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Synthesis and biological activity of triazolo derivative of Dibenzothiazepine

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Abstract: 11-chloro dibenzo[b,f][1,4]thiazepine (**2**) was prepared from dibenzo[b,f][1,4]thiazepin-11(*10H*)-one (**1**), dimethyl aniline and $POCl_3$, which on further treatment with hydrazine hydrate gave 11-hydrazinyl dibenzo[b,f][1,4]thiazepine **(5)**. The resulting 11-hydrazinyl dibenzo[b,f][1,4] thiazepine **(5)** was treated with substituted aromatic aldehydes to give the schiff base **6(b_1-b_{11})** which on treatment with bromine gas in presence of acetic acid gave the final compounds **7(D_1-D_{11})**. The synthesized compounds were characterized by elemental and spectral analysis (IR, ^{1}H NMR and mass spectrometry). All the compounds were screened for their biological activity against different strains of bacteria and fungi. All the compounds were screened for antitubercular activity compared with rifampicin.

Keywords: 11-chloro dibenzo[b,f][1,4]thiazepine, hydrazine hydrate, schiff base, 3-phenyl dibenzo[b,f][1,2,4]triazolo[4,3-d][1,4]thiazepine, antimicrobial activity, antitubercular activity.

Introduction

Heterocyclic compounds play an important role in designing new classes of structural entities of medicinal importance with potentially new mechanisms of action. These heterocyclic compounds are well known to possess diverse pharmacological [1,2] actions including antimicrobial [3,4], anti-tumor [5], antitubercular [6], anti-inflammatory, anticancer [7], antiviral [8], analgesic and antimigrain.

Several drugs containing 1,2,4-triazole group i.e. Etizolam, Alprazolam, Furacylin etc are well known. Literature survey reveals that most of the compounds having 1, 2, 4-triazole nucleus possess outstanding pharmacological activites identified by the medicinal chemists as pyrimidines [7], benzazepinone [8], phthalazine [9], pyrazolyl [10], quinoxaline [11], thiadiazoles [12] are in reported. Triazole and its different

types of derivatives were also synthesized by different method [13-15]. Tricyclic compounds like phenoxazines, acridones, phenothiazine, benzodiazepines and dibenzothiazepine are very important class of anticancer agents[16,17]. Compounds of 11-{4-[2-2- hydroxyethoxy)-ethyl] piperazinyl} dibenzo[b,f][1,4]thiazepine commonly known as quetiapine [18-20] **(2, Figure-1).** Dibenzo[b,f][1,4]thiazepin-11(*10H*)-one and its different types derivatives were also prepared [21-24], some of which were reported to exhibit antitubercular activity [25], useful agents for the prevention and treatment of AIDS [26] or HIV virus [27,28] while others act as leukotriene antagonists [29].

Experimental

General information

Melting points of the synthesized compounds were determined in open-glass capillaries on Stuart SMP10 melting point apparatus and are uncorrected. The purity of the compounds was checked by thin layer chromatography (TLC). Silica gel plates (Kieselgel 0.25 mm, 60G F254), obtained from Merck, Darmstadt (Germany), were used for TLC and the spots were visualized by ultraviolet light as visualizing agents. The IR spectra (ν, cm^{-1}) were obtained with a Perkin-Elmer 1600 FTIR spectrometer in KBr pellets. ^{1}H-NMR and ^{13}C-NMR spectra (δ, ppm) were recorded in DMSO-d_6 solutions on a Bruker-Avance 400 MHz spectrometer using tetramethylsilane as the internal reference. Elemental analysis was performed on an ECS 4010 Elemental Combustion System. The necessary chemicals were used from Loba Chemie, Sigma-Aldrich and analytical reagent grade.

Antimicrobial activity:

All MTCC cultures were collected from Institute of Microbial Technology, Chandigarh and tested against known drugs ampicillin and griseofulvin. Mueller Hinton broth was used as nutrient medium to grow and dilute the drug suspension for the test. Inoculum size for test strain was adjusted to 10^8 CFU (Colony Forming Unit) per milliliter by comparing the turbidity. DMSO was used as diluent to get desired concentration of drugs to test upon standard bacterial strains. Serial dilutions were prepared in primary and secondary screening. The control tube containing no antibiotic was immediately sub cultured (before inoculation) by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37°C overnight. The tubes were then incubated overnight. The MICs of compounds were carried out by broth microdilution method as described by Rattan [30,31]. 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, ampicillin was used as a standard antibacterial agent. Antifungal activity was screened against three fungal species *Candida albicans* MTCC 227, *Aspergillus niger* MTCC 282 and *Aspergillus clavatus* MTCC 1323, griseofulvin was used as a standard antifungal agent.

Synthesis of dibenzo[b,f][1,4]thiazepin-11(*10H*)-one **(1)**

The title compound was synthesized following a reaction according to a procedure described in the literature [22]. Yield 79%, m.p.260-265°C.

Synthesis of 11-hydrazinyl dibenzo [b,f][1,4] thiazepine **5(I_1)**

The mixture of dibenzo[b,f][1,4]thiazepin-11(*10H*)-one (6 gm, 1.0 mol) and dimetyl aniline (0.5 mL) in 25 mL toluene at -5°C to 0°C was added into RBF. $POCl_3$ (18 mL) was drop wise added in reaction mixture at 20-25°C. The reaction mass was heated to raise

the temperature 105-110°C within 45 min. and maintained for 5-6 hours at 105-110°C. The reaction mass was cooled to 20°C and poured into the mixture of 100 mL water and 40 mL toluene at 0-5°C. The reaction mass was stirred for 1 hour at 0-10°C and two phases separated. Aqueous phase was extracted with 20 mL toluene. Organic phase was washed with 10 mL 5% sodium chloride solution and separated. Organic phase was dried with 5 gm sodium sulphate and was filtered. The solution was carried on immediately to the next synthetic step [22]. Hydrazine hydrate (10ml, 99% w/w) in toluene was added dropwise in the reaction mass at 0-10°C. The reaction mass was heated to raise the temperature 60-65°C within 45 min then maintained for 8-10 hours at 60-65°C. After the completion of reaction as evident by TLC, the reaction mixture was washed with cold water and the organic phase was separated then washed with saturated sodium chloride solution, dried with sodium sulphate, acidified by 35 %w/v HCl solution and the solid mass obtained was separated out, filtered and washed with toluene and water, finally dried to give the compound **5(I_1)**.

Off white crystals, m.p. 168°C ; yield 80-85 %; IR (KBr, cm^{-1}): 3363 (-NH_2), 1625 (C=N str.), 1577 (-NH def),1191 (-C-N str.) ; ^{1}H NMR (400.1 MHz, $CHCl_3$): δ_H), 5.40 (d, 2H, NH_2), 6.11 (s, 1H, NH), 6.69-7.76 (m, 8H,Ar-H); ^{13}C NMR (400.0MHz, DMSO): δ_C 125.49 (CH,C-1), 127.17 (CH,C-3), 129.33 (CH,C-7; CH, C-10), 129.97 (CH, C-4), 130.82 (CH, C-9), 131.47 (CH, C-8), 132.27(CH, C-6), 132.73 (CH, C-5), 133.79 (CH, C-11), 137.64 (CH, C-12), 138.18 (CH, C-2), 160.75 (CH, C-13); Anal. Calcd for: $C_{13}H_{11}N_3S$ (241.31); Calaculation (C, 64.47; H, 4.41; N, 17.78; S, 13.04 %); found (C, 64.70; H, 4.59; N, 17.41; S, 13.29 %). MS (EI) *m*/*z*: 241.5 (M^+), 242.5 (M + 1).

Synthesis of (*Z*)-11-(2-(substituted benzylidene) hydrazinyl) dibenzo[b,f][1,4]thiazepine **6 (b_1-b_{11})**

To a stirred solution of hydrazinyl dibenzo[b,f] [1,4]thiazepine (**5**)(2.41 g, 10mmol) in 25 mL of absolute ethanol and 3-4 drops of acetic acid at 25- 30°C temperature in round bottom flask. Substituted aromatic aldehyde (10mmol) was added in reaction mass at 25- 30°C. Raised the temperature of reaction mass at 65-70°C to dissolved the reaction mass and maintain it for 3-4 hours at 65-70°C. The completion of reaction was confirmed by TLC. The reaction mixture was cooled and poured in crushed ice. The product obtained was filtered, washed with ethanol and dried in an oven at low temperature. The product was recrystallized from ethanol to give the compounds **6(b_1-b_{11})**.

Synthesis of substituted phenyl dibenzo[b,f] [1,2,4]triazolo[4,3-d][1,4]thiazepine **7(D_1-D_{11})**
A solution of schiff's base (0.01moles) and anhydrous sodium bicarbonate (0.02moles) in chloroform (20 ml) added at 20°C to 25°C into RBF. The reaction mixture was completely dissolved in chlroform and drop wise addition of bromine (3.0 mL, 0.01 moles) in reaction mixture at 20- 25°C within 30 min completed. The reaction mixture was stirred and maintained for 10-16 hours at 25-30°C and evaporated under vaccum. The residue was poured into crush ice. The product was filtered and washed with cold water. Thus crude product obtained was crystallized from ethanol to give compounds **7(D_1-D_{11})** [13].

2-nitrophenyldibenzo[b,f][1,2,4]triazolo[4,3-d] [1,4]thiazepine **7D_1**
Yellow crystals; m.p. 202°C; yield 74 %; IR (KBr, cm^{-1}): 1650 (C=N) , 1525.74 (NO_2-sy), 1382 (C-N), 839.26 (NO_2-Asy), 870.96 (O-disubstituted); ^{1}H NMR (400.1 MHz, DMSO-d_6, δ_H): 7.01 (m, 1H, DBT), 7.21- 7.32 (m, 3H, DBT and 1H, Ar), 7.39-7.56 (m, 2H, Ar), 7.82-7.84(m, 1H, DBT), 7.89-7.93 (m,2H, DBT), 8.31(m, 1H, DBT and 1H, Ar); ^{13}C NMR (400.1 MHz, DMSO-d_6, δ_c): 124.46 (CH, C-19), 127.43 (CH, C-15), 127.64 (CH, C-1), 129.25 (CH, C-4), 129.41 (CH, C-3), 130.04 (CH,

C-20), 130.16 (CH, C-5), 130.32 (CH, C-8), 130.97 (CH, C-7), 131.32 (CH, C-6), 132.22 (CH, C-2), 133.63 (CH, C-9; CH, C-10), 133.57 (CH, C-16), 135.47 (CH, C-18), 136.25 (CH, C-13), 150.08 (CH, C-17), 150.85 (CH, C-11), 153.45 (CH, C-12; CH, C-14); Anal. Calcd for: $C_{20}H_{12}N_4O_2S$ (372.40); Found (C, 64.43; H, 3.19; N, 13.98; O, 8.53; S, 8.57 %); Required: (C, 64.50; H, 3.25; N, 15.04; O, 8.59; S, 8.61 %).

3-nitrophenyldibenzo[b,f][1,2,4]triazolo[4,3-d][1,4]thiazepine **7D$_2$**

Pale yellow crystals, m.p. 218°C; yield 69 %; IR (KBr, cm^{-1}): 1648 (C=N), 1525.74 (NO_2-sy),1382 (C-N), 839.26 (NO_2-Asy); ^{1}H NMR (400.1 MHz, DMSO-d_6, δ_H): 6.98-8.28 (m, 12H,Ar-H); ^{13}C NMR (400.1 MHz, DMSO-d_6, δ_c): 123.01 (CH, C-17), 124.03 (CH, C-20), 127.64 (CH, C-1), 129.25 (CH, C-4), 129.41 (CH, C-3), 130.04 (CH, C-18), 130.16 (CH, C-5), 130.32 (CH, C-8), 130.97 (CH, C-7), 131.43 (CH, C-15), 131.32 (CH, C-6), 132.22 (CH, C-2), 133.63 (CH, C-9; CH, C-10), 133.57(CH, C-16), 136.25(CH, C-13), 148.38(CH, C-19), 150.85(CH, C-11), 153.45(CH, C-12; CH, C-14); Anal. Calcd for: $C_{20}H_{12}N_4O_2S$ (372.40); Found (C, 64.46; H, 3.22; N, 15.01; O, 8.51; S, 8.56); Required: (C, 64.50; H, 3.25; N, 15.04; O, 8.59; S, 8.61 %)

2,3-dichloro phenyl dibenzo[b,f][1,2,4] triazolo[4,3-d][1,4]thiazepine **7D$_3$**

Off white crystals; m.p. 248°C; yield 72 %; IR (KBr, cm^{-1}): 1628-1453 (C=N, C=C $_{Ar}$), 1382 (C-N), 670.96 (-Cl); ^{1}H NMR (400.1 MHz, DMSO-d_6, δ_H): 6.78-8.04 (m, 10H,Ar-H); ^{13}C NMR (400.1 MHz, DMSO-d_6, δ_c): 127.64 (CH, C-1), 129.25 (CH, C-4), 129.41 (CH, C-3), 129.07 (CH, C-16), 129.87 (CH, C-18), 130.16 (CH, C-5), 130.20 (CH, C-20) 130.32 (CH, C-8), 130.97 (CH, C-7), 131.07 (CH, C-19), 131.32 (CH, C-6), 132.22 (CH, C-2), 133.59 (CH, C-9; CH, C-10), 133.94 (CH, C-17), 136.25 (CH, C-13), 140.03 (CH, C-15), 150.85 (CH, C-11), 153.45 (CH, C-12; CH, C-14); Anal. Calcd for: $C_{20}H_{11}Cl_2N_3S$ (396.29); Found (C, 60.54; H, 2.73; Cl, 17.72; N, 10.53; S, 8.04 %); Required (C, 60.62; H, 2.80; Cl, 17.89; N, 10.60; S, 8.09 %).

4-*N,N*-dimethylaminophenyl dibenzo[b,f][1,2,4]triazolo[4,3-d][1,4]thiazepine **7D$_4$**

Orange crystals ; m.p. 204°C; yield 66 %; IR (KBr, cm^{-1}): 1632-1457 (C=N, C=C $_{Ar}$),1376 (C-N); ^{1}H NMR (400.1 MHz, DMSO-d_6, δ_H): 2.94 (m, 6H, -CH_3), 6.69 (m, 2H, DBT),7.02- 7.04 (m, 1H, DBT), 7.20- 7.22 (m, 2H, Ar), 7.31-7.35 (m, 1H, DBT), 7.42-7.45 (m, 1H, DBT), 7.53-7.58 (m, 2H, Ar), 7.74-7.76 (m, 1H, DBT), 7.85-7.87 (m,1H, DBT), 7.97-7.99 (m, 1H, DBT); ^{13}C NMR (400.1 MHz, DMSO-d_6, δ_c): 41.1 (C, -CH_3-N-CH_3), 111.43 (CH, C-15), 113.01 (CH, C-18; CH, C-19), 127.64 (CH, C-1), 129.25 (CH, C-4), 129.41 (CH, C-3), 129.87 (CH, C-16; CH, C-17), 130.16 (CH, C-5), 130.32 (CH, C-8), 130.97 (CH, C-7), 131.32 (CH, C-6), 132.22 (CH, C-2), 133.87 (CH, C-9; CH, C-10), 136.25 (CH, C-13), 150.85 (CH, C-11), 153.45 (CH, C-12; CH, C-14), 154.38 (CH, C-20); Anal. Calcd for: $C_{22}H_{18}N_4S$ (370.47); Found (C, 71.26; H, 4.83; N, 15.07; S, 8.58 %); Required: (C, 71.32; H, 4.90; N, 15.12; S, 8.66 %); MS (EI) *m/z*: 370.8(M^+), 371.8(M+ 1) and 372.8(M+ 2).

4-flouro phenyl dibenzo[b,f][1,2,4] triazolo[4,3-d][1,4]thiazepine **7D$_5$**

Off white crystals ; m.p. 236°C; yield 68 %; IR (KBr, cm^{-1}): 1628-1453 (C=N, C=C $_{Ar}$),1378 (C-N); ^{1}H NMR (400.1 MHz, DMSO-d_6, δ_H): 6.64-7.80 (m, 11H,Ar-H); ^{13}C NMR (400.1 MHz, DMSO-d_6, δ_c): 116.01 (CH, C-18; CH, C-19), 127.64 (CH, C-1), 129.17 (CH, C-16; CH, C-17), 129.25 (CH, C-4), 129.41 (CH, C-3), 130.03 (CH, C-15), 130.16 (CH, C-5), 130.32 (CH, C-8), 130.97 (CH, C-7), 131.32 (CH, C-6), 132.22 (CH, C-2), 133.87 (CH, C-9; CH, C-10), 136.25 (CH, C-13), 150.85 (CH, C-11), 153.45 (CH, C-12; CH, C-14), 163.08 (CH, C-20); Anal. Calcd for: $C_{20}H_{12}FN_3S$ (345.39); Found (C, 69.49; H, 3.44; F, 5.47; N, 12.08; S,

9.21 %); Required: (C, 69.55; H, 3.50; F, 5.50; N, 12.17; S, 9.28 %).

4-chloro phenyl dibenzo[b,f][1,2,4] triazolo[4,3-d][1,4]thiazepine **7D$_6$**
Off white crystals ; m.p. 198°C; yield 73 %; IR (KBr, cm^{-1}): 1628-1453 (C=N, C=C $_{Ar}$),1378 (C-N); ^{1}H NMR (400.1 MHz, DMSO-d$_6$, δ_H): 7.22(m, 1H, DBT),7.26(m, 2H, DBT), 7.32(m, 1H, DBT), 7.42(m, 2H, DBT), 7.47(m,1H, DBT), 7.56(m, 2H, Ar), 7.61(m, 2H, DBT), 8.12(m, 2H, Ar); ^{13}C NMR (400.1 MHz, DMSO-d$_6$, δ_c): 127.64 (CH, C-1), 129.25 (CH, C-4), 129.41 (CH, C-3), 129.87 (CH, C-16; CH, C-17), 129.87 (CH, C-18; CH, C-19), 130.16 (CH, C-5), 130.32(CH, C-8), 130.97 (CH, C-7), 131.32 (CH, C-6), 132.22 (CH, C-2), 132.80 (CH, C-15), 133.87 (CH, C-9; CH, C-10), 135.21 (CH, C-20), 136.25 (CH, C-13), 150.85 (CH, C-11), 153.45 (CH, C-12; CH, C-14); Anal. Calcd for: $C_{20}H_{12}ClN_3S$ (361.85); Found (C, 66.42; H, 3.32; Cl, 9.76; N, 11.57; S, 8.78 %); Required: (C, 66.39; H, 3.34; Cl, 9.80; N, 11.61; S, 8.86 %.)

2,5-dimethoxy phenyl dibenzo[b,f][1,2,4] triazolo[4,3-d][1,4]thiazepine **7D$_7$**
Off white crystals ; m.p. 226°C; yield 70 %; IR (KBr, cm^{-1}): 1628-1453 (C=N, C=C $_{Ar}$),1378 (C-N); ^{1}H NMR (400.1 MHz, DMSO-d$_6$, δ_H): δ_H 2.94 (d, 6H, OCH_3), 6.64-7.80 (m, 11H,Ar-H); ^{13}C NMR (400.1 MHz, DMSO-d$_6$, δ_c): 55.8 (-OCH_3), 112.24 (CH, C-16), 112.24 (CH, C-19), 115.28 (CH, C-20), 118.58 (CH, C-15), 127.64 (CH, C-1), 129.25 (CH, C-4), 129.41 (CH, C-3), 129.87 (CH, C-8), 130.16 (CH, C-5), 130.97 (CH, C-7), 131.32 (CH, C-6), 132.22 (CH, C-2), 133.87 (CH, C-9; CH, C-10), 136.25 (CH, C-11), 149.4 (CH, C-17), 150.85 (CH, C-13), 153.38 (CH, C-18), 153.61 (CH, C-12; CH, C-14); Anal. Calcd for: $C_{22}H_{17}N_3O_2S$ (387.45); Found (C, 68.16; H, 4.36; N, 10.79; O, 8.19; S, 8.18 %); Required (C, 68.20; H, 4.42; N, 10.85; O, 8.26; S, 8.28 %).

3,4,5-trimethoxy phenyl dibenzo[b,f][1,2,4] triazolo[4,3-d][1,4]thiazepine **7D$_8$**
Off white crystals ; m.p. 214°C; yield 69 %; IR (KBr, cm^{-1}): 1628-1453 (C=N, C=C $_{Ar}$),1378 (C-N); ^{1}H NMR (400.1 MHz, DMSO-d$_6$, δ_H): 2.94 (d, 9H, OCH_3), 6.64-7.80 (m, 10H,Ar-H); ^{13}C NMR (400.1 MHz, DMSO-d$_6$, δ_c): 55.8 (-OCH_3), 60.74 (-OCH_3), 104.24 (CH, C-16; CH, C-17), 125.08 (CH, C-15), 127.64 (CH, C-1), 129.25 (CH, C-4), 129.41 (CH, C-3), 129.87 (CH, C-8), 130.16 (CH, C-5), 130.97 (CH, C-7), 131.32 (CH, C-6), 132.22 (CH, C-2), 133.87 (CH, C-9; CH, C-10), 136.25 (CH, C-11), 139.20 (CH, C-20), 150.85 (CH, C-13), 153.38 (CH, C-18; CH, C-19), 153.61 (CH, C-12; CH, C-14); Anal. Calcd for: $C_{23}H_{19}N_3O_3S$ (417.48); Found (C, 66.09; H, 4.53; N, 10.01; O, 11.42; S, 7.59 %); Required (C, 66.17; H, 4.59; N, 10.07; O, 11.50; S, 7.68 %).

2-chloro phenyl dibenzo[b,f][1,2,4] triazolo[4,3-d][1,4]thiazepine **7D$_9$**
Off white crystals ; m.p. 206°C; yield 71 %; IR (KBr, cm^{-1}): 1628-1453 (C=N, C=C $_{Ar}$),1378 (C-N); ^{1}H NMR (400.1 MHz, DMSO-d$_6$, δ_H): 6.64-7.80 (m, 12H,Ar-H); ^{13}C NMR (400.1 MHz, DMSO-d$_6$, δ_c): 127.36 (CH, C-18), 127.64 (CH, C-1), 129.25 (CH, C-4; CH, C-19), 129.41 (CH, C-3), 129.87 (CH, C-16), 130.16 (CH, C-5; CH, C-20), 130.32 (CH, C-8), 130.97 (CH, C-7), 131.32 (CH, C-6), 132.22 (CH, C-2), 132.82 (CH, C-17), 133.87 (CH, C-9; CH, C-10), 136.25 (CH, C-13), 138.5 (CH, C-15), 150.85 (CH, C-11), 153.45 (CH, C-12; CH, C-14), 154.38 (CH, C-20); Anal. Calcd for: $C_{20}H_{12}ClN_3S$ (361.85); Found (C, 66.44; H, 3.30; Cl, 9.74; N, 11.54; S, 8.81 %); Required: (C, 66.39; H, 3.34; Cl, 9.80; N, 11.61; S, 8.86 %.).

4-methoxy phenyl dibenzo[b,f][1,2,4] triazolo[4,3-d][1,4]thiazepine **7D$_{10}$**
Off white crystals ; m.p. 194°C; yield 73 %; IR (KBr, cm^{-1}): 1628-1453 (C=N, C=C $_{Ar}$), 1378 (C-N); ^{1}H NMR (400.1 MHz, DMSO-d$_6$, δ_H): 2.94 (d, 3H, OCH_3), 6.64-7.80 (m, 12H,Ar-H); ^{13}C NMR (400.1 MHz, DMSO-d$_6$, δ_c): 55.8(-

OCH_3), 114.24 (CH, C-18; CH, C-19), 126.08 (CH, C-15) 127.64 (CH, C-1), 129.25 (CH, C-4), 129.41(CH, C-3), 129.87(CH, C-8), 130.16(CH, C-5), 130.32 (CH, C-16; CH, C-17), 130.97 (CH, C-7), 131.32 (CH, C-6), 132.22 (CH, C-2), 133.87 (CH, C-9; CH, C-10), 136.25 (CH, C-11), 150.85 (CH, C-13), 153.45 (CH, C-12; CH, C-14), 160.2 (CH, C-20); Anal. Calcd for: $C_{21}H_{15}N_3OS$ (357.43); Found (C, 70.53; H, 4.17; N, 11.71; O, 4.43; S, 8.91 %); Required (C, 70.57; H, 4.23; N, 11.76; O, 4.48; S, 8.97%).

4-methyl phenyl dibenzo[b,f][1,2,4] triazolo[4,3-d][1,4]thiazepine **$7D_{11}$**
Off white crystals ; m.p. 212°C; yield 69 %; IR (KBr, cm^{-1}): 1628-1453 (C=N, C=C_{Ar}),1378 (C-N);^{1}H NMR (400.1 MHz, DMSO-d_6, δ_H): 2.94 (d, 3H, CH_3), 6.96 (m, 1H, DBT),7.21-7.32 (m, 3H, DBT and 2H, Ar), 7.39-7.44 (m, 1H, DBT), 7.50-7.56 (m, 2H, Ar), 7.72-7.75(m, 1H, DBT), 7.82-7.85 (m,1H, DBT), 8.02(m, 1H, DBT); ^{13}C NMR (400.1 MHz, DMSO-d_6, δ_c): 23.2 (-CH_3), 126.08 (CH, C-16; CH, C-17) 127.64 (CH, C-1), 129.25 (CH, C-4), 129.41 (CH, C-3), 129.87 (CH, C-18; CH, C-19), 130.16 (CH, C-5), 130.32 (CH, C-8), 130.97 (CH, C-7), 131.32 (CH, C-6), 131.52 (CH, C-15), 132.82 (CH, C-20), 132.22 (CH, C-2), 133.87 (CH, C-9; CH, C-10), 136.25 (CH, C-11), 150.85 (CH, C-13), 153.45 (CH, C-12; CH, C-14); Anal. Calcd for: $C_{21}H_{15}N_3S$ (341.43); Found (C, 73.83; H, 4.39; N, 12.27; S, 9.24 %); Required (C, 73.87; H, 4.43; N, 12.31; S, 9.39 %).

Result and Discussion

Chemistry

The intermediate dibenzo[b,f][1,4]thiazepin-11(*10H*)-one **(1)** was prepared by following literature procedure [15,16] with optimized conditions. Synthesized compounds **7 (D_1-D_{11})** were prepared in good yields and purity. 11-chloro dibenzo[b,f][1,4]thiazepine **(4)** was prepared from dibenzo[b,f][1,4]thiazepin-11(*10H*)-one **(1)**, Dimethyl aniline and $POCl_3$, which on further treatment with hydrazine hydrate gave 11-hydrazinyl dibenzo[b,f][1,4] thiazepine **(5)**.11-hydrazinyl dibenzo[b,f] [1,4]thiazepine (**5**) and substituted aromatic aldehydes in 25 mL of absolute ethanol reacted at room tempurture for 3-5 hours to form schiff base derivatives **6(b_1-b_{11})**, which then cyclized with bromine and sodium carbonate to give final compounds **7 (D_1-D_{11})**. The synthesized compounds were characterized on the basis of the spectral and analytical studies **(Scheme I)**.

Charactication

The IR spectra of compounds **7(D_1-D_{11})** showed the N-H bending vibrations are observed as a sharp medium to strong band at 1540-1500 cm $^{-1}$ in compounds **7(D_1-D_{11})**. The C-S-C linkage of the seven member ring caused a weak and sharp absorption band at 800 - 760 cm^{-1} in all the compounds. Also, for the compounds **$7D_1$** and **$7D_2$**, the vibration bands of the NO_2 group are present in the ranges 1514–1534 cm^{-1} and 1346–1356 cm^{-1}, respectively. The C-H (aliphatic and aromatic), C=C stretching vibrations are observed at their usual positions. Further, ^{1}H NMR spectra exhibited multiplets in the region at δ 6.69-7.99 ppm for 12 aromatic protons **$7D_4$** (8 aromatic protons were dibenzo [b,f][1,4]thiazepines and 4 aromatic protons were benzene). ^{1}H NMR spectra exhibited singlet in the region at δ 2.94 ppm for six protons of dimethyl amine group of dye **$7D_4$**. ^{13}C NMR spectra exhibited multiplets in the region at δ 111.43-153.98 and176.24 ppm for 20 carbons of compounds**$7D_4$** and two carbons of –N $(CH_3)_2$ at 41.3 ppm respectively. Similarly, all these compounds were purified by column chromatography and characterized on the basis of spectral studies.

Biological activity

Antibacterial activity

The minimum inhibitory concentration (MIC) of the tested compounds **7(D_1-D_{11})** are shown in (**Table I, Figure-II**). Most of the compounds tested, exhibited considerable activities against four bacterial species, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococcus pyogenes*. Triazolo compounds **7D_9 (2-Cl)** and **7D_{11} (4-CH_3)** exhibited very good activity at 62.5 µg/mL; **7D_1 (2-NO_2)**, **7D_3 (2,3-Cl)**, and **7D_4 (4-N-(CH_3)$_2$)** exhibited a good activity at 100 µg/mL against *Escherichia coli* as compared to Ampicillin (MIC=100 µg/mL). Compounds **7D_1 (2-NO_2)** and **7D_9 (2-Cl)** exhibited good activity against *Pseudomonas aeruginosa* at 100 µg/mL as compared to Ampicillin (MIC= 100 µg/mL). Compounds **7D_3 (2,3-Cl)**, **7D_7 (2,5- OCH_3)**, **7D_9 (2-Cl)** and **7D_{10} (4-OCH_3)** exhibited very good activity at 100-125 µg/mL; **7D_2 (3-NO_2)**, **7D_5 (4-F)**, **7D_6 (4-Cl)**, **7D_8 (3,4,5-OCH_3)** and **7D_{11} (4-CH_3)** exhibited good activity at 100-250 µg/mL; against *Staphylococcus aureus* as compared to Ampicillin (MIC= 250 µg/mL). Compounds **7D_3 (2,3-Cl)** and **7D_{10} (4-OCH_3)** exhibited good activity against *Streptococcus pyogenes* at 100 µg/mL as compared to Ampicillin (MIC= 100 µg/mL).

Antifungal activity

The minimum inhibitory concentration (MIC) of the tested compounds **7(D_1-D_{11})** is shown in (**Table II, Figure IV**). Most of the compounds possessed very good antifungal activity against *Candida albicans*; their MIC values were in the range between (100-500 µg/ml).

As far as the anti-fungal activity is concerned for triazolo compounds; **7D_3 (2,3-Cl)**, **7D_7 (2,5-OCH_3)** and **7D_9 (2-Cl)** showed excellent activity at 250 µg/mL and compound **7D_6 (4-Cl)** showed good 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.

Antitubercular activity

The encouraging results from the antibacterial studies impelled us to go for preliminary screening against *M. tuberculosis*; the results are summarized in (**Table II, Figure IV**). 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 antitubercular activity data were compared with rifampicin at a 40 µg/ml concentration. Triazole, compounds **7D_2 (3-NO_2)**, **7D_3 (2,3-Cl)** and **7D_5 (4-F)** containing nitro**,** chloro and fluoro substituent showed *M. tuberculosis* MIC value in the range between 62.5 µg/ml which indicated better activity. The highest dilution showing at least 95-99 % inhibition growth is taken as MIC. Remaining compounds showed moderate to weak activity against $H_{37}Rv$ strain.

Conclusion

Compounds **7D_3**, **7D_5**, **7D_7**, **7D_9**, **7D_{10}** and **7D_{11}** were possessed excellent activity comparable to ampicillin for different four species. Compounds **7D_3**, **7D_7** and **7D_9** showed good activity of 250 µg/ml comparable to griseofulvin. Compounds bearing fluoro, chloro, methoxy and methyl derivatives are more effective to inhibit the both bacterial and fungal species. Compounds **7D_2**, **7D_3** and **7D_5** having nitro, chloro and flouro derivatives exhibited *M. tuberculosis* MIC value 62.5 µg/ml comparable with rifampicin. From this observations, we can conclude that nitro, halogen, methyl and methoxy groups can impart a positive effect for biological activity i.e. activity increasing effect. Present work will

be useful for understanding antimicrobial and antitubercular activity of triazolo derivatives of dibenzothiazepines.

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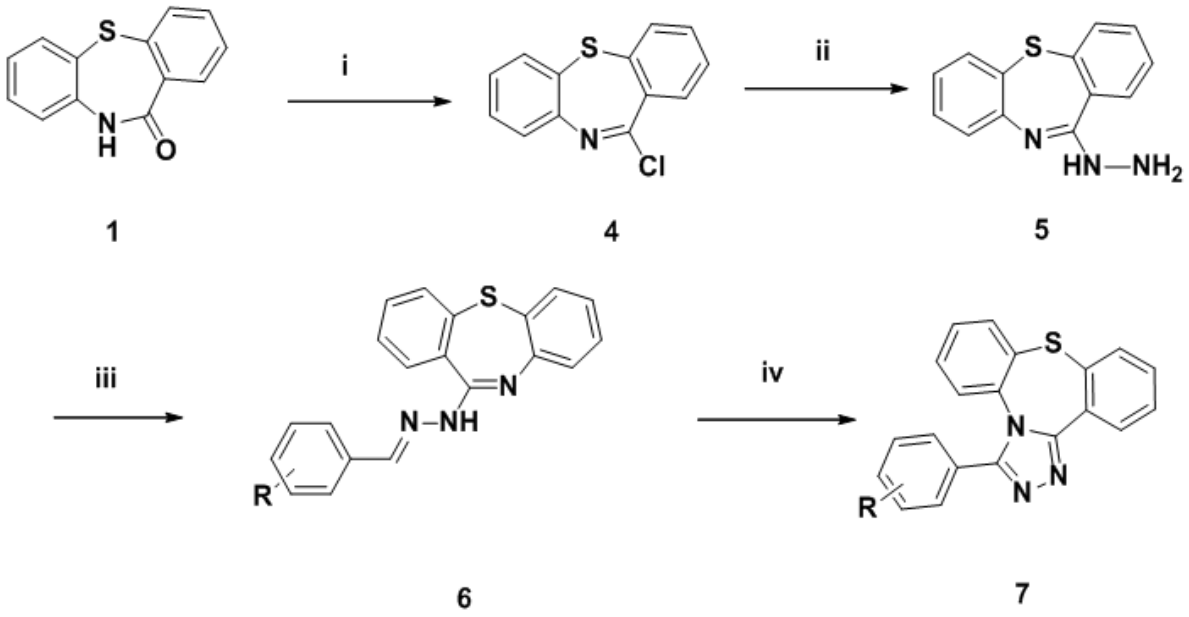
Table I Antimicrobial activity data of synthesized compounds:

Compds. No.	*E. Coli* MTCC 443	*P. Aeruginosa* MTCC 1688	*S. Aureus* MTCC 96	*S. Pyogenus* MTCC 442
$7D_1$	100	100	500	250
$7D_2$	125	250	250	500
$7D_3$	100	125	100	100
$7D_4$	100	250	500	500
$7D_5$	250	250	200	250
$7D_6$	200	200	250	200
$7D_7$	200	250	125	200
$7D_8$	125	250	200	250
$7D_9$	62.5	100	125	200
$7D_{10}$	200	250	125	100
$7D_{11}$	62.5	250	200	200
Ampicillin	100	100	250	100
Chloramphenicol	50	50	50	50

Table-II Antifungal and anti tubercular activity (MIC) of synthesis compounds:

Compds. No.	C.Albicans MTCC 227	A.Niger MTCC 282	A.Clavatus MTCC 1323	H37RV MIC µg/ml
$7D_1$	>1000	500	500	100
$7D_2$	>1000	1000	1000	62.5
$7D_3$	250	>1000	>1000	62.5
$7D_4$	>1000	>1000	>1000	100
$7D_5$	1000	500	500	62.5
$7D_6$	500	500	500	250
$7D_7$	250	1000	1000	500
$7D_8$	1000	>1000	>1000	500
$7D_9$	250	>1000	>1000	100
$7D_{10}$	>1000	500	500	1000
$7D_{11}$	>1000	500	500	250
Griseofulvin	500	100	100	-
Rifampicin	-	-	-	40
Isoniazid	-	-	-	0.2

Scheme-I. Synthesis of sub. phenyl dibenzo[b,f][1,2,4]triazolo[4,3-d][1,4]thiazepine**7 (D_1-D_{12})**



Reagents and Conditions : i) $POCl_3$, Dimethyl aniline, 100-105^{0}C ii) hydrazine hydrate (99% w/v), Na_2CO_3 iii) Aromatic aldehyde, Acetic acid, RT iv) 10-16 hours, RT.

R: 2-NO_2; 3-NO_2; 2,3-Cl; 4-$N(CH_3)_2$; 4-F; 4-Cl; 2,5-OCH_3; 3,4,5-OCH_3; 2-Cl; 4-OCH_3; 4-CH_3.

Figure-I Structures of dibenzo [b,f] [1,4] thiazepine-11(10H)-ones (1), quetiapine (2) and 3-subtituted phenyl dibenzo[b,f][1,2,4]triazolo[4,3-d][1,4] thiazepine derivatives (7)

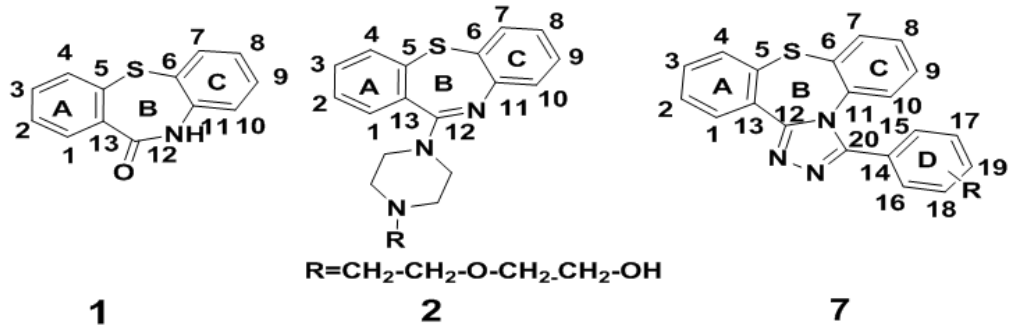


Figure-II Antibacterial activity (MIC) of compounds **$7D_1$-$7D_{11}$**

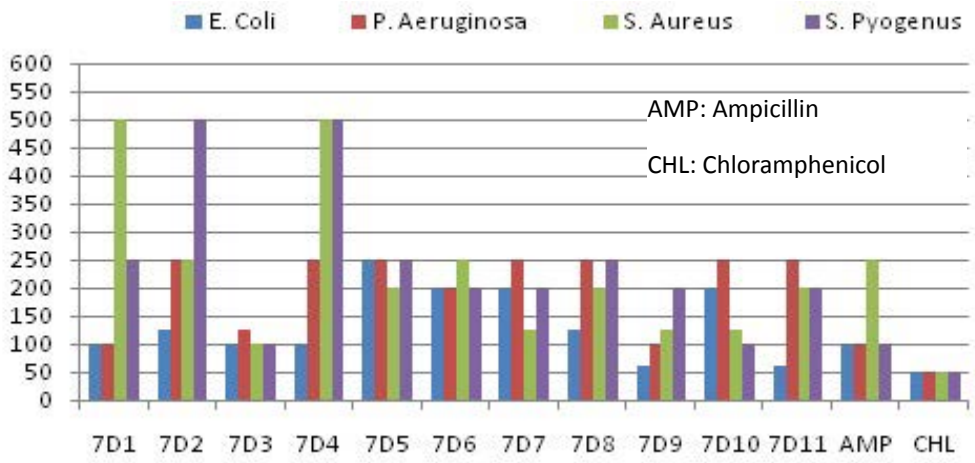


Figure-III Antifungal activity (MFC) of compounds **$7D_1$-$7D_{11}$**

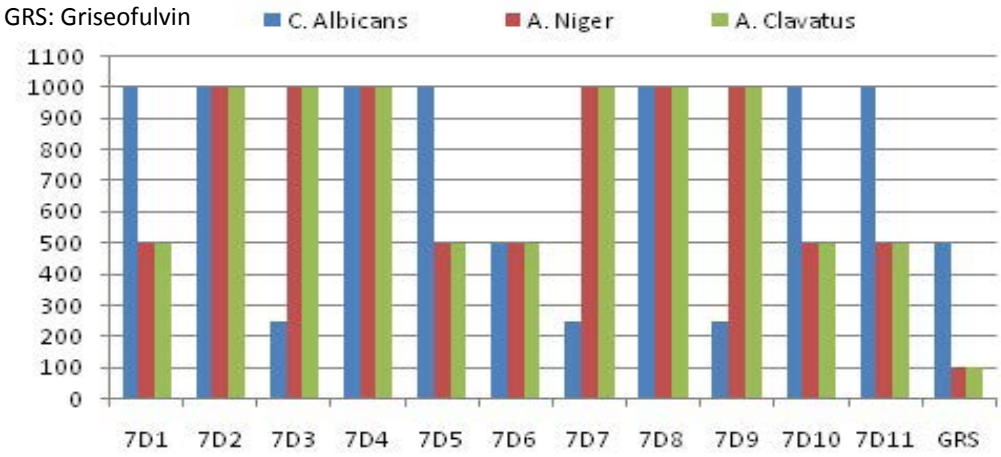
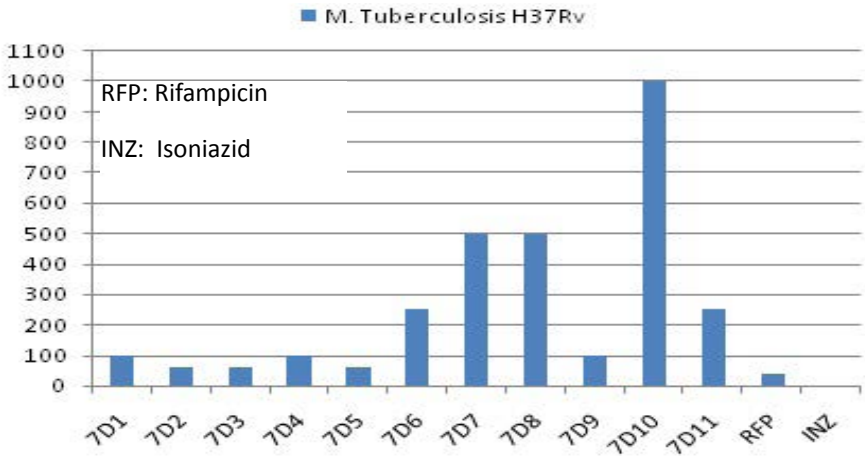


Figure-IV Antitubercular activity (MIC) of compounds **$7D_1$-$7D_{11}$**



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