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RESEARCH ARTICLE

Design and Synthesis of Novel Sulfonamide-Derived Triazoles and Bioactivity Exploration

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Abstract: ***Objective*:** Due to the incidence of resistance, a series of sulfonamide-derived 1,2,4-triazoles were synthesized and evaluated.

***Method*:** The novel sulfonamide-derived 1,2,4-triazoles were prepared starting from commercial acetaniline and chlorosulfonic acid by sulfonylation, aminolysis, N-alkylation and so on. The antimicrobial activity of the synthesized compounds were evaluated *in vitro* by two-fold serial dilution technique.

***Results*:** *In vitro* antimicrobial evaluation found that 2-chlorobenzyl sulfonamide 1,2,4-triazole **7c** exhibited excellent antibacterial activities against MRSA, *B. subtilis*, *B. typhi* and *E. coli* with MIC values of 0.02–0.16 μmol/mL, which were comparable or even better than Chloromycin. The preliminary mechanism suggested that compound **7c** could effectively bind with DNA, and also it could bind with human microsomal heme through hydrogen bonds in molecular docking. Computational chemical studies were performed on compound **7c** to understand the structural features that are essential for activity. Additionally, compound **7c** could generate a small amount of reactive oxygen species (ROS).

***Conclusion*:** Compound **7c** could serve as a potential clinical antimicrobial candidate.

Keywords: Antibacterial, antifungal, antimicrobial agents, cytotoxicity, sulfonamides, triazole.

1. INTRODUCTION

In the past few decades, the incidence of systemic microbial infections has rapidly increased and become a major threat to public health. Various synthetic drugs such as sulfonamides, quinolones, azoles and so on are available throughout the world, however, the overuse of anti-infective drugs for the prevention and treatment of diseases has accelerated the dramatic growing emergence of drug resistance. Especially, the occurrence of multi-drug resistant bacteria and fungi has become a severe problem in both community and hospital-acquired infections. Therefore, the discovery of novel structurally antimicrobial agents with good pharmacological profiles and excellent activity toward resistant strains is highly desirable [1].

Sulfonamides as important artificial antimicrobial agents have been widely used in the clinic since 80 years ago. Currently, sulfonamide compounds have attracted increasing attention due to various biological activities [2] such as antimicrobial [3-5], anticancer [6] and so on [7, 8]. As already reported, sulfonamides could compete with aminobenzoic acid to affect the synthesis of nucleic acid, and then interrupt the growth of microorganisms. Up to now, numerous sulfonamide derivatives containing aromatic rings have been successfully marketed and widely employed in the treatment of infections Fig. (**1**) [9]. Significantly, supramolecular Ag-sulfadiazine used in burn therapy exhibited a better therapeutic effect than the free ligand or $AgNO_3$ Fig. (**1**) [10]. Recently, numerous efforts have been devoted to the further development of the novel sulfonamide derivatives with high activity, broad antimicrobial spectrum and low toxicity [11-14].

1,2,4-Triazole derivatives are known as an important type of poly-nitrogen electron-rich heterocyclic compounds with excellent safety profiles, favorable pharmacokinetic characteristics and the capability of forming hydrogen bonds [15, 16]. Therefore, the introduction of 1,2,4-triazole fragment is beneficial to improve the binding capacity with biomolecular targets and increase water solubility of target compounds. So far, a plenty of predominant triazole-based drugs have been successfully developed and prevalently used in antimicrobial field, such as Fluconazole, Itraconazole, Voriconazole, Posaconazole, Efinaconazole and Terconazole *etc.* [17]. Notably, it is commonly considered that the 1,2,4-triazole ring in Fluconazole can efficiently coordinate with the Fe^{2+} in human microsomal heme protein to restrain the biosynthesis of er-

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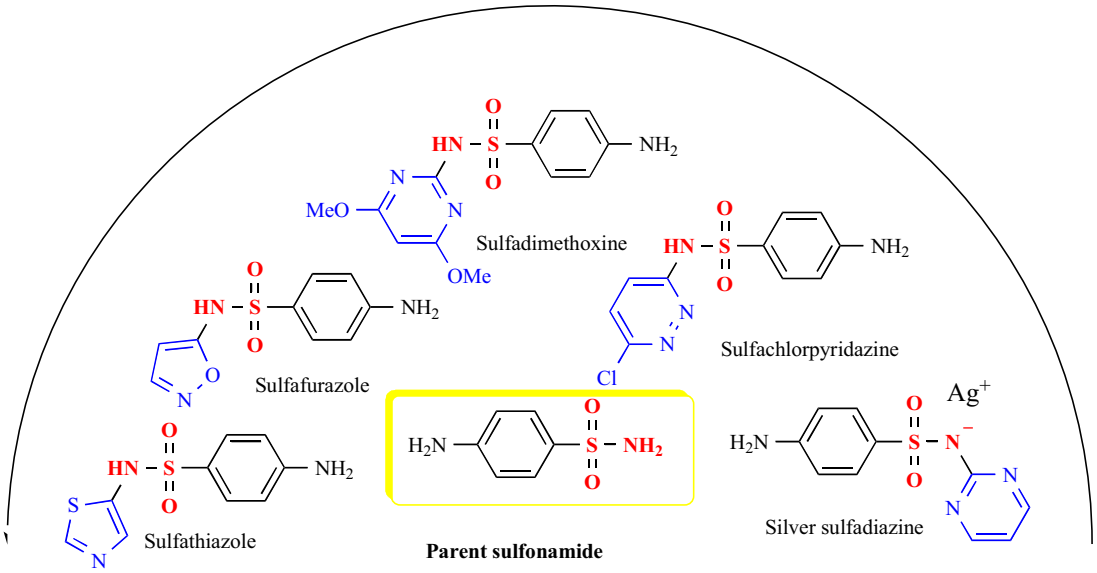


Fig. (1). Structures of sulfonamide-derived clinical drugs.

gosterol, thus inhibiting the growth of fungi [18]. The above observations strongly suggest that 1,2,4-triazole derivatives possess large potentiality as novel antimicrobial agents.

Therefore, the exploration of newly structural molecules with sulfonamide nucleus and 1,2,4-triazole moiety has become one of the predominant directions [19]. Inspired by these observations, a series of novel sulfonamide-derived 1,2,4-triazoles were designed from the following respects Fig. (**1**).

(a) As was reported, tertiary amino moiety as the bioisostere of tertiary alcohol fragment could be employed for the drug design to regulate physicochemical properties of biomolecules and interact with various enzymes and receptors in biological systems to exert bioactivities [20].

(b) Various halobenzyl groups were employed into the target compounds because numerous works has shown that the incorporation of halobenzyl moieties was beneficial to improve biological and pharmacological properties by enhancing the rate of absorption and transport of drugs *in vivo* [21].

(c) Ethylene chain could modulate the molecular flexibility, which might be helpful to improve molecular binding ability with the microbial targets [20].

Based on the above considerations, a series of novel sulfonamide-derived 1,2,4-triazoles were synthesized in two ways. The *in vitro* antibacterial and antifungal activities were evaluated against four Gram-positive bacteria, four Gram-negative bacteria and five fungi. The interaction of the bioactive molecule with calf thymus DNA was performed and molecular computational studies were employed to investigate the possible antibacterial mechanism. Moreover, the cytotoxicity, ROS and docking with human microsomal heme of active compound were also investigated to explore its further biological activity [22, 23].

2. EXPERIMENTAL

2.1. General Methods

2.1.1. Synthesis of 4-acetamidobenzene-1-sulfonyl Chloride (2)

The desired 4-acetamidobenzene-1-sulfonyl chloride **2** was synthesized as white solid [11]. Yield: 90%; mp: 139-140ºC. (literature mp: 142-144ºC).

2.1.2. Synthesis of N- (4-sulfamoylphenyl) acetamide (3)

The N-(4-sulfamoylphenyl) acetamide **3** was obtained as white solid [11]. Yield: 82%; mp: 212–214ºC. (literature mp: 219-220ºC).

2.1.3. Synthesis of N-(4-(N-(2-chlorobenzyl) sulfamoyl) phenyl) acetamide (4a)

A mixture of compound **3** (5.094 g, 23.8 mmol) and potassium carbonate (2.324 g, 16.8 mmol) was stirred in acetone (60 mL) at 50ºC. 1-Chloro-2- (chloromethyl)benzene (3.821 g, 23.7 mmol) was added and the reaction system was stirred at 70ºC continuously after 0.5 h. When the reaction was completed (monitored by TLC, eluent, chloroform/ethyl acetate, 5/1, V/V), the system was filtered and washed with methanol (3 × 25 mL). Compound **4a** was obtained and purified as white solid by silica gel column chromatography (eluent, chloroform/ethyl acetate, 10/1, V/V). Yield: 17%; mp: 180–182ºC; IR (KBr) ν: 3301 (N−H), 3107, 3062 (aromatic C−H), 2924, 2856 (aliphatic C−H), 1678 (C=O), 1592, 1530 (aromatic frame), 1333, 1158, 756 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 10.31 (s, 1H, N*H*COCH$_3$), 8.08 (t, J = 6.1 Hz, 1H, SO_2N*H*), 7.77–7.69 (apparent s, 4H, Ph-*H*), 7.44–7.42 (m, 1H, 2-ClPh-3-*H*), 7.38 (d, J = 7.3 Hz, 1H, 2-ClPh-6-*H*), 7.32–7.26 (m, 2H, 2-ClPh-4,5-*H*), 4.03 (d, J = 6.2 Hz, 2H, 2-ClPh-CH_2), 2.09 (s, 3H, COCH_3) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ: 169.4, 143.3, 135.4, 134.6, 132.6, 130.2, 129.5, 129.4, 128.1, 127.6, 119.1, 44.1, 24.6 ppm.

2.1.4. Synthesis of N-(4-(N-(4-fluorobenzyl) sulfamoyl) phenyl) acetamide (4b)

Compound **4b** was prepared according to the procedure described for compound **4a** starting from compound **3** (3.005 g, 14.0 mmol) and 1-(chloromethyl)-4-fluorobenzene (2.003 g, 13.9 mmol). The pure product **4b** was obtained as white solid. Yield: 7%; mp: 196–198ºC; IR (KBr) ν: 3304 (N−H), 3100, 3048 (aromatic C−H), 2930, 2859 (aliphatic C−H), 1672 (C=O), 1590, 1531 (aromatic frame), 1343, 1163, 748, 611 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 10.30 (s, 1H, N*H*COCH$_3$), 8.02 (t, *J* = 6.2 Hz, 1H, SO_2N*H*), 7.74 (d, *J* = 8.8 Hz, 2H, Ph-2,6-*H*), 7.71 (d, *J* = 8.8 Hz, 2H, Ph-3,5-*H*), 7.27 (dd, *J* = 7.9, 5.9 Hz, 2H, 4-FPh-3,5-*H*), 7.10 (t, *J* = 8.8 Hz, 2H, 4-FPh-2,6-*H*), 3.94 (d, *J* = 6.2 Hz, 2H, 4-FPh-C*H*$_2$), 2.09 (s, 3H, COC*H*$_3$) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ: 169.4, 161.8, 143.2, 134.9, 134.5, 130.1, 128.1, 119.1, 115.5, 45.8, 24.6 ppm.

2.1.5. Synthesis of N-(4-(N-(4-chlorobenzyl) sulfamoyl) phenyl) acetamide (4c)

Compound **4c** was prepared according to the procedure described for compound **4a** starting from compound **3** (5.108 g, 23.8 mmol) and 1-chloro-4-(chloromethyl)benzene (3.124 g, 19.4 mmol). The pure product **4c** was obtained as white solid. Yield: 17%; mp: 189–191ºC; IR (KBr) ν: 3304 (N−H), 3103, 3040 (aromatic C−H), 2928, 2857 (aliphatic C−H), 1670 (C=O), 1593, 1530 (aromatic frame), 1328, 1154, 784 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 10.30 (s, 1H, N*H*COCH$_3$), 8.05 (t, *J* = 6.4 Hz, 1H, SO_2N*H*), 7.74 (d, *J* = 8.8 Hz, 2H, Ph-2, 6-*H*), 7.71 (d, *J* = 8.8 Hz, 2H, Ph-3,5-*H*), 7.34 (d, *J* = 8.3 Hz, 2H, 4-ClPh-3,5-*H*), 7.26 (d, *J* = 8.4 Hz, 2H, 4-ClPh-2,6-*H*), 3.95 (d, *J* = 6.4 Hz, 2H, 4-ClPh-C*H*$_2$), 2.09 (s, 3H, COC*H*$_3$) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ: 169.4, 143.2, 137.4, 134.8, 132.2, 129.9, 128.6, 128.1, 119.1, 45.8, 24.6 ppm.

2.1.6. Synthesis of N-(4-(N-(2, 4-dichlorobenzyl) sulfamoyl) phenyl) acetamide (4d)

Compound **4d** was prepared according to the procedure described for compound **4a** starting from compound **3** (3.007 g, 14.0 mmol) and 2,4-dichloro-1-(chloromethyl)benzene (3.076 g, 14.4 mmol). The pure product **4d** was obtained as white solid. Yield: 3%; mp: 233–235ºC; IR (KBr) ν: 3300 (N−H), 3112, 3054 (aromatic C−H), 2925, 2858 (aliphatic C−H), 1678 (C=O), 1593, 1528 (aromatic frame), 1338, 1153, 763 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 10.39 (s, 1H, N*H*COCH$_3$), 7.81 (apparent s, 4H, Ph-*H*), 7.62 (s, 1H, SO_2N*H*), 7.50–7.39 (m, 3H, 2,4-Cl_2Ph-3,5,6-*H*), 4.31 (s, 2H, 2,4-Cl_2Ph-C*H*$_2$), 2.07 (s, 3H, COC*H*$_3$) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ: 169.4, 144.6, 140.5, 133.9, 130.8, 130.1, 130.0, 129.4, 119.1, 115.6, 115.3, 45.8, 24.6 ppm.

2.1.7. Synthesis of N-(4-(N-(3,4-dichlorobenzyl) sulfamoyl) phenyl) acetamide (4e)

Compound **4e** was prepared according to the procedure described for compound **4a** starting from compound **3** (3.011 g, 14.1 mmol) and 3,4-dichloro-1-(chloromethyl)benzene (2.709 g, 13.9 mmol). The pure product **4e** was obtained as white solid. Yield: 4%; mp: 183–185ºC; IR (KBr) ν: 3305 (N−H), 3103, 3049 (aromatic C−H), 2926, 2857 (aliphatic C−H), 1679 (C=O), 1592, 1529 (aromatic frame), 1369, 1155, 748 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 10.29 (s, 1H, N*H*COCH$_3$), 8.11 (t, *J* = 5.7 Hz, 1H, SO_2N*H*), 7.73 (d, *J* = 8.9 Hz, 2H, Ph-2, 6-*H*), 7.70–7.68 (m, 2H, Ph-3,5-*H*), 7.53 (d, *J* = 8.3 Hz, 1H, 2,3-Cl_2Ph-5-*H*), 7.43 (d, *J* = 1.9 Hz, 1H, 2,3-Cl_2Ph-2-*H*), 7.23 (dd, *J* = 8.3, 2.0 Hz, 1H, 2,3-Cl_2Ph-6-*H*), 3.99 (d, *J* = 5.6 Hz, 2H, 2,3-Cl_2Ph-C*H*$_2$), 2.09 (s, 3H, COC*H*$_3$) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ: 169.4, 143.3, 139.6, 134.7, 131.3, 130.8, 130.1, 129.9, 128.3, 128.1, 119.0, 45.3, 24.6 ppm.

2.1.8. Synthesis of N-(4-(N-(2-bromoethyl)-N-(2-chlorobenzyl) sulfamoyl) phenyl) acetamide (5a)

The mixture of 1,2-dibromoethane (0.340 g, 1.8 mmol), compound **4a** (0.513 g, 1.5 mmol) and potassium carbonate (0.759 g, 5.5 mmol) was reacted in acetone (50 mL) at 50ºC for 8 h. When the reaction was completed (monitored by TLC, eluent, chloroform/ethyl acetate, 5/1, V/V), the residue was extracted with chloroform (3 × 25 mL). Compound **5a** was prepared and purified as white solid. Yield: 82%; mp: 90–92ºC; IR (KBr) *ν*: 3371 (N−H), 3108, 3060 (aromatic C−H), 2929, 2857 (aliphatic C−H), 1703 (C=O), 1591, 1529, 1495 (aromatic frame), 1334, 1156, 752, 548 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 10.38 (s, 1H, N*H*COCH$_3$), 7.81 (apparent s, 4H, Ph-*H*), 7.51 (dd, *J* = 7.0, 2.3 Hz, 1H, 2-ClPh-3-*H*), 7.45 (dd, *J* = 7.2, 2.0 Hz, 1H, 2-ClPh-4-*H*), 7.36–7.33 (m, 2H, 2-ClPh-5,6-*H*), 4.45 (s, 2H, 4-FPh-C*H*$_2$), 3.49 (t, *J* = 7.3 Hz, 2H, NCH$_2$C*H*$_2$), 3.30 (t, *J* = 7.3 Hz, 2H, NC*H*$_2$CH$_2$), 2.11 (s, 3H, COC*H*$_3$) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ: 169.7, 144.0, 134.6, 132.9, 130.7, 130.3, 129.9, 128.8, 128.4, 127.8, 119.3, 50.7, 49.06, 30.4, 24.6 ppm; HRMS (TOF) found, m/z 444.9978 $[M + H]^+$, calcd for $C_{17}H_{19}BrClN_2O_3S$: 444.9983.

2.1.9. Synthesis of N-(4-(N-(2-bromoethyl)-N-(4-fluorobenzyl) sulfamoyl) phenyl) acetamide (5b)

Compound **5b** was prepared according to the procedure described for compound **5a** starting from compound **4b** (0.307 g, 1.0 mmol) and 1,2-dibromoethane (0.434 g, 2.3 mmol). The pure product **5b** was obtained as white solid. Yield: 74%; mp: 132–134ºC; IR (KBr) *ν*: 3295 (N−H), 3102, 3047 (aromatic C−H), 2933, 2865 (aliphatic C−H), 1671 (C=O), 1590, 1536, 1509 (aromatic frame), 1340, 1160, 835, 748, 611 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 10.37 (s, 1H, N*H*COCH$_3$), 7.81 (apparent s, 4H, Ph-*H*), 7.45–7.28 (m, 2H, 4-FPh-2,6-*H*), 7.18 (t, *J* = 8.4 Hz, 2H, 4-FPh-3,5-*H*), 4.31 (s, 2H, 4-FPh-C*H*$_2$), 3.43–3.39 (t, 2H, NCH$_2$C*H*$_2$), 3.27–3.23 (t, 2H, NC*H*$_2$CH$_2$), 2.10 (s, 3H, COC*H*$_3$) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ: 169.5, 161.4, 143.9, 132.7, 130.8, 130.7, 128.7, 119.3, 115.8, 50.0, 49.1, 30.4, 24.6 ppm; HRMS (TOF) found, m/z 429.0273 $[M + H]^+$, calcd for $C_{17}H_{19}BrFN_2O_3S$: 429.0278.

2.1.10. Synthesis of N-(4-(N-(2-bromoethyl)-N-(4-chlorobenzyl) sulfamoyl) phenyl) acetamide (5c)

Compound **5c** was prepared according to the procedure described for compound **5a** starting from compound **4c** (0.515 g, 1.5 mmol) and 1,2-dibromoethane (0.361 g, 1.9 mmol). The pure product **5c** was obtained as yellow syrup. Yield: 70%; IR (KBr) *ν*: 3364 (N−H), 3104, 3042 (aromatic C−H), 2928, 2857 (aliphatic C−H), 1702 (C=O), 1594, 1528,

1492 (aromatic frame), 1326, 1153, 784, 611 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 10.38 (s, 1H, N*H*COCH$_3$), 7.82 (apparent s, 4H, Ph-*H*), 7.43–7.40 (m, 2H, 4-ClPh-2,6-*H*), 7.37–7.34 (m, 2H, 4-ClPh-3,5-*H*), 4.33 (s, 2H, 4-FPh-C*H*$_2$), 3.43 (t, *J* = 7.3 Hz, 2H, NCH$_2$C*H*$_2$), 3.27 (t, *J* = 7.3 Hz, 2H, NC*H*$_2$CH$_2$), 2.10 (s, 3H, COC*H*$_3$) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ: 169.5, 144.0, 132.8, 132.6, 130.5, 128.9, 128.7, 128.5, 119.3, 51.6, 49.1, 30.4, 24.6 ppm; HRMS (TOF) found, m/z 444.9981 $[M + H]^+$, calcd for $C_{17}H_{19}BrClN_2O_3S$: 444.9983.

2.1.11. Synthesis of N-(4-(N-(2-bromoethyl)-N-(2,4-dichlorobenzyl) sulfamoyl) phenyl) acetamide (5d)

Compound **5d** was prepared according to the procedure described for compound **5a** starting from compound **4d** (0.110 g, 0.3 mmol) and 1,2-dibromoethane (0.081 g, 0.4 mmol). The pure product **5d** was obtained as a white solid. Yield: 89%; mp: 164–166ºC; IR (KBr) *v*: 3300 (N−H), 3113, 3055 (aromatic C−H), 2926, 2857 (aliphatic C−H), 1670 (C=O), 1594, 1538, 1502, 1474 (aromatic frame), 1343, 1159, 1095, 763 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 10.38 (s, 1H, N*H*COCH$_3$), 7.87–7.79 (apparent s, 4H, Ph-*H*), 7.41–7.36 (m, 1H, 2,4-Cl$_2$Ph-3-*H*), 7.24 (dd, *J* = 8.7 Hz, 1H, 2,4-Cl$_2$Ph-5-*H*), 7.19–7.11 (m, 1H, 2,4-Cl$_2$Ph-6-*H*), 4.36 (m, 4H, 2,4-Cl$_2$Ph-C*H*$_2$, NCH$_2$C*H*$_2$), 3.31 (m, 2H, NC*H*$_2$CH$_2$), 2.12 (s, 3H, COC*H*$_3$) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ: 169.5, 144.1, 135.8, 133.3, 132.0, 130.3, 128.9, 128.8, 128.4, 127.5, 119.4, 52.2, 50.0, 49.8, 24.6 ppm; HRMS (TOF) found, m/z 478.9597 $[M + H]^+$, calcd for $C_{17}H_{18}BrCl_2N_2O_3S$: 478.9593.

2.1.12. Synthesis of N-(4-(N-(2-bromoethyl)-N-(3,4-dichlorobenzyl) sulfamoyl) phenyl) acetamide (5e)

Compound **5e** was prepared according to the procedure described for compound **5a** starting from compound **4e** (0.150 g, 0.4 mmol) and 1,2-dibromoethane (0.125 g, 0.7 mmol). The pure product **5e** was obtained as yellow syrup. Yield: 79%; IR (KBr) *v*: 3318 (N−H), 3105, 3054 (aromatic C−H), 2925, 2858 (aliphatic C−H), 1678 (C=O), 1591, 1530, 1470 (aromatic frame), 1368, 1156, 746, 612 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 10.38 (s, 1H, N*H*COCH$_3$), 7.81 (apparent s, 4H, Ph-*H*), 7.62 (d, *J* = 8.3 Hz, 1H, 2,3-Cl$_2$Ph-4-*H*), 7.52 (d, *J* = 2.0 Hz, 1H, 2,3-Cl$_2$Ph-5-*H*), 7.34 (dd, *J* = 8.3, 2.0 Hz, 1H, 2,3-Cl$_2$Ph-6-*H*), 4.34 (s, 2H, 2,3-Cl$_2$Ph-C*H*$_2$), 3.47 (t, *J* = 7.1 Hz, 2H, NC*H*$_2$CH$_2$), 3.36 (t, *J* = 6.8 Hz, 2H, NCH$_2$C*H*$_2$), 2.10 (s, 3H, COC*H*$_3$) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ: 169.6, 144.1, 138.8, 132.5, 131.5, 131.1, 130.7, 130.5, 128.8, 128.8, 119.3, 51.1, 50.6, 30.6, 24.6 ppm; HRMS (TOF) found, m/z 478.9589 $[M + H]^+$, calcd for $C_{17}H_{18}BrCl_2N_2O_3S$: 478.9593.

2.1.13. Synthesis of N-(4-(N-(2-(1H-1,2,4-triazol-1-yl) ethyl)-n-benzylsulfamoyl) phenyl) acetamide (6a)

The acetone solution of compound **11** (0.063 g, 1.5 mmol) and potassium carbonate (0.026 g, 0.2 mmol) was reacted at 70ºC for 0.5 h. The benzyl chloride (0.024 g, 1.5 mmol) was added at room temperature, and then the mixture was stirred at 60ºC. When the reaction came to the end (monitored by TLC, eluent, chloroform/methanol, 15/1, V/V), the residue was extracted with chloroform (3 × 20 mL). Compound **6a** was prepared and purified as white solid. Yield: 67%; mp: 179–181ºC; IR (KBr) *v*: 3302 (N−H), 3093, 3040, 3003 (aromatic C−H), 2942, 2869, 2802 (aliphatic C−H), 1691 (C=O), 1592, 1541, 1512 (aromatic frame), 1317, 1151, 992, 732 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 10.33 (s, 1H, N*H*COCH$_3$), 8.28 (s, 1H, TRA C^5-*H*), 7.84 (s, 1H, TRA C^3-*H*), 7.77 (d, *J* = 8.3 Hz, 2H, Ph-2,6-*H*), 7.73 (d, *J* = 8.6 Hz, 2H, Ph-3,5-*H*), 7.36–7.26 (m, 2H, NCH$_2$Ph-2,6-*H*), 7.14 (m, 3H, NCH$_2$Ph-3,4,5-*H*), 4.32 (s, 2H, NC*H*$_2$Ph), 4.21 (t, *J* = 6.2 Hz, 2H, NCH$_2$C*H*$_2$), 3.51 (t, *J* = 6.2 Hz, 2H, NC*H*$_2$CH$_2$), 2.10 (s, 3H, COC*H*$_3$) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ: 169.5, 151.9, 144.7, 132.3, 131.2, 131.1, 128.7, 124.9, 123.7, 123.6, 119.2, 48.2, 48.0, 46.4, 24.6 ppm; HRMS (TOF) found, m/z 400.1435 $[M + H]^+$, calcd for $C_{19}H_{22}N_5O_3S$: 400.1438.

2.1.14. Synthesis of N-(4-(N-(2-(1H-1,2,4-triazol-1-Yl) ethyl)-N-(2-fluorobenzyl) sulfamoyl) phenyl) acetamide (6b)

Compound **6b** was synthesized according to the experimental procedure reported for compound **6a**, starting from compound **11** (0.066 g, 0.2 mmol) and 1-(chloromethyl)-2-fluorobenzene (0.030 g, 0.2 mmol). The pure product **6b** was obtained as white solid. Yield: 81%; mp: 175–177ºC; R (KBr) *v*: 3303 (N−H), 3094, 3044, 3004 (aromatic C−H), 2870, 2802 (aliphatic C−H), 1692 (C=O), 1592, 1541 (aromatic frame), 1343, 1149, 760, 609 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 10.34 (s, 1H, N*H*COCH$_3$), 8.28 (s, 1H, TRA C^5-*H*), 7.84 (s, 1H, TRA C^3-*H*), 7.77 (d, *J* = 8.8 Hz, 2H, Ph-2,6-*H*), 7.73 (d, *J* = 8.7 Hz, 2H, Ph-3,5-*H*), 7.34 (dd, *J* = 6.6 Hz, 1H, 2-FPh-3-*H*), 7.28 (t, *J* = 7.4 Hz, 1H, 2-FPh-4-*H*), 7.14 (t, *J* = 8.1 Hz, 2H, 2-FPh-5,6-*H*), 4.32 (s, 2H, 2-FPh-C*H*$_2$), 4.21 (t, *J* = 6.4 Hz, 2H, NCH$_2$C*H*$_2$), 3.51 (t, *J* = 6.4 Hz, 2H, NC*H*$_2$CH$_2$), 2.10 (s, 3H, COC*H*$_3$) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ: 169.3, 156.4, 148.3, 148.2, 141.2, 127.3, 126.9, 125.2, 118.9, 118.0, 111.8, 108.7, 99.0, 55.6, 37.6, 35.2, 26.8 ppm; HRMS (TOF) found, m/z 418.1347 $[M + H]^+$, calcd for $C_{19}H_{20}FN_5O_3S$: 418.1344.

2.1.15. Synthesis of N-(4-(N-(2-(1h-1,2,4-triazol-1-Yl) ethyl)-N-(2-chlorobenzyl) sulfamoyl) phenyl) acetamide (6c)

A solution of 1*H*-1,2,4-triazole (0.096 g, 1.4 mmol) and potassium carbonate (0.233 g, 1.7 mmol) was reacted in acetonitrile (25 mL) at 70ºC for 0.5 h. Compound **5a** (0.463 g, 1.4 mmol) was added to the mixture at room temperature, and then the system was stirred at 70ºC. When the reaction was completed (monitored by TLC, eluent, chloroform/methanol, 20/1, V/V), the residue extracted with chloroform (3 × 20 mL). Compound **6c** was provided and purified as white solid. Yield: 56%; mp: 187–189ºC; R (KBr) *v*: 3301 (N−H), 3103, 3043 (aromatic C−H), 2865, 2792 (aliphatic C−H), 1689 (C=O), 1590, 1532 (aromatic frame), 1341, 1163, 802, 611 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 10.39 (s, 1H, N*H*COCH$_3$), 8.28 (s, 1H, TRA C^5-*H*), 7.84 (s, 1H, TRA C^3-*H*), 7.81 (d, *J* = 9.1 Hz, 2H, Ph-2,6-*H*), 7.78 (d, *J* = 9.1 Hz, 2H, Ph-3,5-*H*), 7.41 (d, *J* = 8.0 Hz, 1H, 2-ClPh-3-*H*), 7.33–7.26 (m, 3H, 2-ClPh-4,5,6-*H*), 4.34 (s, 2H, 2-ClPh-C*H*$_2$), 4.20 (t, *J* = 6.4 Hz, 2H, NCH$_2$C*H*$_2$), 3.55 (t, *J* =

6.4 Hz, 2H, NCH_2CH$_2$), 2.10 (s, 3H, COCH_3) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ: 169.6, 151.9, 144.7, 144.0, 134.2, 132.8, 132.0, 130.4, 129.9, 129.8, 128.9, 127.7, 119.3, 50.5, 48.6, 48.2, 24.6 ppm; HRMS (TOF) found, m/z 434.1043 [M + H]$^+$, calcd for $C_{19}H_{20}ClN_5O_3S$: 434.1048.

2.1.16. Synthesis of N-(4-(N-(2-(1h-1,2,4-triazol-1-yl) ethyl)-N-(4-fluorobenzyl) sulfamoyl) phenyl) acetamide (6d)

Compound **6d** was synthesized according to the experimental procedure reported for compound **6c**, starting from compound **5b** (0.390 g, 0.9 mmol) and 1*H*-1, 2,4 -triazole (0.065 g, 0.9 mmol). The pure product **6d** was obtained as white solid. Yield: 78%; mp: 177–179ºC; R (KBr) *v*: 3303 (N−H), 3097, 3036 (aromatic C−H), 2996, 2944, 2873, 2804 (aliphatic C−H), 1692 (C=O), 1591, 1543, 1509 (aromatic frame), 1315, 1149, 797, 610 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 10.37 (s, 1H, N*H*COCH$_3$), 8.24 (s, 1H, TRA C^5-*H*), 7.85 (s, 1H, TRA C^3-*H*), 7.79 (d, *J* = 8.9 Hz, 2H, Ph-2,6-*H*), 7.76 (d, *J* = 8.9 Hz, 2H, Ph-3,5-*H*), 7.26 (d, *J* = 8.5 Hz, 2H, 4-FPh-2,6-*H*), 7.13 (d, *J* = 8.5 Hz, 2H, 4-FPh-3,5-*H*), 4.22 (s, 2H, 4-FPh-CH_2), 4.15 (t, *J* = 6.4 Hz, 2H, NCH$_2$CH_2), 3.46 (t, *J* = 6.4 Hz, 2H, NCH_2CH$_2$), 2.10 (s, 3H, COCH_3) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ: 169.5, 161.3, 151.9, 144.7, 143.9, 132.4, 130.6, 128.7, 119.3, 115.8, 115.7, 51.7, 49.1, 48.0, 24.9 ppm; HRMS (TOF) found, m/z 418.1347 [M + H]$^+$, calcd for $C_{19}H_{20}FN_5O_3S$: 418.1344.

2.1.17. Synthesis of N-(4-(N-(2-(1h-1,2,4-triazol-1-yl) ethyl)-N-(4-chlorobenzyl) sulfamoyl) phenyl) acetamide (6e)

Compound **6e** was synthesized according to the experimental procedure reported for compound **6c**, starting from compound **5c** (0.390 g, 0.8 mmol) and 1*H*-1,2,4-triazole (0.064 g, 0.9 mmol). The pure product **6e** was obtained as white solid. Yield: 62%; mp: 195–197ºC; R (KBr) *v*: 3300 (N−H), 3096, 3036 (aromatic C−H), 2997, 2942, 2870, 2804 (aliphatic C−H), 1690 (C=O), 1591, 1543, 1515 (aromatic frame), 1317, 1151, 799, 610 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 10.37 (s, 1H, N*H*COCH$_3$), 8.25 (s, 1H, TRA C^5-*H*), 7.84 (s, 1H, TRA C^3-*H*), 7.78 (apparent s, 4H, Ph-*H*), 7.37 (d, *J* = 8.3 Hz, 2H, 4-ClPh-3,5-*H*), 7.24 (d, *J* = 8.3 Hz, 2H, 4-ClPh-2,6-*H*), 4.23 (s, 2H, 4-ClPh-CH_2), 4.16 (t, *J* = 6.4 Hz, 2H, NCH$_2$CH_2), 3.47 (t, *J* = 6.4 Hz, 2H, NCH_2CH$_2$), 2.10 (s, 3H, COCH_3) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ: 169.5, 151.9, 144.7, 143.9, 136.0, 132.8, 132.35, 130.4, 128.9, 128.7, 119.3, 51.8, 49.1, 48.1, 24.6 ppm; HRMS (TOF) found, m/z 434.1045 [M + H]$^+$, calcd for $C_{19}H_{20}ClN_5O_3S$: 434.1048.

2.1.18. Synthesis of N-(4-(N-(2-(1h-1,2,4-triazol-1-yl) ethyl)-N-(2,4-dichlorobenzyl) sulfamoyl) phenyl) acetamide (6f)

Compound **6f** was synthesized according to the experimental procedure reported for compound **6c**, starting from compound **5d** (0.457 g, 0.9 mmol) and 1*H*-1,2,4 -triazole (0.106 g, 1.54 mmol). The pure product **6f** was obtained as white solid. Yield: 69%; mp: 199–201ºC; R (KBr) *v*: 3306 (N−H), 3096, 3035 (aromatic C−H), 2999, 2971, 2804 (aliphatic C−H), 1694 (C=O), 1591, 1542, 1514 (aromatic frame), 1341, 1152, 792, 611 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 10.37 (s, 1H, N*H*COCH$_3$), 8.30 (s, 1H, TRA C^5-*H*), 7.82 (s, 1H, TRA C^3-*H*), 7.80 (apparent s, 4H, Ph-*H*), 7.54 (s, 1H, 2,4-Cl$_2$Ph-3-*H*), 7.37 (d, 1H, 2,4-Cl$_2$Ph-5-*H*)7.33 (d, 1H, 2,4-Cl$_2$Ph-6-*H*), 4.31 (s, 2H, 2,4-Cl$_2$Ph-CH_2), 4.23 (t, *J* = 6.2 Hz, 2H, NCH$_2$CH_2), 3.55 (t, *J* = 6.1 Hz, 2H, NCH_2CH$_2$), 2.11 (s, 1H, COCH_3) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ: 169.6, 151.9, 144.7, 144.1, 133.7, 133.6, 133.4, 131.8, 129.3, 128.9, 127.9, 119.3, 118.5, 50.2, 48.8, 48.3, 24.6 ppm; HRMS (TOF) found, m/z 468.0653 [M + H]$^+$, calcd for $C_{19}H_{19}Cl_2N_5O_3S$: 468.0658.

2.1.19. Synthesis of N-(4-(N-(2-(1h-1,2,4-triazol-1-yl) Ethyl)-N-(3,4-Dichlorobenzyl) Sulfamoyl) Phenyl) Acetamide (6g)

Compound **6g** was synthesized according to the experimental procedure reported for compound **6c**, starting from compound **5e** (0.193 g, 0.4 mmol) and 1*H*-1,2,4 -triazole (0.051 g, 0.7 mmol). The pure product **6g** was obtained as white solid. Yield: 73%; mp: 195–197ºC; R (KBr) *v*: 3394 (N−H), 3084, 3018 (aromatic C−H), 2960, 2923, 2887 (aliphatic C−H), 1687 (C=O), 1590, 1542, 1511 (aromatic frame), 1332, 1156, 828, 612 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 10.38 (s, 1H, N*H*COCH$_3$), 8.29 (s, 1H, TRA C^5-*H*), 7.83 (s, 1H, TRA C^3-*H*), 7.79 (apparent s, 4H, Ph-*H*), 7.56 (d, *J* = 8.3 Hz, 1H, 2,3-Cl$_2$Ph-4-*H*), 7.35 (d, *J* = 2.0 Hz, 1H, 2,3-Cl$_2$Ph-5-*H*), 7.20 (dd, *J* = 8.3, 2.0 Hz, 1H, 2,3-Cl$_2$Ph-6-*H*), 4.24 (s, 2H, 2,3-Cl$_2$Ph-CH_2), 4.23 (t, *J* = 6.2 Hz, 2H, NCH$_2$CH_2), 3.52 (t, *J* = 6.3 Hz, 2H, NCH_2CH$_2$), 2.11 (s, 1H, COCH_3) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ: 169.5, 162.9, 151.8, 144.7, 144.1, 138.4, 131.5, 131.0, 130.3, 128.8, 128.7, 127.3, 119.3, 51.4, 49.1, 48.1, 24.6 ppm; HRMS (TOF) found, m/z 468.0656 [M + H]$^+$, calcd for $C_{19}H_{19}Cl_2N_5O_3S$: 468.0658.

2.1.20. Synthesis of N-(2-(1h-1,2,4-triazol-1-yl)ethyl)-4-amino-N-benzylbenzenesulfonamide (7a)

0.5 mL 2 mol/L sodium hydroxide solution was added to a solution of compound **6a** in ethanol 15 mL. The mixture was refluxed for 10 h (monitored by TLC, eluent, acetone/petroleum ether, 1/1, V/V). After cooling to the room temperature, the solvent was evaporated and the residue was treated with water (30 mL) and extracted with chloroform (3 × 30 mL). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated in vacuo to give the deprotected compound **7a** as white solid. Yield: 92%; mp: 154–156ºC; R (KBr) *v*: 3453, 3365 (N−H), 3003 (aromatic C−H), 2924, 2856 (aliphatic C−H), 1592, 1503 (aromatic frame), 1324, 1151, 733, 550 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ: 7.84 (s, 1H, TRA C^5-*H*), 7.77 (s, 1H, TRA C^3-*H*), 7.61 (d, *J* = 8.4 Hz, 2H, Ph-2,6-*H*), 7.28 (m, 3H, NCH$_2$Ph-2,5,6-*H*), 7.17–7.11 (m, 2H, NCH$_2$Ph-3,4-*H*), 6.71 (d, *J* = 8.5 Hz, 2H, Ph-3,5-*H*), 4.18 (t, *J* = 6.0 Hz, 2H, NCH$_2$CH_2), 4.08 (s, 2H, NCH_2Ph), 3.43 (t, *J* = 6.3 Hz, 2H, NCH_2CH$_2$) ppm; ^{13}C NMR (151 MHz, CDCl$_3$) δ: 152.1, 150.9, 143.7, 135.8, 129.5, 128.8, 128.6, 128.1, 126.7, 114.2, 53.8, 50.8, 47.7 ppm; HRMS (TOF) found, m/z 358.1335 [M + H]$^+$, calcd for $C_{17}H_{19}N_5O_2S$: 358.1332.

2.1.21. Synthesis of N-(2-(1h-1,2,4-triazol-1-yl) ethyl)-4-amino-N-(2-fluorobenzyl) benzenesulfonamide (7b)

Compound **7b** was obtained as white solid. Yield: 90%; mp: 161–163ºC; IR (KBr) *v*: 3453, 3367 (N−H), 3109 (aro-

matic C−H), 2950, 2924, 2854 (aliphatic C−H), 1592, 1502 (aromatic frame), 1117, 616 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.91 (s, 1H, TRA C^5-*H*), 7.74 (s, 1H, TRA C^3-*H*), 7.57 (d, *J* = 8.5 Hz, 2H, Ph-2,6-*H*), 7.23 (m, 2H, 2-FPh-3,4-*H*), 7.08 (m, 1H, 2-FPh-6-*H*), 6.98 (t, *J* = 9.1 Hz, 1H, 2-FPh-5-*H*), 6.69 (d, *J* = 8.5 Hz, 2H, Ph-3,5-*H*), 4.27 (t, *J* = 6.2 Hz, 2H, NCH_2CH_2), 4.20 (s, 2H, 2-FPh-CH_2), 3.46 (t, *J* = 6.2 Hz, 2H, NCH_2CH_2) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ: 160.0, 152.1, 150.9, 143.7, 131.1, 129.9, 129.9, 129.6, 124.6, 115.6, 115.4, 114.2, 50.8, 48.9, 48.1 ppm; HRMS (TOF) found, m/z 376.1242 $[M + H]^+$, calcd for $C_{17}H_{18}FN_5O_2S$: 376.1238.

2.1.22. Synthesis of N-(2-(1h-1, 2,4-triazol-1-yl) ethyl)-4-2-chlorobenzyl) benzenesulfonamide (7c)

Compound **7c** was obtained as light brown syrup. Yield: 91%; IR (KBr) *v*: 3453, 3366 (N−H), 3128, 3034 (aromatic C−H), 2914, 2859 (aliphatic C−H), 1591, 1504 (aromatic frame), 1326, 1153, 881, 555 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 8.28 (s, 1H, TRA C^5-*H*), 7.84 (s, 1H, TRA C^3-*H*), 7.49 (d, *J* = 8.7 Hz, 2H, Ph-2,6-*H*), 7.40 (dd, *J* = 5.8, 3.5 Hz, 1H, 2-ClPh-3-*H*), 7.33–7.24 (m, 3H, 2-ClPh-4,5,6-*H*), 6.66 (d, *J* = 8.7 Hz, 2H, Ph-3,5-*H*), 4.24 (s, 2H, 2-ClPh-CH_2), 4.19 (t, *J* = 6.5 Hz, 2H, NCH_2CH_2), 3.47 (t, *J* = 6.5 Hz, 2H, NCH_2CH_2) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ: 153.8, 151.9 144.7, 134.6, 132.7, 130.3, 129.8, 129.7, 129.6, 127.68, 123.0, 113.4, 50.5, 49.1, 48.3 ppm; HRMS (TOF) found, m/z 414.0766 $[M + Na]^+$, calcd for $C_{17}H_{18}ClN_5NaO_2S$: 414.0762.

2.1.23. Synthesis of N-(2-(1h-1,2,4-triazol-1-yl) ethyl)-4-amino-N-(4-fluorobenzyl) benzenesulfonamide (7d)

Compound **7d** was obtained as white solid. Yield: 92%; mp: 144-146ºC; R (KBr) *v*: 3450, 3316 (N−H), 3056 (aromatic C−H), 2966, 2906, 2859 (aliphatic C−H), 1594, 1506 (aromatic frame), 1322, 1150, 733, 551 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 8.23 (s, 1H, TRA C^5-*H*), 7.85 (s, 1H, TRA C^3-*H*), 7.46 (d, *J* = 8.7 Hz, 2H, Ph-2,6-*H*), 7.24 (m, 2H, 4-FPh-2,6-*H*), 7.12 (m, 2H, 4-FPh-3,5-*H*), 6.64 (d, *J* = 8.7 Hz, 2H, Ph-3,5-*H*), 6.09 (s, 2H, NH_2), 4.14 (t, *J* = 6.5 Hz, 2H, NCH_2CH_2), 4.12 (s, 2H, 4-FPh-CH_2), 3.38 (t, *J* = 6.5 Hz, 2H, NCH_2CH_2) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ: 161.2, 153.7, 151.8, 144.6, 133.4, 130.6, 130.5, 129.6, 115.6, 113.3, 51.8, 49.0, 48.2 ppm; HRMS (TOF) found, m/z 376.1254 $[M + H]^+$, calcd for $C_{17}H_{18}FN_5O_2S$: 376.1238.

2.1.24. Synthesis of N-(2-(1h-1,2,4-triazol-1-yl) ethyl)-4-amino-N-(4-chlorobenzyl) benzenesulfonamide (7e)

Compound **7e** was obtained as white solid. Yield: 91%; mp: 148–152ºC; R (KBr) *v*: 3479, 3382 (N−H), 3132, 3101 (aromatic C−H), 2961, 2922, 2857 (aliphatic C−H), 1594, 1503 (aromatic frame), 1318, 1145, 875, 546 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.91 (s, 1H, TRA C^5-*H*), 7.78 (s, 1H, TRA C^3-*H*), 7.59 (d, *J* = 8.4 Hz, 2H, Ph-2,6-*H*), 7.24 (d, *J* = 8.1 Hz, 2H, 4-ClPh-3,5-*H*), 7.04 (d, *J* = 8.0 Hz, 2H, 4-ClPh-2,6-*H*), 6.71 (d, *J* = 8.4 Hz, 2H, Ph-3,5-*H*), 4.24 (t, *J* = 6.1 Hz, 2H, NCH_2CH_2), 4.01 (s, 2H, 4-ClPh-CH_2), 3.42 (t, *J* = 6.1 Hz, 2H, NCH_2CH_2) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ: 152.2, 151.0, 144.2, 134.3, 134.1, 129.8, 129.5, 129.0, 126.4, 114.2, 53.1, 49.1, 47.6 ppm; HRMS (TOF) found, m/z 414.0765 $[M + Na]^+$, calcd for $C_{17}H_{18}ClN_5NaO_2S$: 414.0762.

2.1.25. Synthesis of N-(2-(1h-1,2,4-triazol-1-yl) ethyl)-4-amino-N-(2,4-dichlorobenzyl) benzenesulfonamide (7f)

Compound **7f** was obtained as yellow syrup. Yield: 94%; R (KBr) *v*: 3430 (N−H), 3136 (aromatic C−H), 2958, 2925, 2858 (aliphatic C−H), 1599, 1515 (aromatic frame), 1099, 805, 469 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 8.29 (s, 1H, TRA C^5-*H*), 7.82 (s, 1H, TRA C^3-*H*), 7.53 (d, *J* = 1.8 Hz, 1H, 2,4-Cl_2Ph-3-*H*), 7.49 (d, *J* = 8.6 Hz, 2H, Ph-2,6-*H*), 7.37–7.28 (m, 2H, 2,4-Cl_2Ph-5,6-*H*), 6.67 (d, *J* = 8.5 Hz, 2H, Ph-3,5-*H*), 6.13 (s, 2H, NH_2), 4.23 (t, *J* = 6.2 Hz, 2H, NCH_2CH_2), 4.21 (s, 2H, 2,4-Cl_2Ph-CH_2), 3.47 (t, *J* = 6.2 Hz, 2H, NCH_2CH_2) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ: 153.9, 151.8, 144.7, 134.0, 133.6, 133.2, 131.7, 129.8, 129.2, 127.8, 122.7, 113.4, 50.3, 48.8, 48.4 ppm; HRMS (TOF) found, m/z 448.0377 $[M + Na]^+$, calcd for $C_{17}H_{17}Cl_2N_5NaO_2S$: 448.0372.

2.1.26. Synthesis of N-(2-(1h-1,2,4-triazol-1-yl) ethyl)-4-amino-N-(3,4-dichlorobenzyl) benzenesulfonamide (7g)

Compound **7g** was obtained as white solid. Yield: 89%; mp: 157-159ºC; IR (KBr) *v*: 3458, 3330 (N−H), 3145 (aromatic C−H), 2964, 2920, 2863 (aliphatic C−H), 1592, 1502 (aromatic frame), 1323, 1151, 874, 548 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.95 (s, 1H, TRA C^5-*H*), 7.80 (s, 1H, TRA C^3-*H*), 7.58 (d, *J* = 8.5 Hz, 2H, Ph-2,6-*H*), 7.32 (d, *J* = 8.2 Hz, 1H, 3,4-Cl_2Ph-5-*H*), 7.11 (s, 1H, 3,4-Cl_2Ph-2-*H*), 6.93 (d, *J* = 8.1 Hz, 1H, 3,4-Cl_2Ph-6-*H*), 6.71 (d, *J* = 8.5 Hz, 2H, Ph-3,5-*H*), 4.29 (t, *J* = 6.0 Hz, 2H, NCH_2CH_2), 3.97 (s, 2H, 3,4-Cl_2Ph-CH_2), 3.45 (t, *J* = 6.0 Hz, 2H, NCH_2CH_2) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ: 152.2, 151.0, 144.2, 137.8, 134.3, 134.1, 129.8, 129.5, 129.0, 128.5, 126.4, 114.2, 53.1, 49.1, 47.6 ppm; HRMS (TOF) found, m/z 426.0557 $[M + H]^+$, calcd for $C_{17}H_{17}Cl_2N_5O_2S$: 426.0553.

2.1.27. Synthesis of tert-butyl (4-acetamidophenyl) Sulfonyl) carbamate (8)

To solution of the compound **3** (0.214 g, 1.1 mmol) in dichloromethane (20 mL) at 0°C was added triethylamine (0.15 mL, 1.1 mmol), followed by 4-(dimethylamino)-pyridin (0.010 g, 0.08 mmol). The di-tertbutyl dicarbonate (0.327 g, 1.5 mmol) was added to the reaction mixture and stirred at 0 °C for 0.5 h, and then transferred the system to room temperature stirring for another 13 h. After the reaction came to the end (monitored by TLC, eluent, chloroform/methanol = 15/1, V/V), concentrated and chromatography (eluent, dichloromethane/methanol = 4/1, V/V) afforded the intermediates **8** as white solid. Yield: 71%; mp: 137–139ºC; IR (KBr) *v*: 3358 (N−H), 3117 (aromatic C−H), 2980, 2934, 2854 (aliphatic C−H), 1676 (C=O), 1592, 1530 (aromatic frame), 1247, 1151, 739, 613 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 11.47 (s, 1H, SO_2NH), 10.38 (s, 1H, $NHCOCH_3$), 7.80 (apparent s, 4H, Ph-*H*), 2.09 (s, 3H, $COCH_3$), 1.29 (s, 9H, Boc-*H*) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ: 169.6, 150.3, 144.1, 133.6, 129.1, 118.8, 82.5, 28.0, 24.6 ppm; HRMS (TOF) found, m/z 315.1006 $[M + H]^+$, calcd for $C_{13}H_{19}N_2O_5S$: 315.1009.

2.1.28. Synthesis of tert-butyl (4-acetamidophenyl) Sulfonyl) (tert-butyl) carbamate (9)

Compound **9** was obtained as white solid from procedure for the preparation of compound **8**. Yield: 28%; mp: 130–

132 °C; IR (KBr) *v*: 3302 (N−H), 3120, 3059 (aromatic C−H), 2982, 2934 (aliphatic C−H), 1675 (C=O), 1596, 1542 (aromatic frame), 1345, 1143, 623 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 10.36 (s, 1H, N*H*COCH$_3$), 7.89 (d, *J* = 8.8 Hz, 2H, Ph-2,6-*H*), 7.79 (d, *J* = 8.8 Hz, 2H, Ph-3,5-*H*), 2.09 (s, 3H, COC*H*$_3$), 1.45 (s, 9H, N(C*H*$_3$)$_3$), 1.40 (s, 9H, Boc-*H*) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ: 168.9, 155.3, 143.9, 133.2, 128.9, 118.0, 80.4, 49.8, 28.9, 24.3 ppm; HRMS (TOF) found, m/z 371.1638 $[M + H]^+$, calcd for $C_{17}H_{27}N_2O_5S$: 371.1635.

2.1.29. Synthesis of tert-butyl (4-acetamidophenyl) Sulfonyl) (2-bromoethyl) carbamate (10)

The compound **8** (3.314 g, 10.5 mmol) and potassium carbonate (2.170 g, 15.7 mmol) in acetonitrile (100 mL) was stirred at 60°C for 2 h, followed by the addition of 1,2-dibromoethane (4.0 mL, 19.1 mmol), and then the reaction system was stirred at 70 °C for about 10 h. After the reaction came to the end (monitored by TLC, eluent, dichloromethane/methanol = 15: 1, V/V), the solvent was evaporated and the residue was extracted with ethyl acetate (3 × 50 mL). The organic extracts were collected and then dried over anhydrous sodium sulfate and purified by silica gel column chromatography (eluent, petroleum ether/ethyl acetate = 4/1, V/V) to afford white solid of intermediate **10**. Yield: 64%; mp: 150–152 °C; IR (KBr) *v*: 3314 (N−H), 3106, 3048 (aromatic C−H), 2982, 2934 (aliphatic C−H), 1674 (C=O), 1596, 1534 (aromatic frame), 1352, 1159, 731,565 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.86 (d, *J* = 8.7 Hz, 2H, Ph-2,6-*H*), 7.68 (d, *J* = 8.3 Hz, 2H, Ph-3,5-*H*), 4.16 (t, *J* = 7.4 Hz, 2H, NCH$_2$C*H*$_2$), 3.59 (t, *J* = 7.4 Hz, 2H, NC*H*$_2$CH$_2$), 2.12 (s, 3H, COC*H*$_3$), 1.38 (s, 9H, Boc-*H*) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ: 168.7, 150.6, 142.8, 134.2, 129.4, 118.8, 85.1, 47.7, 28.9, 27.9, 24.7 ppm; HRMS (TOF) found, m/z 421.0429 $[M + H]^+$, calcd for $C_{15}H_{22}BrN_2O_5S$: 421.0427.

2.1.30. Synthesis of N-(4-(N-(2-(1h-1,2,4-triazol-1-yl) ethyl) Sulfamoyl) phenyl) acetamide (11)

Compound **11** was synthesized according to the experimental procedure reported for compound **6a**, starting from compound **10** (0.420g, 1.0 mmol) and 1*H*-1, 2,4-triazole (0.069 g, 1.0 mmol). The pure product **11** was obtained as white solid. Yield: 82%; mp: 155–157ºC; IR (KBr) *v*: 3303 (N−H), 3032 (aromatic C−H), 2995, 2924, 2875, 2812 (aliphatic C−H), 1687 (C=O), 1594, 1547, 1512 (aromatic frame), 1323, 1161, 751, 579 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 10.30 (s, 1H, N*H*COCH$_3$), 8.43 (s, 1H, TRA C^5-*H*), 7.94 (s, 1H, TRA C^3-*H*), 7.75 (d, *J* = 8.5 Hz, 2H, Ph-2,6-*H*), 7.71 (s, 1H, SO$_2$N*H*), 7.69 (d, *J* = 8.5 Hz, 1H, Ph-3,5-*H*), 4.22 (t, *J* = 6.1 Hz, 2H, NCH$_2$C*H*$_2$), 3.13 (t, *J* = 6.1 Hz, 2H, NC*H*$_2$CH$_2$), 2.09 (s, 3H, COC*H*$_3$) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ: 169.4, 150.0 144.9, 143.4, 134.2, 128.1, 119.2, 49.0, 42.4, 24.6 ppm; HRMS (TOF) found, m/z 309.3447 $[M + H]^+$, calcd for $C_{12}H_{12}N_5O_3S$: 309.3442.

2.1.31. Synthesis of tert-butyl (2-(1h-1,2,4-triazol-1-yl) ethyl)((4-acetamidophenyl) sulfonyl) carbamate (12)

The by-product **12** was obtained as white solid from procedure for the preparation of compound **11**. Yield: 18%; mp: 147–149ºC; IR (KBr) *v*: 3432 (N−H), 3121, 3034 (aromatic C−H), 299, 2935, 2803 (aliphatic C−H), 1728 (C=O), 1594, 1541, 1510 (aromatic frame), 1357, 1162, 633 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 10.40 (s, 1H, N*H*COCH$_3$), 8.46 (s, 1H, TRA C^5-*H*), 7.98 (s, 1H, TRA C^3-*H*), 7.82 (d, *J* = 9.0 Hz, 2H, Ph-2,6-*H*), 7.79 (d, *J* = 8.8 Hz, 2H, Ph-3,5-*H*), 4.49 (t, *J* = 5.9 Hz, 2H, NCH$_2$C*H*$_2$), 4.16 (t, *J* = 5.9 Hz, 2H, NC*H*$_2$CH$_2$), 2.10 (s, 3H), 1.21 (s, 9H, Boc-*H*) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ: 169.6, 152.0, 150.5, 144.8, 144.5, 133.0, 129.5, 118.7, 84.5, 48.8, 46.6, 27.8, 24.6 ppm; HRMS (TOF) found, m/z 409.1425 $[M + H]^+$, calcd for $C_{17}H_{23}N_5O_5S$: 409.1420.

2.1.32. Synthesis of N-(2-(1h-1,2,4-triazol-1-yl) ethyl)-4-aminobenzenesulfonamide (13)

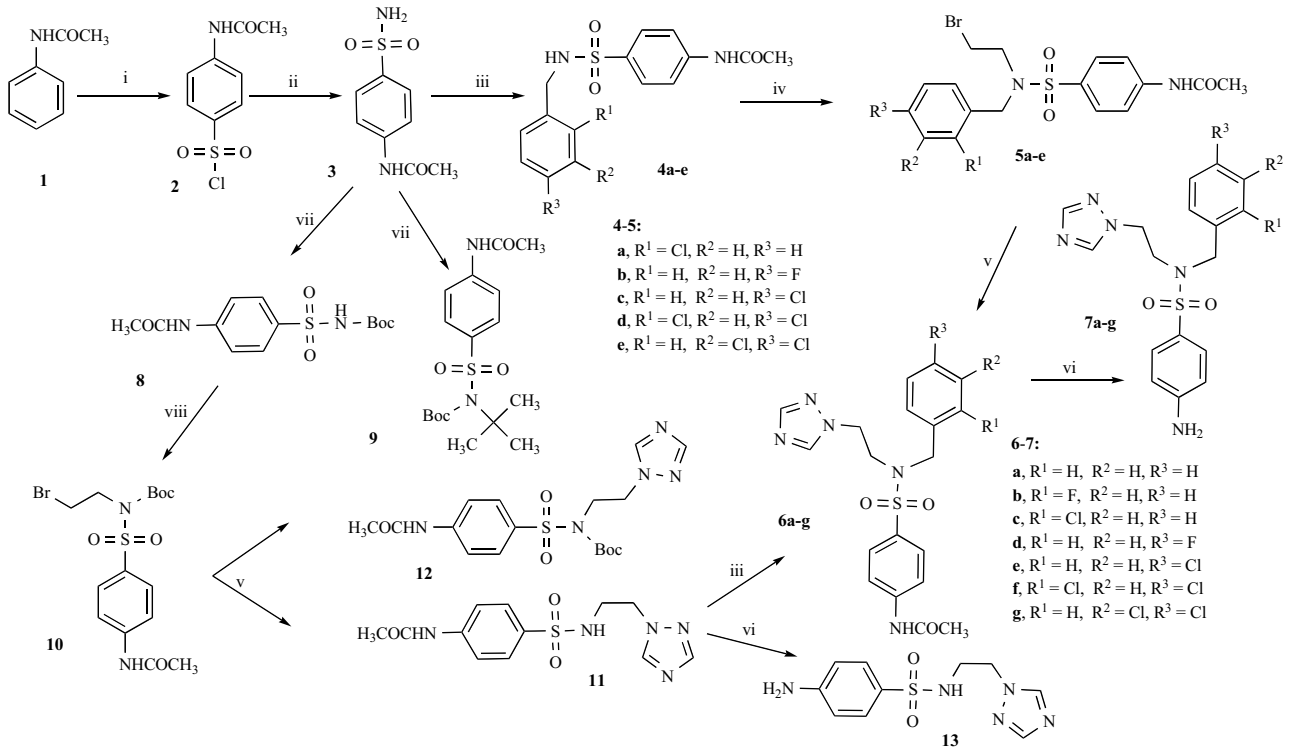
The white solid of target product **13** was obtained according to the experimental procedure reported for compound **7a**, starting from compound **11** (0.052g, 0.2 mmol). Yield: 98%; mp: 161–163ºC; IR (KBr) *v*: 3446, 3355 (N−H), 3114 (aromatic C−H), 2955, 2923, 2853 (aliphatic C−H), 1596, 1503 (aromatic frame), 1299, 1145, 688 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 8.41 (s, 1H, TRA C^5-*H*), 7.94 (s, 1H, TRA C^3-*H*), 7.39 (d, *J* = 8.5 Hz, 2H, Ph-2,6-*H*), 7.33 (s, 1H, SO$_2$N*H*), 6.61 (d, *J* = 8.6 Hz, 2H, Ph-3,5-*H*), 5.94 (s, 2H, N*H*$_2$), 4.20 (t, *J* = 6.2 Hz, 2H, NCH$_2$C*H*$_2$), 3.07 (t, *J* = 6.1 Hz, 2H, NC*H*$_2$CH$_2$) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ: 153.1, 151.9, 144.8, 128.9, 125.5, 113.2, 48.9, 42.4 ppm; HRMS (TOF) found, m/z 290.0689 $[M + H]^+$, calcd for $C_{10}H_{13}FN_5O_2S$: 290.2967.

3. RESULTS AND DISCUSSION

3.1. Chemistry

The synthetic routes of sulfonamide-derived 1,2,4-triazoles were outlined in Scheme **1**. During the procedure, the *N*-protected sulfonyl chloride **2** was prepared with superior yield of 91% by the reaction of acetanilide with chlorosulfonic acid, and it was further treated by ammonium hydroxide to provide *p*-acetylaminobenzene sulfonamide **3** in 82% yield. Subsequent *N*-alkylation of compound **3** was performed with a series of halobenzyl halides to afford the secondary amine derivatives **4a**–**e** with yields of 3%–17%. Intermediates **4a**–**e** further reacted with 1,2-dibromoethane to obtain the tertiary amine sulfonamides **5a**–**e** in good yields of 70%–89%. Sulfonamide triazole intermediates **6a**–**e** were efficiently obtained by the N-alkylation of compounds **5a**–**e** with 1,2,4-triazole in 56%–78% yields.

To improve the yield of the target compounds, the second synthetic route was designed by using *t*-butyloxy carbonyl (Boc) group to protect one hydrogen atom of sulfonamide **3**. Thus the Boc-protected sulfonamide **8** and the by-product **9** were achieved from *p*-acetylaminobenzene sulfonamide **3** in yields of 71% and 28%, respectively, and then compound **8** reacted with 1,2-dibromoethane to afford *tert*-*N*-sulfonamide **10** in yield of 64%. Subsequently, compound **10** experienced nucleophilic substitution to conveniently afford the desired sulfonamide intermediate **11** in a high yield of 82% and Boc deprotected by-product **12** at a low yield of 18%. Further N-alkylation of secondary amine **11** with halobenzyl halides produced intermediates **6a**–**g** with yields ranging from 67% to 81%. Finally, intermediates **6a**–**g** and **11** were further transformed into the deprotected sulfonamide derivatives **7a**-



Reagents and conditions: (i) chlorosulfonic acid, 0ºC; (ii) ammonium hydroxide, 0ºC; (iii) halobenzyl halide, potassium carbonate, acetone, 50–70ºC; (iv) 1,2-dibromoethane, potassium carbonate, acetone, 50ºC; (v) 1,2,4-triazole, potassium carbonate, acetonitrile, 60–70ºC; (vi) 2 mol/L NaOH, ethanol, reflux; (vii) di-tertbutyl dicarbonate, 4-(dimethylamino)-pyridine, triethylamine, dichloromethane, 0ºC–r.t.; (viii) 1,2-dibromoethane, potassium carbonate, acetonitrile, 60–70ºC.

Scheme 1. Synthesis of sulfonamide-derived 1,2,4-triazoles **4**-**13**.

g and **13** in ethanol in order to explore their influence on the bioactivity.

3.2. Analysis of Spectra

For the IR, ^{1}H NMR and ^{13}C NMR spectra, all the absorption bands were observed at the expected regions. The presence of acetylamino moiety of sulfonamide compounds **4**–**6** and **8**–**12** in IR spectra was confirmed by the broad absorption in 3394–3295 cm^{-1} for NH group and 1728–1670 cm^{-1} for characteristic C=O bands, whereas in ^{1}H NMR spectra, the CH_3 protons linked to the amide moiety were observed singlets at 2.07–2.12 ppm, and in ^{13}C NMR spectra, the carbonyl carbon was found at δ 169.7–168.7 ppm.

3.3. Biological Activity

The *in vitro* antibacterial and antifungal screening of the sulfonamide compounds was explored normally [24]. The antibacterial and antifungal data were displayed in Table **1** and Table **2**.

3.3.1. Antibacterial Activity

As shown in Table **1**, the sulfonamides **5a**–**e** exhibited some activity against the tested bacterial strains with MIC values ranging from 0.27 to 1.19 μmol/mL.

Some important effects of substituents on the benzene ring on biological activity were observed. Non-substituted derivative **6a** possessed relatively weaker antibacterial activity in comparison with halogen substituted compounds **6b**–**g**, but it exerted stronger anti-*E. coli* (DH52) activity (MIC = 0.04 μmol/mL) than Chloromycin. Among halobenzyl sulfonamide derivatives, sulfonamide **6d** bearing 4-fluorobenzyl group showed better activities than compounds **6b** and **6e** with 2-fluorobenzyl and 4-chlorobenzyl groups, however, it displayed relatively lower potencies in inhibiting the growth of the tested strains than other substituted compounds. The 2-chlorobenzyl compound **6c** displayed equivalent inhibitory potency to compounds **6f** and **6g** with dichlorobenzyl group against the tested strains. Especially, replacement of 2-chlorobenzyl moiety with 2,4-dichlorobenzyl group, which generated compound **6f**, resulted in good inhibitory potency against Gram-negative *S. dysenteriae* with MIC value of 0.27 μmol/mL.

Most of deprotected compounds **7a**–**g** exerted relatively superior activities in inhibiting the growth of the tested bacteria to the corresponding protected ones to some extent, and compound **13** without halobenzyl group showed lower biological activities than halobenzyl contained ones.

Noticeably, the 1,2,4-triazole-based sulfonamide **7c** bearing 2-chlorobenzyl moiety showed the strongest inhibition towards Gram-negative *E. coli* (DH52 and JM109) strains (MIC= 0.02 μmol/mL), which was 5-fold more potent than Chloromycin. Additionally, it displayed equivalent inhibitory potency against MRSA to Chloromycin (MIC = 0.16 μmol/mL). This indicated that compound **7c** could be further studied as potential novel antibacterial agents. The compounds **7b** and **7c** bearing chlorobenzyl moieties exerted

Table 1. Antibacterial data as MIC (μmol/mL) for compounds 5–13[a,b,c].

Compds	Gram-Positive Bacteria				Gram-Negative Bacteria			
	MRSA	*S. aureus*	*B. subtilis*	*M. luteus*	*B. typhi*	*E. coli* (DH52)	*E. coli* (JM109)	*S. dysenteriae*
5a	0.57	0.29	0.57	0.29	0.57	1.15	1.15	1.15
5b	1.19	1.19	1.19	1.19	0.60	0.60	0.30	1.19
5c	1.15	0.57	0.57	0.57	1.15	0.57	1.15	0.57
5d	1.07	1.07	0.53	1.07	0.53	0.27	1.07	1.07
5e	0.27	1.07	1.07	0.53	1.07	0.27	0.53	1.07
6a	0.64	0.64	1.28	1.28	1.28	0.04	0.64	1.28
6b	0.61	1.23	1.23	1.23	1.23	1.23	0.61	1.23
6c	0.29	0.59	0.29	0.59	1.18	0.29	0.59	1.18
6d	0.61	0.61	0.31	1.23	0.61	0.61	1.23	0.61
6e	1.18	0.59	0.59	0.59	0.59	1.18	1.18	1.18
6f	0.27	0.27	0.27	1.10	1.10	0.27	0.55	0.27
6g	1.10	1.10	0.27	0.55	1.10	0.27	1.10	1.10
7a	1.43	1.43	1.43	1.43	1.43	1.43	1.43	1.43
7b	1.36	1.36	1.36	1.36	1.36	1.36	1.36	1.36
7c	0.16	0.65	0.04	0.65	0.08	0.02	0.02	0.65
7d	1.36	1.36	0.68	1.36	0.68	0.68	1.36	1.36
7e	0.65	0.33	0.33	0.65	0.33	0.02	0.08	0.65
7f	1.20	0.60	0.04	0.30	0.60	0.30	1.20	0.60
7g	1.20	1.20	0.60	1.20	0.60	1.20	0.60	1.20
8	0.18	0.09	0.18	0.18	0.18	0.09	0.18	0.18
9	0.69	0.64	1.38	0.69	1.38	1.38	1.38	1.38
10	0.61	0.61	1.22	0.61	1.22	0.30	1.22	1.22
11	1.66	0.83	1.66	1.66	1.66	1.66	0.83	1.66
12	1.25	1.25	1.25	1.25	1.25	0.31	0.63	1.25
13	0.48	1.92	1.92	0.48	0.96	1.92	1.92	1.92
Chloromycin	0.05	0.05	0.10	0.02	0.10	0.10	0.10	0.05
Norfloxacin	0.03	0.01	0.01	0.01	0.01	0.003	0.003	0.05

[a]Minimal inhibitory concentrations were determined by micro broth dilution method for microdilution plates.
[b]*S. aureus*, Staphylococcus aureus (ATCC25923); MRSA, Methicillin-Resistant Staphylococcus aureus (N315); *B. subtilis*, Bacillus subtilis; *M. luteus*, Micrococcus luteus (ATCC4698); *B. proteus*, Bacillus proteus (ATCC13315); *E. coli*, Escherichia coli (JM109); *P. aeruginosa*, Pseudomonas aeruginosa; *B. typhi*, Bacillus typhi.
[c]ClogP values were calculated by ChemDraw Ultra 10.0.

Table 2. Antifungal data as MIC (μmol/mL) for compounds 5–13[d].

Compds	*C. albicans*	*C. mycoderma*	*C. utilis*	*S. cerevisiae*	*A. flavus*
5a	1.19	0.30	1.19	1.19	1.19
5b	0.57	1.15	0.57	1.15	0.29

Table 2. contd…

Compds	*C. albicans*	*C. mycoderma*	*C. utilis*	*S. cerevisiae*	*A. flavus*
5c	0.29	0.14	1.15	0.29	0.29
5d	0.53	0.53	1.07	1.07	0.53
5e	0.53	0.27	1.07	0.13	0.53
6a	1.23	1.23	0.61	1.23	1.23
6b	0.59	0.29	1.18	1.18	0.59
6c	0.29	0.15	1.18	0.29	0.29
6d	1.10	0.55	0.55	0.55	1.10
6e	0.27	1.10	1.10	1.10	0.27
6f	1.28	0.64	1.28	1.28	1.28
6g	1.23	0.15	1.23	1.23	1.23
7a	1.36	0.68	0.17	1.36	0.68
7b	0.08	0.08	0.33	0.16	0.33
7c	0.08	0.02	0.33	0.65	0.33
7d	0.04	1.20	1.20	1.20	1.20
7e	0.60	1.20	1.20	0.30	1.20
7f	1.43	1.43	1.43	1.43	1.43
7g	0.34	1.36	0.68	1.36	1.36
8	0.18	0.05	0.09	0.18	0.18
9	1.38	0.35	0.04	0.69	1.38
10	1.22	0.61	0.30	1.22	1.22
11	1.66	0.05	0.83	1.66	1.66
12	1.25	0.63	0.63	1.25	1.25
13	1.92	1.92	0.96	0.96	1.92
Fluconazole	0.003	0.01	0.03	0.05	0.84

[d]*C. albicans*, Candida albicans (ATCC76615); *C. mycoderma*, Candida mycoderma; *C. utilis*, Candida utilis; *S. cerevisia*, Saccharomyces cerevisia; *A. flavus*, Aspergillus flavus.

relatively better activity than the dichlorobenzyl group substituted ones **7f** and **7g**, which might probably be attributed to change of the electronic distribution and physicochemical properties, thereby affecting the absorption, distribution and metabolism of the bioactive molecules. Moreover, sulfonamide **8** with Boc moiety exhibited high inhibitory activities against *S. aureus* and *E. coli* DH52 strains with MIC values of 0.09 μmol/mL. The deprotected sulfonamide triazole **11** displayed higher activity than the Boc-protected compound **12** to some extent. These results suggested that the Boc group possessed remarkable effects on biological activities. The good hydrophilicity of Boc moiety in these compounds might make it easy for them be delivered to the binding sites.

3.3.2. Antifungal Activity

As depicted in Table **2**, the *in vitro* antifungal data indicated that some target sulfonamide-derived 1,2,4-triazoles displayed moderate inhibitory potencies against the tested fungal strains. Sulfonamide intermediates **5a**–**e** showed moderate to good antifungal activities with MIC values ranging from 0.27 to 1.19 μmol/mL, and notably compound **5e** with a 3,4-dichlorobenzyl group exhibited significant inhibitory activity against *S. cerevisiae* with MIC value of 0.13 μmol/mL, which was equipotent to Fluconazole.

Among the halobenzyl sulfonamide 1,2,4-triazoles **6a**–**g** and **7a**-**g**, compounds **6a** and **7a** without halogen atom showed low activities in inhibiting the growth of all the tested fungal strains. Moreover, 2-fluorobenzyl and 2-chlorobenzyl substituted compounds **6b** and **6c** gave low MIC value of 0.15 μmol/mL against *C. mycoderma*, which was better than compound **6d** with 4-fluorobenzyl group. Intriguingly, 2-chlorobenzyl derivative **7c** without acetyl group exerted better anti-*A. flavus* activity (MIC = 0.33 μmol/mL) than Fluconazole (MIC = 0.84 μmol/mL), and it also exhibited equivalent activity against *C. mycoderma* in comparison with Fluconazole (MIC = 0.02 μmol/mL). Compound **7d** with 4-fluorobenzyl group showed better inhibitory against *C. utilis* (MIC = 0.17 μmol/mL) than 2-fluorobenzyl derivative **7b**, whereas the latter exhibited better activity against *C. albicans* than compound **7d**. Sulfona-

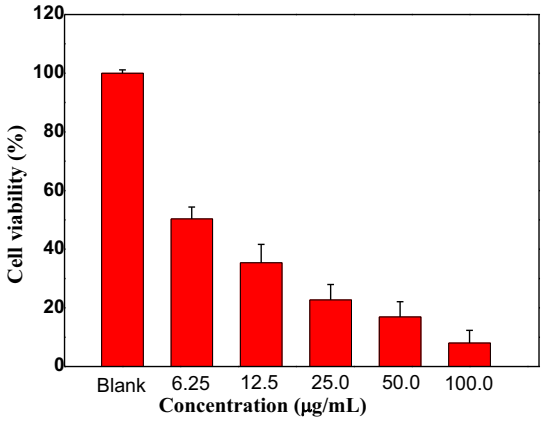


Fig. (2). Cytotoxic assay of target compound **7c** on human breast cancer cell line (MCF-7) by CCK-8 Kit. Each data bar represents an average of three parallels, and error bars indicate one standard deviation from the mean (Blank: PBS). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

mide derivatives **7c** and **7e–g** with chlorine atom had relatively better antifungal activity than fluorinated ones **7b** and **7d**, which indicated that the replacement of fluoro substituent with chloro moiety was beneficial for the antifungal activity.

Compound **8** with a Boc moiety showed higher inhibitory activity against Fluconazole-insensitive *A. flavus* with the MIC value of 0.18 μmol/mL than Fluconazole (MIC = 0.84 μmol/mL). The *t*-butyl-derived by-product **9** exhibited excellent inhibitory efficiency against *C. utilis* strains with MIC value of 0.04 μmol/mL, which was superior to Fluconazole (MIC = 0.03 μmol/mL). Sulfonamide 1,2,4-triazole **12** showed higher antifungal activity in comparison with the corresponding Boc-deprotected one **11**, which might be attributed to the improved water solubility.

As mentioned above, it was demonstrated that the antimicrobial efficacies might be closely related to acetyl fragment, Boc moiety and different halobenzyl groups to some extent.

4. CELL TOXICITY

The highly active compound **7c** was further investigated for its cytotoxic properties on human breast cancer cell lines (MCF-7) by using the Cell-Counting Kit-8 (CCK-8) [25]. The phosphate buffered saline (PBS) was selected as a positive control (blank). Compound **7c** was dissolved in a mixture of ethanol and water to prepare the stock solutions, which then was diluted by PBS to obtain the required concentrations of 6.25, 12.5, 25.0, 50.0 and 100.0 μg/mL, respectively. The CKK-8 assay showed that compound **7c** had high cytotoxicity against MCF-7 with an IC_{50} value of 6.33 μg/mL Fig. (**2**). With the increase of the concentration of the compound **7c**, the cell viability decreased.

5. EVALUATION OF ROS GENERATION IN MCF-7 CELLS

Although the relationship between antimicrobial mechanism and cell toxicity had not been fully elucidated [26], this work studied the ROS level using DCFH-DA as a fluorescence probe and imaged by fluorescence microscope [27, 28]. To some extent, the amount of ROS produced in MCF-7 cells was positively correlated with anticancer activity. However, excessive ROS might cause cellular injury and thus lead to cell death and DNA damage. As shown in Fig. (**3**), the generated amount of ROS increased with the increasing concentration of compound **7c**, thereby the anticancer activity also increased. Especially, compound **7c** showed lower ROS generation than hydrogen peroxide (H_2O_2) at a concentration of 100 μg/mL (safe dose to normal human cells). Therefore, the newly synthesized compound **7c** exhibited better safety than the reference by downregulating ROS generation.

6. INTERACTIONS WITH CALF THYMUS DNA

Calf thymus deoxyribonucleic acid (DNA) was employed to study the interaction behavior of compound **7c** with it to explore the possible antimicrobial mechanism [29, 30]. In the experiments, the UV-vis spectra gave a proportional increase and slight red shift with the increasing concentration of compound **7c** and a fixed concentration of DNA Fig. (**4**). Besides, the sum value of free DNA and free compound **7c** was a little greater than the absorption value of **7c**–DNA complex (the inset of Fig. **4**), which demonstrated that a weak hypochromic effect is present between compound **7c** and DNA. The spectral changes might agree with the intercalation of compound **7c** into the helix and the overlap of π-π* states of DNA bases [31, 32]. The binding constant (K) was

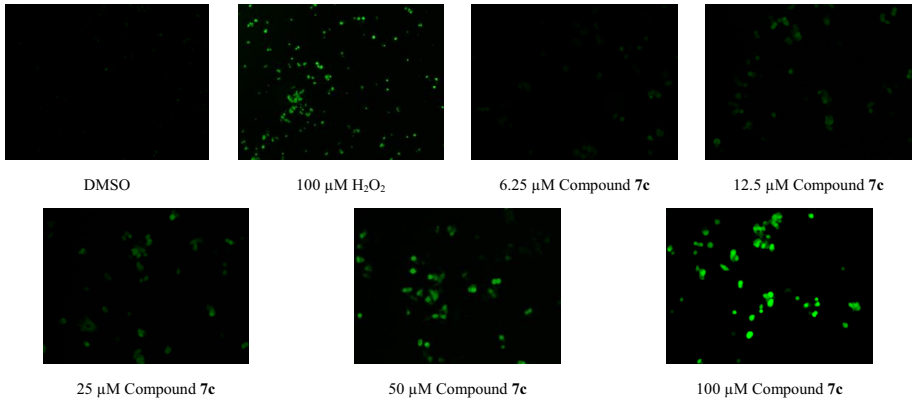


Fig. (3). Compound **7c**-induced ROS formation in MCF-7 cells and H_2O_2 as positive control. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

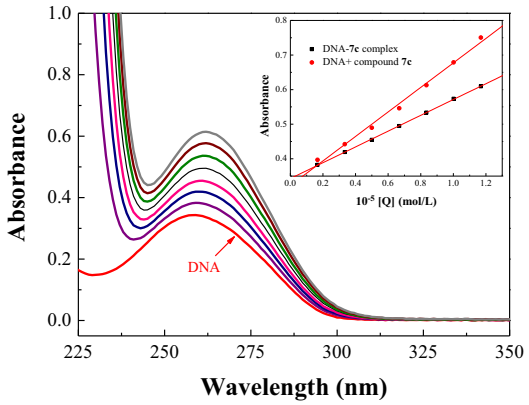


Fig. (4). UV absorption spectra of DNA with different concentrations of compound **7c** (pH = 7.4, T = 293 K). Inset: comparison of absorption at 260 nm between the **7c**–DNA complex and the sum values of free DNA and free compound **7c**. *c*(DNA) = 4.85 × 10^{-5} mol/L, and *c*(compound **7c**) = 0–1.17 × 10^{-5} mol/L for curves *a–g* respectively at increment 0.167 × 10^{-5}. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

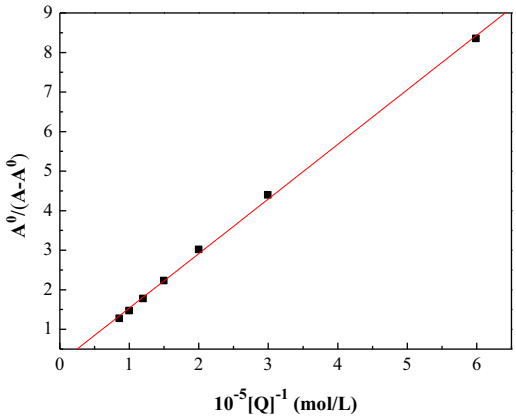


Fig. (5). The plot of $A^0/(A-A^0)$ versus 1/[compound **7c**]. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

calculated using equation 1. The plot of $A^0/(A-A^0)$ *versus* 1/[compound **7c**] was obtained by using the absorption titration data and linear fitting Fig. (**5**), $K = 1.14 \times 10^4$ L/mol, R = 0.999, SD = 0.08 (R is the correlation coefficient. SD is standard deviation).

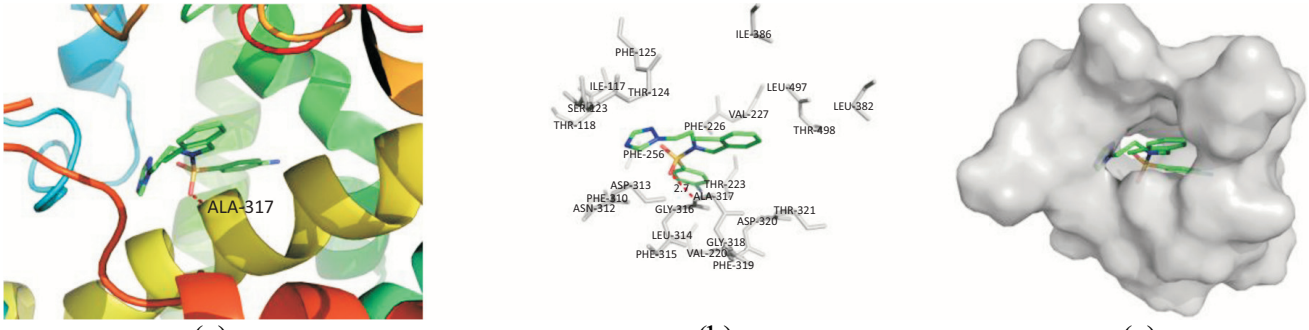
7. MOLECULAR MODELING STUDIES

Docking study could offer more insights into understanding the interactions of sulfonamide-derived 1,2,4-triazoles and the structural features of the active site of protein. The crystal structure data of human microsomal heme (PDB code: 2HI4) was obtained from the Protein Data Bank (PDB), which was a representative target to investigate the antibacterial mechanism of 1,2,4-triazole derivatives. Target compound **7c** was selected to dock into the heme (the hemoglobin complex Fe^{2+} of heme protein) to form a coordination bond with the nitrogen atom in the 1,2,4-triazole ring, which made the hemoglobin lose its chance of binding to oxygen and inhibited the lanolin sterol 14α site demethylation reaction, thereby the growth of the microorganism was inhibited [33].

As shown in Fig. (**6**), it showed the detailed binding mode between the active sites of human microsomal heme and the most active derivative **7c** bearing a 2-chlorobenzyl group. The predominant intermolecular force of hydrogen bond was labeled by a dashed line to understand the interaction of the complex. The analyses of hydrogen bond interaction confirmed that amino acid residue Ala 317 played a relatively important role in binding potency. The backbone of Ala 317 was inclined to form a hydrogen bond with one of the oxygen atoms at -SO_2NR in compound **7c**, and the distance was 2.70 Å. The result demonstrated that compound **7c** could act with the heme protein through hydrogen bonds.

8. COMPUTATIONAL CHEMICAL STUDIES

In an attempt to understand the further possible mechanism of the excellent biological activity and low toxicity of active compound **7c** bearing 2-chlorobenzyl groups, computational chemical assays were done and shown in Fig. (**7**). Meanwhile, molecular electrostatic potential (MEP) and atomic polar tensor (APT) charges had been performed to explore the electrostatic binding characteristic through the surface and atomic level of molecule, respectively Fig. (**7b-c**). This MEP map was generated for a selection of compound at the neutral state *via* the *B3LYP/6-31C** theoretical computation [34, 35], and the MEP surface gave an indication of the charged surface area and hydrophilicity of compound (Fig. **7b**). The results revealed that compound **7c** possessed more negative charge regions (in red) on the oxygen and nitrogen atoms of -SO_2NR than nitrogen atoms of



(a) (b) (c)

Fig. (6). (**a**) Molecular modeling of compound **7c** docked into the binding site of human microsomal heme (PDB: 2HI4). The dashed line represent the hydrogen bonding interactions between compound **7c** and heme; (**b**) Three-dimensional conformation of compound **7c** docked in heme; (**c**) Stereoview of the conformation of compound **7c** intercalated to heme to form **7c**–heme complex. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

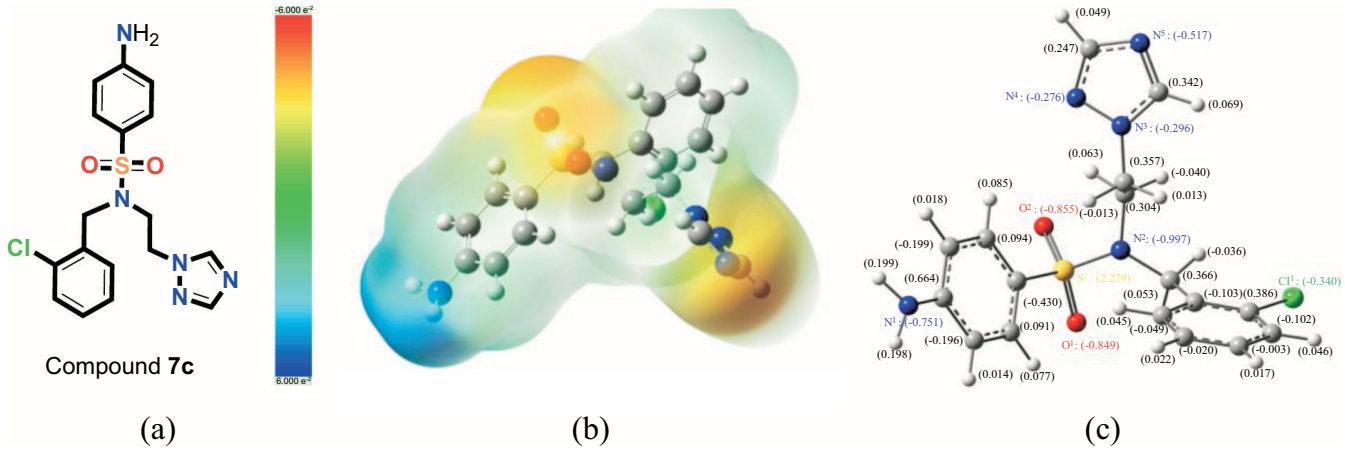


Fig. (7). (**a**) Structure of active compound **7c**; (**b**) Electrostatic potential of compound **7c**; (**c**) APT atomic charges of compound **7c**. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

1,2,4-triazole ring (in yellow). The oxygen and nitrogen atoms of SO_2NR were electronically available with their lone pairs, which were probably oriented toward the outer part of the molecule and therefore were accessible to interact with their surroundings.

On the other hand, the APT atomic charges of compound **7c** *via* the *Gaussian 09* theoretical calculations were showed in Fig. (**7c**). It was found that the APT charge of oxygen and nitrogen atoms in -SO_2NR moiety was lower than other atoms; especially the nitrogen atom had the lowest APT charge. This data demonstrated that the oxygen and nitrogen atoms in -SO_2NR moiety were most likely to form hydrogen bonds. Because of the π–π conjugative effect and steric hindrance, the nitrogen lone pairs in SO_2NR moiety were buried in the structure of compound **7c**, which was favorable for forming hydrogen bonds. It might indicate that the capability of forming hydrogen bond was related with the nitrogen atoms of -SO_2NR moiety. These results were in agreement with the binding mode obtained from above docking study.

CONCLUSION

In this work, a series of sulfonamide–derived 1,2,4-triazoles were successfully synthesized in two ways starting from commercial commercial acetanilide and chlorosulfonic acid. All the structures of the new compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and HRMS. The antimicrobial evaluation *in vitro* revealed that some target compounds showed effective antibacterial activity with suitable Clog*P* values, and even displayed equipotent or superior activities to the reference drugs. Structure-activity relationships demonstrated that 1,2,4-triazole and sulfonyl fragments exerted a significant influence on biological activity. Noticeably, 2-chlorobenzyl group substituted compound **7c** exhibited particularly strong antibacterial activity against most of the tested bacterial and fungal strains (MIC = 0.02–0.65 μmol/mL) and also displayed an objective cancer toxicity against MCF-7 cells by evaluating cell toxicity and ROS generation. The interaction of active compound **7c** with calf thymus DNA evidenced that it could properly bind with calf thymus DNA, which might be a factor to exert its powerful bioactivity. Molecular docking indicated that compound **7c** could act with the residue of Ala 317 in human microsomal heme protein through hydrogen bonds. The MEP surface and APT atomic charges studies indicated the capability of hydrogen bond formation with one of the oxygen atoms in sulfonyl moiety, which were in agreement with the binding mode obtained from the above docking study. All these results sufficiently indicated that it should be a promising starting point to optimize the structures of sulfonamide-derived 1,2,4-triazoles as potential clinical antimicrobial candidates.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are the basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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