (CO*NH*). DEPT-135: δ 23.41 (↓), 24.90 (↓), 28.05 (↓), 37.05 (↓) (CO*CH*$_2$S), 38.96 (↑) (SO$_2$*CH*$_3$), 59.65 (↑), 121.92 (↑), 128.78 (↑), 133.06 (↑). Anal. Calcd for $C_{19}H_{20}N_4O_6S_3$: C, 45.95; H, 4.06. Found: C, 45.96; H, 4.08.

*N-[2-(4-Methoxyphenyl)-4-oxothiazolidin-3-yl]-2-(methylsulfonamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**6d**)* Mp 152 °C (aq. alcohol); Yield: 65 %. IR (KBr, cm^{-1}): 3314 (br. CONH), 3267 (br. NHSO$_2$), 1741 (N*CO*CH$_2$), 1664 (*CO*NH), 1337 (*SO*$_2$Me unsym. str.), 1168 (*SO*$_2$Me unsym. str.). ^{1}H NMR (300 MH$_Z$, CDCl$_3$): 1.52–1.79 (m, 4H, *CH*$_2$*-5,6*), 2.62–2.78 (m, 4H, *CH*$_2$*-4,7*), 2.78 (s, 3H, –SO$_2$*CH*$_3$), 4.18 (s, 1H, *NH*SO$_2$Me), 4.78 (d, 1H, $J = 2.7$ Hz, S*CH*$_a$), 4.81(d, 1H, $J = 2.7$ Hz, S*CH*$_b$), 6.34 (s, 1H, N*CHϕ*), 7.10–7.54 (m, 4H, Ar*H*), 9.83 (s, 1H, CO*NH*). ^{13}C NMR (75 MH$_Z$, CDCl$_3$): 23.6, 24.1, 24.7, 36.1 (CO*CH*$_2$S), 40.9 (SO$_2$*CH*$_3$), 55.9 (*OCH*$_3$), 58.4 (N*CHϕ*), 114.5, 116.2, 125.3, 129.6, 131.2, 136.2, 139.3, 159.1, 164.5 (*CO*CH$_2$S), 168.2 (CO*NH*). DEPT-135: δ 23.41 (↓), 24.90 (↓), 28.05 (↓), 37.05 (↓) (CO*CH*$_2$S), 38.96 (↑) (SO$_2$*CH*$_3$), 59.65 (↑) (N*CHϕ*), 117.92 (↑), 128.92 (↑), 129.06 (↑). Anal. Calcd for $C_{20}H_{23}N_3O_5S_3$: C, 49.88; H, 4.81. Found: C, 49.85; H, 4.80.

*N-[2-(4-Chlorophenyl)-4-oxothiazolidin-3-yl]-2-(methyl sulfonamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**6e**)* Mp 132 °C (aq. alcohol); Yield: 73 %. IR (KBr, cm^{-1}): 3320 (br. CO*NH*), 3261 (br. *NH*SO$_2$Me), 1741 (N*CO*CH$_2$), 1672 (*CO*NH), 1353 (*SO*$_2$Me unsym. str.), 1162 (*SO*$_2$Me unsym. str.). ^{1}H NMR (300 MH$_Z$, CDCl$_3$): 1.82–1.94 (m, 4H, *CH*$_2$*-5,6*), 2.58–2.74 (m, 4H, *CH*$_2$*-4,7*), 2.97 (s, 3H, –SO$_2$*CH*$_3$), 4.17 (s, 1H, *NH*SO$_2$Me), 4.86 (d, 1H, $J = 2.1$ Hz, S*CH*$_a$), 4.98 (d, 1H, $J = 2.1$ Hz, S*CH*$_b$), 6.36 (s, 1H, N*CHϕ*), 7.23–7.67 (m, 4H, Ar*H*), 9.63 (s, 1H, CO*NH*). ^{13}C NMR (75 MH$_Z$, CDCl$_3$): 23.3, 23.9, 24.4, 36.2 (CO*CH*$_2$S), 39.3 (SO$_2$*CH*$_3$), 57.7 (N*CHϕ*), 115.5, 123.4, 125.1, 128.4, 130.2, 132.8, 136.9, 138.2, 139.0, 163.8 (*CO*CH$_2$S), 168.7 (CO*NH*). DEPT-135: δ 23.32 (↓), 24.05 (↓), 28.35 (↓), 37.42 (↓) (CO*CH*$_2$S), 38.96 (↑) (SO$_2$*CH*$_3$), 59.60 (↑) (N*CHϕ*), 128.61 (↑), 130.29 (↑), 132.06 (↑). Anal. Calcd for $C_{19}H_{20}ClN_3O_4S_3$: C, 46.95; H, 4.15. Found: C, 46.96; H, 4.18.

*N-[2-(3,4-Dimethoxyphenyl)-4-oxothiazolidin-3-yl]-2-(methylsulfonamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**6f**)* Mp 124 °C (aq. alcohol); Yield: 71 %. IR (KBr, cm^{-1}): 3311 (br. CO*NH*), 3267 (br. *NH*SO$_2$Me), 1723 (N*CO*CH$_2$), 1680 (*CO*NH), 1338 (*SO*$_2$Me unsym. str.), 1154 (*SO*$_2$Me unsym. str.). ^{1}H NMR (300 MH$_Z$, CDCl$_3$): 1.64–1.81 (m, 4H, *CH*$_2$*-5,6*), 2.59–2.87 (m, 4H, *CH*$_2$*-4,7*), 2.85 (s, 3H, –SO$_2$*CH*$_3$), 3.84 (s, 2H, *OCH*$_3$), 4.16 (s, 1H, *NH*SO$_2$Me), 4.64 (d, 1H, $J = 2.7$ Hz, S*CH*$_a$), 4.87 (d, 1H, $J = 2.7$ Hz, S*CH*$_b$), 6.63 (s, 1H, N*CHϕ*), 6.84–7.61 (m, 3H, Ar*H*), 9.85 (s, 1H, CO*NH*). ^{13}C NMR (75 MH$_Z$, CDCl$_3$): 23.3, 23.8, 24.3, 35.9 (CO*CH*$_2$S), 39.8 (SO$_2$*CH*$_3$), 56.3 (*OCH*$_3$), 58.4 (N*CHϕ*), 114.5, 116.2, 123.4, 125.3, 132.6, 136.2, 139.3, 146.7, 149.1, 164.5 (*CO*CH$_2$S), 168.2 (*CO*NH). DEPT-135: δ 23.41 (↓), 24.90 (↓), 28.05 (↓), 37.05 (↓) (CO*CH*$_2$S), 38.96 (↑) (SO$_2$*CH*$_3$), 59.65 (↑) (N*CHϕ*), 117.92 (↑), 128.92 (↑), 129.06 (↑). *Anal. Calcd for* $C_{21}H_{25}N_3O_6S_3$: C, 49.30; H, 4.93. Found: C, 49.33; H, 4.90.

*N-[2-(4-Nitrophenyl)-4-oxo-thiazolidin-3-yl]-2-(methanes ulfonamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide, (**6g**)* Mp 149 °C (aq. alcohol); Yield: 79 %. IR (KBr, cm^{-1}): 3341 br. CO*NH*), 3268 (br. *NH*SO$_2$Me), 1752 (N*CO*CH$_2$), 1668 (*CO*NH), 1347 (*SO*$_2$Me unsym. str.), 1149 (*SO*$_2$Me unsym. str.). 1352 (*NO*$_2$ unsym. str.),

1327 (NO_2 sym. str.). ^{1}H NMR (300 MH_Z, $CDCl_3$): 1.65–1.89 (m, 4H, *CH$_2$-5,6*), 2.58–2.88 (m, 4H, *CH$_2$-4,7*), 2.90 (s, 3H, –SO_2CH_3), 4.19 (s, 1H, *NH*SO_2Me), 4.93 (d, 1H, $J = 2.4$ Hz, S*CH*$_a$), 4.98 (d, 1H, $J = 2.4$ Hz, S*CH*$_b$), 6.31 (s, 1H, N*CHϕ*), 7.02–8.12 (m, 4H, Ar*H*), 9.80 (s, 1H, CO*NH*). ^{13}C NMR (75 MH_Z, $CDCl_3$): 23.3, 23.6, 24.4, 36.1 (CO*CH$_2$*S), 39.7 (SO_2CH_3), 56.1 (N*CHϕ*), 114.9, 123.4, 125.2, 128.6, 132.7, 135.8, 139.6, 146.5, 163.8 (*CO*CH_2S), 168.7 (*CO*NH). DEPT-135: δ 23.41 (↓), 24.90 (↓), 28.05 (↓), 37.05 (↓) (CO*CH$_2$*S), 38.96 (↑) (SO_2CH_3), 59.65 (↑), 121.92 (↑), 128.78 (↑), 131.06 (↑), 134.53 (↑). Anal. Calcd for $C_{19}H_{20}N_4O_6S_3$: C, 45.95; H, 4.06. Found: C, 45.96; H, 4.08

N-[2-(Indol-3-yl)-4-oxo-thiazolidin-3-yl]-2-(methanesulfonamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide, ***(6h)*** Mp 135 °C (aq. alcohol); Yield: 73 %. IR (KBr, cm^{-1}): 3320 (br. CO*NH*), 3261 (br. *NH*SO_2Me), 1741 (N*CO*CH_2), 1673 (*CO*NH), 1452 (–NH *of indol-3-yl*), 1334 (*SO$_2$*Me unsym. str.), 1146 (*SO$_2$*Me unsym. str.). ^{1}H NMR (300 MH_Z, $CDCl_3$): 1.66–1.79 (m, 4H, *CH$_2$-5,6*), 2.72–2.85 (m, 4H, *CH$_2$-4,7*), 2.84 (s, 3H, –SO_2CH_3), 4.20 (s, 1H, *NH*SO_2Me), 4.81 (d, 1H, $J = 2.1$ Hz, S*CH*$_a$), 4.97 (d, 1H, $J = 2.1$ Hz, S*CH*$_b$), 6.38 (s, 1H, N*CHϕ*), 6.80–7.43 (m, 5H, Ar*H*), 9.89 (s, 1H, CO*NH*), 11.32 (s, 1H, *NH*-indol-3-yl). ^{13}C NMR (75 MH_Z, $CDCl_3$): 23.1, 23.8, 24.6, 35.9 (CO*CH$_2$*S), 39.7 (SO_2CH_3), 55.9 (N*CHϕ*), 111.2, 114.5, 119.3, 122.8, 123.4, 125.2, 128.0, 130.2, 135.8, 136.9, 139.4, 164.5 (*CO*CH_2S), 168.3 (*CO*NH).DEPT-135: 23.41 (↓), 24.90 (↓), 28.05 (↓), 37.05 (↓) (CO*CH$_2$*S), 38.96 (↑) (SO_2CH_3), 59.65 (↑) (N*CHϕ*), 111.92 (↑), 118.78 (↑), 119.78 (↑), 122.78 (↑), 124.78 (↑), 127.87 (↑).

N-[2-(4-Oxo-4H-chromen-2-yl)-4-oxo-thiazolidin-3-yl]-2-(methanesulfonamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide, ***(6i)*** Mp 139 °C (aq. alcohol); Yield: 65 %. IR (KBr, cm^{-1}): 3340 (br. CO*NH*), 3272 (br. *NH*SO_2 Me), 1770 (N*CO*CH_2), 1733 (*CO* of chromone), 1661 (*CO*NH), 1353 (*SO$_2$*Me unsym. str.), 1156 (*SO$_2$*Me unsym. str.). ^{1}H NMR (300 MH_Z, $CDCl_3$): 1.61–1.82 (m, 4H, *CH$_2$-5,6*), 2.77–2.94 (m, 4H, *CH$_2$-4,7*), 2.97 (s, 3H, –SO_2CH_3), 4.13 (s, 1H, *NH*SO_2Me), 4.68 (d, 1H, $J = 2.1$ Hz, S*CH*$_a$), 4.84 (d, 1H, $J = 2.1$ Hz, S*CH*$_b$), 6.30 (s, 1H, N*CHϕ*), 6.23 (s, 1H, H-2′), 7.18–8.10 (m, 4H, Ar*H*), 9.76 (s, 1H, CO*NH*). ^{13}C NMR (75 MH_Z, $CDCl_3$): 23.2, 23.5, 24.3, 36.8 (CO*CH$_2$*S), 39.4 (SO_2CH_3), 59.6 (N*CHϕ*), 109.4, 114.9, 123.4, 125.2, 135.8, 139.6, 156.4, 163.8, 164.5 (*CO*CH_2S), 168.7 (*CO*NH), 179.1 (*CO* of chromone). DEPT-135: δ 23.41 (↓), 24.90 (↓), 28.05 (↓), 37.05 (↓) (CO*CH$_2$*S), 39.86 (↑) (SO_2CH_3), 59.65 (↑) (N*CHϕ*), 111.92 (↑), 118.78 (↑), 119.78 (↑), 122.78 (↑), 124.78 (↑). Anal. Calcd for $C_{22}H_{21}N_3O_6S_3$: C, 50.85; H, 4.07. Found: C, 50.83; H, 4.09.

N-[2-(2-Chloroquinolin-3-yl)-4-oxo-thiazolidin-3-yl]-2-(Methanesulfonamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide, ***(6j)*** Mp 165 °C (aq. alcohol); Yield: 65 %. IR (KBr, cm^{-1}): 3320 (br. CO*NH*), 3265 (br. *NH*SO_2Me), 1741 (N*CO*CH_2), 1665 (*CO*NH), 1337 (*SO$_2$*Me unsym. str.), 1156 (*SO$_2$*Me unsym. str.).^{1}H NMR (300 MH_Z, $CDCl_3$): 1.52–1.79 (m, 4H, *CH$_2$-5,6*), 2.62–2.78 (m, 4H, *CH$_2$-4,7*), 2.92 (s, 3H, –SO_2CH_3), 4.01 (s, 1H, *NH*SO_2Me), 4.76 (d, 1H, $J = 2.4$ Hz, S*CH*$_a$), 4.84 (d, 1H, $J = 2.4$ Hz, S*CH*$_b$), 6.18 (s, 1H, N*CHϕ*), 7.61–8.42 (m, 5H, Ar*H*), 9.86 (s, 1H, CO*NH*). ^{13}C NMR (75 MH_Z, $CDCl_3$): 23.1, 23.8, 24.6, 35.9 (CO*CH$_2$*S), 39.7 (SO_2CH_3), 53.1 (N*CHϕ*), 114.9, 125.2, 126.4, 127.3, 129.6, 130.2, 135.8, 136.8, 139.6, 145.6, 163.8 (*CO*CH_2S), 168.7 (*CO*NH). DEPT-135: δ 23.41 (↓), 24.90 (↓), 28.05 (↓), 37.12 (↓) (CO*CH$_2$*S), 39.86 (↑) (SO_2CH_3), 54.65 (↑) (N*CHϕ*), 114.92 (↑), 124.78 (↑), 125.78 (↑), 126.78 (↑), 127.48 (↑), 129.48 (↑), 131.92 (↑). Anal. Calcd for $C_{22}H_{22}ClN_4O_4S_3$: C, 49.11; H, 4.12. Found: C, 49.07; H, 4.15.

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