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Conventional and Microwave-Assisted CuAAC Synthesis of Novel Sulphadimidine–1,2,3-Triazole Hybrids: Spectral Characterization, ADMET Analysis and Antimicrobial Evaluation

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A series of novel sulphadimidine–1,2,3-triazole hybrid derivatives (**6a-o**) was synthesized through copper-catalysed azide–alkyne cycloaddition (CuAAC) reactions under both conventional and microwave-assisted conditions. The synthetic approach involved *N*-propargylation of sulphadimidine followed by regioselective cycloaddition with various aromatic azides to afford 1,4-disubstituted 1,2,3-triazole derivatives in good to excellent yields. Reaction optimization demonstrated that microwave-assisted synthesis significantly enhanced reaction efficiency by reducing reaction time from several hours to a few minutes while improving product yields up to 97%. The synthesized compounds were characterized using FT-IR, ^{1}H NMR, ^{13}C NMR, mass spectrometry and elemental analysis, confirming the successful formation of the target sulphadimidine–triazole framework. The lipophilicity and *in silico* ADMET properties of the synthesized derivatives were evaluated using the SwissADME platform. Most compounds exhibited acceptable lipophilic behaviour with moderate log P values, although high molecular weights and elevated TPSA values suggested limited oral bioavailability for certain derivatives. Antimicrobial screening revealed moderate antibacterial activity against selected bacterial strains, whereas antifungal activity was comparatively weaker. Among the tested derivatives, compounds **6b**, **6e** and **6k** demonstrated relatively improved antibacterial activity, while compound **6c** exhibited comparatively better antifungal activity against *Candida albicans*, *Aspergillus niger* and *Aspergillus clavatus*. The study demonstrates that structural modification of sulphadimidine through triazole incorporation provides promising hybrid scaffolds for further optimization toward biologically active antimicrobial agents.

Keywords: Lipophilicity, Antimicrobial activity, Sulphadimidine, Pharmacokinetic.

INTRODUCTION

Sulphadimidine is an important antimicrobial agent widely used in both human and veterinary medicine. As one of the earliest extensively studied sulphonamide antibiotics, it played a significant role in controlling bacterial infections and advancing the understanding of infectious microorganisms and disease mechanisms [1]. Most sulphadimidine derivatives exert their antibacterial activity by inhibiting dihydropteroate synthase through structural similarity to *para*-aminobenzoic acid (PABA), thereby disrupting bacterial folate metabolism and suppressing microbial growth. Although their clinical use declined after the introduction of penicillin and other antibiotics, sulphadimidine derivatives have regained considerable interest due to their synergistic antibacterial activity, particularly in combination with trimethoprim [2]. In addition, nitrogen- and sulphur-containing heterocyclic sulphadimidine derivatives have attracted significant attention in the development of novel anticancer agents owing to their diverse biological and pharmacological properties [3].

Sulphadimidine is considered a highly significant bioactive moiety [4], possessing a wide array of biological properties, including antibacterial, anti-hypertensive [5], antioxidant activity [6], anticancer [7]. Also, a large number of readily available medications containing the sulphadimidine heterocycle in their structures illustrate the importance of sulphadimidine and its derivatives in the development of innovative therapeutic drug moieties [8]. Recently, it is reported that cyclic sulphadimidine exhibits promising resistance against SARS-CoV-2 [9].

The copper-catalysed Huisgen 1,3-dipolar cycloaddition reaction between azides and terminal alkynes, commonly referred to as click chemistry, is an efficient and versatile method for the synthesis of structurally diverse 1,2,3-triazole derivatives [10,11]. In present study, the synergistic integration of bioactive sulphadimidine and 1,2,3-triazole pharmacophores was

explored through the synthesis of novel 1,4-disubstituted 1,2,3-triazole derivatives containing sulphadimidine linkages *via* Cu(I)-catalysed 1,3-dipolar cycloaddition reactions. Copper were employed as catalytic systems for the efficient synthesis of the target compounds.

The present work focuses on the rational design and synthesis of novel sulphadimidine–1,2,3-triazole hybrid molecules through CuAAC click chemistry under conventional and microwave-assisted conditions using different catalytic systems. A pharmacophore hybridization strategy combined with systematic structural modification was employed to investigate the influence of substituents on lipophilicity, ADMET properties and biological activity, while optimizing reaction efficiency and product yield through sustainable synthetic approaches. In addition to synthetic and biological investigations, the computational tools such as AutoDock and SwissADME were utilized for molecular docking, pharmacokinetic prediction, drug-likeness evaluation and medicinal chemistry assessment.

EXPERIMENTAL

Chemicals supplied by Loba, SRL, Merck, Spectrochem, Combi-Blocks and CDH, were used as received, without additional purification. Melting points were determined using electrothermal equipment with open capillaries and the values are uncorrected. Thin-layer chromatography (TLC) was performed on precoated silica gel 60 F_{254} plates from Merck. The compounds were visualised under UV light at 254-365 nm or by exposure to iodine vapour. Microwave-assisted reactions were carried out using a CEM Discover laboratory microwave synthesizer equipped with automatic temperature and pressure control systems. The reactions were performed in sealed glass vessels under controlled microwave irradiation at a power range of 120-150 W and a temperature range of 70-80 ºC with continuous magnetic stirring. Infrared spectra were recorded using the ATR technique with a Bruker ALPHA II Compact FT-IR spectrometer. ^{1}H NMR & ^{13}C NMR spectra were acquired on a Bruker Ascend spectrometer using DMSO-d_6 as the solvent at 400 MHz and 101 MHz, respectively. Mass spectra were obtained using a Waters Acquity QDa ultra mass spectrometer equipped with a direct input probe. The physico-chemical properties, lipophilicity (log Po/w) and ADMET parameters of the synthesised compounds were predicted using the Swiss-ADME online tool.

Herein, the reactions were carried out under both conventional stirring and microwave-assisted irradiation to evaluate the influence of reaction conditions on reaction efficiency, time and product yield.

General synthesis of 4-amino-*N*-(4,6-dimethylpyrimidin-2-yl)-*N*-(pro*p*-2-yn-1-yl)benzenesulphonamide (3): To synthesise of sulphadimidine (1 mmol) was dissolved in 10 mL of anhydrous DMF in a round-bottom flask. Then, (2 mmol) of K_2CO_3 was added as a base. Propargyl bromide (1.2 mmol) was subsequently introduced dropwise to the mixture while stirring continuously at room temperature (25-30 ºC). The progress of the reaction was monitored using TLC over a period of 4-6 h of stirring. Upon completion, the reaction mixture was poured into ice water to precipitate the product, which was then filtered, washed with water and dried under vacuum.

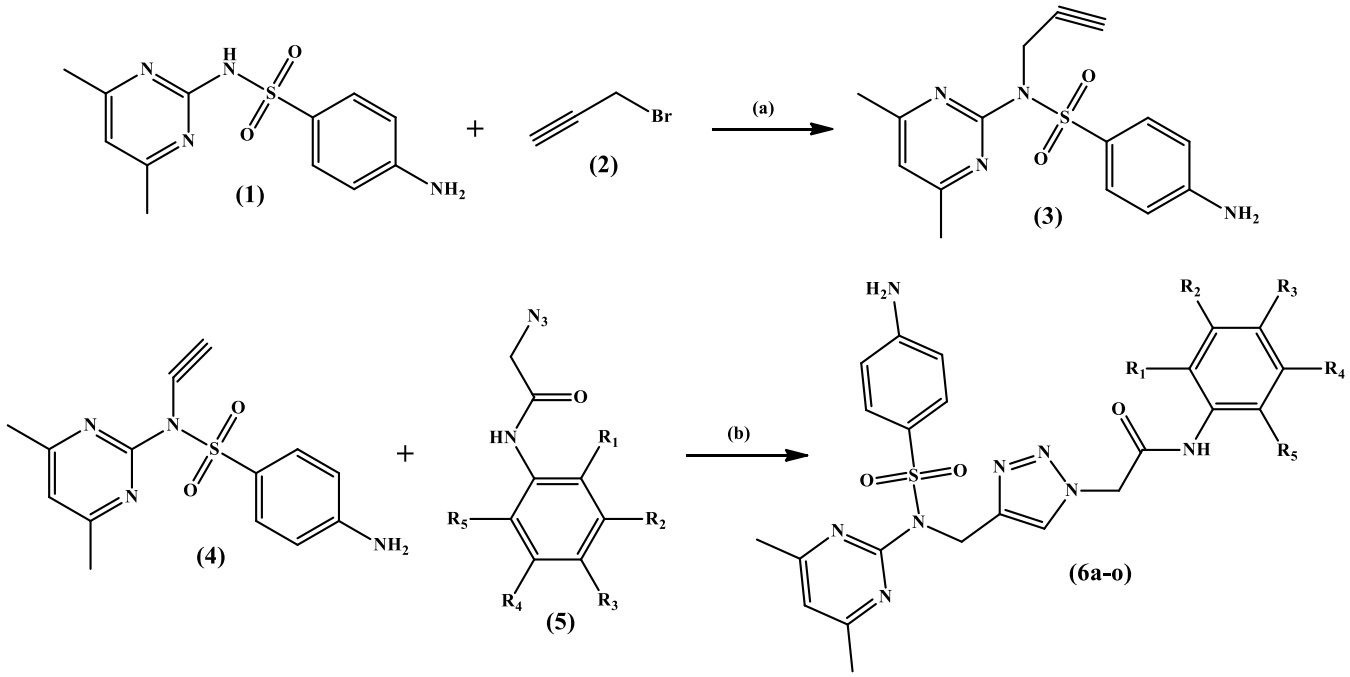
General synthesis of 2-(4-(((4-amino-*N*-(4,6-dimethylpyrimidin-2-yl)phenyl)sulphonamido)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-bromophenyl)acetamide (6): In a round bottom flask, a mixture of DMF and water (9:1 v/v) was used to dissolve 4-amino-*N*-(4,6-dimethylpyrimidin-2-yl)-*N*-(prop-2-yn-1-yl)benzenesulphonamide (**3**, 1 mmol) and 2-azido-*N*-phenylacetamide (1.2 mmol). The reaction was catalysed by adding (0.1 mmol) of $CuSO_4 \cdot 5H_2O$ and (0.2 mmol) of sodium ascorbate. The mixture was stirred at room temperature (25-30 ºC) for 6-8 h, with its progress monitored using TLC (**Scheme-I**). Upon completion, the solvent was evaporated under reduced pressure and the residue was treated with water.

2-(4-(((4-Amino-*N*-(4,6-dimethylpyrimidin-2-yl)phenyl)-sulphonamido)methyl)-1*H*-1,2,3-triazol-1-yl)-N-(*p*-tolyl)-acetamide (6a): Yield: 90%, m.p.: 244-246 ºC, IR (KBr, ν_{max}, cm^{-1}): 3361.09 (NH), 1696.38 (C=O), 1254.72 (C–O); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 10.35 (s, 1H, NH), 7.97 (s, 1H, CH), 7.62 (d, 2H, CH, *J* = 8.5 Hz), 7.47 (d, 2H, CH, *J* = 8.0 Hz), 7.14 (d, 2H, CH, *J* = 8.1 Hz), 6.82 (s, 1H, CH), 6.53 (d, 2H, CH, *J* = 8.5 Hz), 6.03 (s, 2H,CH_2), 5.43 (s, 2H, CH_2), 5.28 (s, 2H, CH_2), 2.30 (s, 6H, CH_3), 2.26 s (3H,CH_3). ^{13}C NMR (101 MHz, DMSO-d_6, δ ppm): 167.51, 164.46, 157.37, 153.58, 136.42, 133.14, 131.75, 129.77, 126.10, 124.98, 119.64, 114.57, 112.02, 52.52, 41.13, 23.70, 20.92; Mass: *m/z* 506.59 $[M + H]^+$. Elemental anal. of $C_{24}H_{26}N_8O_3S$ (*m.w.* 506.59): calcd. (found) %: C, 56.93 (56.90); H, 5.22 (5.17); N, 22.18 (22.12).

2-(4-(((4-Amino-*N*-(4,6-dimethylpyrimidin-2-yl)-phenyl)sulphonamido)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-bromophenyl)acetamide (6b): Yield: 84%, m.p.: 261-263 ºC; IR (KBr, ν_{max}, cm^{-1}): 3345.81 (NH), 1661.13 (C=O), 1238.73 (C–O); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 10.60 (s, 1H, NH), 7.97 (d, 1H, CH, *J* = 8.3 Hz,), 7.57 (dt, 6H, CH, *J* = 25.3, 8.8 Hz,) 6.82 (s, 1H, CH_2), 6.52 (d, 2H, CH, *J* = 8.5 Hz,), 6.05 (s, 2H, CH_2), 5.42 (s, 2H, CH_2), 5.31 (s, 2H, CH_2), 2.89 (s, 2H, NH_2), 2.30 (s, 5H, CH_3); ^{13}C NMR (101 MHz, DMSO-d_6, δ ppm): 169.55-155.47 (m), 153.57, 135.31, 131.75, 126.19, 124.96, 121.44, 115.99, 114.57, 52.49, 41.13, 23.69. Mass: *m/z* 571.45 $[M + H]^+$. Elemental anal. of $C_{23}H_{23}BrN_8O_3S$ (*m.w.* 571.45): calcd. (found) %: C, 48.40 (48.34); H, 4.15 (4.06); N, 19.74 (19.61).

2-(4-(((4-Amino-N-(4,6-dimethylpyrimidin-2-yl)phenyl)-sulphonamido)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-fluoro-phenyl)acetamide (6c): Yield: 93%, m.p.: 269-271 ºC; IR (KBr, ν_{max}, cm^{-1}): 3351.68 (NH), 1654.11 (C=O), 1214.95 (C–O); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 10.51 (s, 1H, NH), 7.97 (d, 2H, CH, *J* = 9.4 Hz), 7.68 (s, 1H, NH_2), 7.61 (t, 3H, CH, *J* = 7.7 Hz), 7.18 (t, 2H, CH, *J* = 8.7 Hz), 6.81 (s, 1H, NH_2), 6.66 (s, 1H,CH), 6.52 (d, 1H, CH, *J* = 8.4 Hz), 6.04 (s, 2H, CH_2), 5.42 (s, 2H, CH_2), 5.30 (s, 2H, CH_2), 2.29 (s, 5H, CH_3); ^{13}C NMR (101 MHz, DMSO-d_6, δ ppm): 169.55-155.47 (m), 153.57, 135.31, 131.75, 126.19, 124.96, 121.44, 115.99, 114.57, 52.49, 41.13, 23.69. Mass: *m/z* 510.55 $[M + H]^+$. Elemental anal. of $C_{23}H_{23}FN_8O_3S$ (*m.w.* 510.55): calcd. (found) %: C, 54.16 (54.11); H, 4.59 (4.54); N, 21.98 (21.95).

2-(4-(((4-Amino-*N*-(4,6-dimethylpyrimidin-2-yl)phenyl)-sulphonamido)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-chloro-phenyl)acetamide (6d): Yield: 81%, m.p.: 245-247 ºC; IR (KBr, ν_{max}, cm^{-1}): 3389.13 (NH), 1592.72 (C=O), 1311.32



Compound	R_1	R_2	R_3	R_4	R_5	R_6
6a	-H	-H	-H	$-CH_3$	-H	-H
6b	-H	-H	-H	-Br	-H	-H
6c	-H	-H	-H	-F	-H	-H
6d	-H	-H	-H	-Cl	-H	-H
6e	-H	-H	-H	$-OCH_3$	-H	-H
6f	-H	-H	-Cl	-H	-H	-H
6g	-H	-Cl	-H	-Cl	-Cl	-H
6h	-H	-F	-H	-H	-H	-F
6i	-H	-Br	-H	-Br	-H	-Br
6j	-H	$-CH_3$	-H	$-CH_3$	-H	-H
6k	-H	$-CH_3$	-H	$-CH_3$	-H	$-CH_3$
6l	-H	-H	-H	$-NO_2$	-H	-H
6m	-H	$-NO_2$	-H	-H	-H	-H
6n	-H	-H	-Cl	-H	-H	-H
6o	-H	$-CH_3$	-H	-H	-H	$-CH_3$

Scheme-I: Synthesis of the sulfadimidine containing 1,2,3-triazoles derivatives [Reaction condition: (a) K_2CO_3, DMF, room temperature; (b) $CuSO_4$, sodium ascorbate, DMF:H_2O, room temperature]

(C–O); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 10.59 (s, 1H, NH), 7.98 (s, 1H, CH), 7.67 (d, 1H, NH_2, J = 10.6 Hz,), 7.61 (d, 4H, CH, J = 8.2 Hz), 7.40 (d, 2H, CH, J = 8.4 Hz,), 6.82 (s, 1H, CH), 6.51 (d, 2H, CH, J = 8.4 Hz), 6.04 (s, 2H, NH_2), 5.42 (s, 2H,CH_2), 5.31 (s, 2H,CH_2), 2.30 (s, 6H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6, δ ppm): 167.51, 164.95, 157.37, 153.57, 137.88, 131.75, 129.33, 127.75, 124.95, 121.20, 114.57, 112.02, 52.52, 41.11, 23.70. Mass: *m/z* 527.00 $[M + H]^+$. Elemental anal. of $C_{23}H_{23}ClN_8O_3S$ (*m.w.* 527.00): calcd. (found) %: C, 52.49 (52.42); H, (4.46) 4.40; N, 21.30 (21.26).

2-(4-(((4-Amino-N-(4,6-dimethylpyrimidin-2-yl)phenyl)-sulphonamido)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-methoxy-phenyl)acetamide (6e): Yield: 96%, m.p.: 230-232 ºC; IR (KBr, ν_{max}, cm^{-1}): 3354.04 (NH), 1683.93 (C=O), 1244.12 (C–O); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 10.31 (s, 1H, NH), 7.97 (s, 1H, CH), 7.62 (d, 2H, CH, J = 8.6 Hz), 7.55-7.44 (m, 2H, CH), 6.96-6.85 (m, 2H, CH), 6.82 (s, 1H, CH), 6.57-6.47 (m, 2H, CH), 6.04 (s, 2H, CH_2), 5.42 (s, 2H, CH_2), 5.26 (s, 2H, CH_2), 3.72 (s, 3H, CH_3), 2.30 (s, 6H, CH_3); ^{13}C NMR (101 MHz, DMSO-d_6, δ ppm): 167.51, 164.18, 157.37, 155.95, 153.58, 132.03, 131.75, 124.96, 121.18, 114.57, 114.49, 112.02, 55.62, 52.47, 41.14, 23.70. Mass: *m/z* 522.58 $[M + H]^+$. Elemental anal. of $C_{24}H_{26}N_8O_4S$ (*m.w.* 522.58): calcd. (found) %: C, 55.20 (55.16); H, 5.08 (5.02); N, 21.49 (21.44).

2-(4-(((4-Amino-N-(4,6-dimethylpyrimidin-2-yl)phenyl)-sulphonamido)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(3-chloro-phenyl) acetamide (6f): Yield: 86%, m.p.: 233-235 ºC; IR (KBr, ν_{max}, cm^{-1}): 3372.21 (NH), 1632.48 (C=O), 1204.66 (C–O); Mass: *m/z* 527.00 $[M + H]^+$. Elemental anal. of $C_{23}H_{23}ClN_8O_3S$ (*m.w.* 527.00): calcd. (found) %: C, 52.49 (52.42); H, 4.47 (4.40); N, 21.30 (21.26).

2-(4-(((4-Amino-N-(4,6-dimethylpyrimidin-2-yl)phenyl)-sulphonamido)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(2,4,5-tri-

chlorophenyl) acetamide (6g): Yield: 85%, m.p.: 253-255 ºC; IR (KBr, ν_{max}, cm^{-1}): 3347.53 (NH), 1633.91 (C=O), 1351.10 (C–O); Mass: *m/z* 595.88 $[M + H]^+$. Elemental anal. of $C_{23}H_{21}Cl_3N_8O_3S$ (*m.w.* 595.88): calcd. (found) %: C, 46.36 (46.36); H, 3.55 (3.55); N, 18.81 (18.81).

2-(4-(((4-Amino-*N*-(4,6-dimethylpyrimidin-2-yl)phenyl)-sulphonamido)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(2,6-difluorophenyl)acetamide (6h): Yield: 82%, m.p.: 263-265 ºC; IR (KBr, ν_{max}, cm^{-1}): 3367.58 (NH), 1634.57 (C=O), 1237.02 (C–O); Mass: *m/z* 528.54 $[M + H]^+$. Elemental anal. of $C_{23}H_{22}F_2N_8O_3S$ (*m.w.* 528.54): calcd. (found) %: C, 52.30 (52.27); H, 4.28 (4.20); N, 21.25 (21.20).

2-(4-(((4-Amino-N-(4,6-dimethylpyrimidin-2-yl)phenyl)-sulphonamido)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(2,4,6-tribromophenyl)acetamide (6i): Yield: 93%, m.p.: 239-241 ºC; IR (KBr, ν_{max}, cm^{-1}): 3294.53 (NH), 1599.10 (C=O), 1153.12 (C–O); Mass: *m/z* 729.25 $[M + H]^+$. Elemental anal. of $C_{23}H_{21}Br_3N_8O_3S$ (*m.w.* 729.25): calcd. (found) %: C, 37.90 (37.88); H, 2.96 (2.90); N, 15.45 (15.37).

2-(4-(((4-Amino-*N*-(4,6-dimethylpyrimidin-2-yl)phenyl)-sulphonamido)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(2,4-dimethylphenyl)acetamide (6j): Yield: 92%, m.p.: 235-237 ºC; IR (KBr, ν_{max}, cm^{-1}): 3365.57 (NH), 1641.56 (C=O), 1147.44 (C–O); Mass: *m/z* 520.61 $[M + H]^+$. Elemental anal. of $C_{25}H_{28}N_8O_3S$ (*m.w.* 520.61): calcd. (found) %: C, 57.70 (57.68); H, 5.48 (5.42); N, 21.55 (21.52).

2-(4-(((4-Amino-*N*-(4,6-dimethylpyrimidin-2-yl)phenyl)-sulphonamido)methyl)-1*H*-1,2,3-triazol-1-yl)-N-mesitylacetamide (6k): Yield: 87%, m.p.: 246-248 ºC; IR (KBr, ν_{max}, cm^{-1}): 3355.98 (NH), 1634.75 (C=O), 1152.66 (C–O); Mass: *m/z* 534.64 $[M + H]^+$. Elemental anal. of $C_{26}H_{30}N_8O_3S$ (*m.w.* 534.64): calcd. (found) %: C, 58.48 (58.41); H, 5.73 (5.66); N, 21.99 (20.96).

2-(4-(((4-Amino-*N*-(4,6-dimethylpyrimidin-2-yl)phenyl)-sulphonamido)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-nitrophenyl)acetamide (6l): Yield: 91%, m.p.: 263-265 ºC; IR (KBr, ν_{max}, cm^{-1}): 3348.23 (NH), 1632.71 (C=O), 1260.23 (C–O); Mass: *m/z* 537.56 $[M + H]^+$. Elemental anal. of $C_{23}H_{23}N_9O_5S$ (*m.w.* 537.56): calcd. (found) %: C, 51.44 (51.39); H, 4.39 (4.31); N, 23.50 (23.45).

2-(4-(((4-Amino-N-(4,6-dimethylpyrimidin-2-yl)phenyl)-sulphonamido)methyl)-1*H*-1,2,3-triazol-1-yl)-N-(2-nitrophenyl)acetamide (6m): Yield: 86%, m.p.: 276-278 ºC; IR (KBr, ν_{max}, cm^{-1}): 3352.46 (NH), 1630.44 (C=O), 1248.84 (C–O); Mass: *m/z* 537.56 $[M + H]^+$. Elemental anal. of $C_{23}H_{23}N_9O_5S$ (*m.w.* 537.56): calcd. (found) %: C, 51.44 (51.39); H, 4.39 (4.31); N, 23.50 (23.45).

2-(4-(((4-Amino-*N*-(4,6-dimethylpyrimidin-2-yl)phenyl)-sulphonamido)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(3-chloro-4-fluorophenyl)acetamide (6n): Yield: 88%, m.p.: 251-253 ºC; IR (KBr, ν_{max}, cm^{-1}): 3346.89 (NH), 1631.04 (C=O), 1142.95 (C–O); Mass: *m/z* 544.99 $[M + H]^+$. Elemental anal. of $C_{23}H_{22}ClFN_8O_3S$ (*m.w.* 544.97): calcd. (found) %: C, 50.75 (50.69); H, 4.15 (4.07); N, 20.62 (20.56).

2-(4-(((4-Amino-*N*-(4,6-dimethylpyrimidin-2-yl)phenyl)-sulphonamido)methyl)-1*H*-1,2,3-triazol-1-yl)-N-(2,6-dimethylphenyl)acetamide (6o): Yield: 84%, m.p.: 238-240 ºC; IR (KBr, ν_{max}, cm^{-1}): 3353.97 (NH), 1652.43 (C=O), 1148.59 (C–O); Mass: *m/z* 520.62 $[M + H]^+$. Elemental anal. of $C_{25}H_{28}N_8O_3S$ (*m.w.* 520.61): calcd. (found) %: C, 57.77 (57.68); H, 5.48 (5.42); N, 21.58 (21.52).

Antimicrobial activity: The antimicrobial activity of the synthesized sulphadimidine–1,2,3-triazole hybrid derivatives (**6a-o**) was evaluated using the agar well diffusion methods against selected bacterial and fungal strains [12]. The bacterial strains included *Staphylococcus aureus* and *Streptococcus pyogenes*, while antifungal activity was evaluated against *Candida albicans*, *Aspergillus niger* and *Aspergillus clavatus*. Test microorganisms were cultured in suitable nutrient media and incubated at 37 ºC for 18-24 h prior to analysis. The synthesized compounds were dissolved in DMSO to prepare stock solutions of the desired concentrations. For the agar well diffusion method, sterile nutrient agar plates were uniformly inoculated with microbial cultures using sterile cotton swabs. Wells of suitable diameter were prepared in the agar medium and filled with the compound solutions. The plates were incubated at 37 ºC for 24 h and antimicrobial activity was assessed by measuring the diameter of the inhibition zones around the wells. Chloramphenicol and griseofulvin were employed as standard antibacterial and antifungal drugs, respectively, while DMSO was used as the negative control. All antimicrobial experiments were performed in triplicate to ensure the accuracy, reliability and reproducibility of the obtained results.

ADMET Prediction: The 2D structures of the synthesised compounds were converted into simplified SMILES notation using the freely accessible SwissADME platform to evaluate their *in silico* pharmacokinetic and molecular properties [13]. The evaluated parameters included molecular weight, hydrogen bond acceptors (HBA), hydrogen bond donors (HBD), topological polar surface area (TPSA), lipophilicity (log Po/w), water solubility (log S), gastrointestinal absorption (GIA), skin permeation (log Kp), Lipinski's rule of five (RoF) and synthetic accessibility (SA).

RESULTS AND DISCUSSION

The present work focuses on the design and synthesis of novel sulphadimidine–1,2,3-triazole hybrid derivatives using CuAAC click chemistry with the objective of developing biologically active antimicrobial compounds [14]. As illustrated in **Scheme-I**, the synthetic route involved the N-propargylation of sulphadimidine using propargyl bromide and K_2CO_3 in DMF at room temperature, affording the corresponding terminal alkyne intermediate in 92% yield. The obtained alkyne was subsequently reacted with various organic azides under copper(I)-catalysed azide–alkyne cycloaddition conditions to produce a series of 1,4-disubstituted 1,2,3-triazole derivatives (**6a–o**) containing amide functionality. The Cu(I) active species was generated in situ from $CuSO_4$ and sodium ascorbate, where Cu(I) initially forms a copper acetylide intermediate with the terminal alkyne, followed by cycloaddition with the azide to generate the regioselective 1,4-disubstituted triazole framework. The high regioselectivity towards the 1,4-isomer is attributed to the stabilization of the copper acetylide intermediate and controlled orientation of the reacting species.

The synthesis of sulphadimidine-based 1,2,3-triazole derivatives (**6a-o**) was optimized by investigating the influence of

solvent systems, catalysts and reaction conditions under both conventional and microwave-assisted methods, as summarized in Table-1. Initially, reactions performed in DMF:H_2O using CuI as the catalyst under conventional conditions afforded lower yields (25-35%) with prolonged reaction times of 7-13 h (Table-1, entries 1 and 3). Under microwave irradiation, the reaction time was significantly reduced to 20-40 min with improved yields of 55-70%, indicating the positive effect of microwave-assisted heating on CuAAC efficiency. Similar behaviour was observed in *t*-BuOH:H_2O using CuI, where the yield increased from 38% under conventional conditions to 73% under microwave irradiation with a substantial reduction in reaction time (Table 1, entry 4).

A considerable improvement in reaction efficiency was observed when $CuSO_4 \cdot 5H_2O$ and sodium ascorbate were employed as the catalytic system due to the *in situ* generation of active Cu(I) species. In both DMF:H_2O and *t*-BuOH:H_2O solvent systems, the yields increased significantly under microwave-assisted conditions compared with conventional stirring. Reactions catalysed by $CuSO_4 \cdot 5H_2O$/sodium ascorbate afforded yields up to 85-94% within 12-15 min under microwave irradiation, whereas the corresponding conventional reactions required several hours (Table-1, entries 5-9). Among the catalytic systems investigated, $Cu(OAc)_2$ mixed with sodium ascorbate in DMF:H_2O exhibited the best performance, affording excellent yields of 91-97% within 10-11 min under microwave conditions compared with 87-93% after 9-10 h under conventional conditions (Table-1, entries 8 and 10).

The enhanced efficiency observed under microwave irradiation can be attributed to rapid and uniform heating, improved energy transfer and accelerated formation of the copper acetylide intermediate during the CuAAC process. The results clearly demonstrate that both the solvent system and catalyst type strongly influence the cycloaddition reaction, while microwave-assisted synthesis provides a rapid, efficient and sustainable approach for the synthesis of sulphadimidine-linked 1,2,3-triazole derivatives with higher yields and significantly reduced reaction times.

In the ^{1}H NMR spectra confirmed the presence of the key functional groups in the synthesized compounds. The NH protons of sulphonamide and amide functionalities appeared as singlets in the downfield region (~9.5-10.5 ppm), while aromatic protons resonated between ~6.5-8.0 ppm with characteristic doublet patterns corresponding to substituted aromatic rings [15]. The characteristic singlet observed at ~7.97 ppm confirmed the formation of the 1,2,3-triazole ring [16]. The methylene protons attached to nitrogen atoms appeared as singlets at ~5.43 and 6.03 ppm, whereas methyl protons resonated at ~2.26-2.30 ppm. The ^{13}C NMR spectra further supported the proposed structures. The amide carbonyl carbons appeared in the downfield region at ~165-170 ppm, while aromatic and triazole carbons resonated between ~110-145 ppm. The methylene carbons attached to nitrogen atoms were observed at ~41-53 ppm and methyl carbons appeared at ~21-24 ppm. The observed chemical shifts, splitting patterns and integration values were in good agreement with the proposed molecular structures, confirming the successful synthesis of the target sulphadimidine–triazole derivatives (**6a-o**).

Lipophilicity study: Lipophilicity is an important physicochemical property commonly expressed as the partition coefficient (C log P) between water and a nonpolar solvent such as octanol. It significantly influences the absorption, distribution, membrane permeability, solubility and overall biological activity of drug molecules [17]. The calculated C log P values of the synthesized sulphadimidine derivatives (**6a-o**) were evaluated to assess their lipophilic characteristics and drug-likeness.

Compounds with moderate C log P values (0.95-1.64), such as **6a**, **6b**, **6d**, **6f**, **6j**, **6n** and **6o**, exhibited balanced lipophilicity, which is generally favourable for oral bioavailability and membrane permeability. In contrast, compounds with higher C log P values (>2), including **6g** and **6i**, showed increased lipophilic character, which may enhance membrane permeability but could reduce aqueous solubility. Conversely, compounds **6l** and **6m** with low or negative C log P values (-0.31) displayed higher hydrophilicity, indicating improved aqueous solubility but potentially lower membrane permeability (Table-2). These results suggest that structural modifications significantly influence the lipophilic behaviour of the synthesized derivatives and may affect their pharmacokinetic properties and biological performance.

ADMET properties: In the drug development process, many potential drug candidates are often eliminated because of inadequate physico-chemical and pharmacokinetic proper-

TABLE-1
OPTIMISATION OF THE REACTION CONDITIONS FOR 2-(4-(((4-AMINO-N-(4,6-DIMETHYLPYRIMIDIN-2-YL)PHENYL)SULFONAMIDO)METHYL)-1*H*-1,2,3-TRIAZOL-1-YL)-N-(*p*-TOLYL) ACETAMIDE

Entry	Solvent	Catalyst	Conventional method		Microwave method	
			Time (h)	Yield (%)[a]	Time (min)	Yield (%)[a]
1	DMF:H_2O	CuI	7	25	40	55
2	*t*-BuOH:H_2O	$CuSO_4$, sodium ascorbate	11	28	35	68
3	DMF:H_2O	CuI	13	35	20	70
4	*t*-BuOH:H_2O	CuI	19	38	18	73
5	DMF:H_2O	$CuSO_4$, sodium ascorbate	22	46	26	82
6	*t*-BuOH:H_2O	$CuSO_4$, sodium ascorbate	28	67	15	85
7	*t*-BuOH:H_2O	$CuSO_4$, sodium ascorbate	8	73	12	88
8	DMF:H_2O	$Cu(OAc)_2$, sodium ascorbate	9	87	10	91
9	*t*-BuOH:H_2O	$CuSO_4$, sodium ascorbate	7	90	12	94
10	DMF:H_2O	$Cu(OAc)_2$, sodium ascorbate	10	93	11	97

[a]Isolated yield after crystallisation form DMF.

TABLE-2
CALCULATED LIPOPHILIC CHARACTERS
OF THE SYNTHESISED COMPOUNDS (**6a-o**)

Compounds	C log P	Compounds	C log P
6a	0.95	**6i**	2.79
6b	1.34	**6j**	1.30
6c	0.71	**6k**	1.64
6d	1.22	**6l**	-0.31
6e	0.54	**6m**	-0.31
6f	1.22	**6n**	1.32
6g	2.43	**6o**	1.30
6h	0.81		

Calculated C log P values representing the lipophilic character of the synthesised sulfadimidine derivatives (**6a-o**).

ties. The molecular weights of the synthesized derivatives ranged from 506.59 to 729.25 Da, with several compounds exceeding the recommended 500 Da limit of Lipinski's rule, which may negatively influence oral bioavailability. The lipophilicity values (log Po/w = 1.88-3.39) remained within an acceptable range, indicating a favourable balance between membrane permeability and aqueous solubility. However, relatively high TPSA values (~157-203 Å^2) and moderate to low water solubility (log S = -3.90 to -6.57) contributed to the predicted low gastrointestinal absorption for most compounds. These findings suggest that although the synthesized derivatives possess acceptable lipophilic characteristics, their high molecular weight and polarity may limit oral absorption (Table-3). Nevertheless, these compounds may still serve as promising lead molecules for further structural optimization or for development through non-oral delivery routes.

Antimicrobial activities: The synthesized derivatives (**6a-o**) exhibited moderate to weak antimicrobial activity compared with the standard drugs chloramphenicol and griseofulvin. Among the tested compounds, derivatives **6b**, **6e** and **6k** showed relatively better antibacterial activity against selected bacterial strains, although their potency remained lower than chloramphenicol (MIC = 50 μg/mL). Compound **6k** displayed comparatively broad-spectrum activity, showing improved inhibition against *S. aureus* (241 μg/mL) and *S. pyogenus* (210 μg/mL) (Table-4). The antifungal activity of the synthesised compounds was generally limited, with most derivatives exhibiting high MIC values. Among them, compound **6c** showed comparatively better antifungal activity against *C. albicans*, *A. niger* and *A. clavatus*, although its activity was still significantly lower than that of griseofulvin, which exhibited MIC values of 500 μg/mL for *C. albicans* and 100 μg/mL for *A. niger* and *A. clavatus* (Table-4).

Conclusion

In this study, a series of novel sulphadimidine-1,2,3-triazole hybrid derivatives (**6a-o**) were successfully synthesized through CuAAC click chemistry using both conventional and microwave-assisted methods. Microwave irradiation proved to be a highly efficient and sustainable synthetic method by significantly reducing reaction times and improving product yields compared with conventional conditions. The spectral characterization using FT-IR, ^{1}H NMR, ^{13}C NMR, mass spectrometry and elemental analysis confirmed the successful formation of the target triazole-linked sulphadimidine derivatives. The lipophilicity and ADMET investigations revealed that the synthesized compounds possess acceptable membrane permeability and drug-like characteristics, although the relatively high molecular weight and TPSA values may limit oral bioavailability in some cases. The biological evaluation demonstrated moderate antibacterial activity and comparatively weaker antifungal activity, indicating that the nature of substituents strongly influences antimicrobial performance. Compounds **6b**, **6e** and **6k** exhibited comparatively improved antibacterial activity, whereas compound **6c** showed better antifungal behaviour among the synthesised derivatives.

TABLE-3
PHYSICO-CHEMICAL, PHARMACOKINETIC AND MEDICINAL
CHEMISTRY PROPERTIES OF THE SYNTHESISED COMPOUNDS **6a-o**

Compound	Physicochemical properties						Pharmacokinetic		Medicinal chemistry	
	MW	HBA	HBD	TSPA	Log $P_{o/w}$	Log S	GIA	Log Kp	RoF (V)	SA
6a	506.59	7	2	157.37	2.45	-4.14	LOW	-7.95	NO	3.89
6b	571.45	7	2	157.37	2.99	-4.74	LOW	-8.12	NO	3.82
6c	510.55	8	2	157.37	2.15	-3.99	LOW	-8.16	NO	3.79
6d	527.00	7	2	157.37	2.33	-4.43	LOW	-7.89	NO	3.79
6e	522.58	8	2	166.60	2.80	-3.91	LOW	-8.33	NO	3.90
6f	527.00	7	2	157.37	2.73	-4.43	LOW	-7.89	NO	3.80
6g	595.88	7	2	157.37	3.16	-5.62	LOW	-7.41	NO	3.87
6h	528.54	9	2	157.37	2.39	-4.15	LOW	-8.20	NO	3.83
6i	729.25	7	2	157.37	2.97	-6.57	LOW	-8.09	NO	3.86
6j	520.61	7	2	157.37	2.72	-4.44	LOW	-7.78	NO	4.02
6k	534.64	7	2	157.37	3.39	-4.75	LOW	-7.60	NO	4.14
6l	537.56	9	2	203.19	1.88	-3.90	LOW	-8.52	NO	3.90
6m	537.56	9	2	203.19	1.91	-4.25	LOW	-8.13	NO	4.00
6n	544.99	8	2	157.37	2.67	-4.59	LOW	-7.93	NO	3.81
6o	520.61	7	2	157.37	2.94	-4.44	LOW	-7.78	NO	4.02
Chloramphenicol	323.13	5	3	115.38	1.17	-3.16	High	-7.46	Yes	2.78

[a]MW Molecular weight, HBA H-bond acceptor, HBD H-bond donor, TPSA-topological polar surface area, Log $P_{o/w}$-lipophilicity, Log S-water solubility, GIA- gastrointestinal absorption, Log Kp skin permeation, RoF (V)- Lipinski's rule of five, SA- synthetic.

TABLE-4
MINIMAL INHIBITORY CONCENTRATION (MIC) BIOLOGICAL ACTIVITY DATA OF SYNTHESISED COMPOUNDS (**6a-o**)

Compound	Antimicrobial activity				Antifungal activity		
	E. coli (MTCC 443)	*P. aeruginosa* (MTCC 1688)	*S. aureus* (MTCC 96)	*S. pyogenus* (MTCC 442)	*C. albicans* (MTCC 227)	*A. niger* (MTCC 282)	*A. clavatus* (MTCC 1323)
6a	112.5	130	105	98	520	980	990
6b	76	108	190	118	745	970	950
6c	138	84	235	189	1015	1025	1025
6d	92	215	114	90	465	510	495
6e	68	124	122	188	510	240	275
6f	215	143	95	134	1085	565	548
6g	108	218	117	204	268	965	945
6h	272	194	106	112	525	1015	980
6i	131	118	113	109	235	498	460
6j	81	109	196	238	482	1012	1005
6k	69	132	241	210	995	970	920
6l	102	186	88	103	476	1018	965
6m	120	266	107	129	1022	489	471
6n	205	97	133	108	498	515	495
6o	265	139	119	105	478	990	1012
Chloramphenicol	50	50	50	50	–	–	–
Griseofulvin	–	–	–	–	500	100	100

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

DECLARATION OF AI-ASSISTED TECHNOLOGIES

During the preparation of this manuscript, the authors used an AI-assisted tool(s) to improve the language. The authors reviewed and edited the content and take full responsibility for the published work.

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