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Original article

Synthesis of novel sulfanilamide-derived 1,2,3-triazoles and their evaluation for antibacterial and antifungal activities

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ABSTRACT

A series of novel sulfanilamide-derived 1,2,3-triazole compounds were synthesized in excellent yields *via* 1,3-dipolar cycloaddition and confirmed by MS, IR and NMR spectra as well as elemental analyses. All the compounds were screened *in vitro* for their antibacterial and antifungal activities. Preliminary results indicated that some target compounds exhibited promising antibacterial potency. Especially, 4-amino-*N*-((1-dodecyl-1H-1,2,3-triazol-4-yl)methyl) benzenesulfonamide, *N*-((1-(2,4-dichlorobenzyl)- 1*H*-1,2,3-triazol-4-yl)methyl)-4-aminobenzenesulfonamide and 4-amino-*N*-((1-(2,4-difluorobenzyl)- 1*H*-1,2,3-triazol-4-yl)methyl) benzenesulfonamide were found to be the most potent compounds against all the tested strains except for *Candida albicans* (ATCC76615) and *Candida mycoderma*.

1. Introduction

The alarming rates of emerging and reemerging microbial threats coupled with the growing emergence of antimicrobial resistance in hospitals are major concerns to the public health and scientific communities worldwide, especially in regard to multi-drug-resistant Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) [1]. Thus, these trends have emphasized the urgent need for new, more effective and safe antimicrobial agents. Among the attractive approaches to achieve this goal, the development of structurally new classes of antimicrobial agents with novel mechanism of action and the structural modification or optimization of the existing agents by improving both the binding affinity and spectrum of activity while retaining bioavailability and safety profiles, have provoked special interest in the realm of medical chemistry. However, the increasing prevalence of one such strategy that has been pursued in recent years employs a combination of two different active fragments in one molecule [2]. With this strategy, each drug moiety is designed to bind independently to two different biological targets and synchronously accumulate at both target sites. Such dual-action drugs, or hybrid drugs, offer the possibility to overcome the current resistance and reduce the appearance of new resistant strains [3].

Sulfonamides which were extensively employed as effective antimicrobial antifolic agents for the prevention and cure of bacterial infections in human biological systems as early as 70 years ago, have aroused considerable interest in biology and medicine for their diversified pharmacological activities including carbonic anhydrase inhibitors [4], antifungal [5], antiviral [6], antitumor [7], and anti-inflammatory ones [8] in recent years. Meanwhile, sulfonamides have attracted increasing attention in the supramolecular chemistry and supramolecular medicinal chemistry [9], since it combined the features required for various biological activities and the metal coordination through phenylamino and sulfonyl amino groups. In particular, Ag-sulfadiazine has been proved to be an effective topical antimicrobial agent, and to be of significance in burn therapy, better than the free ligand or $AgNO_3$. Furthermore, sulfonamides combined with trimethoprin were confirmed to considerably enhance their antibacterial efficacy by a well known synergistic effect. For instance, sulfamethoxazole in combination with trimethoprim is a very active pharmaceutical compound and has been extensively used in clinic as the first choice in the treatment of pneumonia and urinary tract bacterial infections, toxoplasmosis [10] and pneumocystosis in HIV infected patients [11]. Nevertheless, numerous researches have been still focusing on the structure modification of sulfanilamide through the phenylamino and sulfonyl amino groups to afford sulfanilamide-

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based bioactive molecules in order to broaden their antimicrobial spectrum of activity and improve their potency. Recently, a large number of literatures manifested that the sulfanilamide moiety **1** retaining the structural $-SO_2NH-$ feature, which was incorporated into nitrogen-containing aromatic heterocyclic groups with different biological activities, could exhibit various pharmacological activities or even enhance activities in comparison with the sulfanilamide precursor [12]. Up to now, several sulfanilamide derivatives (Fig. 1) bearing aromatic heterocyclic groups such as isoxazole, thiazole, pyridazine, pyrimidine and so on at the N1-position, have been successfully used in clinics owing to their excellent antimicrobial activities.

1,2,3-Triazole and its derivatives are an important class of nitrogen-containing aromatic heterocyclic compounds, and have attracted a great deal of interest due to their diverse biological activities such as antitubercular [13], anti-HIV [14], antifungal [15], antibacterial [16], and anticancer activities [17], along with the introduction of 'click chemistry' for their easy synthesis. 1,2,3-Triazole moiety is stable to metabolic degradation and capable of hydrogen bonding, which could be favorable in binding of biomolecular targets and increasing solubility [18]. Moreover, 1,2,3-triazoles as attractive linker units which could connect two pharmacophores to give an innovative bifunctional drugs, have become increasingly useful and important in constructing bioactive molecules and functional molecules [19]. Noticeably, the bioisosteric replacement between 1,2,3-triazole moiety and its bioisoster 1,2,4-triazole has received special attention in medical chemistry, which represented an efficient concept for the discovery and development of novel triazole drugs, significantly extending the chemical space of triazole scaffolds possessing potent activities or enhancing biological activities [20]. Additionally, many investigations showed that the incorporation of alkyl chains and/or variable aromatic substituents have an important effect on the antimicrobial activities [21], especially some halogen-substituted aromatic compounds such as 2,4-difluorobenzyl, 2,4-dichlorobenzyl, fluorobenzyl, chlorobenzyl and so on, were found to be biologically important and could improve antimicrobial activities.

Based on all above considerations and as an extension of our studies on the development of novel triazole antimicrobial agents [22], we disclosed the synthesis of novel sulfanilamide-derived 1,2,3-triazoles **6a**–**f** and **7a**–**i** with different lengths of alkyl chains or haloaryl compounds *via* a Cu(I) catalyzed 1,3-dipolar cycloaddition. The synthesized compounds have also been screened for their antibacterial and antifungal activities *in vitro*. Various functional groups were introduced into the target compounds in order to investigate their preliminary structure-activity relationships.

2. Results and discussion

2.1. Chemistry

The synthetic route of target compounds was outlined in Scheme 1. The target sulfanilamide-derived 1,2,3-triazoles **6a**–**f** and **7a**–**i** were synthesized by using commercially available acetaniline as starting material. The intermediate **3**, prepared according to the reference described [23], was upon *N*-alkylation with 3-bromoprop-1-yne to yield the *N*-acetyl-protected sulfanilamide **4**, and then the removal of the acetyl group in compound **4** by acidic hydrolysis with concentrated hydrochloric acid gave propargyl sulfonamide **5**. The 1,3-dipolar cycloaddition of propargyl sulfonamide **5** with alkyl or aryl azides using catalytic amount of copper sulfate and sodium ascorbate in *t*-BuOH/H_2O at 60 °C afforded sulfanilamide-derived 1,4-disubstituted 1,2,3-triazoles **6a**–**f** and **7a**–**i** in moderate to good yields ranging from 68.6% to 90.2%.

Generally, the 1,3-dipolar cycloaddition of terminal acetylenes with organic azides produces two isomers 1,4-disubstituted 1,2,3-triazoles and 1,5-disubstituted ones. Numerous researches showed that this type of cycloaddition by the copper(I) catalysis could regioselectively yield 1,4-disubstituted 1,2,3-triazoles, the related reaction mechanism has been systematically discussed in literatures [24]. This catalytic process is involved in the Cu(I) acetylide complex which coordinated the azide following by rearrangement of the complex into a six-membered metallocycle and further into the copper-metallated triazole and then the Cu-triazole complex eventually released the free 1,4-disubstituted 1,2,3-triazole. In our work all experiments showed that the Cu(I) ion could efficiently affect the regioselectivity of 1,3-dipolar cycloaddition to produce 1,4-disubstituted 1,2,3-triazole derivatives, while 1,5-disubstituted 1,2,3-triazole ones were not almost obtained.

Furthermore, the experimental results also indicated that reaction temperature, various substrates as well as the nature of solvent exerted great influences on the 1,3-dipolar cycloaddition. In general, lowering the reaction temperature would make the cycloaddition reaction more stable and safe, which benefited the formation of target products and diminished the complexity of the reaction. However, temperature below 60 °C would greatly decrease the reactivity and make the reaction sluggish, thus leading to poor yields. On the other side, the effect of solvent is another quite important factor in the cycloaddition. Our observations indicated that the mixture of *t*-BuOH/H_2O or DMSO/H_2O (V/V, 1/1) could give good reactivity and excellent yields. Additionally, it was also found that the structure of reaction substrates influenced efficiencies of

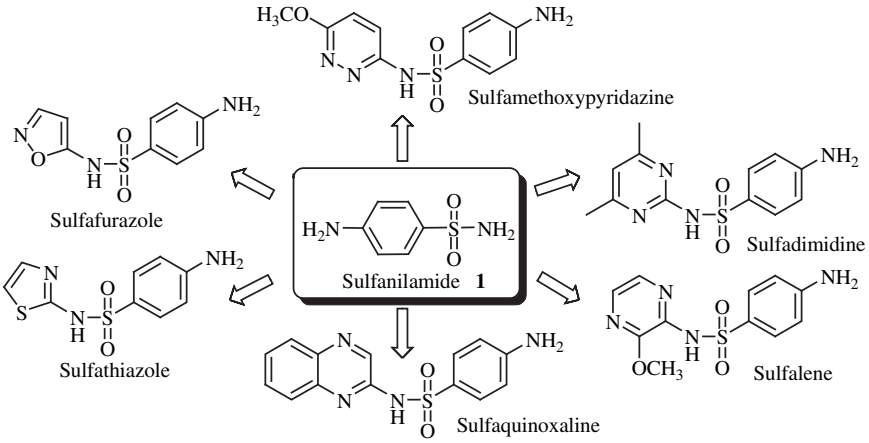
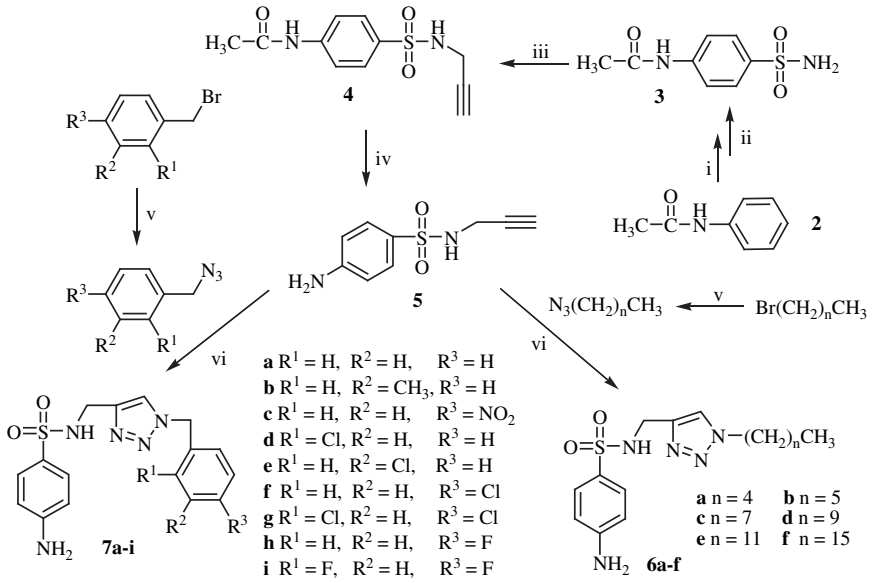


Fig. 1. Structures of some sulfanilamide-derived drugs.



Scheme 1. Synthetic route of novel sulfanilamide-derived 1,2,3-triazoles **6a**–**f** and **7a**–**i**. Reagents and conditions: (i) sulfurochloridic acid, 60 °C; (ii) 30% NH_3 aq., acetone, 0 °C; (iii) 3-bromoprop-1-yne, acetone, 45 °C; (iv) conc. HCl, EtOH, reflux; $NaOH/H_2O$; (v) NaN_3, CH_3COCH_3/H_2O, reflux; (vi) sodium ascorbate (0.2 equiv), $CuSO_4 \cdot 5H_2O$ (0.1 equiv), *t*-BuOH/H_2O (1/1, V/V), 60 °C.

cycloaddition significantly. For example, the short alkyl azides would increase the reactivity of propargyl sulfonamide **5**, while the long alkyl azides showed lower reactivity.

2.2. Analysis of spectra

All the newly synthesized compounds were characterized by MS, IR and NMR spectra as well as elemental analyses listed in the experimental section. The spectral analyses were in accordance with the assigned structures, and the mass spectra of target compounds showed a major fragment of $[M+H]^+$ or $[M+Na]^+$ according to their molecular formula.

2.2.1. IR spectra

The IR spectra of propargyl sulfonamide **5** exhibited three moderate absorption bands at 3404, 3339 and 3250 cm^{-1}, which were respectively attributable to the stretching vibration of N–H in the phenylamino and sulfonamide moiety and C–H in the terminal alkyne (≡C–H). The absorption bands of all synthesized sulfanilamide-derived 1,2,3-triazoles **6a**–**f** and **7a**–**i** associated with functional groups appeared in the expected regions. Moreover, it was found that all the vibration frequency of N–H in halobenzyl 1,2,3-triazoles was slightly shifted to higher wave numbers compared with alkyl 1,2,3-triazoles (Table 1), which was mainly responsible for the inductive effects of the electron-withdrawing character of halogen- or nitro-substituted aryl moieties, especially nitro-substituted sulfanilamide-derived 1,2,3-triazole **7c**.

2.2.2. ^1H NMR spectra

The ^1H NMR spectra revealed that two singlets at the region of 4.50–4.65 ppm and 4.31–5.76 ppm were assigned to the methylene protons of SO_2NHCH_2 and triazole-CH_2–R (R = alkyl or aryl) moiety in all title compounds respectively. In addition, the methylene protons of triazole-CH_2–R in aryl substituted 1,2,3-triazoles **7a**–**i** appeared obvious downfield shifts in comparison with that in alkyl-substituted 1,2,3-triazoles **6a**–**f** as a result of the strong electron-withdrawing character of halogen-substituted aryl moieties in compounds **7a**–**i**, as seen in Table 1. On the basis of the ^1H NMR spectra, it was also observed that all the methylene protons of the SO_2NHCH_2 group in sulfanilamide-derived 1,2,3-triazoles **6a**–**f** and **7a**–**i** displayed larger shifts at 4.50–4.65 ppm in contrast to propargyl sulfonamide **5** (δ 4.06 ppm) owing to the electron-withdrawing character of 1,2,3-triazole group in the newly synthesized compounds. In addition, the acetyl group results in slightly downfield chemical shift at 4.17 ppm for the methylene protons of SO_2NHCH_2 in *N*-acetyl-protected sulfanilamide **4** in comparision with deprotected propargyl sulfonamide **5** (δ 4.06 ppm).

2.2.3. ^{13}C NMR spectra

The ^{13}C NMR spectral analyses were consistent with the assigned structures. No large differences were found in ^{13}C chemical shifts for the methylene carbon of SO_2NHCH_2 (δ 37.9–41.5 ppm) moiety and triazole-CH_2-R group (δ 50.7–52.9 ppm) in all title compounds. The SO_2NHCH_2 moiety in propargyl sulfonamide **5** gave slight upfield chemical shift at 31.6 ppm in contrast to *N*-acetyl-protected sulfanilamide **4** (δ 32.4 ppm). However, the methylene carbon of triazole-CH_2–R in aryl substituted 1,2,3-

Table 1
Some spectral data of synthesized compounds **5**–**7**.

Compds.	IR (ν/cm^{-1})	^1H NMR (δ/ppm)		^{13}C NMR (δ/ppm)	
	N–H	SO_2NHCH_2	triazole-CH_2–R	SO_2NHCH_2	triazole-CH_2–R
5	3404, 3339	4.06	–	31.6	–
6a	3353, 3308, 3275	4.61	4.44	39.5	51.0
6b	3352, 3311, 3269	4.50	4.33	39.6	50.8
6c	3353, 3308, 3271	4.61	4.45	39.4	50.8
6d	3351, 3308, 3269	4.52	4.35	41.1	50.7
6e	3352, 3310, 3269	4.50	4.31	41.0	50.7
6f	3353, 3311, 3269	4.65	4.50	41.5	50.8
7a	3360, 3269	4.45	5.51	37.9	52.7
7b	3390, 3296	4.49	5.48	38.1	52.9
7c	3383, 3330	4.37	5.76	37.9	51.8
7d	3379, 3269	4.50	5.67	37.9	51.6
7e	3380, 3332	4.50	5.50	37.9	51.8
7f	3381, 3334	4.48	5.49	38.4	51.8
7g	3366, 3336	4.35	5.65	38.3	51.6
7h	3381, 3336	4.59	5.53	38.4	51.9
7i	3379, 3335	4.48	5.53	37.9	52.1

triazoles **7a**–**i** appeared small downfield shifts at 51.6–52.9 ppm in comparison with that in alkyl-substituted 1,2,3-triazoles **6a**–**f** at 50.7–51.0 ppm as a result of the strong electron-withdrawing character of halogen-substituted aryl moieties in compounds **7a**–**i**. Moreover, the introduction of 1,2,3-triazole ring also results in large downfield ^{13}C shifts for the methylene carbon of SO_2NHCH_2 moiety in either alkyl-substituted 1,2,3-triazoles **6a**–**f** (δ 39.4–41.5 ppm) or aryl ones **7a**–**i** (δ 37.9–38.4 ppm), compared with their precursor propargyl sulfonamide **5** (δ 31.6 ppm), as seen in Table 1.

2.3. Biological activity

These sulfanilamide-derived 1,2,3-triazoles **6a**–**f** and **7a**–**i** containing alkyl and halobenzyl groups were evaluated for their *in vitro* antimicrobial activities against the representative bacterial strains including *S. aureus* (ATCC25923), methicillin-resistant *S. aureus* (MRSA) (N315), and *Bacillus subtilis* (ATCC6633), *Ealmonella typhosa*, *Pseudomonas aeruginosa*, *Shigella dysenteriae*, and *Escherichia coli* (JM109), as well as two fungal strains such as *Candida albicans* (ATCC76615) and *Candida mycoderma* using the two-fold serial dilution technique [25]. The minimal inhibitory concentration (MIC, μg/mL) was determined, taking Chloramphenicol and Fluconazole as the reference drugs. The bioactive data were summarized in Table 2.

2.3.1. Antibacterial activity

The results of antimicrobial activities indicated that some of the title compounds showed moderate activities against certain tested stains *in vitro*. As seen in Table 2, alkyl-substituted sulfanilamide-derived 1,2,3-triazoles **6d**–**f** exhibited comparable antibacterial activities against *P. aeruginosa* with MIC values ranging from 32 to 64 μg/mL, with corresponding reference drug Chloramphenicol. Meanwhile, it was also observed that these alkyl-substituted compounds displayed good antibacterial activities against *E. typhosa* and *S. dysenteriae* with MIC values ranging from 32 to 128 μg/mL. Additionally, compound **6d** bearing decyl moiety showed moderate antibacterial activities against *B. subtilis* compared with the reference drug Chloramphenicol with an MIC value of 64 μg/mL. Notably, compound **6e** with dodecyl group possessed the most potent biological activities against all tested strains with MIC values between 32 and 64 μg/mL. However, the antibacterial results showed no obvious inhibition for compounds **6a** and **6b** with short C5–C6 alkyl chains. Furthermore, 4-amino-N-((1-hexadecyl-1H-1,2,3-triazol-4-yl)methyl) benzenesulfonamide **6f** displayed reduction in inhibitory activity against the tested stains, compared to compound **6e** with C12 alkyl chain. Therefore, the introduction of alkyl chain with different lengths into sulfanilamide-derived 1,2,3-triazoles has remarkable effect on antibacterial activities, and it was unfavorable in enhancing activity to the incorporation of alkyl chain with lengths too short or too long.

From the bioactive data, it was found that the antibacterial activities of halobenzyl-substituted sulfanilamide-derived 1,2,3-triazoles **7a**–**i** were generally better than that of alkyl-substituted compounds **6a**–**f**. Among these halobenzyl-substituted series, compounds **7g**–**i** containing 2,4-dichlorobenzyl, 4-flurorobenzyl and 2,4-diflurorobenzyl groups respectively, displayed moderate activities against some tested strains at the concentration of 16–128 μg/mL, superior to that of chlorobenzyl substituted 1,2,3-triazoles. Noticeably, compounds **7g** and **7i** with dichlorobenzyl and 2,4-diflurorobenzyl moieties respectively, exhibited good antibacterial activities against all tested strains with MIC values ranging from 16 to 128 μg/mL except for MRSA. Particularly, sulfanilamide-derived 1,2,3-triazole **7i** containing 2,4-difluorobenzyl moiety showed excellent antibacterial activities against *S. dysenteriae* and *P. aeruginosa* in comparison with the reference drug Chloramphenicol with an MIC value of 16 μg/mL. This result was probably ascribed to the high electro-negativity of fluorine moiety, which could modify the electronic distribution in the molecule, and thereby influence the absorption, distribution and metabolism of the bioactive molecules [21]. These findings indicated that the type of substitution in the benzene ring has significant influence on antibacterial activities.

In addition, it was specially noteworthy that propargyl sulfonamide **5** as the precurosor of the target compounds, was no inhibitory activity against all tested strains, while the incorporation of 1,2,3-triazole dramatically enhanced the antibacterial activities

Table 2
In vitro antibacterial and antifungal activities of compounds **5, 6a**–**f** and **7a**–**i**.[a, b, c]

Minimum inhibitory concentration (MIC, μg/mL)									
Fungal strains			Bacterial strains						
Compds.	*C. albicans*	*C. mycoderma*	*S. aureus*	*B. subtilis*	*P. aeruginosa*	*E. coli*	*S. dysenteriae*	*MRSA*	*E. typhosa*
5	>512	>512	>512	>512	>512	>512	>512	>512	>512
6a	>512	>512	>512	>512	512	>512	512	>512	512
6b	>512	>512	512	256	256	>512	256	512	>512
6c	>512	512	>512	256	128	512	256	512	256
6d	>512	>512	256	64	64	512	128	512	128
6e	512	256	128	128	32	64	32	128	64
6f	>512	>512	256	256	64	256	128	512	128
7a	>512	>512	512	>512	512	>512	512	256	512
7b	>512	>512	>512	512	>512	>512	>512	>512	512
7c	>512	>512	>512	256	>512	>512	>512	256	>512
7d	>512	>512	>512	>512	512	>512	512	>512	>512
7e	>512	>512	512	>512	512	>512	>512	256	256
7f	>512	>512	512	>512	>512	>512	>512	>512	512
7g	512	512	64	128	64	128	32	128	128
7h	>512	>512	128	>512	128	256	128	>512	256
7i	256	512	64	128	16	128	16	128	128
A	–	–	4	2	8	4	4	2	2
B	0.5	4	–	–	–	–	–	–	–

[a] Minimum inhibitory concentrations were determined by two-fold serial dilution method for microdilution plates.
[b] **A**, chloramphenicol; **B**, fluconazole.
[c] *C. albicans*, *Candida albicans* (ATCC76615); *C. mycoderma*, *Candida mycoderma*; *S. aureus*, *Staphylococcus aureus* (ATCC25923); *B. subtilis*, *Bacillus subtilis* (ATCC6633); *P. aeruginosa*, *Pseudomonas aeruginosa*; *E. coli*, *Escherichia coli* (JM109); *S. dysenteriae*, *Shigella dysenteriae*; *MRSA*, Methicillin-Resistant *Staphylococcus aureus* (N315); *E. typhosa*, *Eberthella typhosa*.

of the sulfonamide. This results manifested that 1,2,3-triazole and its derivatives are of biological significance, which were expected to become a new member of antimicrobial agents.

In a word, the halobenzyl-substituted sulfanilamide-derived 1,2,3-triazoles **7g**–**i** bearing 2,4-dichlorobenzyl, 4-flurorobenzyl and 2,4-diflurorobenzyl groups respectively, as well as the alkyl-substituted compounds **6d**–**f** with decyl, dodecyl and hexadecyl moieties respectively, showed more potent antibacterial activities than other new compounds against some tested bacteria species, while the halobenzyl-substituted compounds exhibited enhanced activity in contrast to the alkyl-substituted sulfanilamide-derived 1,2,3-triazoles. More importantly, the incorporation of 1,2,3-triazole is beneficial to improve the inhibition activity of the sulfonamide precurosor *in vitro*. All the results suggested the significant effect of the introduction of 1,2,3-triazole into the sulfanilamide, the substitution of benzyl group as well as the lengths of linear alkyl chain in the 1,2,3-triazole ring on antibacterial activities.

2.3.2. Antifungal activity

Unfortunately, the antifungal evaluation revealed that almost all the synthesized alkyl-substituted and halobenzyl-substituted sulfanilamide-derived 1,2,3-triazoles exhibited poor antifungal activities against *C. albicans* and *C. mycoderm*, which were relatively weak in comparison with their antibacterial activities. These results also validated the fact that sulfanilamide derivatives have no obvious antifungal activity *in vitro*, although 1,2,3-triazole ring was incorporated into the sulfanilamide scaffold.

3. Conclusion

In conclusion, a series of novel sulfanilamide-derived 1,2,3-triazoles with different lengths of alkyl chains and halobenzyl groups were synthesized successfully *via* cyclization of azides and terminal alkyne by 'click chemistry'. All these new compounds were confirmed by MS, IR and NMR spectra as well as elemental analyses. Their antimicrobial activities were evaluated against *S. aureus*, *MRSA*, *E. typhosa*, *P. aeruginosa*, *S. dysenteriae, B. subtilis*, *E. coli*, as well as *C. albicans* and *C. mycoderma* using the two-fold serial dilution technique. The results showed that most of the synthesized sulfanilamide derivatives exhibited moderate antimicrobial activities *in vitro*. Especially, compounds **6e**, **7g** and **7i** bearing dodecyl, 2,4-dichlorobenzyl and 2,4-difurobenzyl group, respectively, showed the most potent antibacterial activities against all tested bacterial strains with the MIC values ranging from 32 to 128 μg/mL. The lengths of the alkyl chain and substitution in the benzyl moiety played important roles in the antimicrobial activities of the title compounds. More importantly, the incorporation of 1,2,3-triazole is helpful to improve the inhibition activity of the sulfonamide precurosor *in vitro*. These findings demonstrated that sulfanilamide-derived 1,2,3-triazoles are of biological significance, which have the perspective to become a new member of antimicrobial agents.

4. Experimental

4.1. Chemistry

Melting points were uncorrected and were recorded on X-6 melting point apparatus. TLC analysis was done using pre-coated silica gel plates. FT-IR spectra were carried out on Bruker RFS100/S spectrophotometer (Bio-Rad, Cambridge, MA, USA) using KBr pellets in the 400–4000 cm^{-1} range. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AV 300 pectrometer or Varian-Mercury 400 spectrometer using TMS as an internal standard. The chemical shifts were reported in parts per million (ppm), the coupling constants (J) are expressed in hertz (Hz) and signals were described as singlet (s), doublet (d), triplet (t), quartet (q), broad (br) as well as multiplet (m). The mass spectra were recorded on FINNIGAN TRACE GC/MS (Thermo Electron Corporation, Bremen, Germany). Elemental analyses were carried out on a ERBA1106 (Carlo Erba, Milan, Italy). All chemicals and solvents were commercially available, and were used without further purification.

4.2. Synthesis of alkyl or benzyl azides

To a stirred solution of alkyl or benzyl bromides (0.5 mmol) in acetone (20 mL) was added equal equimolar of NaN_3 at room temperature, then the water (10 mL) was added into the solution. The reaction mixture was refluxed overnight at 60 °C for 10–14 h (monitored by TLC, eluent, petroleum ether). After cooling to the room temperature, the solution was evaporated in vacuo and then water (30 mL) was added. Subsequently, the mixture was extracted with chloroform (3×30 mL), and all organic phases were combined, dried over anhydrous Na_2SO_4 and then evaporated under reduced pressure to produce liquid azides [26]. The azides were used in the following reaction without further purification.

4.3. Synthesis of 4-(N-acetylamino)benzenesulfonamide (*3*)

To a stirred solution of acetaniline (5.0 g, 37 mmol) in acetone (25 mL) was added chlorosulfonic acid (13 mL, 195 mmol) at 0 °C. The reaction mixture was heated to 60 °C, stirred for 1 h, then cooled to room temperature and poured into crushed ice. A white solid was formed, which was isolated by filtration, then dissolved in acetone (40 mL). At 0 °C, ammonium hydroxide (10 mL) was added. The mixture was stirred at room temperature for 1 h, and then the solvent was removed in vacuo to give the intermediate **3** as white solid in 81% yield which was used in the following reaction without further purification, mp 217–219 °C in agreement with the commercial material (mp 219–220 °C).

4.4. Synthesis of the intermediate (*4*)

To a stirred mixture of compound **3** (2.0 g, 8 mmol) in acetone (10 mL) in the presence of potassium carbonate (1.6 g, 11.6 mmol) was added 3-bromoprop-1-yne (1.8 mL, 23 mmol) at room temperature. After one hour, tetrabutyl ammonium iodide (TBAI) (5.0 mg) was added, and then the resulting mixture was stirred under 45–50 °C for 10–12 h (monitored by TLC, eluent, chloroform/ethyl acetate). The solvent was evaporated and then water (30 mL) was added. Subsequently, the mixture was extracted with chloroform (3×30 mL), dried over anhydrous Na_2SO_4 and then evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, chloroform/ethyl acetate) to give the terminal propargyl intermediate **4** as yellow solid in 65.2% yield, mp 126–128 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, 2H, $J = 8.6$ Hz, Ar 2, 6-H), 7.67 (d, 2H, $J = 8.6$ Hz, Ar 3, 5-H), 7.51 (s, 1H, CH_3CONH), 4.17 (s, 2H, SO_2NHCH_2), 2.20 (s, 3H, CH_3), 2.07 (s, 1H, ≡CH) ppm; ^{13}C NMR (100 MH_Z, $CDCl_3$): δ 167.2 (C═O), 143.6 (Ph 4-C), 133.8 (Ph 1-C), 127.9 (Ph 2, 6-C), 113.6 (Ph 3, 5-C), 80.6 (C≡CH), 72.4 (≡CH), 32.4 (SO_2NHCH_2), 24.1 (CH_3) ppm; MS (m/z): 275 $[M + Na]^+$, 253 $[M + H]^+$; Anal. Calcd. for $C_{11}H_{12}N_2O_3S$: C, 52.37; H, 4.79; N, 11.10. Found: C, 52.35; H, 4.78; N, 11.11.

4.5. Synthesis of 4-amino-N-(prop-2-ynyl)benzenesulfonamide (*5*)

Concentrated hydrochloric acid (10 mL) was added under stirring to a solution of propargyl intermediate **4** in ethanol (20 mL) at room temperature. The mixture was refluxed for 30 min (monitored by

TLC, eluent, chloroform). After cooling to the room temperature, the pH of the solution was adjusted to the alkaline with sodium hydroxide, then the solvent was removed in vacuo to give the deprotected propargyl sulfonamide **5** as light yellow solid in 92% yield, mp 131–132 °C; IR (KBr): ν 3404, 3339, 3275 (NH), 3250 (≡CH), 2925, 2117, 1601, 1523, 1441, 1150, 1097 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.83 (d, 2H, $J = 8.6$ Hz, Ar 2, 6-H), 6.77 (d, 2H, $J = 8.6$ Hz, Ar 3, 5-H), 4.70 (s, 2H, NH_2), 4.49 (s, 1H, NH), 4.06 (d, 2H, $J = 3.4$ Hz, SO_2NHCH_2), 2.33 (s, 1H, ≡CH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.2 (Ph 4-C), 131.2 (Ph 1-C), 128.6 (Ph 2, 6-C), 112.6 (Ph 3, 5-C), 80.2 (C≡CH), 71.6 (≡CH), 31.6 (SO_2NHCH_2) ppm; MS (*m*/*z*): 233 $[M + Na]^+$, 211 $[M + H]^+$; Anal. Calcd. for $C_9H_{10}N_2O_2S$: C, 51.41; H, 4.79; N, 13.32. Found: C, 51.42; H, 4.50; N, 13.31.

4.6. General procedure for synthesis of sulfanilamide-derived alkyl 1,2,3-triazoles (**6a–f**)

To a solution of propargyl sulfonamide **5** (100 mg, 0.48 mmol) in a *t*-BuOH/H_2O mixture (10 mL, 1/1, V/V) was added sodium ascorbate (0.20 equiv) and copper (II) sulfate pentahydrate (0.10 equiv) successively. Hereafter excess alkyl azide (0.50 mmol) was added, and the mixture was stirred for 30–60 min at 60 °C (monitored by TLC, eluent, chloroform/ethyl acetate). The reaction system was cooled to room temperature, and the solvent was evaporated under reduced pressure. Subsequently, the resulting mixture was poured into water (30 mL) and extracted with ethyl acetate (3 × 30 mL). After that, the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography (eluent, chloroform/ethyl acetate) to afford the desired cyclization products **6a–f.**

4.6.1. 4-Amino-N-((1-pentyl-1H-1,2,3-triazol-4-yl)methyl) benzenesulfonamide (**6a**)

Compound **6a** (121 mg) was obtained as yellow solid in 78.6% yield, mp 148–150 °C; IR (KBr): ν 3353, 3308, 3275 (NH), 3160, 2955, 2862, 2932, 1604, 1526, 1467, 1321, 1146, 1097 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.83 (d, 2H, $J = 7.6$ Hz, Ar 2,6-H), 7.56 (s, 1H, triazole H), 6.78 (d, 2H, $J = 7.3$ Hz, Ar 3,5-H), 4.94 (bs, 1H, NH), 4.61 (s, 2H, SO_2NHCH_2), 4.44 (s, 2H, triazole-CH_2), 2.38 (s, 2H, triazole-CH_2CH_2), 1.43 (s, 4H, $(CH_2)_2CH_3$), 1.00 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.2 (Ph 4-C), 145.3 (triazole 4-C), 130.8 (Ph 1-C), 129.0 (Ph 2, 6-C), 122.8 (triazole 5-C), 112.6 (Ph 3, 5-C), 51.0 (triazole-CH_2), 39.5 (SO_2NHCH_2), 29.5 ($CH_3CH_2CH_2$), 28.2 (triazole-CH_2CH_2), 22.6 (CH_2CH_3), 14.2 (CH_3) ppm; MS (*m*/*z*): 346 $[M + Na]^+$, 324 $[M + H]^+$; Anal. Calcd. for $C_{14}H_{21}N_5O_2S$: C, 51.99; H, 6.54; N, 21.65. Found: C, 51.96; H, 6.56; N, 21.62.

4.6.2. 4-Amino-N-((1-hexyl-1H-1,2,3-triazol-4-yl)methyl) benzenesulfonamide (**6b**)

Compound **6b** (143 mg) was obtained as white solid in 88.8% yield, mp 138–140 °C; IR (KBr): ν 3352, 3311, 3269 (NH), 3157, 2956, 2850, 2919, 1606, 1526, 1468, 1321, 1146, 1056 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, 2H, $J = 8.2$ Hz, Ar 2,6-H), 7.44 (s, 1H, triazole H), 6.66 (d, 2H, $J = 8.3$ Hz, Ar 3,5-H), 4.70 (bs, 2H, NH_2), 4.50 (s, 2H, SO_2NHCH_2), 4.33 (t, 2H, $J = 7.1$ Hz, triazole-CH_2), 1.89 (s, 2H, triazole-CH_2CH_2), 1.31–1.25 (m, 6H, $(CH_2)_3CH_3$), 0.88 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.5 (Ph 4-C), 145.8 (triazole 4-C), 131.2 (Ph 1-C), 128.5 (Ph 2, 6-C), 122.3 (triazole 5-C), 112.3 (Ph 3, 5-C), 50.8 (triazole-CH_2), 39.6 (SO_2NHCH_2), 31.6 ($CH_3CH_2CH_2$), 30.7 (triazole-CH_2CH_2), 26.6 (triazole-$CH_2CH_2CH_2$), 22.9 (CH_2CH_3), 14.5 (CH_3) ppm; MS (*m*/*z*): 360 $[M + Na]^+$; Anal. Calcd. for $C_{15}H_{23}N_5O_2S$: C, 53.39; H, 6.87; N, 20.75. Found: C, 53.35; H, 6.90; N, 20.72.

4.6.3. 4-Amino-N-((1-octyl-1H-1,2,3-triazol-4-yl)methyl) benzenesulfonamide (**6c**)

Compound **6c** (151 mg) was obtained as yellow solid in 86.8% yield, mp 129–131 °C; IR (KBr): ν 3353, 3308, 3271 (NH), 3151, 2954, 2855, 2924, 1605, 1526, 1467, 1321, 1146, 1096 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.83 (d, 2H, $J = 7.7$ Hz, Ar 2,6-H), 7.56 (s, 1H, triazole H), 6.78 (d, 2H, $J = 7.8$ Hz, Ar 3,5-H), 4.84 (s, 2H, NH_2), 4.61 (s, 2H, SO_2NHCH_2), 4.45 (s, 2H, triazole-CH_2), 2.00 (s, 2H, triazole-CH_2CH_2), 1.41–1.37 (m, 10H, $(CH_2)_5CH_3$), 0.99 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.8 (Ph 4-C), 145.5 (triazole 4-C), 130.0 (Ph 1-C), 129.1 (Ph 2, 6-C), 122.6 (triazole 5-C), 112.8 (Ph 3, 5-C), 50.8 (triazole-CH_2), 39.4 (SO_2NHCH_2), 32.4 ($CH_3CH_2CH_2$), 31.0 (CH_2), 29.8 (CH_2), 29.7 (triazole-CH_2CH_2), 27.2 (triazole-$CH_2CH_2CH_2$), 23.3 (CH_2CH_3), 14.8 (CH_3) ppm; MS (*m*/*z*): 388 $[M + Na]^+$, 366 $[M + H]^+$; Anal. Calcd. for $C_{17}H_{27}N_5O_2S$: C, 55.86; H, 7.45; N, 19.16. Found: C, 55.88; H, 7.43; N, 19.14.

4.6.4. 4-Amino-N-((1-decyl-1H-1,2,3-triazol-4-yl)methyl) benzenesulfonamide (**6d**)

Compound **6d** (130 mg) was obtained as yellow solid in 69.6% yield, mp 145–147 °C; IR (KBr): ν 3351, 3308, 3269 (NH), 3162, 2954, 2852, 2922, 1607, 1526, 1466, 1321, 1145, 1096 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, 2H, $J = 8.3$ Hz, Ar 2,6-H), 7.44 (s, 1H, triazole H), 6.68 (d, 2H, $J = 8.2$ Hz, Ar 3,5-H), 4.71 (bs, 2H, NH_2), 4.52 (s, 2H, SO_2NHCH_2), 4.35 (s, 2H, triazole-CH_2), 1.89 (s, 2H, triazole-CH_2CH_2), 1.32–1.27 (m, 14H, $(CH_2)_7CH_3$), 0.87 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.4 (Ph 4-C), 144.5 (triazole 4-C), 133.0 (Ph 1-C), 128.7 (Ph 2, 6-C), 121.1 (triazole 5-C), 112.2 (Ph 3, 5-C), 50.7 (triazole-CH_2), 41.4 (SO_2NHCH_2), 32.0 ($CH_3CH_2CH_2$), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.1 (triazole-CH_2CH_2), 26.6 (triazole-$CH_2CH_2CH_2$), 22.8 (CH_2CH_3), 14.2 (CH_3) ppm; MS (*m*/*z*): 416 $[M + Na]^+$, 394 $[M + H]^+$; Anal. Calcd. for $C_{19}H_{31}N_5O_2S$: C, 57.99; H, 7.94; N, 17.80. Found: C, 58.02; H, 7.92; N, 17.76.

4.6.5. 4-Amino-N-((1-dodecyl-1H-1,2,3-triazol-4-yl)methyl) benzenesulfonamide (**6e**)

Compound **6e** (166 mg) was obtained as yellow solid in 82.6% yield, mp 141–143 °C; IR (KBr): ν 3352, 3310, 3269 (NH), 3161, 2954, 2851, 2921, 1606, 1526, 1467, 1321, 1146, 1097 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, 2H, $J = 8.6$ Hz, Ar 2,6-H), 7.44 (s, 1H, triazole H), 6.67 (d, 2H, $J = 8.6$ Hz, Ar 3,5-H), 4.86 (bs, 1H, NH), 4.71 (bs, 2H, NH_2), 4.50 (d, 2H, $J = 5.1$ Hz, SO_2NHCH_2), 4.31 (t, 2H, $J = 7.3$ Hz, triazole-CH_2), 1.89 (t, 2H, $J = 6.4$ Hz, triazole-CH_2CH_2), 1.31–1.25 (m, 18H, $(CH_2)_9CH_3$), 0.88 (t, 3H, $J = 6.4$ Hz, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.4 (Ph 4-C), 144.2 (triazole 4-C), 133.6 (Ph 1-C), 128.4 (Ph 2, 6-C), 121.6 (triazole 5-C), 111.8 (Ph 3, 5-C), 50.7 (triazole-CH_2), 41.0 (SO_2NHCH_2), 32.4 ($CH_3CH_2CH_2$), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 28.1 (triazole-CH_2CH_2), 26.1 (triazole-$CH_2CH_2CH_2$), 21.8 (CH_2CH_3), 14.6 (CH_3) ppm; MS (*m*/*z*): 444 $[M + Na]^+$, 422 $[M + H]^+$; Anal. Calcd. for $C_{21}H_{35}N_5O_2S$: C, 59.83; H, 8.37; N, 16.61. Found: C, 59.79; H, 8.35; N, 16.64.

4.6.6. 4-Amino-N-((1-hexadecyl-1H-1,2,3-triazol-4-yl)methyl) benzenesulfonamide (**6f**)

Compound **6f** (160 mg) was obtained as white solid in 70.2% yield, mp 144–145 °C; IR (KBr): ν 3353, 3311, 3269 (NH), 3157, 2954, 2850, 2919, 1606, 1526, 1468, 1321, 1146, 1097 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, 2H, $J = 8.3$ Hz, Ar 2, 6-H), 7.44 (s, 1H, triazole H), 6.66 (d, 2H, $J = 8.3$ Hz, Ar 3,5-H), 4.84 (bs, 1H, NH), 4.65 (s, 2H, SO_2NHCH_2), 4.50 (s, 2H, triazole-CH_2), 4.33 (s, 2H, NH_2), 1.89 (s, 2H, triazole-CH_2CH_2), 1.30–1.25 (m, 26H, $(CH_2)_{13}CH_3$), 0.88 (t, 3H, $J = 6.3$ Hz, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.6 (Ph 4-C), 144.8 (triazole 4-C), 133.2 (Ph 1-C), 127.9 (Ph 2, 6-C), 121.4 (triazole 5-C), 112.3 (Ph 3, 5-C), 50.8 (triazole-CH_2), 41.5 (SO_2NHCH_2),

31.8 ($CH_3CH_2CH_2$), 29.8 (CH_2), 29.1 (CH_2), 28.6 (CH_2), 28.5 (triazole-CH_2CH_2), 27.5 (triazole-$CH_2CH_2CH_2$), 22.9 (CH_2CH_3), 14.5 (CH_3) ppm; MS (*m*/*z*): 500 $[M+Na]^+$, 478 $[M+H]^+$; Anal. Calcd. for $C_{25}H_{43}N_5O_2S$: C, 62.86; H, 9.07; N, 14.66. Found: C, 62.87; H, 9.05; N, 14.64.

4.7. General procedure for synthesis of sulfanilamide-derived aryl 1,2,3-triazoles (**7a**–**i**)

To a solution of propargyl sulfonamide **5** (100 mg, 0.48 mmol) in a *t*-BuOH/H_2O mixture (10 mL, 1/1, V/V) were added sodium ascorbate (0.2 equiv) and copper (II) sulfate pentahydrate (0.1 equiv) successively. Hereafter excess aryl azide (0.50 mmol) was added, and the mixture was stirred at 60 °C. After 25–45 min, the reaction came to the end (monitored by TLC, eluent, chloroform/ethyl acetate), and then solvent was evaporated under reduced pressure. Subsequently, the resulting mixture was poured into water (30 mL) and extracted with ethyl acetate (3 × 30 mL). After that, the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude material, which was purified by silica gel column chromatography (eluent, chloroform/ethyl acetate) to afford the desired cyclization products **7a**–**i**.

4.7.1. 4-Amino-N-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl) benzenesulfonamide (**7a**)

Compound **7a** (147 mg) was obtained as yellow solid in 90.2% yield, mp 136–137 °C; IR (KBr): *ν* 3360, 3269 (NH), 3149, 3060, 2865, 1601, 1519, 1455, 1312, 1148, 1097 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 7.66 (d, 2H, *J* = 8.3 Hz, Ar H), 7.49 (s, 1H, triazole H), 7.40–7.27 (m, 4H, Ar H), 6.64 (d, 2H, *J* = 8.4 Hz, Ar H), 5.94 (s, H, NH), 5.51 (s, 2H, triazole-CH_2), 4.45 (d, 2H, *J* = 5.5 Hz, SO_2NHCH_2) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 150.9 (*p*-NH_2Ph 4-C), 145.2 (triazole 4-C), 136.1 (CH_2Ph 1-*C*), 130.5 (*p*-NH_2Ph 1-C), 128.6 (CH_2Ph 2, 6-*C*), 128.0 (CH_2Ph 3, 5-*C*), 127.8 (*p*-NH_2Ph 2, 6-C), 127.2 (CH_2Ph 4-*C*), 122.9 (triazole 5-C), 111.1 (*p*-NH_2Ph 3, 5-C), 52.7 (triazole-CH_2), 37.9 (SO_2NHCH_2) ppm; MS (*m*/*z*): 366 $[M+Na]^+$; Anal. Calcd. for $C_{16}H_{17}N_5O_2S$: C, 55.96; H, 4.99; N, 20.39. Found: C, 55.98; H, 4.97; N, 20.38.

4.7.2. 4-Amino-N-((1-(3-methyl)-1H-1,2,3-triazol-4-yl)methyl) benzenesulfonamide (**7b**)

Compound **7b** (133 mg) was obtained as white solid in 78.3% yield, mp 195–197 °C; IR (KBr): *ν* 3390, 3296 (NH), 3148, 3067, 2943, 2859, 2915, 1595, 1517, 1460, 1313, 1142, 1034 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 7.71 (d, 2H, *J* = 8.4 Hz, Ar H), 7.38 (s, 1H, triazole H), 7.19–7.07 (m, 3H, Ar H), 6.65 (d, 2H, *J* = 8.3 Hz, Ar H), 5.48 (s, 2H, triazole-CH_2), 4.61 (s, 2H, NH_2), 4.49 (s, 2H, SO_2NHCH_2), 2.34 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 151.1 (*p*-NH_2Ph 4-C), 145.3 (triazole 4-C), 138.1 (*m*-CH_3Ph 3-*C*), 136.1 (*m*-CH_3Ph 1-*C*), 130.7 (*m*-CH_3Ph 2-*C*), 128.8 (*p*-NH_2Ph 1-C), 128.8 (*m*-CH_3Ph 5-*C*), 128.6 (*p*-NH_2Ph 2, 6-C), 127.4 (*m*-CH_3Ph 4-*C*), 125.1 (*m*-CH_3Ph 6-*C*), 123.1 (triazole 5-C), 111.3 (*p*-NH_2Ph 3, 5-C), 52.9 (triazole-CH_2), 38.1 (SO_2NHCH_2), 21.0 (CH_3) ppm; MS (*m*/*z*): 380 $[M+Na]^+$; Anal. Calcd. for $C_{17}H_{19}N_5O_2S$: C, 57.12; H, 5.36; N, 19.59. Found: C, 57.13; H, 5.34; N, 19.57.

4.7.3. N-((1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-4-aminobenzenesulfonamide (**7c**)

Compound **7c** (162 mg) was obtained as yellow solid in 87.5% yield, mp 167–168 °C; IR (KBr): *ν* 3383, 3330 (NH), 3151, 2865, 1605, 1523, 1314, 1149, 1111 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): *δ* 8.23 (d, 2H, *J* = 8.6 Hz, Ar H), 8.11 (s, 1H, triazole H), 7.51 (m, 4H, Ar H), 6.87 (s, H, NH), 6.69 (d, 2H, *J* = 8.4 Hz, Ar H), 5.76 (s, 2H, triazole-CH_2), 4.37 (d, 2H, *J* = 5.4 Hz, SO_2NHCH_2) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 150.7 (*p*-NH_2Ph 4-C), 147.2 (*p*-NO_2Ph 4-C), 145.2 (triazole 4-C), 143.3 (*p*-NO_2Ph 1-C), 128.8 (*p*-NO_2Ph 2, 6-C), 128.6 (*p*-NH_2Ph 1-C), 128.3 (*p*-NH_2Ph 2, 6-C), 127.2 (triazole 5-C), 123.7 (*p*-NO_2Ph 3, 5-C) 111.1 (*p*-NH_2Ph 3, 5-C), 51.8 (triazole-CH_2), 37.9 (SO_2NHCH_2) ppm; MS (*m*/*z*): 412 $[M+Na]^+$; Anal. Calcd. for $C_{16}H_{16}N_6O_4S$: C, 49.48; H, 4.15; N, 21.64. Found: C, 49.49; H, 4.13; N, 21.63.

4.7.4. 4-Amino-N-((1-(2-chlorobenzyl)-1H-1,2,3-triazol-4-yl) methyl)benzenesulfonamide (**7d**)

Compound **7d** (123 mg) was obtained as white solid in 68.6% yield, mp 176–178 °C; IR (KBr): *ν* 3379, 3269 (NH), 3153, 2868, 1604, 1520, 1475, 1312, 1149, 1098 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 7.73 (d, 2H, *J* = 8.7 Hz, Ar H), 7.44 (s, 1H, triazole H), 7.10–7.07 (m, 4H, Ar H), 6.67 (d, 2H, *J* = 8.7 Hz, Ar H), 5.67 (s, 2H, triazole-CH_2), 4.62 (bs, 2H, NH_2), 4.50 (s, 2H, SO_2NHCH_2) ppm; ^{13}C NMR (100 MH_Z, DMSO-d_6): δ 150.8 (*p*-NH_2Ph 4-C), 145.0 (triazole 4-C), 133.2 (*o*-ClPh 1-C), 132.4 (*o*-ClPh 2-C), 130.5 (*o*-ClPh 6-C), 130.2 (*p*-NH_2Ph 1-C), 130.0 (*o*-ClPh 3-C), 129.5 (*p*-NH_2Ph 2, 6-C), 127.6 (*o*-ClPh 4-C), 127.1 (*o*-ClPh 5-C), 123.3 (triazole 5-C), 111.1 (*p*-NH_2Ph 3, 5-C), 51.6 (triazole-CH_2), 37.9 (SO_2NHCH_2) ppm; MS (*m*/*z*): 400 $[M+Na]^+$, 378 $[M+H]^+$; Anal. Calcd. for $C_{16}H_{16}ClN_5O_2S$: C, 50.86; H, 4.27; N, 18.53. Found: C, 50.88; H, 4.26; N, 18.51.

4.7.5. 4-Amino-N-((1-(3-chlorobenzyl)-1H-1,2,3-triazol-4-yl) methyl)benzenesulfonamide (**7e**)

Compound **7e** (141 mg) was obtained as white solid in 78.3% yield, mp 151–153 °C; IR (KBr): *ν* 3380, 3332 (NH), 3153, 2865, 1603, 1520, 1472, 1313, 1149, 1098 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 7.72 (d, 2H, *J* = 8.6 Hz, Ar H), 7.61 (s, 1H, triazole H), 7.40–7.15 (m, 4H, Ar H), 6.65 (d, 2H, *J* = 8.6 Hz, Ar H), 5.50 (s, 2H, triazole-CH_2), 4.62 (s, 2H, NH_2), 4.50 (s, 2H, SO_2NHCH_2) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 150.8 (*p*-NH_2Ph 4-C), 145.2 (triazole 4-C), 138.4 (*m*-ClPh 1-C), 133.1 (*m*-ClPh 3-C), 130.5 (*m*-ClPh 5-C), 127.9 (*p*-NH_2Ph 1-C), 127.6 (*m*-ClPh 2-C), 127.1 (*p*-NH_2Ph 2, 6-C), 126.5 (*m*-ClPh 6-C), 123.0 (triazole 5-C), 111.0 (*p*-NH_2Ph 3, 5-C), 51.8 (triazole-CH_2), 37.9 (SO_2NHCH_2) ppm; MS (*m*/*z*): 400 $[M+Na]^+$, 378 $[M+H]^+$; Anal. Calcd. for $C_{16}H_{16}ClN_5O_2S$: C, 50.86; H, 4.27; N, 18.53. Found: C, 50.88; H, 4.26; N, 18.51.

4.7.6. 4-Amino-N-((1-(4-chlorobenzyl)-1H-1,2,3-triazol-4-yl) methyl)benzenesulfonamide (**7f**)

Compound **7f** (124 mg) was obtained as yellow solid in 68.9% yield, mp 152–153 °C; IR (KBr): *ν* 3381, 3334 (NH), 3151, 2864, 1603, 1520, 1471, 1315, 1150, 1010 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 7.71 (d, 2H, *J* = 8.6 Hz, Ar H), 7.47 (s, 1H, triazole H), 7.18–7.26 (m, 4H, Ar H), 6.64 (d, 2H, *J* = 8.6 Hz, Ar H), 5.49 (s, 2H, triazole-CH_2), 4.63 (bs, 1H, NH), 4.48 (s, 2H, SO_2NHCH_2) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 150.8 (*p*-NH_2Ph 4-C), 145.2 (triazole 4-C), 135.0 (*p*-ClPh 1-C), 132.7 (*p*-ClPh 4-C), 130.5 (*p*-ClPh 2, 6-C), 129.7 (*p*-NH_2Ph 1-C), 128.6 (*p*-ClPh 3, 5-C), 127.1 (*p*-NH_2Ph 2, 6-C), 122.9 (triazole 5-C), 111.0 (*p*-NH_2Ph 3, 5-C), 51.8 (triazole-CH_2), 38.4 (SO_2NHCH_2) ppm; MS (*m*/*z*): 400 $[M+Na]^+$; Anal. Calcd. for $C_{16}H_{16}ClN_5O_2S$: C, 50.86; H, 4.27; N, 18.53. Found: C, 50.88; H, 4.26; N, 18.51.

4.7.7. N-((1-(2,4-dichlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-4-aminobenzenesulfonamide (**7g**)

Compound **7g** (177 mg) was obtained as yellow solid in 90.2% yield, mp 147–149 °C; IR (KBr): *ν* 3366, 3336 (NH), 3145, 2865, 1597, 1513, 1474, 1334, 1153, 1052 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): *δ* 7.72 (d, 2H, *J* = 8.5 Hz, Ar H), 7.43 (s, 1H, triazole H), 6.88 (m, 2H, Ar H), 6.64 (d, 2H, *J* = 8.6 Hz, Ar H), 5.65 (s, 2H, triazole-CH_2), 4.73 (bs, 1H, NH), 4.35 (s, 2H, SO_2NHCH_2) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 150.5 (*p*-NH_2Ph 4-C), 143.9 (triazole 4-C), 134.3 (2, 4-Cl_2Ph 1-C), 133.4 (2, 4-Cl_2Ph 2-C), 131.3 (2, 4-Cl_2Ph 4-C), 130.9 (2, 4-Cl_2Ph

6-C), 130.7 (2, 4-Cl_2Ph 3-C), 128.9 (*p*-NH_2Ph 1-C), 127.3 (*p*-NH_2Ph 2, 6-C), 127.2 (2, 4-Cl_2Ph 5-C), 122.9 (triazole 5-C), 111.1 (*p*-NH_2Ph 3, 5-C), 51.6 (triazole-CH_2), 38.3 (SO_2NHCH_2) ppm; MS (*m*/*z*): 437 $[M+Na]^+$; Anal. Calcd. for $C_{16}H_{15}Cl_2N_5O_2S$: C, 46.61; H, 3.67; N, 16.99. Found: C, 46.63; H, 3.66; N, 16.97.

4.7.8. 4-Amino-N-((1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl) methyl)benzenesulfonamide (**7h**)

Compound **7h** (118 mg) was obtained as white solid in 68.6% yield, mp 162–164 °C; IR (KBr): ν 3381, 3336 (NH), 3152, 2928, 2864, 1605, 1512, 1472, 1315, 1222, 1149, 1010 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.83 (d, 2H, $J = 7.5$ Hz, Ar H), 7.48 (s, 1H, triazole H), 7.20 (m, 2H, Ar H), 6.76 (d, 2H, $J = 7.4$ Hz, Ar H), 5.61 (s, 2H, triazole-CH_2), 4.91 (bs, 1H, NH), 4.75 (s, 2H, NH_2), 4.59 (s, 2H, SO_2NHCH_2) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.0, 160.5 (*p*-FPh 4-C), 150.9 (*p*-NH_2Ph 4-C), 145.2 (triazole 4-C), 132.3 (*p*-FPh 1-C), 130.5 (*p*-NH_2Ph 1-C), 130.2, 130.1 (*p*-FPh 2, 6-C), 127.2 (*p*-NH_2Ph 2, 6-C), 122.8 (triazole 5-C), 115.6, 115.4 (*p*-FPh 3, 5-C), 111.1 (*p*-NH_2Ph 3, 5-C), 51.9 (triazole-CH_2), 38.4 (SO_2NHCH_2) ppm; MS (*m*/*z*): 384 $[M+Na]^+$, 362 $[M+H]^+$; Anal. Calcd. for $C_{16}H_{16}FN_5O_2S$: C, 53.17; H, 4.46; N, 19.38. Found: C, 53.15; H, 4.48; N, 19.36.

4.7.9. 4-Amino-N-((1-(2,4-difluorobenzyl)-1H-1,2,3-triazol-4-yl) methyl)benzenesulfonamide (**7i**)

Compound **7i** (160 mg) was obtained as white solid in 88.5% yield, mp 172–174 °C; IR (KBr): ν 3379, 3335 (NH), 3156, 2866, 1604, 1520, 1475, 1314, 1149, 1098 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, 2H, $J = 8.6$ Hz, Ar H), 7.47 (s, 1H, triazole H), 6.91 (m, 3H, Ar H), 6.65 (d, 2H, $J = 8.6$ Hz, Ar H), 5.53 (s, 2H, triazole-CH_2), 4.79 (bs, 1H, NH), 4.63 (s, 2H, NH_2), 4.48 (s, 2H, SO_2NHCH_2) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.6, 163.5, 161.5, 161.4 (2,4-F_2Ph 2-C), 161.1, 161.0, 159.1, 159.0 (2,4-F_2Ph 4-C), 150.8 (*p*-NH_2Ph 4-C), 145.1 (triazole 4-C), 132.1, 132.0 (2,4-F_2Ph 6-C), 130.5 (*p*-NH_2Ph 1-C), 127.2 (*p*-NH_2Ph 2, 6-C), 122.9 (triazole 5-C), 119.4, 119.2 (2,4-F_2Ph 1-C), 111.9, 111.6 (2,4-F_2Ph 5-C), 111.1 (*p*-NH_2Ph 3, 5-C), 104.4, 104.1, 103.9 (2,4-F_2Ph 3-C), 52.1 (triazole-CH_2), 37.9 (SO_2NHCH_2) ppm; MS (*m*/*z*): 402 $[M+Na]^+$, 380 $[M+H]^+$; Anal. Calcd. for $C_{16}H_{15}F_2N_5O_2S$: C, 50.65; H, 3.99; N, 18.46. Found: C, 50.66; H, 4.01; N, 18.44.

4.8. Antibacterial and antifungal assays

The *in vitro* minimal inhibitory concentrations (MICs) of the target compounds were determined using the two-fold serial dilution technique in 96-well microtest plates according to the National Committee for Clinical Laboratory Standards. The tested microorganism strains were provided by the School of Pharmaceutical Sciences, Southwest University and the College of Pharmacy, Third Military Medical University. Chloramphenicol and Fluconazole were used as standard drugs.

4.8.1. Antibacterial assays

The prepared compounds **5**, **6a**–**f** and **7a**–**i** were evaluated for their antibacterial activities against *S. aureus* (ATCC25923), *MRSA* (N315) and *B. subtilis* (ATCC6633) as Gram-positive, *E. coli* (JM109), *P. aeruginosa*, *S. dysenteriae* and *E. typhosa* as Gram-negative bacteria. The bacterial suspension was adjusted with sterile saline to a concentration of 1×10^5 CFU. The tested compounds were dissolved in DMSO to prepare the stock solutions. The tested compounds and reference drugs were prepared in Mueller–Hinton broth (Guangdong huaikai microbial sci.& tech co., Ltd, Guangzhou, Guangdong, China) by two-fold serial dilution to obtain the required concentrations of 512, 256, 128, 64, 32, 16, 8, 4, 2, 1, 0.5 μg/mL. These dilutions were inoculated and incubated at 37 °C for 24 h. To ensure that the solvent had no effect on bacterial growth, a control test was performed with test medium supplemented with DMSO at the same dilutions as used in the experiment.

4.8.2. Antifungal assays

The newly synthesized compounds were evaluated for their antifungal activity against *C. albicans* (ATCC76615) and *C. mycoderma*. A spore suspension in sterile distilled water was prepared from 1-day old culture of the fungi growing on Sabouraud agar (SA) media. The final spore concentration was $1–5 \times 10^3$ spore mL^{-1}. From the stock solutions of the tested compounds and reference antifungal Fluconazole, dilutions in sterile RPMI 1640 medium (Neuronbc Laboraton Technology CO., Ltd, Beijing, China) were made resulting in eleven desired concentrations (0.5–512 μg/mL) of each tested compound. These dilutions were inoculated and incubated at 35 °C for 24 h. The drug MIC was defined as the first well with an approximate 80% reduction in growth compared to the growth of the drug-free well. The minimum inhibitory concentration values (MICs) (in μg/mL) were summarized in Table 2.

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