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Synthesis, Biological Activity, and Molecular Docking Assessment of Some New Sulfonylated Tetrazole Derivatives

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Abstract—The designed molecular structures have been subjected to computational analysis for calculating their physicochemical properties and drug likeness. The calculated data indicate that most of the compound possess the bioactivity score in the active zone. Synthetic approach to the target compounds is straightforward and easy to handle. Structures of the new compounds are supported by FT-IR, ^{1}H, and ^{13}C NMR, and mass spectra. Antimicrobial tests of the products against pathogens (*S. aureus*, *S. epidermidis*, *E. coli*, and *P. mirabilis*) indicate the products as active or highly active. Their cyto-toxicity is determined to be 92–98% at concentration of 3.125 μmol/L. The molecular docking analysis carried out for the target compounds against the receptor Glc-N-6P exhibits low binding energy and various binding sites of those.

Keywords: Sulfonilated tetrazole, computational approach, synthesis, characterization, biological screening

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Tetrazole derivatives are characterized by versatile biological properties including chemotherapeutic and anti-cancer effects [1–3]. Earlier we have reported the synthesis and anticancer potential of novel piperonyl-tetrazole derivatives [4] and *N*-(pyrimidine-2-yl)benzene-sulfonamide derivatives [5, 6]. In the current study we synthesized some new sulfonylated tetrazole derivatives with enhanced chemotherapeutic potential.

EXPERIMENTAL

The reagents and solvents were purchased from Sigma Aldrich and Merck, Germany. The processes were monitored by TLC on pre-coated silica gel aluminium sheets and visualized under UV light. Melting points were determined on a Melt-Temp instrument. Elemental analysis was carried out on a Heraeus Vario EL III analyzer. FTIR spectra were recorded on a Perkin-Elmer model 1600 FT-IR RX1 spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance 300 MHz spectrometer using DMSO-d_6 as a solvent and TMS as a standard. Mass spectra were measured on a Micromass Quattro II triple quadrupole mass spectrometer. The antibacterial study was carried out under laminar flow, and percent viability of the cells was recorded by ELISA.The bioactivity score and the physicochemical properties were calculated by Molinspration software. The computational assessment (drug likeness and physicochemical properties) was performed with the software available online (www.molinspiration.com), according to the route discussed in [7–12]. Structure of the molecules were drawn with ChemDraw Ultra 8.0, and their smile files were generated with the online available software same as above, and the parameters like molecular mass, milogP, TPSA, N_{atoms}, N_{ON}, N_{OHNH}, Nviolationsn Nrot, Volume, GPCR ligand, Ion channel modulator, Kinase inhibitor, Nuclear receptor ligand, Protease inhibitor and Enzyme inhibitor were calculated.

Synthesis of benzene-1,4-dicarbonitrile. The mixture of (*Z*,*Z*)-benzene-1,4-diylbis(*N*-hydroxymethanimine) with 20 mL of acetic anhydride was refluxed. Upon completion of the reaction the reaction mixture was poured into ice cold water. The precipitate was filtered off and dried under vacuum, purified by column chromatography using hexane–chloroform. Brown crystals, yield 85%. FT-IR spectrum, ν, cm^{-1}: 2955 (CH-Ar), 2222 (CN). ^{1}H NMR spectrum, δ, ppm: 7.123–7.169 d (2H, Ar-H), 7.540–7.582 d (2H, Ar-H).

Synthesis of 5,5'-benzene-1,4-diylbis(1*H*-tetrazole). The mixture of equimolar amounts of benzene-1,4-dicarbonitrile, sodium azide and zinc bromoide water

solution, and 40 mL of isopropyl alcohol (10 mL) was refluxed refluxed. 5,5'-Benzene-1,4-diylbis(1*H*-tetrazole) was filtered off and dried under vacuum. Creamy-white crystals, yield 90%. FT-IR spectrum, ν, cm^{-1}: 3255 (NH), 3312 (NH), 2924 (CH-Ar), 1617 (C=N), 1596 (C=N). ^1H NMR spectrum, δ, ppm: 7.470–7.508 d (2H, Ar-H), 7.431–7.478 d (2H, Ar-H), 10.922 s (1H, NH), 11.145 s (1H, NH).

Synthesis of sulfonylated tetrazole derivatives (1–12). The equimolar amounts of 5,5'-benzene-1,4-diylbis(1*H*-tetrazole) and the corresponding sulfonyl chloride were mixed with NaOH solution (40 mL, 10%) and refluxed. Upon completion of the process (TLC), the reaction mixture was poured into ice cold water, neutralized by dil. HCl, the precipitate of the corresponding compound was filtered off and dried under vacuum, purified by column chromatography and recrystallized from methanol.

5,5'-Benzene-1,4-diylbis[1-(phenylsulfonyl)-1*H*-tetrazole] (1). White crystals, yield 85%, mp 122–124°C. FT-IR spectrum, ν, cm^{-1}: 1027 (SO_2, sym.), 1030 (SO_2, sym.), 1045 (C–N), 1049 (C–N), 1575 (SO_2, asym.), 1577 (SO_2, asym.), 1620 (C=N), 1624 (C=N), 2987 (CH-Ar). ^1H NMR spectrum, δ, ppm: 7.72–7.75 d (2H, CH-Ar), 7.92–7.98 d (2H, CH-Ar), 8.20–8.25 m (3H, CH-Ar), 8.42–8.48 m (3H, CH-Ar), 9.00–9.03 d (2H, CH-Ar), 9.09–9.10 d (2H, CH-Ar). ^{13}C NMR spectrum, δ, ppm: 119.36 (Ar-C), 120.45 (Ar-C), 120.70 (Ar-C), 121.63 (Ar-C), 122.02 (Ar-C), 122.31 (Ar-C), 123.01 (Ar-C), 124.13 (Ar-C), 124.30 (Ar-C), 124.67 (Ar-C), 125.12 (Ar-C), 125.30 (Ar-C), 125.55 (Ar-C), 126.02 (Ar-C), 126.31 (Ar-C), 126.70 (Ar-C), 127.19 (Ar-C), 127.53 (Ar-C), 127.93 (Ar-C), 158.33 (C–N), 160. 82 (C–N), 166.91 (C=N), 167.82 (C=N). ESI-MS: *m/z*: 495.08 $[M + H]^+$. Found, %: C 48.55, H 2.87, N 22.69. $C_{20}H_{14}N_8O_4S_2$. Calculated, %: C 48.58, H 2.85, N 22.6.

5,5'-Benzene-1,4-diylbis{1-[(4-chlorophenyl)-sulfonyl]-1*H*-tetrazole} (2). White crystals, yield 85%, mp 125–127°C. FT-IR spectrum, ν, cm^{-1}: 1021 (SO_2, sym.), 1028 (SO_2, sym.), 1043 (C–N), 1044 (C–N), 1571 (SO_2, asym.), 1573 (SO_2, asym.), 1621 (C=N), 1626 (C=N), 2980 (CH-Ar). ^1H NMR spectrum, δ, ppm: 7.72–7.74 d (2H, CH-Ar), 7.92–7.97 d (2H, CH-Ar), 8.23–8.25 d (2H, CHAr), 8.42–8.45 d (2H, CH-Ar), 9.01–9.05 d (2H, CH-Ar), 9.08–9.11 d (2H, CH-Ar). ^{13}C NMR spectrum, δ, ppm: 119.49 (Ar-C), 120.16 (Ar-C), 120.79 (Ar-C), 121.31 (Ar-C), 122.31 (Ar-C), 122.47 (Ar-C), 123.75 (Ar-C), 124.35 (Ar-C), 123.91 (Ar-C), 124.38 (Ar-C), 125.19 (Ar-C), 125.93 (Ar-C), 125.27 (Ar-C), 126.15 (Ar-C), 126.71 (Ar-C), 126.37 (Ar-C), 127.08 (Ar-C), 127.30 (Ar-C), 127.41 (Ar-C), 159.08 (C–N), 160. 93 (C–N), 164.31 (C=N), 166.20 (C=N). ESI-MS: *m/z*: 562.94 $[M + H]^+$. Found, %: C 42.62, H 2.19, N 19.90. $C_{20}H_{12}Cl_2N_8O_4S_2$. Calculated, %: C 42.64, H 2.15, N 19.89.

5,5'-Benzene-1,4-diylbis{1-[(4-bromophenyl) sulfonyl]-1*H*-tetrazole} (3). White crystals, yield 80%, mp 118–120°C. FT-IR spectrum, ν, cm^{-1}: 1029 (SO_2, sym.), 1033 (SO_2, sym.), 1045 (C–N), 1047 (C–N), 1569 (SO_2, asym.), 1577 (SO_2, asym.), 1625 (C=N), 1628 (C=N), 2993 (CH-Ar). ^1H NMR spectrum, δ, ppm: 7.71–7.73 d (2H, CH-Ar), 7.92–7.97 d (2H, CH-Ar), 8.23–8.26 d (2H, CH-Ar), 8.42–8.45 d (2H, CH-Ar), 9.01–9.04 d (2H, CH-Ar), 9.06–9.10 d (2H, CH-Ar). ^{13}C NMR spectrum, δ, ppm: 119.14 (Ar-C), 119.24 (Ar-C), 120.35 (Ar-C), 121.21 (Ar-C), 121.29 (Ar-C), 122.55 (Ar-C), 122.98 (Ar-C), 123.77 (Ar-C), 124.08 (Ar-C), 124.77 (Ar-C), 125.00 (Ar-C), 125.85 (Ar-C), 126.17 (Ar-C), 126.88 (Ar-C), 127.00 (Ar-C), 127.11 (Ar-C), 127.51 (Ar-C), 127.77 (Ar-C), 127.99 (Ar-C), 157.11 (C–N), 161. 33 (C–N), 165.17 (C=N), 165.27 (C=N). ESI-MS: *m/z*: 650.85 $[M + H]^+$. Found, %: C 36.85, H 1.88, N 17.21. $C_{20}H_{12}Br_2N_8O_4S_2$. Calculated, %: C 36.83, H 1.85, N 17.18.

5,5'-Benzene-1,4-diylbis{1-[(3-bromophenyl)-sulfonyl]-1*H*-tetrazole} (4). White crystals, yield 83%, mp 123–125°C. FT-IR spectrum, ν, cm^{-1}: 1021 (SO_2, sym.), 1041 (SO_2, sym.), 1051 (C–N), 1059 (C–N), 1561 (SO_2, asym.), 1573 (SO_2, asym.), 1627 (C=N), 1633 (C=N), 2990 (CH-Ar). ^1H NMR spectrum, δ, ppm: 7.71–7.73 d (2H, CH-Ar), 7.91–7.93 d (2H, CH-Ar), 8.27–8.29 d (2H, CH-Ar), 8.43–8.50 m (2H, CH-Ar), 9.11–9.13 d (2H, CH-Ar), 9.22–9.25 d (2H, CH-Ar). ^{13}C NMR spectrum, δ, ppm: 119.77 (Ar-C), 120.19 (Ar-C), 120.77 (Ar-C), 121.37 (Ar-C), 121.85 (Ar-C), 122.97 (Ar-C), 122.41 (Ar-C), 123.35 (Ar-C), 124.11 (Ar-C), 124.65 (Ar-C), 125.18 (Ar-C), 125.77 (Ar-C), 126.35 (Ar-C), 126.86 (Ar-C), 127.01 (Ar-C), 127.57 (Ar-C), 127.78 (Ar-C), 127.90 (Ar-C), 127.99 (Ar-C), 150.44 (C–N), 164. 14 (C–N), 166.33 (C=N), 167.22 (C=N). ESI-MS: *m/z*: 650.85 $[M + H]^+$. Found, %: C 36.85, H 1.88, N 17.21. $C_{20}H_{12}Br_2N_8O_4S_2$. Calculated, %: C 36.83, H 1.85, N 17.18.

5,5'-Benzene-1,4-diylbis{1-[(4-methylphenyl)-sulfonyl]-1*H*-tetrazole} (5). Creamy crystals, yield 86%, mp 120–122°C. FT-IR spectrum, ν, cm^{-1}: 1030 (SO_2,

sym.), 1033 (SO_2, sym.), 1055 (C–N), 1061 (C–N), 1569 (SO_2, asym.), 1570 (SO_2, asym.), 1634 (C=N), 1639 (C=N), 2989 (CH-Ar). ^{1}H NMR spectrum, δ, ppm: 7.72–7.75 d (2H, CH-Ar), 7.91–7.94 d (2H, CH-Ar), 8.27–8.29 d (2H, CH-Ar), 8.43–8.46 d (2H, CH-Ar), 9.11–9.15 d (2H, CH-Ar), 9.21–9.25 d (2H, CH-Ar), 2.51 s (3H, CH_3), 2.57 s (3H, CH_3). ^{13}C NMR spectrum, δ, ppm: 25.77 (CH_3), 26.17 (CH_3), 119.35 (Ar-C), 120.23 (Ar-C), 120.77 (Ar-C), 121.30 (Ar-C), 121.85 (Ar-C), 122.21 (Ar-C), 122.78 (Ar-C), 123.30 (Ar-C), 124.08 (Ar-C), 124.45 (Ar-C), 125.17 (Ar-C), 125.79 (Ar-C), 126.21 (Ar-C), 126.75 (Ar-C), 127.02 (Ar-C), 127.11 (Ar-C), 127.25 (Ar-C), 127.58 (Ar-C), 127.95 (Ar-C), 150.91 (C–N), 164. 70 (C–N), 166.55 (C=N), 167.57 (C=N). ESI-MS: *m/z*: 523.11 $[M + H]^+$. Found, %: C 50.55, H 3.49, N 21.46. $C_{22}H_{18}N_8O_4S_2$. Calculated, %: C 50.57, H 3.47, N 21.44.

5,5'-Benzene-1,4-diylbis{1-[(4-methoxyphenyl)-sulfonyl]-1*H*-tetrazole} (6). White crystals, yield 88%, mp 125–127°C. FT-IR spectrum, ν, cm^{-1}: 1037 (SO_2, sym.), 1041 (SO_2, sym.), 1057 (C–N), 1059 (C–N), 1572 (SO_2, asym.), 1575 (SO_2, asym.), 1637 (C=N), 1643 (C=N), 2995 (CH-Ar). ^{1}H NMR spectrum, δ, ppm: 7.74–7.76 d (2H, CH-Ar), 7.92–7.95 d (2H, CH-Ar), 8.28–8.29 d (2H, CH-Ar), 8.45–8.47 d (2H, CH-Ar), 9.11–9.15 d (2H, CH-Ar), 9.21–9.25 d (2H, CH-Ar), 3.87 s (3H, OCH_3), 2.89 s (3H, OCH_3). ^{13}C NMR spectrum, δ, ppm: 55.78 (OCH_3), 55.98 (OCH_3), 120.08 (Ar-C), 120.25 (Ar-C), 120.90 (Ar-C), 121.12 (Ar-C), 121.78 (Ar-C), 122.51 (Ar-C), 122.91 (Ar-C), 123.35 (Ar-C), 124.15 (Ar-C), 124.95 (Ar-C), 125.37 (Ar-C), 125.89 (Ar-C), 126.30 (Ar-C), 126.76 (Ar-C), 127.99 (Ar-C), 127.02 (Ar-C), 127.12 (Ar-C), 127.25 (Ar-C), 127.62 (Ar-C), 153.00 (C–N), 164.19 (C–N), 167.33 (C=N), 168.08 (C=N). ESI-MS: *m/z*: 555.07 $[M + H]^+$. Found, %: C 47.67, H 3.28, N 20.23. $C_{22}H_{18}N_8O_6S_2$. Calculated, %: C 47.65, H 3.27, N 20.21.

5,5'-Benzene-1,4-diylbis{1-[(4-ethoxyphenyl)-sulfonyl]-1*H*-tetrazole} (7). White crystals, yield 81%, mp 121–125°C. FT-IR spectrum, ν, cm^{-1}: 1022 (SO_2, sym.), 1037 (SO_2, sym.), 1055 (C–N), 1063 (C–N), 1579 (SO_2, asym.), 1583 (SO_2, asym.), 1633 (C=N), 1647 (C=N), 2999 (CH-Ar). ^{1}H NMR spectrum, δ, ppm: 7.76–7.78 d (2H, CH-Ar), 7.93–7.96 d (2H, CH-Ar), 8.27–8.29 d (2H, CH-Ar), 8.44–8.47 d (2H, CH-Ar), 9.11–9.15 d (2H, CH-Ar), 9.22–9.24 d (2H, CH-Ar), 1.28-1.33 t (3H, CH_3), 4.11-4.18 q (2H, CH_2). ^{13}C NMR spectrum, δ, ppm: 25.71 (CH_3), 55.57 (CH_2), 67.35 (O-CH_2), 120.10 (Ar-C), 120.72 (Ar-C), 120.99 (Ar-C), 121.10 (Ar-C), 121.58 (Ar-C), 122.11 (Ar-C), 122.59 (Ar-C), 123.55 (Ar-C), 124.13 (Ar-C), 124.90 (Ar-C), 125.30 (Ar-C), 125.82 (Ar-C), 126.15 (Ar-C), 126.88 (Ar-C), 127.00 (Ar-C), 127.10 (Ar-C), 127.52 (Ar-C), 127.69, (Ar-C), 127.95 (Ar-C), 153.33 (C–N), 164.52 (C–N), 167.21 (C=N), 168.11 (C=N). ESI-MS: *m/z*: 583.00 $[M + H]^+$. Found, %: C 49.39, H 3.285, N 19.18. $C_{24}H_{22}N_8O_6S_2$. Calculated, % C 49.48, H 3.81, N 19.23.

5,5'-Benzene-1,4-diylbis{1-[(4-nitrophenyl)-sulfonyl]-1*H*-tetrazole} (8). Yellow crystals, yield 80%, mp 119–121°C. FT-IR spectrum, ν, cm^{-1}: 1021 (SO_2, sym.), 1036 (SO_2, sym.), 1051 (C–N), 1055 (C–N), 1567 (SO_2, asym.), 1573 (SO_2, asym.), 1628 (C=N), 1635 (C=N), 2985 (CH-Ar). ^{1}H NMR spectrum, δ, ppm: 7.86–7.789 d (2H, CH-Ar), 7.78–7.80 d (2H, CH-Ar), 8.36–8.38 d (2H, CH-Ar), 8.55–8.59 d (2H, CH-Ar), 8.90–8.94 d (2H, CH-Ar), 9.08–9.11 d (2H, CH-Ar). ^{13}C NMR spectrum, δ, ppm: 120.19 (Ar-C), 120.97 (Ar-C), 121.05 (Ar-C), 121.33 (Ar-C), 121.59 (Ar-C), 122.17 (Ar-C), 122.88 (Ar-C), 123.07 (Ar-C), 124.36 (Ar-C), 125.79 (Ar-C), 126.09 (Ar-C), 126.73 (Ar-C), 126.97 (Ar-C), 127.35 (Ar-C), 127.49 (Ar-C), 127.95 (Ar-C), 128.07 (Ar-C), 128.19 (Ar-C), 128.31 (Ar-C), 154.92 (C–N), 163.00 (C–N), 165.19 (C=N), 167.08 (C=N). ESI-MS: *m/z*: 585.07 $[M + H]^+$. Found, %: C 41.13, H 2.04, N 23.41. $C_{20}H_{12}N_{10}O_8S_2$. Calculated, %: C 41.10, H 2.07, N 23.96.

5,5'-Benzene-1,4-diylbis{1-[(4-methylsulfonyl-phenyl)sulfonyl]-1*H*-tetrazole} (9). Yellow crystals, yield 83%, mp 125–127°C. FT-IR spectrum, ν, cm^{-1}: 1037 (SO_2, sym.), 1040 (SO_2, sym.), 1057 (C–N), 1065 (C–N), 1560 (SO_2, asym.), 1578 (SO_2, asym.), 1633 (C=N), 1678 (C=N), 2990 (CH-Ar). ^{1}H NMR spectrum, δ, ppm: 7.93–7.97 d (2H, CH-Ar), 7.89–7.92 d (2H, CH-Ar), 8.76–8.79 d (2H, CH-Ar), 8.68–8.71 d (2H, CH-Ar), 9.01–9.06 d (2H, CH-Ar), 9.23–9.27 d (2H, CH-Ar), 2.62 s (3H, CH_3), 2.54 s (3H, CH_3). ^{13}C NMR spectrum, δ, ppm: 25.13 (CH_3), 26.94 (CH_3), 119.88 (Ar-C), 120.12 (Ar-C), 120.28 (Ar-C), 121.55 (Ar-C), 121.98 (Ar-C), 122.10 (Ar-C), 122.55 (Ar-C), 123.17 (Ar-C), 123.99 (Ar-C), 124.40 (Ar-C), 125.11 (Ar-C), 125.39 (Ar-C), 126.18 (Ar-C), 126.70 (Ar-C), 127.05 (Ar-C), 127.18 (Ar-C), 127.51 (Ar-C), 127.83 (Ar-C), 127.99, (Ar-C), 151.08 (C–N), 164.79 (C–N), 166.39 (C=N), 167.11 (C=N). ESI-MS: *m/z*: 523.11 $[M + H]^+$. Found, %: C 40.64, H 2.80, N 17.23. $C_{22}H_{18}N_8O_8S_4$. Calculated, %: C 40.61, H 2.79, N 17.22.

5,5'-Benzene-1,4-diylbis{1-[(4-sulfanilamidephenyl)sulfonyl]-1*H*-tetrazole} (10). Yellow crystals, yield 89%, mp 135–137°C. FT-IR spectrum, ν, cm^{-1}: 1038 (SO_2, sym.), 1043 (SO_2, sym.), 1057 (C–N), 1065 (C–N), 1563 (SO_2, asym.), 1571 (SO_2, asym.), 1631 (C=N), 1675 (C=N), 2990 (CH-Ar), 3312 (NH_2). ^{1}H NMR spectrum, δ, ppm: 9.91 s (2H, NH_2), 9.96 s (2H, NH_2); 9.15–9.19 d (2H, CH-Ar), 9.22–9.25 d (2H, CH-Ar), 8.79–8.81 d (2H, CH-Ar), 8.57–8.59 d (2H, CH-Ar), 7.96–7.99 d (2H, CH-Ar), 7.82–7.86 d (2H, CH-Ar). ^{13}C NMR spectrum, δ, ppm: 120.12 (Ar-C), 120.71 (Ar-C), 120.88 (Ar-C), 121.19 (Ar-C), 121.75 (Ar-C), 122.03 (Ar-C), 122.72 (Ar-C), 123.19 (Ar-C), 123.79 (Ar-C), 124.37 (Ar-C), 125.33 (Ar-C), 125.69 (Ar-C), 126.27 (Ar-C), 126.59 (Ar-C), 127.17 (Ar-C), 127.39 (Ar-C), 127.54 (Ar-C), 127.75 (Ar-C), 127.97 (Ar-C), 150.93 (C–N), 164.37 (C–N), 167.06 (C=N), 168.33 (C=N). ESI-MS: *m/z*: 653.00 [*M* + H]$^+$. Found, %: C 36.90, H 2.45, N 21.45. $C_{20}H_{16}N_{10}O_8S_4$. Calculated, %: C 36.81, H 2.47, N 21.46.

5,5'-Benzene-1,4-diylbis{1-[(4-thiomethylphenyl) sulfonyl]-1*H*-tetrazole} (11). Yellow crystals, yield 80%, mp 129–131°C. FT-IR spectrum, ν, cm^{-1}: 1025 (SO_2, sym.), 1031 (SO_2, sym.), 1057 (C–N), 1067 (C–N), 1572 (SO_2, asym.), 1578 (SO_2, asym.), 1637 (C=N), 1643 (C=N), 2999 (CH-Ar). ^{1}H NMR spectrum, δ, ppm: 9.29–9.32 d (2H, CH-Ar), 9.12–9.16 d (2H, CH-Ar), 8.57–8.60 d (2H, CH-Ar), 8.36–8.39 d (2H, CH-Ar), 7.92–7.96 d (2H, CH-Ar), 7.77–7.80 d (2H, CH-Ar), 2.51 s (3H, CH_3), 2.57 s (3H, CH_3). ^{13}C NMR spectrum, δ, ppm: 25.54 (CH_3), 25.88 (CH_3), 120.37 (Ar-C), 120.91 (Ar-C), 121.39 (Ar-C), 121.95 (Ar-C), 122.67 (Ar-C), 122.84 (Ar-C), 123.59 (Ar-C), 124.58 (Ar-C), 124.88 (Ar-C), 125.82 (Ar-C), 125.86 (Ar-C), 126.57 (Ar-C), 126.88 (Ar-C), 127.14, (Ar-C), 127.23 (Ar-C), 127.51 (Ar-C), 127.67 (Ar-C), 127.99 (Ar-C), 150.37 (C–N), 160.55 (C–N), 167.37 (C=N), 168.15 (C=N). ESI-MS: *m/z*: 587.08 [*M* + H]$^+$. Found, %: C 45.10, H 3.12, N 19.12. $C_{22}H_{18}N_8O_4S_4$. Calculated, %: C 45.04, H 3.09, N 19.10.

5,5'-Benzene-1,4-diylbis{1-[(4-trifluoromethylphenyl)sulfonyl]-1*H*-tetrazole} (12). Creamy crystals, yield 85%, mp 126–128°C. FT-IR spectrum, ν, cm^{-1}: 1017 (SO_2, sym.), 1026 (SO_2, sym.), 1061 (C–N), 1069 (C–N), 1573 (SO_2, asym.), 1579 (SO_2, asym.), 1644 (C=N), 1659 (C=N), 2972 (CH-Ar). ^{1}H NMR spectrum, δ, ppm: 9.11–9.16 d (2H, CH-Ar), 8.98–9.02 d (2H, CH-Ar), 8.87–8.92 d (2H, CH-Ar), 8.69–8.74 d (2H, CH-Ar), 8.15–8.19 d (2H, CH-Ar), 7.96–7.99 d (2H, CH-Ar). ^{13}C NMR spectrum, δ, ppm: 150.35 (C–N), 160.19 (C–N), 167.04 (C=N), 168.39 (C=N), 120.19 (Ar-C), 120.85 (Ar-C), 121.19 (Ar-C), 121.90 (Ar-C), 122.41 (Ar-C), 122.71 (Ar-C), 122.90 (Ar-C), 123.77 (Ar-C), 124.71 (Ar-C), 124.97 (Ar-C), 125.32 (Ar-C), 125.77 (Ar-C), 126.81 (Ar-C), 126.95 (Ar-C), 127.00, (Ar-C), 127.08 (Ar-C), 127.16 (Ar-C), 127.50 (Ar-C), 127.89 (Ar-C). ESI-MS: *m/z*: 663.09 [*M* + H]$^+$. Found, %: C 39.85, H 1.85, N 16.93. $C_{22}H_{12}F_6N_8O_6S_2$. Calculated, %: C 39.88, H 1.83, N 16.91.

Antimicrobial activity. The synthesized compounds **1**–**12** were assessed for antimicrobial activity against gram positive and negative strains of the pathogens [*S. aureus* (ATCC-25923), *S. epidermidis* (ATCC-29887), *E. coli* (ATCC-25922), *P. mirabilis* (ATCC-25933)]. The tests were carried out by the developed earlier method [13-19]. The pathogens (*S. aureus, S. epidermidis*, *P. mirabilis*, and *E. coli*) were sub-cultured in nutrient agar medium and left for incubation at 37°C for 24 h. To yield the suspension of about 10^5 CFU/Ml, the bacteria cells were suspended in the saline solution. The mixture (10 mL of suspension + 10 mL of sterile antibiotic agar) was heated to 40°C and poured on the agar plate in a laminar flow cabinet. To 100 mL of DMSO, was added 1 g of the compound for yielding the stock solution, one gram of each test compound was added. The 6 mm diameter paper discs were dipped in the solutions of the test compounds, diluted to different concentrations, fixed on agar plate, and incubated for 18 h for determining the inhibition zone.

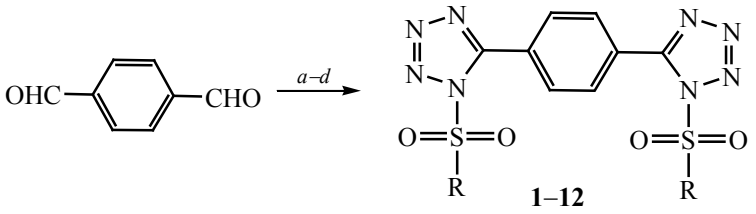
MTT assay. To assess toxicity status of the products **1**–**12**, hepatocellular carcinoma Hep G2 cells were harvested in DMEM (Dulbecco's modified Eagle's medium) with a mixture of 10% FBS (heat inactivated) with 100 units/mL penicillin, 100 mg/mL streptomycin and 2.5 mg/mL amphotericin B) at 37°C. The process was continued until reaching 80% confluent level. The percent viability of the cells was tested in accordance with the developed protocol [20, 21].

Molecular docking. Molecular docking of the compounds **1**–**12** was carried out by Auto-dock tools 1.5.6 [22–24]. Chem Draw Ultra 8.0 was used for drawing the structures **1**–**12**. The smiles files were generated and converted to the PDBs by the online smile translator.

RESULTS AND DISCUSSION

The four steps synthetic approach to the target compounds (Scheme 1) started with the reaction

Scheme 1. Synthetic approach to compounds **1**–**12**.



a. $NH_2OH \cdot HCl$, $NaHCO_3$, H_2O, reflux; *b*. Acetic anhydride, H_2O, reflux;
c. NaN_3, $ZnBr_2$, 2-Propanol, H_2O, reflux; *d.* Sulfonyl chloride, NaOH, reflux.

R = Ph (**1**), 4-Cl-Ph (**2**), 4-Br-Ph (**3**), 3-Br-Ph (**4**), 4-CH_3Ph (**5**), 4-OCH_3-Ph (**6**), 4-OC_2H_5-Ph (**7**), 4-NO_2-Ph (**8**), 4-CH_3SO_2-Ph (**9**), 4-NH_2SO_2-Ph (**10**), 4-SCH_3-Ph (**11**), 4-OCF_3-Ph (**12**).

of the aldehyde and hydroxylamine hydrochloride in water which gave (*Z*,*Z*)-benzene-1,4-diylbis(*N*-hydroxymethanimine). Its following refluxing with acetic anhydride led to benzene-1,4-dicarbonitrile, cyclization of which with sodium azide and zinc bromide led to formation of 5,5'-benzene-1,4-diylbis(1*H*-tetrazole). Sulfonylation of the tetrazole intermediate by various substituted sulfonyl chlorides gave the target compounds **1**–**12**. Structures of the synthesized compounds were supported by FT-IR, ^1H and ^{13}C NMR, and mass spectra. Completion of the last step of the synthesis was indicated by the absence of N-H bands in the range of 3255–3312 cm^{-1} and disappearance of the characteristic singlet of tetrazole N**H** in the range of 10.922–11.145 ppm in ^1H NMR spectra of the products **1**–**12**.

Drug likeness and physicochemical properties of compounds 1–12. The molecular structures of compounds **1**–**12** were designed, and their physicochemical properties and bioactivity score were calculated. The calculations indicated that all compounds did not have the molecular weight in accordance with the Lipinski rule of Five, except the compound **1.** The other parameters including milogP, TPSA, Natoms, Non, Nohnh, Nviolationsn Nrot, and Volume correlated with the Lipinski rule of Five for active compounds (Tables 1, 2).

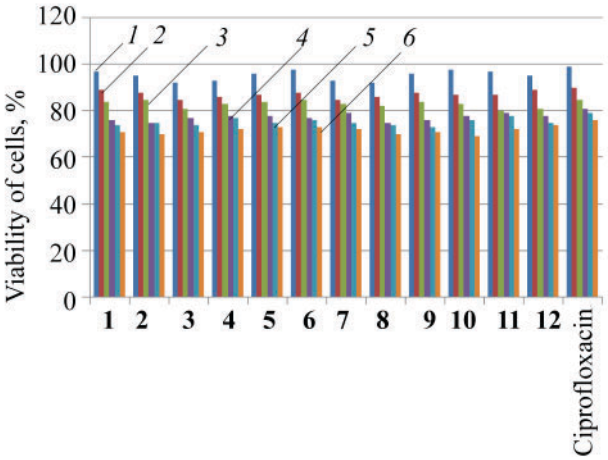
Table 1. Physicochemical properties of compounds **1**–**12** and ciprofloxacin

Compound	Physicochemical property score								
	miLogP	TPSA	Natoms	MW	nON	nOHNH	Nviolations	Nrotb	Volume
1	2.750	155.500	34	494.520	12	0	1	6	378.340
2	4.100	155.500	36	563.410	12	0	2	6	405.410
3	4.370	155.500	36	652.310	12	0	2	6	414.110
4	4.320	155.500	36	652.310	12	0	2	6	414.110
5	3.600	155.500	36	522.570	12	0	2	6	411.460
6	2.860	173.970	38	554.570	14	0	2	8	429.430
7	3.610	173.970	40	582.620	14	0	2	10	463.030
8	2.670	247.150	40	584.510	18	0	2	8	425.000
9	0.490	223.790	42	650.700	16	0	2	8	474.320
10	0.140	275.830	42	652.680	18	4	2	8	463.780
11	3.610	155.500	38	586.710	12	0	2	8	447.720
12	4.690	173.970	44	662.510	14	0	2	10	458.900
Ciprofloxacin	–0.071	74.569	24	331.347	6	2	0	3	285.460

Table 2. Bioactivity score of the compounds **1**–**12** and ciprofloxacin

Compound	Bioactivity score					
	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	0.06	–0.16	–0.05	–0.23	–0.04	0.02
2	0.05	–0.19	–0.06	–0.23	–0.07	0.00
3	–0.02	–0.24	–0.08	–0.29	–0.12	–0.03
4	–0.03	–0.26	–0.10	–0.32	–0.12	–0.03
5	0.01	–0.26	–0.10	–0.24	–0.09	–0.03
6	0.02	–0.30	–0.08	–0.22	–0.08	–0.03
7	–0.01	–0.42	–0.16	–0.26	–0.10	–0.11
8	–0.06	–0.40	–0.19	–0.33	–0.14	–0.13
9	–0.01	–0.59	–0.18	–0.29	0.04	–0.06
10	–0.01	–0.59	–0.18	–0.29	0.04	–0.06
11	–0.05	–0.55	–0.18	–0.48	0.04	–0.08
12	0.00	–0.28	–0.10	–0.22	–0.06	–0.02
Ciprofloxacin	0.12	–0.04	–0.07	–0.19	–0.21	0.28

Antimicrobial activity. The synthesized compounds **1**–**12** were tested for antimicrobial activity against gram positive and gram negative pathogens (*S. aureus*, *S. epidermidis*, *E. coli,* and *P. mirabilis*). All compounds demonstrated substantial values of activity that were higher or close to that of ciprofloxacin (Table 3).



Percent viability of cells determined for the compounds **1**–**12** and ciprofloxacin: (*1*) 3.125, (*2*) 6.25, (*3*) 12.5, (*4*) 25, (*5*) 50, and (*6*) 100 μmol/L.

MTT assay. The synthesized compounds were tested according to MTT assay using HepG2 cells. The cells were cultured in DMEM and the percent viability of cells was determined. HepG2 Cells were treated by the solutions of compounds within the concentration range 3.125–100 μmol/L. The determined cyto-toxicity was concentration dependent (see the figure).

Molecular docking. Molecular docking assessment carried out for compounds **1**–**12** against Glc-N-6P synthase (PDB: 2VF5) revealed their formation of H-bonds with the amino acids, including SR 303, CYS 300, SER 349, SER 401, VAL 399, ILE 397, GLY 398, THR 302, ILU 397, GLU 396, THR 352, GLN 348, SER 347, GLU 488. H-Bonding with SER-401 and VAL 399 residues was observed for all compounds. Also H-bonding was indicated for compounds **1**–**5**, **7** and **11** with SER 303, for **1**, **4**, **7**, and **8** with CYS 300, for **1**, **3**, **4**, and **6**–**12** with SER 349, for **2**, **10**, and **11** with ILE 397, for **2**, **5**, **9**, and **10** with GLY 398, for **2**, **5**, **6**, **9**, **10**, and **12** with THR 302, for **3** and **11** with ILU 397, for **3**, **9**–**11** with GLU 396, for **6**, **8**–**10**, and **12** with THR 352, for **9**, **10**, and **12** with GLU 488. Ciprofloxacin was likely to form H-bonding with VAL 567 and TYR 576. The above data strongly stimulate further experimental studies.

Table 3. Zones of inhibition and the minimum inhibitory concentrations of tetrazole derivatives **1**–**12** and ciprofloxacin

Compound	Zones of inhibition, mm				Minimum inhibitory concentration, μg/mL			
	gram positive		gram negative		gram positive		gram negative	
	S. aureus	*S. epidermidis*	*E. coli*	*P. mirabilis*	*S. aureus*	*S. epidermidis*	*E. coli*	*P. mirabilis*
1	20.44±0.18	22.53±0.17	23.06±0.14	20.24±0.22	6.25	3.125	12.5	25
2	20.90±0.27	22.22±0.22	23.55±0.30	20.58±0.31	6.25	3.125	12.5	25
3	20.76±0.17	21.76±0.40	22.11±0.22	19.98±0.17	6.25	3.125	12.5	25
4	20.10±0.29	21.22±0.23	22.30±0.19	20.28±0.25	6.25	3.125	12.5	25
5	20.31±0.20	22.31±0.33	23.73±0.32	21.14±0.27	6.25	3.125	12.5	25
6	21.15±0.35	22.50±0.27	23.98±0.10	20.76±0.35	6.25	3.125	6.25	12.5
7	20.93±0.17	21.29±0.20	21.18±0.20	20.35±0.28	6.25	3.125	6.25	12.5
8	21.76±0.22	21.79±0.19	23.98±0.23	20.88±0.18	6.25	3.125	6.25	12.5
9	21.85±0.30	22.98±0.21	23.77±0.26	20.70±0.17	6.25	3.125	6.25	12.5
10	22.12±0.20	22.85±0.25	23.19±0.50	20.34±0.27	6.25	3.125	6.25	12.5
11	21.12±0.18	21.59±0.43	22.49±0.36	20.55±0.40	6.25	3.125	12.5	25
12	21.22±0.20	21.70±0.30	22.88±0.24	20.34±0.38	6.25	3.125	12.5	25
Ciprofloxacin	21.39±0.21	22.87±0.37	23.69±0.81	22.34±0.21	6.25	3.125	6.25	12.5

CONCLUSIONS

A new sequence of twelve sulfonynated analogues of bis-tetrazole is designed and computationally screened for physicochemical properties and drug likeness. The readily synthesized compounds are tested for antimicrobial activity and cytotoxicity. The tests reveal that all compounds demonstrate the significant antimicrobial activity with the low toxic effect.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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