Journal of Advanced Scientific Research

Available online through https://sciensage.info

ISSN

0976-9595

Research Article

Synthesis, Characterisation and Biological Assessment of 2,4,6-Trisubstituted 1,3,5-Triazine Derivatives

Mayur L. Chandera[1*], Kinjal J. Sabalpara[1], Chetana M. Rajyaguru[1], Jatin J. Upadhyay[1]

Department of Chemistry, Matrushri Virbai Mahila Science & Home Science College, Saurashtra University, Rajkot, Gujarat, India.

*Corresponding author: chanderamayur419@gmail.com

Received: 14-08-2025; Accepted: 07-09-2025; Published: 30-09-2025

https://doi.org/10.55218/JASR.2025160902

ABSTRACT

2,4,6-trichloro-1,3,5-triazine (Cyanuric Chloride) and 4-(4-aminophenyl)morpholin-3-one were converted into a new series of 2,4,6-trisubstituted 1,3,5-triazine derivatives by a regioselective reaction, which was followed by reflux with substituted thiophenole in the presence of a catalytic amount of triethyl amine. IR, ^{1}H-NMR, mass, and elemental analysis were used to characterise each of the synthesised substances. All the synthesized compounds were tested for their *in vitro* antimicrobial activity against gram-positive strains, such as *Staphylococcus aureus* and *Bacillus subtilis,* as well as gram-negative strains, such as *Escherichia coli* and *Pseudomonas aeruginosa,* by using ampicillin, chloramphenicol and tetracycline as standard drugs. *In-vitro* antifungal activity was tested against three different fungal strains, such as *Candida albicans*, *Aspergillus flavus* and *Aspergillus niger.* Most of the compounds showed moderate to good activity. Among them, compound CML-1F is most active against bacterial species and compound CML-1H exhibited potent antifungal activity.

Keywords: 2,4,6-trichloro-1,3,5-triazine, 4-(4-aminophenyl)morpholin-3-one, substituted thiophenol, Regioselective reaction, Antimicrobial activity.

INTRODUCTION

Heterocyclic motifs with six members that have three nitrogen atoms in their ring structure are called triazines. Because of its reactivity and diverse functionalisation, this family of heteroaromatics is extensively studied and used. The synthesis of a wide variety of heterocyclic systems is made easier by the potential ring transformations. Furthermore, nucleophilic aromatic addition or substitution is made possible by the triazine ring's electrophilicity. They are crucial for creating bioactive chemicals because of their high reactivity, which allows them to be further modified via a range of potential pathways. Triazines are therefore widely used in the synthesis of natural products or in the creation of novel materials with a variety of unique characteristics, such as sensing, luminescence, liquid crystal, etc. There are three analogues of triazines, depending on where the nitrogen is situated in the ring.

1,2,3-triazine

1,2,4-triazine

1,3,5-triazine

According to a review of the literature, the 1,3,5-triazine nucleus has long attracted the interest of chemists and researchers because of its important biological properties and wide range of applications [1]. Their strong biological activity is the primary reason they continue to attract a lot of attention.

Numerous advantageous pharmacological actions, including A2A antagonism [2], NF-κB inhibition [3], antibacterial [4-6], antimalarial [7,8], and antifungal activities [9], are exhibited by 1,3,5-triazine, a heterocyclic nucleus. Additionally, 1,3,5-triazine exhibits anti-cancer efficacy through targeting multiple RTKs, including mTOR [15,16], EGFR [10], RET [11], and VEGFR [12], but most significantly, PI3K [13,14]. The s-triazine nucleus is found in several heterocyclic compounds that are employed as antitumor [21], anti-protozoal [17], oestrogen receptor modulators [18], cyclin dependent kinase modulators [19], and antimicrobials [20], and antitumor [21].

Various 1,3,5-triazine morpholine-containing compounds show excellent inhibitory activity against PI3K/mTOR kinases and are at various stages of drug development.

MATERIAL AND METHODS

All the chemicals used to synthesize the library were purchased from CDH Chemicals, Delhi, of AR grade and were used as available without further purification. The progress of reaction was monitored by thin-layer chromatography (TLC) on silica gel-G plates (G60 F254 (Merck)) of 0.5 mm thickness, and the developed spots were made visualized with ultraviolet light (254 and 365 nm) and Iodine vapor. Melting points of the synthesized compounds were measured by the open capillary method and are uncorrected. IR spectra were recorded on an FTIR-8400 spectrophotometer (Shimadzu, Kyoto, Japan), using the DRS probe KBr pellet method. 1H-NMR spectra

of the synthesized compounds were recorded on a Bruker Advance-II (400 MHz) spectrometer using DMSO-d6 solvent. Chemical shift values are expressed in δ ppm by using TMS as an internal standard. Mass spectra were determined using a direct inlet probe on a QC-LCMS-QP 2010 mass spectrometer (Shimadzu, Kyoto, Japan).

Reaction scheme/synthetic pathway

The synthetic pathway for the targeted compounds CML-1A to CML-1N is shown in Fig.1a, and the physical parameters of the synthesized products are shown in Table 1. The first step of synthesis involves the Regioselective reaction of 2,4,6-trichloro-1,3,5-triazine (Cyanuric Chloride) with 4-(4-aminophenyl)morpholin-3-one (Aromatic amine) to form 4-(4-((4,6-dichloro-1,3,5- triazin-2-yl) amino)phenyl)morpholin-3-one(INT-1). The second step is the synthesis of the target molecule, which is achieved by reflux of INT-1 with various substituted thiophenols in the presence of a catalytic amount of triethylamine.

Experimental procedure

General synthesis of 4-(4-((4,6-dichloro-1,3,5-triazin-2-yl)amino) phenyl) morpholin-3-one (INT-01)

To a stirred solution of 2,4,6-trichloro-1,3,5-triazine (10 g,0.054 mol) in anhydrous acetone (150 mL) 4-(4-aminophenyl)morpholin-3-one (10.09 g, 0.054 mol) was drop wise added dropwise at 0°C. The resulting reaction mixture was stirred at this temperature for 2 hours. Then Aqu. Solution of $NaHCO_3$ (5.48 g, 0.054 mol) was added and stirring was continued for another 5 h. The reaction mixture was then treated with crushed ice, followed by neutralization with dilute HCl, and filtered, dried, and recrystallized from acetone to afford int-1. Yield 88%, m.p. 259°C.

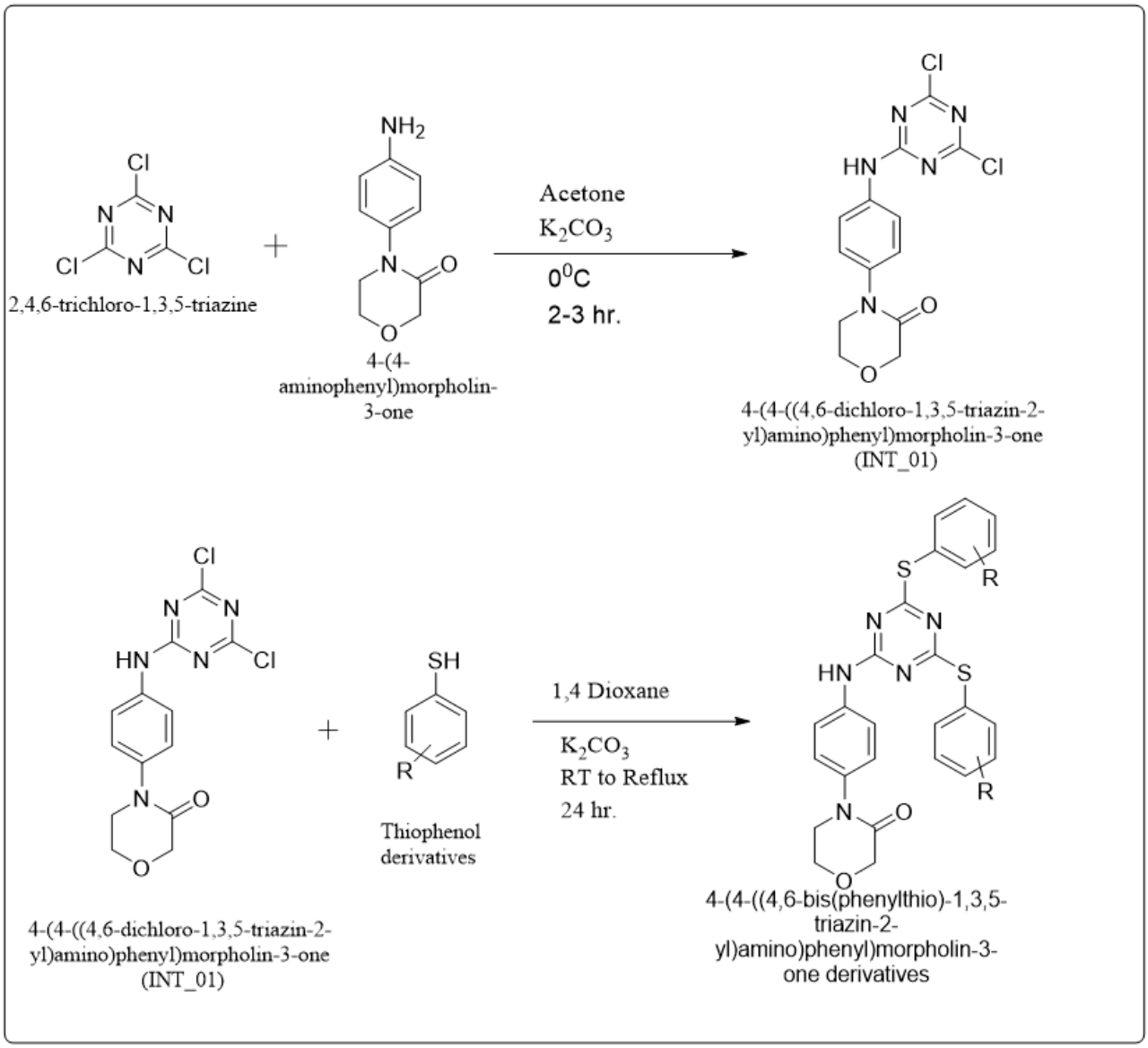


Fig. 1a: The synthetic pathway for the targeted compounds (CML-1A to CML-1N)

General synthesis of 4-(4-((4,6-bis(phenylthio)-1,3,5-traizin-2-yl)amino) phenyl)morpholin-3-one derivatives (CML-1A to CML-1N)

To a solution of 4-(4-((4,6-dichloro-1,3,5-triazin-2-yl)amino)phenyl) morpholin-3-one, INT-01 (0.01 mol) in 1,4-dioxane (30 mL), the respective substituted Thiophenol derivative was added(2equivalent) and the reaction mixture was stirred at RT for 24h. Potassium carbonate (2 equivalents) was used for neutralization of the reaction mixture. The progress of the reaction was monitored by TLC using toluene: acetone (8:2) as eluent. The mixture was then treated with crushed ice and neutralized by dilute HCl. The precipitate thus obtained was filtered off, dried and recrystallized from THF to afford the desired compounds.

Biological Assessment

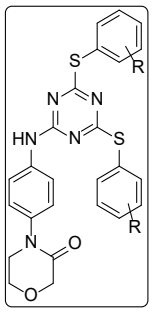
All the synthesized compounds were tested for their *in vitro* antimicrobial activity against Gram +ve strains, such as *Staphylococcus aureus* and *Bacillus subtilis* as well as Gram -ve strains, such as *Escherichia coli* and *Pseudomonas aeruginosa,* by using ampicillin, chloramphenicol and tetracycline as standard drugs. *In vitro* antifungal activity was tested against three different fungal strains, such as *Candida albicans*, *Aspergillus flavus* and *Aspergillus Niger*. To prepare a solution with 2000 µg/mL of each target molecule, the target compounds (2 mg) were dissolved in DMSO (1-mL). An additional stepwise two-fold dilution in Muller-Hinton broth was carried out to achieve the Minimum concentrations of 1000, 500, 250, 125, 62.5, and 31.25 µg/mL. The control test was performed by using a medium supplemented with DMSO at the same dilutions used in the experiment to ensure that the solvent was not affecting the growth of bacteria.

Suspension of fresh bacterial and fungal cultures was prepared in N-broth and potato dextrose broth, respectively. In primary screening, 1000, 500, and 250 µg/mL concentrations of the synthesized drugs were used. The active synthesized drugs found in this primary screening were further tested in the second set of dilutions at 125, 62.5, and 31.25 µg/mL concentration against all microorganisms. The tubes were inoculated with 108 bacterial CFU/mL and incubated at 37°C for 24 hours. The MIC was reported.

RESULTS AND DISCUSSION

All the tri-substituted triazine derivatives were synthesized in a simple way and in moderate to high yield. Newly synthesized compounds were characterized by spectral analysis such as IR, ^{1}H-NMR and Mass Spectra and structures were confirmed. The synthesized compounds were examined for their antibacterial and antifungal activity. Most of the compounds showed moderate to good activity. Among them, compound CML-1F is most active against bacterial species and compound CML-1H exhibited potent antifungal activity

Table 1: Physical parameters of 4-(4-((4,6-bis(phenylthio)-1,3,5-triazin-2-yl)amino)phenyl) morpholin-3-one derivatives (CML-1A to CML-1N)



Compound code	*Mol. Formula*	*'R' Substitution*	*Mol.Weight*	*% ofYield*	*M.P (^{0}C)*
CML-1A	$C_{25}H_{21}N_5O_2S_2$	H	487.60	79	312–314
CML -1B	$C_{25}H_{19}Cl_2N_5O_2S_2$	4-chloro	556.48	71	332–334
CML -1C	$C_{27}H_{25}N_5O_2S_2$	4-methyl	515.65	65	285–287
CML -1D	$C_{27}H_{25}N_5O_4S_2$	4-methoxy	547.65	62	296–298
CML -1E	$C_{25}H_{17}Cl_4N_5O_2S_2$	2,4-dichloro	625.36	65	343–345
CML -1F	$C_{29}H_{29}N_5O_6S_2$	2,4-dimethoxy	607.70	54	321–323
CML -1G	$C_{27}H_{23}Cl_2N_5O_2S_2$	3-chloro-2-methyl	584.53	63	285–293
CML -1H	$C_{25}H_{19}F_2N_5O_2S_2$	4-fluoro	523.58	70	294–305
CML -1I	$C_{25}H_{19}Br_2N_5O_2S_2$	4-bromo	645.39	81	352–354
CML -1J	$C_{25}H_{19}N_7O_6S_2$	4-nitro	577.59	65	363–365
CML -1K	$C_{25}H_{17}N_9O_{10}S_2$	2,4-dinitro	667.58	63	376–378
–CML -1L	$C_{29}H_{29}N_5O_2S_2$	4-ethyl	543.70	65	292–294
CML -1M	$C_{27}H_{25}N_5O_2S_2$	2-methyl	515.65	62	286–288
CML -1N	$C_{25}H_{17}Br_2C_{l2}N_5O_2S_2$	4-bromo-2-chloro	714.27	65	358–360

(Tables 2 and 3).

Spectral Analysis of Synthesized Compounds

4-(4-((4,6-bis(phenylthio)-1,3,5-triazin-2-yl)amino)phenyl) morpholin-3-one (CML- 1A)

White Solid, Yield: 71%. IR (KBr, νmax, cm-1): 3457 & 3411 (N-H stretching, primary or secondary amines), 3089.96(C-H stretching aromatics), 2911, 2871 (C-H stretching, alkane), 1680 (-CO-NH, amide carbonyl), 1513.84, 1467.94 (C=C stretching in ring, aromatic), 1389,1314 (C-N stretching aromatic 3° amine), 1247.85 (C-N stretching, aromatic amines), 1155.07 (C-O stretching of ether), 1122.41, 1038.38, 994.81 (C-N stretching, aliphatic amines), 919.48(in plane Ar-C-H bending), 841.88 (p-substituted aromatic), 747.15, 686.52 (Ar-C-H out of plane bending, monosubst, Ar ring), 644.59(C-S stretching). 1H NMR (400 MHz, DMSO) in δ ppm: a=3.67 (2H, t, -CH2-), b=3.96(2H, t, -CH2-), c=4.18 (2H, s, -CH2-), d=7.10-7.12 (2H, complex, Ar-H), e=7.19-7.26 (2H, complex, Ar-H), f, f'=7.45-7.47 (4H, complex, Ar-H), g, g'=7.52 (2H, complex, Ar-H), h,h'=7.54-7.66(4H, complex, Ar-H), i=10.26 (1H, s, -NH-) Elemental Analysis: Cal.: C; 57.48%, H; 4.05%, Cl;13.57%, N; 18.77%, O; 6.13%, Found: C; 57.52%, H; 4.09%, Cl; 13.52, N; 18.73%, O; 6.12%.

4-(4-((4,6-bis((4-chlorophenyl)thio)-1,3,5-triazin-2-yl) amino)phenyl)morpholin-3-one (CML-1B)

White Solid, Yield: 71 %. IR (KBr, ν_{max}, cm^{-1}): 3496.55 (N-H stretching, primary or secondary amines), 3101.19, 3058.08 (C-H stretching aromatics), 2992.08, 2952.90, 2831.55 (C-H stretching, alkane),1689.17 (-CO-NH, amide carbonyl), 1587.27, 1493.27, 1455.72 (C=C stretching in ring, aromatic), 1385.48,1347.83 (C-N stretching aromatic 3° amine), 1296.39, 1250.28 (C-N stretching, aromatic amines), 1176.63 (C-O stretching of ether), 1183.27, 1145.49, 1113.04, 1033.12, 1004.88 (C-N stretching, aliphatic amines), 919.40(in plane Ar-C-H bend.), 850.07(p-substituted aromatic), 832.28, 759.62 (C-Cl stretching), 640.67 (C-S stretching). ^{1}H- NMR (400 MHz, DMSO) in δ ppm: a=3.63 (2H, t, -CH_2-), b=3.94 (2H, t, -CH_2-), c=4.18 (2H, s, -CH_2-), d=7.02-7.04 (2H, complex, Ar-H), e=7.39-7.41 (2H, complex, Ar-H), f, f'=7.22-7.29 (4H, complex, Ar-H), g, g'=7.48-7.60 (4H, complex, Ar-H), h=10.21 (1H, s, -NH-). Elemental Analysis: Cal.: C; 53.96%, H; 3.44%, Cl; 12.74%, N; 12.59%, O; 5.75%. Found: C; 53.92%, H; 3.47%, Cl; 12.71%, N; 12.62%, O; 5.71%.

4-(4-((4,6-bis(p-tolylthio)-1,3,5-triazin-2-yl)amino)phenyl) morpholin-3-one (CML- 1C)

Off white solid, Yield: 65%. IR (KBr, νmax, cm-1): 3285.55 (N-H stretching, primary or secondary amines), 3111.08, 3058.26 (C-H stretching aromatics), 2982.14, 2913.36, 2871.32 (C-H stretching, alkane), 1687.17 (-CO-NH, amide carbonyl), 1516.16, 1474.12, (C=C stretching in ring, aromatic), 1389.48,1337.83 (C-N stretching aromatic 3° amine), 1243.00 (C-N stretching, aromatic amines), 1179.63 (C-O stretching of ether), 1119.84, 992.94 (C-N stretching, aliphatic amines), 922.40 (in plane Ar-C-H bend.), 855.07(p-substituted aromatic), 792.39,725.53 680.41 (Ar-C-H out of plane bending, monosubst. Ar ring), 645.67 (C-S stretching). ^{1}H-NMR (400 MHz, DMSO) in δ ppm: a=3.64-3.66 (2H, t, -CH_2-), b=3.94-3.96(2H, t, -CH_2-), c=4.18 (2H, s, -CH_2-), d=7.02-7.04 (2H, complex, Ar- H), e=7.18-7.20 (2H, complex, Ar-H), f, f'=7.23-7.28 (4H, complex, Ar-H), g, g'=7.37-7.46 (4H, complex, Ar- H), h,h'=2.37-2.40(6H, s, 2(-CH_3)), I =10.16 (1H, s, -NH-).. Elemental Analysis: Cal.: C; 62.89%, H; 4.89%, N; 13.58%, O; 6.21, S; 12.43 Found: C; 62.93%, H;4.94%, Cl; 13.52, N; 13.53%, O; 6.25, S; 12.47%

4-(4-((4,6-bis((4-methoxyphenyl)thio)-1,3,5-triazin-2-yl) amino)phenyl)morpholin-3-one (CML-1D)

Off white solid, Yield: 62%.IR (KBr, νmax, cm-1): 3279.33, 3130.51 (N-H stretching, primary or seconadry amines), 3115.26, 3057.70 (C-H stretching aromatics), 2958.67, 2852.10, 2833.65 (C-H stretching, alkane), 1633.62(C=O stretching, ketone), 1690(-CO-NH, amide carbonyl) 1545.25, 1496.67, 1423.56 (C-C stretching in ring, aromatic), 1375.48,1345.83 (C-N stretching aromatic 3° amine), 1296.14, 1253.29 (C-N stretching, aromatic amines), 1171.29,1149.32,1112.89,1037.32 (C-N stretching, aliphaticamines).1187.63(C-O stretching of ether),918.40(in plane Ar-C-H bend.),859.07(p-substituted aromatic), 792.39,725.53 680.41 (Ar-C-H out of plane bending, monosubst. Ar ring), 642.67 (C-S stretching). 1H NMR (400 MHz, DMSO) in δ ppm: 1.898(6H, s, -CH_3), 3.710-3.734(2H, t, -CH_2-), 3.931-3.968 (2H, t, -CH_2-), 4.195 (2H, s, -CH_2-), 6.799-7.462(8H, complex, Ar-H), 7.628- 7.735 (4H, complex, -Ar-H), 9.208 (1H, s, -NH-). Elemental Analysis: Cal. (%): C; 59.22%, H; 4.60%, N; 12.79%, O; 11.69, S; 11.71 %. Found: C; 59.18%, H; 4.63%, N;12.77%, O; 11.72%, S; 11.68 %

4-(4-((4,6-bis((2,4-dichlorophenyl)thio)-1,3,5-triazin-2-yl)amino)phenyl)morpholin-3-one (CML-1E)

Off white solid, Yield: 65%. IR (KBr, νmax, cm-1): 3492.53, 3475.78 (N-H stretching, primary or seconadry amines), 3121.58, 3054.26 (C-H stretching aromatics), 2994.29, 2955.62, 2834.73 (C-H stretching, alkane), 1591.42, 1496.28, 1456.73 (C-C stretching (in ring), aromatic), 1355.27, 1298.02, 1248.29 (C-N stretching, aromatic amines), 1153.48,1125.72, 1030.87 (C-N stretching, aliphatic amines), 1179.63 (C-O stretching of ether), 845.20 (p-substituted aromatic ring),829.23, 762.78 (C-Cl stretching), 740.15(ortho disubstituted aromatic ring). 1H NMR (400 MHz, DMSO) in δ ppm: 3.710-3.734 (2H, t, -CH2-), 3.931-3.968 (2H, t, -CH2-), 4.195 (2H, s, -CH2-), 6.799-7.462(2H, d, Ar-H), 7.633-7.7779 (2H, d,-Ar-H), 7.825(2H, s, Ar-H), 7.628-7.735 (4H, complex, -Ar-H), 9.208 (1H, s, -NH-). Elemental Analysis: Cal.: C; 48.02%, H; 2.74%, N; 11.20%, O; 5.12 %, S; 10.25 %, Cl; 22.67 %. Found: C; 48.05%, H; 2.71%, N;12.77%, O; 5.09%, S; 10.27%, Cl; 22.64 %.

4-(4-((4,6-bis((2,4-dimethoxyphenyl)thio)-1,3,5-triazin-2-yl)amino)phenyl)morpholin-3-one (CML-1F)

Off white solid, Yield: 54%.IR (KBr, νmax, cm-1): 3490.34, 3477.27 (N-H stretching, primary or seconadry amines), 3125.37, 3058.64 (C-H stretching aromatics), 2998.65, 2952.87, 2832.38 (C-H stretching, alkane),2850 (O-CH_3, methyl ether C-H

stretching),1639.62(C=O stretching, ketone), 1491.63, 1458.35 (C-C stretching (in ring), aromatic), 1367.14(C-O stretching of ether), 1289.87, 1243.09 (C-N stretching, aromatic amines), 1152.29, 1122.55,1033.73(C-N stretching, aliphatic amines), 855(p-disubstituted aromatic ring),750(ortho disubstituted aromatic ring), 640.02(C-S stretching). 1H NMR (400 MHz, DMSO) in δ ppm: 3.710(2H, t, - CH2-), 3.737 (6H, s, -OCH3), 3.680(6H, s, -OCH3), 3.948-3.960 (2H, t, -CH2-), 4.182 (2H, s, -CH2-), 6.859-6.880(4H, d, Ar-H), 7.235-7.256(2H, d, Ar-H), 7.638-7.777 (2H, d, -Ar-H), 7.821(2H, s, Ar-H), 9.208 (1H, s, -NH-). Elemental Analysis: Cal.: C; 57.32%, H; 4.81%, N;11.52%, O; 15.80 %, S; 10.55 %. Found: C; 57.36%, H; 4.79%, N;11.54%, O; 15.77 %, S; 10.58%.

4-(4-((4,6-bis((3-chloro-2-methylphenyl)thio)-1,3,5-triazin-2-yl)amino)phenyl)morpholin-3-one (CML-1G)

Off white solid, Yield: 63%. IR (KBr, νmax, cm-1): 3589.97, 3413.94 (N-H stretching, primary or seconadry amines), 3191.33, 2974.66 (C-H stretching aromatics), 2922.39, 2850.37 (C-H stretching, alkane), 1674 (-CO-NH, amide carbonyl), 1728.06(C=O stretching), 1538.10, 1447.11 (C-C stretching in ring aromatic), 1378.52, 1345.95, 1308.17 (C-N stretching aromatic 30 amine), 1160.20, 1071.22, 1015.67 (C-N stretching, aliphatic amines), 782.93(C-Cl stretching), 789,875(meta disubstituted aromatic ring),750 (ortho disubstituted aromatic ring), 678.18,689.16,699.12 (C-S stretching of Aryl thioether). ^{1}H-NMR (400 MHz, DMSO) in δ ppm: 3.709(2H, t, - CH2-), 3.293 (6H, s, -CH3) , 3.938-3.950 (2H, t, -CH2-), 4.192 (2H, s, -CH2-), 7.628- 7.735 (2H, comple, -Ar-H), 6.869-7.819(2H, d, Ar-H), 7.825-7.833(2H, d, Ar-H),6.84-7.03(2H, d-d, Ar-H) 9.208 (1H, s, -NH-).Elemental Analysis: Cal.: C; 58.91%, H; 4.58%, N; 17.81%, O; 5.81%, Cl; 12.88%. Found: C; 58.98%, H; 4.50%, N; 17.84%, O; 5.75, Cl; 12.92%.

Table 2: Antibacterial activity of synthesized compounds CML-1A to CML-1L

Compound code	*Antibacterial activity*			
	Minimum Inhibitory Concentration: µg/mL			
	Gram + ve bacteria		*Gram - ve bacteria*	
	S. aureus	*B. subtilis*	*P. aeruginosa*	*E. coli*
CML-1A	500	62.5	125	31.25
CML-1B	-	250	-	250
CML-1C	250	62.5	250	62.5
CML-1D	250	250	-	125
CML-1E	500	-	250	-
CML-1F	125	31.25	125	31.25
CML-1G	250	500	250	125
CML-1H	125	62.5	250	62.5
CML-1I	125	62.5	250	62.5
CML-1J	-	250	-	250
CML-1K	-	250	-	125
CML-1L	250	125	250	125
Ampicillin	500	7.8	125	7.8
Chloramphenicol	125	3.9	125	3.95
Tetracycline	7.8	1.95	15.6	3.95

Table 3: Antifungal activity of synthesized compounds CML-1A to CML-1L

Compound code	*Antifungal activity*		
	Minimum Inhibitory Concentration: µg/ml.		
	Candida albicans	*Aspergillus flavus*	*Aspergillus niger*
CML-1A	125	250	125
CML-1B	125	-	250
CML-1C	-	-	125
CML-1D	250	125	-
CML-1E	-	-	125
CML-1F	62.5	125	31.2
CML-1G	125	250	125
CML-1H	31.2	31.2	31.2
CML-1I	31.2	62.5	-
CML-1J	-	-	250
CML-1K	250	250	-
CML-1L	62.5	125	31.2
Nystatin	1.25	12.5	25
Griseofulvin	49.92	0.5	2.0

4-(4-((4,6-bis((4-fluorophenyl)thio)-1,3,5-triazin-2-yl)amino)phenyl)morpholin-3-one (CML-1H)

Off white solid, Yield: 70%. IR (KBr, νmax, cm-1): 3490.27 (N-H stretching, primaryor secondary amines),3113.83, 3057.45 (C-H stretching aromatics), 2996.26, 2955.27, 2835.38 (C-H stretching, alkane), 1680 (-CO-NH, amide carbonyl), 1587.35, 1494.72, 1455.38 (C-C stretching in ring, aromatic), 1358.24, 1295.98, 1254.46 (C-N stretching, aromatic 3^{0} amines), 1154.07 (C-O stretching of ether), 1190.45, 1147.49, 1120.27 (C-N stretching, aliphatic amines), 982.28, 1050.39, 1095.41 (C-F stretching), 845.90 (p-substituted aromatic ring).1H NMR (400 MHz, DMSO) in δ ppm: 3.809(2H, t, - CH_2-), 3.938-3.950 (2H, t, -CH_2-), 4.192 (2H, s, -CH_2-), 6.869-7.219(4H, complex, Ar-H), 7.290-7.401(8H, complex, Ar-H) 9.208 (1H, s, -NH-). Elemental Analysis: Cal.: C; 57.35%, H; 3.66%, N; 13.38%, O; 6.11%, F; 7.26%, S;12.25%. Found: C; 57.38%, H;3.64%, N; 13.41%, O; 6.15, F; 7.29%, S;12.22%.

4-(4-((4,6-bis((4-bromophenyl)thio)-1,3,5-triazin-2-yl)amino)phenyl)morpholin-3-one (CML-1I)

White solid, Yield: 81%. IR (KBr, νmax, cm-1): 3491.05 (N-H stretching, primary or secondary amines), 3103.78, 3054.38 (C-H stretching aromatics), 2996.27, 2951.99, 2832.02 (C-Hstretching, alkane), 1670 (-CO-NH, amide carbonyl), 1586.98, 1492.38, 1450.37(C-C stretching in ring, aromatic), 1354.28, 1290.87, 1253.52 (C-N stretching, aromatic amines), 1183.72, 1147.38, 1119.52, 1033.12, 1004.88 (C-N stretching, aliphatic amines), 835.58 (p-substituted aromatic ring)612.28, 639.62 (C-Br stretching). 1H NMR (400 MHz, DMSO) in δ ppm: 3.709(2H, t, - CH2-), 3.938-

3.950 (2H, t, -CH2-), 4.192 (2H, s, -CH2-), 6.869-7.239(4H, complex, Ar-H), 7.580-7.801(8H, complex, Ar-H), 9.208 (1H, s, -NH-). Elemental Analysis: Cal.: C; 46.53%, H; 2.97%, N; 10.85%, O; 4.96%, Br; 24.76%, S;9.94%. Found: C; 46.50%, H; 2.95%, N; 10.89%, O; 4.94%, Br; 24.79%, S;9.91%.

4-(4-((4,6-bis((4-nitrophenyl)thio)-1,3,5-triazin-2-yl)amino) phenyl)morpholin-3-one (CML-1J)

Off white solid, Yield: 65%. IR (KBr, νmax, cm-1): 3277.65, 3129.51, 3115.26, 3058.70, 2958.67, 2852.10, 2833.65, 1634.62, 1545.25, 1496.67, 1423.56, 1296.14, 1253.29, 1173.29, 1149.32, 1112.89, 1038.32. 1H NMR (400 MHz, DMSO) in δ ppm: 1.923(6H, s, -CH3), 3.708-3.735(2H, t, -CH2-), 3.938-3.968 (2H, t, -CH2-), 4.195 (2H, s, -CH2-), 6.799-6.810(4H, d, ortho Ar-H), 7.242-7.262(2H, d, Ar-H), 7.618- 7.745 (6H, d, -Ar-H), 9.053 (2H, singlet, -NH-), 9.218 (1H, s, -NH-). Elemental Analysis: Cal. (%): C; 67.34, H; 5.65, N; 20.36, O; 6.64. Found: C; 67.27, H; 5.74, N; 20.27, O; 6.67.

4-(4-((4,6-bis((2,4-dinitrophenyl)thio)-1,3,5-triazin-2-yl) amino)phenyl)morpholin-3-one (CML-1K)

Off white solid, Yield: 62%. IR (KBr, νmax, cm-1): 3279.33, 3130.51, 3115.26, 3057.70, 2958.67, 2852.10, 2833.65, 1633.62, 1545.25, 1496.67, 1423.56, 1296.14, 1253.29, 1171.29, 1149.32, 1112.89, 1037.32. 1H NMR (400 MHz, DMSO) in δ ppm: 1.898(6H, s, -CH3), 3.710-3.734(2H, t, -CH2-), 3.931-3.968 (2H, t, -CH2-), 4.195 (2H, s, -CH2-), 6.799-7.462(8H, complex, Ar-H), 7.628-7.735 (4H, complex, -Ar-H), 9.043 (2H, singlet, -NH-), 9.208 (1H, s, -NH-). Elemental Analysis: Cal. (%): C; 67.34, H; 5.65, N; 20.36, O; 6.64. Found (%): C; 67.27, H; 5.74, N; 20.27, O; 6.67.

4-(4-((4,6-bis((4-ethylphenyl)thio)-1,3,5-triazin-2-yl)amino) phenyl)morpholin-3-one (CML-1L)

Off white solid, Yield: 65%. IR (KBr, νmax, cm-1): 3490.45, 3472.78, 3118.34, 3055.09, 2996.56, 2955.62, 2835.34, 1586.43, 1496.65, 1452.55, 1357.48, 1294.38, 1250.66, 1158.26, 1127.37, 1035.87, 829.23, 762.78. 1H NMR (400 MHz, DMSO) in δ ppm: 3.715-3.739 (2H, t, -CH2-), 3.970-3.984 (2H, t, -CH2-), 4.203 (2H, s, -CH2-), 7.270-7.310 (4H, complex, Ar-H), 7.339-7.354 (2H, doublet, Ar H), 7.501-7.513 (2H, doublet, Ar-H) 7.782 (2H, singlet, -Ar-H), 9.460 (1H, singlet, -NH-), 9.482 9.496 (2H, multiplet, -NH-). Elemental Analysis: Cal. (%): C; 44.15, H; 2.82, Br; 23.50, Cl; 10.42, N; 14.41, O; 4.70. Found: C; 44.23, H; 2.87, Br; 23.43, Cl; 10.45, N; 14.35, O; 4.67.

CONCLUSION

In summary, we have synthesized 2,4,6-trisubstituted 1,3,5-triazine derivatives. The synthesis was carried out in two steps by using cyanuric chloride as a starting material. Various spectroscopic techniques confirmed the structures of the synthesized compounds. The reaction is regioselective and the products were obtained in good to excellent yields without any further formation of any side products. It has gained significant importance for the synthesis of substituted 1,3,5 triazines. The present work is important for the synthesis of a wide variety of biologically active triazine heterocyclic derivatives.

ACKNOWLEDGMENTS

The authors are thankful to the Principal, M.V.M. Science and Home Science College Rajkot.

REFERENCES

1. Hollink E, Simanek EE, Bergbreiter DE. Strategies for protecting and manipulating triazine derivatives. Tetrahedron letters. 2005 Mar 21;46(12). https://doi.org/10.1016/j.tetlet.2005.01.150
2. Masih A, Singh S, Agnihotri AK, Giri S, Shrivastava JK, Pandey N, Bhat HR, Singh UP. Design and development of 1, 3, 5-triazine-thiadiazole hybrids as potent adenosine A2A receptor (A2AR) antagonist for benefit in Parkinson's disease. Neuroscience Letters. 2020 Sep 14;735:135222. https://doi.org/10.1016/j.neulet.2020.135222
3. Srivastava JK, Awatade NT, Bhat HR, Kmit A, Mendes K, Ramos M, Amaral MD, Singh UP. Pharmacological evaluation of hybrid thiazolidin-4-one-1, 3, 5-triazines for NF-κB, biofilm and CFTR activity. RSC advances. 2015;5(108):88710-8. https://doi.org/10.1039/C5RA09250G
4. Singh B, Bhat HR, Kumawat MK, Singh UP. Structure-guided discovery of 1, 3, 5-triazine–pyrazole conjugates as antibacterial and antibiofilm agent against pathogens causing human diseases with favorable metabolic fate. Bioorganic & Medicinal Chemistry Letters. 2014 Aug 1;24(15):3321-5. https://doi.org/10.1016/j.bmcl.2014.05.103
5. Singh UP, Bhat HR, Kumawat MK, Singh RK. Utilisation of Home Laundry Effluent (HLE) as a catalyst for expeditious one-pot aqueous phase synthesis of highly functionalised 4-thiazolidinones. SpringerPlus. 2013 Sep 16;2(1):466. https://doi.org/10.1186/2193-1801-2-466
6. Bhat HR, Masih A, Shakya A, Ghosh SK, Singh UP. Design, synthesis, anticancer, antibacterial, and antifungal evaluation of 4-aminoquinoline-1, 3, 5-triazine derivatives. Journal of Heterocyclic Chemistry. 2020 Jan;57(1):390-9. https://doi.org/10.1002/jhet.3791
7. Bhat HR, Singh UP, Thakur A, Ghosh SK, Gogoi K, Prakash A, Singh RK. Synthesis, antimalarial activity and molecular docking of hybrid 4-aminoquinoline-1, 3, 5-triazine derivatives. Experimental Parasitology. 2015 Oct 1;157:59-67. https://doi.org/10.1016/j.exppara.2015.06.016
8. Gahtori P, Ghosh SK, Parida P, Prakash A, Gogoi K, Bhat HR, Singh UP. Antimalarial evaluation and docking studies of hybrid phenylthiazolyl-1, 3, 5-triazine derivatives: a novel and potential antifolate lead for Pf-DHFR-TS inhibition. Experimental parasitology. 2012 Mar 1;130(3):292-9. https://doi.org/10.1016/j.exppara.2011.12.014
9. Singh UP, Bhat HR, Gahtori P, Singh RK. Hybrid phenylthiazole and 1, 3, 5-triazine target cytosolic leucyl-tRNA synthetase for antifungal action as revealed by molecular docking studies. In Silico Pharmacology. 2013 Feb 12;1(1):3. doi:10.1186/2193-9616-1-3
10. Srivastava JK, Pillai GG, Bhat HR, Verma A, Singh UP. Design and discovery of novel monastrol-1, 3, 5-triazines as potent anti-breast cancer agent via attenuating epidermal growth factor receptor tyrosine kinase. Scientific Reports. 2017 Jul 19;7(1):5851. https://doi.org/10.1038/s41598-017-05934-5
11. Pathak P, Naumovich V, Grishina M, Shukla PK, Verma A, Potemkin V. Quinazoline based 1, 3, 5-triazine derivatives as cancer inhibitors by impeding the phosphorylated RET tyrosine kinase pathway: Design, synthesis, docking, and QSAR study. Archiv der Pharmazie. 2019 Sep;352(9):1900053. https://doi.org/10.1002/ardp.201900053
12. Pathak P, Shukla PK, Kumar V, Kumar A, Verma A. Quinazoline clubbed 1, 3, 5-triazine derivatives as VEGFR2 kinase inhibitors: design, synthesis, docking, in vitro cytotoxicity and in ovo antiangiogenic activity. Inflammopharmacology. 2018 Dec;26(6):1441-53. https://

doi.org/10.1007/s10787-018-0471-3
13. Yaguchi SI, Fukui Y, Koshimizu I, Yoshimi H, Matsuno T, Gouda H, Hirono S, Yamazaki K, Yamori T. Antitumor activity of ZSTK474, a new phosphatidylinositol 3-kinase inhibitor. Journal of the National Cancer Institute. 2006 Apr 19;98(8):545-56. https://doi.org/10.1093/jnci/djj133
14. Venkatesan AM, Dehnhardt CM, Delos Santos E, Chen Z, Dos Santos O, Ayral-Kaloustian S, Khafizova G, Brooijmans N, Mallon R, Hollander I, Feldberg L. Bis (morpholino-1, 3, 5-triazine) derivatives: potent adenosine 5′-triphosphate competitive phosphatidylinositol-3-kinase/mammalian target of rapamycin inhibitors: discovery of compound 26 (PKI-587), a highly efficacious dual inhibitor. Journal of medicinal chemistry. 2010 Mar 25;53(6):2636-45. https://doi.org/10.1021/jm901830p
15. Rageot D, Bohnacker T, Keles E, McPhail JA, Hoffmann RM, Melone A, Borsari C, Sriramaratnam R, Sele AM, Beaufils F, Hebeisen P. (S)-4-(Difluoromethyl)-5-(4-(3-methylmorpholino)-6-morpholino-1, 3, 5-triazin-2-yl) pyridin-2-amine (PQR530), a potent, orally bioavailable, and brain-penetrable dual inhibitor of class I PI3K and mTOR kinase. Journal of medicinal chemistry. 2019 Jun 7;62(13):6241-61. https://doi.org/10.1021/acs.jmedchem.9b00525
16. Peterson EA, Andrews PS, Be X, Boezio AA, Bush TL, Cheng AC, Coats JR, Colletti AE, Copeland KW, DuPont M, Graceffa R. Discovery of triazine-benzimidazoles as selective inhibitors of mTOR. Bioorganic & medicinal chemistry letters. 2011 Apr 1;21(7):2064-70. https://doi.org/10.1016/j.bmcl.2011.02.007
17. Baliani A, Bueno GJ, Stewart ML, Yardley V, Brun R, Barrett MP, Gilbert IH. Design and synthesis of a series of melamine-based nitroheterocycles with activity against trypanosomatid parasites. Journal of medicinal chemistry. 2005 Aug 25;48(17):5570-9. https://doi.org/10.1021/jm050177+
18. Henke BR, Consler TG, Go N, Hale RL, Hohman DR, Jones SA, Lu AT, Moore LB, Moore JT, Orband-Miller LA, Robinett RG. A new series of estrogen receptor modulators that display selectivity for estrogen receptor β. Journal of medicinal chemistry. 2002 Dec 5;45(25):5492-505. https://doi.org/10.1021/jm020291h
19. Kuo GH, DeAngelis A, Emanuel S, Wang A, Zhang Y, Connolly PJ, Chen X, Gruninger RH, Rugg C, Fuentes-Pesquera A, Middleton SA. Synthesis and identification of [1, 3, 5] triazine-pyridine biheteroaryl as a novel series of potent cyclin-dependent kinase inhibitors. Journal of medicinal chemistry. 2005 Jul 14;48(14):4535-46. https://doi.org/10.1021/jm040214h
20. Koc ZE, Bingol H, Saf AO, Torlak E, Coskun A. Synthesis of novel tripodal-benzimidazole from 2, 4, 6-tris (p-formylphenoxy)-1, 3, 5-triazine: structural, electrochemical and antimicrobial studies. Journal of hazardous materials. 2010 Nov 15;183(1-3):251-5. https://doi.org/10.1016/j.jhazmat.2010.07.018
21. Cascioferro S, Parrino B, Spanò V, Carbone A, Montalbano A, Barraja P, Diana P, Cirrincione G. 1, 3, 5-Triazines: A promising scaffold for anticancer drugs development. European journal of medicinal chemistry. 2017 Dec 15;142:523-49. https://doi.org/10.1016/j.ejmech.2017.09.035

HOW TO CITE THIS ARTICLE: Chandera ML, Sabalpara KJ, Rajyaguru CM, Upadhyay JJ. Synthesis, Characterisation and Biological Assessment of 2,4,6-Trisubstituted 1,3,5-Triazine Derivatives. *J Adv Sci Res*. 2025;16(09): 8-14 **DOI:** 10.55218/JASR.2025160902