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5*H*-Dibenz[b,f]azepine based pyrazole sulphonamides: A privileged platform for probing the antimicrobial and antioxidative properties

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ABSTRACT

In rummage around for a novel antimicrobial and antioxidant agent with improved potency, we designed and synthesized a series of 5*H*-dibenz[b,f]azepine based pyrazole sulphonamides (20-40) by expedient five steps route. All compounds were characterized by physico-chemical and spectroscopic techniques. In order to probe the antimicrobial and antioxidant activities, the newly synthesized compounds were assayed for their *in vitro* activities. Among the compounds of the particular interest, compounds 38 and 39 emerged as outperformed antimicrobial agents than standard streptomycin and fluconazole. Molecular docking studies of compound 38 and 39 into *S. aureus* tyrosyl-tRNA synthetase active site was performed, and the tight fitting of the compounds in the active site and the associated high binding energy might be the reason for their antimicrobial activity. On the other hand, compounds 28-30 were found to exert positive efficacy towards antioxidant activity comparable to butylated hydroxy anisole.

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1. Introduction

The biological activity manifested by tricyclic, nitrogen-containing heterocyclic compounds, makes them attractive targets for synthetic chemists [1-3]. The seven-membered ring 5*H*-dibenz[*b,f*]azepine nucleus (**1**) is a pharmaceutically important structure and constitutes the key subunit in tricyclic antidepressant drug substances such as carbamazepine (**1a**) and oxcarbazepine (**1b**) (Figure 1) [4]. These anticonvulsant and mood stabilizing drugs are primarily used for the treatment of epilepsy, bipolar disorder [5-7], trigeminal neuralgia [8], and other neurological disorders [9]. Sulphonamides represent an important class of medicinally important molecules and are known to possess wide varieties of biological activities, hence sulphonamides moieties are an integral part of many antimicrobial drugs, saluretics, carbonic anhydrase inhibitors, antithyroid agents, antitumour drugs, *etc.* [10-19]. Sulphonamides remain the most widely used antibacterial agents in the world because of their low cost, low toxicity and excellent activity against common bacterial diseases.

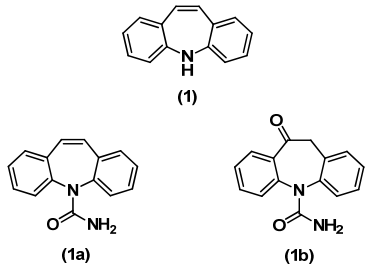

Figure 1. Some pharmaceutically important structure of 5*H*-dibenz[*b,f*]azepine (**1**) and its analogues (**1a** and **b**).

Recently, we have reported the synthesis and the antioxidant properties of 5*H*-dibenz[*b,f*]azepine analogues functionalized with amino acids (**1c**) and aminophenols (**1d**) (Figure 2) [20,21]. The literature survey approaching towards synthesis of sulphonamide linked pyrazole gathered with 5*H*-dibenz[*b,f*]azepine moiety indicates the lack of reference available.

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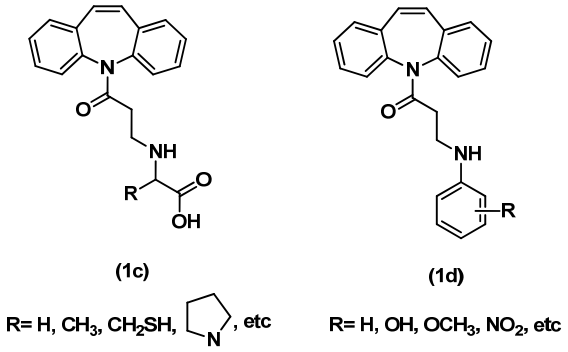


Figure 2. 5*H*-Dibenz[*b,f*]azepine analogues functionalized with amino acids (**1c**) and aminophenols (**1d**).

In view of these observation and in persistence of our earlier work on different bioactive heterocyclic derivatives [22-26], we envision our approach towards gathering two bioactive entities, 5*H*-dibenz[*b,f*]azepine and pyrazole sulphonamide in one compact structure for probing the antimicrobial and antioxidant potentials.

2. Experimental

2.1. Materials and methods

All reagents and solvents were purchased from Merck (Darmstadt, Germany) chemical AR grade and were used as provided. 1 1-diphenyl-2-picrylhydrazyl (DPPH) and butylated hydroxy anisole (BHA) were purchased from Sigma-Aldrich chemical Co. (St. Louis, MO, USA). TLC analysis was performed on alumina sheets precoated with silica gel $60F_{254}$ and SiO_2, 150 mesh (Merck) was used for column chromatography. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Bruker spectrometer in the appropriate deuterated dimethyl sulphoxide (DMSO-d_6) solvent. Melting points were obtained on a Reichert thermopan melting point apparatus, equipped with a microscope and are uncorrected. Mass spectra were obtained by Water-Q-TOF ultima spectrometer. Micro analytical data were obtained by Elemental-Vario EL-III.

2.2. Synthesis

2.2.1. Procedure for synthesis of 4-(5H-dibenzo[b,f]azepin-5-yl)benzaldehyde (3)

The mixure of 4-chlorobenzaldehyde (**2**) (0.8 mol) was refluxed at 65 °C in the appropriate amount of 5*H*-dibenzo [*b,f*]azepine (**1**) (0.8 mol) for 4 hrs. The progress of the reaction was monitored by using TLC. After completion of the reaction, the reaction mass was poured on ice cold water (50 mL) to give white solid precipitate which was then filtered, dried and recrystallized in ethanol to give the pure solid product (**3**) (Scheme 1).

4-(5H-Dibenzo[b,f]azepin-5-yl)benzaldehyde (**3**): Color: Yellow solid. Yield: 66%. M.p: 124-125 °C. FT-IR (KBr, ν, cm^{-1}): 2900-2700 (Ar-H), 1701 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 10.1 (s, 1H, CHO), 6.99 (s, 2H, Azepine-H), 6.86-7.34 (m, 12H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 190.8 (1C, CHO), 150.1 (1C, C-N), 137-119 (19C, Ar-C). MS (ESI, *m/z* (%)): 297.11 (M$^+$, 100). Anal. calcd. for $C_{21}H_{15}NO$: C, 84.82; H, 5.08; N, 4.71. Found: C, 84.63; H, 4.99; N, 4.51%.

(E)-3-(4-(5H-Dibenz[b, f]azepin-5-yl)phenyl)-1-phenylprop-2-en-1-one (**7**): Color: Yellow solid. Yield: 88%. M.p: 164-167 °C. FT-IR (KBr, ν, cm^{-1}): 3131-2973 (Ar-CH), 1705 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 8.06 (d, 1H, beta-H), 6.63-7.89 (m, 17H, Ar-Hs), 6.99 (s, 2H, Azepine-H), 7.59 (d, 1H, Alpha-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 189.7 (1C, C=O), 145.1, 137.9, 137.8, 134.5, 132.0, 131.1, 129.7, 129.6, 129.5, 129.2, 128.8, 128.5, 124.9, 123.0, 121.3, 119.3 (28C, Ar-C). MS (ESI, *m/z* (%)): 399.16 (M$^+$, 100). Anal. calcd. for $C_{29}H_{21}NO$, C, 87.19; H, 5.30; N, 3.51. Found: C, 87.15; H, 5.36; N, 3.53%.

(E)-3-(4-(5H-Dibenz[b, f]azepin-5-yl)phenyl)-1-(4-hydroxy phenyl)prop-2-en-1-one (**8**): Color: Yellow solid. Yield: 65%. M.p: 180-183 °C. FT-IR (KBr, ν, cm^{-1}): 3139-2970 (Ar-CH), 1704 (C=O), 3602 (OH) (Phenolic-OH). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 10.2 (s, 1H, OH), 8.06 (d, 1H, beta-H), 6.63-8.05 (m, 16H, Ar-Hs), 6.99 (s, 2H, azepine-H), 7.59 (d, 1H, Alpha-H), 5.35 (s, 1H, O-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 164.3 (1C, C=O), 145.1, 137.8, 132.0, 131.3, 131.1, 130.5, 129.7, 129.6, 129.5, 128.8, 124.9, 123.0, 121.3, 119.3, 116.4 (28C, Ar-C). MS (ESI, *m/z* (%)): 415.16 (M$^+$). Anal. calcd. for $C_{29}H_{21}NO_2$, C, 83.83; H, 5.09; N, 3.37. Found: C, 83.86; H, 5.06; N, 3.33%.

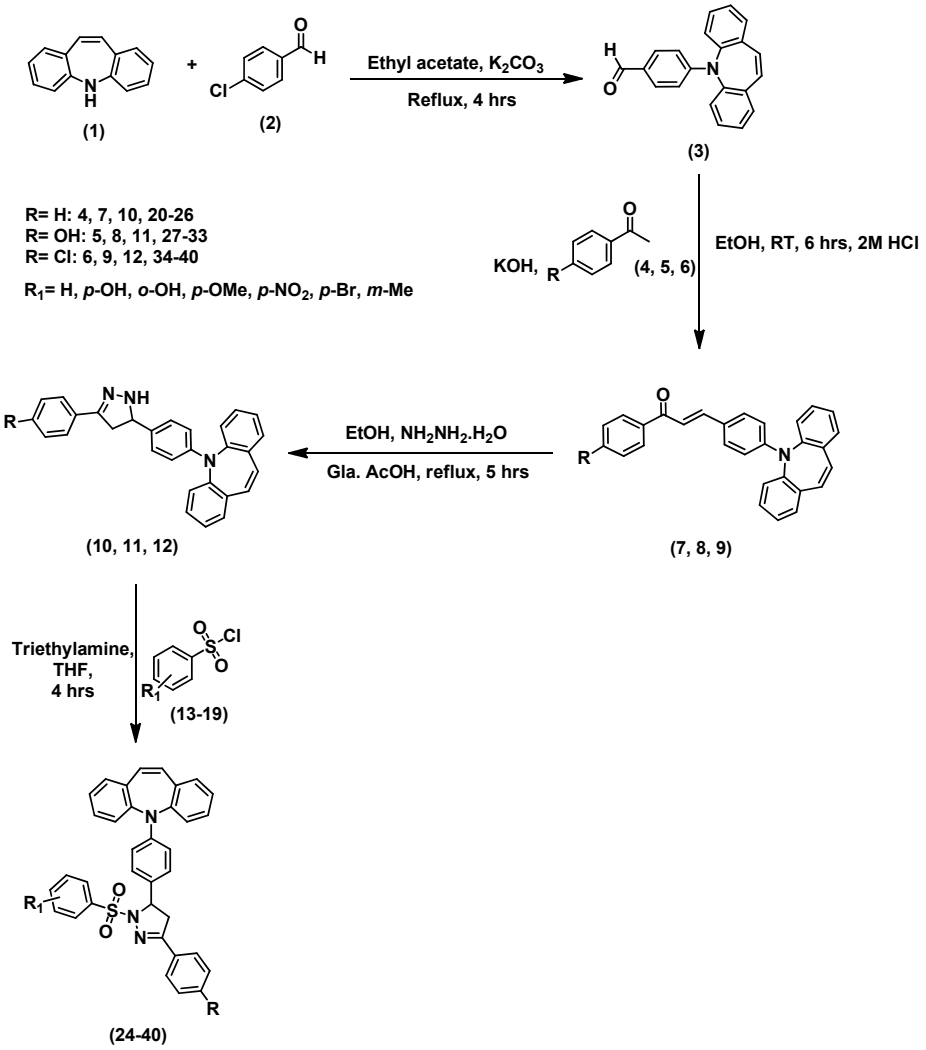
(E)-3-(4-(5H-Dibenz[b, f]azepin-5-yl)phenyl)-1-(4-chloro phenyl)prop-2-en-1-one (**9**): Color: Yellow solid. Yield: 55%. M.p: 185-188 °C. FT-IR (KBr, ν, cm^{-1}): 3136-2972 (Ar-CH), 1706 (C=O), 3045 (Ar-CH), 3605 (OH) (Phenolic-OH), 813 (C-Cl), 1361 (C-N). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 8.06 (d, 1H, Beta-H), 7.59 (d, 1H, Alpha-H), 6.63-7.65 (m, 16H, Ar-H), 6.99 (s, 2H, Azepine-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 189.5 (1C, C=O), 145.1, 140.3, 137.8, 136.0, 132.0, 131.2, 130.3, 129.5, 129.3, 128.8, 124.7, 123.0, 122.4, 122.8, 121.3, 119.0 (C28, Ar-C). MS (ESI, *m/z* (%)): 433.12 (M$^+$). Anal. calcd. for $C_{29}H_{20}ClNO$, C, 80.27; H, 4.65; N, 3.23. Found: C, 80.20; H, 4.60; N, 3.21%.

2.2.2. Procedure for synthesis of 5H-dibenz[b,f]azepine based pyrazoles (10-12) *via cyclization of compound* 7-9 *with hydrazine hydrate*

Hydrazine hydrate (10 mmol) was added to a round bottom flask containing 5 mL ethanolic solution of compound **7-9** (1 mmol). The reaction mass was heated at reflux for 3 hrs and glacial acetic acid (1 mmol) was added. Heating was continued for 2 hrs. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature. At the end, 10 mL of cold water was slowly added to the flask. The separated product was filtered off and washed with cold water for several times. The final compounds **10-12** were recrystallized from ethanol (Scheme 1).

5-(4-(3-Phenyl-4, 5-dihydro-1H-pyrazol-5-yl)phenyl)-5H-dibenz[b,f]azepine (**10**): Color: Yellow solid. Yield: 74%. M.p: 206-209 °C. FT-IR (KBr, ν, cm^{-1}): 3059-2985 (Ar-CH), 3352 (NH), 1624 (C=N, Pyrazole), 1366 (C-N). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 6.63-7.67 (m, 17H, Ar-Hs), 7.10 (d, 1H, N-H), 6.99 (s, 2H, Azepine-H), 3.69 (d, 2H, Pyrazzole alpha-H), 3.90 (m, 1H, Pyrazzole beta-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 151.7 (1C, C=N), 143.9, 137.9, 137.8, 136.4, 132.0, 131.1, 131.0, 129.5, 129.2, 128.8, 128.2, 127.8, 123.0, 119.3 (26C, Ar-C), 51.1 (1C, C-CN) (Pyrole), 42.6 (1C, CH_2) (Pyrole). MS (ESI, *m/z* (%)): 413.19 (M$^+$). Anal. calcd. for $C_{29}H_{23}N_3$, C, 84.23; H, 5.61; N, 10.16. Found: C, 84.25; H, 5.63; N, 10.15%.

4-(5-(4-(5H-Dibenz[b,f]azepin-5-yl)phenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenol (**11**): Color: Brown solid. Yield: 56%. M.p: 190-193 °C. FT-IR (KBr, ν, cm^{-1}): 3049-2972 (Ar-CH), 3602 (OH), 3356 (NH), 1628 (C=N, Pyrazole), 1359 (C-N). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 10.2 (s, 1H, OH), 6.63-7.85 (m, 16H, Ar-H), 7.15 (s, 1H, N-H), 6.99 (s, 2H, Azepine-H), 3.74 (d, 2H, Pyrazole alpha-H), 3.85 (m, 1H, Pyrazole beta-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 160.8 (1C, C-OH), 151.7, 143.9, 137.9, 132.0, 131.1, 129.5, 129.2, 129.1, 129.0, 128.8, 127.8, 123.0, 119.3, 116.0 (26C, Ar-C), 51.1 (1C, C-NH) (Pyrazole), 42.6 (1C, CH_2). MS (ESI, *m/z* (%)): 429.18 (M$^+$). Anal. calcd. for $C_{29}H_{23}N_3O$, C, 81.09; H, 5.40; N, 9.78. Found: C, 81.06; H, 5.42; N, 9.77%.



Scheme 1

5-(4-(3-(4-Chlorophenyl)-4, 5-dihydro-1H-pyrazol-5-yl) phenyl)-5H-dibenz[b,f]azepine (**12**): Color: Light brown solid. Yield: 72%. M.p: 182-185 °C. FT-IR (KBr, ν, cm^{-1}): 3345 (NH), 3045-2896 (Ar-CH), 1635 (C=N, Pyrazole), 1364 (C-N), 813 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.98-6.63 (m, 16H, Ar-H), 7.10 (s, 1H, NH), 6.99 (s, 2H, Azepine-H), 3.94 (d, 2H, Pyrazole Alpha-H), 3.93 (m, 1H, Pyrazole Beta-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 151.7 (1C, C=N) (Pyrazole), 151.0 (1C, C-N), 145.9, 143.9, 137.9, 137.8, 132.0, 131.2, 131.1, 129.5, 129.2, 128.8, 127.8, 124.6, 123.0, 122.9, 119.3, 115.5 (25C, Ar-C) (aromatic), 51.5 (1C, C-NH) (Pyrazole), 42.1 (1C, CH_2) (Pyrazole). MS (ESI, *m/z* (%)): 447.15 (M^+). Anal. calcd. for $C_{29}H_{22}ClN_3$, C, 77.76; H, 4.95; N, 9.38. Found: C, 77.70; H, 4.91; N, 9.42%.

2.2.3. General procedure for synthesis of 5H-dibenz[b,f] azepine based pyrazole sulphanamides (20-40)

To a well stirred solution of compounds **10**-**12** (1 mmol) in 5-10 mL of dry tetrahydrofuran (THF), triethylamine (TEA) (1.2 mmol) was added slowly and stirred for 4 h at room temperature. After completion of the reaction, the reaction mixture was quenched with ice cold water and the product was extracted in dichloromethane (DCM). The organics were washed with sodium bicarbonate (Na_2HCO_3) and dried over anhydrous sodium sulphate (Na_2SO_4) and concentrated under rota evaporator to get desired products **20**-**40** (Scheme 1).

5-(4-(3-Phenyl-1-(phenylsulfonyl)-4, 5-dihydro-1H-pyrazol-5-yl)phenyl)-5H-dibenz[b,f]azepine (**20**): Color: Green solid. Yield: 75%. M.p: 248-251 °C. FT-IR (KBr, ν, cm^{-1}): 3124-2981 (Ar-CH), 1624 (C=N, Pyrazole), 1353 (C-N). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 6.58-7.67 (m, 24H, Ar-Hs), 3.90 (d, 2H, Pyrazole CH_2), 4.1 (m, 1H, CH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 151.5 (1C, C=N) (Pyrazole), 144.4, 143.5, 137.9, 137.6, 136.4, 132.0, 131.5, 131.0, 129.5, 129.1, 128.8, 128.2, 127.8, 127.3, 123.0, 119.3 (32C, Ar-C) (aromatic), 49.5 (1C, C-N) (Pyrazole), 39.0 (1C, CH_2) (Pyrazole). MS (ESI, *m/z* (%)): 553.18 (M^+). Anal. calcd. for $C_{35}H_{27}N_3O_2S$, C, 75.92; H, 4.92; N, 7.59; O, 5.78; S, 5.79; found: C, 75.90; H, 4.89; N, 7.66; O, 5.73; S, 5.83%.

4-(5-(4-(5H-Dibenz[b, f]azepin-5-yl)phenyl)-3-phenyl-4, 5-dihydro-1H-pyrazol-1-ylsulfonyl)phenol (**21**): Color: Green solid. Yield: 77%. M.p: 235-238 °C. FT-IR (KBr, ν, cm^{-1}): 3097-2973 (Ar-CH), 1628 (C=N, Pyrazole), 1362 (C-N). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 6.58-7.67 (m, 21H, Ar-H), 6.99 (s, 2H, Azepine-H), 5.32 (s, 1H, OH), 3.95 (m, 1H, Pyrazole beta-H), 3.69 (d, 2H, Pyrazole alpha-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 143.8 (1C, C-OH), 141.2 (Pyrazole), 138.4, 138.0, 137.8,

136.1, 132.0, 131.4, 131.3, 152.0, 129.5, 129.3, 129.0, 128.8, 128.3, 127.5, 123.0, 119.0, 49.3 (31C, Ar-C), 39.0 (1C, C-N) (Pyrzole), 21.3 (1C, CH_2) (Pyrazole). MS (ESI, *m/z* (%)): 569.18 (M^+). Anal. calcd. for $C_{35}H_{27}N_3O_3S$, C, 73.79; H, 4.78; N, 7.38. Found: C, 73.72; H, 4.73; N, 7.35%.

2-(5-(4-(5H-Dibenz[b, f]azepin-5-yl)phenyl)-3-phenyl-4, 5-dihydro-1H-pyrazol-1-ylsulfonyl)phenol (**22**): Color: Green solid. Yield: 55%. M.p: 232-236 °C. FT-IR (KBr, ν, cm^{-1}): 3085-2970 (Ar-CH), 1620 (C=N, Pyrazole), 1368 (C-N). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 6.58-7.65 (m, 21H, Ar-H), 6.93 (s, 2H, Azepine-H), 5.35 (s, 1H, OH), 3.92 (m, 1H, Pyrazole beta-H), 3.65 (d, 2H, Pyrazole alpha-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 143.5 (1C, C-OH) (phenolic OH), 141.0, 138.5, 138.0, 137.8, 136.0, 132.3, 131.4, 131.0, 152.0, 129.5, 129.3, 129.0, 128.8, 128.2, 127.3, 123.1, 119.3, 49.0 (32C, C-Ar) (aromatic), 39.2 (1C, C-N) (Pyrazole), 21.4 (1C, CH_2) (Pyrazole). MS (ESI, *m/z* (%)): 569.17 (M^+). Anal. calcd. for $C_{35}H_{27}N_3O_3S$, C, 73.79; H, 4.78; N, 7.38. Found: C, 73.74; H, 4.82; N, 7.44%.

5-(4-(1-(4-Methoxyphenylsulfonyl)-3-phenyl-4, 5-dihydro-1H-pyrazol-5-yl)phenyl)-5H-dibenz[b,f]azepine (**23**): Color: Brown solid. Yield: 54%. M.p: 165-168 °C. FT-IR (KBr, ν, cm^{-1}): 3089-2968 (Ar-CH), 1625 (C=N, Pyrazole), 1374 (C-N). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 6.50-7.62 (m, 21H, Ar-H), 6.96 (s, 2H, Azepine-H), 3.92 (m, 1H, Pyrazole beta-H), 3.83 (s, 3H, OCH_3), 3.61 (d, 2H, Pyrazole alpha-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 163.8 (1C, C-OMe) (Aromatic C-OMe), 151.8 (1C, C=N) (pyrazole), 143.9, 137.8, 137.5, 136.5, 136.0, 132.0, 131.1, 129.5, 129.0, 128.8, 128.2, 127.8, 126.1, 123.0, 119.3, 114.6 (31C, Ar-C), 55.8 (1C, OCH_3) (Methoxy), 49.5 (1C, C-N) (Pyrazole), 39.0 (1C, CH_2) (Pyrazole). MS (ESI, *m/z* (%)): 583.19 (M^+). Anal. calcd. for $C_{36}H_{29}N_3O_3S$, C, 74.08; H, 5.01; N, 7.20. Found: C, 74.12; H, 4.95; N, 7.23%.

5-(4-(1-(4-Nitrophenylsulfonyl)-3-phenyl-4, 5-dihydro-1H-pyrazol-5-yl)phenyl)-5H-dibenz[b,f]azepine (**24**): Color: Green solid. Yield: 63%. M.p: 192-194 °C. FT-IR (KBr, ν, cm^{-1}): 3137-2971 (Ar-CH), 1632 (C=N, Pyrazole), 1374 (C-N), 1562, 1346 (N-O). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 6.58-8.39 (m, 21H, Ar-H), 6.99 (s, 2H, Azepine-H), 3.72 (d, 2H, Pyrazole alpha-H), 3.95 (m, 1H, Pyrazole beta-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 151.7 (1C, C=N) (Pyrazole), 150.5 (1C, C-NO_2) (Nitro phenol), 143.9, 137.4, 137.1, 135.9, 132.0, 131.4, 131.0, 129.6, 129.1, 128.8, 128.3, 127.5, 124.4, 123.1, 119.2 (31C, Ar-C), 49.8 (1C, C-N) (Pyrazole), 39.2 (1C, CH_2) (Pyrazole). MS (ESI, *m/z* (%)): 598.17 (M^+). Anal. calcd. for $C_{35}H_{26}N_4O_4S$, C, 70.22; H, 4.38; N, 9.36. Found: C, 70.20; H, 4.34; N, 9.34%.

5-(4-(1-(4-Bromophenylsulfonyl)-3-phenyl-4,5-dihydro-1H-pyrazol-5-yl)phenyl)-5H-dibenz[b,f]azepine (**25**): Color: Green solid. Yield: 91%. M.p: 172-174 °C. FT-IR (KBr, ν, cm^{-1}): 3045-2854 (Ar-CH), 1371 (C-N). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 6.58-7.80 (m, 21H, Ar-H), 6.99 (s, 2H, Azepine-H), 3.90 (m, 1H, Pyrazole beta-H), 3.72 (d, 2H, Pyrazole alpha-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 151.9 (1C, C=N) (Pyrazole), 143.9, 142.5, 137.9, 137.8, 137.6, 136.4, 132.8, 132.4, 131.6, 129.5, 129.2, 129.0, 128.9, 128.7, 128.2, 127.4, 123.0, 119.3 (32C, Ar-C), 49.5 (1C, C-N) (Pyrazole), 38.9 (1C, CH_2) (Pyrazole). MS (ESI, *m/z* (%)): 631.09 (M^+). Anal. calcd. for $C_{35}H_{26}BrN_3O_2S$, C, 66.46; H, 4.14; N, 6.64. Found: C, 66.42; H, 4.10; N, 6.60%.

5-(4-(3-Phenyl-1-tosyl-4, 5-dihydro-1H-pyrazol-5-yl)phenyl)-5H-dibenz[b,f]azepine (**26**): Color: Green solid. Yield: 58.90%. M.p: 187-189 °C. FT-IR (KBr, ν, cm^{-1}): 3097-2973 (Ar-CH), 1628 (C=N, Pyrazole), 1362 (C-N). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 6.58-7.67 (m, 21H, Ar-H), 6.99 (s, 2H, Azepine-H), 3.95 (m, 1H, Pyrazole beta-H), 3.69 (d, 2H, Pyrazole alpha-H), 2.34 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 143.8 (1C, C=N) (Pyrazole), 141.2, 138.4, 138.0, 137.8, 136.1, 132.0, 131.4, 131.3, 152.0, 129.5, 129.3, 129.0, 128.8, 128.3, 127.5, 123.0, 119.0 (32C, Ar-C), 49.3 (1C, C-N) (Ppyrazole), 39.0 (1C, CH_2) (Pyrazole), 21.3 (1C, CH_3) (Methyl). MS (ESI, *m/z* (%)): 567.20 (M^+). Anal. calcd. for $C_{36}H_{29}N_3O_2S$, C, 76.16; H, 5.15; N, 7.40. Found: C, 76.14; H, 5.19; N, 7.43%.

4-(5-(4-(5H-Dibenz[b, f]azepin-5-yl)phenyl)-1-(phenyl sulfonyl)-4, 5-dihydro-1H-pyrazol-3-yl)phenol (**27**): Color: Reddish brown solid. Yield: 63%. M.p.: 240-243 °C. FT-IR (KBr, ν, cm^{-1}): 3042-2774 (Ar-CH), 3602 (OH), 1641 (C=N, Pyrazole), 1360 (C-N). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 6.55-7.85 (m, 21H, Ar-H), 6.95 (s, 2H, Azepine-H), 5.35 (s, 1H, OH), 3.95 (m, 1H, Pyrazole beta-H), 3.62 (d, 2H, Pyrazole alpha-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 160.7 8 (1C, C-OH) (phenolic OH), 151.8 (1C, C=N) (Pyrazole), 144.2, 143.5, 137.5, 132.0, 131.5, 131.0, 129.5, 129.2, 129.0, 128.8, 127.6, 127.3, 123.0, 119.3, 116.0, 49.3 (32C, Ar-C), 38.7 (1C, CH_2). MS (ESI, *m/z* (%)): 569.17 (M^+). Anal. calcd. for $C_{35}H_{27}N_3O_3S$, C, 73.79; H, 4.78; N, 7.38. Found: C, 73.75; H, 4.83; N, 7.42%.

4-(5-(4-(5H-Dibenzo[b, f]azepin-5-yl)phenyl)-1-(4-hydroxy phenylsulfonyl)-4,5-dihydro-1H-pyrazol-3-yl)phenol (**28**): Color: Green semisolid. Yield: 80.30%. FT-IR (KBr, ν, cm^{-1}): 3038-2770 (Ar-CH), 3585 (OH), 1638 (C=N, Pyrazole), 1372 (C-N). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 6.58-7.85 (m, 20H, Ar-H), 6.90 (s, 2H, Azepine-H), 5.33 (s, 2H, OH), 3.92 (m, 1H, Pyrazole beta-H), 3.65 (d, 2H, Pyrazole alpha-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 161.5 8 (1C, C-OH) (Phenolic OH), 160.7 (Phenolic OH), 151.5 (1C, C=N) (Pyrazole), 143.5, 137.8, 137.5, 137.0, 132.0, 131.0, 130.0, 129.5, 129.2, 129.0, 128.8, 127.7, 126.6, 123.3, 119.2, 116.0 (30C, Ar-C), 49.6 3 (1C, C-N), 39.3 (1C, CH_2) (Pyrazole). MS (ESI, *m/z* (%)): 585.17 (M^+). Anal. calcd. for $C_{35}H_{27}N_3O_4S$, C, 71.78; H, 4.65; N, 7.17. Found: C, 71.73; H, 4.60; N, 7.23%.

2-(5-(4-(5H-Dibenz[b, f]azepin-5-yl)phenyl)-3-(4-hydroxy phenyl)-4,5-dihydro-1H-pyrazol-1-ylsulfonyl)phenol (**29**): Color: Light yellow solid. Yield: 66%. M.p: 199-202 °C. FT-IR (KBr, ν, cm^{-1}): 3030-2778 (Ar-CH), 3583 (OH), 1642 (C=N, Pyrazole), 1370 (C-N). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 6.55-7.83 (m, 20H, Ar-H), 6.89 (s, 2H, Azepine-H), 5.35 (s, 2H, OH), 3.95 (m, 1H, Pyrazole Beta-H), 3.66 (d, 2H, Pyrazole Alpha-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 161.8 8 (1C, C-OH) (Phenolic OH), 160.8 8 (1C, C-OH) (Phenolic OH), 151.3 (1C, C=N) (Pyrazole), 143.4, 137.5, 137.6, 137.1, 131.9, 131.3, 130.0, 129.8, 129.1, 129.0, 128.8, 127.8, 126.5, 123.0, 119.3, 116.3 (30C, Ar-H), 49.5 (1C, C-N), 39.5 (1C, CH_2) (Pyrazole). MS (ESI, *m/z* (%)): 585.18 (M^+). Anal. calcd. for $C_{35}H_{27}N_3O_4S$, C, 71.78; H, 4.65; N, 7.17. Found: C, 71.82; H, 4.69; N, 7.15%.

4-(5-(4-(5H-Dibenz[b, f]azepin-5-yl)phenyl)-1-(4-methoxy phenylsulfonyl)-4,5-dihydro-1H-pyrazol-3-yl)phenol (**30**): Color: Yellow solid. Yield: 67%. M.p: 205-207 °C. FT-IR (KBr, ν, cm^{-1}): 3035-2770 (Ar-CH), 3589 (O-H), 1651 (C=N, Pyrazole), 1365 (C-N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.58-7.86 (m, 20H, Ar-H), 6.89 (s, 2H, Azepine-H), 3.98 (m, 1H, Pyrazole beta-H), 3.84 (s, 3H, OCH_3), 3.68 (d, 2H, Pyrazole alpha-H), 10.2 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 163.7 (1C, C-OMe) (Aromatic C-OMe), 160.5 8 (1C, C-OH) (Phenolic OH), 151.8 (1C, C=N) (Pyrazole), 144.0, 138.2, 137.8, 136.5, 132.5, 131.1, 129.5, 129.0, 128.9, 128.7, 127.5, 126.0, 123.0, 119.5, 116.2, 114.0 (30C, Ar-H), 55.8 (1C, OCH_3) (Methoxy), 49.6, 39.0 (1C, CH_2) (Pyrazole). MS (ESI, *m/z* (%)): 599.18 (M^+). Anal. calcd. for $C_{36}H_{29}N_3O_4S$, C, 72.10; H, 4.87; N, 7.01. Found: C, 72.10; H, 4.87; N, 7.01%.

4-(5-(4-(5H-Dibenz[b,f]azepin-5-yl)phenyl)-1-(4-nitrophenyl sulfonyl)-4, 5-dihydro-1H-pyrazol-3-yl)phenol (**31**): Color: Brown solid. Yield: 64%. M.p: 224-226 °C. FT-IR (KBr, ν, cm^{-1}): 3110-2693 (Ar-CH), 3602 (OH), 1562, 1346 (N-O), 1641 (C=N Pyrazole), 1360 (C-N). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 6.58-8.39 (m, 20H, Ar-H), 6.97 (s, 2H, Azepine-H), 5.35 (s, 1H, O-H), 3.93 (m, 1H, Pyrazole beta-H), 3.65 (d, 2H, Pyrazole alpha-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 160.8 8 (1C, C-OH) (phenolic OH), 151.1 (1C, C=N) (Pyrazole), 150.5 (1C, C=N) (pyrazole), 143.8, 138.0, 137.8, 132.0, 131.3, 129.6, 129.2, 129.1, 129.0, 128.8, 128.4, 127.2, 124.2, 123.0, 119.6, 116.4 (30C, Ar-C), 49.6 (1C, C-N), 39.2 (1C, CH_2) (Pyrazole). MS (ESI, *m/z* (%)): 614.16 (M^+). Anal. calcd. for $C_{35}H_{26}N_4O_5S$, C, 68.39; H, 4.26; N, 9.11. Found: C, 68.37; H, 4.25; N, 9.14%.

4-(5-(4-(5H-Dibenz[b, f]azepin-5-yl)phenyl)-1-(4-bromo phenylsulfonyl)-4,5-dihydro-1H-pyrazol-3-yl)phenol (**32**): Color: Green semisolid. Yield: 88%. FT-IR (KBr, ν, cm^{-1}): 3129-2977 (Ar-CH), 3607(O-H) 1638 (C=N, Pyrazole), 1358 (C-N), 858 (C-Br). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 6.58-7.90 (m, 20H, Ar-H), 6.97 (s, 2H, Azepine-H), 5.35 (s, 1H, OH), 3.94 (m, 1H, Pyrazole beta-H), 3.73 (d, 2H, Pyrazole alpha-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 160.8 8 (1C, C-OH) (Phenolic OH), 151.7 (1C, C=N) (Pyrazole), 143.9, 142.6, 137.8, 137.4, 132.6, 131.1, 130.5, 129.9, 129.6, 129.3, 128.9, 128.7, 127.6, 123.1, 119.1, 116.0 (31C, Ar-C), 49.2 (1C, C-N), 38.7 (1C, CH_2) (Pyrazole). MS (ESI, *m/z* (%)): 647.08 (M^+). Anal. calcd. for $C_{35}H_{26}BrN_3O_3S$, C, 64.82; H, 4.04; N, 6.48. Found: C, 64.80; H, 4.10; N, 6.45%.

4-(5-(4-(5H-Dibenz[b, f]azepin-5-yl)phenyl)-1-(m-tolylsulfon yl)-4, 5-dihydro-1H-pyrazol-3-yl)phenol (**33**): Color: Brown solid. Yield: 62%. M.p: 203-205 °C. FT-IR (KBr, ν, cm^{-1}): 3105-2879 (Ar-CH), 3602 (O-H), 1625 (C=N, Pyrazole), 1374 (C-N). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 6.58-7.85 (m, 20H, Ar-H), 6.94 (s, 2H, Azepine-H), 5.30 (s, 1H, O-H), 3.92 (m, 1H, Pyrazole beta-H), 3.75 (d, 2H, Pyrazole alpha-H), 2.34 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 160.4 8 (1C, C-OH) (Phenolic OH), 151.5 (1C, C=N) (Pyrazole), 143.8, 141.4, 138.0, 137.8, 137.6, 132.0, 131.1, 129.5, 129.2, 129.0, 128.5, 128.0, 127.6, 123.0, 119.1, 116.0 (31C, Ar-C), 49.2 (1C, C-N), 39.0(1C, CH_2) (Pyrazole), 21.3 (1C, CH_3) (Methyl). MS (ESI, *m/z* (%)): 583.19 (M^+). Anal. calcd. for $C_{36}H_{29}N_3O_3S$, C, 74.08; H, 5.01; N, 7.20. Found: C, 74.04; H, 5.02; N, 7.24%.

5-(4-(3-(4-Chlorophenyl)-1-(phenylsulfonyl)-4, 5-dihydro-1H-pyrazol-5-yl)phenyl)-5H-dibenz[b,f]azepine (**34**): Color: Yellow solid. Yield: 71%. M.p: 215-217 °C. FT-IR (KBr, ν, cm^{-1}): 3136-2969 (Ar-CH), 2826 (C-H), 1639 (C=N, Pyrazole), 1364 (C-N), 821 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 6.58-7.25 (m, 21H, Ar-Hs), 6.85 (s, 2H, Azepine-H), 3.95 (m, 1H, Pyrazole beta-H), 3.81 (d, 2H, Pyrazole alpha-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 151.5 (1C, C=N) (Pyrazole), 144.4, 143.9, 137.5, 137.4, 136.6, 134.4, 132.0, 131.8, 131.0, 129.5, 129.2, 129.0, 128.7, 128.5, 128.2, 127.8, 127.3, 123.0, 119.3 (32C, Ar-C), 49.5 (1C, C-N), 39.2 (1C, CH_2) (Pyrazole). MS (ESI, *m/z* (%)): 587.14 (M^+). Anal. calcd. for $C_{35}H_{26}ClN_3O_2S$, C, 71.48; H, 4.46; N, 7.14. Found: C, 71.55; H, 4.39; N, 7.10%.

4-(5-(4-(5H-Dibenz[b, f]azepin-5-yl)phenyl)-3-(4-chloro phenyl)-4,5-dihydro-1H-pyrazol-1-ylsulfonyl)phenol (**35**): Color: Brown solid. Yield: 80%. M.p: 255-257 °C. FT-IR (KBr, ν, cm^{-1}): 3130-2965 (Ar-CH), 2835 (C-H), 1642 (C=N, pyrazole), 1368 (C-N), 835 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 6.54-7.30 (m, 20H, Ar-H), 6.92 (s, 2H, Azepine-H), 5.35 (s, 1H, OH), 3.96 (m, 1H, Pyrazole beta-H), 3.75 (d, 2H, Pyrazole alpha-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 161. 8 8 (1C, C-OH) (phenolic OH), 151.8 (1C, C=N) (Pyrazole), 144.2, 143.5, 137.7, 137.3, 136.5, 134.5, 132.3, 131.0, 129.4, 129.2, 129.0, 128.8, 128.4, 128.0, 127.8, 127.2, 123.6, 119.0 (32C, Ar-C), 49.8 (1C, C-N), 39.3 (1C, CH_2) (Pyrazole). MS (ESI, *m/z* (%)): 603.14 (M^+). Anal. calcd. for $C_{35}H_{26}ClN_3O_3S$, C, 69.58; H, 4.34; N, 6.96. Found: C, 69.62; H, 4.38; N, 6.92%.

2-(5-(4-(5H-Dibenz[b, f]azepin-5-yl)phenyl)-3-(4-chloro phenyl)-4,5-dihydro-1H-pyrazol-1-ylsulfonyl)phenol (**36**): Color: Green solid. Yield: 70%. M.p: 273-276 °C. FT-IR (KBr, ν, cm^{-1}): 3135-2968 (Ar-CH), 2842 (C-H), 1637 (C=N, Pyrazole), 1375 (C-N), 838 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 6.58-7.32 (m, 20H, Ar-H), 6.99 (s, 2H, Azepine-H), 5.32 (s, 1H, OH), 3.95 (m, 1H, Pyrazole beta-H), 3.75 (d, 2H, Pyrazole alpha-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 161. 3 8 (1C, C-OH) (Phenolic OH), 151.5 (1C, C=N) (Pyrazole), 144.0, 143.8, 137.9, 137.4, 136.8, 134.5, 132.2, 131.4, 129.4, 129.1, 129.0, 128.7, 128.4, 128.2, 127.4, 127.0, 123.6, 119.3 (31C, Ar-C), 49.5 (1C, C-N), 39.0 (1C, CH_2) (Pyrazole). MS (ESI, *m/z* (%)): 603.13 (M^+). Anal. calcd. for $C_{35}H_{26}ClN_3O_3S$, C, 69.58; H, 4.34; N, 6.96. Found: C, 69.64; H, 4.40; N, 6.95%.

5-(4-(3-(4-Chlorophenyl)-1-(4-methoxyphenylsulfonyl)-4,5-dihydro-1H-pyrazol-5-yl)phenyl)-5H-dibenz[b, f]azepine (**37**): Color: Green solid. Yield: 71%. M.p: 240-242 °C. FT-IR (KBr, ν, cm^{-1}): 3138-2972 (Ar-CH), 2838 (C-H), 1651 (C=N, Pyrazole), 1373 (C-N), 842 (C-Cl).^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 6.54-7.30 (m, 20H, Ar-H), 6.92 (s, 2H, Azepine-H), 3.95 (m, 1H, Pyrazole beta-H), 3.83 (s, 3H, OCH_3), 3.78 (d, 2H, Pyrazole alpha-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 163.8 (1C, C-OMe) (Aromatic C-OMe), 151.4 (1C, C=N) (Pyrazole), 144.4, 143.1, 137.8, 137.4, 136.7, 134.4, 132.6, 131.4, 129.3, 129.1, 129.0, 128.8, 128.4, 128.2, 127.5, 127.0, 123.6, 119.5 (32C Ar-C), 55.8 (1C, OCH_3) (Methoxy), 49.3, 39.0 (1C, CH_2) (Pyrazole). MS (ESI, *m/z* (%)): 617.15 (M^+). Anal. calcd. for $C_{36}H_{28}ClN_3O_3S$, C, 69.95; H, 4.57; N, 6.80. Found: C, 70.03; H, 4.62; N, 6.17%.

5-(4-(3-(4-Chlorophenyl)-1-(4-nitrophenylsulfonyl)-4, 5-dihydro-1H-pyrazol-5-yl)phenyl)-5H-dibenz[b, f]azepin (38): Color: Green solid. Yield: 78%. M.p: 219-221 °C. FT-IR (KBr, ν, cm^{-1}): 3128-2970 (Ar-CH), 815 (C-Cl) 1568, 1344 (N-O) 1637 (C=N, Pyrazole), 1359 (C-N). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 6.58-8.39 (m, 20H, Ar-H), 6.97 (s, 2H, Azepine-H), 3.94 (d, 2H, Pyrazole alpha-H), 3.85 (m, 1H, Pyrazole beta-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 151.9 (1C, C=N) (Pyrazole), 151.5, 151.0, 145.7, 143.8, 138.2, 137.8, 132.0, 131.6, 131.1, 129.9, 129.2, 128.6, 128.3, 127.7, 124.6, 124.2, 123.4, 122.9, 119.6, 115.4 (32C, Ar-C), 49.6 (1C, C-N), 38.3 (1C, CH_2) (Pyrazole). MS (ESI, *m/z* (%)): 632.12 (M^+). Anal. calcd. for $C_{35}H_{25}ClN_4O_4S$, C, 66.40; H, 3.98; N, 8.85. Found: C, 66.45; H, 4.02; N, 8.89%.

5-(4-(1-(4-Bromophenylsulfonyl)-3-(4-chlorophenyl)-4, 5-dihydro-1H-pyrazol-5-yl)phenyl)-5H-dibenz[b, f]azepine (**39**): Color: Green semisolid. Yield: 64%. FT-IR (KBr, ν, cm^{-1}): 3140-2961 (Ar-CH), 1642 (C=N Pyrazole), 1353 (C-N), 829, 816 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 6.58-7.80 (m, 20H, Ar-H), 6.95 (s, 2H, Azepine-H), 3.95 (m, 1H, Pyrazole beta-H), 3.87 (d, 2H, Pyrazole alpha-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 151.7 (1C, C=N) (Pyrazole), 151.3, 145.9, 143.8, 138.4, 137.9, 137.1, 132.0, 131.6, 131.1, 129.5, 129.0, 128.7, 127.8, 124.6, 123.1, 122.9, 119.0, 115.5 (32C, Ar-C), 49.5 (1C, C-N), 38.5 (1C, CH_2) (Pyrazole). MS (ESI, *m/z* (%)): 665.05 (M^+). Anal. calcd. for $C_{35}H_{25}BrClN_3O_2S$, C, 63.02; H, 3.78; N, 6.30. Found: C, 63.10; H, 3.72; N, 6.24%.

5-(4-(3-(4-Chlorophenyl)-1-(m-tolylsulfonyl)-4,5 -dihydro-1H-pyrazol-5-yl)phenyl)-5H-dibenzo[b, f]azepine (**40**): Color: Green solid. Yield: 66%. M.p: 210-212 °C. FT-IR (KBr, ν, cm^{-1}): 3099-2682 (Ar-CH), 818 (C-Cl), 1632 (C=N pyrazole), 1368 (C-N). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 6.58-7.40 (m, 20H, Ar-H), 6.97 (s, 2H, Azepine-H), 3.94 (d, 2H, Pyrazole alpha-H), 3.89 (m, 1H, Pyrazole beta-H) 23.4 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 151.9 (1C, C=N) (Pyrazole), 151.6, 143.9, 143.6, 137.9, 137.6, 132.4, 131.4, 131.1, 129.4, 129.3, 129.0, 128.8, 128.2, 127.8, 124.6, 123.3, 122.9, 119.3, 115, (32C, Ar-C), 49.3 (1C, C-N), 38.5 (1C, CH_2) (Pyrazole), 21.3 (1C, CH_3) (Methyl). MS (ESI, *m/z* (%)): 601.15 (M^+). Anal. calcd. for $C_{36}H_{28}ClN_3O_2S$, C, 71.81; H, 4.69; N, 6.98. Found: C, 71.83; H, 4.72; N, 7.02%.

2.3. Antimicrobial studies

2.3.1. Antibacterial studies

The antibacterial activities of newly synthesized compounds **20-40** were determined by well plate method in Mueller-Hinton Agar [27-29]. The antibacterial activity was carried out against 24 h old cultures of bacterial strains like *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeroginosa*. The test compounds were dissolved in dimethyl sulfoxide (DMSO) at concentration of 1000 and 500 µg/mL. Sterilized agar media (20 mL) was poured into each pre-sterilized Petri dish. Excess of suspension was decanted and plates were dried by placing them in an incubator at 37 °C for an hour. About 60 mL of 24 hrs old culture suspensions were poured and neatly swabbed with the pre-sterilized cotton swabs. Six millimeter diameter well were then punched

carefully using a sterile cork borer and 30 mL of test solutions of different concentrations were added into each labeled well. The plates were then incubated at 37 °C for 24 hrs. The inhibition zone that appeared after 24 hrs, around the well in each plate were measured as zone of inhibition in mm. Experiments were carried out in triplicates and standard deviation was calculated.

2.3.2. Antifungal studies

Antifungal studies of newly synthesized compounds **20**-**40** were carried out against *A. flavus, C. keratinophilum* and *C. albicans.* Sabourands agar media was prepared by dissolving peptone (10 g), D-glucose (40 g) and agar (20 g) in distilled water (1000 mL) and adjusting the pH to 5.7. Normal saline was used to make a suspension of spore of fungal strains for lawning. A loopful of particular fungal strain was transferred to 3 mL saline to get a suspension of the corresponding species. Agar media (20 mL) was poured into each petri dish. Excess of suspension was decanted and plates were dried by placing them in an incubator at 37 °C for 1 hr. Wells were made on these seeded agar plates using sterile cork borer and different concentrations of the test compounds in DMSO were added into each of the labeled wells. A control was also prepared for the plates in the same way using DMSO. The Petri dishes were prepared in triplicate and maintained at 25 °C for 72 hrs. Antifungal activity was determined by measuring the diameter of inhibition zone. Activity of each compound was compared with fluconazole as standard. Zones of inhibition were determined for compounds **20**-**40**.

2.4. Protocol of docking study

Synthesized molecules were drawn using Java molecular editor (JME) Molecular Editor and their 3-Dimensional structures were created and energy minimized using the PRODRG Server [30]. Crystal structure of *S. aureus* tyrosyl-tRNA synthetase (TyrRS) in complex with its inhibitor (1jij.pdb) was downloaded. All the hetero-atoms and water molecules were removed from the crystal structure and the energy minimized compounds were placed in the binding pocket, using PyMOL version 1.4.1.23. The resultant structure was used for the molecular docking studies using AutoDock version 4.2.

AutoDock 4.2 consists of two programs: Autodock, which performs the docking of the ligand to a set of grids describing the target protein and autogrid pre-calculates these grids. First, Autogrid was used to create the 3-D grid box of 60*60*60 Å size with a spacing of 0.375 Å. The center of the grid was choosen as -12.0, 12.0 and 83.0. Then AutoDock part of the software was used to calculate the binding energy between the synthesized compounds and TyrRS enzyme. The Genetic Algorithm with local search (GA-LS) was chosen as the docking algorithm with 100 runs, population size of 150, maximum number of 27,000 generations, 2,500,000 number of energy evaluations, a mutation rate of 0.02 and a crossover rate of 0.8. These parameters were set using the software ADT (AutoDock Tools package version 1.5.4). Results differing by less than 2 Å in root mean square deviation (RMSD) were clustered together and the model with the most favorable binding energy was selected as the resultant complex structure.

Electrostatic and hydrophobic interactions existing between TyrRS and the ligands were analyzed by Ligand-Protein Contacts & Contacts of Structural Units (LPC/CSU) online server [31]. Hydrogen bonds in the resultant complex structure were deduced from LPC/CSU online server results after checking for proper geometry in PyMol.

2.5. Antioxidant studies

2.5.1. DPPH free radical scavenging assay

The evaluation of antioxidant activity of newly synthesized compounds **20**-**40** were done by DPPH radical scavenging activity assay [32]. Internal standard, BHA and the synthesized compounds of different concentrations were prepared in distilled ethanol. 1 mL of Each compound solutions having different concentrations (10, 25, 50, 100, 200 and 500 µM) were taken in different test tubes and 4 mL of 0.1 mM ethanol solution of 1,1-diphenyl-2-picrylhydrazyl (DPPH) was added and shaken vigorously. The tubes were then incubated in the dark room at room temperature for 20 min. A DPPH blank was prepared without the compound, and ethanol was used for the baseline correction. Changes (decrease) in the absorbance at 517 nm were measured using a UV-visible spectrophotometer and the remaining DPPH was calculated. The percent decrease in the absorbance was recorded for each concentration, and percent quenching of DPPH was calculated on the basis of the observed decreased in absorbance of the radical. The radical scavenging activity was expressed as the inhibition percentage and was calculated using the formula:

$$\text{Radical scavenging activity (\%)} = [(A_o\text{-}A_1)/A_o \times 100] \quad (1)$$

where A_o is the absorbance of the control (without compound) and A_1 is the absorbance of the compound.

2.5.2. Inhibition of microsomal lipid peroxidation assay

Liver excised from adult male Wister rats, was homogenized (20 g/100 mL Tris buffer) in 0.02 mol/L, *tris*-buffer (pH = 7.4). Microsomes were isolated by calcium aggregation method. 100 µL of Liver microsomal suspension (0.5 mg protein) was incubated with 1 mmol/L each of $FeSO_4$ and ascorbic acid with or without compounds in a total volume of 1 mL in 0.1 mol/L phosphate buffer (pH = 7.4). After incubation at 37 °C for 60 min, the reaction mixture was boiled with thiobarbutaric acid (TBA) (0.67 g/100 mL water) for 15 min. Formation of TBA reactive substances (TBARS) was calculated from the absorbance at 535 nm. BHA was used as the positive control.

The inhibition ratio (%) was calculated using the following formula:

$$\text{Inhibition ratio (\%)} = [(A_0 - A_1)/A_0 \times 100] \quad (2)$$

where, A_0 is the absorbance of the control and A_1 is the absorbance of the test sample.

3. Results and discussion

3.1. Chemistry

5*H*-Dibenz[*b,f*]azepine was readily prepared according to the literature method [33]. Coupling reaction of 5*H*-dibenz[*b,f*] azepine (**1**) with 4-chlorobenzaldehyde (**2**) afforded 4-(5*H*-dibenz[*b,f*]azepine-5-yl)benzaldehyde (**3**). 5*H*-Dibenz[*b,f*] azepine based chalcones (**7**-**9**) were synthesized *via* Aldol condensation by treating 4-(5*H*-dibenz[*b,f*]azepine-5-yl)benz aldehyde (**3**) with substituted acetophenones (**4**-**6**) in dilute ethanolic solution of potassium hydroxide at ambient temperature. Further, Claissan-Schmidt condensation of respective chalcones (**7**-**9**) with hydrazine hydrate in the presence of glacial acetic acid gave pyrazole substituted 5*H*-dibenz[*b,f*] azepine derivatives (**10**-**12**). Finally, coupling of commercially available phenylsulfonyl chlorides (**13**-**19**) with **10**-**12** in the presence of triethylamine furnished 5*H*-dibenz[b,f]azepine based pyrazole sulphonamides (**20**-**40**) in good yields (Scheme 1).

Table 1. Inhibitory zone (diameter) mm of the synthesized compounds against tested bacterial strains by well plate method. Each value represents mean±SD (n = 3) *.

Compound	*Escherichia coli*		*Staphylococcus aureus*		*Pseudomonas aeroginosa*	
	1000 (µg/mL)	500 (µg/mL)	1000 (µg/mL)	500 (µg/mL)	1000 (µg/mL)	500 (µg/mL)
10	NA	NA	NA	NA	NA	NA
11	NA	NA	NA	NA	NA	NA
12	4±0.02	3±0.03	2±0.01	1±0.01	3±0.02	2±0.02
20	6±0.01	4±0.01	3±0.02	1±0.02	4±0.02	3±0.01
27	5±0.01	4±0.01	3±0.01	1±0.01	4±0.01	3±0.01
34	5±0.03	4±0.02	3±0.01	1±0.02	4±0.02	3±0.02
21	6±0.01	5±0.01	3±0.02	2±0.01	6±0.01	3±0.01
28	7±0.02	6±0.01	9±0.01	7±0.01	5±0.01	3±0.02
35	9±0.01	6±0.02	8±0.02	6±0.02	6±0.02	4±0.01
22	5±0.02	4±0.01	3±0.01	2±0.01	4±0.01	3±0.02
29	4±0.01	3±0.01	3±0.02	1±0.02	3±0.03	3±0.01
36	6±0.01	5±0.03	5±0.02	2±0.02	6±0.02	4±0.02
23	4±0.01	4±0.01	4±0.02	2±0.02	6±0.02	4±0.02
30	4±0.01	3±0.02	3±0.01	2±0.01	4±0.01	3±0.01
37	5±0.02	5±0.02	4±0.02	2±0.02	4±0.02	3±0.02
24	5±0.01	4±0.01	3±0.01	1±0.01	5±0.01	4±0.01
31	5±0.02	5±0.01	3±0.02	1±0.02	7±0.02	5±0.01
38	20±0.01	16±0.01	16±0.02	12±0.01	21±0.01	17±0.01
25	4±0.02	3±0.02	3±0.01	2±0.01	4±0.01	3±0.02
32	6±0.02	5±0.01	4±0.01	3±0.02	4±0.02	3±0.01
39	22±0.02	19±0.02	17±0.01	11±0.01	19±0.01	16±0.01
26	8±0.01	6±0.01	5±0.02	4±0.01	8±0.02	6±0.01
33	7±0.01	6±0.02	5±0.01	3±0.01	4±0.01	3±0.02
40	6±0.01	5±0.01	4±0.01	3±0.01	6±0.02	4±0.01
Streptomycin	18±0.01	10±0.01	15±0.02	10±0.01	18±0.01	12±0.02

* NA: no activity.

Table 2. Inhibitory zone (diameter) mm of the synthesized compounds against tested fungal strains by well plate method. Each value represents mean±SD (n = 3) *.

Compound	*Aspergillus flavus*		*Chrysosporium keratinophilum*		*Candida albicans*	
	1000 (µg/mL)	500 (µg/mL)	1000 (µg/mL)	500 (µg/mL)	1000 (µg/mL)	500 (µg/mL)
10	NA	NA	NA	NA	NA	NA
11	NA	NA	NA	NA	NA	NA
12	2±0.02	1±0.01	3±0.02	2±0.02	2±0.02	1±0.02
20	4±0.01	2±0.02	4±0.01	3±0.01	4±0.01	2±0.01
27	2±0.02	10±0.01	5±0.02	3±0.01	3±0.01	2±0.01
34	2±0.03	1±0.02	5±0.01	3±0.01	3±0.02	3±0.01
21	3±0.01	1±0.01	5±0.02	3±0.01	3±0.01	2±0.01
28	6±0.02	5±0.01	4±0.01	3±0.01	5±0.01	4±0.02
35	5±0.01	3±0.02	5±0.02	4±0.02	4±0.02	2±0.01
22	3±0.02	1±0.01	4±0.01	3±0.01	3±0.01	2±0.02
29	3±0.01	1±0.01	4±0.02	3±0.02	3±0.02	2±0.01
36	3±0.02	1±0.01	5±0.02	4±0.01	3±0.01	2±0.01
23	4±0.01	1±0.01	5±0.02	4±0.01	3±0.01	2±0.02
30	4±0.01	1±0.02	4±0.01	3±0.02	4±0.01	2±0.01
37	3±0.02	1±0.02	4±0.02	3±0.02	4±0.02	3±0.02
24	2±0.01	2±0.01	4±0.01	3±0.01	4±0.01	3±0.01
31	4±0.02	1±0.01	4±0.02	3±0.02	5±0.02	3±0.01
38	16±0.01	13±0.02	19±0.01	17±0.01	25±0.01	21±0.01
25	4±0.02	3±0.02	4±0.01	4±0.01	3±0.01	3±0.02
32	4±0.02	2±0.01	5±0.02	4±0.02	3±0.02	4±0.01
39	17±0.03	14±0.01	21±0.02	18±0.01	27±0.01	22±0.01
26	3±0.01	2±0.02	6±0.01	5±0.01	9±0.01	8±0.02
33	5±0.01	4±0.01	3±0.02	3±0.01	5±0.02	3±0.01
40	6±0.01	5±0.01	5±0.01	2±0.01	5±0.01	4±0.01
Fluconazole	13±0.01	12±0.02	17±0.02	16±0.01	22±0.02	20±0.02

* NA: no activity.

Structures of all the synthesized compounds were confirmed by physico-chemical and spectroscopic techniques like IR, mass, ^{1}H and ^{13}C NMR.

3.2. Antimicrobial activity

The antimicrobial activity of newly synthesized compounds **20**-**40** were determined by well plate method [27-29]. The supremacy of the synthesized compounds as antimicrobials was assessed for their antibacterial studies against different human pathogenic strains of bacteria namely *Escherichia coli* (ATCC25922), *Staphylococcus aureus* (ATCC25923), and *Pseudomonas aeruginosa* (ATCC27853). Antifungal studies were performed against human pathogenic fungi strains such as *Aspergillus flavus* (MTCC3306), *Chrysosporium keratinophilum* (MTCC3017) and *Candida albicans* (MTCC2827). The test compounds were dissolved in dimethyl sulphoxide at concentrations of 1000 and 500 µg/mL and the results obtained as zone of inhibition (mm) are presented in Table 1 and 2.

3.2.1. Antibacterial activity

The antibacterial screening revealed that some of the tested compounds showed good inhibition against various tested microbial strains (Table 1). Initially, pyrazole substituted 5*H*-dibenz[*b,f*]azepine derivatives (**10**,**11**) showed negligible activity whereas, compound **12** possessing electro negative chlorine group exhibited reasonable activity. Further, introduction of phenyl sulphonyl chlorides into the pyrazole ring accounted for the enhanced activity. It is to be noted that the nature of the substituent present on the phenyl ring of 3-substituted pyrazole and phenyl sulphonyl terminus was found to have the strongest influence on the activity and this was confirmed by the fact that the presence of electron withdrawing chloro and bromo group in compound **39** displayed excellent activity (even more active than standard).

Table 3. Comparison of experimentally determined Inhibitory zone diameter for *S. aureus* with the molecular docking results of compound **38** and **39** and streptomycin with *S. aureus* tyrosyl-tRNA synthetase.

Compound	Binding energy (kcal/mol)	Inhibition constant (nM)	Inhibitory zone (diameter) mm for *S. aureus* by well plate method (1000 µg/mL)
38	-11.11	7.21	14±0.02
39	-12.74	0.46	17±0.01
Streptomycin	-13.01	0.29	15±0.02

Compound **38** having functionalities like nitro and chloro at para position on benzene ring of sulfonamide terminus and 3-substituted pyrazole ring terminus displayed 4-12 fold more activity than compound **12** against all the tested bacterial strains and in fact the same compound displayed more activity than Streptomycin, an internal standard. From the studies, the analogues holding electron donating hydroxyl, methyl and methoxy groups were not demanded for enhanced activity against all bacterial strains. This might be the reason for decreased activity in compounds **21**-**23**, **28**-**30**, **35**-**37** and **26**, **33**, **40** compared to other analogues and standard drug as well.

3.2.2. Antifungal activity

The investigation of antifungal activity divulge that compound **39** possessing electro negative bromo and chloro moiety on phenylsulphonyl ring and 3-substituted pyrazole ring respectively, emerged as the active antifungal agent against *A. flavus, C. keratinophilum* and *C. albicans* compared with an internal standard, fluconazole as well as against other compounds (Table 2). Whereas compound **38**, holding nitro and chloro group was the next effective antifungal species. The remaining compounds **20**-**23**, **27**-**30**, **34**-**37** and **24**-**25**, **31**-**33**, **38**-**40** showed completely insusceptible activity against all the tested fungicidal strains. Therefore, modification of phenyl sulfonamides moiety with diversified functional groups at different positions can significantly improve the antifungal activity.

3.3. Molecular docking

To explain the promising activity of the synthesized compounds, molecular docking studies of synthesized compounds within the binding pocket of tyrosyl-tRNA synthetase (TyrRS) was performed. TyrRS is an enzyme which ligates tyrosine to its tRNA molecules and thus plays an important role in protein production [34]. Very recently, 3-aryl-4-aminofuranes-2(5*H*)-ones were reported as potent inhibitors of TyrRS and several of them showed excellent antibacterial activity [35]. Therefore, creating novel TyrRS inhibitors can act as new antimicrobial agents by arresting cellular protein production. Autodock 4.2, the molecular docking software for studying the binding affinity of small molecule to enzyme target was used to study the interactions between the active compounds and the TyrRS binding site [36]. Compounds **38** and **39** which showed the highest activity among the synthesized compounds and Streptomycin were docked into the binding site of TyrRS based on the crystal structure of TyrRS complex structure (1jij.pdb) [37].

The docking results showed that compound **38** and **39** and Streptomycin are held to the active site by several electrostatic and hydrophobic interactions. The computational determined binding energy and inhibition constant values of compound **38** and **39** matches closely with that of Streptomycin (Table 3). In the docking model generated for compound **39** (the most active compound), the seven-membered ring 5*H*-dibenz[*b*,*f*] azepine nucleus moiety and the pharmacologically important sulphonamide linked pyrazole moiety are located towards the entrance of the cavity (Figure 3 and 4). This causes the substituted phenyl ring attached to the pyrazole moiety to interact with active site residues inside the cavity. The 5*H*-dibenz[*b*,*f*]azepine nucleus moiety forms hydrophobic interaction with Ala43, His47, His50 and Trp241 whereas sulphonamide linked pyrazole moiety forms hydrophobic interaction with Ala39, His50, Pro53. Due to the strong hydrophobic interaction of the above moieties at the entrance of the cavity, we predict that our compounds act as a competitive inhibitor by preventing substrate binding, thus leading to higher potency. The bromine atom in the phenyl sulphonamide moiety as acceptor forms H-bond with H (-CH_2) of Pro53 at 3.3 Å and H (-CH_2) of Gly193 at 3.6 Å. Carbonyl oxygen of Gln196 forms a strong H-bond with -NH of the pyrazole ring at 2.7 Å and -NH_2 hydrogen of Gln196 forms a hydrogen bond with N of pyrazole moiety at 3.7 Å. Oxygen atom (-SO_2) of the sulphonamide moiety as acceptor forms H-bond with H (–SH) of Cys37 at 2.7 Å. Chlorine atom of the substituted phenyl ring attached to the pyrazole moiety forms H-bonding interactions with H (meta-CH) of Tyr36 at 3.0 Å, H (-CH_2) of Gln174 at 2.9 Å and H (-CH_2) of Asp177 at 3.1 Å (Figure 5).

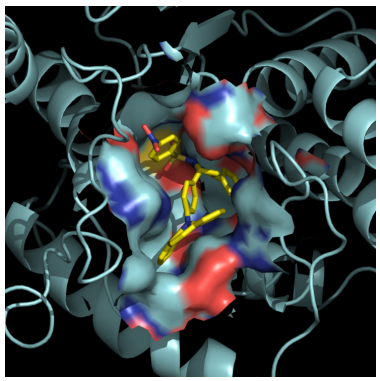


Figure 3. High ranked compound **38** docked in the binding site of *S. aureus* tyrosyl-tRNA synthetase. Protein is represented as cartoons, residues with less than 6 Å from ligand as surface and ligand as sticks. This figure was made using PyMol.

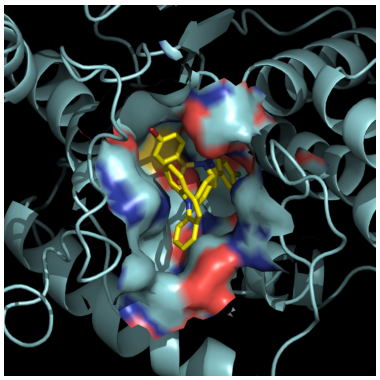


Figure 4. High ranked compound **39** docked in the binding site of *S. aureus* tyrosyl-tRNA synthetase. Protein is represented as cartoons, residues with less than 6 Å from ligand as surface and ligand as sticks. This figure was made using PyMol.

Thus, compound **39** being the most active compound can be attributed to the several H-bonds and hydrophobic

interactions it forms with TyrRS (Figure 6). The above discussed docking results unveiled that the seven-membered ring 5*H*-dibenz[*b,f*]azepine nucleus moiety and the electron withdrawing group in the sulphonamide linked pyrazole moiety had an significant effect on the interactions of the TyrRS-**39** complex and thus were crucial to the TyrRS binding. Bulkiness of -NO_2 group in compound **38** causes the 5*H*-dibenz[*b,f*]azepine nucleus moiety to be located at a different part of the active site compared to compound **39** due to steric hindrance (Figure 3 and 4), causing slight decrease in binding energy, which is supported by the decrease in inhibitory zone diameter (Table 3).

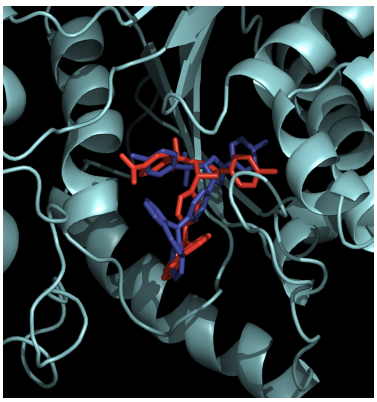


Figure 5. Superposition of compound **38** and **39** docked in the binding site of aaTYrS. Compound **38** and **39** are represented as red and blue respectively. This figure was made using PyMol.

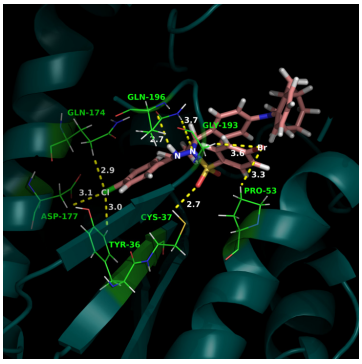


Figure 6. Hydrogen bonding interaction of compound **39** docked in the binding site of *S. aureus* tyrosyl-tRNA synthetase. Hydrogen bonding interactions are shown in dash. Hydrogen-bonded residues are labeled and shown as sticks. This figure was made using PyMol.

3.4. Antioxidant activity

3.4.1. DPPH free radical scavenging activity

In order to probe the antioxidant potential of the newly synthesized compounds, *in vitro* models were adopted for evaluation. Antioxidant activity for the newly synthesized compounds were done by using two assays: 2,2-diphenyl-1-picryl-hydrazyl (DPPH) radical scavenging activity [32] and inhibition of microsomal lipid peroxidation (LPO) [38]. The antioxidant properties were expressed as 50% inhibitory concentration (IC_{50}) (Table 4). The DPPH radical scavenging evaluation is a standard assay in antioxidant activity studies and offers a rapid technique for screening the radical scavenging activity (RSA) of specific compounds. Interaction of the synthesized compounds with stable DPPH free radical indicates their free radical scavenging ability. 5*H*-Dibenz[*b,f*]azepine based pyrazole scaffold compound **10** and **12** displayed less activity but compound **11** exhibited substantial activity, this could be due to the presence of electron donating hydroxyl group at 3-substituted phenyl ring and also the presence of N-H functional group in the pyrazole moiety (Table 4) [39]. Eventually, coupling of phenyl sulphonyl chlorides to compound **10**-**12** enhanced the activity significantly. Majority of the tested compounds in the series **20**-**40** showed moderate to high activity. Interestingly, compounds **28** and **29** possessing two-hydroxyl groups and compound **30** holding methoxy and hydroxyl group on the *N*-substituted phenyl sulphonamide ring of the pyrazole skeleton as well as in 3-substituted phenyl ring were standout as the most efficacious scaffolds. Whereas, compound **28** and **29** possessing one-hydroxyl group at different position on the phenyl ring showed 13-14 fold more activity than the scaffold (**11**). The electron or hydrogen donating ability of nitrogen based DPPH radical, which eventually become stable diamagnetic material plays a significant role for the enhanced antioxidant activity of these compounds among the synthesized compounds and internal standard as well. The introduction of phenyl sulphonyl chlorides holding electron withdrawing groups (NO_2 and Br) to compound **10**-**12** was inadequate for the enhanced activity in compound **24**, **25**; **31**, **32**; **38**, **39** whereas, the compounds **22**, **23**, **36** and **37** containing electron releasing hydroxyl and methoxy groups at different position of sulphonamide phenyl ring exhibited 2-4 fold more RSA activity than the scaffolds (**10**-**12**) (Table 4). Since, compound **20**, **27** and **34** does not have any substituent on the sulphonamide phenyl ring as well as in 3-substituted phenyl ring, it was the least active scaffold among the compounds.

Table 4. 50% Inhibition of DPPH radical and microsomal LPO inhibition by prepared compounds. Each value represents mean±SD (n = 3).

Compound	DPPH activity IC_{50} (μM/mL) [a]	LPO inhibition IC_{50} (μM/mL) [b]
10	158±0.43	175±0.75
11	125±0.55	143±0.22
12	188±0.61	203±0.63
20	80±0.33	92±0.42
27	28±0.10	33±0.11
34	70±0.53	81±0.67
21	20±0.44	34±0.60
28	08±0.60	12±0.01
35	81±0.31	97±0.78
22	55±0.77	63±0.82
29	09±0.11	13±0.10
36	83±0.23	90±0.95
23	79±0.23	88±0.94
30	10±0.33	16±0.45
37	40±0.12	50±0.12
24	38±0.38	67±0.77
31	33±0.14	45±0.70
38	160±0.66	180±0.65
25	55±0.72	78±0.44
32	47±0.33	62±0.36
39	73±0.52	85±0.07
26	124±0.11	116±0.47
33	132±0.70	150±0.66
40	95±0.42	106±0.42
BHA	11±0.01	16±0.32

[a] IC_{50} = The concentration exhibiting 50% inhibition of DPPH radical.
[b] IC_{50} = The concentration exhibiting 50% inhibition of LPO oxidation.

3.4.2. Inhibition of microsomal lipid peroxidation activity

Inhibition of lipid peroxidation property of the newly synthesized compounds were performed by the formation of thiobarbutaric acid reactive species (TBARS) using liver excised from adult male Wister rats. The free radicals tend to stabilize by a molecular rearrangement to produce a conjugated diene, which then readily reacts with oxygen molecule to give a peroxy radical. In this assay, all the newly synthesized compounds **20**-**40** inhibited the ferric chloride induced lipid peroxidation by varying degree compared to the standard antioxidant BHA (Table 4). Compounds **28**-**30** which contains

hydroxyl (-OH) and methoxy (-OMe) groups on the sulphonamide phenyl ring and 3-substituted phenyl ring of pyrazole moiety ideally suits for the enhanced activity. In general, the presence of electron-donating groups on the phenyl ring favors the activity. This might be the reason for the 12-17 fold enhancement of activity compared to compound **10**-**12**. Whereas, compound **24**, **25**; **31**, **32**; **38**, **39** holding electron withdrawing groups (NO_2, Cl and Br) on the phenyl rings was not demanded for improved antioxidant efficacy.

5. Conclusions

In this study, we have achieved a convenient protocol for the synthesis of *5H-dibenz[b,f]azepine based pyrazole sulphonamides* (**20**-**40**) by simple and efficient reaction pathway and there *in vitro* antioxidant and antimicrobial activities were evaluated. Among the analogues, compounds **38** and **39** possessing electron withdrawing groups like Cl, Br and NO_2 on the phenyl rings showed excellent antimicrobial activity against all tested microbial strains and displayed even more activity than their corresponding internal standard. Molecular docking study showed good binding of these compounds to the tyrosyl-tRNA synthetase active site. It is noteworthy that compounds **28**-**30** possessed potent antioxidant activity than the standard because of having highest phenolic content. Overall, the biological tests revealed that the introduction of phenyl sulfonyl chlorides into *5H-dibenz[b,f]azepine* based pyrazole core moiety leads the exceptional platform for probing the bioactivity.

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