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Synthesis, characterization and biological activities of sulfonamide tagged 1,2,3-triazoles

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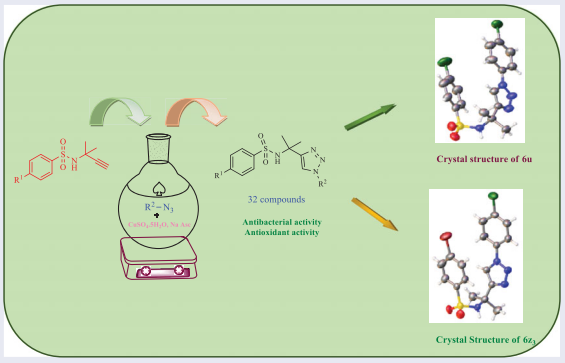
ABSTRACT

The present paper elicits a marvelous synthesis of a series of sulfonamide containing 1,4-disubstituted 1,2,3-triazoles through click reaction of terminal alkynes with aromatic azides. The synthesized triazoles were characterized by FTIR, ^{1}H NMR,^{13}C NMR and HRMS techniques. Further, the structures of synthesized compounds **6u** (CCDC 1954932) and **6z$_3$** (CCDC 1954931) were also confirmed by X-ray crystallography. The synthesized triazoles were evaluated for *in vitro* antibacterial activity against *S. aureus, B.subtilis*, *E. coli* and *K. pneumoniae* by serial dilution method. Among the series, compound 4-bromo-*N*-(2-(1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)propan-2-yl)benzenesulfonamide, **6z$_4$** (MIC = 0.025 μM/mL) and 4-bromo-*N*-(2-(1-(naphthalen-1-yl)-1*H*-1,2,3-triazol-4-yl)propan-2-yl)benzenesulfonamide **6z$_6$** (MIC = 0.027 μM/mL) exhibited the appreciable antibacterial activity against *Staphylococcus aureus* and *Bacillus subtilis*. Further, the molecular docking studies of above potent analogs with dihydropteroate synthase was performed to have an insight for binding interactions. Synthesized molecules were also explored for antioxidant activity, reflecting compound **6m** as better radical scavenging agent with IC_{50} value of 1.96 μM/mL.

GRAPHICAL ABSTRACT



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Introduction

In the present scenario, the synthesis of newer heterocycles is the need of time to come out with an effective pharmacophore with broad biological spectrum. In this sequence, nitrogen containing heteroaromatics received considerable attention due to their wide biological applications. Among these, 1,2,3-triazoles are of key importance possessing varied pharmaceutical applications in form of anticancer,[1–4] antimicrobial,[5–9] antiviral,[10,11] antitubercular,[12–14] antioxidant,[15,16] anti-depressant,[17] anti-inflammatory,[18–20] anti-malarial,[21,22] anti-protozoal,[23] anti-leishmanial,[24] anti-adipogenic,[25] Cholinesterase inhibitory[26] agents. An effective and concrete synthesis of substituted 1,2,3-triazoles was put forward by Sharpless[27,28] and coworkers, through click chemistry, involving cycloaddition reaction between terminal alkynes and azides using copper(I) as a catalyst yielding 1,4-disubstituted isomer selectively. These copper(I) catalyzed synthesis are quiet efficient, can be performed under mild reaction conditions and leads to interesting products having different functionalities/moieties with encouraging yields. Monocyclic 1,2,3-triazoles are remarkably stable toward hydrolysis, oxidative/reductive conditions, and enzymatic degradation. Some unique features like hydrogen bond formation, dipole-dipole and π stacking interactions of triazoles have increased their significance in the field of medicinal chemistry due to their effective binding with the biological targets. The triazole also serves as synthetic intermediates in many industrial applications such as agrochemicals,[29] corrosion inhibitors,[30,31] additives, dyes, polymer,[32,33] etc.

It has been stated that free radicals containing reactive oxygen species (ROS) like superoxide (O_2), hydroxyl (HO), peroxyl (ROO), alkoxyl (RO), and nitric oxide (NO) radicals are highly reactive molecules and are believed to be associated with multiple diseases conditions such as carcinogenesis, inflammation, mutagenesis, arthritis, cancer and genotoxicity. In order to prevent the deleterious effects caused by free radicals in the human body, there is need to cater the potential antioxidative agents in form of newer molecules with broad biological significance.

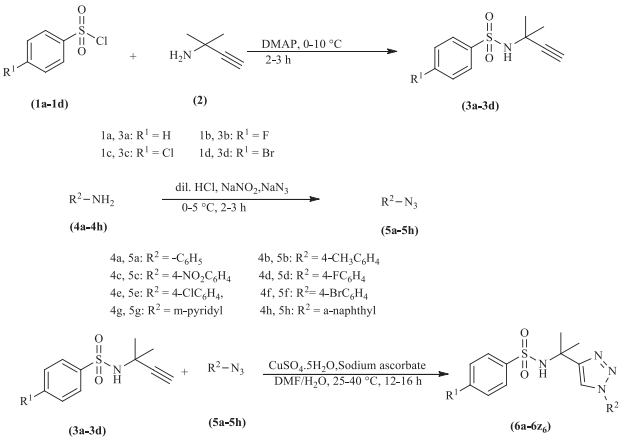
Nowadays, antibiotic-resistant microbes are also making their inexorable march, throwing a tough challenge to the organic chemists to synthesize more effective molecules having an edge over existing drugs. Sulfonamides[34–36] were the first effective chemotherapeutic agents to prevent and cure the bacterial infection in human beings as early as 70 years ago.

Owing to the biological significance of sulfonamide moiety, it has been thought to carry out synthesis of sulfonamide tagged 1,4-disubstituted 1,2,3-triazoles through copper(I) catalyzed cycloaddition reaction between terminal alkynes and azides and to evaluate the biological activity of synthesized triazoles in form of antibacterial (against *Staphylococcus aureus, Bacillus subtilis, Klebsiella pneumoniae, Escherichia coli*) and antioxidant agents.

Result and discussion

Chemistry

The work describes the synthesis of a series of sulfonamide tagged 1,4-disubstituted 1,2,3-triazoles (Scheme 1). In the first step, propargylation of commercially available



Compounds	R^1	R^2	Reaction time (h)	Yield (%)
6a	H	C_6H_5	4	82
6b	H	4-$CH_3C_6H_4$	5	82
6c	H	4-$NO_2C_6H_4$	5	78
6d	H	4-FC_6H_4	7	84
6e	H	4-ClC_6H_4	8	85
6f	H	4-BrC_6H_4	6	75
6g	H	m-pyridyl	10	82
6h	H	α-naphthyl	8	82
6i	F	C_6H_5	5	78
6j	F	4-$CH_3C_6H_4$	6	76
6k	F	4-$NO_2C_6H_4$	6	86
6l	F	4-FC_6H_4	5	72
6m	F	4-ClC_6H_4	6	82
6n	F	4-BrC_6H_4	8	86
6o	F	m-pyridyl	10	84
6p	F	α-naphthyl	8	84
6q	Cl	C_6H_5	5	85
6r	Cl	4-$CH_3C_6H_4$	4	78
6s	Cl	4-$NO_2C_6H_4$	4	83
6t	Cl	4-FC_6H_4	6	76
6u	Cl	4-ClC_6H_4	5	72
6v	Cl	4-BrC_6H_4	5	78
6w	Cl	m-pyridyl	9	88
6x	Cl	α-naphthyl	7	68
6y	Br	C_6H_5	6	88
6z	Br	4-$CH_3C_6H_4$	6	81
6z$_1$	Br	4-$NO_2C_6H_4$	6	91
6z$_2$	Br	4-FC_6H_4	5	68
6z$_3$	Br	4-ClC_6H_4	6	85
6z$_4$	Br	4-BrC_6H_4	8	64
6z$_5$	Br	m-pyridyl	11	82
6z$_6$	Br	α-naphthyl	9	82

Scheme 1. Synthesis of sulfonamide containing 1,4-disubstituted 1,2,3-triazoles (**6a–6z$_6$**).

aromatic sulfonyl chlorides[37,38] (**1a–1d**) was carried out by 1,1-dimethylpropargylamine (**2**) in the presence of 4-(dimethylamino)pyridine (DMAP) in dichloromethane. The aromatic azides (**5a–5h**) were synthesized from aromatic amines by dropwise addition of dilute HCl and $NaNO_2$ followed by the addition of sodium azide in

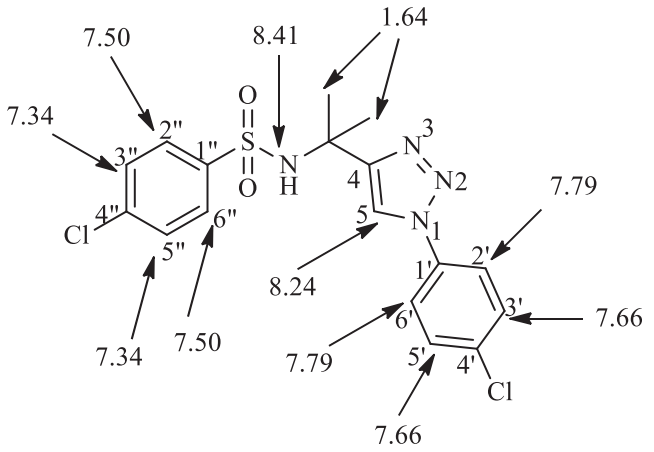


Figure 1. Chemical shift (δ) values of ^{1}H NMR of compound **6u**.

dichloromethane. After this, the terminal alkynes (**3a–3d**) were subjected to the reaction with aromatic azides (**5a–5h**), in the presence of catalytic amount of copper sulfate pentahydrate and sodium ascorbate in DMF: H_2O (8:2) to furnish desired triazoles (**6a–6z$_6$**) in good yields.

The structure of all the synthesized triazoles was established on the basis of various analytical techniques i.e., FTIR, ^{1}H and ^{13}C NMR, HRMS. The FTIR spectra of the synthesized triazoles (**6a–6z$_6$**) displayed characteristic absorption bands in the regions at 3118–3308 and 3007–3153 cm^{-1} due to the N–H and C–H stretching vibrations of triazole ring, respectively. The S=O asymmetric and symmetric stretching bands of sulfonamide were observed in the regions 1311–1342 and 1143–1161 cm^{-1} respectively. The ^{1}H NMR spectra of all the compounds, exhibited characteristic singlet due to triazolyl proton in the region δ 7.79–8.68 and the singlet due to N–H proton appeared at δ 8.33–8.99. A singlet in the region of δ 1.60–1.69 was assigned to the six protons of two aliphatic methyl groups. Moreover, in ^{13}C NMR spectra, the appearance of signals in the region of δ 141.0–143.0 and δ 119.8–121.0 assigned to C4 and C5 of triazole ring confirmed the formation of target compounds. Further, the results obtained from high-resolution mass spectrometry (HRMS) were found in accordance with theoretically predicted molecular masses. The structure of compound **6u** and **6z$_3$** was further confirmed by X-ray crystallography.

To have a better clarity between two aromatic rings present in the synthesized molecule it has been thought to utilize 2 D-NMR spectroscopy (COSY, TOCSY, HSQC and HMBC). The structure of representative molecule **6u** was further confirmed by X-ray crystallography study.

FTIR spectrum of **6u** displayed absorption at 3142 (N–H str.), 3086 (C–H str., triazole ring), 2985 (C–H str., aliphatic), 1546, 1454 (C=C str., aromatic ring), 1323 (S=O asym. str., sulfonamide), 1143 (S=O sym. str., sulfonamide) cm $^{-1}$. ^{1}H NMR spectrum of **6u** (Figure 1) exhibited one proton singlet in the most downfield region centered at δ 8.44 was expediently assigned to N–H and another one proton singlet at δ 8.25 due to C_5–H. Four doublets at 7.79, 7.66, 7.50, 7.34 each integrating for two protons were assigned to $C_{2'}$, $C_{3'}$, $C_{2''}$ and $C_{3''}$ respectively and another singlet at δ 1.64 due to six

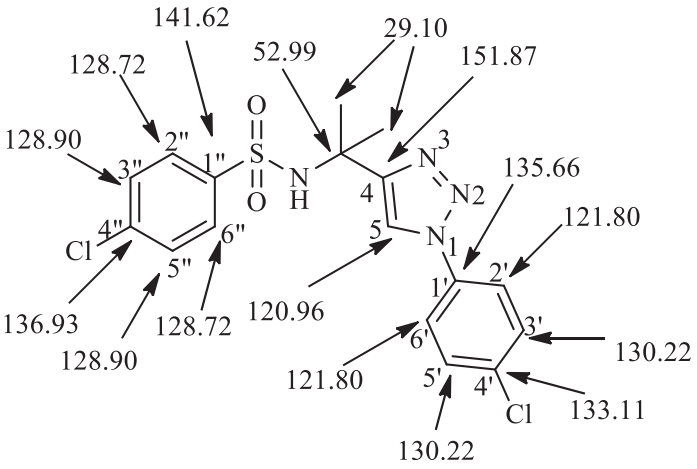


Figure 2. Chemical shift (δ) values of ^{13}C NMR of compound **6u**.

protons of –**C**$(CH_3)_2$. The ^{13}C NMR spectrum of **6u** (Figure 2) exhibited a signal in the most downfield region at δ 151.87 ppm, which was safely attributed to C_4 of the triazole ring. The peak in the most shielded region at 29.10 ppm was assigned to –C(**C**$H_3)_2$ and another peak at 52.99 ppm was attributed to the –**C**$(CH_3)_2$. 135-DEPT spectrum of compound **6u** confirmed the presence five carbon signal of methine and one carbon signal of methyl carbon. These assignments were further confirmed by 2 D NMR spectral studies i.e., ^{1}H–^{1}H COSY, TOCSY, ^{1}H –^{13}C HSQC and HMBC. The ^{1}H–^{1}H correlations between δ 7.79 ($C_{2'}$–H) and 7.66 ($C_{3'}$–H); δ 7.50 ($C_{2''}$–H) and δ 7.34 ($C_{3''}$–H) were established through COSY spectrum. The HSQC experiments revealed the assignment of carbon signals at 121.80 ($C_{2'}$), 130.22 ($C_{3'}$), 128.72 ($C_{2''}$), 128.90 ($C_{3''}$), 120.96 (C_5), 29.10 [–C(**C**$H_3)_2$] because the key correlation (^{1}H–^{13}C) was observed as: d 7.79 ($C_{2'}$–H)/dC 121.80 ($C_{2'}$); dH 7.66 ($C_{3'}$–H)/dC 130.22 ($C_{3'}$), dH 7.50 ($C_{2''}$–H)/dC 128.72 ($C_{2''}$), dH 7.34 ($C_{3''}$–H)/dC 128.90 ($C_{3''}$), dH 8.25 (C_5–H)/dC 120.96 (C_5) and dH 1.64 –C(**C**$H_3)_2$/dC 29.10. Heteronuclear Multiple Bond Correlation (HMBC) experiment reflected the linkage involving hydrogen with other carbons through multiple bond correlation of signals at δ 1.64–29.1, 52.9, 151.8 (C_4); δ 8.24–29.1, 52.9, 151.8; δ 7.50–136.9, 128.72, 141.6 ($C_{1''}$); δ 7.34–136.9, 128.72, 141.6 ($C_{1''}$). Additionally, HMBC and 135-DEPT spectra of **6u** proved helpful toward chemical shift assignments of proton and carbon signals. Further HRMS analysis result of **6u** was found in full agreement with its molecular weight (vide experimental).

X-ray crystallographic study

Single crystals of 4-chloro-N-(2-(1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)propan-2-yl)benzenesulfonamide (**6u**) (Table 1; Figure 3) and 4-bromo-N-(2-(1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)propan-2-yl)benzenesulfonamide (**6z$_3$**) (Table 2; Figure 4) were grown in ethyl acetate and methanol (3:1) using the slow evaporation technique. Single crystal data for compounds **6u** and **6z$_3$** was deposited in the Cambridge Crystallographic Data Center and assigned to the CCDC 1954932 and CCDC 1954931, respectively, which is available online at www.ccdc.cam.ac.uk/conts/retrieving.html.

Table 1. Crystal data and structure refinement for 4-chloro-*N*-(2-(1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)propan-2-yl)benzenesulfonamide (**6u**).

Property	Data
Empirical formula	$C_{17}H_{16}N_4O_2SCl_2$
Formula weight	411.30
Temperature/K	293
Crystal system	Monoclinic
Space group	$P2_1/c$
a/Å	9.6248(4)
b/Å	10.5238(5)
c/Å	18.3928(10)
$\alpha/^\circ$, $\beta/^\circ$, $\gamma/^\circ$	90, 91.214(5), 90
Volume/Å^3	1862.59(16)
Z	4
ρ_{calc}g/cm^3	1.467
μ/mm^{-1}	4.357
F(000)	848.0
Crystal size/mm^3	$0.81 \times 0.75 \times 0.229$
Radiation	CuKα ($\lambda = 1.54184$)
2Θ range for data collection/$^\circ$	9.19 to 146.374
Index ranges	$-11 \leq h \leq 9$, $-8 \leq k \leq 12$, $-20 \leq l \leq 22$
Reflections collected	6953
Independent reflections	3605 [$R_{int} = 0.0966$, $R_{sigma} = 0.0939$]
Data/restraints/parameters	3605/0/238
Goodness-of-fit on F^2	1.265
Final R indexes [$I >= 2\sigma$ (I)]	$R_1 = 0.1094$, $wR_2 = 0.2827$
Final R indexes [all data]	$R_1 = 0.1310$, $wR_2 = 0.3369$

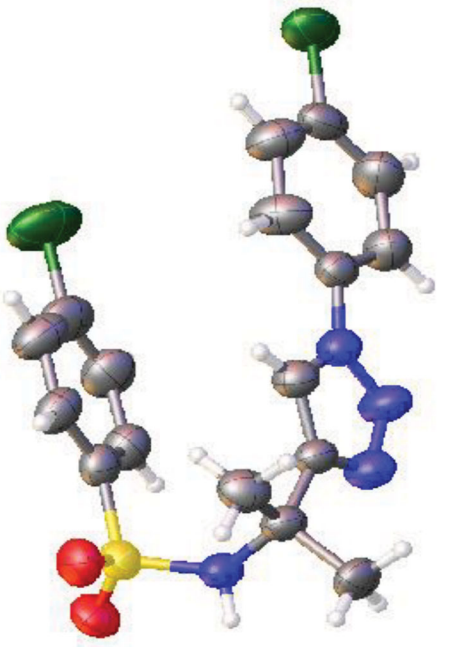


Figure 3. Crystal structure of 4-chloro-*N*-(2-(1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)propan-2-yl)benzenesulfonamide (**6u**) [CCDC 1954932].

Table 2. Crystal data and structure refinement for 4-bromo-*N*-(2-(1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)propan-2-yl)benzenesulfonamide (**6z$_3$**).

Property	Data
Empirical formula	$C_{17}H_{16}N_4O_2SClBr$
Formula weight	455.76
Temperature/K	293
Crystal system	Monoclinic
Space group	$P2_1/n$
a/Å	20.8494(13)
b/Å	10.4818(4)
c/Å	9.7097(5)
$\alpha/^\circ$ $\beta/^\circ$ $\gamma/^\circ$	90, 117.828(7), 90
Volume/Å^3	1876.5(2)
Z	4
ρ_{calc}g/cm^3	1.613
μ/mm^{-1}	5.510
F(000)	920.0
Crystal size/mm^3	$0.98 \times 0.677 \times 0.221$
Radiation	CuKα ($\lambda = 1.54184$)
2Θ range for data collection/$^\circ$	9.108 to 146.598
Index ranges	$-25 \leq h \leq 23$, $-12 \leq k \leq 12$, $-11 \leq l \leq 12$
Reflections collected	10,734
Independent reflections	3672 [$R_{int} = 0.1103$, $R_{sigma} = 0.0743$]
Data/restraints/parameters	3672/0/238
Goodness-of-fit on F^2	1.358
Final R indexes [$I >= 2\sigma$ (I)]	$R_1 = 0.1154$, $wR_2 = 0.3046$
Final R indexes [all data]	$R_1 = 0.1375$, $wR_2 = 0.3513$
Largest diff. peak/hole / e Å^{-3}	1.78/−1.15

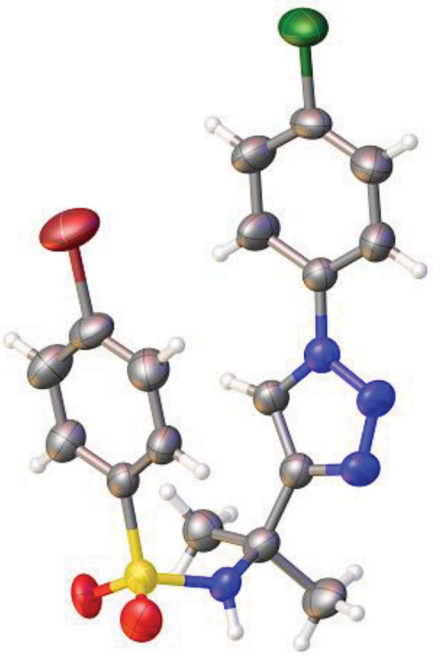


Figure 4. Crystal structure of 4-bromo-*N*-(2-(1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)propan-2-yl)benzenesulfonamide (**6z$_3$**) [CCDC 1954931].

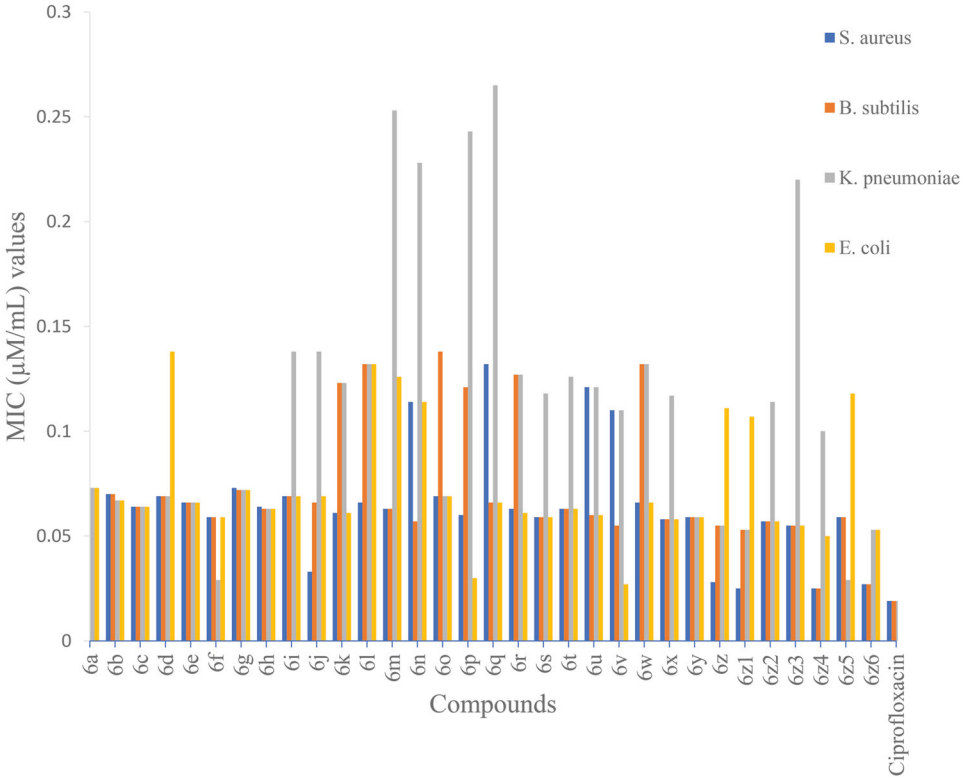


Figure 5. In vitro antibacterial activity of the synthesized compounds (**6a–6z$_6$**) in terms of Minimum inhibitory concentration (MIC) (μmol/mL).

Antibacterial activity

All the synthesized compounds were assessed for *in vitro* antibacterial activity against *S. aureus, B. subtilis, K. pneumoniae, E. coli*. Antibacterial activities of synthesized compounds were evaluated by following the procedure reported by Kaushik et al.[39] Minimum Inhibitory Concentration (MIC) is reflected in μmol/mL as presented in Figure 5 and Table 3. Ciprofloxacin was used as a standard drug.

Among the synthesized series, the compounds **6j** (MIC 0.033)**, 6z** (MIC 0.028), **6z$_1$** (MIC 0.025), **6z$_4$** (MIC 0.025), **6z$_6$** (MIC 0.027 μM/mL) against *S. aureus*, compounds **6z** (MIC 0.028), **6z$_4$** (MIC 0.025) and **6z$_6$** (MIC 0.027) against B. subtilis, compounds **6f** (MIC 0.029) and **6z$_5$** (MIC 0.029) against *K. pneumoniae*, compounds **6p** (MIC 0.030) and **6v** (MIC 0.027) against *E. coli*. exhibited significant antibacterial activity in comparison to reference drug.

It has been observed that the antibacterial is quite influenced by the nature of the substituent present on triazole ring. The antibacterial data in Table 3 showed that all the tested compounds exhibited a marked degree of activity against all the tested bacterial strain compared with standard drug. Structure with relation to biological activity reflected that substitution of aromatic ring hydrogen attached to nitrogen of triazole ring increases the antibacterial activity in most of the cases. The presence of bromo group on the aromatic ring attached to the nitrogen of triazole showed enhanced activity in comparison to F and Cl. The presence of nitro group on the aromatic ring attached to the N of triazole showed improved activity in

Table 3. In vitro antibacterial activity of compounds **6a–6z$_6$** (MIC in μmol/mL).

Compounds	*Staphylococcus aureus (MTCC 7443)*	*Bacillus subtilis (MTCC 441)*	*Klebsiella pneumoniae (NCDC 138)*	*Escherichia coli (MTCC1231)*
6a	0.073	0.073	0.073	0.073
6b	0.070	0.070	0.067	0.067
6c	0.064	0.064	0.064	0.064
6d	0.069	0.069	0.069	0.138
6e	0.066	0.066	0.066	0.066
6f	0.059	0.059	0.029	0.059
6g	0.073	0.072	0.072	0.072
6h	0.064	0.063	0.063	0.063
6i	0.069	0.069	0.138	0.069
6j	0.033	0.066	0.138	0.069
6k	0.061	0.123	0.123	0.061
6l	0.066	0.132	0.132	0.132
6m	0.063	0.063	0.253	0.126
6n	0.114	0.057	0.228	0.114
6o	0.069	0.138	0.069	0.069
6p	0.060	0.121	0.243	0.030
6q	0.132	0.066	0.265	0.066
6r	0.063	0.127	0.127	0.061
6s	0.059	0.059	0.118	0.059
6t	0.063	0.063	0.126	0.063
6u	0.121	0.060	0.121	0.060
6v	0.110	0.055	0.110	0.027
6w	0.066	0.132	0.132	0.066
6x	0.058	0.058	0.117	0.058
6y	0.059	0.059	0.059	0.059
6z	0.028	0.055	0.055	0.111
6z$_1$	0.025	0.053	0.053	0.107
6z$_2$	0.057	0.057	0.114	0.057
6z$_3$	0.055	0.055	0.220	0.055
6z$_4$	0.025	0.025	0.100	0.050
6z$_5$	0.059	0.059	0.029	0.118
6z$_6$	0.027	0.027	0.053	0.053
Ciprofloxacin	0.019	0.019	0.019	0.019

comparison to methyl group i.e., electron donating group showed better activity than electron withdrawing group. Replacement of phenyl ring attached to nitrogen of triazole with naphthyl ring also increases the activity of the compounds. Also, substituent on phenyl ring attached to sulfonamide group enhanced antibacterial potential. Bromo group on aromatic ring attached to nitrogen of sulfonamide showed better antibacterial activity than their halo counterparts.

Antioxidant activity

The *in vitro* antioxidant activity of synthesized compounds was performed spectrophotometrically using 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging assay with as standard by following the procedure reported by Shaikh et al.[40] DPPH radical scavenging procedure is a rapid and convenient assay for screening the antioxidant activities of products. Figure 6 and Table 4 summarize the radical scavenging activities of all compounds, compared to the synthetic antioxidant. Compound **6p** was found to be most active with IC_{50} value of 1.96 μM/mL. Compounds **6i, 6k, 6l, 6n** also showed good radical scavenging activity with IC_{50} value of 2.44, 2.42, 2.40, 2.64 μM/mL respectively.

Compounds containing naphthyl ring were found to exhibit diligent activity as compared to phenyl ring attached to nitrogen of triazole. Triazoles having nitro substituent

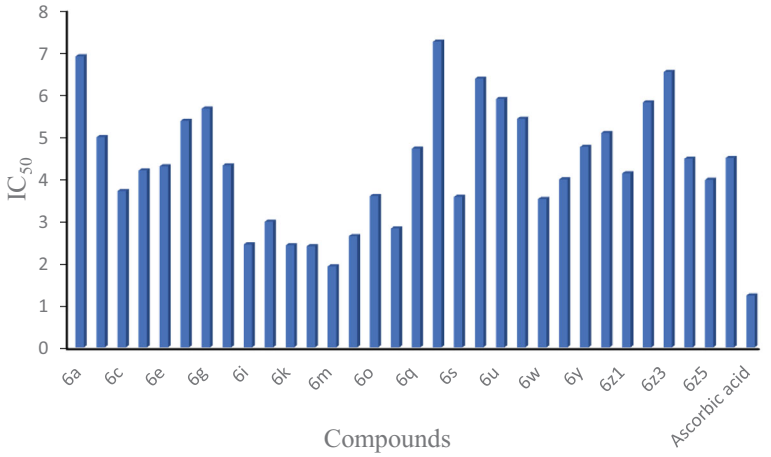


Figure 6. In vitro antioxidant activity of compounds **6a–6z$_6$** (IC_{50} value in µmol/mL).

Table 4. In vitro antioxidant activity of compounds **6a–6z$_6$** (IC_{50} value in µmol/mL).

Compound	IC_{50}	Compound	IC_{50}
6a	6.9	**6r**	7.25
6b	4.98	**6s**	3.57
6c	3.71	**6t**	6.37
6d	4.19	**6u**	5.89
6e	4.29	**6v**	5.42
6f	5.37	**6w**	3.52
6g	5.66	**6x**	3.98
6h	4.31	**6y**	4.75
6i	2.44	**6z**	5.08
6j	2.98	**6z$_1$**	4.12
6k	2.42	**6z$_2$**	5.81
6l	2.4	**6z$_3$**	6.53
6m	1.92	**6z$_4$**	4.47
6n	2.64	**6z$_5$**	3.97
6o	3.59	**6z$_6$**	4.49
6p	2.82	**Ascorbic acid**	1.23
6q	4.71		

have better inhibition as compared to methyl substituted triazoles. In case of scaffolds carrying halogens, those with fluoro substituent are more active than chloro and bromo congeners. Pyridyl derivatives showed enhanced activity as compared to phenyl group containing triazoles in most of the cases. Overall data suggested that to achieve antioxidant activity against DPPH the nature of substituent on the phenyl ring was important.

Docking studies

Antibiotics containing sulfonamide moiety inhibits dihydropteroate synthase (DHPS) which is an important enzyme in folate pathway in bacteria. These drugs compete with p-aminobenzoic acid for condensation with 6-hydroxymethyl-7,8–dihydropterin-pyrophosphate. Keeping these facts in view, compounds **6z$_4$** and **6z$_6$** with better antimicrobial activity were docked in active site of enzyme DHPS. The docked compounds along with interacting residues are shown in Figures 7 and 8. Figure 9 shows binding

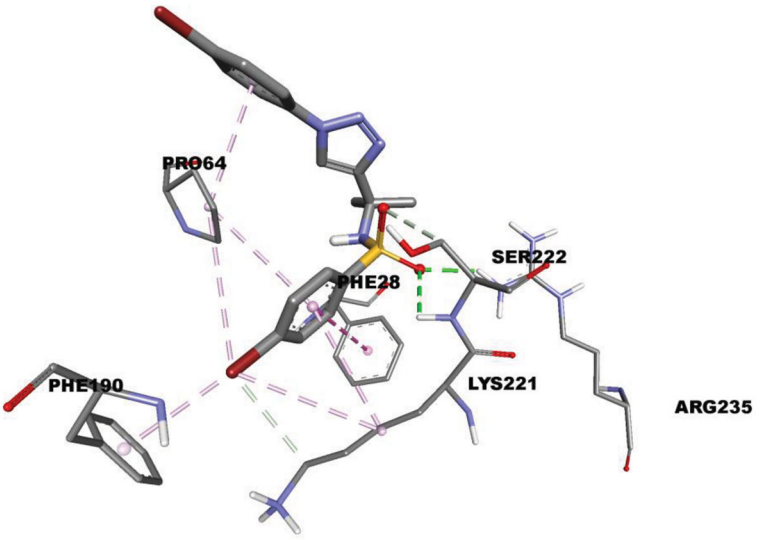


Figure 7. Interactions of compound $\mathbf{6z_4}$ with active site residues of DHPS.

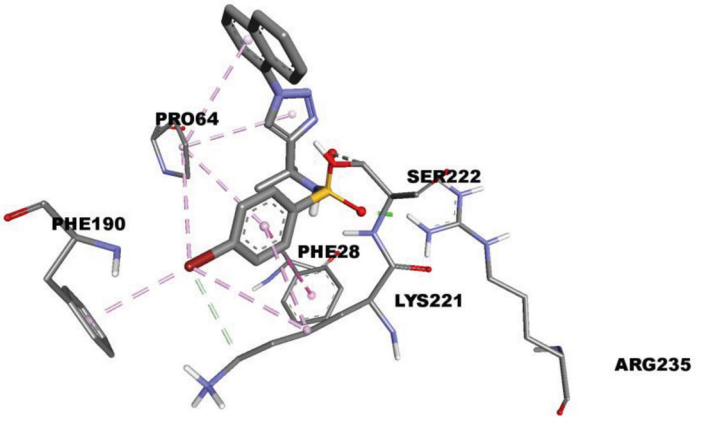


Figure 8. Interactions of compound $\mathbf{6z_6}$ with active site residues of DHPS.

interactions of co-crystallized sulfamethoxazole. One oxygen atom of sulfonamide moiety of compound $\mathbf{6z_4}$ created hydrogen bonds with Ser222 and Arg235. Bromine atom made a carbon hydrogen bond with Lys221. Bromophenyl ring attached with sulfur was involved in T-shaped pi-pi stacking interactions with Phe28. Pro64 and Phe190 were involved in hydrophobic interactions with $\mathbf{6z_4}$. Compound $\mathbf{6z_6}$ also interacted with the same residues but hydrogen bond with Ser222 was absent in this case which is crucial for binding of p-aminobenzoic acid as well as sulfonamide drugs. The binding affinity of these compounds was −6.8 kcal/mol and −6.6 kcal/mol respectively, which are also in correlation with their activity against *Staphylococcus aureus*, *Bacillus subtilis*, and *Escherichia coli*. Docked confirmation of these two compounds along with sulfamethoxazole is exhibited in cartoon diagram in Figure 10. 2 D depiction of interactions of compound (a) $\mathbf{6z_4}$ (b) $\mathbf{6z_6}$ and (c) sulfamethoxazole (SMX) with active site residues of DHPS shown in Figure 11. Detailed interactions of docked compounds are given in Table 5.

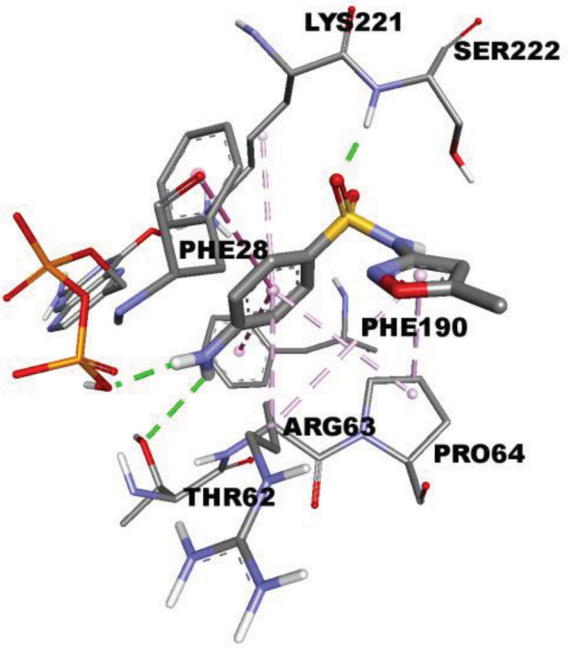


Figure 9. Interactions of sulfamethoxazoe with active site residues of DHPS.

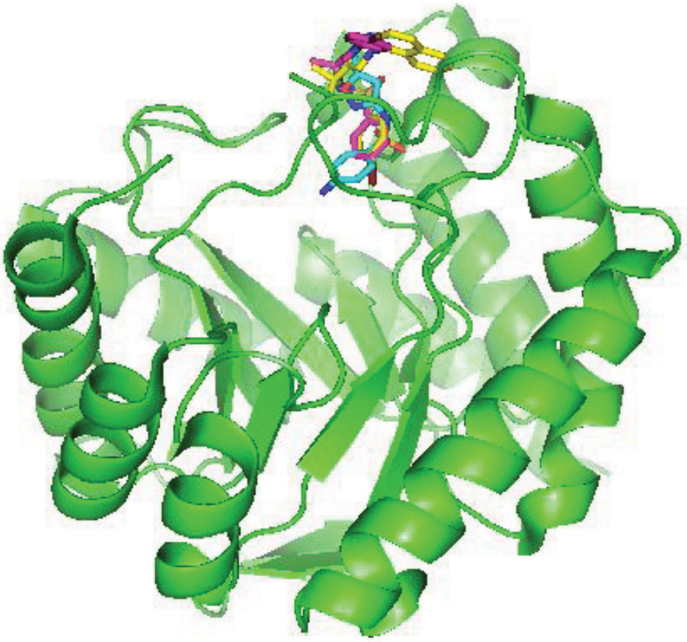


Figure 10. Docked conformation of compounds **6z$_4$** and **6z$_6$** along with co-crystallized sulfamethoxazole in DHPS.

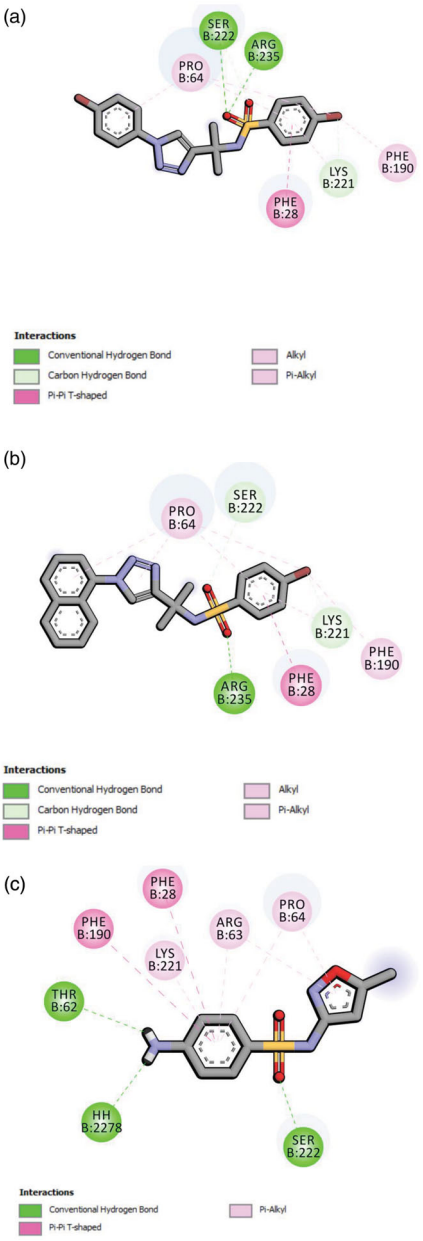


Figure 11. 2 D depiction of interactions of compound (a) **6z$_4$** (b) **6z$_6$** and (c) sulfamethoxazole (SMX) with active site residues of DHPS.

Experimental

General information

The starting materials were purchased from Sigma-Aldrich, Alfa-Aesar, Hi-Media and used without any further purification. Melting points (°C) were determined by open capillaries and are uncorrected. Analytical Thin-layer chromatography (TLC) was performed using

Table 5. Details of interactions of docked compounds.

Compound	Residue	Category of interaction	Type of interaction	Distance
6z4				
	SER222	Hydrogen Bond	Conventional Hydrogen Bond	2.90782
	ARG235	Hydrogen Bond	Conventional Hydrogen Bond	2.24872
	LYS221	Hydrogen Bond	Carbon Hydrogen Bond	3.66251
	SER222	Hydrogen Bond	Carbon Hydrogen Bond	3.22237
	PHE28	Hydrophobic	Pi-Pi T-shaped	4.80826
	PRO64	Hydrophobic	Alkyl	5.32876
	LYS221	Hydrophobic	Alkyl	4.89105
	PRO64	Hydrophobic	Pi-Alkyl	4.60217
	LYS221	Hydrophobic	Pi-Alkyl	4.55286
	PRO64	Hydrophobic	Pi-Alkyl	4.35504
	PHE190	Hydrophobic	Pi-Alkyl	3.6359
6z6				
	ARG235	Hydrogen Bond	Conventional Hydrogen Bond	1.96964
	LYS221	Hydrogen Bond	Carbon Hydrogen Bond	3.70799
	SER222	Hydrogen Bond	Carbon Hydrogen Bond	3.08307
	PHE28	Hydrophobic	Pi-Pi T-shaped	4.75137
	PRO64	Hydrophobic	Alkyl	5.1749
	LYS221	Hydrophobic	Alkyl	4.81249
	PRO64	Hydrophobic	Pi-Alkyl	4.90514
	PRO64	Hydrophobic	Pi-Alkyl	4.69767
	LYS221	Hydrophobic	Pi-Alkyl	4.55152
	PRO64	Hydrophobic	Pi-Alkyl	5.01427
	PHE190	Hydrophobic	Pi-Alkyl	3.88686
SMX				
	HH2278	Hydrogen Bond	Conventional Hydrogen Bond	2.10511
	THR62	Hydrogen Bond	Conventional Hydrogen Bond	2.7681
	SER222	Hydrogen Bond	Conventional Hydrogen Bond	1.98315
	PHE28	Hydrophobic	Pi-Pi T-shaped	5.01272
	PHE190	Hydrophobic	Pi-Pi T-shaped	5.13468
	ARG63	Hydrophobic	Pi-Alkyl	5.14762
	PRO64	Hydrophobic	Pi-Alkyl	4.94372
	LYS221	Hydrophobic	Pi-Alkyl	4.84487
	ARG63	Hydrophobic	Pi-Alkyl	5.33765
	PRO64	Hydrophobic	Pi-Alkyl	3.78151

silica gel plates (SIL G/UV254, ALUGRAM) to monitor the progress of reaction and to check the purity of compounds. The IR spectra were taken on SHIMAZDU IR AFFINITY-I FTIR spectrometer using potassium bromide (KBr) powder and values are given in cm^{-1}. Nuclear magnetic resonance (NMR) spectra were recorded on BRUKER AVANCE II instrument operating at 400 MHz (^{1}H) and 100 MHz (^{13}C), in DMSO, and chemical shifts (δ) are recorded in parts per million downfield from the internal standard trimethylsilane (TMS). Coupling constant (J) values were observed in Hertz (Hz). HRMS were observed on Bruker micro TOF Q-II spectrometer.

Procedure for synthesis of N-(2-(1-phenyl-1H-1,2,3-triazol-4-yl)propan-2-yl)benzenesulfonamide (6a)

N-(2-methylbut-3-yn-2-yl)benzenesulfonamide (**3a**) was synthesized by dropwise addition of 1,1-dimethylpropargyl amine (**2**) (1.0 mmol) to the stirred solution of benzenesulfonylchlorides (1.0 mmol) (**1a**) in dichloromethane in presence of 4-(dimethylamino)pyridine (DMAP) as base at 0–10 °C for 2–3 h.

Azidobenzene (**5a**) was synthesized by reaction of aniline (**4a**) (1.0 mmol) and dilute HCl, saturated solution of sodium nitrite was added dropwise at 0–5 °C. Stirred the content for 30 minutes, then aqueous solution of sodium azide (3.0 mmol) was added to the reaction mixture at 0–5 °C and stirred further for 2–3 h at same temperature.

Finally, N-(2-(1-phenyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl)benzenesulfonamide (**6a**) was synthesized from reaction of N-(2-methylbut-3-yn-2-yl)benzenesulfonamide (**3a**) (1.0 mmol) and Azidobenzene (**5a**) (1.0 mmol) using dimethylformamide:water (8:2) as solvent in the presence of copper sulfate pentahydrate (0.2 mmol) and sodium ascorbate (0.4 mmol) with continuous stirring at 40 °C for 4 h. Progress of the reaction was monitored by TLC, after completion of reaction, reaction mixture was quenched with ice-cold water and ammonia solution, product was extracted with ethyl acetate to get white solid product in 82% yield, mp: 152–156 °C; FTIR (KBr): ν_{max} = 3207 (N–H str.), 3026 (C–H str., triazole ring), 2881 (C–H str., aliphatic), 1504, 1456 (C=C str., aromatic ring), 1327 (S=O asym. str., sulfonamide), 1149 (S=O sym. str., sulfonamide) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (s, 1H, –NH), 8.12 (s, 1H, C-H triazole), 7.74 (d, J = 8.0 Hz, 2H), 7.59–7.55 (m, 4H), 7.47 (t, J = 8.0 Hz, 1H), 7.39–7.31 (m, 3H), 1.62 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.35 (C_4 triazole), 143.18, 137.01, 132.01, 130.22, 128.87, 126.74, 120.80 (C_5 triazole), 120.39, 53.07, 29.20; HRMS (*m/z*) calculated for $C_{17}H_{18}N_4O_2S$ $[M+H]^+$: 343.1150. Found: 343.1086.

X-ray crystallographic study

Single crystals of $C_{17}H_{16}N_4O_2SClBr$ (**6u**) and $C_{17}H_{16}N_4O_2SCl_2$ (**6z$_3$**) was selected and determined on a SuperNova, Single source at offset, Titan diffractometer. The crystal was kept at 293 K during data collection. Using Olex2,[41] the structure was solved with the ShelXT[42] structure solution program using Direct Methods and refined with the ShelXL refinement package using Least Squares minimization.

General procedure for *in vitro* antibacterial evaluation

Two Gram-positive bacterial strains: *S. aureus* (MTCC 3160), *B. subtilis* (MTCC 441) and two Gram-negative bacterial strain: *E. coli* (MTCC 443), *K. pneumoniae* (NCDC 138) were used for *in vitro* antibacterial screening of synthesized triazole derivatives by serial dilution technique.[43,44] To get the stock solution of 200 µg/mL concentration, 2.0 mg of synthesized compound was dissolved in 10 mL of DMSO. Fresh nutrient broth was used as a culture media for bacterial strains. Initially, 1 mL of nutrient broth was taken in each test tube and 1 mL of stock solution was added in one test tube to get the solution of 100 µg/mL concentration. Further, the concentration of 50–3.12 µg/ml were also obtained through serial dilution technique. After that, 0.1 mL of respective microorganism in sterile saline was inoculated in each test tube and then incubated at 37 °C for 24 h.

General procedure for *in vitro* antioxidant activity

The *in vitro* antioxidant activity of synthesized compounds was performed spectrophotometrically using 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging assay.[45] Stock solutions of the compounds (100 µg/mL) were prepared in methanol and diluted to different concentrations in the range of 20–100 µg/mL in methanol. Methanol, DPPH solution and standard drugs were used as blank, control and reference respectively. Solution of organic compounds were taken in test tubes (2 mL) and then freshly prepared DPPH solution (1 mL) (0.004 g DPPH in 100 mL methanol) was added to every test tube. The samples were kept in the dark for 30 min after which absorbance was read against a blank at 517 nm (at an absorption maximum of DPPH) with UV-Visible spectrophotometer and the percentage of scavenging activity was calculated. The percentage of radical scavenging activity (RSA %) (I %) of the tested compounds was calculated according to the following equation:

$$\text{RSA } \% = (A_0 - A_1)/A_0 \times 100$$

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

Docking

The desired protein dihydropteroate synthase (PDB ID: 3TZF) was taken from protein data bank[46] as this protein is complexed with known sulfonamide drug sulfamethoxazole and protein preparation was performed using Chimera tool.[47] The structures of small compounds were prepared and optimized with MarvinSketch[48] and results were visualized with Discovery studio[49] and PyMOL.[50] Docking studies were carried out with Autodock Vina program[51] and the docking protocols were validated by redocking of the co-crystallized ligand SMX which resulted into the conformation within 2Å RMSD of the co-crystallized conformation. These docking protocols with search box of dimensions center_x = 28.923181887, center_y = −1.2838, center_z = 9.0701, size_x = 20.0934362261, size_y = 25.0, size_z = 25.0 were used for final study.

Conclusion

In precise, we have reported a series of composite scaffold having sulfonamide tagged 1,4-disubstituted 1,2,3-triazoles obtained through Cu(I)-catalyzed click reaction of aromatic azides and sulfonamide containing alkynes. All the synthesized 1,2,3-triazoles were characterized by analytical techniques—IR, ^{1}H NMR, ^{13}C NMR and HRMS. Further, structures of compounds **6u** (CCDC 1954932) and **6z$_3$** (CCDC 1954931) were also confirmed by X-ray crystallography. Antibacterial activity of all the synthesized triazoles has been evaluated against four bacterial strains reflected moderate to good efficacy, however, the compound **6z$_4$** (MIC = 0.025 µM/mL) exhibited appreciable antibacterial activity against *B. subtilis* and *S. aureus*. Molecular docking investigation for the broadly active compound was in parallel to the in vitro antibacterial potency results. Further, the synthesized molecules were also examined for antioxidant activity,

in which compound **6m** (IC_{50} = 1.96 μM/mL) revealed best radical scavenging activity among the synthesized triazoles.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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