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ARTICLE

Synthesis, characterization, and antiplasmodial efficacy of sulfonamide-appended [1,2,3]-triazoles

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Abstract

A series of benzenesulfonamide-appended [1,2,3]-triazole hybrids was synthesized by using [3 + 2] cycloaddition of primary, secondary, and tertiary sulfonamide azides with various phenoxymethylacetylenes under click reaction conditions. After structural characterization, the compounds were subjected to *in-silico* absorption, distribution, metabolism, excretion and toxicity (ADMET) screening to evaluate their drug-likeness and other pharmacokinetic parameters. Furthermore, their in vitro antiplasmodial potential was assessed against *Plasmodium falciparum* (3D7) strain, and some of the synthesized compounds displayed promising antimalarial potency. On cytotoxicity evaluation using MTT cell viability assay, the most active candidate *N*-(4,6-dimethylpyridin-2-yl)-4-(4-(4-nitrophenoxy)methyl)-1*H*-[1,2,3]-triazol-1-yl)benzenesulfonamide (**14**; IC_{50} 6.2 μg/mL) demonstrated CC_{50} 7.5 μg/mL against human hepatocarcinoma (HUH-7) cells.

1 | INTRODUCTION

Malaria is one of the leading causes of mortality and morbidity worldwide, especially in countries of sub-Saharan Africa and Southeast Asia. This disease is caused by the parasite of genus *Plasmodium* and is transmitted by the bites of infected female *Anopheles* mosquitoes. A total of five species of *Plasmodium*, namely, *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, and *Plasmodium knowlesi*, are known to infect humans out of which *P. falciparum* is responsible for the majority of severe malaria cases and deaths worldwide. The *World Malaria Report 2018* accounted for approximately 219 million malaria cases and an estimated 435 000 deaths worldwide in the year 2017.[1] One of the primary reasons of not being able to completely abrogate the disease is the rapid emergence and dissemination of drug resistance, especially in *P. falciparum*. Historically, chloroquine was the first major primary antimalarial drug for which the resistance in *P. falciparum* emerged in the Southeast Asia and later spread to South America and Africa.[2,3] Later, *P. falciparum* became resistant to other commonly used antimalarials. To overcome the problem of drug resistance, combination therapy, particularly artemisinin combination therapy (ACT) was introduced by the World Health Organization (WHO), as the first line treatment for uncomplicated *P. falciparum* malaria,[4] which combines a fast-acting artemisinin derivative such as artesunate or artemether and slow-acting partner drug(s) such as lumefantrine or sulfadoxine-pyrimethamine.[5] However, artemisinin resistance has been knocking our doors since past few years, and reduced efficacy to artemisinin has already been witnessed from various parts of Southeast Asia[6] and India.[7] In case, artemisinin-resistant parasites spread to other parts of the world, such as sub-Saharan Africa, it can have disastrous consequences as an effective and safe transmission-blocking drug is

currently unavailable for the entire malaria-susceptible population.[8,9]

Meanwhile, continued and focused efforts should be directed towards the development of novel antiplasmodial drugs in order to overcome drug resistance and also to be one step ahead of malaria parasite. To this end, the sulfonamide scaffold, a constituent of several types of drugs collectively termed as sulfonamides or sulfa drugs, is a suitable base for the development of novel antimalarial drugs. One such sulfonamide-based antimalarial drug, sulfadoxine, is used as a part of first line ACT for malaria treatment along with artesunate and pyrimethamine.[10] Moreover, sulfadoxine, along with pyrimethamine, is also used as a first line antimalarial drug therapy in intermittent preventive treatment in pregnancy.[10] Apart from sulfadoxine, sulfadiazine and sulfalene are also available in the market as antimalarial drugs in which sulfonamide group is directly linked to a six-membered nitrogen heterocycle (Figure 1).[11] Besides, the sulfonamide moiety is found to be a constituent of many other pharmacologically active molecules having antimicrobial,[12] antiepileptic,[13] carbonic anhydrase inhibitory,[13,14] antiprotozoal,[15] hypoglycemic,[16] diuretic,[17] anticancer,[18,19] anti-inflammatory,[19] and antiviral[19,20] properties.

However, it is hypothesized that the prospective antimalarial compounds would show similar cross-resistance patterns to other established sulfonamides such as sulfadoxine, in areas with reported sulfadoxine resistance due to the presence of the same sulfonamide moiety. So, in order to diversify the chemical structure, another molecule of significant pharmacological importance, [1,2,3]-triazole, was introduced into the structure to create a sulfonamide-triazole hybrid. [1,2,3]-Triazoles, possess multitude of medicinal properties, which includes, but not limited to, antifungal,[21] antibacterial,[22] and antitubercular properties.[23] Studies suggest that [1,2,3]-triazole group cannot only play a role of being a passive linker between two scaffolds, but [1,2,3]-triazoles can themselves act as critical constituents of antimalarials.[24,25] Therefore, hybrids based on these two distinct pharmacophores, namely, sulfonamides and [1,2,3]-triazoles, are expected to possess multiple mechanisms of action and minimum risk of development of drug resistance. In the backdrop of drug resistance, our aim was to synthesize novel hybrid compounds with two "biologically active" moieties that can act at multiple target sites and to evaluate these hybrids for their absorption, distribution, metabolism, excretion and toxicity (ADMET) profile and antiplasmodial activity. We herein report synthesis, structural characterization, and in vitro antiplasmodial activity of a panel of new benzenesulfonamide-appended [1,2,3]-triazoles.

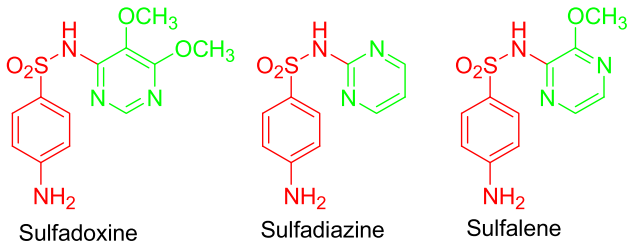


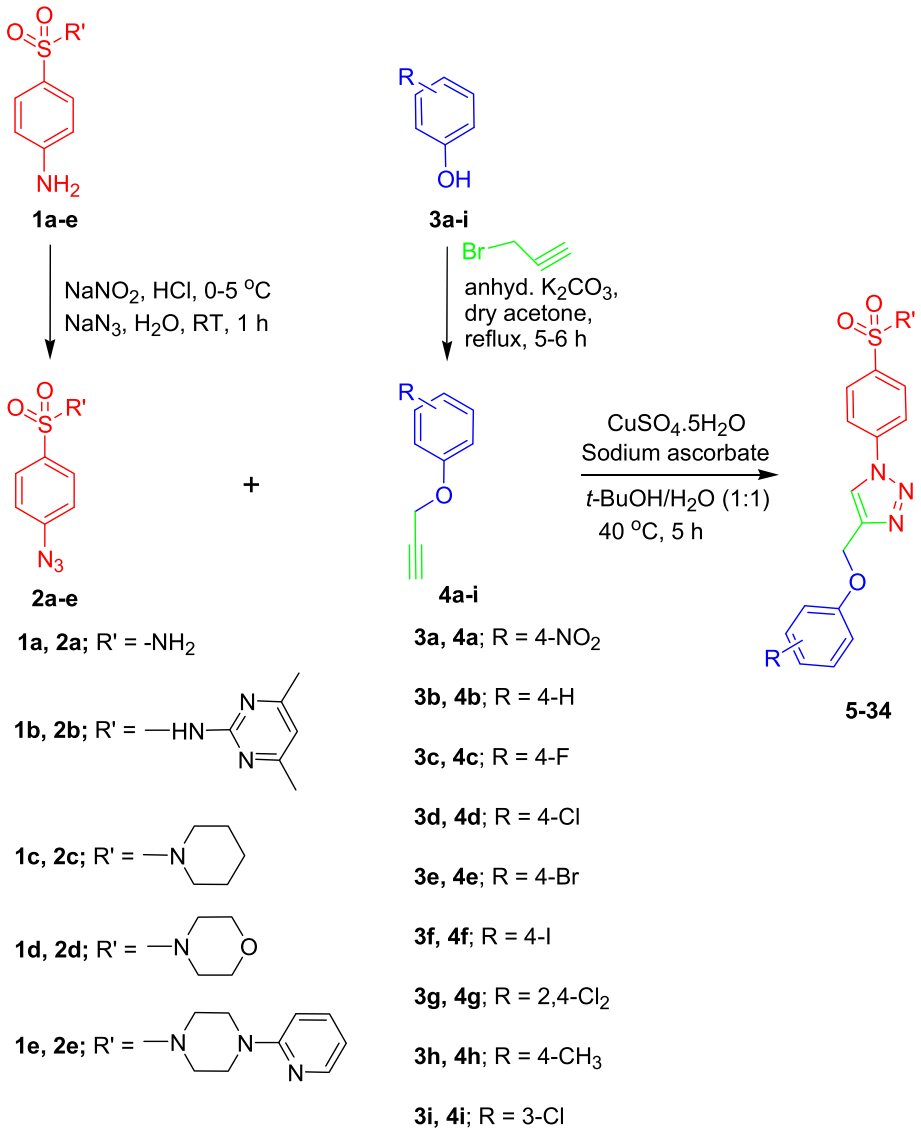
FIGURE 1 Representative examples of sulfonamide-based antimalarial drugs

2 | RESULTS AND DISCUSSION

2.1 | Synthesis and structural characterization

To synthesize a new series of benzenesulfonamide-appended [1,2,3]-triazoles (**5-34**) as antimalarials, a common approach of click chemistry has been adapted, by reacting various 4-azidobenzenesulfonamides with phenoxymethylacetylenes as depicted in Scheme 1. The sulfonamide (**1a**) and sulfamethazine (**1b**) were procured from Aldrich, and tertiary sulfonamide-based amines (**1c-e**) were synthesized by reacting 4-acetamidobenzenesulfonyl chloride with cyclic secondary amines such as piperidine, morpholine, and 1-pyridin-2-yl-piperazine in water at ambient temperature followed by the hydrolysis using concentrated hydrochloric acid at 100°C.[26,27] Further, these 4-aminobenzenesulfonamides (**1a-e**) were diazotized on treatment with $NaNO_2$ in the presence of conc. HCl at 0°C followed by the reaction with NaN_3 in water to afford the corresponding azide precursors (**2a-e**) in good yields.[28,29] In addition, phenoxymethylacetylenes (**4a-i**) have been prepared in good to excellent yields from substituted phenols after the reaction with propargyl bromide in dry acetone-containing anhydrous K_2CO_3.[30,31] Lastly, the construction of desired benzenesulfonamide-appended [1,2,3]-triazoles (**5-34**) was accomplished via Cu(I)-catalyzed Huisgen [3 + 2] cycloaddition reaction of 4-azidobenzenesulfonamides (**2a-e**) with substituted phenoxymethylacetylenes (**4a-i**) in the presence of $CuSO_4 \cdot 5H_2O$ and sodium ascorbate in 50% *t*-butanol in water at 40°C for 5 hours.[32] All the prepared products were obtained in good to excellent yields, and their structural characterization was done on the basis of spectral data analysis. The infrared (IR) spectrum of a representative compound, 1-((4-(4-(phenoxymethyl)-1*H*-1,2,3-triazol-1-yl)phenyl)sulfonyl)-piperidine (**18**) showed a characteristic absorption peak at 1242 cm^{-1} corresponding to the

SCHEME 1 Synthesis of benzenesulfonamide-appended [1,2,3]-triazoles

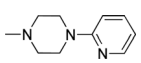


SO_2 group. In the ^{1}H NMR of compound **18**, a peak at δ 9.11 ppm was observed as a singlet due to the presence of triazole proton, whereas a singlet at δ 5.25 ppm corresponds to CH_2O protons. Also, a characteristic triplet for 4 protons at δ 2.93 ppm and two sets of multiplets in the range of δ 1.33 to 1.57 ppm for 4 and 2 protons, respectively, were assigned for the piperidine ring. The protons of aromatic ring were appeared either as doublet or triplet in the down field region between δ 8.20 and 6.96 ppm. Similarly, the characteristic peaks at δ 158.06 and 60.92 ppm in ^{13}C NMR of molecule **18** correspond to the carbons of 1,2,3-triazole and OCH_2, respectively. Additionally, the peaks at δ 46.81, 24.85, and 22.97 ppm were assigned to the carbons of the piperidine moiety. Further, the formation of the product **18** was confirmed on the basis of mass spectral analysis, which displayed $[M + H]^+$ peak at m/z 399.1485 for molecular formula $C_{20}H_{23}N_4O_3S$.

2.2 | ADMET prediction

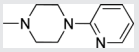
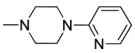
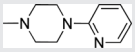
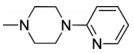
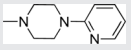
Various physically significant descriptors and pharmaceutically relevant properties such as molecular weight, lipophilicity, donor/acceptor hydrogen bonds, volume, solvent accessible surface area (SASA), percentage of human gastrointestinal (GI) absorption, Caco-2 (human epithelial colorectal adenocarcinoma), and madin-darby canine kidney (MDCK) cell permeability, aqueous solubility, human serum albumin (HSA) binding, and drug-likeness parameters of synthesized benzenesulfonamide-appended 1,2,3-triazoles were predicted by using Qikprop 3.5 module offered by Schrodinger.[33] In the context of pharmacokinetics and pharmacodynamics, lipophilicity of drug candidates is a major driving force for determining the ease of their passage through intestinal lipid bilayers and binding to the receptor targets.[34] This is determined from octanol/water partition coefficient (log

TABLE 1 Isolated yields and in vitro antiplasmodial potency of benzenesulfonamide-appended [1,2,3]-triazoles (**5-34**)

Compounds	R′	R	Yield (%)	Antiplasmodial activity (after 42 h)	
				IC_{50} (μg/mL)	IC_{50} (μM)
5	$-NH_2$	4-NO_2	70	>50	>133.31
6	**$-NH_2$**	**4-H**	**99**	**15**	**45.44**
7	**$-NH_2$**	**4-F**	**94**	**15.4**	**44.24**
8	**$-NH_2$**	**4-Cl**	**92**	**44**	**120.86**
9	$-NH_2$	4-Br	83	>50	>122.55
10	$-NH_2$	4-I	65	>50	>109.65
11	$-NH_2$	2,4-Cl_2	93	>50	>125.62
12	$-NH_2$	4-CH_3	88	>50	>145.31
13	**$-NH_2$**	**3-Cl**	**93**	**28**	**76.91**
14		**4-NO_2**	**65**	**6.2**	**12.88**
15		4-H	63	>50	>114.64
16		**2,4-Cl_2**	**56**	**16.7**	**33.13**
17		4-NO_2	90	>50	>112.83
18		4-H	82	>50	>125.58
19		4-F	73	>50	>120.15
20		4-Cl	88	>50	>115.71
21		4-Br	80	>50	>105.03
22		4-I	83	>50	>95.23
23		4-NO_2	69	>50	>112.33
24		4-H	91	>50	>124.96
25		**4-F**	**88**	**48**	**114.80**
26		4-Cl	92	>50	>115.18
27		**4-Br**	**70**	**48**	**100.41**
28		4-I	77	>50	>95.05
29		4-NO_2	65	>50	>95.94

(Continues)

TABLE 1 (Continued)

Compounds	R′	R	Yield (%)	Antiplasmodial activity (after 42 h)	
				IC_{50} (μg/mL)	IC_{50} (μM)
30		**4-H**	**72**	**48.5**	**101.85**
31		4-F	75	>50	>101.18
32		4-Cl	89	>50	>98.01
33		**4-Br**	**79**	**46**	**83.02**
34		**4-I**	**81**	**12**	**19.93**
CQ	-	-	-	0.034	0.066

Abbreviation: CQ, chloroquine.

Po/w), which is predicted to be positive and on the higher side for all the synthesized compounds. This is also evident from oral absorption profile of the compounds as all compounds demonstrated >50% human oral absorption with 4 compounds showing >90% absorption and 5 compounds showing 100% absorption through oral route. Majority of compounds were predicted to have good cell permeability profile (MDCK values and/or Caco-2 values greater than 500). Out of 30 compounds, 21 compounds were found to have no Lipinski rule[35] violation, 8 compounds showed one violation while one compound showed 2 violations (Table S1 in supporting information). All other properties such as volume, SASA, and human serum albumin binding were in the range of recommended values for the majority of compounds. Compounds were also scored according to their overall drug-likeness by ADMET compliance score (indicated by #stars), which indicates the number of properties or descriptor values which are on the outside of the 95% range of similar values for known drugs. In short, all of these compounds showed promising ADMET profile and were subsequently used for in vitro experiments.

2.3 | Biological evaluation

The antiplasmodial potential of benzenesulfonamide-appended 1,2,3-triazoles (**5-34**) was evaluated against *P. falciparum* (3D7) strain by using radioactive [^{3}H] hypoxanthine incorporation method.[36] Chloroquine was used as a positive control for our experiments. IC_{50} values (half maximal inhibitory concentration) of the tested compounds are summarized in Table 1.

Among the screened compounds, *N*-(4,-6-dimethylpyridin-2-yl)-4-(4-(4-nitrophenoxy)methyl)-1*H*-[1,2,3]-triazol-1-yl)benzene-sulfonamide (**14**) was found to be the most effective candidate against *P. falciparum* (3D7) strain with IC_{50} 6.2 μg/mL, followed by 1-((4-(4-((4-iodophenoxy)methyl)-1*H*-[1,2,3]-triazol-1-yl)-phenyl)sulfonyl)-4-(pyridine-2-yl)-piperazine (**34**; IC_{50} 12 μg/mL), 4-(4-(phenoxymethyl)-1*H*-[1,2,3]-triazol-1-yl)benzene-sulfonamide (**6**; IC_{50} 15 μg/mL), 4-(4-((4-fluorophenoxy)methyl)-1*H*-[1,2,3]-triazol-1-yl)-benzenesulfonamide (**7**; IC_{50} 15.4 μg/mL) and 4-(4-(2,4-dichlorophenoxy)methyl)-1*H*-[1,2,3]-triazol-1-yl)-*N*-(4,6-dimethyl-pyrimidin-2-yl)benzenesulfonamide (**16**; IC_{50} 16.7 μg/mL). The structure-activity relationship revealed that in case of triazoles of primary benzenesulfonamides, the presence of *p*-fluoro substituent on the phenoxymethyl moiety such as compound (**7**) increases the antimalarial potency as compared with other halogen containing molecules (**8-10**). The triazole-benzenesulfonamide conjugate (**6**), having no substitution on the phenoxymethyl group enhances the antimalarial potency as compared to the compound (**12**) containing an electron donating *p*-methylphenoxymethyl substituent on the [1,2,3]-triazole scaffold. On the contrary, secondary benzenesulfonamide based [1,2,3]-triazole (**15**) having no substitution on phenoxymethyl group was found to be inactive. However, the secondary

benzenesulfonamide-[1,2,3]-triazole hybrids (**14** and **16**) containing electron withdrawing 4-nitrophenoxymethyl- and 2,4-dichlorophenoxymethyl substituents displayed significant potency with IC_{50} 6.2 and 16.7 μg/mL, respectively. In contrast, a series of tertiary sulfonamide-[1,2,3]-triazoles (**17-22**) having a piperidine ring attached to the SO_2 group demonstrated no positive effect on the potency as all the compounds exhibited IC_{50} values >50 μg/mL. Further by replacing the piperidine with morpholine, a significant antiplasmodial activity (IC_{50} 48 μg/mL) was observed in the case of compounds (**25** and **27**) decorated with *p*-fluoro- and *p*-bromophenoxymethyl groups, respectively. In addition, the presence of 1-pyridin-2-yl-piperazine moiety along with either unsubstituted phenoxymethyl group or 4-bromo- or 4-iodophenoxymethyl groups such as in benzenesulfonamide-1,2,3-triazole hybrids (**30**, **33**, and **34)** demonstrated antiplasmodial potency in the range of IC_{50} 12 to 48.5 μg/mL. Furthermore, the most potent compound, *N*-(4,-6-dimethylpyridin-2-yl)-4-(4-(4-nitrophenoxy)methyl)-1*H*-[1,2,3]-triazol-1-yl)benzenesulfonamide (**14**) has demonstrated CC_{50} 7.5 μg/mL against human hepatocarcinoma (HUH7) cells in MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) cell viability assay.[37,38]

3 | CONCLUSIONS

In conclusion, a series of benzenesulfonamide-appended [1,2,3]-triazoles was synthesized in good to excellent yields via [3 + 2] cycloaddition reaction between primary, secondary, and tertiary sulfonamide-based azides and various phenoxymethyl-acetylenes. After spectroscopic characterization, their ADMET properties were predicted by *in silico* tools, and compounds were evaluated for their in vitro antiplasmodial activity against *P. falciparum* (3D7) strain. Majority of the compounds showed promising pharmacokinetic profiles and displayed variable antiplasmodial potency. The most active candidate (**14**) demonstrated IC_{50} and CC_{50} (human HUH7 cells) values 6.2 and 7.5 μg/mL, respectively. Although sulfonamide moiety is known to be part of some major antimalarial drugs of today (eg, sulfadoxine), *P. falciparum* has already become resistant to such drugs. Appending the sulfonamide moiety with other pharmacologically active functional groups (eg, [1,2,3]-triazoles) will result in hybrids that might surpass the drug resistance markers and might give rise to the second generation of sulfonamide-based antimalarials. Futuristic studies would definitely be aimed towards evaluating the potency of these sulfonamide based [1,2,3]-triazoles against sulfadoxine-resistant malaria parasites. The lead molecule of this study has the potential to be further investigated as the prototype for the antimalarials of the future.

4 | EXPERIMENTAL SECTION

4.1 | Chemistry

The reagents and solvents used in the synthesis of target compounds were procured from Sigma-Aldrich and Merck and utilized as received without further purification. The progress of the reactions was monitored by thin layer chromatography using silica gel 60 F_{254} (pre-coated aluminum sheets) from Merck, and the spots were visualized under ultraviolet (UV) light. The synthesized compounds were purified by column chromatography on silica gel (60-120 mesh). ^1H and ^{13}C NMR spectra were recorded in dimethyl sulfoxide (DMSO-d_6) using tetramethylsilane (TMS) as an internal standard on Jeol ECX 400 MHz nuclear magnetic resonance (NMR) spectrometer. The chemical shifts are reported in parts per million (ppm) and coupling constants (*J*) are expressed in Hertz (Hz). Infrared spectra were recorded on Perkin-Elmer IR spectrometer, and absorption maxima (ν_{max}) are given in cm^{-1}. High-resolution mass spectra were recorded on Agilent G6530 AA LC-HRMS Q-TOF system. The melting points were determined in open-capillary tubes on Buchi M-560 melting point apparatus and are uncorrected. The 4-azidobenzenesulfonamides (**2a-e**) and phenoxymethylacetylenes (**4a-i**) were synthesized according to the literature methods.[28–31]

4.2 | General synthetic protocol for benzenesulfonamide-appended [1,2,3]-triazoles (5-34)

To a suspension of 4-azidobenzenesulfonamides (**2a-e**; 0.51 mmol) and phenoxymethylacetylenes (**4a-i**; 0.56 mmol) in *t*-BuOH (8 mL) was added a solution of sodium ascorbate (0.30 mmol) in water (4 mL) followed by the addition of a solution of $CuSO_4{\cdot}5H_2O$ (0.20 mmol) in water (4 mL). The reaction mixture was stirred at 40°C under inert atmosphere for 5 hours. The completion of the reaction was monitored by TLC. After completion of the reaction, the desired products were extracted from ethyl acetate (5 × 20 mL). The organic layers were combined, washed with water (5 × 20 mL) followed by brine solution (5 × 20 mL), and dried over anhydrous Na_2SO_4. Finally, the organic solvent was evaporated to dryness under reduced pressure to afford the crude solid, which after purification on silica-gel column using ethyl acetate: hexane (7:3) as eluent, afforded the pure products in good

to excellent yields. The compounds (**5-14)** are known, and their spectral data were found to be in agreement with the reported data.[32] The characterization data of unknown sulfonamide-appended [1,2,3]-triazoles (**15-34**) are given below.

4.2.1 | *N*-(4,6-Dimethylpyrimidin-2-yl)-4-(4-(4-phenoxymethyl)-1*H*-[1,2,3]-triazol-1-yl)benzene-sulfonamide (15)

Dark brown solid; yield 65%; mp 198-200°C; IR (Nujol) ν_{max}: 3151, 1728, 1589, 1548, 1496, 1425, 1377, 1282, 1242, 1139, 1111, 1080, 981, 869, 835, 790, 754, 692, 638, 607, 569, 507 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.03 (s, 1H, triazole H), 8.16 (d, 2H, J = 8.79 Hz, ArH), 8.10 (d, 2H, J = 8.79 Hz, ArH), 7.58 (d, 1H, J = 1.46 Hz, ArH), 7.41 (d, 4H, J = 2.93 Hz, ArH), 6.74 (s, 1H, ArH), 5.35 (s, 2H, CH_2O), 2.26 (s, 6H, $2CH_3$) ppm; HRMS (ESI): Calcd for $C_{21}H_{21}N_6O_3S$: m/z 437.1390 $[M + H]^+$. Found: 437.1396.

4.2.2 | 4-(4-(2,4-Dichlorophenoxy) methyl)-1*H*-[1,2,3]-triazol-1-yl)-*N*-(4,6-dimethylpyrimidin-2-yl) benzenesulfonamide (16)

Brown solid; yield 56%; mp 189-192°C; IR (Nujol) ν_{max}: 3105, 1593, 1550, 1500, 1431, 1386, 1336, 1298, 1255, 1147, 1097, 1018, 850, 758, 700 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.03 (s, 1H, triazole H), 8.16 (d, 2H, J = 8.05 Hz, ArH), 8.09 (d, 2H, J = 8.05 Hz, ArH), 7.58 (d, 1H, J = 1.40 Hz, ArH), 7.41 (d, 2H, J = 2.93 Hz, ArH), 6.74 (s, 1H, ArH), 5.36 (s, 2H, CH_2O), 2.26 (s, 6H, $2CH_3$) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.42, 143.45, 138.90, 138.67, 129.84, 129.41, 128.11, 125.03, 123.44, 122.60, 119.82, 118.93, 115.69, 79.15, 62.15, 28.99 ppm; HRMS (ESI): Calcd for $C_{21}H_{19}N_6O_3SCl_2$: m/z 505.0611 $[M + H]^+$. Found: 505.0598.

4.2.3 | 1-((4-(4-((4-Nitrophenoxy) methyl)-1*H*-[1,2,3]-triazol-1-yl)phenyl)-sulfonyl)piperidine (17)

Off white solid; yield 90%; mp 200-202°C; IR (Film) ν_{max}: 3081, 2923, 2854, 1917, 1712, 1609, 1594, 1513, 1497, 1463, 1338, 1263, 1160, 1044, 923, 824, 750, 689 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.14 (s, 1H, triazole H), 8.24 (d, 2H, J = 8.79 Hz, ArH), 8.19 (d, 2H, J = 9.52 Hz, ArH), 7.95 (d, 2H, J = 8.79 Hz, ArH), 7.30 (d, 2H, J = 9.52 Hz, ArH), 5.45 (s, 2H, CH_2O), 2.93 (t, 4H, J = 5.13 Hz, piperidine H), 1.57-1.52 (m, 4H, piperidine H), 1.39-1.34 (m, 2H, piperidine H) ppm; HRMS (ESI): Calcd for $C_{20}H_{22}N_5O_5S$: m/z 444.1336 $[M + H]^+$. Found: 444.1336.

4.2.4 | 1-((4-(4-(Phenoxymethyl)-1*H*-[1,2,3]-triazol-1-yl)phenyl)sulfonyl)-piperidine (18)

Crimson solid; yield 82%; mp 155-157°C; IR (KBr) ν_{max}: 2939, 2855, 1598, 1339, 1242, 1163, 1044, 927, 834, 746, 607, 583 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.11 (s, 1H, triazole H), 8.20 (d, 2H, J = 8.79 Hz, ArH), 7.94 (d, 2H, J = 8.79 Hz, ArH), 7.32 (t, 2H, J = 8.05 Hz, ArH), 7.07 (d, 1H, J = 8.05 Hz, ArH), 6.96 (t, 2H, J = 8.05 Hz, ArH), 5.25 (s, 2H, CH_2O), 2.93 (t, 4H, J = 5.13 Hz, piperidine H), 1.57-1.52 (m, 4H, piperidine H), 1.39-1.33 (m, 2H, piperidine H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.06, 144.63, 139.59, 135.53, 129.82, 129.60, 123.30, 121.28, 120.83, 114.91, 60.92, 46.81, 24.85, 22.97 ppm; HRMS (ESI): Calcd for $C_{20}H_{23}N_4O_3S$: m/z 399.1485 $[M + H]^+$. Found: 399.1484.

4.2.5 | 1-((4-(4-((4-Fluorophenoxy) methyl)-1*H*-[1,2,3]-triazol-1-yl)phenyl)-sulfonyl)piperidine (19)

Light yellow solid; yield 73%; mp 178-180°C; IR (KBr) ν_{max}: 2924, 2857, 1600, 1508, 1339, 1208, 1162, 1096, 1044, 926, 823, 735, 605, 581, 507 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.09 (s, 1H, triazole H), 8.20 (d, 2H, J = 8.05 Hz, ArH), 7.94 (d, 2H, J = 8.05 Hz, ArH), 7.17-7.07 (m, 4H, ArH), 5.23 (s, 2H, CH_2O), 2.93 (t, 4H, J = 5.13 Hz, piperidine H), 1.57-1.51 (m, 4H, piperidine H), 1.39-1.33 (m, 2H, piperidine H) ppm; HRMS (ESI): Calcd for $C_{20}H_{22}FN_4O_3S$: m/z 417.1397 $[M + H]^+$. Found: 417.1385.

4.2.6 | 1-((4-(4-((4-Chlorophenoxy) methyl)-1*H*-[1,2,3]-triazol-1-yl)phenyl)-sulfonyl)piperidine (20)

Light brown solid; yield 88%; mp 191-193°C; IR (KBr) ν_{max}: 2926, 2857, 1598, 1492, 1338, 1247, 1162, 1044, 927, 822, 755, 605, 582 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.09 (s, 1H, triazole H), 8.19 (d, 2H, J = 8.79 Hz, ArH), 7.94 (d, 2H, J = 8.79 Hz, ArH), 7.35 (d, 2H, J = 8.79 Hz, ArH), 7.10 (d, 2H, J = 8.79 Hz, ArH), 5.26 (s, 2H, CH_2O), 2.93 (t, 4H, J = 5.13 Hz, piperidine H), 1.57-1.51 (m, 4H, piperidine H), 1.39-1.33 (m, 2H,

piperidine H) ppm; HRMS (ESI): Calcd for $C_{20}H_{22}ClN_4O_3S$: m/z 433.1096 $[M + H]^+$. Found: 433.1093.

4.2.7 | 1-((4-(4-((4-Bromophenoxy) methyl)-1*H*-[1,2,3]-triazol-1-yl)phenyl)-sulfonyl)piperidine (21)

Light yellow solid; yield 80%; mp 163-165°C; IR (KBr) ν_{max}: 2941, 2856, 1598, 1490, 1338, 1248, 1163, 1044, 927, 774, 603, 582 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.07 (s, 1H, triazole H), 8.19 (d, 2H, J = 8.79 Hz, ArH), 7.94 (d, 2H, J = 8.79 Hz, ArH), 7.47 (d, 2H, J = 8.79 Hz, ArH), 7.05 (d, 2H, J = 8.79 Hz, ArH), 5.26 (s, 2H, CH_2O), 2.93 (t, 4H, J = 5.13 Hz, piperidine H), 1.57-1.51 (m, 4H, piperidine H), 1.39-1.32 (m, 2H, piperidine H) ppm; HRMS (ESI): Calcd for $C_{20}H_{22}BrN_4O_3S$: m/z 477.0591 $[M + H]^+$. Found: 477.0582 and 479.0566 [(M + H) + 2].

4.2.8 | 1-((4-(4-((4-Iodophenoxy)methyl)-1*H*-[1,2,3]-triazol-1-yl)phenyl)-sulfonyl) piperidine (22)

Yellow solid; yield 83%; mp 195-197°C; IR (KBr) ν_{max}: 2936, 2853, 1598, 1487, 1338, 1248, 1162, 1097, 1043, 928, 839, 811, 773, 582 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.09 (s, 1H, triazole H), 8.19 (d, 2H, J = 8.79 Hz, ArH), 7.94 (d, 2H, J = 8.79 Hz, ArH), 7.61 (d, 2H, J = 8.79 Hz, ArH), 6.93 (d, 2H, J = 8.79 Hz, ArH), 5.25 (s, 2H, CH_2O), 2.93 (t, 4H, J = 5.13 Hz, piperidine H), 1.57-1.51 (m, 4H, piperidine H), 1.38-1.32 (m, 2H, piperidine H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.03, 144.33, 139.63, 138.57, 135.64, 129.68, 123.50, 120.96, 117.91, 84.04, 61.16, 46.90, 24.93, 23.06 ppm; HRMS (ESI): Calcd for $C_{20}H_{22}IN_4O_3S$: m/z 525.0452 $[M + H]^+$. Found: 525.0446.

4.2.9 | 4-((4-(4-((4-Nitrophenoxy) methyl)-1*H*-[1,2,3]-triazol-1-yl)phenyl)-sulfonyl)morpholine (23)

Light brown solid; yield 69%; mp 227-229°C; IR (KBr) ν_{max}: 2918, 2867, 1595, 1507, 1341, 1267, 1161, 1108, 1044, 949, 832, 747, 595, 538 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.13 (s, 1H, triazole H), 8.22 (brs, 4H, ArH), 7.95 (d, 2H, J = 8.79 Hz, ArH), 7.30 (d, 2H, J = 8.79 Hz, ArH), 5.44 (s, 2H, CH_2O), 3.63 (brs, 4H, morpholine H), 2.92 (brs, 4H, morpholine H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.24, 143.56, 134.39, 129.82, 126.08, 123.74, 122.34, 120.94, 115.55, 65.39, 61.82, 46.03 ppm; HRMS (ESI): Calcd for $C_{19}H_{20}N_5O_6S$: m/z 446.1129 $[M + H]^+$. Found: 446.1110.

4.2.10 | 4-((4-(4-Phenoxymethyl)-1*H*-[1,2,3]-triazol-1-yl)phenyl)sulfonyl)-morpholine (24)

Crimson solid; yield 91%; mp 163-165°C; IR (KBr) ν_{max}: 2976, 2864, 1596, 1492, 1350, 1251, 1165, 1110, 1043, 946, 750, 600, 543 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.11 (s, 1H, triazole H), 8.22 (brs, 2H, ArH), 7.95 (brs, 2H, ArH), 7.30 (brs, 2H, ArH), 7.06 (brs, 2H, ArH), 6.95 (brs, 1H, ArH), 5.26 (s, 2H, CH_2O), 3.61 (brs, 4H, morpholine H), 2.89 (brs, 4H, morpholine H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.97, 144.53, 139.78, 134.21, 129.73, 129.67, 123.23, 121.13, 120.76, 114.78, 65.35, 60.86, 45.96 ppm; HRMS (ESI): Calcd for $C_{19}H_{21}N_4O_4S$: m/z 401.1278 $[M + H]^+$. Found: 401.1274.

4.2.11 | 4-((4-(4-((4-Fluorophenoxy) methyl)-1*H*-[1,2,3]-triazol-1-yl)phenyl)-sulfonyl)morpholine (25)

Light yellow solid; yield 88%; mp 172-174°C; IR (KBr) ν_{max}: 2976, 2858, 1595, 1506, 1347, 1257, 1178, 1095, 1045, 939, 831, 761, 733, 598, 538 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.12 (s, 1H, triazole H), 8.23 (d, 2H, J = 8.70 Hz, ArH), 7.96 (d, 2H, J = 8.70 Hz, ArH), 7.17-7.07 (m, 4H, ArH), 5.24 (s, 2H, CH_2O), 3.64 (t, 4H, J = 4.58 Hz, morpholine H), 2.92 (t, 4H, J = 4.58 Hz, morpholine H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.81 (d, $^1J_{C\text{-}F}$ = 235.78 Hz), 154.27, 144.3, 139.74, 134.21, 129.70, 123.24, 120.73, 116.17 (d, $^3J_{C\text{-}F}$ = 8.63 Hz), 115.98 (d, $^2J_{C\text{-}F}$ = 23.00 Hz), 65.32, 61.53, 45.93 ppm; HRMS (ESI): Calcd for $C_{19}H_{20}FN_4O_4S$: m/z 419.1184 $[M + H]^+$. Found: 419.1178.

4.2.12 | 4-((4-(4-((4-Chlorophenoxy) methyl)-1*H*-[1,2,3]-triazol-1-yl)phenyl)-sulfonyl)morpholine (26)

Light brown solid; yield 92%; mp 180-182°C; IR (KBr) ν_{max}: 2849, 1490, 1351, 1245, 1169, 1113, 1003, 950, 826, 757, 598, 540 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.09 (s, 1H, triazole H), 8.21 (d, 2H, J = 8.79 Hz, ArH), 7.95 (d, 2H, J = 8.79 Hz, ArH), 7.34 (d, 2H, J = 8.79 Hz, ArH), 7.09 (d, 2H, J = 8.79 Hz, ArH), 5.26 (s, 2H, CH_2O), 3.63 (m, 4H, morpholine H), 2.91 (m, 4H, morpholine H)

ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.99, 144.43, 139.94, 134.52, 130.02, 129.68, 125.13, 123.58, 121.11, 116.92, 65.60, 61.41, 46.20 ppm; HRMS (ESI): Calcd for $C_{19}H_{20}ClN_4O_4S$: m/z 435.0888 $[M + H]^+$. Found: 435.0884.

4.2.13 | 4-((4-(4-((4-Bromophenoxy) methyl)-1*H*-[1,2,3]-triazol-1-yl)phenyl)-sulfonyl)morpholine (27)

Light brown solid; yield 70%; mp 190-191°C; IR (KBr) ν_{max}: 2927, 2852, 1591, 1483, 1350, 1245, 1168, 1112, 949, 824, 757, 597, 539 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.09 (s, 1H, triazole H), 8.21 (d, 2H, J = 8.79 Hz, ArH), 7.95 (d, 2H, J = 8.79 Hz, ArH), 7.47 (d, 2H, J = 8.79 Hz, ArH), 7.05 (d, 2H, J = 8.79 Hz, ArH), 5.26 (s, 2H, CH_2O), 3.63 (m, 4H, morpholine H), 2.92 (m, 4H, morpholine H) ppm; HRMS (ESI): Calcd for $C_{19}H_{20}BrN_4O_4S$: m/z 479.0383 $[M + H]^+$. Found: 479.0372 and 481.0360 [(M + H) + 2].

4.2.14 | 4-((4-(4-((4-Iodophenoxy) methyl)-1*H*-[1,2,3]-triazol-1-yl)phenyl)-sulfonyl)morpholine (28)

Light brown solid; yield 77%; mp 201-203°C; IR (KBr) ν_{max}: 2924, 1476, 1349, 1244, 1166, 1111, 948, 824, 775, 615, 596 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.09 (s, 1H, triazole H), 8.21 (d, 2H, J = 8.79 Hz, ArH), 7.95 (d, 2H, J = 8.79 Hz, ArH), 7.61 (d, 2H, J = 8.79 Hz, ArH), 6.93 (d, 2H, J = 8.79 Hz, ArH), 5.25 (s, 2H, CH_2O), 3.63 (brs, 4H, morpholine H), 2.91 (brs, 4H, morpholine H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.03, 144.38, 138.39, 134.50, 130.00, 123.57, 121.09, 117.93, 65.58, 61.15, 46.18 ppm; HRMS (ESI): Calcd for $C_{19}H_{20}IN_4O_4S$:m/z 527.0244 $[M + H]^+$. Found: 527.0236.

4.2.15 | 1-((4-(4-((4-Nitrophenoxy) methyl)-1*H*-[1,2,3]-triazol-1-yl)phenyl)-sulfonyl)-4-(pyridine-2-yl)piperazine (29)

White solid; yield 65%; mp 244-246°C; IR (Film) ν_{max}: 2922, 2853, 1722, 1592, 1463, 1341, 1260, 1164, 1097, 799, 774 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.13 (s, 1H, triazole H), 8.22 (t, 4H, J = 9.16 Hz, ArH), 8.06 (d, 1H, J = 6.87 Hz, pyridyl H), 7.98 (d, 2H, J = 8.70 Hz, ArH), 7.50 (t, 1H, J = 6.87 Hz, pyridyl H), 7.29 (d, 2H, J = 9.16 Hz, ArH), 6.80 (d, 1H, J = 8.82 Hz, pyridyl H), 6.62 (d, 1H, J = 6.87 Hz, pyridyl H), 5.43 (s, 2H, CH_2O), 3.60 (t, 4H, J = 4.58 Hz, piperazine H), 3.03 (t, 4H, J = 4.58 Hz, piperazine H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.14, 158.27, 147.55, 143.43, 141.20, 139.62, 137.78, 134.61, 129.63, 125.96, 123.62, 120.81, 115.43, 113.65, 107.52, 61.75, 45.60, 44.02 ppm; HRMS (ESI): Calcd for $C_{24}H_{24}N_7O_5S$: m/z 522.1533 $[M + H]^+$. Found: 522.1550.

4.2.16 | 1-((4-(4-(Phenoxymethyl)-1*H*-[1,2,3]-triazol-1-yl)phenyl)sulfonyl)-4-(pyridine-2-yl)piperazine (30)

Off white solid; yield 72%; mp 184-186°C; IR (Film) ν_{max}: 2916, 2852, 1594, 1491, 1349, 1314, 1246, 1161, 1043, 948, 853, 775, 749 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.09 (s, 1H, triazole H), 8.21 (d, 2H, J = 8.70 Hz, ArH), 8.06 (d, 1H, J = 5.50 Hz, pyridyl H), 7.97 (d, 2H, J = 8.70 Hz, ArH), 7.50 (t, 1H, J = 7.79 Hz, ArH), 7.31 (t, 2H, J = 7.79 Hz, ArH), 7.06 (d, 2H, J = 7.79 Hz, ArH), 6.96 (t, 1H, J = 7.79 Hz, pyridyl H), 6.80 (d, 1H, J = 8.70 Hz, pyridyl H), 6.63 (t, 1H, J = 5.50 Hz, pyridyl H), 5.24 (s, 2H, CH_2O), 3.59 (t, 4H, J = 4.58 Hz, piperazine H), 3.03 (t, 4H, J = 4.58 Hz, piperazine H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.50, 158.11, 147.77, 144.69, 139.88, 138.10, 134.72, 129.90, 123.39, 121.37, 121.01, 114.97, 113.99, 107.80, 60.95, 45.82, 44.28 ppm; HRMS (ESI): Calcd for $C_{24}H_{25}N_6O_3S$: m/z 477.1703 $[M + H]^+$. Found: 477.1696.

4.2.17 | 1-((4-(4-((4-Fluorophenoxy) methyl)-1*H*-[1,2,3]-triazol-1-yl)phenyl)-sulfonyl)-4-(pyridine-2-yl)piperazine (31)

White solid; yield 75%; mp 194-196°C; IR (Film) ν_{max}: 2854, 2636, 1506, 1349, 1203, 1161, 1041, 950, 828, 737 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.07 (s, 1H, triazole H), 8.20 (d, 2H, J = 7.33 Hz, ArH), 8.06 (d, 1H, J = 5.50 Hz, pyridyl H), 7.97 (d, 2H, J = 7.33 Hz, ArH), 7.50 (t, 1H, J = 7.79 Hz, pyridyl H), 7.15-7.05 (m, 4H, ArH), 6.79 (d, 1H, J = 7.79 Hz, pyridyl H), 6.62 (t, 1H, J = 5.50 Hz, pyridyl H), 5.22 (s, 2H, CH_2O), 3.59 (brs, 4H, piperazine H), 3.02 (brs, 4H, piperazine H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.24 (d, $^1J_{C\text{-}F}$ = 246.33 Hz), 154.40, 147.74, 144.51, 139.85, 138.06, 134.70, 129.85, 123.39, 120.97, 116.37 (d, $^3J_{C\text{-}F}$ = 8.63 Hz), 116.17 (d, $^2J_{C\text{-}F}$ = 23.00 Hz), 113.93, 107.76, 61.62, 45.80, 44.24 ppm; HRMS (ESI): Calcd for $C_{24}H_{24}FN_6O_3S$: m/z 495.1609 $[M + H]^+$. Found: 495.1599.

4.2.18 | 1-((4-(4-((4-Chlorophenoxy) methyl)-1*H*-[1,2,3]-triazol-1-yl)phenyl)-sulfonyl)-4-(pyridine-2-yl)piperazine (32)

Pale white solid; yield 89%; mp 206-208°C; IR (Film) ν_{max}: 2919, 2855, 1595, 1490, 1438, 1349, 1240, 1163, 1042, 950, 822, 772, 750 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.09 (s, 1H, triazole H), 8.20 (d, 2H, J = 8.24 Hz, ArH), 8.06 (d, 1H, J = 5.95 Hz, pyridyl H), 7.97 (d, 2H, J = 8.24 Hz, ArH), 7.52 (t, 1H, J = 7.79 Hz, pyridyl H), 7.34 (d, 2H, J = 8.70 Hz, ArH), 7.09 (d, 2H, J = 8.70 Hz, ArH), 6.83 (d, 1H, J = 7.79 Hz, pyridyl H), 6.64 (t, 1H, J = 5.95 Hz, pyridyl H), 5.25 (s, 2H, CH_2O), 3.61 (brs, 4H, piperazine H), 3.03 (brs, 4H, piperazine H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.63, 156.93, 144.33, 139.87, 138.94, 134.76, 129.89, 129.61, 125.03, 123.49, 121.03, 120.60, 116.84, 113.91, 108.53, 61.35, 45.72, 44.42 ppm; HRMS (ESI): Calcd for $C_{24}H_{24}ClN_6O_3S$: m/z 511.1314 $[M + H]^+$. Found: 511.1303.

4.2.19 | 1-((4-(4-((4-Bromophenoxy) methyl)-1*H*-[1,2,3]-triazol-1-yl)phenyl)-sulfonyl)-4-(pyridine-2-yl)piperazine (33)

Light brown solid; yield 79%; mp 216-218°C; IR (Film) ν_{max}: 1474, 1344, 1245, 1159, 1041, 947, 813, 770 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.09 (s, 1H, triazole H), 8.20 (d, 2H, J = 8.24 Hz, ArH), 8.06 (d, 1H, J = 5.50 Hz, pyridyl H), 7.97 (d, 2H, J = 8.24 Hz, ArH), 7.51 (d, 1H, J = 8.70 Hz, pyridyl H), 7.46 (d, 2H, J = 9.16 Hz, ArH), 7.04 (d, 2H, J = 9.16 Hz, ArH), 6.88 (d, 1H, J = 8.70 Hz, pyridyl H), 6.63 (t, 1H, J = 5.50 Hz, pyridyl H), 5.24 (s, 2H,CH_2O), 3.60 (brs, 4H, piperazine H), 3.02 (brs, 4H, piperazine H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.47, 157.36, 147.74, 144.27, 139.83, 138.07, 134.73, 132.48, 129.86, 123.49, 120.99, 117.35, 113.96, 112.74, 107.77, 61.26, 45.80, 44.25 ppm; HRMS (ESI): Calcd for $C_{24}H_{24}BrN_6O_3S$: m/z 555.0808 $[M + H]^+$. Found: 555.0784 and 557.0781 [M + H) + 2].

4.2.20 | 1-((4-(4-((4-Iodophenoxy) methyl)-1*H*-[1,2,3]-triazol-1-yl)phenyl)-sulfonyl)-4-(pyridine-2-yl)piperazine (34)

Light brown solid; yield 82%; mp 226-228°C; IR (Film) ν_{max}: 2856, 1593, 1481, 1436, 1352, 1315, 1278, 1244, 1163, 1120, 1093, 1041, 954, 815, 777, 748, 615, 596, 569, 441 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.09 (s, 1H, triazole H), 8.20 (d, 2H, J = 7.79 Hz, ArH), 8.06 (d, 1H, J = 4.58 Hz, pyridyl H), 7.97 (d, 2H, J = 7.79 Hz, ArH), 7.61 (d, 2H, J = 8.24 Hz, ArH), 7.50 (t, 1H, J = 7.79 Hz, pyridyl H), 6.92 (d, 2H, J = 8.24 Hz, ArH), 6.82 (d, 1H, J = 8.70 Hz, pyridyl H), 6.62 (t, 1H, J = 5.95 Hz, pyridyl H), 5.23 (s, 2H,CH_2O), 3.59 (brs, 4H, piperazine H), 3.03 (brs, 4H, piperazine H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.23, 157.77, 147.49, 144.02, 138.02, 137.95, 137.73, 134.51, 129.58, 123.25, 120.68, 117.62, 117.57, 113.61, 107.49, 60.99, 45.57, 44.00 ppm; HRMS (ESI): Calcd for $C_{24}H_{24}IN_6O_3S$: m/z 603.0700 $[M + H]^+$. Found: 603.0656.

4.3 | ADMET prediction

ADMET prediction of targeted benzenesulfonamide-appended [1,2,3]-triazoles was carried out using *Qikprop 3.5* module offered by Schrödinger.[33] *Qikprop* predicts physically significant descriptors and pharmaceutically relevant properties either individually or in batches. The procedure used for *Qikprop* is described below.

1. Structures of the compounds were sketched by *Chemdraw 8.0*/builder module of Schrödinger and saved using .mol file extension.
2. Structures were imported into the Maestro Graphical User Interface (GUI).
3. All the structures were processed using *Ligprep* tool of Maestro. "Neutralize" option was selected as *Qikprop* is unable to successfully process ligands which contain charged groups or molecules.
4. Structures were eventually processed by *Ligprep* and saved using .mae file extension for further use in *Qikprop*.
5. *Qikprop* module was selected in Maestro GUI and compounds were processed in normal mode.
6. Predicted properties were exported to Microsoft excel for further analysis.

4.3.1 | In vitro cultivation of *P. falciparum*

Cryopreserved strain 3D7 of *P. falciparum* was revived according to standard protocols and introduced into the culture. Asexual erythrocytic stages were cultivated by the procedures of Trager and Jensen with minor modifications.[39] The parasites were cultivated in RPMI-1640 medium containing 2 g/L sodium bicarbonate, 40 μg/mL gentamicin sulfate supplemented with 0.5% AlbuMAX-II. Human erythrocytes at 10% hematocrit were used to

culture the parasites, and the cultures were maintained at 37°C in the presence of mixture of gasses, 5% CO_2, 5% O_2, and 90% N_2.

4.4 | Evaluation of antimalarial activity of sulfonamide-appended [1,2,3]-triazoles (5-34) against *P. falciparum* 3D7 strain

For the evaluation of antimalarial activity, [^{3}H]-hypoxanthine incorporation inhibition assay was performed as reported earlier.[36] Chloroquine was used as a positive control. The test compounds and chloroquine were solublized in DMSO and double distilled water, respectively, and the working solutions were prepared in RPMI-1640 medium at two-fold dilutions and plated in 96 well plates (final solvent concentration <0.5%). Separate wells were prepared without the test compounds/chloroquine and used as negative control for our experiments. Asynchronous *P. falciparum* cultures suspended in 2% parasitemia and 4% final hematocrit were added to each well. After 24 hours of incubation, 20 μL of 0.2 μCi per well [^{3}H] hypoxanthine was added to each well for an additional 18 hours. At the end of incubation, the contents in each well were harvested on a glass-fiber filter mat (Whatman GF/C) using a 96-well Skatron semi-automated cell harvester. The radioactive associated nucleic acids on the filters were transferred to 5 mL of toluene-based scintillation cocktail, and radioactive counts were determined using Perkin Elmer liquid scintillation beta-counter. The IC_{50} values were determined by plotting the drug concentration against the percentage of viability of the parasites after 42 hours of growth assay period.

4.5 | Evaluation of in-vitro cytotoxicity of *N*-(4,6-dimethylpyrimidin-2-yl)-(4-(4-((4-nitrophenoxy)methyl)-1*H*-[1,2,3]-triazol-1-yl)benzenesulfonamide (14)

Cytotoxicity of the lead compound (**14**) was investigated against human hepatocarcinoma cell line (HUH7) using MTT cell viability assay as described elsewhere with certain modifications.[37,38] HUH7 cells were seeded at 6×10^3 cells per well into 96 well plate containing 100 μL of DMEM medium supplemented with 10% fetal bovine serum. The test compound was added to the wells 20 hours post-seeding to obtain a range of concentrations viz 1, 5, 10, 20, and 50 μM. After 48 hours of incubation with the test compound, 10 μL of MTT (Sigma, 5 mg/mL in phosphate-buffered saline [PBS]) was added to each well and the plates were incubated in the dark for 4 hours. The by-product (dark blue formazan) formed by viable cells was dissolved in DMSO, and absorbance was recorded at 570 nm by using a Biotek Synergy HT microplate reader. A 50% cytotoxic concentration (CC_{50}) was determined using nonlinear regression analysis. The CC_{50} obtained in μM was converted to μg/mL for further analysis.

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REFERENCES

[1] WHO. World malaria report; *World Heath* Organization, **2018**.
[2] N. J. White, *J. Clin. Invest.* **2004**, *113*, 1084.
[3] R. G. Ridley, *Nature* **2002**, *415*, 686.
[4] WHO. WHO Guidelines of Malaria Treatment 3rd Edition; *World Health Organization*, **2015**.
[5] T. K. Mutabingwa, *Acta Trop.* **2005**, *95*, 305.
[6] A. P. Phyo, E. A. Ashley, T. J. Anderson, Z. Bozdech, V. I. Carrara, K. Sriprawat, S. Nair, M. M. White, J. Dziekan, C. Ling, *Clin. Infect. Dis.* **2016**, *63*, 784.
[7] N. Mishra, K. Kaitholia, B. Srivastava, N. K. Shah, J. P. Narayan, V. Dev, S. Phookan, A. R. Anvikar, R. Rana, R. S. Bharti, *Malar. J.* **2014**, *13*, 284.
[8] I. Wadi, C. R. Pillai, A. R. Anvikar, A. Sinha, M. Nath, N. Valecha, *Malar. J.* **2018**, *17*, 11.
[9] I. Wadi, A. R. Anvikar, M. Nath, C. R. Pillai, A. Sinha, N. Valecha, *Future Med. Chem.* **2018**, *10*, 2619.
[10] A. H. Beavogui, A. A. Djimde, A. Gregson, A. M. Toure, A. Dao, B. Coulibaly, D. Ouologuem, B. Fofana, A. Sacko, M. Tekete, *Int. J. Parasitol.* **2010**, *40*, 1213.
[11] A. Ryckebusch, R. Deprez-Poulain, M. A. Debreu-Fontaine, R. Vandaele, E. Mouray, P. Grellier, C. Sergheraert, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2595.
[12] Y. Genc, R. Ozkanca, Y. Bekdemir, *Ann. Clin. Microbiol Antimicrob.* **2008**, *7*, 17.
[13] B. Masereel, S. Rolin, F. Abbate, A. Scozzafava, C. T. Supuran, *J. Med. Chem.* **2002**, *45*, 312.
[14] A. Thiry, J.-M. Dogne, C. T. Supuran, B. Masereel, *Curr. Pharm. Des.* **2008**, *14*, 661.
[15] K. Chibale, H. Haupt, H. Kendrick, V. Yardley, A. Saravanamuthu, A. H. Fairlamb, S. L. Croft, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2655.
[16] A. Loubatières, *Ann. N. Y. Acad. Sci.* **1957**, *71*, 192.
[17] V. Zubkov, T. Tsapko, I. Gritsenko, A. Zagayko, L. Galuzinskaya, *Russ. Chem. Bull.* **2012**, *61*, 1969.

[18] C. T. Supuran, A. Casini, A. Scozzafava, *Med. Res. Rev.* **2003**, *23*, 535.
[19] A. Casini, A. Scozzafava, C. T. Supuran, *Expert Opin. Ther. Pat.* **2002**, *12*, 1307.
[20] C. T. Supuran, A. Innocenti, A. Mastrolorenzo, A. Scozzafava, *Mini-Rev. Med. Chem.* **2004**, *4*, 189.
[21] N. G. Aher, V. S. Pore, N. N. Mishra, A. Kumar, P. K. Shukla, A. Sharma, M. K. Bhat, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 759.
[22] J. A. Demaray, J. E. Thuener, M. N. Dawson, S. J. Sucheck, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4868.
[23] R. P. Tripathi, A. K. Yadav, A. Ajay, S. S. Bisht, V. Chaturvedi, S. K. Sinha, *Eur. J. Med. Chem.* **2010**, *45*, 142.
[24] N. Batra, V. Rajendran, D. Agarwal, I. Wadi, P. C. Ghosh, R. D. Gupta, M. Nath, *ChemistrySelect* **2018**, *3*, 9790.
[25] I. Wadi, D. Prasad, N. Batra, K. Srivastava, A. R. Anvikar, N. Valecha, M. Nath, *ChemMedChem.* **2019**, *14*, 484.
[26] P. Wang, C. Liu, T. Sanches, Y. Zhong, B. Liu, J. Xiong, N. Neamati, G. Zhao, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4574.
[27] H. Khalid, M. Aziz-ur-Rehman, *Int. J. Pharm. Sci.* **2012**, *4*, 443.
[28] D. Prasad, N. Aggarwal, R. Kumar, M. Nath, *Indian J. Chem.* **2012**, *51B*, 731.
[29] R. X. Yao, L. Kong, Z. S. Yin, F. L. Qing, *J. Fluor. Chem.* **2008**, *129*, 1003.
[30] V. P. R. Lingam, R. Vinodkumar, K. Mukkanti, A. Thomas, B. Gopalan, *Tetrahedron Lett.* **2008**, *49*, 4260.
[31] M. Pal, K. Parasuraman, K. R. Yeleswarapu, *Org. Lett.* **2003**, *5*, 349.
[32] N. Batra, B. Roy, S. Mazumder, M. Nath, *Indian J. Chem.* **2015**, *54B*, 650.
[33] QikProp 3.5, Schrödinger, LLC, New York, NY.
[34] J. A. Arnott, S. L. Planey, *Expert Opin. Drug Discov.* **2012**, *7*, 863.
[35] C. A. Lipinski, F. Lombardo, B. W. Dominy, P. J. Feeney, *Adv. Drug Del. Rev.* **1997**, *23*, 3.
[36] V. Rajendran, C. Singh, P. C. Ghosh, *Can. J. Physiol. Pharmacol.* **2018**, *96*, 1145.
[37] T. Mosmann, *J. Immunol. Methods* **1983**, *65*, 55.
[38] F. Denizot, R. Lang, *J. Immunol. Methods* **1986**, *89*, 271.
[39] W. Trager, J. B. Jensen, *Science* **1976**, *193*, 673.

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