

Design, Synthesis, Characterization, *In silico* Evaluation, and Antimicrobial Potential of Novel 1,3,5-Triazine-amino-benzenesulfonamide Derivatives: Part 2

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In continuation of our previous work, a series of 1,3,5-triazine-aminobenzenesulfonamide derivatives (**A13-A25**) was synthesized through sequential nucleophilic substitution reactions of cyanuric chloride and evaluated for their structural, antimicrobial and pharmacokinetic properties. The synthesized compounds were characterized by FTIR, ¹H NMR, ¹³C NMR and mass spectrometry. The spectral data supported the presence of the triazine, sulfonamide and substituted amino functionalities. The antimicrobial activity was assessed by the tube dilution method against selected Gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*), Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) and fungal strains (*Candida albicans* and *Aspergillus niger*) using trimethoprim as the reference drug. Molecular docking against dihydrofolate reductase was performed to examine the binding behaviour of the synthesized derivatives. The calculated binding affinities ranged from -8.5 to -10.2 kcal mol⁻¹, compared with -7.6 kcal mol⁻¹ for trimethoprim. Compound **A23** showed the most favourable docking score (-10.2 kcal mol⁻¹), followed by **A22** (-9.8 kcal mol⁻¹) and **A24** (-9.7 kcal mol⁻¹). SwissADME-based analysis predicted favourable gastrointestinal absorption for several derivatives, particularly **A19**, **A21** and **A22**, while most compounds showed limited BBB penetration. The ADMET profile revealed high plasma protein binding for most derivatives and variable CYP enzyme interactions.

Keywords: Antimicrobial resistance, DHFR, Molecular docking, ADMET, *In silico*.

INTRODUCTION

Heterocyclic compounds are the important medicinal chemistry scaffolds due to their structural diversity and tunable physico-chemical properties. Nitrogen-containing heterocycles are particularly valuable in drug design, as ring nitrogen atoms influence electron distribution, basicity, hydrogen bonding and molecular recognition. Strategic substitution of these rings enables optimization of molecular properties and structure-activity relationships for biological activity [1-5]. Among nitrogen-rich heterocycles, 1,3,5-triazine is a versatile medicinal chemistry scaffold owing to its electron-deficient aromatic ring and high reactivity toward nucleophilic substitution [6-8]. Its three carbon centers enable diverse functionalization, allowing systematic tuning of electronic, steric and hydrophobic properties. 1,3,5-Triazine derivatives exhibit broad biological activities, particularly antimicrobial, antifungal, anticancer and antiviral effects and have been explored extensively in the antimicrobial and antifolate research [9-12].

Sulphonamides are also the well-established pharmacophores in medicinal chemistry, with polarized S=O groups and hydrogen-bonding sites that facilitate interactions with biological targets [13,14]. Their incorporation can modulate molecular properties and target recognition, contributing to diverse antibacterial, antifungal, anti-inflammatory, anticancer and enzyme-inhibitory activities [13,15,16]. Benzene-sulfonamide is an important scaffold for enzyme-inhibitor design, particularly the carbonic anhydrase inhibitors and structural modification of its aromatic substituents enables systematic optimization of potency and selectivity [14,17]. Hybridization of the sulphonamide pharmacophore with an electron-deficient heterocycle such as 1,3,5-triazine provides a rational approach for integrating complementary molecular recognition features and exploring new antimicrobial agents [18-20].

The search for new antimicrobial chemotypes is increasingly important due to the global rise of antimicrobial resistance (AMR). Reduced susceptibility of bacterial and fungal pathogens limits therapeutic options and increases morbidity,

mortality and healthcare costs. Extensive antimicrobial use and the acquisition and spread of resistance determinants have accelerated the loss of efficacy of established agents [21,22]. The flexible 1,3,5-triazine-amino-benzenesulfonamide framework provides a tunable platform for antimicrobial research by combining the biological relevance of both pharmacophores. Substitution on the triazine ring enables systematic modulation of electronic, steric and hydrophobic properties, while the sulphonamide group contributes hydrogen-bonding and polarity features [23,24]. Correlating the antimicrobial activity with DHFR binding and predicted ADMET profiles can provide preliminary structure-activity relationships and support further optimization of this hybrid scaffold.

The present study was undertaken to synthesize a new series of 1,3,5-triazine-amino-benzenesulfonamide derivatives and investigate their structural and biological properties. The synthesized compounds were characterized by FTIR, ^1H NMR, ^{13}C NMR spectroscopy and mass spectrometry. Their potential interaction with dihydrofolate reductase was investigated by molecular docking using the selected protein structure from the Protein Data Bank, with emphasis on ligand orientation and interactions within the active-site region. The antimicrobial activity of the derivatives was evaluated by the tube dilution method against selected Gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*), Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) and fungal strains (*Aspergillus niger* and *Candida albicans*). *In silico* ADMET profiling was also carried out to assess their predicted pharmacokinetic and toxicity-related properties.

EXPERIMENTAL

All reagents and starting materials were of analytical grade and obtained from commercial suppliers including Loba Chemie Pvt. Ltd. and HiMedia Laboratories Pvt. Ltd. (New Delhi, India). Reaction progress was monitored by thin-layer chromatography (TLC) on silica gel G plates using ethyl acetate-*n*-hexane as the developing solvent system. Melting points were determined using a Sonar melting-point apparatus (Sunbim, India) and are uncorrected. ^1H NMR spectra were recorded on a Bruker 400 MHz spectrometer using DMSO as the solvent. Mass spectra were obtained using a Micromass Q-ToF Micro mass spectrometer. Antimicrobial minimum inhibitory concentration (MIC) assays were performed using a laminar airflow biosafety cabinet and a BOD incubator (Laborate Pharmaceutical India Ltd., India).

Synthesis: Cyanuric chloride (1 equiv.) was dissolved in dry acetone and cooled to 0–5 °C with stirring, followed by gradual addition of 4-aminobenzenesulfonamide (1 equiv.). The reaction was monitored by TLC using *n*-hexane/acetone (2:3) until completion. Aqueous NaOH (1.7 M) was added gradually to neutralize the liberated HCl, and the mixture was stirred for a further 10 min. The reaction mixture was poured onto crushed ice and the precipitated *N'*-(4,6-dichloro-1,3,5-triazin-2-yl)benzenesulfonamide was filtered, washed and dried under vacuum at 30–40 °C. The resulting dichlorotriazine intermediate (0.01 mol) was treated with the appropriate substituted aniline (0.01 mol) in acetone (15 mL) in the presence of K_2CO_3 or NaOH at room temperature and stirred for 5–12 h.

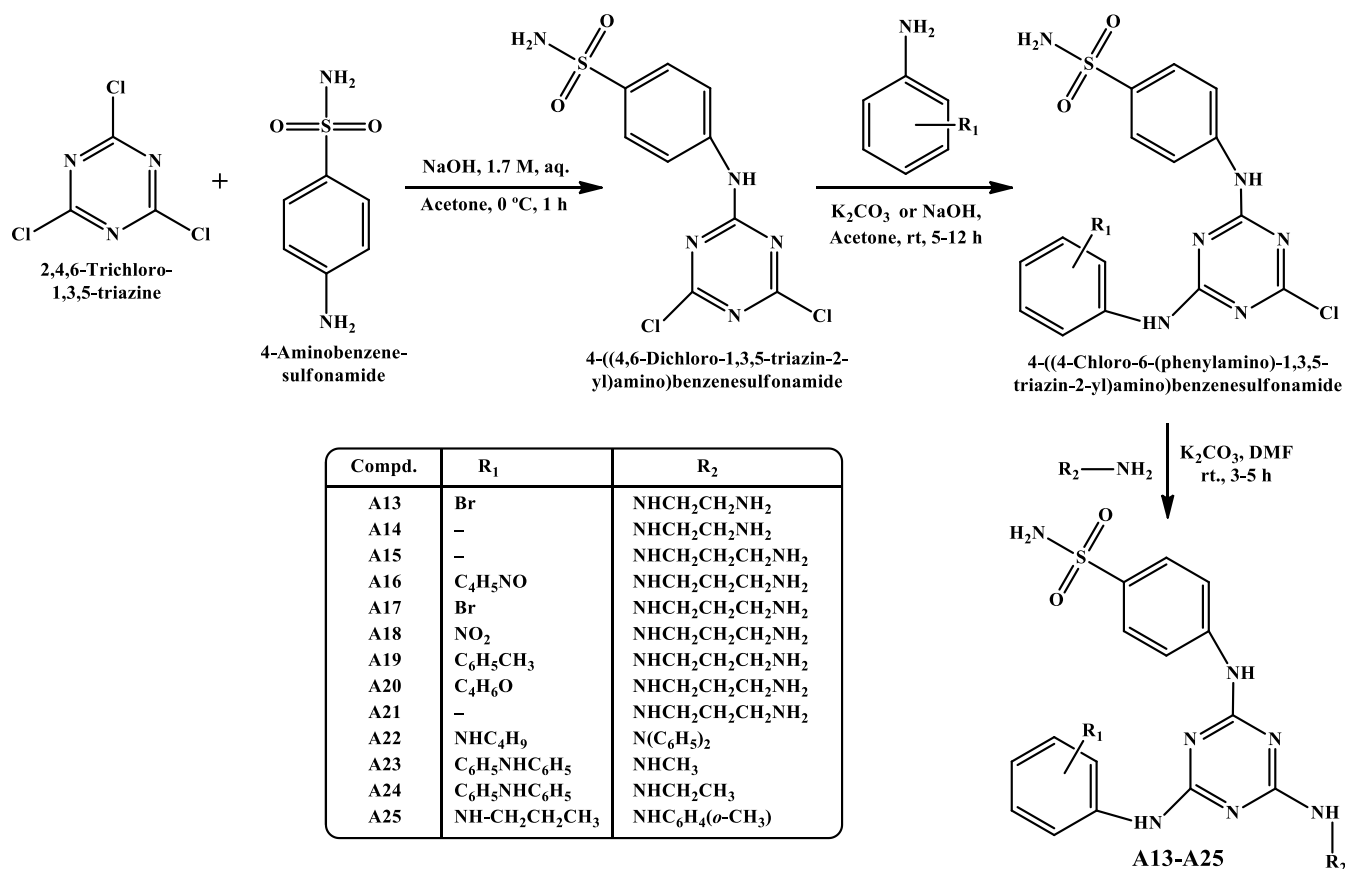
After completion, the reaction mixture was poured onto crushed ice and acidified with dilute HCl. The precipitated *N'*-[4-chloro-6-(arylamino)-1,3,5-triazin-2-yl]benzenesulfonamide was filtered, washed with water, dried and recrystallized. In next step, the resulting chloro intermediate (0.01 mol) was subsequently reacted with the appropriate amine (0.01 mol) in DMF (15 mL) in the presence of K_2CO_3 at room temperature for 3–5 h (**Scheme-I**). The reaction mixture was poured onto crushed ice, acidified with dilute HCl and the precipitated 1,3,5-triazine-amino-benzenesulfonamide derivatives (**A13–A25**) were filtered, washed, dried and recrystallized.

4-((4-(4-Bromophenyl)amino)-6-(propylamino)-1,3,5-triazin-2-yl)amino)benzene-sulphonamide (A13): Yield: 45%, m.p.: 240–242 °C, R_f : 0.37; m.f.: $\text{C}_{18}\text{H}_{20}\text{BrN}_7\text{O}_2\text{S}$; IR (KBr, ν_{max} , cm^{-1}): 3300 (N–H str.), 3100 (C–H str., Ar.), 2984 (C–H str., aliph.), 1650 (C=N str., 1,3,5-triazine), 1350 (SO_2 asym. str.), 1150 (SO_2 sym. str.), 750 (C–S str.), 550 (C–Br str.); ^1H NMR (500 MHz, DMSO- d_6 , δ ppm): 9.92 (s, 1H), 9.20 (s, 1H), 8.05 (br s, 2H, SO_2NH_2), 7.64 (d, 2H), 7.52 (d, 2H), 7.40 (d, 2H), 7.16 (d, 2H), 7.50 (s, 1H), 3.18 (q, 2H), 1.54–1.47 (m, 2H), 0.91 (t, 3H); ^{13}C NMR (125 MHz, DMSO- d_6 , δ ppm): 169.0, 167.5, 165.3, 145.2, 138.4, 132.1, 131.6, 129.2, 128.8, 124.7, 121.8, 116.5, 41.3, 22.5, 11.8; EI-MS calcd. (found): m/z 478.37 (477.05) [M^{+1}].

4-((4-(Phenylamino)-6-(propylamino)-1,3,5-triazin-2-yl)amino)benzene sulphonamide (A14): Yield: 41%, m.p.: 210–212 °C, R_f : 0.42; m.f.: $\text{C}_{18}\text{H}_{21}\text{N}_7\text{O}_2\text{S}$; IR (KBr, ν_{max} , cm^{-1}): 3300 (N–H str.), 3100 (C–H str., Ar.), 2984 (C–H str., aliph.), 1650 (C=N str.), 1350 (SO_2 asym. str.), 1150 (SO_2 sym. str.), 750 (C–S str.); ^1H NMR (500 MHz, DMSO- d_6 , δ ppm): 9.84 (s, 1H), 9.18 (s, 1H, NH), 8.04 (s, 2H), 7.63 (d, J = 8.6 Hz, 2H), 7.38–7.32 (m, 2H), 7.28–7.22 (m, 2H), 7.15–7.10 (m, 1H), 7.40 (d, J = 8.6 Hz, 2H), 7.49 (s, 1H), 3.18 (q, J = 6.8 Hz, 2H), 1.54–1.47 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO- d_6 , δ ppm): 168.9, 167.4, 165.2, 145.2, 139.3, 129.5, 128.8, 127.4, 124.8, 121.6, 118.4, 114.9, 41.2, 22.5, 11.8; EI-MS calcd. (found): m/z 400.51 (399.14) [M^{+1}].

4-((4-(Butylamine)-6-((4-chlorophenyl)amino)-1,3,5-triazin-2-yl)amino)benzene sulphonamide (A15): Yield: 48%, m.p.: 212–214 °C, R_f : 0.36; m.f.: $\text{C}_{19}\text{H}_{21}\text{ClN}_7\text{O}_2\text{S}$; IR (KBr, ν_{max} , cm^{-1}): 3300 (N–H str.), 3100 (C–H str., Ar.), 2984 (C–H str., aliph.), 1650 (C=N str., 1,3,5-triazine), 1350 (SO_2 asym. str.), 1150 (SO_2 sym. str.), 750 (C–S str.), 650 (C–Cl str.); ^1H NMR (500 MHz, DMSO- d_6 , δ ppm): 9.88 (s, 1H), 9.20 (s, 1H), 8.04 (s, 2H), 7.63 (d, J = 8.6 Hz, 2H), 7.37 (d, J = 8.7 Hz, 2H), 7.40 (d, J = 8.6 Hz, 2H), 7.12 (d, J = 8.7 Hz, 2H), 7.48 (br s, 1H), 3.17 (q, J = 6.8 Hz, 2H), 1.48–1.42 (m, 2H), 1.32–1.26 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO- d_6 , δ ppm): 169.0, 167.5, 165.3, 145.2, 138.6, 130.8, 129.6, 128.8, 127.2, 124.9, 121.6, 116.2, 42.1, 31.2, 20.1, 13.8; EI-MS calcd. (found): m/z 446.93 (446.13) [M^{+1}].

4-((4-(Butylamino)-6-(4H-1,4-oxazin-4-yl)-1,3,5-triazin-2-yl)amino)benzene sulphonamide (A16): Yield: 62%, m.p.: 232–234 °C, R_f : 0.37; m.f.: $\text{C}_{17}\text{H}_{24}\text{N}_6\text{O}_3\text{S}$; IR (KBr, ν_{max} , cm^{-1}): 3300 (N–H str.), 3100 (C–H str., Ar.), 2984 (C–H str., aliph.), 1650 (C=N str., 1,3,5-triazine), 1350 (SO_2 asym. str.), 1150 (SO_2 sym. str.), 1050 (C–O–C str., oxazine), 750 (C–S



Scheme-I: Synthetic route for the synthesis of 1,3,5-triazine-sulphonamide derivatives

str.); ¹H NMR (500 MHz, DMSO-*d*₆, δ ppm): 9.22 (s, 1H), 8.03 (s, 2H), 7.62 (d, *J* = 8.6 Hz, 2H), 7.39 (d, *J* = 8.6 Hz, 2H), 7.46 (br s, 1H), 3.80-3.75 (m, 4H), 3.61-3.55 (m, 4H), 3.18 (q, *J* = 6.8 Hz, 2H), 1.48-1.42 (m, 2H), 1.31-1.25 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (125 MHz, DMSO-*d*₆, δ ppm): 168.9, 166.8, 165.2, 145.3, 128.9, 126.7, 118.3, 114.9, 66.5, 49.7, 42.0, 31.1, 20.0; EI-MS calcd. (found): *m/z* 392.16 (391.16) [M⁺].

4-((4-(4-Bromophenyl)amino)-6-(butylamino)-1,3,5-triazin-2-yl)amino)benzene sulphonamide (A17): Yield: 45%, m.p.: 240-242 °C, R_f: 0.39; m.f.: C₁₉H₂₂BrN₇O₂S; IR (KBr, ν_{max}, cm⁻¹): 3300 (N-H *str.*), 3100 (C-H *str.*, Ar.), 2984 (C-H *str.*, aliph.), 1650 (C=N *str.*, 1,3,5-triazine), 1350 (SO₂ asym. *str.*), 1150 (SO₂ sym. *str.*), 750 (C-S *str.*), 550 (C-Br *str.*); ¹H NMR (500 MHz, DMSO-*d*₆, δ ppm): 9.90 (s, 1H), 9.21 (s, 1H), 8.04 (br s, 2H), 7.63 (d, *J* = 8.6 Hz, 2H), 7.52 (d, *J* = 8.7 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.16 (d, *J* = 8.7 Hz, 2H), 7.49 (br s, 1H), 3.18 (q, *J* = 6.8 Hz, 2H), 1.48-1.42 (m, 2H), 1.31-1.25 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (125 MHz, DMSO-*d*₆, δ ppm): 169.0, 167.5, 165.3, 145.2, 138.4, 132.1, 131.6, 129.2, 128.8, 124.7, 121.8, 116.5, 42.1, 31.2, 20.1, 13.8; EI-MS calcd. (found): *m/z* 492.40 (491.07) [M⁺].

4-((4-(Butylamino)-6-((4-nitrophenyl)amino)-1,3,5-triazin-2-yl)amino)benzene sulphonamide (A18): Yield: 40%, m.p.: 218-220 °C, R_f: 0.40; m.f.: C₁₉H₂₂N₈O₂S; IR (KBr, ν_{max}, cm⁻¹): 3300 (N-H *str.*), 3100 (C-H *str.*, Ar.), 2984 (C-H *str.*, aliph.), 1650 (C=N *str.*, 1,3,5-triazine), 1520

(NO₂ asym. *str.*), 1350 (NO₂ sym. *str.*), 1300 (SO₂ asym. *str.*), 1150 (SO₂ sym. *str.*), 750 (C-S *str.*); ¹H NMR (500 MHz, DMSO-*d*₆, δ ppm): 10.10 (s, 1H), 9.23 (s, 1H), 8.05 (br s, 2H), 8.18 (d, *J* = 8.9 Hz, 2H), 7.63 (d, *J* = 8.6 Hz, 2H), 7.48 (d, *J* = 8.9 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.49 (br s, 1H), 3.18 (q, *J* = 6.8 Hz, 2H), 1.48-1.42 (m, 2H), 1.31-1.25 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (125 MHz, DMSO-*d*₆, δ ppm): 169.1, 167.6, 165.4, 147.8, 145.3, 141.6, 129.4, 128.8, 125.3, 124.6, 121.7, 116.0, 42.1, 31.2, 20.1, 13.8; EI-MS calcd. (found): *m/z* 458.50 (458.14) [M⁺].

4-((4-(Butylamino)-6-(*o*-tolylamino)-1,3,5-triazin-2-yl)amino)benzenesulfonamide (A19): Yield: 42%, m.p.: 223-225 °C, R_f: 0.35; m.f.: C₂₀H₂₅N₇O₂S; IR (KBr, ν_{max}, cm⁻¹): 3300 (N-H *str.*), 3100 (C-H *str.*, Ar.), 2984 (C-H *str.*, aliph.), 1650 (C=N *str.*, 1,3,5-triazine), 1350 (SO₂ asym. *str.*), 1150 (SO₂ sym. *str.*), 750 (C-S *str.*/Ar. C-H bending); ¹H NMR (500 MHz, DMSO-*d*₆, δ ppm): 9.78 (s, 1H), 9.19 (s, 1H), 8.04 (s, 2H), 7.62 (d, *J* = 8.6 Hz, 2H), 7.34-7.18 (m, 4H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.47 (br s, 1H), 3.18 (q, *J* = 6.8 Hz, 2H), 2.23 (s, 3H), 1.49-1.42 (m, 2H), 1.33-1.26 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (125 MHz, DMSO-*d*₆, δ ppm): 169.0, 167.5, 165.3, 145.2, 136.8, 135.1, 130.7, 129.8, 128.8, 127.5, 126.2, 124.9, 121.7, 116.2, 42.1, 31.2, 20.3, 20.0, 13.8; EI-MS calcd. (found): *m/z* 427.53 (427.17) [M].

4-((4-(Butylamino)-6-((4-hydroxyphenyl)amino)-1,3,5-triazin-2-yl)amino)benzene sulphonamide (A20): Yield: 65%, m.p.: 226-228 °C, R_f: 0.42; m.f.: C₁₉H₂₃N₇O₂S; IR (KBr, ν_{max}, cm⁻¹): 3300 (O-H/N-H *str.*), 3100 (C-H *str.*, Ar.), 2984

(C–H *str.*, aliph.), 1650 (C=N *str.*, 1,3,5-triazine), 1350 (SO₂ asym. *str.*), 1250 (C–O *str.*, phenolic), 1150 (SO₂ sym. *str.*), 750 (C–S *str.*); ¹H NMR (500 MHz, DMSO-*d*₆, δ ppm): 9.82 (s, 1H), 9.56 (s, 1H), 9.20 (s, 1H), 8.04 (br s, 2H), 7.62 (d, *J* = 8.6 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.08 (d, *J* = 8.7 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 7.48 (br s, 1H), 3.18 (q, *J* = 6.8 Hz, 2H), 1.48–1.42 (m, 2H), 1.32–1.25 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (125 MHz, DMSO-*d*₆, δ ppm): 169.0, 167.4, 165.2, 156.2, 145.2, 135.8, 129.4, 128.8, 124.9, 121.7, 116.3, 115.6, 42.1, 31.2, 20.1, 13.8; EI-MS calcd. (found): *m/z* 429.50 (429.17) [*M*⁺].

4-((4-(Butylamino)-6-(phenylamino)-1,3,5-triazin-2-yl)amino)benzene sulphonamide (A21): Yield: 40%, m.p.: 248–250 °C, *R*_f: 0.38; m.f.: C₁₉H₂₁N₇O₂S; IR (KBr, *v*_{max}, cm^{–1}): 3300 (N–H *str.*), 3100 (C–H *str.*, Ar.), 2984 (C–H *str.*, aliph.), 1650 (C=N *str.*, 1,3,5-triazine), 1350 (SO₂ asym. *str.*), 1150 (SO₂ sym. *str.*), 750 (C–S *str.*); ¹H NMR (500 MHz, DMSO-*d*₆, δ ppm): 9.82 (s, 1H), 9.20 (s, 1H), 8.04 (br s, 2H), 7.62 (d, *J* = 8.6 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.34–7.27 (m, 2H), 7.18–7.12 (m, 2H), 7.03–6.98 (m, 1H), 7.48 (br s, 1H), 3.18 (q, *J* = 6.8 Hz, 2H), 1.48–1.42 (m, 2H), 1.32–1.25 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (125 MHz, DMSO-*d*₆, δ ppm): 169.0, 167.5, 165.3, 145.2, 139.4, 129.5, 128.9, 127.4, 124.9, 121.7, 118.5, 115.0, 42.1, 31.2, 20.1, 13.8; EI-MS calcd. (found): *m/z* 413.50 (413.50) [*M*⁺].

4-((4-(Butylamino)-6-(diphenyl amino)-1,3,5-triazin-2-yl)amino)benzene sulphonamide (A22): Yield: 41%, m.p.: 243–245 °C, *R*_f: 0.47; m.f.: C₂₅H₂₇N₇O₂S; IR (KBr, *v*_{max}, cm^{–1}): 3300 (N–H *str.*), 3100 (C–H *str.*, Ar.), 2984 (C–H *str.*, aliph.), 1650 (C=N *str.*, 1,3,5-triazine), 1350 (SO₂ asym. *str.*), 1150 (SO₂ sym. *str.*), 750 (C–S *str.*/Ar. C–H bending); ¹H NMR (500 MHz, DMSO-*d*₆, δ ppm): 9.18 (s, 1H), 8.03 (br s, 2H), 7.62 (d, *J* = 8.6 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.35–7.28 (m, 4H), 7.22–7.14 (m, 4H), 7.08–7.02 (m, 2H), 7.46 (br s, 1H), 3.17 (q, *J* = 6.8 Hz, 2H), 1.48–1.42 (m, 2H), 1.32–1.25 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (125 MHz, DMSO-*d*₆, δ ppm): 169.2, 167.6, 165.4, 145.3, 147.2, 129.8, 129.2, 128.9, 127.6, 125.8, 124.9, 123.4, 121.8, 119.6, 116.3, 42.1, 31.2, 20.1, 13.8; EI-MS calcd. (found): *m/z* 489.59 (489.19) [*M*⁺].

4-((4-(Butylamino)-6-(diphenyl amino)-1,3,5-triazin-2-yl)amino)benzene sulphonamide (A23): Yield: 54%, m.p.: 232–234 °C, *R*_f: 0.38; m.f.: C₂₂H₂₁N₇O₂S; IR (KBr, *v*_{max}, cm^{–1}): 3350 (N–H *str.*), 3260 (N–H *str.*), 3060 (C–H *str.*), 2955 (C–H *str.*), 2868 (C–H *str.*), 1648 (C=N *str.*), 1595 (C=C *str.*), 1345 (SO₂), 1155 (SO₂ sym. *str.*), 830 (Ar. C–H bending), 750 (Ar. C–H bending); ¹H NMR (500 MHz, DMSO-*d*₆, δ ppm): 9.20 (s, 1H), 8.05 (s, 2H), 7.63 (d, *J* = 8.5 Hz), 7.41 (d, *J* = 8.5 Hz, 2H), 7.36–7.28 (m, 4H, Ar–H), 7.22–7.14 (m, 4H, Ar–H), 7.10–7.03 (m, 2H, Ar–H), 7.46 (br s, 1H), 3.20 (q, *J* = 6.8 Hz, 2H), 1.50–1.43 (m, 2H), 1.34–1.25 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (125 MHz, DMSO-*d*₆, δ ppm): 169.3, 167.7, 165.5, 145.5, 144.8, 141.8, 129.7, 129.1, 128.8, 127.5, 125.8, 124.7, 123.5, 121.7, 119.5, 42.0, 31.1, 20.1, 13.8; EI-MS calcd. (found): *m/z* 447.14 (447.52) [*M*⁺].

4-((4-(Diphenylamino)-6-(ethylamino)-1,3,5-triazin-2-yl)amino)benzenesulfonamide (A24): Yield: 57%, m.p.:

219–221 °C, *R*_f: 0.28; m.f.: C₂₃H₂₃N₇O₂S; IR (KBr, *v*_{max}, cm^{–1}): 3357 (N–H *str.*), 3265 (N–H *str.*), 3068 (C–H *str.*), 2960 (C–H *str.*), 2870 (C–H *str.*), 1650 (C=N *str.*), 1590 (C=C *str.*), 1345 (SO₂), 1150 (SO₂ sym. *str.*), 835 (Ar. C–H bending), 757 (Ar. C–H bending); ¹H NMR (500 MHz, DMSO-*d*₆, δ ppm): 9.20 (s, 1H), 8.05 (s, 2H, SO₂NH₂), 7.65 (d, *J* = 8.5 Hz), 7.41 (d, *J* = 8.5 Hz, 2H, Ar–H), 7.38–7.26 (m, 4H, Ar–H), 7.22–7.14 (m, 4H), 7.10–7.03 (m, 2H), 7.46 (br s, 1H), 3.20 (q, *J* = 6.8 Hz), 1.05 (t, *J* = 7.3 Hz); ¹³C NMR (125 MHz, DMSO-*d*₆, δ ppm): 169.3, 167.7, 165.5, 145.5, 144.8, 141.8, 129.7, 129.1, 128.8, 127.5, 125.8, 124.7, 123.5, 121.7, 119.5, 42.0, 15.0; EI-MS calcd. (found): *m/z* 461.54 (461.16) [*M*⁺].

4-((4-(Propylamino)-6-(*o*-tolylamino)-1,3,5-triazin-2-yl)amino)benzenesulfonamide (A25): Yield: 66%, m.p.: 240–242 °C, *R*_f: 0.37; m.f.: C₁₉H₂₃N₇O₂S; IR (KBr, *v*_{max}, cm^{–1}): 3345 (N–H *str.*), 3265 (N–H *str.*), 3060 (C–H *str.*, Ar.), 2958 (C–H *str.*), 2876 (C–H *str.*), 1645 (C=N *str.*), 1598 (C=C *str.*, Ar.), 1348 (SO₂ asym. *str.*), 1155 (SO₂ sym. *str.*), 825 (Ar. C–H bending), 755 (Ar. C–H bending); ¹H NMR (500 MHz, DMSO-*d*₆, δ ppm): 9.25 (s, 1H), 8.10 (s, 2H, SO₂NH₂), 7.62 (d, *J* = 8.5 Hz, 2H, Ar–H), 7.40 (d, *J* = 8.5 Hz, 2H, Ar–H), 7.30–7.22 (m, 2H, *o*-tolyl Ar–H), 7.18–7.10 (m, 2H, *o*-tolyl Ar–H), 7.08 (br s, 1H, –NHCH₂–), 3.25 (q, *J* = 6.8 Hz, 2H), 1.65–1.52 (m, 2H, –CH₂–), 0.92 (t, *J* = 7.3 Hz, 3H), 2.25 (s, 3H, Ar–CH₃). ¹³C NMR (125 MHz, DMSO-*d*₆, δ ppm): 169.2, 167.5, 165.4, 145.6, 141.8, 136.8, 130.5, 129.7, 129.1, 127.5, 126.8, 125.4, 124.1, 122.8, 119.5, 42.5, 22.8, 17.5, 11.2; EI-MS calcd. (found): *m/z* 413.50 (413.16) [*M*⁺].

Docking analysis: ChemDraw Professional 15.0 was used to construct the two-dimensional chemical structures, which were converted into three-dimensional models using Chem3D 15.0. The ligand geometries were energy-minimized using the steepest-descent method and the MMFF94 force field. The optimized structures were converted to the required docking format using Open Babel. Further energy minimization was performed using Swiss-PdbViewer with 20 steepest-descent steps. The ligand structures were prepared in PDBQT format by adding polar hydrogens and assigning Gasteiger partial charges using AutoDock Tools. Molecular docking was performed using AutoDock Vina, with trimethoprim used as the reference ligand to validate the docking protocol [25,26]. The binding affinity was estimated from the Vina scoring function, which accounts for intermolecular interactions and conformational contributions associated with ligand binding. Docking poses were ranked according to their predicted binding energies and the lowest-energy conformations were selected for interaction analysis.

***In silico* pharmacokinetics (drug-likeness) and toxicity analysis:** The pharmacokinetic properties and drug-likeness of the synthesized compounds were predicted using the SwissADME web tool [27]. The compounds were submitted as SMILES strings and key physico-chemical and drug-likeness parameters including molecular weight (MW), lipophilicity (logP), topological polar surface area (TPSA), rotatable bonds (RB), hydrogen-bond acceptors (HBA) and donors (HBD) were evaluated. Predicted ADME profiles covering absorption, distribution, metabolism and excretion were used to assess the pharmacokinetic suitability of the compounds.

in vitro Antimicrobial activity: The synthesized compounds (**A13-A25**) were evaluated for their *in vitro* antimicrobial activity using standard tube dilution method [28] against Gram-positive bacteria, *Staphylococcus aureus* (MTCC 3160) and *Bacillus subtilis* (MTCC 441), Gram-negative bacteria, *Pseudomonas aeruginosa* (MTCC 2488) and *Escherichia coli* (MTCC 443) and fungal strains, *Candida albicans* (MTCC 227) and *Aspergillus niger* (MTCC 281). Trimethoprim was used as the standard antibacterial drug. Serial dilutions of the test and standard compounds were prepared in double-strength nutrient broth for bacterial strains and Sabouraud dextrose broth for fungal strains. The inoculated tubes were incubated at 37 ± 1 °C for 24 h for bacterial strains, 37 ± 1 °C for 48 h for *C. albicans* and 25 ± 1 °C for 7 days for *A. niger*. Antimicrobial activity was assessed in terms of the minimum inhibitory concentration (MIC).

RESULTS AND DISCUSSION

The synthesized compounds **A13-A25** comprise a 1,3,5-triazine-aminobenzenesulfonamide scaffold obtained through sequential nucleophilic substitution of cyanuric chloride. 4-Aminobenzenesulfonamide first replaces one chlorine atom, followed by reaction with substituted anilines and suitable alkyl-amines or cyclic amines. This synthetic sequence permits the preparation of unsymmetrical triazine derivatives with variation in steric, electronic and hydrophobic features. The reported yields of 40-66% are moderate to good, and the high melting points are consistent with the presence of sulfonamide, amino and triazine functionalities.

The FTIR spectra contain the characteristic absorptions expected for the proposed structures. N–H stretching bands occur around $3357\text{--}3300\text{ cm}^{-1}$, while aromatic and aliphatic C–H stretching bands appear near $3100\text{--}3060$ and $2984\text{--}2968\text{ cm}^{-1}$, respectively. The triazine C=N vibration occurs around $1650\text{--}1645\text{ cm}^{-1}$, whereas strong bands near $1350\text{--}1345$ and $1155\text{--}1150\text{ cm}^{-1}$ correspond to the asymmetric and symmetric SO_2 stretching, which support the presence of benzenesulfonamide moiety. Derivative-specific bands for C–O–C,

NO_2 , phenolic C–O and halogen groups are present where applicable. The ^1H NMR spectra are largely consistent with the assigned structures. Triazine-linked NH protons occur in the δ 9.18–10.10 ppm region, while the SO_2NH_2 protons appear near δ 8.0 ppm. Aromatic protons are distributed mainly over δ 6.8–8.2 ppm depending on the substituent. Propyl- and butyl-amino groups give characteristic CH_2 and terminal CH_3 resonances in the aliphatic region, while tolyl derivatives exhibit a methyl signal near δ 2.2 ppm. The ^{13}C NMR spectra display three downfield signals around δ 165–169 ppm, which assigned to the three carbon atoms of the 1,3,5-triazine ring. Aromatic carbons occur mainly within δ 115–145 ppm, with further resonances arising from the different substituents. The aliphatic carbon signals are compatible with the reported alkyl-amino groups.

Antimicrobial activity: The novel 1,3,5-triazine-aminobenzenesulfonamide derivatives (**A13-A15**) exhibited variable antimicrobial activity against Gram-positive bacteria (*S. aureus* and *B. subtilis*), Gram-negative bacteria (*P. aeruginosa* and *E. coli*) and fungi (*A. niger* and *C. albicans*) (Table-1). Compound **A19** showed the strongest activity against *P. aeruginosa* ($9.25 \pm 0.25\text{ }\mu\text{g mL}^{-1}$) and *E. coli* ($8.94 \pm 0.24\text{ }\mu\text{g mL}^{-1}$), while compound **A25** was most active against *C. albicans* ($9.04 \pm 0.24\text{ }\mu\text{g mL}^{-1}$).

Egg-boil diagram: The SwissADME Egg-Boiled plot provides a graphical prediction of gastrointestinal absorption (HIA) and blood-brain barrier (BBB) permeability for synthesized compounds **A13-A25** and trimethoprim. The white region represents the HIA zone, while the yellow yolk represents the BBB permeation zone (Fig. 1). The plot is mainly influenced by WLOGP and TPSA, which are important determinants of passive membrane permeability and oral absorption. Most synthesized compounds are located within or close to the HIA region, which suggest the favourable predicted gastrointestinal absorption (Fig. 1).

Their WLOGP values are mainly around 2–5, while the TPSA values are relatively high. The high TPSA arises from the triazine, sulfonamide and amino functionalities and may restrict passive membrane diffusion despite the predicted

TABLE-1
ANTIMICROBIAL ACTIVITY DATA OF NEWLY SYNTHESIZED DERIVATIVES (**A13-A25**)

Compd.	Minimum inhibitory concentration (MIC, $\mu\text{g mL}^{-1}$)					
	<i>S. aureus</i>	<i>B. subtilis</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>A. niger</i>	<i>C. albicans</i>
A13	5.10 ± 0.17	3.65 ± 0.12	2.65 ± 0.09	1.06 ± 0.05	2.65 ± 0.09	1.66 ± 0.06
A14	1.09 ± 0.05	4.00 ± 0.14	5.22 ± 0.18	–	–	2.44 ± 0.09
A15	–	2.55 ± 0.09	1.65 ± 0.06	3.30 ± 0.11	3.30 ± 0.11	–
A16	3.30 ± 0.11	1.32 ± 0.06	2.20 ± 0.08	6.00 ± 0.19	8.11 ± 0.23	1.04 ± 0.05
A17	–	4.20 ± 0.15	2.32 ± 0.08	3.10 ± 0.11	2.12 ± 0.08	1.44 ± 0.06
A18	4.50 ± 0.15	3.12 ± 0.11	–	2.15 ± 0.08	–	2.45 ± 0.09
A19	1.09 ± 0.05	8.00 ± 0.22	8.94 ± 0.24	9.25 ± 0.25	3.44 ± 0.12	2.12 ± 0.08
A20	–	–	1.45 ± 0.06	2.10 ± 0.08	7.42 ± 0.22	1.04 ± 0.05
A21	3.12 ± 0.11	3.30 ± 0.11	2.78 ± 0.10	1.44 ± 0.06	–	1.14 ± 0.05
A22	–	3.26 ± 0.11	–	2.20 ± 0.08	3.33 ± 0.11	2.14 ± 0.08
A23	–	2.40 ± 0.09	2.66 ± 0.09	1.55 ± 0.06	1.14 ± 0.05	–
A24	3.11 ± 0.11	2.22 ± 0.08	4.24 ± 0.15	1.33 ± 0.06	3.32 ± 0.11	2.00 ± 0.07
A25	3.05 ± 0.10	2.10 ± 0.08	–	–	7.40 ± 0.22	9.04 ± 0.24
Trimethoprim	11.10 ± 0.28	15.10 ± 0.35	14.00 ± 0.32	12.10 ± 0.30	–	–

Note: Sign (–) represents no activity

TABLE-2
ADSORPTION PROPERTIES OF TRIAZINE SULPHONAMIDE DERIVATIVES

Compd.	Caco-2	MDCK (10 ₆)	Pgp-inhi.	Pgp-subs.	HIA	F20%	F30%	F50%
A13	-5.028	-5.0745	0.99960	1.18	0.24877	0.00804	0.79994	0.99985
A14	-5.199	-4.8973	0.99990	2.34	0.04033	0.00060	0.41825	0.99996
A15	-5.199	-4.8973	0.99990	2.30	0.04030	0.00060	0.41825	0.99996
A16	-5.130	-4.9847	0.99980	5.20	0.04194	0.00050	0.23636	0.99988
A17	-5.134	-5.1356	0.71820	0.09	0.73842	0.18768	0.79185	0.93762
A18	-5.344	-4.7052	0.94138	0.59	0.00728	0.00115	0.04949	0.96910
A19	-5.111	-5.1319	0.99990	7.53	0.98464	0.02782	0.97146	0.99997
A20	-4.919	-4.8727	0.99990	0.02	0.24708	0.01877	0.93525	0.99998
A21	-5.132	-5.0629	0.99590	1.86	0.75347	0.02360	0.98510	0.99999
A22	-4.969	-4.8801	0.99998	4.36	0.85820	0.04248	0.99231	0.99990
A23	-4.792	-5.0566	0.99992	2.90	0.12812	0.00476	0.86664	0.99963
A24	-4.980	-5.0369	0.99938	1.14	0.00921	0.00075	0.32453	0.99949
A25	-4.950	-5.0400	0.99000	2.90	0.04900	0.00300	0.55000	0.99000
Trimethoprim	-5.860	-5.2200	4.67000	0.98	0.00100	7.49000	0.00	0.12

Note: Empirical decision for P-gp, HIA and F: 0–0.3, excellent; 0.3–0.7, good; 0.7–1.0, poor.

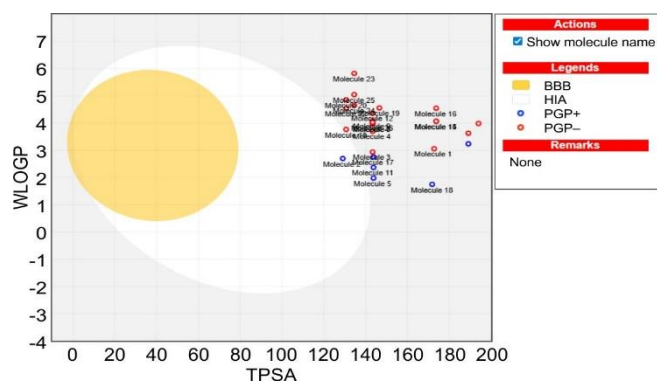


Fig. 1. Egg-boil diagram for compounds **A1**–**A25** and trimethoprim

gastrointestinal absorption. Most compounds remain outside the BBB region, suggesting a low probability of CNS penetration (Fig. 1). The relatively high polarity, hydrogen-bonding capacity and TPSA of the triazine–sulfonamide scaffold are likely to contribute to this behaviour. Compounds positioned closer to the BBB boundary may possess somewhat greater permeability, while increased lipophilicity alone does not appear sufficient to ensure BBB penetration.

The plot further provides P-glycoprotein (P-gp) predictions, with the different marker types representing predicted P-gp substrate/non-substrate behaviour. P-gp-mediated efflux may influence intestinal and systemic exposure and should be considered alongside the ADMET parameters (Table-2). The Egg-Boiled plot suggests a favourable predicted gastrointestinal absorption profile with limited BBB permeability for most compounds. These results are computational predictions rather than experimental measurements and the relatively high TPSA and multiple hydrogen-bonding groups remain important factors governing their permeability characteristics.

ADMET studies: The *in silico* ADMET profile of compounds **A13**–**A25** was evaluated using the absorption, distribution, metabolism, excretion and toxicity parameters presented in Tables 2–5, together with the SwissADME Egg-Boiled plot (Fig. 1). The compounds display considerable variation in predicted absorption and pharmacokinetic behaviour, which can be related to differences in their triazine substituents.

Absorption: The Caco-2 and MDCK values in Table-2 are negative for all derivatives, while HIA values vary considerably. Compound **A19** shows the highest predicted HIA (0.98464), followed by **A22** (0.85820), **A21** (0.75347) and **A17** (0.73842). **A14**, **A15**, **A16**, **A18** and **A24** have much lower HIA values. The F20%, F30% and F50% values likewise vary among the compounds, with several derivatives attaining high F30% and F50% values. Compounds **A19**, **A22** and **A21** occupy relatively favourable positions for gastrointestinal absorption, whereas the high polarity of the scaffold may limit CNS penetration.

Distribution: Plasma protein binding is high for most derivatives, with values generally above 98%. Compound **A18** is an exception, with a lower value of 84.95% (Table-3). BBB penetration remains relatively low for most compounds, with values from 0.05 for **A17** to 8.30 for **A20**. **A20** and **A22** show the highest predicted BBB penetration, while **A17** and **A18** have very low values.

TABLE-3
DRUG DISTRIBUTION PROPERTIES OF
TRIAZINE SULPHONAMIDE DERIVATIVES

Compounds	Parameter		
	Plasma protein binding (%)	BBB penetration	FU (%)
A13	98.82709	4.07	0.813977
A14	98.52239	1.59	1.203553
A15	98.52239	1.59	1.203553
A16	99.20962	2.64	0.444393
A17	98.61870	0.05	1.178355
A18	84.95418	0.13	12.29284
A19	98.89295	1.32	0.796868
A20	98.63931	8.30	0.939530
A21	98.87428	1.56	0.893212
A22	98.97547	5.68	0.607770
A23	99.29764	2.93	0.429830
A24	98.95398	5.03	0.609709
A25	99.08224	3.25	0.486542
Trimethoprim	98.61870	1.56	0.939530

Abbreviations: PPB, plasma protein binding; BBB, blood–brain barrier; FU, fraction unbound. Note: Empirical decision for BBB: 0–0.3, excellent; 0.3–0.7, good; 0.7–1.0, poor

TABLE-4
METABOLISM PROPERTIES OF TRIAZINE SULPHONAMIDE DERIVATIVES

Compound	CYP1A2		CYP2C19		CYP2D6	
	Inhi	Subs	Inhib	Subs	Inhibitor	Subs
A13	0.006082	0.001123	0.075518	0.00032	8.060600	0.030201
A14	0.031646	0.000555	0.676258	0.00140	0.000182	0.032062
A15	0.139889	0.000555	0.676258	0.00140	0.000182	0.032062
A16	0.607787	0.017340	0.758177	0.00279	0.000336	0.013287
A17	0.599723	0.005071	0.002436	5.15000	1.170600	0.014625
A18	0.789222	1.730000	0.953279	0.04781	0.136681	0.110463
A19	0.789222	0.151150	0.138656	5.10050	2.570000	0.000240
A20	0.599723	0.999583	0.983781	0.02721	5.895000	0.001643
A21	0.030263	0.006155	0.085503	0.00011	8.840500	0.065654
A22	0.743469	0.560593	0.594209	0.00079	0.000343	0.002610
A23	0.529975	0.011514	0.351485	0.00020	0.000907	0.027050
A24	0.058606	0.101777	0.332849	0.00012	1.027050	0.078060
A25	0.043202	0.115291	0.351272	0.00430	0.000254	0.000344
Trimethoprim		0.886237	0.280645	2.91070	6.380800	1.070800

Note: Empirical decision: 0–0.3, excellent; 0.3–0.7, good; 0.7–1.0, poor.

Metabolism: Table-4 shows variable interaction with CYP1A2, CYP2C19 and CYP2D6. Compounds **A18**, **A19** and **A20** show relatively high CYP1A2 inhibition values, while **A18** and **A20** display strong CYP2C19 inhibition, whereas compounds **A13**, **A19–A21** show significant CYP2D6 inhibition values.

Excretion: Clearance values range from approximately 2.00 to 3.91 mL/min/kg (Table-5). Compounds **A20** and **A21** have the highest clearance values, whereas compound **A25** has the lowest value. The reported half-lives are relatively short, remaining below approximately 1 h, with compounds **A14** and **A15** among the higher values. The variation in the clearance and half-life suggests differences in the predicted systemic persistence of the derivatives.

Toxicity: The toxicity predictions (Table-6) show the substantial variation among the synthesized compounds. Several derivatives have low predicted hERG liability, while compounds **A19** and **A22** show markedly higher values. Skin-sensitivity, carcinogenicity and respiratory-toxicity predictions are high for several compounds, particularly for compounds **A15–A17** and **A19–A23**.

TABLE-5
EXCRETION PROPERTIES OF TRIAZINE
SULPHONAMIDE DERIVATIVES

Compound	Clearance (mL/min/kg)	Half-life ($t^{1/2}$)
A13	2.441371	0.630191
A14	2.363078	0.865643
A15	2.363078	0.865643
A16	2.790634	0.654864
A17	3.471548	0.720146
A18	3.48845	0.791113
A19	3.709996	0.426684
A20	3.907073	0.50474
A21	3.968008	0.714996
A22	3.037428	0.614657
A23	2.356505	0.450742
A24	2.04945	0.482562
A25	1.999702	0.521152
Trimethoprim	3.267287	0.493057

Note: Empirical decision for $T_{1/2}$: 0–0.3, excellent; 0.3–0.7, good; 0.7–1.0, poor.

TABLE-6
TOXICITY PROFILE OF TRIAZINE SULPHONAMIDE DERIVATIVES

Compound	Parameters					
	hERG	Skin sensitivity	Carcinogenicity	Respiratory	Neurotoxicity	Ototoxicity
A13	0.725086	0.004228	0.859158	0.147955	0.288594	0.439096
A14	0.613583	0.022507	0.908188	0.423346	0.017556	0.345064
A15	0.000111	1.000000	0.999998	1.000000	0.000182	7.340900
A16	0.000111	1.000000	0.999998	1.000000	0.000182	7.340900
A17	1.530000	1.000000	0.999857	1.000000	0.024931	3.821000
A18	0.351872	0.036092	0.962857	0.050549	0.186908	0.333740
A19	9.330000	1.000000	0.999993	1.000000	0.000723	4.210900
A20	0.530549	0.007646	0.941852	0.790215	0.160656	0.570276
A21	0.547032	0.878895	0.760096	0.840672	0.039550	0.226145
A22	9.070000	1.000000	0.999852	1.000000	0.007926	3.041000
A23	0.666578	0.927817	0.647664	0.835526	0.037631	0.174361
A24	0.646684	0.007560	0.872341	0.173347	0.382899	0.595968
A25	0.548612	0.002576	0.821202	0.473088	0.646686	0.621827
Trimethoprim	0.595255	0.002140	0.915325	0.296754	0.629601	0.593359

Thus, the ADMET profile suggests favourable gastrointestinal absorption for compounds **A19**, **A21** and **A22**, with limited BBB penetration predicted for most derivatives. Moreover, compound **A20** requires closer attention due to its relatively high BBB penetration and CYP inhibition. These computational findings provide useful preliminary insights into the pharmacokinetic behaviour of the compounds but *in vivo* studies are needed to confirm their therapeutic potential.

Molecular docking: Molecular docking was performed to examine the binding behaviour of compounds **A13**–**A25** toward the selected molecular target, with trimethoprim used as a reference ligand. The calculated binding affinities ranged from -8.5 to -10.2 kcal mol⁻¹ as compared to -7.6 kcal mol⁻¹ for trimethoprim (Table-7). Most of the synthesized derivatives showed more favourable predicted binding than the reference drug, supporting their potential interaction with the target site.

TABLE-7
MOLECULAR DOCKING ANALYSIS
OF DIFFERENT COMPOUNDS

Compd.	Binding affinity (kcal/mol)	Compd.	Binding affinity (kcal/mol)
A13	-8.5	A20	-8.5
A14	-8.6	A21	-8.7
A15	-8.5	A22	-9.8
A16	-8.6	A23	-10.2
A17	-8.5	A24	-9.7
A18	-8.7	A25	-8.7
A19	-8.5	Trimethoprim	-7.6

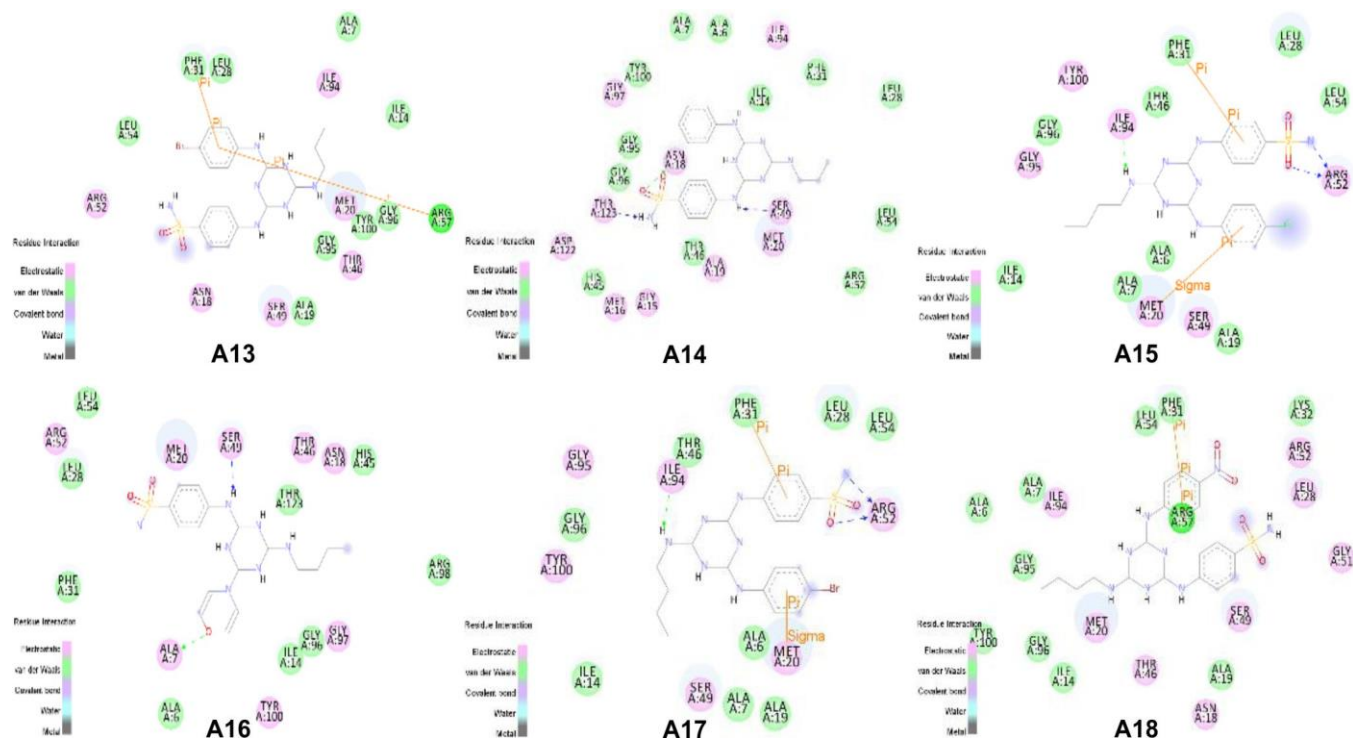
Among the tested compounds, compound **A23** showed the strongest binding affinity (-10.2 kcal mol⁻¹), followed by compound **A22** (-9.8 kcal mol⁻¹) and **A24** (-9.7 kcal mol⁻¹). Compounds **A18**, **A21** and **A25** showed binding affinities of

-8.7 kcal mol⁻¹, while compounds **A14** and **A16** gave -8.6 kcal mol⁻¹. The remaining derivatives exhibited values around -8.5 kcal mol⁻¹. The relatively strong binding of compounds **A22**–**A24** may be related to their larger aromatic substituents, which provide greater hydrophobic surface area and additional possibilities for non-covalent interactions within the binding pocket.

The two-dimensional interaction diagrams (Fig. 2) indicate that the docked compounds are stabilized through a combination of hydrogen bonding, hydrophobic contacts and other non-covalent interactions with residues surrounding the active site. The triazine and sulfonamide functionalities provide hydrogen-bonding sites, while the substituted aromatic groups can participate in hydrophobic and π -related interactions. The interaction pattern observed for compound **A23** is consistent with its lowest predicted binding energy.

Conclusion

A series of 1,3,5-triazine-aminobenzenesulfonamide derivatives **A13**–**A25** was synthesized through sequential substitution of cyanuric chloride, providing a structurally diverse set of triazine-based compounds in moderate to good yields. FTIR, ¹H NMR and ¹³C NMR data supported the proposed triazine-sulfonamide framework and the incorporation of different aryl, alkyl and heterocyclic substituents. Molecular docking provided further insight into their possible interaction with dihydrofolate reductase. Compound **A23** exhibited the most favourable predicted binding affinity (-10.2 kcal mol⁻¹), followed by compounds **A22** and **A24**, with the docked complexes involving hydrogen-bonding, hydrophobic and other non-covalent interactions. The computational ADMET profile suggested favourable gastrointestinal absorption for selected derivatives, particularly **A19**, **A21** and **A22**, while most compounds showed limited predicted BBB penetration.





During the preparation of this manuscript, the authors used an AI-assisted tool(s) to improve the language and no data, results or scientific conclusions were generated by AI. All analyses, interpretations and conclusions are the authors' own. The authors reviewed and edited the content and take full responsibility for the published work.

1. H.F. Hetta, Y.N. Ramadan, A.I. Al-Harbi, E.A. Ahmed, B. Battah, N.H. Abd Ellah, S. Zanetti and M.G. Donadu, *Biomedicines*, **11**, 413 (2023);
<https://doi.org/10.3390/biomedicines11020413>
2. N.S. Radulovic, P.D. Blagojevic, Z.Z. Stojanovic-Radic and N.M. Stojanovic, *Curr. Med. Chem.*, **20**, 932 (2013);
<https://doi.org/10.2174/092986713805219136>
3. A.P. Taylor, R.P. Robinson, Y.M. Fobian, D.C. Blakemore, L.H. Jones and O. Fadeyi, *Org. Biomol. Chem.*, **14**, 6611 (2016);
<https://doi.org/10.1039/C6OB00936K>
4. S. Chandu, A. Manupathi, S. Gundekari and M. Varkolu, *Curr. Org. Chem.*, **30**, 691 (2026);
<https://doi.org/10.2174/0113852728379590251112105811>
5. J. Jatin, S. Murugappan, S. Kirad, C. Ala, P.V. Kuthe, C.S. Kondapalli and M. Sankaranarayanan, *RSC Med. Chem.*, **16**, 1941 (2025);
<https://doi.org/10.1039/D4MD00995A>
6. J. Kumawat, S. Jain, N. Misra, J. Dwivedi and D. Kishore, *Mini Rev. Med. Chem.*, **24**, 2019 (2024);
<https://doi.org/10.2174/0113895575309800240526180356>

7. F. Örcü and G.Ö. Dalkılıç, Author identification using N-grams and SVM, *The* (2010) 1-5.
8. M. Makosza and K. Wojciechowski, *Chem. Rev.*, **104**, 2631 (2004); <https://doi.org/10.1021/cr020086+>
9. C. Thalluri, M. Vasam, R. Jampala, S. Alagarsamy, A. Dubey, A. Lather and T. Hooda, *Pharm. Nanotechnol.*, **13**, e22117385350217 (2024); <https://doi.org/10.2174/0122117385350217241122151638>
10. A. Lather, V. Gupta, A.K. Chaudhary, R. Singh, P. Bansal, P. Ghaiye and R. Bansal, *Pak. J. Pharm. Sci.*, **25**, 693 (2012).
11. A. Lather, S. Sharma and A. Khatkar, *Sci. Rep.*, **10**, 13903 (2020); <https://doi.org/10.1038/s41598-020-70895-1>
12. S. Neelam, S. Ahlawat, A. Shankar, A. Lather, A. Khatkar and K.K. Sharma, *3 Biotech*, **11**, 70 (2021); <https://doi.org/10.1007/s13205-020-02636-0>
13. S. Zerbib, N. Cruz-Martins and L. Bouissane, *Arch. Pharm.*, **359**, e70180 (2026); <https://doi.org/10.1002/ardp.70180>
14. F. Carta, C. T. Supuran and A. Scozzafava, *Future Med. Chem.*, **6**, 1149 (2014); <https://doi.org/10.4155/fmc.14.68>
15. N. Kakeya, M. Aoki, A. Kamada and N. Yata, *Chem. Pharm. Bull.*, **17**, 1010 (1969); <https://doi.org/10.1248/cpb.17.1010>.
16. R. Gitto, F.M. Damiano, P. Mader, L. De Luca, S. Ferro, C.T. Supuran, D. Vullo, J. Brynda, P. Řezáčová and A. Chimirri, *J. Med. Chem.*, **55**, 3891 (2012); <https://doi.org/10.1021/jm300112w>.
17. M.T.M. Nemr, A.M. AboulMagd, H.M. Hassan, A.A. Hamed, M.I.A. Hamed and M.T. Elsaadi, *RSC Adv.*, **11**, 26241 (2021); <https://doi.org/10.1039/D1RA05277B>
18. N. Lolak, M. Boga, M. Tuneg, G. Karakoc, S. Akocak and C.T. Supuran, *J. Enzyme Inhib. Med. Chem.*, **35**, 424 (2020); <https://doi.org/10.1080/14756366.2019.1707196>
19. M. Ceruso, D. Vullo, A. Scozzafava and C.T. Supuran, *Bioorg. Med. Chem.*, **21**, 6929 (2013); <https://doi.org/10.1016/j.bmc.2013.09.031>
20. N.C. Desai, A.H. Makwana and R.D. Senta, *J. Saudi Chem. Soc.*, **20**, 686 (2016); <https://doi.org/10.1016/j.jscs.2015.01.004>
21. M. Ferri, E. Ranucci, P. Romagnoli and V. Giaccone, *Crit. Rev. Food Sci. Nutr.*, **57**, 2857 (2017); <https://doi.org/10.1080/10408398.2015.1077192>
22. M.A. Salam, M.Y. Al-Amin, M.T. Salam, J.S. Pawar, N. Akhter, A.A. Rabaa and M.A. Alqumber, *Healthcare*, **11**, 1946 (2023); <https://doi.org/10.3390/healthcare11131946>
23. A.H. Makwana, N.C. Desai and R.D. Senta, *J. Saudi Chem. Soc.*, **21S1**, S25 (2017); <https://doi.org/10.1016/j.jscs.2013.09.006>
24. R.A. Mohamed-Ezzat and G. H. Elgemeie, *BMC Chem.*, **18**, 58 (2024); <https://doi.org/10.1186/s13065-024-01164-9>
25. O. Trott and A.J. Olson, *J. Comput. Chem.*, **31**, 455 (2010); <https://doi.org/10.1002/jcc.21334>
26. T.A. Halgren, *J. Comput. Chem.*, **17**, 490 (1996); [https://doi.org/10.1002/\(SICI\)1096-987X\(199604\)17:5/6<490::AID-JCC1>3.0.CO;2-P](https://doi.org/10.1002/(SICI)1096-987X(199604)17:5/6<490::AID-JCC1>3.0.CO;2-P)
27. A. Daina, O. Michielin and V. Zoete, *Sci. Rep.*, **7**, 42717 (2017); <https://doi.org/10.1038/srep42717>
28. S. Yadav, B. Narasimhan, S. M. Lim, K. Ramasamy, M. Vasudevan, S.A.A. Shah and A. Mathur, *Egypt. J. Basic Appl. Sci.*, **5**, 100 (2018); <https://doi.org/10.1016/j.ejbas.2017.11.001>