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Synthesis, Characterisation, Molecular Docking and Antimicrobial Evaluation of Certain Cyclic Amine-Containing Trisubstituted 1,3,5-Triazine Derivatives

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A series of novel tri-substituted 1,3,5-triazine derivatives **(5a-l)** was synthesised and characterised using analytical and spectroscopic techniques including IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry. The antimicrobial efficacy of the synthesised compounds was evaluated against four bacterial strains (*Escherichia coli* MTCC 443, *Pseudomonas aeruginosa* MTCC 1688, *Staphylococcus aureus* MTCC 96 and *Streptococcus pyogenes* MTCC 442) and three fungal strains (*Candida albicans* MTCC 227, *Aspergillus niger* MTCC 282 and *Aspergillus clavatus* MTCC 1323). Compound **5i** showed the lowest MIC against *S. aureus* (MIC 62.5 µg/mL), while compound **5b** demonstrated moderate broad-spectrum antibacterial activity with MIC values of 50-100 µg/mL, representing the most active member of the series (MIC 50 µg/mL *vs*. ciprofloxacin MIC 25 µg/mL). Compound **5k** showed significant antifungal activity against *C. albicans* (MIC 100 µg/mL), superior to griseofulvin for this specific strain (MIC 500 µg/mL). Molecular docking studies against *S. aureus* DNA gyrase (PDB: 3FY8) revealed that compound **5e** exhibited the highest binding affinity among the synthesised compounds (docking score: -7.074 kcal/mol), lower than the reference ciprofloxacin (-7.778 kcal/mol). The compounds demonstrated interactions with key active-site residues *via* hydrophobic contacts, hydrogen bonding with TYR 98, halogen bonding and electrostatic interactions with ASP 27 and LYS 45, suggesting DNA gyrase as a possible target for further exploration. These findings indicate that 1,3,5-triazine scaffolds are promising leads for the development of antimicrobial agents targeting DNA gyrase.

Keywords: Heterocyclic, Derivatives, Cyclic amine, Antimicrobial activities.

INTRODUCTION

s-Triazine, also known as 1,3,5-triazine, is a nitrogen-rich aromatic heterocycle consisting of a six-membered ring with three symmetrically positioned nitrogen atoms and is a well-studied structural motif in medicinal chemistry [1,2]. The pharmaceutical significance of *s*-triazine derivatives is evidenced by several clinically approved drugs containing this scaffold. Notable examples include 6-azacytosine, an antiviral agent; 6-azauracil, employed in antitumor therapy; tirapazamine, utilised in cancer treatment; lamotrigine, a widely prescribed anticonvulsant and metribuzin, used as a herbicide [3-5]. These diverse applications underscore the versatility and therapeutic potential of triazine-based compounds across the multiple therapeutic areas [6].

The core for obtaining several *s*-triazine derivatives is 2,4,6-trichloro-1,3,5-triazine, due to its low cost and the ease with which its three independent, easily adjustable ring locations can be manipulated. This enables nucleophilic substitution processes to occur sequentially with almost all nucleophiles including sulfur, oxygen and nitrogen [7-13]. Furthermore, significant class of chemicals is represented by *s*-triazine derivatives due to their potential biological activity and are recognised as antimicrobials [14], cyclin-dependent kinase modulators [15], estrogen receptor modulators [16], anti-malarials [17], anticancer drugs [18] and anti-protozoal [19].

Cyanuric chloride is a cheap, readily accessible reagent that has been used extensively in organic reactions because it is less corrosive and hazardous than similar reagents [20]. An affordable, commercially available reagent for preparing a range of *s*-triazine derivatives is cyanuric chloride (1,3,5-triazine). The reagent's usefulness for the synthesis of mono-, di- and tri-substituted 1,3,5-triazine derivatives at regulated temperatures is increased by the ease with which different nucleophiles can displace the chlorine atoms in cyanuric chloride [21]. In the present study, we report the synthesis of a new class of asymmetrical triazinyl compounds derived from O-[(2*E*)-3-chloroprop-2-en-1-yl]hydroxylamine. The derivatives were synthesised through nucleophilic substitution reactions involving various amines. The structural elucidation of the synthesised compounds (**5a-l**) was performed using spectroscopic techniques and their antimicrobial activity was evaluated against the Gram-positive *Staphylococcus aureus* and the fungal pathogen *Candida albicans* to assess their potential as bioactive agents.

EXPERIMENTAL

The solvents and other chemical reagents needed for the synthetic processes were purchased from Merck Ltd., India, SD Fine Chemicals and Sigma-Aldrich Chemicals Ltd.. Before being used, the reagent-grade compounds were refined by either distillation or recrystallisation. Thin-layer chromatography was used to assess the purity of the synthesised compounds. Melting points were measured uncorrected using an electrical digital melting point device VMP-PM-digital melting/boiling point apparatus. Using TMS as the internal standard, ^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Bruker Avance Neo 500 MHz spectrometer. The mass spectra were obtained using a Triple Quadrupole LC-MS/MS (LC-MS-8060NX) spectrometer.

Synthesis of O-[(2*E*)-3-chloroprop-2-en-1-yl] hydroxylamine (2): In a 500 mL glass flask with a stirring apparatus, a mixture of 0.15 mol of hydroxylamine in water, 0.15 mol of methyl acetate and 100 mL of water was prepared. Following this, 0.15 mol of 4% NaOH solution was added in 60 min and after 2-3 h, a solution of 1,3-dichloropropene was slowly added dropwise while simultaneously adding (0.20 mol) of 4% NaOH solution. The reaction temperature was maintained at 0-5 ºC and the mixture was stirred for approximately 2-4 h until the starting material disappeared, as confirmed by TLC examination. Subsequently, the reaction mass was heated to 50 ºC and 0.45 mol of conc. HCl solution was added. The mixture was stirred for about 5-6 h until the starting material disappeared, as confirmed by TLC examination. After that, 200 mL of CCl_4 was added and the pH was neutralised with 4% NaOH solution and the organic layer was separated. The organic solvent was then evaporated under reduced pressure using a rotary evaporator to obtain compound **2**. The compound **2** was purified by column distillation. Elemental anal. of C_3H_6ClNO (*m.w.* 107.54): Calcd. (found) %: C, 33.52 (33.51); H; 5.61 (5.62); Cl, 32.96 (32.97); N, 13.05 (13.03); O, 14.87 (14.88); ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 4.26 (2H, d, J = 6.9 Hz), 5.75 (1H, dt, J = 14.0, 6.9 Hz), 6.22 (1H, d, J = 14.0 Hz); ^{13}C NMR (500 MHz, $CDCl_3$, δ ppm): δ 69.2 (1C, s), 119.3 (1C, s), 131.1 (1C, s).

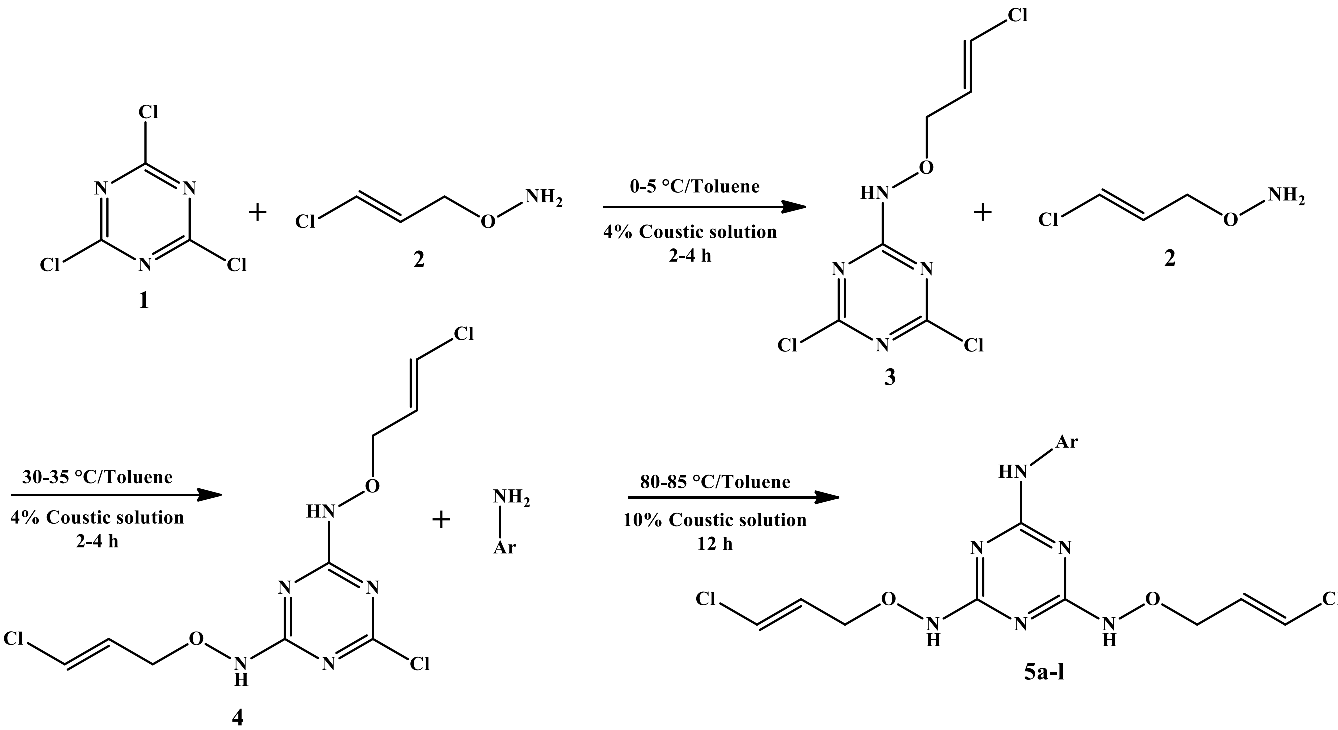
Synthesis of 4,6-dichloro-*N*-{[(2*E*)-3-chloroprop-2-en-1-yl]oxy}-1,3,5-triazin-2-amine (3): *s*-Triazine (**1**, 0.05 mol), 4% NaOH (0.1 mol) and 100 mL methylbenzene were fed into a 500 mL glass flask equipped with a stirrer. Compound (**2**, 0.05 mol) dissolved in 50 mL methyl benzene was added dropwise into the flask. The reaction temperature was kept at 0-5 ºC and the mixture was stirred for about 2-4 h until the starting material disappeared. The inorganic material was filtered off and the filtrate was washed with water. The organic layer (methylbenzene) was separated and evaporated under reduced pressure using a rotary evaporator to obtain compound **3** in 89% yield. Elemental anal. of $C_6H_5Cl_3N_4O$ (*m.w.* 255.49): Calcd. (found) %: C (28.21%) H (1.97%) Cl (41.63%) N (21.93%) O (6.26%); IR (KBr, ν_{max}, cm^{-1}): 3373 (N-H), 3208 (C-H), 1565 (C=C), 1419 (C=N),1171 (C-N), 752 (Cl-C).^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 4.54 (2H, d, J = 6.4 Hz), 5.82 (1H, dt, J = 14.0, 6.4 Hz), 6.22 (1H, d, J = 14.0 Hz); ^{13}C NMR (500 MHz, $CDCl_3$, δ ppm): 69.2 (1C, s), 119.3 (1C, s), 131.1 (1C, s), 160.9 (2C, s), 162.8 (1C, s).

Synthesis of 6-chloro-N^2,N^4-*bis*{[(2E)-3-chloroprop-2-en-1-yl]oxy}-1,3,5-triazine-2,4-diamine (4): 4,6-Dichloro-N-{[(2*E*)-3-chloroprop-2-en-1-yl]oxy}-1,3,5-triazin-2-amine (**3**, 0.05 mol), 4% NaOH (0.1 mol) and 100 mL methyl benzene were fed into a 500 mL glass flask equipped with a stirrer followed by the addition of compound (**2**, 0.05 mol) dissolved in 50 mL methyl benzene. The reaction temperature was kept at 30-35 ºC and the mixture was stirred for about 8-10 h until the starting material disappeared examined by TLC, the inorganic material was filtered off and the filtrate washed with water. The separate out organic layer methylbenzene evaporated under reduced pressure by rota evaporator to obtain **4** (yield: 93%), Elemental anal. of $C_9H_{10}Cl_3N_5O_2$ (*m.w.* 326.57): Calcd. (found) %: C, 33.10 (33.09); H, 3.09 (3.07); Cl, 32.57 (32.61); N, 21.45 (21.40); O, 9.80 (9.86); IR (KBr, ν_{max}, cm^{-1}): 3361 (N-H), 1670 (C=C), 1447 (C=N), 1290 (C-N), 761 (Cl-C); ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 69.2 (2C, s), 119.3 (2C, s), 131.1 (2C, s), 160.9 (1C, s), 162.8 (2C, s); ^{13}C NMR (500 MHz, $CDCl_3$, δ ppm): 4.54 (4H, d, J = 6.4 Hz), 5.82 (2H, dt, J = 14.0, 6.4 Hz), 6.22 (2H, d, J = 14.0 Hz).

General procedures for the synthesis of compounds 5a-l

Synthesis of 4,6-*bis*((((E)-3-chloroallyl)oxy)amino)-N-cyclopropyl-1,3,5-triazin-2-amine derivatives (5a): In a three-necked 500 mL flask, a solution of compound **4** (0.05 mol) in methyl benzene (100 mL) and 10% NaOH (0.1 mol) were added, followed by the dropwise addition of cyclopropylamine in 50 mL toluene (0.05 mol). The reaction mixture was stirred at reflux for 12-16 h until the starting material had disappeared, as monitored by TLC. Then, ice water (100 mL) was added to the semi-dry precipitate. The solid was collected by vacuum filtration, washed with water, dried and recrystallised from chloroform/*n*-hexane to give a colourless crystalline **5a** (yield: 85%, m.p.: 112 ºC) (**Scheme-I**). Elemental anal. of $C_{12}H_{16}Cl_2N_6O_2$ (*m.w.* 347.21): Calcd. (found) %: C, 41.51 (41.43); H, 4.65 (4.56); Cl, 20.42 (20.19); N, 24.21 (24.16); O, 9.22 (9.29); IR (KBr, ν_{max}, cm^{-1}): 3029 (N-H), 3008 (C-H), 1558 (C=C), 1451 (C=N), 1262 (C-N), 803 (Cl-C); ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 0.45 (4H, dddd, J = 8.1, 7.8, 7.5, 6.7 Hz), 2.97 (1H, tt, J = 8.1, 7.5 Hz), 4.54 (4H, d, J = 6.4 Hz), 5.82 (2H, dt, J = 14.0, 6.4 Hz), 6.22 (2H, d, J = 14.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 6.6 (2C, s), 23.3 (1C, s), 69.2 (2C, s), 119.9 (2C, s), 131.1 (2C, s), 162.7 (1C, s), 162.8 (2C, s).

4,6-*bis*((((*E*)-3-Chloroallyl)oxy)amino)-*N*-cyclobutyl-1,3,5-triazin-2-amine (5b): Yield (%): 85, m.p.: 112 ºC; Elemental anal. of $C_{13}H_{18}Cl_2N_6O_2$ (*m.w.* 361.23): Calcd. (found) %: C, 43.23 (43.25); H, 5.02 (5.04), Cl, 19.63 (19.60),



Scheme-I: Synthetic route for the preparation of tri-substituted 1,3,5-triazine derivatives (**5a-l**)

N, 23.27 (23.25); O, 8.86 (8.85); IR (KBr, ν_{max}, cm^{-1}): 3347 (N-H), 3165 (C-H), 1633 (C=C), 1465 (C=N), 1221 (C-N), 794 (Cl-C); ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 1.74-1.93 (6H, 1.82 (d, *J* =4.5 Hz), 1.85 (d, *J* =4.5 Hz), 3.70 (1H, d, *J* = 6.7 Hz), 4.20 (4H, d, *J* = 6.4 Hz), 5.87 (2H, d, *J* = 6.4 Hz), 6.29 (2H, d, *J* = 14.0 Hz); ^{13}C NMR (500 MHz, $CDCl_3$, δ ppm): 18.3 (1C, s), 24.5 (2C, s), 48.5 (1C, s), 73.9-77.3 (2C, s), 124.1- (2C, s), 136.2 (2C, s), 165.0-169.1 (3C, 165.0 (s), 168.3 (s), MS (ESI) *m/z*: 361.2, calcd: 361.25.

4,6-*bis*(((E)-3-Chloroallyl)oxy)amino)-N-cyclopentyl-1,3,5-triazin-2-amine (5c): Yield (%): 87, m.p.: 127 ºC; Elemental anal. of $C_{14}H_{20}Cl_2N_6O_2$ (*m.w.* 375): Calcd. (found) %: C, 44.81 (44.84); H, 5.37 (5.36); Cl, 18.89 (18.88); N, 22.40 (22.41); O, 8.53 (8.52); IR (KBr, ν_{max}, cm^{-1}): 3402 (N-H), 3170 (C-H), 1594 (C=C), 1500 (C=N), 1245(C-N), 831 (Cl-C); ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 1.50-1.69 (4H, 1.59 (m, *J* = 13.3, 6.5, 5.4, 4.1 Hz), 1.60 (m, *J* = 13.3, 8.2, 5.3, 3.5 Hz), 1.71-1.91 (4H, 1.79 m, 1.81 m), 3.82 (1H, m), 4.19 (4H, d, *J* = 6.4 Hz), 5.87 (2H, dt, *J* = 14.0, 6.4 Hz), 6.29 (2H, d, *J* = 14.0 Hz); ^{13}C NMR (500 MHz, $CDCl_3$, δ ppm): 24.1 (2C, s), 31.3 (2C, s), 50.1 (1C, s), 73.9 (2C, s), 124.1 (2C, s), 131.1 (2C, s), 165.0-169.11 (3C, 165.05 (s), 168.33 (s); MS (ESI) *m/z*: 374.2, calcd: 375.26.

4,6-*bis*((((*E*)-3-Chloroallyl)oxy)amino)-*N*-cyclohexyl-1,3,5-triazin-2-amine (5d): Yield (%): 83, m.p.: 121 ºC; Elemental anal. of $C_{15}H_{22}Cl_2N_6O_2$ (*m.w.* 389.29): Calcd. (found) %: C, 46.28 (46.30); H, 5.70 (5.71); Cl, 18.21 (18.18), N, 21.59 (21.57); O, 8.22 (8.24); IR (KBr, ν_{max}, cm^{-1}): 3469 (N-H), 3107 (C-H), 1572 (C=C), 1470 (C=N), 1213 (C-N), 745 (Cl-C); ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 1.29-1.56 (6H, 1.37 m, 1.48 m), 1.76 (4H, dt, *J* = 13.3, 6.5 Hz), 3.69 (1H, m), 4.54 (4H, d, *J* = 6.4 Hz), 5.82 (2H, dt, *J* = 14.0, 6.4 Hz), 6.22 (2H, d, *J* = 14.0 Hz); ^{13}C NMR (500 MHz, $CDCl_3$, δ ppm): 25.0 (2C, s), 25.7 (1C, s), 33.5 (2C, s), 51.8 (1C, s), 69.2 (2C, s), 119.3 (2C, s), 131.1 (2C, s), 162.7 (1C, s), 162.8 (2C, s), MS (ESI) *m/z*: 389.2, calcd.: 389.29.

4,6-*bis*((((*E*)-3-Chloroallyl)oxy)amino)-*N*-cycloheptyl-1,3,5-triazin-2-amine (5e): Yield (%): 81, m.p.: 147 ºC; Elemental anal. of $C_{16}H_{24}Cl_2N_6O_2$ (*m.w.* 403.31): Calcd. (found) %: C, 47.65 (47.66); H, 6.00 (6.02); Cl, 17.58 (17.57); N 20.84 (20.85); O, 7.93 (7.91); IR (KBr, ν_{max}, cm^{-1}): 3387 (N-H), 3103 (C-H), 1570 (C=C), 1437 (C=N), 1277 (C-N), 742 (Cl-C); ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 1.45-1.66 (12H, 1.54 m, 1.54 m, 1.58 m), 3.72 (1H, m), 4.54 (4H, d, *J* = 6.4 Hz), 5.82 (2H, dt, *J* = 14.0 Hz), 6.22 (2H, d, *J* = 14.0 Hz); ^{13}C NMR (500 MHz, $CDCl_3$, δ ppm): 23.4 (2C, s), 27.9 (2C, s), 33.8 (2C, s), 57.7 (1C, s), 69.2 (2C, s), 119.3 (2C, s), 131.1 (2C, s), 162.7 (1C, s), 162.8 (2C, s); MS (ESI) *m/z*: 403.3, calcd.: 403.31.

4,6-*bis*((((*E*)-3-Chloroallyl)oxy)amino)-*N*-cyclooctyl-1,3,5-triazin-2-amine (5f): Yield (%): 78, m.p.: 147 ºC; Elemental anal. of $C_{17}H_{26}Cl_2N_6O_2$ (*m.w.* 417.34): Calcd. (found) %: C, 48.93 (48.91); H, 6.28 (6.29); Cl, 16.99 (16.98); N, 20.14 (20.16); O, 7.67 (7.69); IR (KBr, ν_{max}, cm^{-1}): 3468 (N-H), 3108 (C-H), 1570 (C=C), 1476 (C=N),1277 (C-N), 742 (Cl-C); ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 1.36-1.68 (14H, 1.44 m, 1.48 m, 1.52 m, 1.59 m, 3.50 (1H, t, *J* = 9.6 Hz), 4.54 (4H, d, *J* =6.4 Hz), 5.82 (2H, dt, *J* = 14.0, 6.4 Hz), 6.22 (2H, d, *J* =14.0 Hz); ^{13}C NMR (500 MHz, $CDCl_3$, δ ppm): 25.1 (2C, s), 25.6 (1C, s), 27.1 (2C, s), 29.2 (2C, s), 69.2 (2C, s), 76.8 (1C, s), 119.3 (2C, s), 131.1 (2C, s), 162.7 (1C, s), 162.8 (2C, s); MS (ESI) *m/z*: 417.3, calcd.: 417.34.

4,6-*bis*((((*E*)-3-Chloroallyl)oxy)amino)-*N*-(2-methyl-cyclopropyl)-1,3,5-triazin-2-amine (5g): Yield (%): 68, m.p.: 137 ºC; Elemental anal. of $C_{13}H_{18}Cl_2N_6O_2$ (*m.w.* 361.23): Calcd. (found) %: C, 43.23 (43.24); H, 5.02 (5.01); Cl, 19.63 (19.64); N, 23.27 (23.26); O, 8.86 (8.87); IR (KBr, ν_{max}, cm^{-1}): 3452 (N-H), 3106 (C-H), 1571 (C=C), 1476 (C=N), 1273 (C-N), 746 (Cl-C); ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 0.28-0.51 (2H, 0.36 m, 0.44 m, 0.79 (1H, m), 1.21 (3H, d, *J* = 6.9 Hz), 2.94 (1H, m), 4.48-4.60 (4H, 4.54 (d, *J* = 6.4 Hz), 4.54 (d, *J* = 6.4 Hz), 5.82 (2H, m), 6.23 (2H, d, *J* = 14.0 Hz); ^{13}C NMR (500 MHz, $CDCl_3$, δ ppm): 11.9 (1C, s), 12.4 (1C, s), 18.4 (1C, s), 49.9 (1C, s), 69.2 (2C, s), 119.9 (2C, s), 131.1 (2C, s), 162.7 (1C, s), 162.8 (2C, s); MS (ESI) *m/z*: 361.2, calcd. 361.23.

4,6-*bis*((((*E*)-3-chloroallyl)oxy)amino)-*N*-(2-ethylcyclopropyl)-1,3,5-triazin-2-amine (5h): Yield (%): 88, m.p.: 107 ºC; Elemental anal. of $C_{14}H_{20}Cl_2N_6O_2$ (*m.w.* 375.26): Calcd. (found) %: C, 44.81 (44.82); H, 5.37 (5.35); Cl, 18.89 (18.91); N, 22.40 (22.42); O, 8.53 (8.55); IR (KBr, ν_{max}, cm^{-1}): 3455 (N-H), 3101 (C-H), 1573 (C=C), 1466 (C=N),1279 (C-N), 746 (Cl-C); ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 0.29-0.52 (2H, 0.37 m, 0.44 m, 0.93 (3H, dd, *J* = 7.1 Hz), 1.10 (1H, m), 1.52-1.70 (2H, 1.61 m, 1.61 m, 2.90 (1H, m), 4.48-4.60 (4H, 4.54 (d, *J* = 6.4 Hz), 4.54 (d, *J* = 6.4 Hz), 5.82 (2H, m), 6.23 (2H, d, *J* = 14.0 Hz); ^{13}C NMR (500 MHz, $CDCl_3$, δ ppm): 12.1 (1C, s), 12.4 (1C, s), 17.1 (1C, s), 21.6 (1C, s), 49.9 (1C, s), 69.2 (2C, s), 119.9 (2C, s), 131.1 (2C, s), 162.7 (1C, s), 162.8 (2C, s); MS (ESI) *m/z*: 375.31, calcd.: 376.26.

4,6-*bis*((((*E*)-3-Chloroallyl)oxy)amino)-*N*-(2-propylcyclopropyl)-1,3,5-triazin-2-amine (5i): Yield (%): 78, m.p.: 116 ºC; Elemental anal. of $C_{15}H_{22}Cl_2N_6O_2$ (*m.w.* 389.29): Calcd. (found) %: C, 46.28 (46.29); H, 5.70 (5.71); Cl (18.21); N, 21.59 (21.62); O, 8.22 (8.20); IR (KBr, ν_{max}, cm^{-1}): 3469 (N-H), 3110 (C-H), 1566 (C=C), 1471 (C=N), 1280 (C-N), 746 (Cl-C); ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 0.30-0.52 (2H, 0.37 m, 0.45 m), 0.89 (3H, dd, *J* = 6.6, 6.6 Hz), 1.09 (1H, m), 1.26-1.55 (4H, 1.35 m, 1.35 m, 1.48 m), 2.91 (1H, m), 4.48-4.60 (4H, 4.54 (d, *J* = 6.4 Hz), 4.54 (d, *J* = 6.4 Hz), 5.82 (2H, m), 6.23 (2H, d, *J* = 14.0 Hz); ^{13}C NMR (500 MHz, $CDCl_3$, δ ppm): 12.4 (1C, s), 13.7 (1C, s), 17.1 (1C, s), 19.6 (1C, s), 32.2 (1C, s), 49.9 (1C, s), 69.2 (2C, s), 119.9 (2C, s), 131.1 (2C, s), 162.7 (1C, s), 162.8 (2C, s); MS (ESI) *m/z*: 389.218, calcd.: 389.29.

4,6-*bis*((((*E*)-3-Chloroallyl)oxy)amino)-*N*-(2-isopropylcyclopropyl)-1,3,5-triazin-2-amine (5j): Yield (%): 88, m.p.: 119 ºC; Elemental anal. of $C_{15}H_{22}Cl_2N_6O_2$ (*m.w.* 389.29): Calcd. (found) %: C, 46.28 (46.29); H, 5.70 (5.71); Cl, 18.21 (18.24); N, 21.59 (21.55); O, 8.22 (8.20); IR (KBr, ν_{max}, cm^{-1}): 3459 (N-H), 3113 (C-H), 1570 (C=C), 1459 (C=N),1293 (C-N), 744 (Cl-C); ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 0.30-0.52 (2H, 0.37 m, 0.44 m), 0.82-0.94 (6H, 0.88 (d, *J* = 6.8 Hz), 0.88 (d, *J* = 6.8 Hz), 1.09 (1H, m), 1.67 (1H, m), 2.91 (1H, m), 4.48-4.60 (4H, 4.54 (d, *J* = 6.4 Hz), 4.54 (d, *J* = 6.4 Hz), 5.82 (2H, m), 6.23 (2H, d, *J* = 14.0 Hz); ^{13}C NMR (500 MHz, $CDCl_3$, δ ppm): 12.4 (1C, s), 17.8 (1C, s), 21.0-21.1 (2C, 21.0 (s), 21.0 (s), 27.9 (1C, s), 49.9 (1C, s), 69.2 (2C, s), 119.9 (2C, s), 131.1 (2C, s), 162.7 (1C, s), 162.8 (2C, s); MS (ESI) *m/z*: 389.17, calcd: 389.29.

***N*-(2-(*tert*-Butyl)cyclopropyl)-4,6-*bis*((((*E*)-3-chloroallyl)-oxy)amino)-1,3,5-triazin-2-amine (5k):** Yield (%): 71, m.p.: 161 ºC; Elemental anal. of $C_{16}H_{24}Cl_2N_6O_2$ (*m.w.* 403.31): Calcd. (found) %: C, 47.65 (47.68); H, 6.00 (6.01); Cl, 17.58 (17.61); N, 20.84 (20.83); O, 7.93 (7.92); IR (KBr, ν_{max}, cm^{-1}): 3441 (N-H), 3116 (C-H), 1572 (C=C), 1459 (C=N), 1274 (C-N), 744 (Cl-C); ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 0.28-0.53 (2H, 0.35 m, 0.45 m), 0.91 (9H, s), 1.08 (1H, m), 2.94 (1H, m), 4.48-4.60 (4H, 4.54 (d, *J* = 6.4 Hz), 4.54 (d, *J* = 6.4 Hz), 5.82 (2H, m), 6.23 (2H, d, *J* = 14.0 Hz); ^{13}C NMR (500 MHz, $CDCl_3$, δ ppm): δ 12.4 (1C, s), 21.4 (1C, s), 27.6 (3C, s), 30.7 (1C, s), 49.9 (1C, s), 69.2 (2C, s), 119.9 (2C, s), 131.1 (2C, s), 162.7 (1C, s), 162.8 (2C, s); MS (ESI) *m/z*: 403.28, calcd: 404.31.

4,6-*bis*((((*E*)-3-Chloroallyl)oxy)amino)-*N*-(2-isobutylcyclopropyl)-1,3,5-triazin-2-amine (5l): Yield (%): 80, m.p.: 149 ºC; Elemental anal. of $C_{16}H_{24}Cl_2N_6O_2$ (*m.w.* 403.81): Calcd. (found) %: C, 47.65 (47.64); H, 6.00 (6.02); Cl, 17.58 (17.59); N, 20.84 (20.82); O, 7.93 (7.91); IR (KBr, ν_{max}, cm^{-1}): 3448 (N-H), 3103 (C-H), 1571 (C=C), 1451 (C=N), 1269 (C-N), 747 (Cl-C); ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 0.30-0.53 (2H, 0.38 m, 0.45 m), 0.75-0.87 (6H, 0.81 (d, *J* = 6.6 Hz), 0.81 (d, *J* = 6.6 Hz), 0.99-1.28 (3H, 1.09 m, 1.21 (dd, *J* = 6.9, 6.7 Hz), 1.21 (dd, *J* = 6.9, 6.7 Hz), 1.51 (1H, m), 2.92 (1H, m), 4.48-4.60 (4H, 4.54 (d, *J* = 6.4 Hz), 4.54 (d, *J* = 6.4 Hz), 5.82 (2H, m), 6.23 (2H, d, *J* = 14.0 Hz); ^{13}C NMR (500 MHz, $CDCl_3$, δ ppm): 12.4 (1C, s), 17.1 (1C, s), 22.7-22.8 (2C, 22.8 (s), 22.8 (s), 26.5 (1C, s), 38.5 (1C, s), 49.9 (1C, s), 69.2 (2C, s), 119.9 (2C, s), 131.1 (2C, s), 162.7 (1C, s), 162.8 (2C, s), MS (ESI) *m/z*: 403.76, calcd.: 403.81.

Antimicrobial activity: The *in vitro* antimicrobial activity of the synthesised compounds (**5a-l**) was evaluated using the broth microdilution method in accordance with standard guidelines [22,23]. Bacterial strains (*Escherichia coli* MTCC 443, *Pseudomonas aeruginosa* MTCC 1688, *Staphylococcus aureus* MTCC 96 and *Streptococcus pyogenes* MTCC 442) were cultured in Mueller-Hinton broth, while fungal strains (*Candida albicans* MTCC 227, *Aspergillus niger* MTCC 282 and *Aspergillus clavatus* MTCC 1323) were maintained in Sabouraud dextrose broth. Stock solutions of the test compounds were prepared in DMSO and serially diluted in sterile broth to obtain concentrations ranging from 1000 to 50 μg/mL. The microbial suspensions were adjusted to a standard inoculum (≈10^6 CFU/mL for bacteria and ≈10^5 spores/mL for fungi) and added to each well of a 96-well microtiter plate containing the test compounds. The plates were incubated at 37 ºC for 24 h for bacteria and at 28 ºC for 48-72 h for fungi. Minimum inhibitory concentration (MIC) values were determined as the lowest concentration of the compound showing no visible growth. Ciprofloxacin and griseofulvin were used as standard antibacterial and antifungal agents, respectively, while wells containing only medium and DMSO served as controls.

Molecular docking studies: Molecular docking studies were conducted using the Glide module of Schrödinger Suite (Schrödinger, LLC, New York, NY) to assess the binding affinity of the test compound with the co crystal structure of *S. aureus* (PDB ID: 3FY8). The crystal structure was retrieved from the RCSB Protein Data Bank and prepared using the Protein Preparation Wizard, which included hydrogen atom addition, bond order assignment and optimisation of the hydrogen bonding network using PROPKA at pH 7.4. Water molecules beyond 5 Å from heteroatoms were deleted and the structure was energy-minimised using the OPLS4 force field until RMSD convergence to 0.30 Å. The ligand was prepared *via* LigPrep with ionisation states generated at pH 7.4 ± 2.0 using Epik, followed by tautomer and stereoisomer generation. A receptor grid of 20 Å × 20 Å × 20 Å was centered on the ATP-binding site of the co-crystal structure 3FY8, with van der Waals scaling set to 1.0 for atoms with partial charges < 0.25. Glide XP (Extra Precision) docking was performed with a flexible ligand and rigid receptor. The optimal binding pose was selected based on GScore, Emodel and interaction analysis. Binding interactions and free energies were evaluated using the Glide XP Visualizer and MM-GBSA calculations in Prime [24,25].

RESULTS AND DISCUSSION

The synthetic pathway involves stepwise nucleophilic substitution of cyanuric chloride with O-[(2E)-3-chloroprop-2-en-1-yl]hydroxylamine under controlled temperature to yield intermediates **3** and **4**. Subsequent substitution of the remaining chloro groups with aryl/cyclic amines in basic medium (NaOH, toluene) under reflux affords the target triazine derivatives (**5a-l**). All the compounds were characterised through mass spectrometry, ^{1}H NMR and ^{13}C NMR analysis. In the ^{1}H NMR spectra of all compounds, a broad singlet or doublet attributable to the N–H proton of the cyclic amine linkage (triazine–NH) was observed in the range δ 5.0-6.5 ppm (1H, br s). Additionally, broad signals in the δ 7.5-8.5 ppm region are assigned to the two allyloxyamine N–H protons (2H, br s). These N–H assignments were confirmed by D_2O exchange experiments, in which the relevant signals disappeared upon addition of D_2O. The integration values reported in the experimental section account for all protons including these exchangeable N–H signals.

Antibacterial activity: The antibacterial data revealed that all synthesised compounds (**5a-l**) exhibited moderate activity against the tested bacterial strains, with MIC values ranging from 50 to 250 μg/mL (Table-1). Among all compounds, compound **5b** demonstrated the most active broad-spectrum antibacterial profile in the series, showing MIC values of 50 μg/mL against both *E. coli* (MTCC 443) and *P. aeruginosa* (MTCC 1688) and 50 μg/mL against *S. pyogenes* (MTCC 442). It should be observed that these values remain 2-fold higher than those of the reference drug ciprofloxacin (MIC: 25-50 μg/mL) and therefore the synthesised compounds are best described as moderate antibacterial agents rather than potent ones. Compound **5i** showed the lowest MIC against *S. aureus* (MTCC 96) at 62.5 μg/mL, representing the best result for that strain within the series. Against Gram-negative bacteria, compounds **5a**, **5f**, **5g** and **5h** displayed moderate activity against *E. coli* and *P. aeruginosa* with MIC values of 100-125 μg/mL. For Gram-positive bacteria, compound **5e** exhibited activity against both *S. aureus* (MTCC 96) and *S. pyogenes* with MIC values of 100 μg/mL, while compounds **5c**, **5d**, **5h, 5i, 5j** and **5l** demonstrated MIC values of 100 μg/mL against *S. aureus.*

Antifungal activity: The antifungal evaluation revealed that most compounds exhibited moderate to weak antifungal activity with MIC values ranging from 100 to 1000 μg/mL. Compound **5k** displayed the most prominent antifungal activity against *C. albicans* (MTCC 227) with an MIC of 100 μg/mL, which is 5-fold lower than the MIC of the standard drug griseofulvin (MIC: 500 μg/mL) against this strain. Against *A. niger* (MTCC 282), compound **5b** showed moderate activity with an MIC value of 250 μg/mL, weaker than standard griseofulvin (MIC: 100 μg/mL) against this strain. For *A. clavatus* (MTCC 1323), compound **5b** demonstrated the best activity with an MIC of 100 μg/mL, equivalent to that of griseofulvin. Only compounds **5a**, **5g** and **5j** showed selective antifungal activity against *C. albicans* with MIC values of 250-500 μg/mL while maintaining moderate antibacterial properties.

Molecular docking results: Molecular docking studies against *S. aureus* DNA gyrase (PDB: 3FY8) revealed that all the synthesised compounds (**5a-l**) exhibited favourable binding interactions within the active site, with docking scores ranging from -4.381 to -7.074 kcal/mol (Table-2). Compound **5e** demonstrated the highest binding affinity among the synthesised series (-7.074 kcal/mol), though this value remains lower than that of the reference antibiotic ciprofloxacin (-7.778

TABLE-1
MINIMUM INHIBITORY CONCENTRATIONS (MIC, μg/mL) OF SYNTHESISED TRIAZINE DERIVATIVES (**5a-l**) AGAINST BACTERIAL AND FUNGAL STRAINS

Compound	*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)
5a	125	100	200	250	500	500	500
5b	50	50	100	50	500	250	100
5c	200	250	125	100	500	1000	1000
5d	200	100	100	200	1000	500	500
5e	250	200	100	100	500	500	1000
5f	100	100	200	125	1000	500	500
5g	100	100	250	250	250	500	500
5h	125	100	100	125	500	1000	1000
5i	125	200	62.5	100	1000	500	500
5j	200	250	100	100	250	500	500
5k	250	200	250	250	100	500	1000
5l	200	100	100	250	500	1000	1000
Ciprofloxacin	25	25	50	50	–	–	–
Grieseofulvin	–	–	–	–	500	100	100

TABLE-2
MOLECULAR DOCKING RESULTS OF SYNTHESISED TRIAZINE DERIVATIVES (**5a-l**) WITH *S. aureus* DNA GYRASE (PDB ID: 3FY8)

Compound	Docking score (kcal/mol)	Interacting amino acids			
		Hydrophobic interactions	Polar interactions	H-bond	Others
5a	-5.247	VAL 6, VAL 31, ALA 7, LEU 5, LEU 20, ILE 14, ILE 50, PHE 92, TYR 98, TRP 22, GLY 43, GLY 93, GLY 94	THR 46, THR 96, THR 111, THR 121, GLN 19, GLN 95, ASN 18, SER 49	TYR 98 (H-bond with O), GLY 94 (halogen bond with Cl)	ASP 27 (charged negative), LYS 45 (charged positive)
5b	-5.897	VAL 6, ALA 7, LEU 5, LEU 20, LEU 97, ILE 14, ILE 50, PHE 92, TYR 98, TRP 22, GLY 15, GLY 43, GLY 93, GLY 94	THR 46, THR 96, THR 121, GLN 19, GLN 95, ASN 18, SER 49	ASN 18 (H-bond with NH)	LYS 45 (charged positive)
5c	-6.357	VAL 6, VAL 31, ALA 7, LEU 5, LEU 20, LEU 28, ILE 14, ILE 50, PHE 92, TYR 98, GLY 15, GLY 93, GLY 94	THR 121, GLN 19, GLN 95, ASN 18, SER 49	TYR 98 (H-bond with cyclopentyl NH), LEU 20 (halogen bond with Cl)	ASP 27 (charged negative), LYS 45 (charged positive)
5d	-5.811	VAL 6, VAL 31, ALA 7, LEU 5, LEU 20, LEU 28, ILE 14, ILE 50, PHE 92, TYR 98, GLY 15, GLY 93, GLY 94	THR 46, THR 96, THR 121, GLN 19, GLN 95, ASN 18, SER 49	TYR 98 (H-bond with THR 96), LEU 20 (halogen bond with Cl)	ASP 27 (charged negative), LYS 45 (charged positive)
5e	-7.074	VAL 6, VAL 31, ALA 7, LEU 5, LEU 28, ILE 14, ILE 50, PHE 92, TYR 98, TRP 22, GLY 43, GLY 93, GLY 94	THR 46, THR 96, THR 121, GLN 19, GLN 95, ASN 18, SER 49	LEU 97 (halogen bond with Cl)	ASP 27 (charged negative), LYS 45 (charged positive)
5f	-6.815	VAL 6, VAL 31, ALA 7, LEU 5, LEU 28, LEU 54, ILE 14, PHE 92, TYR 98, GLY 43, GLY 93, GLY 94	THR 46, THR 96, THR 121, GLN 19, GLN 95, ASN 18, SER 49	–	LYS 45 (charged positive)
5g	-4.381	VAL 6, VAL 31, ALA 7, LEU 5, LEU 20, LEU 28, ILE 14, ILE 50, PHE 92, TYR 98, GLY 15, GLY 43, GLY 93, GLY 94	THR 46, THR 96, THR 111, GLN 19, GLN 95, ASN 18, SER 49	TYR 98 (H-bond with NH), GLY 94 (halogen bond with Cl)	ASP 27 (charged negative), LYS 45 (charged positive)
5h	-6.219	VAL 6, VAL 31, ALA 7, LEU 5, LEU 20, ILE 14, PHE 92, GLY 15, GLY 93, GLY 94	THR 46, THR 96, THR 121, GLN 95, ASN 18, SER 49	–	LYS 45 (charged positive)
5i	-5.342	VAL 6, VAL 31, ALA 7, LEU 5, LEU 20, LEU 28, LEU 97, ILE 14, PHE 92, TYR 98, TRP 22, GLY 15, GLY 93, GLY 94	THR 46, THR 96, THR 121, GLN 19, GLN 95, ASN 18, SER 49	GLN 95 (H-bond with O)	LYS 45 (charged positive)
5j	-6.081	VAL 6, VAL 31, ALA 7, LEU 5, LEU 28, ILE 14, PHE 92, TYR 98, GLY 15, GLY 93, GLY 94	THR 46, THR 96, THR 111, THR 121, GLN 19, GLN 95, ASN 18, SER 49	TYR 98 (H-bond with O)	ASP 27 (charged negative), LYS 45 (charged positive)
5k	-6.773	VAL 6, VAL 31, ALA 7, LEU 5, LEU 97, ILE 14, ILE 50, PHE 92, TYR 98, TRP 22, GLY 15, GLY 43, GLY 93, GLY 94	THR 46, THR 96, THR 121, GLN 19, GLN 95, ASN 18, SER 49	LEU 97 (halogen bond with Cl)	LYS 45 (charged positive)
5l	-6.642	VAL 6, VAL 31, ALA 7, LEU 5, LEU 20, LEU 28, LEU 54, LEU 97, ILE 14, ILE 50, PHE 92, TYR 98, GLY 15, GLY 43, GLY 93, GLY 94	THR 46, THR 96, THR 121, GLN 19, GLN 95, ASN 18, SER 49	LEU 97 (halogen bond with Cl)	ASP 27 (charged negative), LYS 45 (charged positive)
Ciprofloxacin	-7.778	VAL 6, VAL 31, ALA 7, LEU 5, LEU 20, LEU 28, LEU 54, ILE 14, ILE 50, PHE 92, TYR 98, TRP 22, PRO 21, GLY 15, GLY 93, GLY 94	THR 46, GLN 19, ASN 18, SER 49	TYR 98 (H-bond with OH)	–
Griseofulvin	-3.691	ILE 14, LEU 97, PHE 42, PHE 47, PHE 122, MET 42, GLY 43, GLY 93, GLY 94	THR 46, THR 96, THR 121, GLN 95, ASN 18	THR 46 (H-bond with O)	ASP 120 (charged negative), GLU 17 (charged negative), GLU 99 (charged negative), LYS 45 (charged positive), ARG 44 (charged positive)

kcal/mol). Compound **5g** showed the weakest interaction (-4.381 kcal/mol). It is noteworthy that docking scores do not directly correlate with *in vitro* MIC values, as compound 5b showed the highest antibacterial activity despite a moderate docking score (-5.897 kcal/mol), whereas compound **5e** exhibited the best docking score but comparatively weaker MIC values. This discrepancy indicates that pharmacokinetic factors, membrane permeability and other cellular processes may significantly influence antibacterial activity and DNA gyrase inhibition cannot be considered the sole mechanism at this stage.

The binding mode analysis revealed that all compounds occupied the same binding pocket and formed extensive interactions with key active-site residues. Hydrophobic interactions predominantly involved VAL 6, ALA 7, LEU 5, ILE 14, PHE 92, TYR 98 and GLY 93/94, which formed a stable hydrophobic core essential for ligand stabilisation. Polar residues including THR 46, THR 96, GLN 19, GLN 95, ASN 18 and SER 49 contributed to the binding stability through van der Waals contacts and electrostatic interactions.

Several compounds formed hydrogen bonds with TYR 98 (**5a**, **5c**, **5d**, **5g**, **5j**), a catalytically important residue in the DNA gyrase active site, similar to ciprofloxacin. This interaction pattern suggests DNA gyrase inhibition as a plausible, though speculative, mechanism. Compound **5e**, despite lacking direct hydrogen bonding, exhibited halogen bonding with LEU 97 (Cl) and extensive hydrophobic contacts, explaining its superior computational score. Halogen bonding interactions were observed in compounds **5a**, **5c**, **5d**, **5e**, **5k** and **5l**, providing additional stabilisation within the binding pocket.

Charged interactions with ASP 27 (negative) and LYS 45 (positive) were observed in several compounds, **5a**, **5c**, **5d**, **5e**, **5j**, **5l**, further anchoring the ligands within the binding pocket. The electrostatic interactions, combined with hydrogen bonding and halogen bonding, contributed to the enhanced computational binding scores of the more active compounds. Infrared spectral analysis of the synthesised compounds provided meaningful diagnostic information. Interestingly, griseofulvin, included as a reference antifungal agent, exhibited the weakest binding affinity (-3.691 kcal/mol) and a distinct binding orientation, engaging primarily peripheral residues (PHE 42, PHE 47, PHE 122) rather than core active-site residues. This distinct interaction profile correlates with its lack of antibacterial activity against *S. aureus.*

SAR studies: The structure-activity relationship analysis provided several useful observations, albeit from a limited set of structural variations. Among compounds bearing simple cyclic amine substituents **5a-f**, a non-linear relationship between ring size and antibacterial activity was observed. The four-membered cyclobutyl derivative **5b** exhibited the best antibacterial activity in the series (MIC 50 μg/mL against *E. coli* and *S. pyogenes*), outperforming the smaller cyclopropyl analogue **5a** (MIC 125-250 μg/mL) and the larger cyclopentyl (**5c**), cyclohexyl (**5d**), cycloheptyl (**5e**) and cyclooctyl (**5f**) analogues. This suggests an optimal ring size around carbons for antibacterial activity, consistent with earlier SAR reports on triazine-based antimicrobials where moderate steric bulk enhanced membrane permeation and target engagement [26]. The cyclooctyl derivative **5f** showed a marked decrease in activity (MIC 100-200 μg/mL), possibly due to increased

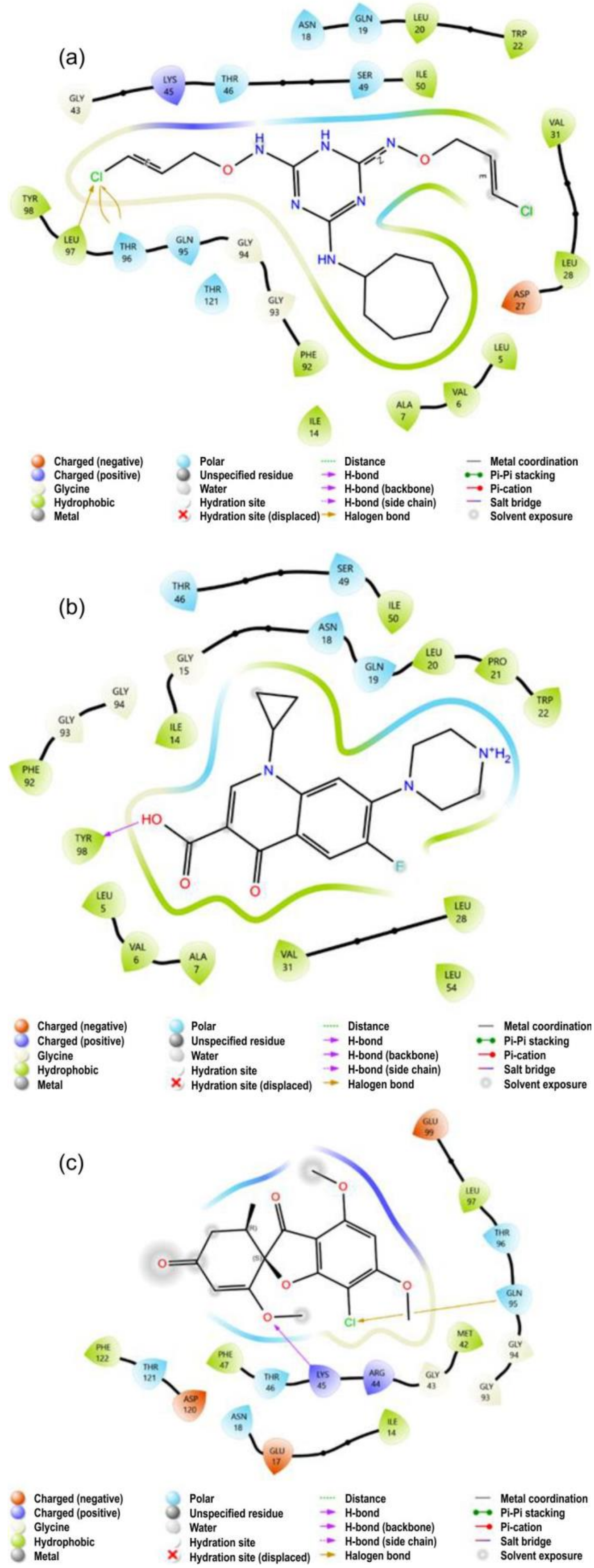


Fig. 1. 2D interaction diagram of compound **5e** (a), cipro-floxacin (b) and griseofulvin (c) with *S. aureus* DNA gyrase (PDB ID: 3FY8)

lipophilicity impeding aqueous solubility and thus cellular uptake. Among the substituted cyclopropylamine series (**5g-l**), compounds bearing bulkier substituents such as isopropyl (**5j**, MIC 100 µg/mL *vs.* *S. aureus*) and *tert*-butyl (**5k**, MIC 100 µg/mL *vs.* *C. albicans*) showed distinct selectivity profiles, with **5k** displaying notably superior antifungal activity. The presence of branched alkyl substituents on the cyclopropyl ring appears to influence selectivity between bacterial and fungal targets, which may reflect differences in cell-wall composition and membrane sterol content. It must be observed that the structural variation explored in this series was confined to the cyclic amine substituent at the C-2 position of the triazine ring, while the two O-[(2*E*)-3-chloroallyl]oxyamine groups remained constant. Broader SAR exploration varying all three triazine positions would be required to draw stronger conclusions. These computational findings, while supporting DNA gyrase as one potential target, should be interpreted alongside the biological data with the caveat that the poor docking score-MIC correlation indicates other cellular factors are likely operative (Fig. 1).

Conclusion

The sequential nucleophilic substitution of cyanuric chloride provides an efficient, operationally simple synthetic route to a diverse array of trisubstituted *s*-triazine derivatives. Antimicrobial evaluation revealed that compound **5i** showed the lowest MIC against *S. aureus* (MIC 62.5 µg/mL), while compound **5b** was the most active antibacterial member of the series (MIC 50-100 µg/mL), though remaining weaker than the reference ciprofloxacin. Compound **5k** showed significant antifungal activity against *C. albicans* (MIC 100 µg/mL) compared to griseofulvin. Molecular docking studies against *S. aureus* DNA gyrase indicated that compound **5e** exhibited the highest computational binding affinity (-7.074 kcal/mol) among the synthesised compounds, with key interactions involving TYR 98, halogen bonding with LEU 97 and electrostatic contacts with ASP 27/LYS 45. Although a direct correlation between docking scores and MIC values was not observed, the obtained data suggest that DNA gyrase may be a relevant, albeit not exclusive, target for further investigation. These results suggest that the synthesised triazine derivatives are moderate yet promising lead scaffolds, deserving further optimisation, particularly in terms of cyclic amine ring size and substituent effects.

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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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