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Synthesis and biological evaluation of 2-azetidinone and thiazolidine-4-one derivatives containing dibenzothiazepine nucleus

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In the present study, 3-chloro-1-(dibenzo[b,*f*][1,4]thiazepin-11-ylamino)-4-(substituted phenyl)azetidin-2-one **2a–k** and 3-(dibenzo[b,*f*][1,4]thiazepin-11-ylamino)-2-(substituted phenyl)thiazolidin-4-one **3a–k** derivatives have been synthesized *via* the reaction of (*Z*)-11-(2-(substituted benzylidene) hydrazinyl) dibenzo[b,*f*][1,4] thiazepine **1a-k** with chloro acetyl chloride and thiogycolic acid respectively under mild reaction conditions. The structures of all synthesised compounds have been assigned on the basis of FT-IR, ^{1}H and ^{13}C NMR spectral data as well as elemental analysis. The title compounds have been screened for their preliminary *in vitro* antimicrobial activity against a panel of pathogenic strains and *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis H37 Rv*.

Keyword: Dibenzo[b,*f*][1,4]thiazepine hydrazone, chloro acetylchloride, thioglycolic acid, antimycobacterial activity, antimicrobial activity

A wide variety of biologically active synthetic and natural compounds are known to have heterocycles containing the 1,4-thiazepine moiety[1-4]. Among them, aryl- and heteroaryl-fused derivatives of this heterocycle represent an important group of compounds with interesting pharmaceutical properties[5-8]. For instance, thiazepine is the important class of heterocycles that possess a wide range of biological and pharmacological activities and can act as an antimicrobial, anti-tumor, antitubercular, anti-inflammatory, anticancer, antiviral, analgesic and antimigrain agents[9-14].

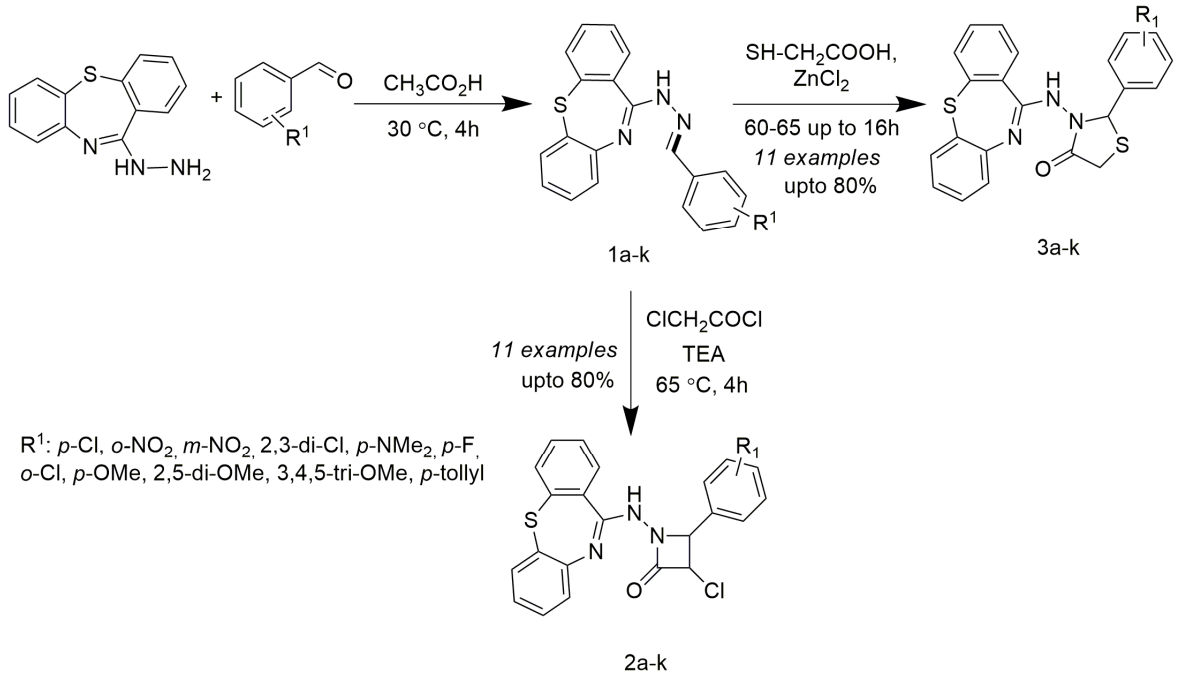
2-Azetidinone and thiazolidine-4-one skeleton belongs to the penicillin family. The ring ultimately proved to be the main component of the pharmacophore, so the term possesses both medicinal and chemical significance. Penicillins, cephalosporins, carbapenems, nocardicins, monobactams, clavulanic acid, troglitazone and pioglitazone are well known drugs containing 2-azetidinone[15-18] and thiazolidine-4-one core[19-22] but combination of dibenzo[b,*f*][1,4]thiazepine with 2-azetinone or thiazolidine-4-one derivatives are not reported yet.

From the synthetic point of view, the opportunity to prepare biologically important heterocyclic molecule in limited steps under mild reaction condition is an exciting goal for every modern organic chemists. Although a number of methods are available for the synthesis of simple substituted 2-azetinones and thiazolidine-4-ones, they typically require multistep synthesis and expensive reagents[21-24]. Recently, we have reported the synthesis of substituted phenyl dibenzo[b,*f*][1,2,4]triazolo[4,3-*d*][1,4]thiazepine (A) through heterocyclization of the corresponding arylidene hydrazone under reflux condition[25]. Herein we report the synthesis and antitubercular and antimicrobial evaluation of some azetidin-2-one and thiazolidin-4-one derivatives containing dibenzo[b,*f*][1,4]thiazepine core.

Results and Discussion

Chemistry

The 2-azetidinones and thiazolidin-4-ones have their synthetic route *via* the Staudinger reaction. The synthetic pathway includes heterocyclization reaction of (*Z*)-11-(2-(substituted benzylidene) hydrazinyl) dibenzo[b,*f*][1,4]thiazepine **1a-k** with chloro acetyl chloride or thiogycolic acid to give direct access to the desired 3-chloro-1-(dibenzo[b,*f*][1,4]thiazepin-11-ylamino)-4-(substituted phenyl) azetidin-2-one **2a-k** or 3-(dibenzo[b,*f*][1,4] thiazepin-11-ylamino) -2-(substituted phenyl) thiazolidin-4-one **3a-k**, respectively (Scheme I). All these new heterocyclic derivatives were fully characterised by means of spectroscopic techniques such as FTIR, ^{1}H and ^{13}C NMR as well as elemental analysis.



Scheme I — Synthesis of azetidin-2-one and thiazolidin-4-one of dibenzothiazepine

The IR spectrum of compound **2k**, a broad stretching band and a sharp medium to strong band for the N-H group were observed at 3180-3140 cm^{-1} and 1540-1500 cm^{-1}, the C-S-C linkage of the seven member ring caused a weak and sharp absorption band at 760- 800 cm^{-1} and the C=O group was observed as a strong and sharp band at 1620-1700 cm^{-1}. Also, for the compounds **2k**, the vibration bands of the NO_2 group were observed at 1514–1534 cm^{-1} and 1346–1356 cm^{-1}, respectively. The C-H (aliphatic and aromatic), C=C stretching vibrations were observed at their usual positions. Electron-donating ketene substituents and electron-withdrawing imine substituents accelerate the direct ring closure, leading to a preference for *cis*-β-lactam formation. In contrast, electron-withdrawing ketene substituents and electron-donating imine substituents slow the direct ring closure, leading to a preference for trans-β-lactam formation. The isomers were confirmed by coupling constants of H-3 and H-4, which were calculated to be greater than 4.0 Hz for the *cis*-isomers (**2j**, **2k**) and less than 2.5 Hz for the *trans*-isomers (**2a-i**) (Table I). In the ^{1}H NMR spectrum of compound **2k**, multiplets in the region at δ 7.01-8.36 were exhibited for 12 aromatic protons (8 aromatic protons were dibenzo[b,*f*][1,4]thiazepines and 4 aromatic protons were benzene), one proton present in –NH group was found to resonate as singlet at δ 8.87 and two protons present in azetidinone ring *i.e.* N-CH-Ar and C-CH-Cl were found to resonate as doublets at δ 4.56 and 4.66. The ^{13}C NMR spectrum of compound **2k** exhibited multiplets in the region of δ 121.20-150.25 for 13 aromatic carbons dibenzo[b, *f*][1,4]thiazepinone and four carbons of benzene, the C=O group is observed at δ 162.25 and two carbons present in N-CH-Ar and C-CH-Cl group were found to resonate as singlet at δ 45.50 and 41.37 respectively.

Table I — Stereochemistry of azetidin-2-one compounds **2a-k**

Entry	R_1	Isolated isomer
2a	-CH_3	*Trans*
2b	-OCH_3	*Trans*
2c	2,5-OCH_3	*Trans*
2d	3,4,5-OCH_3	*Trans*
2e	4-Cl	*Trans*
2f	2-Cl	*Trans*
2g	2,3-Cl	*Trans*
2h	4-$N(CH_3)_2$	*Trans*
2i	4-F	*Trans*
2j	2-NO_2	*Cis*
2k	3-NO_2	*Cis*

The IR spectrum of compound **3h**, a broad stretching band and a sharp medium to strong band for the N-H group were observed at 3180-3140 cm^{-1} and 1540-1500 cm^{-1}, the C=O group was observed as a strong and sharp band at 1620-1700 cm^{-1} and the S-CH_2 group of 4-thiazolidinone ring was observed as sharp absorption band at 1460-1485 cm^{-1}. Also, for

the compounds **3i** and **3k**, the vibration bands of the $-NO_2$ group were observed at 1514–1534 cm^{-1} and 1346–1356 cm^{-1}, respectively. The C-H (aliphatic and aromatic), C=C stretching vibrations were observed at their usual positions.

The ^1H NMR spectrum of compound **3h** exhibited multiplets in the region at δ 7.15-7.75 for 11 aromatic protons (8 aromatic protons were dibenzo[b, *f*][1,4]thiazepines and 3 aromatic protons were benzene), one proton present in –NH group was found to resonate as singlet at δ 8.87 and three protons present in 4-thiazolidinone ring *i.e.* one proton of N-CH-Ar and two protons of S-CH_2- were found to resonate as singlet at δ 5.83 and 3.82-4.08 respectively. The ^{13}C NMR spectrum of compound **3h**, exhibited multiplets in the region at δ 103.9-154.24 for 13 aromatic carbons of dibenzo[b,*f*][1,4]thiazepinone and four carbons of benzene, the two C=O of amide group is observed at δ 169.13. One carbon present in N-CH-Ar and two carbons present in S-CH_2-group were found to resonate as singlet at δ 60.59 and 35.12.

All synthesized compounds *i.e.* azetidin-2-one 2a-k and thiazolidin-4-one 3a-k were tested *in vitro* for their biological activity against pathogenic micro-organisms. The experimental results of anti-bacterial, anti-fungal and anti-tuberculosis activity indicated a variable degree of efficacy of the compounds against different strains of microbes (Table II and Table III).

Azetidinone compound 2d exhibited very good activity at 62.5 µg/mL and compounds 2f and 2h at 100 µg/mL against *Escherichia coli* as compared to Ampicillin (MIC=100 µg/mL). Azetidinone compounds 2a, 2b, 2d, 2e, 2f, 2h, 2i, 2g and 2j exhibited good activity at 100-125 µg/mL against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococcus pyogenes* compared to Ampicillin (MIC=100 µg/mL). Azetidinone compounds 2a (4-CH_3), 2c (2,5-OCH_3), 2e (4-Cl), 2f (2-Cl), 2h (4-$N(CH_3)_2$) and 2i (4-F), exhibited good activity at 250 µg/mL; against *Staphylococcus aureus* as compared to ampicillin (MIC= 250 µg/mL). As far as the anti-fungal activity is concerned for azetidinone compounds 2b and 2f showed excellent activity at 250 µg/mL and compounds 2e, 2j and 2k showed good activity at 500 µg/mL against *Candida albicans* as compared to griseofulvin (MIC= 500 µg/mL).

Table II — Antibacterial activities of (MIC) of synthesis compounds

Entry	*E. coli* MTCC 443	*P. aeruginosa* MTCC 1688	*S. aureus* MTCC 96	*S. pyogenes* MTCC 442
2a	200	125	100	100
2b	250	200	200	250
2c	250	200	250	250
2d	62.5	100	100	100
2e	250	200	200	100
2f	100	125	250	200
2g	250	100	125	200
2h	100	125	250	250
2i	200	250	250	100
2j	250	250	500	250
2k	200	250	100	250
3a	250	200	500	250
3b	500	500	500	500
3c	200	100	250	250
3d	200	100	250	250
3e	100	100	200	200
3f	100	100	200	200
3g	125	250	250	100
3h	125	200	250	250
3i	200	250	125	200
3j	250	200	100	125
3k	200	250	200	250
Ampicillin	100	100	250	100
Chloramphenicol	50	50	50	50
Standard deviation	±5	±5	±5	±5
Control (DMSO)	–	–	–	–

Thiazolidin-4-one compounds 3c, 3d, 3e, 3h, 3i, 3g and 3j exhibited good activity at 100-125 µg/mL against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococcus pyogenes* compared to ampicillin (MIC=100 µg/mL). Thiazolidin-4-one compounds 3c, 3d, 3e, 3f, 3g, 3h and 3k exhibited good activity at 250 µg/mL; against *Staphylococcus aureus* as compared to ampicillin (MIC= 250 µg/mL).

As far as the anti-fungal activity concerned for thiazolidin-4-one, compounds 3b and 3i showed excellent activity at 250 µg/mL and compounds 3e, 3f and 3g showed moderate activity at 500 µg/mL against *Candida albicans* as compared to griseofulvin (MIC= 500 µg/mL). All the screened compounds were less active against *Aspergillus niger* and *Aspergillus clavatus*. The other compounds tested showed less activity against the fungal species. The encouraging results from the antibacterial studies prompted us to go for preliminary screening against *M. tuberculosis*; the results are summarized in Table III.

In this screening 1000, 500 and 250 µg/mL concentrations of the compounds were taken. The compounds which were found active in this screening were further tested in a secondary screening against *M. tuberculosis* $H_{37}Rv$ in L. J. Medium (conventional method). The compounds found active in primary screening were similarly diluted to obtain 200, 100, 50, 25, 12.5, 6.250 and 3.50 µg/mL concentrations. The highest dilution showing at least 95–99% inhibition growth is taken as MIC. All compounds showed moderate to weak activity against $H_{37}Rv$ strain.

Experimental Section

Preliminary analysis of reaction samples was performed using TLC plates and visualized by UV(365nm) irradiation or by staining with I_2. LC-MS was recorded by using LCMS-6410 from Agilent technology. The IR spectra (ν, cm^{-1}) were obtained with a Perkin-Elmer 1600 FT-IR spectrometer in KBr pellets. Finally isolated compounds were confirmed by ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) of Bruker Avance II in DMSO-d_6 solvent. All chemicals were used as received.

Antimicrobial activity

All MTCC (Microbial Type Culture Collection) cultures were collected from Institute of Microbial

Table III — Antifungal and anti tubercular activity (MIC) of synthesis compounds

Compd	*C. albicans* MTCC 227	*A. niger* MTCC 282	*A. clavatus* MTCC 1323	H37RV MIC µg/mL
2a	1000	>1000	>1000	1000
2b	250	>1000	>1000	1000
2c	>1000	1000	1000	500
2d	>1000	250	1000	250
2e	500	>1000	>1000	100
2f	250	500	500	100
2g	>1000	>1000	>1000	500
2h	>1000	>1000	>1000	1000
2i	500	>1000	>1000	1000
2j	500	>1000	>1000	1000
3a	1000	500	500	1000
3b	250	500	500	1000
3c	1000	>1000	>1000	500
3d	1000	>1000	>1000	500
3e	500	>1000	>1000	100
3f	500	500	500	250
3g	500	>1000	>1000	500
3h	>1000	>1000	>1000	1000
3i	250	500	500	250
3j	1000	200	100	125
3k	1000	250	200	250
Griseofulvin	500	100	100	–
Rifampicin	–	–	–	40
Standard deviation	±5	±5	±5	±5
Control (DMSO)	–	–	–	–

Technology, Chandigarh and tested against known drugs like ampicilin (antibacterial) and griseofulvin (antifungal) as reference drugs. Mueller Hinton broth was used as nutrient medium for bacterial and fungal strain to grow and dilute the concentrations of 1000 g/mL, 500 g/mL, 250 g/mL, 125 g/mL, 100 g/mL, 50 g/mL, 25 g/mL, 12.5 g/mL, 6.250 g/mL, 3.125 g/mL and 1.5625 g/mL drug suspension for the test. DMSO was used as diluent to get desired concentration of drugs to test upon standard bacterial strains. Inoculum size for tested strain was adjusted to 10^8 CFU (Colony Forming Unit) per milliliter by comparing the turbidity. The control plate without antibiotic was sub-cultured by spreading a loopful of testing organisms evenly over a quarter of plate on nutrient medium and put for incubation at 37°C overnight. The MICs of compounds were obtained by broth micro dilution method as described by Rattan[26,27]. Antibacterial activity was screened against two gram positive (*Staphylococcus aureus* MTCC 96, *Streptococcus pyogenus* MTCC 443) and two gram negative (*Escherichia coli* MTCC 442, *Pseudomonas aeruginosa* MTCC 2488) bacteria. Antifungal activity was screened against three fungal species *Candida albicans* MTCC 227, *Aspergillus niger* MTCC 282 and *Aspergillus clavatus* MTCC 1323.

General procedure for the synthesis of 3-chloro-1-(dibenzo [*b*,*f*][1,4]thiazepin-11-yl amino)-4-(substituted phenyl) azetidin-2-one, 2a-k

To the stirred solution of (*Z*)-11-(2-(substituted benzylidene) hydrazinyl) dibenzo[b,*f*][1,4] thiazepine 1a-k (3.43 g, 0.01 mol) in 20 mL of dioxane, triethyl amine (1.68 g, 0.02 mol) was added at 0°C. The solution of chloroacetyl chloride (1.68 g, 0.02 mol) in 5 mL dioxane was added drop-wise at the same temperature. The resulting reaction mixture was stirred for 1 h at 0°C. It was then heated up to 60-65°C and stirred for 6 h. Completion of reaction was checked on TLC. The reaction solvent was distilled out under vacuum at 60-65°C. The residue was poured into crushed ice. The resultant solid was filtered off and washed with 5% sodium bicarbonate solution to neutralise the acidic impurities. The white colour product was recrystallized with ethanol which yielded 3-chloro-1-(dibenzo[b,*f*][1,4]thiazepin-11-*yl* amino)-4-(substituted phenyl) azetidin-2-one 2a-k. The structure of the compounds 2a-k was confirmed by ^{1}H NMR, ^{13}C NMR and HRMS analysis. Yield 75%. m.p.138-140°C. IR (KBr): 3363, 1625, 1577, 1191 cm^{-1}; ^{1}H NMR(400 MHz, DMSO-d_6): δ 2.94 (s, 3H), 4.47- 4.52 (*J* = 2.25 Hz, d, 1H, H-4), 4.72-4.79 (*J* = 2.32 Hz, d, 1H, H-3), 6.78-7.98 (m, 12H, Ar-H), 8.7 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.11, 45.11, 48.98, 114.07, 114.07, 118.64, 127.54, 127.54, 129.31, 129.78, 130.03, 130.03, 130.38, 131.04, 131.46, 132.20, 133.94, 135.40, 136.22, 138.40, 153.45, 153.98, 160.42; EI-MS: *m/z* 419.93 (M^+), 420.98 (M + 1). Anal. Calcd for $C_{23}H_{18}ClN_3OS$ (419.93): C, 65.73; H, 4.25; Cl, 8.41; N, 9.96; O, 3.79; S, 7.63. Found: C, 65.78; H, 4.32; Cl, 8.44; N, 10.01; O, 3.81; S, 7.64%.

3-Chloro-1-(dibenzo[*b*,*f*][1,4]thiazepin-11-yl amino)-4-(4-methoxy phenyl)azetidin -2-one, 2b: The product was isolated as off white solid; Yield 80%. m.p.110–114°C. IR (KBr): 670, 1377, 1672, 3363 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.89 (s, 3H), 4.45-4.51 (*J* = 2.34 Hz, d, 1H, H-4), 4.76-4.82 (*J* = 2.12 Hz, d, 1H, H-3), 6.98 (m, 2H), 7.23 (s, 1H), 7.26 (m, 2H), 7.31 (s, 1H), 7.41–7.43 (m, 2H), 7.49 (m, 1H), 7.61 (s, 1H), 7.96 (m, 2H), 8.67 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 45.11, 48.98, 55.8, 114.2, 126.1, 127.6, 129.2, 129.4, 129.9, 130.2, 130.3, 131.0, 131.3, 132.2, 133.9, 136.3, 150.9, 153.5, 160.2. Anal. Calcd for $C_{23}H_{18}ClN_3O_2S$ (435.93): C, 70.57; H, 4.23; N, 11.76; O, 4.48; S, 8.97. Found: C, 70.52; H, 4.20; N, 11.72; S, 8.96%.

3-Chloro-1-(dibenzo[b,*f*][1,4]thiazepin-11-yl amino)-4-(2,5-dimethoxy phenyl) azetidin-2-one, 2c: The product was obtained as off white solid, Yield 74%. m.p.136-138°C. IR (KBr, cm^{-1}): 1025, 1381, 1668, 3063, 3405 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.72 (s, 1H, NH), 6.64-7.80 (m, 11H, Ar-*H*), 4.78-4.82 (*J* = 2.11 Hz, d, 1H, H-4), 4.46-4.47 (*J* = 2.34 Hz, d, 1H, H-3), 3.64 (s, 6H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 45.34, 49.53, 55.17, 113.49, 115.68, 116.28, 118.23, 127.08, 127.67, 127.82, 129.51, 129.89, 130.28, 130.65, 131.93, 132.26, 133.79, 139.49, 149.07, 153.64, 156.27, 161.16, 161.16. Anal. Calcd for $C_{25}H_{22}ClN_3O_4S$ (495.98): C, 61.93; H, 4.25; Cl, 7.56; N, 8.86; O, 10.23; S, 6.83. Found: C, 61.86; H, 4.33; Cl, 7.61; N, 9.02; O, 10.30; S, 6.88%.

3-Chloro-1-(dibenzo[b,*f*][1,4]thiazepin-11-yl amino)-4-(3,4,5-tri methoxy phenyl) azetidin-2-one, 2d: The product was isolated as off white needles, Yield 76%. m.p.136-138°C. IR (KBr, cm^{-1}): 1381, 1668, 3063, 3405 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.59 (s, 1H, NH), 6.64-7.80 (m, 10H, Ar-*H*), 4.78 (*J* = 2.40 Hz, d, 1H, H-4), 4.46 (*J* = 2.12 Hz, d, 1H, H-3), 3.64 (s, 9H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 45.86, 49.48, 55.17, 58.60, 59.87, 99.8,

107.28, 113.94, 127.08, 127.24, 128.47, 128.47, 129.49, 129.89, 130.65, 131.93, 132.26, 133.79, 139.49, 143.02, 152.02, 156.27, 159.02, 160.29, 161.02. Anal. Calcd for: $C_{25}H_{22}ClN_3O_4S$ (495.98): C, 60.43; H, 4.45; Cl, 7.06; N, 8.41; O, 12.83; S, 6.39. Found: C, 60.54; H, 4.47; Cl, 7.15; N, 8.47; O, 12.90; S, 6.47%.

3-Chloro-1-(dibenzo[b,*f*][1,4]thiazepin-11-yl amino)-4-(4-chloro phenyl)azetidin-2-one, 2e: The product was obtained as off white solid, Yield 73%. m.p.124–126°C. IR (KBr, cm^{-1}): 670.96, 1377, 1662, 3363 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.67 (s, 1H, NH), 6.64-7.80 (m, 12H, Ar-*H*), 4.88-4.98 (*J* = 2.26 Hz, d, 1H, H-4), 4.64- 4.65 (*J* = 2.12 Hz, d, 1H, H-3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 45.24, 49.49, 117.09, 126.94, 127.05, 127.14, 127.14, 127.47, 127.97, 128.47, 128.47, 129.49, 130.05, 131.80, 132.27, 132.39, 133.87, 136.6, 139.59, 153.52, 156.45, 160.49. Anal. Calcd for: $C_{22}H_{15}Cl_2N_3OS$ (440.35); C, 59.93; H, 3.37; Cl, 16.04; N, 9.43; O, 3.57; S, 7.23. Found: C, 60.01; H, 3.43; Cl, 16.10; N, 9.54; O, 3.63; S, 7.28%.

3-Chloro-1-(dibenzo[b,*f*][1,4]thiazepin-11-yl amino)-4-(2-chloro phenyl)azetidin-2-one, 2f: The product was obtained as off white solid, Yield 78%. m.p.152–154°C. IR (KBr, cm^{-1}): 670, 1377, 1662, 3363 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.62 (s, 1H, NH), 6.74-8.08 (m, 12H, Ar-*H*), 4.86 (*J* = 2.26 Hz, d, 1H, H-4), 4.62 (*J* = 2.20 Hz, d, 1H, H-3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 45.18, 49.68, 117.09, 126.94, 126.78, 126.92, 127.47, 129.49, 129.73, 130.05, 130.12, 130.82, 132.26, 132.27, 132.39, 133.87, 133.96, 134.60, 139.73, 153.57, 156.52, 160.79. Anal. Calcd for: $C_{22}H_{15}Cl_2N_3OS$ (440.35); C, 59.93; H, 3.29; Cl, 16.01; N, 9.46; O, 3.57; S, 7.23. Found: C, 60.01; H, 3.43; Cl, 16.10; N, 9.54; O, 3.63; S, 7.28%.

3-Chloro-1-(dibenzo[b,*f*][1,4]thiazepin-11-yl amino)-4-(2,3-di chloro phenyl) azetidin-2-one, 2g: The product was obtained as off white soild, Yield 75%; mp 184–186°C. IR (KBr, cm^{-1}): 670, 1384, 1670, 3429 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.67 (s, 1H), 6.64-7.86 (m, 11H, Ar-*H*), 4.64 (*J* = 2.16 Hz, d, 1H, H-4); 4.51 (*J* = 2.06 Hz, d, 1H, H-3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 45.32, 49.54, 119.42, 125.65, 127.45, 128.12, 129.02, 129.19, 129.27, 130.08, 130.27, 130.76, 131.98, 131.71, 131.71, 133.47, 133.87, 136.05, 137.98, 139.04, 153.45, 161.29. Anal. Calcd for: $C_{22}H_{14}Cl_3N_3OS$ (474.79); C, 55.43; H, 2.65; Cl, 22.62; N, 8.56; O, 3.23; S, 6.79. Found: C, 55.65; H, 2.97; Cl, 22.40; N, 8.85; O, 3.37; S, 6.75%.

3-Chloro-1-(dibenzo[b,*f*][1,4]thiazepin-11-yl amino)-4-(4-*N*,*N*-Dimethyl amino phenyl) azetidin -2-one, 2h: The product was obtained as orange crystals, Yield 70%. m.p.104–106°C. IR (KBr, cm^{-1}): 670, 1662, 1377, 3363 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.7 (s, 1H, NH), 6.69-7.99 (m, 12H, Ar-*H*), 4.79-5.01 (*J* = 2.28 Hz, d, 1H, H-4), 4.59-4.63 (*J* = 2.18 Hz, d, 1H, H-3), 2.94 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 41.1, 45.16, 49.57, 111.42, 111.42, 119.42, 123.56, 127.45, 127.64, 128.12, 128.12, 129.02, 129.19, 129.27, 130.27, 131.98, 133.47, 136.05, 137.98, 139.45, 153.85, 161.24, 160.42. Anal. Calcd for: $C_{24}H_{21}ClN_4OS$ (448.11); C, 64.10; H, 4.67; Cl, 7.82; N, 12.44; O, 3.51; S, 7.14. Found: C, 64.20; H, 4.71; Cl, 7.90; N, 12.48; O, 3.56; S, 7.14%.

3-Chloro-1-(dibenzo[b,*f*][1,4]thiazepin-11-yl amino)-4-(4-flourophenyl)azetidin-2-one, 2i: The product was isolated as off white solid; Yield 68%. m.p.142-145°C; IR (KBr, cm^{-1}): 670, 1377, 1227, 1682, 3363 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.63 (s, 1H, NH), 6.72-7.91 (m, 12H, Ar-*H*), 4.66-4.71 (*J* = 2.10 Hz, d, 1H, H-3), 4.52-4.58 (*J* = 2.02 Hz, d, 1H, H-3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 45.27, 49.61, 115.42, 115.42, 117.72, 127.38, 127.69, 128.14, 128.14, 129.12, 129.19, 129.27, 130.27, 131.98, 133.77, 136.13, 138.98, 139.63, 153.52, 156.45, 160.28, 161.13. Anal. Calcd for: $C_{22}H_{15}ClFN_3OS$ (423.89); C, 62.23; H, 3.55; Cl, 8.32; F, 4.43; N, 9.86; O, 3.73; S, 7.49. Found: C, 62.34; H, 3.57; Cl, 8.36; F, 4.48; N, 9.91; O, 3.77; S, 7.56%.

3-Chloro-1-(dibenzo[b,*f*][1,4]thiazepin-11-yl amino)-4-(2-nitro phenyl)azetidin-2-one, 2j: The product was obtained as off white crystals, Yield 78%. m.p.194–198°C. IR (KBr, cm^{-1}): 670, 1348, 1525, 1662, 3379 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.76 (s, 1H), 7.00-8.20 (m, 12H, Ar-*H*), 4.64 (*J* = 5.80 Hz, d, 1H, H-3), 4.48 (*J* = 5.62 Hz, d, 1H, H-3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 45.31, 49.57, 121.92, 125.65, 128.27, 129.05, 129.24, 129.39, 129.77, 129.77, 130.27, 130.89, 131.98, 132.79, 133.47, 133.87, 136.05, 137.98, 138.41, 147.69, 161.29, 162.11; EI-MS: *m/z* 450.9 (M^+), 451.8 (M + 1), 452.8 (M + 2). Anal. Calcd for: $C_{22}H_{15}ClN_4O_3S$ (450.90); C, 58.53; H, 3.23; N, 12.38; O, 10.59; S, 6.98. Found: C, 58.60; H, 3.35; Cl, 7.86; N, 12.43; O, 10.65; S, 7.11%.

3-Chloro-1-(dibenzo[b,*f*][1,4]thiazepin-11-yl amino)-4-(3-nitro phenyl)azetidin-2-one, 2k: The product was isolated as pale yellow soild, Yield 60%. m.p.246-248°C. IR (KBr, cm^{-1}): 670, 1348, 1525, 1666, 3393 cm^{-1}; ^{1}H NMR (400.0 MHz, DMSO-d_6): δ

8.61 (s, 1H, NH), 7.01-8.30 (m, 12H, Ar-*H*), 4.72 (*J* = 6.06 Hz, d, 1H, H-4), 4.56-4.59 (*J* = 5.68 Hz, d, 1H, H-3); ^{13}C NMR (400.0 MHz, DMSO-d_6): δ 45.50, 49.52, 121.92, 122.56, 125.65, 129.05, 129.24, 129.39, 129.39, 129.77, 130.08, 130.27, 131.98, 132.79, 133.47, 133.83, 136.05, 137.98, 138.41, 147.69, 150.57, 162.11; EI-MS: *m/z* 450.9 (M^+), 451.8 (M + 1), 452.8 (M + 2). Anal. Calcd for: $C_{22}H_{15}ClN_4O_3S$ (450.90): C, 58.23; H, 3.05; Cl, 7.62; N, 12.86; O, 10.03; S, 6.79. Found: C, 58.60; H, 3.35; Cl, 7.86; N, 12.43; O, 10.65; S, 7.11%.

General procedure for the synthesis of 3-(dibenzo[*b,f*][1,4]thiazepin-11-yl amino)-2-(substituted phenyl) thiazolidin-4-one, 3a-k: To the stirred solution of (*Z*)-11-(2-(substituted benzylidene) hydrazinyl) dibenzo[b,*f*][1,4]thiazepine **1a-k** (3.43 g, 0.01 mol) in 20 mL of dioxane, catalytic amount of $ZnCl_2$ (1.68 g, 0.02 mol) was added at 0°C. The solution of thioglycolic acid (1.68 g, 0.02 mol) in 5 mL dioxane was then added drop wise at the same temperature. The resulting reaction mixture was stirred for 16 h at 80-85°C. Completion of reaction was checked on TLC, the reaction mixture was concentrated under vacuum at 60-65°C to remove dioxane. The residue was poured into crushed ice, the reaction mixture was neutralized with 5% sodium bicarbonate solution and resultant solid was filtered off and washed with cold water. The white product was recrystallized with ethanol to afford 3-(dibenzo[b,*f*][1,4]thiazepin-11-yl amino)-2-(substituted phenyl) thiazolidin-4-one **3a-k**. The structure of the compound **3a-k** was confirmed by ^{1}H NMR, ^{13}C NMR and HRMS analysis. mp: 214–216°C. IR (KBr): 3363, 1704, 1632, 1572, 1470, 1405, 1374 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.34 (d, 3H), 3.89 (d,1H), 3.99 (d, 1H), 5.82 (s, 1H, CH), 7.06 (m, 2H), 7.12–7.15 (m, 2H), 7.23–7.27 (m, 2H), 7.29–7.31 (m, 2H), 7.41 (s, 1H), 7.59 (s, 1H), 7.61–7.63 (m, 2H), 8.34 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.11, 35.22, 60.78, 114.27, 114.27, 118.64, 127.54, 127.54, 129.31, 129.78, 130.03, 130.03, 130.38, 131.04, 131.46, 132.20, 133.94, 136.22, 138.40, 153.45, 154.98, 156.40, 168.96; EI-MS: *m/z* 417.58 (M^+), 418.64 (M+1), 419.64 (M+2). Anal. Calcd for: $C_{23}H_{19}N_3OS_2$ (417.55): C, 66.16; H, 4.59; N, 10.06; O, 3.83; S, 15.36. Found: C, 66.23; H, 4.48; N, 10.16; O, 3.76; S, 15.28%.

3-(Dibenzo[b,*f*][1,4]thiazepin-11-yl amino)-2-(4-methoxy phenyl)thiazolidin-4-one, 3b: The product was obtained as off white soild, Yield 68%. m.p. 194–196°C. IR (KBr): 3384, 1696, 1629, 1583, 1470, 1405, 1383, 758 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.91 (s, 3H), 3.89 (d, 1H), 3.99 (d, 1H), 5.82 (s, 1H), 7.12–7.15 (m, 2H), 7.23–7.27 (m, 3H), 7.29–7.31 (m, 3H), 7.41 (s, 1H), 7.59 (s, 1H), 7.69–7.70 (m, 2H), 8.29 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 35.22, 55.17, 60.78, 118.64, 114.62, 114.62, 127.17, 128.67, 128.67, 129.33, 129.97, 130.82, 131.47, 132.27, 132.73, 133.79, 135.25, 138.18, 154.64, 155.64, 156.52, 168.96. Anal. Calcd for: $C_{23}H_{19}N_3O_2S_2$ (433.55): C, 63.72; H, 4.42; N, 9.69; O, 7.38; S, 14.79. Found: C, 63.93; H, 4.55; N, 9.86; O, 7.29; S, 14.68%.

3-(Dibenzo[b,*f*][1,4]thiazepin-11-yl amino)-2-(2,5-dimethoxy phenyl)thiazolidin-4-one, 3c: The product was obtained as white needles, Yield 72%. m.p.226–228°C. IR (KBr): 3384, 1702, 1640, 1572, 1478, 1376, 759 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.94 (d, 6H), 3.81 (d, 1H), 3.94 (d,1H), 5.81 (s, 1H), 6.95 (s, 1H), 7.17–7.19 (m, 2H), 7.22–7.25 (m, 3H), 7.32 (s, 1H), 7.40–7.42 (m, 2H), 7.61–7.62 (s, 1H), 8.10 (s, 1H), 8.63 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 35.22, 55.87, 56.17, 60.78, 112.47, 113.47, 113.92, 113.92, 117.27, 124.06, 125.65, 129.05, 129.05, 129.24, 130.08, 130.76, 132.79, 133.83, 136.05, 138.41, 150.69 , 154.24, 169.13. Anal. Calcd for: $C_{24}H_{21}N_3O_3S_2$ (463.10): C, 62.18; H, 4.57; N, 9.06; O, 10.35; S, 13.83. Found: C, 62.23; H, 4.52; N, 9.19; O, 10.42; S, 13.71%.

3-(Dibenzo[b,*f*][1,4]thiazepin-11-yl amino)-2-(3,4,5-trimethoxy phenyl)thiazolidin -4-one, 3d: The product was obtained as yellow needles, Yield 70%. mp 286–288°C. IR (KBr): 3367, 1679, 1634, 1570, 1468, 1368, 763 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.94 (d, 9H), 3.91 (d,1H), 4.02 (d,1H), 5.76 (s, 1H), 7.14 (m, 2H), 7.22–7.25 (m, 3H), 7.32 (s, 2H), 7.44 (s, 1H), 7.61–7.62 (s, 1H), 8.38 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 35.22, 55.17, 58.60, 59.87, 60.78, 107.28, 107.28, 113.94, 127.08, 128.47, 128.47, 129.49, 129.89, 130.65, 131.93, 132.26, 133.79, 134.04, 136.02, 139.49, 153.12, 153.14, 156.27, 160.29, 168.22. Anal. Calcd for: $C_{25}H_{23}N_3O_4S_2$ (493.60): C, 63.83; H, 4.70; N, 8.51; O, 12.97; S, 12.99. Found: C, 63.89; H, 4.63; N, 8.66; O, 12.89; S, 12.89%.

3-(Dibenzo[b,*f*][1,4]thiazepin-11-yl amino)-2-(4-chloro phenyl)thiazolidin-4-one, 3e: The product was obtained as white needles, Yield 65%; mp 196–198°C. IR (KBr): 3342, 1697, 1628, 1568, 1470, 689, 659 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.93-3.94 (d, 1H), 4.00-4.11 (d, 1H), 5.81 (s, 1H), 7.16 (s, 1H), 7.26–7.27 (m, 3H), 7.32 (s, 1H), 7.42–7.43 (m, 2H), 7.47 (s, 1H), 7.55–7.56 (m, 2H), 7.61–7.63

(m, 2H), 8.12 (s, 1H), 8.62 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 35.12, 60.59, 124.06, 125.65, 129.05, 129.05, 129.24, 129.77, 129.77, 130.08, 130.27, 130.27, 130.76, 132.45, 132.79, 133.83, 136.05, 137.71, 138.41, 150.69, 154.24, 169.13. Anal. Calcd for: $C_{22}H_{16}ClN_3OS_2$ (437.96): C, 60.33; H, 3.68; Cl, 8.09; N, 9.59; O, 3.65; S, 14.64. Found: C, 60.42; H, 3.62; Cl, 8.16; N, 9.67; O, 3.58; S, 14.53%.

3-(Dibenzo[b,*f*][1,4]thiazepin-11-yl amino)-2-(2-chloro phenyl)thiazolidin-4-one, 3f: The product was obtained as white needles, Yield 76%; mp 204–206°C. IR (KBr): 3358, 1703, 1630, 1582, 1474, 1371, 706, 662 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.89 (d, 1H, 5-H_b), 3.99 (d,1H, 5-H_a), 5.82 (s, 1H, CH, N-CH-Ar), 7.16 (s, 1H), 7.26–7.27 (m, 3H), 7.32 (s, 1H), 7.42–7.43 (m, 2H), 7.47 (s, 1H), 7.55–7.56 (m, 2H), 7.61–7.63 (m, 2H), 8.12 (s, 1H), 8.62 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 35.22, 60.78, 101.82, 117.90, 126.94, 126.78, 126.92, 127.47, 129.49, 129.73, 130.05, 130.12, 130.82, 132.27, 132.39, 133.87, 133.96, 139.7, 153.57, 156.52, 168.34. Anal. Calcd for: $C_{22}H_{16}ClN_3OS_2$ (437.96): C, 60.33; H, 3.68; Cl, 8.09; N, 9.59; O, 3.65; S, 14.64. Found: C, 60.42; H, 3.62; Cl, 8.16; N, 9.67; O, 3.58; S, 14.53%.

3-(Dibenzo[b,*f*][1,4]thiazepin-11-yl amino)-2-(2,3-dichloro phenyl)thiazolidin-4-one, 3g: The product was obtained as brown needles. Yield 74%. m.p. 246–248°C. IR (KBr): 3349, 1698, 1650, 1513, 1470, 1378, 761 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.88-3.92 (d, 1H), 4.04-4.08 (d, 1H), 5.81 (s, 1H), 6.94-7.40 (m, 5H), 7.41-7.43 (s, 1H), 7.52-7.59 (m, 2H), 7.72-7.75 (s, 1H), 7.83-7.85 (s, 1H), 7.99-7.01 (s, 1H), 8.40 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 35.1, 60.5, 103.9, 124.0, 125.6, 129.0, 129.2, 129.3, 129.7, 130.1, 130.3, 130.8, 132.8, 133.5, 133.8, 136.0, 138.4, 150.7, 154.3, 169.11. Anal. Calcd for: $C_{22}H_{15}C_{l2}N_3OS_2$ (472.41): C, 55.43; H, 3.34; Cl, 15.12; N, 8.67; O, 3.41; S, 13.53. Found: C, 55.93; H, 3.20; Cl, 15.01; N, 8.89; O, 3.39; S, 13.58%.

3-(Dibenzo[b,*f*][1,4]thiazepin-11-yl amino)-2-(4-dimethyl amino phenyl) thiazolidin-4-one, 3h: The product was obtained as Orange crystals, Yield 70%; mp 204–206°C. IR (KBr): 3359, 1702, 1634, 1472, 1378, 759 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.94 (s, 6H), 3.70-3.71 (d, 1H), 3.87-3.89 (d, 1H), 5.81(s, 1H), 6.69-6.71(m, 2H), 7.02-7.04 (s, 1H), 7.31 -7.35 (m, 2H), 7.42-7.45 (s, 1H), 7.53-7.59 (m, 2H), 7.74-7.76 (s, 1H), 7.85-7.89 (s, 1H), 7.97-7.99 (m, 2H), 8.42 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 35.12, 41.20, 60.59, 112.61, 112.62, 124.06, 125.65, 129.05, 129.05, 129.24, 129.39, 129.77, 129.77, 130.08, 130.76, 132.79, 133.83, 136.05, 138.41, 154.69, 150.69, 154.24, 169.13; EI-MS: *m/z* 372.60 (M^+), 373.56 (M+1). Anal. Calcd for: $C_{24}H_{22}N_4OS_2$ (446.59): C, 64.55; H, 4.97; N, 12.55; O, 3.58; S, 14.36. Found: C, 64.43; H, 5.03; N, 12.68; O, 3.53; S, 14.29%.

3-(Dibenzo[b,*f*][1,4]thiazepin-11-yl amino)-2-(4-fluoro phenyl)thiazolidin-4-one, 3i: The product was botanized as white needles, Yield 68%; mp 234–236°C. IR (KBr): 3371, 1692, 1652, 1572, 1474, 1378, 1239, 763 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.81-3.82 (d, 1H), 3.98-4.0 (d, 1H), 5.86 (s, 1H), 7.17–7.19 (m, 2H), 7.22–7.25 (m, 3H), 7.32– 7.35 (m, 3H), 7.44 (s, 1H), 7.61–7.62 (s, 1H), 7.81 (m, 2H), 8.38 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 35.12, 60.59, 115.74, 115.74, 124.06, 125.65, 129.05, 129.05, 129.24, 130.08, 130.27, 130.27, 130.76, 132.79, 133.47, 133.83, 136.05, 138.41, 150.69, 154.24, 161.19, 169.13. Anal. Calcd for: $C_{22}H_{16}FN_3OS_2$ (421.07): C, 62.69; H, 3.83; F, 4.51; N, 9.97; O, 3.80; S, 15.21. Found: C, 62.93; H, 3.92; F, 4.47; N, 9.86; O, 3.83; S, 15.18%.

3-(Dibenzo[b,*f*][1,4]thiazepin-11-yl amino)-2-(2-nitro phenyl)thiazolidin-4-one, 3j: The product was obtained as yellow needles. Yield 72%. m.p.202–204°C. IR (KBr): 3280, 1678, 1650, 1527, 1525, 1350, 1474, 870 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.86 (d, 1H), 4.02 (d, 1H), 5.89 (s, 1H), 7.17–7.19 (m, 2H), 7.22–7.24 (m, 3H), 7.31 (s, 1H), 7.39 (s, 1H), 7.61 (s, 1H), 7.81 (s, 1H), 8.26–8.29 (m, 2H), 8.46–8.49 (s, 1H), 8.67 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 35.12, 60.59, 122.77, 124.06, 124.94, 125.65, 129.05, 129.05, 129.24, 129.39, 130.08, 130.76, 132.79, 133.83, 136.05, 138.41, 140.41, 149.07, 153.69, 154.24, 169.13. Anal. Calcd for: $C_{22}H_{16}N_4O_3S_2$ (448.52): C, 58.91; H, 3.60; N, 12.49; O, 10.70; S, 14.30. Found: 58.83; H, 3.45; N, 12.86; O, 10.63; S, 14.39%.

3-(Dibenzo[b,*f*][1,4]thiazepin-11-yl amino)-2-(3-nitro phenyl)thiazolidin-4-one, 3k: The product was obtained as yellow needles. Yield 74%. m.p.218–220°C. IR (KBr): 3280, 1678, 1650, 1527, 1525, 1350, 1474, 870 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.86 (d, 1H), 4.02 (d, 1H), 5.89 (s, 1H, CH), 7.17–7.19 (m, 2H), 7.22–7.24 (m, 3H), 7.31 (s, 1H), 7.39 (s, 1H), 7.61 (s, 1H), 7.81 (s, 1H), 8.26–8.29 (m, 2H), 8.46–8.49 (s, 1H), 8.83 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 35.12, 60.59, 122.77, 124.06, 124.94, 125.65, 129.05,

129.05, 129.24, 129.39, 130.08, 130.76, 132.79, 133.83, 136.05, 138.41, 140.41, 149.07, 153.69, 154.24, 169.13; EI-MS: *m/z* 448.58 (M^+), 449.52 (M+1). Anal. Calcd for: $C_{22}H_{16}N_4O_3S_2$ (448.52): C, 58.91; H, 3.60; N, 12.49; O, 10.70; S, 14.30. Found: 58.83; H, 3.45; N, 12.86; O, 10.63; S, 14.39%.

Conclusion

We have described here a simple approach for the synthesis of 2-azetidinone and thiazolidine-4-one derivatives of dibenzothiazepine. Synthesized compounds were screened for antibacterial, antifungal and antitubercular activity. From our observations, we can conclude that nitro, halogen, methyl and methoxy groups can impart a positive effect for biological activity *i.e*. activity increasing effect. The present work will be useful for understanding antimicrobial and antitubercular activity of 2-azetidinone and thiazolidine-4-one of dibenzothiazepines.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

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