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Synthesis and characterization of biological activities of various pyrimidine-cyanuric derivatives

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Abstract: Triazine-pyrimidine derivatives (13a-n) has been synthesized by substitution of chlorides one by one with primary amine containing pyrimidine derivatives, 6-methyl-*N*-(4-pyridin-3-yl-pyrimidin-2-yl)-benzene-1,3-diamine and 3-aminoadamantanol. The structures of all synthesized compounds were characterized by elemental analysis, FT-IR, Mass and 1*H*-NMR spectroscopy. Triazine-pyrimidine derivatives have been screened for antimicrobial activity against bacteria and fungi by using MIC determination. In vitro antibacterial, antifungal activity antimalarial and antitubercular activity.

Key words; Triazine-pyrimidine, 3-aminoadamantanol, antibacterial, antifungal activity antimalarial and antitubercular activity

Introduction: Hetero atom/atoms such as Nitrogen, Oxygen, Sulphur etc. containing five and six-membered ring are the well-known hetero cyclic organic compounds having great characteristics of pharmacological. [1-3]. Triazines also has unique importance having three nitrogen atoms in pharmaceutical chemistry. Different transformations synthesized by using triazines [4]. Various triazine such as 1,2,3-triazine, 1,2,4-triazine and 1,3,5-triazine are known, among them 1,3,5-triazine isomer are used with remarkable applications because of many pharmacological activities such as antimicrobial activity [5-8]. Triazine derivatives undergo more frequently nucleophilic substitution reaction while it showed difficulty towards electrophilic substitution reaction because of their resonance energy is less than benzene ring. [9-10]. Because of the presence of an electron-donating group such as amino group at position 2,4 or 6 of the 1,3,5-triazine, restriction of free rotation is more caused by the formation of stronger bond [11].

Experiment:

Preparation of 2-methyl-5-nitroaniline (2)
To H_2SO_4 (16g) cooled at 0-5ºC, *o*-toluidine (1) (0.01mol) was added dropwise with vigorous stirring. Mixture of 10g of 65% HNO_3 and 35g of H_2SO_4 was then added dropwise during 2 hours at 0-5ºC. After the completion of reaction, the reaction mixture was then poured into crushed ice and was made alkaline by using aqueous sodium hydroxide. The solid obtained was collected by filtration and air-dried. Subsequent recrystallization was done using 50% ethanol. Yield; 81%, melting point; 105-107ºC, **(Scheme-1).**

Preparation of *N*-(2-methyl-5-nitrophenyl) guanidinium nitrate (3)
2-methyl-5-nitroaniline (2) (0.01mol) was dissolved in n-butanol (15mL) and then 65% nitric acid (3mL) was added dropwise to the solution, followed by a 50% aqueous solution of cyanamide (0.01mol). The reaction mixture was refluxed for 12 hours. After the completion of reaction, the reaction mixture cooled to 0ºC. The solid mass obtained which was collected by filtration and washed with chilled solution of methanol and diethyl ether (1:1, 20mL) and air-dried to afford 18.48 g (53%) of the title product as a yellow solid, melting point; 216-218ºC, **(Scheme-1).**

Preparation of *N*-(2-methyl-5-nitrophenyl)-4-pyridin-3-yl-pyrimidin-2-yl-amine (5)
3-dimethylamino-1-(pyridin-3-yl)-propanone (4) (0.01mol) and *N*-(2-methyl-5-nitrophenyl)-guanidinium nitrate (3) (0.015mol) were dissolved in n-butanol (100mL), solid sodium hydroxide (0.02mol) was added. The reaction mixture was refluxed for 16 hours and then cooled to 0ºC. The solid mass was collected by filtration and washed with methanol and diethyl ether, and air-dried. Yellow solid, yield; 79% melting point; 196-197ºC, **(Scheme-1).**

Preparation of 6-methyl-*N*-(4-pyridin-3-yl-pyrimidin-2-yl)-benzene-1,3-diamine (6)
To the solution of stannous chloride dihydrate (0.01mol) in hydrochloric acid (10mL) cooled at 0ºC, *N*-(2-methyl-5-nitrophenyl)-4-pyridin-3-yl-pyrimidin-2-ylamine (5) (0.01mol) was added in portions the mixture was vigorously stirred for 6 hours. The mixture was then poured into crushed ice, made alkaline with solid sodium hydroxide, and extracted three times with ethyl acetate (50mL). The combined organic phase was dried over anhydrous sodium sulphate and the filtrate was evaporated to dryness in vacuo. The residue was recrystallized from methylene chloride. Yellow solid, yield; 72% melting point; 142-144ºC, **(Scheme-1).**

Preparation of various pyrimidine derivatives (9a-n)
Mixture of various chalcone derivatives (7a-n) (0.01mol) and guanidine nitrate (8) (0.012mol) was taken into 20mL ethanol in RBF. The reaction mixture was heated with continuous stirring with reflux condenser. Sodium ethoxide solution (0.01mol sodium in ethanol) was added slowly and drop wise during 30 minutes time period. The reaction mixture was refluxed further for 12-13 hours. The completion of reaction was checked by using TLC. After the completion of reaction, the reaction mixture was cooled to room temperature and poured in to ice-bath. The solid obtained which was filtered, washed with cold distilled water several times, dried and recrystalized from ethanol to give compounds (9a-n), **(Scheme-2).**

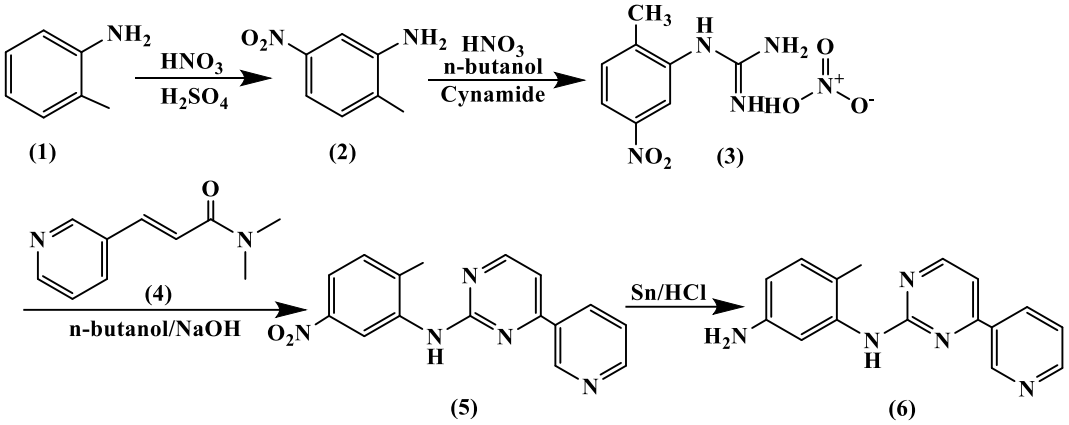
Preparation of *N*-(4,6-dichloro-1,3,5-triazin-2-yl)-4-methyl-*N*-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (10)
0.01 mol cyanuric chloride (7) was taken in 25mL acetone and stirred at 0-5ºC. 0.01mol 6-methyl-*N*-(4-pyridin-3-yl-pyrimidin-2-yl)-benzene-1,3-diamine (6) was dissolved in 15mL acetone and was added to the above solution drop-wise at 0-5ºC with maintaining neutral reaction medium by the addition 10% sodium bicarbonate aqueous solution from time to time as per requirement of reaction condition. The reaction mixture was stirred for further 3 hours. After the completion of reaction, the reaction mixture was poured into ice. The solid mass was obtained, which was collected by filtration and dried. The crude product was recrystallized from alcohol to get compound (10), **(Scheme-3).**

Preparation of 6-chloro-*N*-(4,6-diphenylpyrimidin-2-yl)-*N*-(4-methyl-3-((4-(pyridin-3-yl) pyrimidin-2-yl)amino)phenyl)-1,3,5-triazine-2,4-diamine derivatives (11a-n)
N-(4,6-dichloro-1,3,5-triazin-2-yl)-4-methyl-*N*-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (10) (0.01mol) was dissolved in 25mL DMF with continuous stirring. Various pyrimidine derivatives (9a-n) (0.01mol) was dissolved in 15mL DMF and added drop wise into the above solution with continuous stirring. The reaction conditions such as 35-40ºC and pH was maintained by the addition 10% sodium bicarbonate solution during the reaction period. After the addition was completed the reaction temperature slowly raised up to 45ºC for additional 3 hours. After the completion of reaction, the reaction mixture was dumped into ice-cold water and the solid mass was obtained. The solid was filtered and dried. The crud product was purified by recrystallisation from ethanol to get compound (11a-n), **(Scheme-4).**

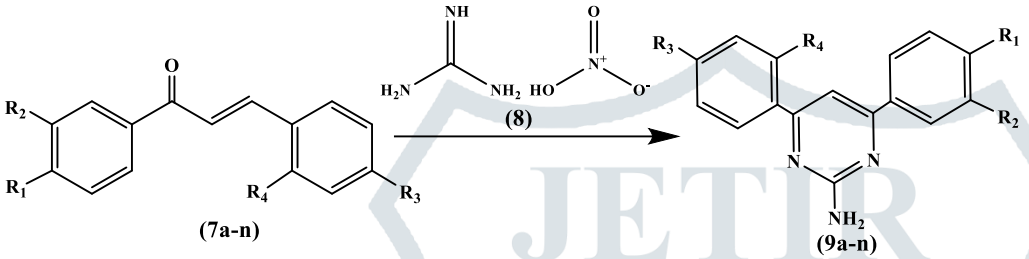
Preparation of 3-((4-((4,6-diphenylpyrimidin-2-yl)amino)-6-((4-methyl-3-((4-(pyridin-3-yl) pyrimidin-2-yl)amino)phenyl)amino)-1,3,5-triazin-2-yl)amino)adamantan-1-ol derivatives (13a-n) (VJT$_1$ to VJT$_{14}$)
Compound 6-chloro-*N*-(4,6-diphenylpyrimidin-2-yl)-*N*-(4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)-1,3,5-triazine-2,4-diamine derivative (11a-n) (0.01mol) was dissolved in 25mL DMF with stirring. The reaction mixture was heated slowly in oil bath. 3-aminoadamantanol (12) (0.01mol) was dissolved in 15mL DMF. This dissolved mixture was added to the above heated solution slowly and temperature was maintained 80-90ºC and pH was maintained by the addition of 10% sodium bicarbonate solution during the reaction period. After completion of addition the reaction temperature slowly raised up to 100ºC for additional 4 hours. After the completion of reaction, the reaction mixture was dumped into ice-cold water and the solid mass was obtained. The solid compound was filtered and dried. The crude product was purified and recrystalized from ethanol to get compound (13a-n), **(Scheme-5).**

Reaction Scheme

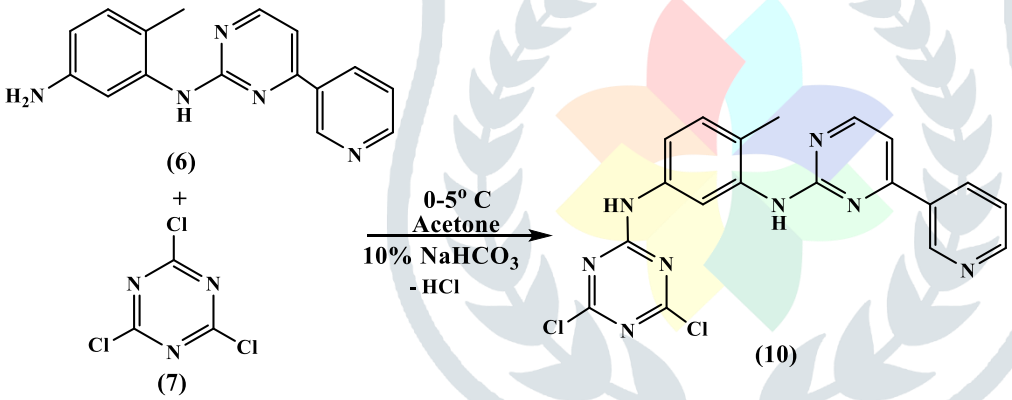
Scheme 1 Preparation of 6-methyl-*N*-(4-pyridin-3-yl-pyrimidin-2-yl)-benzene-1,3-diamine (6)



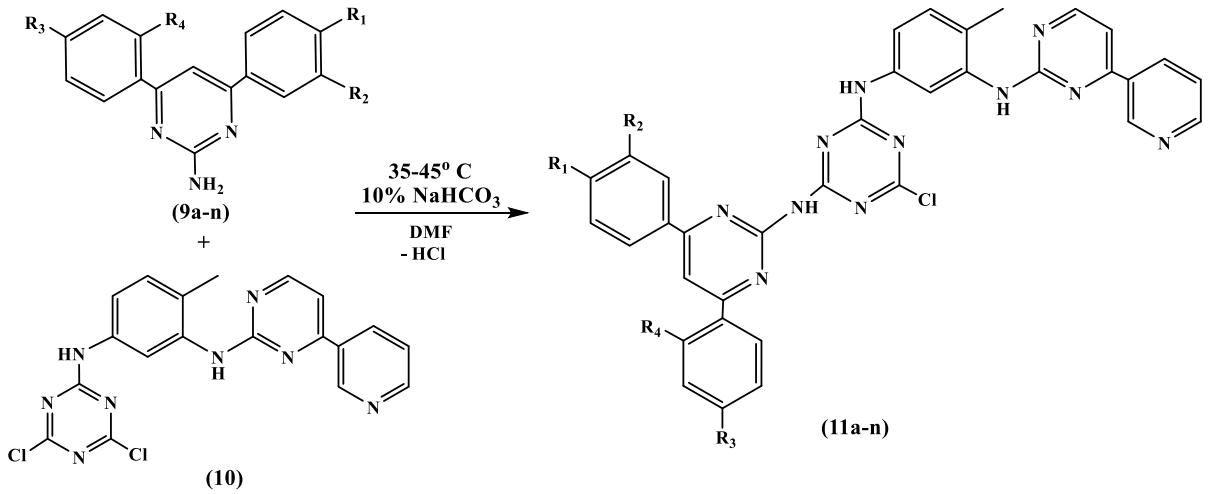
Scheme 2 Preparation of various pyrimidine derivatives (9a-n)



Scheme 3 Preparation of *N*-(4,6-dichloro-1,3,5-triazin-2-yl)-4-methyl-*N*-(4-(pyridin-3-yl) pyrimidin-2-yl)benzene-1,3-diamine (10)



Scheme 4 Preparation of 6-chloro-*N*-(4,6-diphenylpyrimidin-2-yl)-*N*-(4-methyl-3-((4-(pyridine-3-yl)pyrimidin-2-yl)amino)phenyl)-1,3,5-triazine-2,4-diamine derivatives (11a-n)



Scheme 5 Preparation of triazine-pyrimidine derivatives (13a-n) (VJT_1 to VJT_{14})

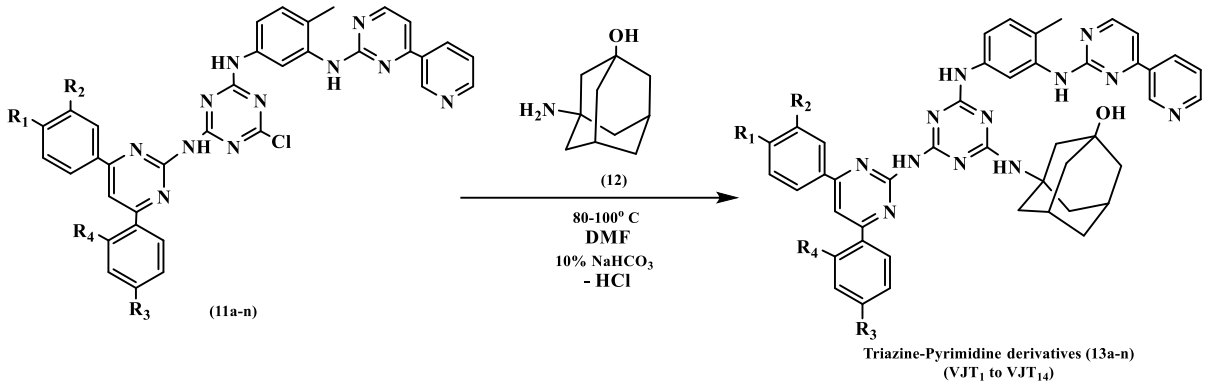


Table 5.1 Physical data of synthesized triazine-pyrimidine derivatives

No	Sample	Sample Code	Molecular Formula	Substituent				Melting Point (°C)
				R_1	R_2	R_3	R_4	
1	13a	VJT_1	$C_{46}H_{43}BrN_{12}O_2$	-Br	-H	$-OCH_3$	-H	265-268° C
2	13b	VJT_2	$C_{45}H_{40}BrClN_{12}O$	-Br	-H	-Cl	-H	271-272° C
3	13c	VJT_3	$C_{45}H_{40}BrClN_{12}O$	-Br	-H	-H	-Cl	275-276° C
4	13d	VJT_4	$C_{45}H_{40}Cl_2N_{12}O$	-Cl	-H	-Cl	-H	266-268° C
5	13e	VJT_5	$C_{45}H_{40}Cl_2N_{12}O$	-Cl	-H	-H	-Cl	270-271° C
6	13f	VJT_6	$C_{47}H_{46}ClN_{13}O$	-Cl	-H	$-(CH)_2N$	-H	259-260° C
7	13g	VJT_7	$C_{46}H_{43}ClN_{12}O$	$-CH_3$	-H	-Cl	-H	263-264° C
8	13h	VJT_8	$C_{45}H_{40}ClN_{13}O_3$	$-NO_2$	-H	-Cl	-H	280-282° C
9	13i	VJT_9	$C_{45}H_{40}ClN_{13}O_3$	$-NO_2$	-H	-H	-Cl	277-278° C
10	13j	VJT_{10}	$C_{45}H_{41}ClN_{12}O_2$	-OH	-H	-Cl	-H	265-267° C
11	13k	VJT_{11}	$C_{46}H_{43}ClN_{12}O_2$	$-OCH_3$	-H	-Cl	-H	248-250° C
12	13l	VJT_{12}	$C_{45}H_{40}ClN_{13}O_3$	-H	$-NO_2$	-Cl	-H	275-277° C
13	13m	VJT_{13}	$C_{45}H_{41}ClN_{12}O_2$	-H	-OH	-Cl	-H	263-264° C
14	13n	VJT_{14}	$C_{46}H_{43}ClN_{12}O_2$	-H	$-OCH_3$	-Cl	-H	248-250° C

Table 5.2 Elementary analysis data of triazine-pyrimidine derivatives

No	Sample Code	Elementary Analysis											
		Calculated (%)						Found (%)					
		C	H	O	N	Cl	Br	C	H	N	O	Cl	Br
1	VJT_1	62.44	5.08	10.40	9.10	-	12.98	62.39	4.98	10.36	9.00	-	12.90
2	VJT_2	60.06	4.55	7.74	9.04	5.72	12.89	59.99	4.48	7.68	8.98	5.68	12.78
3	VJT_3	60.06	4.55	7.74	9.04	5.72	12.89	59.89	4.52	7.71	8.99	5.71	12.82
4	VJT_4	64.70	4.90	8.34	9.74	12.32	-	64.68	4.85	8.31	9.70	12.25	-
5	VJT_5	64.70	4.90	8.34	9.74	12.32	-	64.64	4.86	8.29	9.71	12.26	-
6	VJT_6	67.86	5.87	8.22	11.99	6.07	-	67.81	5.79	8.18	11.89	6.00	-
7	VJT_7	69.24	5.63	8.65	10.09	6.39	-	69.18	5.59	8.62	10.00	6.29	-
8	VJT_8	63.53	4.82	13.65	11.95	6.05	-	63.49	4.79	13.59	11.89	5.99	-
9	VJT_9	63.53	4.82	13.65	11.95	6.05	-	63.48	4.72	13.58	11.89	5.98	-
10	VJT_{10}	66.84	5.25	11.49	10.06	6.36	-	66.81	5.20	11.38	9.88	6.34	-
11	VJT_{11}	67.30	5.47	11.21	9.81	6.21	-	67.28	5.42	11.18	9.78	6.18	-
12	VJT_{12}	63.53	4.82	13.65	11.95	6.05	-	63.48	4.78	13.56	11.89	5.98	-
13	VJT_{13}	66.84	5.25	11.49	10.06	6.36	-	66.78	5.21	11.47	9.89	6.31	-
14	VJT_{14}	67.30	5.47	11.21	9.81	6.21	-	67.22	5.44	11.14	9.78	6.16	-

Spectral data Analysis (1H NMR, 13C NMR, IR, LCMS)

^{1}H NMR data of VJT$_1$ (500 MHz, DMSO-*d*$_6$) δ; 2.28 (s, 3H of methyl group), 3.80 (s, 3H of methoxy group), 8.49 (s, -NH of pyrimidine ring), 9.29 (s, -NH of benzene ring), 7.43 (s, -NH of admentanol), 8.36 (s, NH of pyrimidine ring), 7.48-9.30 (m, 4H of pyridine ring), 7.60-8.39 (m, 2H of pyrimidine ring), 7.17-8.86 (m, 3H of benzene ring), 5.09 (s, -OH group of admentanol), 1.48-2.32 (m, 14H of admentanol), 7.96 (s, 1H of pyrimidine ring), 6.86-7.79 (m, 4H of benzene ring), 7.60-7.94 (m, 4H of benzene ring).

^{1}H NMR data of VJT$_2$ (500 MHz, DMSO-*d*$_6$) δ; 2.32 (s, 3H of methyl group), 8.44 (s, -NH of pyrimidine ring), 9.27 (s, -NH of benzene ring), 7.41 (s, -NH of admentanol), 8.37 (s, -NH of pyrimidine ring), 7.47-9.31 (m, 4H of pyridine ring), 7.60-8.39 (m, 2H of pyrimidine ring), 7.17-8.86 (m, 3H of benzene ring), 5.12 (s, -OH group of admentanol), 1.48-2.32 (m, 14H of admentanol), 7.96 (s, 1H of pyrimidine ring), 6.86-7.79 (m, 4H of benzene ring), 7.60-7.94 (m, 4H of benzene ring).

^{1}H NMR data of VJT$_3$ (500 MHz, DMSO-*d*$_6$) δ; 2.31(s, 3H of methyl group), 8.47 (s, -NH of pyrimidine ring), 9.29 (s, -NH of benzene ring), 7.42 (s, -NH of admentanol), 8.38 (s, -NH of pyrimidine ring), 7.43-9.31 (m, 4H of pyridine ring), 7.61-8.40 (m, 2H of pyrimidine ring), 7.17-8.88 (m, 3H of benzene ring), 5.03 (s, -OH group of admentanol), 1.48-2.29 (m, 14H of admentanol), 7.95 (s, 1H of pyrimidine ring), 6.86-7.79 (m, 4H of benzene ring), 7.60-7.95 (m, 4H of benzene ring).

^{13}C NMR data of VJT$_1$ (500 MHz, DMSO-*d*$_6$) δ; 17.65, 29.84, 35.91, 43.26, 44.25, 47.07, 50.76, 55.35, 69.19, 108.07, 109.34, 110.56, 114.18, 117.26, 122.82, 124.16, 124.47, 127.00, 129.48, 130.07, 131.55, 131.77, 134.32, 135.81, 140.63, 141.58, 149.55, 150.72, 157.49, 158.13, 158.20, 159.41, 159.78, 159.89, 160.56, 161.12, 162.99, 163.69.

^{13}C NMR data of VJT$_2$ (500 MHz, DMSO-*d*$_6$) δ; 17.65, 29.18, 29.84, 35.91, 41.50, 42.49, 43.70, 44.25, 47.07, 50.76, 69.19, 108.09, 109.34, 110.56, 117.26, 122.82, 124.16, 124.47, 127.00, 127.71, 128.70, 129.48, 129.76, 130.90, 131.55, 132.74, 133.81, 134.32, 135.26, 135.81, 140.63, 141.58, 149.55, 150.72, 156.16, 157.00, 158.13, 158.99, 159.78, 160.56, 161.93, 162.99, 163.69.

IR data of VJT$_1$ (KBr, cm^{-1}) ν; C-H 1266cm^{-1}, N-H 1552cm^{-1} secondary amine, O-H 3924cm^{-1}, C-H 1348cm^{-1} of Ar-CH_3, C-H 2861cm^{-1} of -OCH_3, C-H 3414cm^{-1}, C-Br 754cm^{-1}.

IR data of VJT$_2$ (KBr, cm^{-1}) ν; C-H 1254cm^{-1}, N-H 1538cm^{-1} secondary amine, O-H 3926cm^{-1}, C-H 1332cm^{-1} of Ar-CH_3, C-H 2854cm^{-1} of OCH_3, C-H 3413cm^{-1}, C-Br 619cm^{-1}, C-Cl 735cm^{-1}.

Table 5.3 Antibacterial activity of triazine-pyrimidine derivatives

Antibacterial activity					
Minimum Inhibition Concentration					
Sample	**Sample Code**	***E. Coli* MTCC443**	***P. Aeruginosa* MTCC1688**	***S. Aureus* MTCC96**	***S. Pyogenes* MTCC442**
13a	VJT$_1$	150	200	200	100
13b	VJT$_2$	62.5	62.5	100	100
13c	VJT$_3$	50	100	100	150
13d	VJT$_4$	100	100	200	200
13e	VJT$_5$	200	150	250	250
13f	VJT$_6$	150	200	50	100
13g	VJT$_7$	100	150	150	150
13h	VJT$_8$	150	200	200	200
13i	VJT$_9$	50	50	100	100
13j	VJT$_{10}$	125	100	125	200
13k	VJT$_{11}$	62.5	150	100	100
13l	VJT$_{12}$	100	100	200	100
13m	VJT$_{13}$	62.5	100	100	100
13n	VJT$_{14}$	100	200	200	150
Ampicillin		100	100	250	100
Chloramphenicol		50	50	50	50

Norfloxacin	10	10	10	10
Ciprofloxacin	25	25	50	50

Table 5.4 Antifungal activity and antitubercular activity of triazine-pyrimidine derivatives

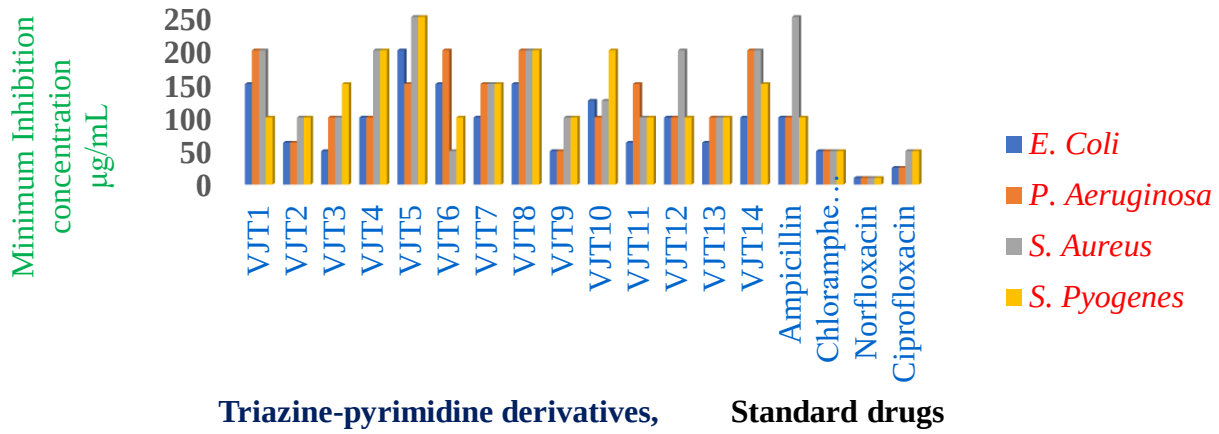
Antifungal activity and antitubercular activity					
Minimum Inhibition Concentration					
Sample	**Sample Code**	***C. Albicans* MTCC227**	***A. Niger* MTCC282**	***A. Clavatus* MTcc1323**	**$H_{37}RV$ MIC µg/mL**
13a	VJT_1	100	150	250	100
13b	VJT_2	62.5	100	100	250
13c	VJT_3	150	200	250	250
13d	VJT_4	200	250	250	1000
13e	VJT_5	100	150	250	100
13f	VJT_6	50	62.5	100	100
13g	VJT_7	100	150	250	100
13h	VJT_8	200	250	200	500
13i	VJT_9	150	200	250	250
13j	VJT_{10}	200	250	200	500
13k	VJT_{11}	150	250	250	100
13l	VJT_{12}	200	250	250	200
13m	VJT_{13}	150	200	250	200
13n	VJT_{14}	150	200	250	250
Nystatin		100	100	100	-
Griseofulvin		500	100	100	-
Rifampicin		-	-	-	40
Isoniazid		-	-	-	0.2

Table 5.5 Antimalarial activity of triazine-pyrimidine derivatives

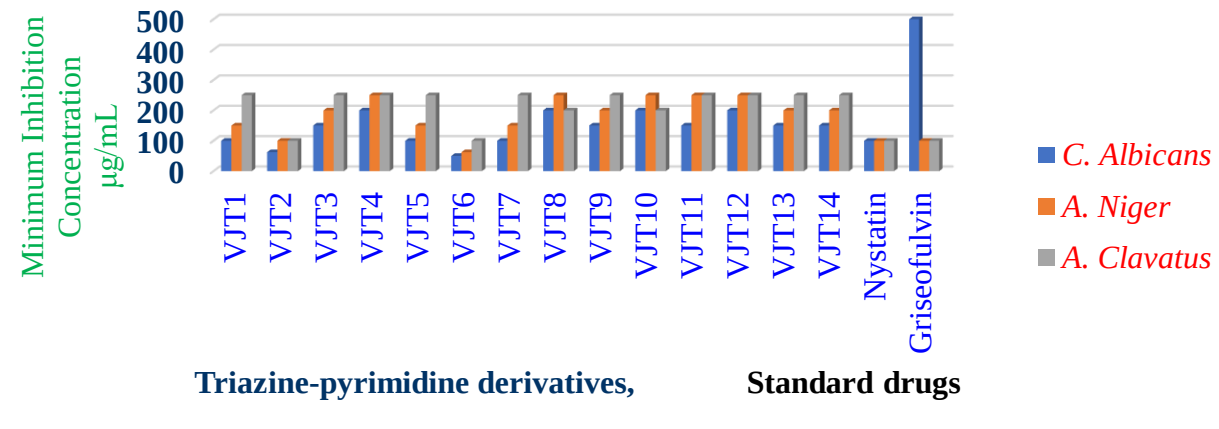
Antimalarial activity		
Minimum Inhibition Concentration		
Sample	**Sample Code**	**Mean Values**
13a	VJT_1	0.29µg/mL
13b	VJT_2	1.37µg/mL
13c	VJT_3	1.20µg/mL
13d	VJT_4	1.19µg/mL
13e	VJT_5	1.22µg/mL
13f	VJT_6	1.20µg/mL
13g	VJT_7	0.74µg/mL
13h	VJT_8	0.72µg/mL
13i	VJT_9	0.89µg/mL
13j	VJT_{10}	0.28µg/mL
13k	VJT_{11}	1.01µg/mL
13l	VJT_{12}	1.27µg/mL
13m	VJT_{13}	0.39µg/mL
13n	VJT_{14}	0.26µg/mL
Chloroquine		0.020µg/mL
Quinine		0.268µg/mL

Graph section

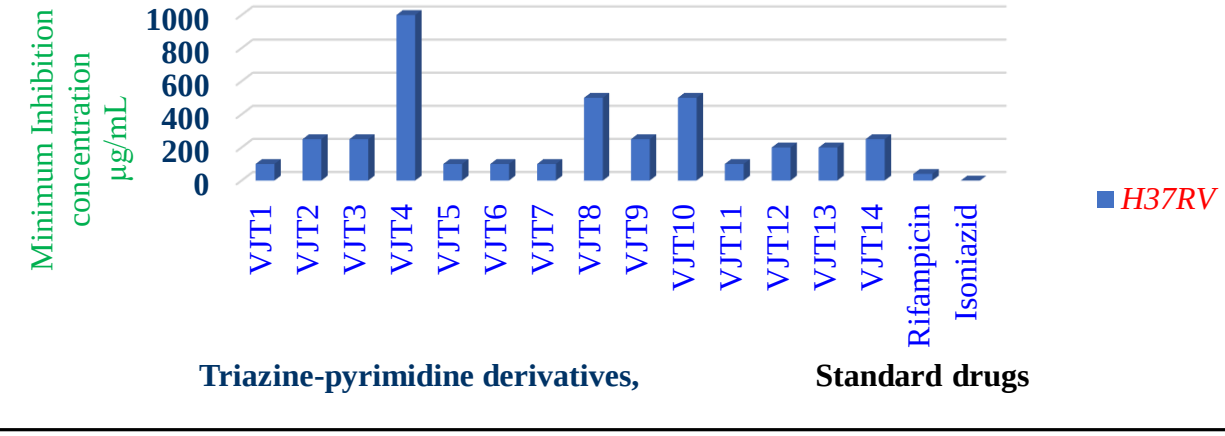
Graph-5.1 Antibacterial activity of triazine-pyrimidine derivatives (VJT_1 to VJT_{14})



Graph-5.2 Antifungal activity of triazine-pyrimidine derivatives (VJT_1 to VJT_{14})



Graph-5.3 Antitubercular activity of triazine-pyrimidine derivatives (VJT_1 to VJT_{14})



Results and discussion

At 0-5ºC temperature, *o*-toluidine (1) was added dropwise into sulfuric acid with vigorous stirring. In this mixture, nitrating mixture (H_2SO_4 and HNO_3) was added at 0-5ºC for nitration. Finally, alkaline solution was added to yield 2-methyl-5-nitroaniline (2). *N*-(2-methyl-5-nitrophenyl) guanidinium nitrate (3) was prepared from reaction

between 2-methyl-5-nitroaniline (2), nitric acid and cyanamide. The reaction mixture was refluxed in butanol for 12 hours. Reaction between *N*-(2-methyl-5-nitrophenyl) guanidinium nitrate (3) and *N*-(2-methyl-5-nitrophenyl)-4-pyridin-3-yl-pyrimidin-2-yl-amine (5). *N*-(2-methyl-5-nitrophenyl)-4-pyridin-3-yl-pyrimidin-2-yl-amine (5) was reduced using stannous chloride dihydrate in hydrochloric acid at 0ºC which gave 6-methyl-*N*-(4-pyridin-3-yl-pyrimidin-2-yl)-benzene-1,3-diamine (6).

Various chalcone derivatives (7a-n) were prepared in ethanol at room temperature by Claisen-Schmidt condensation reaction between various substituted aldehydes and various substituted acetophenones. The condensation reaction was carried out by 20% (W/W) aqueous solution of NaOH. Unreacted carbaldehyde and/or acetophenone was removed by using ethyl acetate and n-hexane. First the chalcone derivative (7a-n) was dissolved into minimum ethyl acetate and kept inside water-bath and n-hexane was added drop by drop to obtain crystalline product. These chalcone derivatives (7a-n) and guanidine nitrate (8) in methanol solvent was heated slowly with continuous string. Drop by drop sodium methoxide was added and refluxed for about 11-12 hours and cooled to room temperature. It gave various pyrimidine derivatives (9a-n).

Cyanuric chloride (7) was taken in acetone and stirred at 0-5ºC. 6-methyl-*N*-(4-pyridin-3-yl-pyrimidin-2-yl)-benzene-1,3-diamine (6) was dissolved in 15mL acetone and was added to the above solution drop-wise at 0-5ºC maintaining reaction medium neutrals by the addition 10% sodium bicarbonate aqueous solution from time to time as per requirement of reaction condition. The reaction mixture was stirred for further 3 hours. The crude product was recrystallized from alcohol to get compound *N*-(4,6-dichloro-1,3,5-triazin-2-yl)-4-methyl-*N*-(4-(pyridin-3-yl) pyrimidin-2-yl)benzene-1,3-diamine (10).

N-(4,6-dichloro-1,3,5-triazin-2-yl)-4-methyl-*N*-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (10) was dissolved in DMF with continuous stirring. Various pyrimidine derivatives (9a-n) were dissolved in DMF and added drop wise into the above solution with continuous stirring. The reaction condition; such as 35-40ºC and pH was maintained by the addition 10% sodium bicarbonate solution during the reaction period. After the addition was completed the reaction temperature was slowly raised up to 45º C. The crude product was purified by recrystallisation from ethanol to get compound 6-chloro-*N*-(4,6-diphenylpyrimidin-2-yl)-*N*-(4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino) phenyl)-1,3,5-triazine-2,4-diamine derivatives (11a-n).

6-chloro-*N*-(4,6-diphenylpyrimidin-2-yl)-*N*-(4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino) phenyl)-1,3,5-triazine-2,4-diamine derivatives (11a-n) was dissolved in DMF with stirring and heated slowly in oil bath. 3-aminoadamantanol (12) was dissolved in DMF. The dissolved mixture was slowly added to previously heated solution and further heated at 80-90ºC and pH was maintained by the addition of 10% sodium bicarbonate solution during the reaction period. After the completion of addition, the reaction temperature was slowly raised up to 100ºC. The crude product was purified by recrystallisation from ethanol to get compound (13a-n).

The structure of the synthesized compounds was confirmed by the FT-IR spectra obtained using KBr pellets on Perkin-Elmer 1600 FTIR, ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 500MHz in DMSO-d_6 as a solvent using tetramethyl silane (TMS) as internal standard respectively. LC-MS were obtained using LCMS. These triazine-pyrimidine derivatives (13a-n) were confirmed by ^{1}H NMR data such as, -OH group showed value of δ near **5.03-5.12,** -NH group of admentanol showed value of δ near **7.41-7.43,** -NH group of pyrimidine ring showed value of δ near **8.44-8.49,** methyl group showed value of δ near **2.28-2.32,** methoxy group showed value of δ near **3.80.** These triazine-pyrimidine derivatives (13a-n) were confirmed by IR data such as, N-H (2° amine) was confirmed by value of ν near **1550cm^{-1},** O-H group was confirmed by value of ν near **3920cm^{-1}**, C-H of Ar-CH_3 was confirmed by value of ν near **1348cm^{-1},** C-H of -OCH_3 was confirmed by value of ν near **3414cm^{-1}. Figure; 5.11** to **5.13** shows ^{1}H NMR spectra of the compounds **VJT$_1$, VJT$_2$** and **VJT$_3$** respectively. **Figure; 5.14** to **5.15** shows ^{13}C NMR spectra of the compounds **VJT$_1$** and **VJT$_2$** respectively. **Figure; 5.16** to **5.17** shows IR spectra of the compounds **VJT$_1$** and **VJT$_2$** respectively. **Figure; 5.18** shows LCMS spectra of the compounds **VJT$_1$** and **VJT$_2$.**

Biological activity

Antibacterial activity

The minimum inhibition concentration of the triazine-pyrimidine derivatives **(VJT_1 to VJT_{14})** is shown in **Table-5.3** (Graph-5.1). The results showed that most of the compounds exhibited considerable activities against *E. Coli, P. Aeruginosa, S. Aureus*, *S. Pyogenes.* According to data of antibacterial activity of triazine-pyrimidine derivatives such as, **VJT_3** (R_1 = -Br and R_4 = -Cl) and **VJT_9** (R_1 = $-NO_2$ and R_4 = -Cl) exhibited the best activity at **50µg/mL, VJT_2** (R_1 = -Br and R_3 = -Cl), **VJT_{11}** (R_1 = $-OCH_3$ and R_3 = -Cl) and **VJT_{13}** (R_2 = -OH and R_3 = -Cl) exhibited good activity at **62.5µg/mL**, **VJT_4** (R_1 = -Cl and R_3 = -Cl), **VJT_7** (R_1 = $-CH_3$ and R_3 = -Cl), **VJT_{12}** (R_2 = $-NO_2$ and R_3 = -Cl) and **VJT_{14}** (R_2 = $-OCH_3$ and R_3 = -Cl) exhibited good activity at **100µg/mL** against *E. Coli* as compared to Ampicillin (MIC=100µg/mL). From the results triazine-pyrimidine derivatives such as, **VJT_9** (R_1 = $-NO_2$ and R_4 = -Cl) exhibited the best activity at **50µg/mL, VJT_2** (R_1 = -Br and R_3 = -Cl) exhibited good activity at **62.5µg/mL**, **VJT_3** (R_1 = -Br and R_4 = -Cl), **VJT_4** (R_1 = -Cl and R_3 = -Cl), **VJT_{10}** (R_1 = -OH and R_3 = -Cl), **VJT_{12}** (R_2 = $-NO_2$ and R_3 = -Cl) and **VJT_{13}** (R_2 = -OH and R_3 = -Cl) exhibited good activity at **100µg/mL** against *P. Aeruginosa* as compared to Ampicillin (MIC=100µg/mL) and equal as Chloramphenicol (MIC=50µg/mL). Antibacterial activity triazine-pyrimidine derivatives such as, **VJT_6** (R_1 = -Cl and R_3 = $-N(CH_3)_2$) exhibited the best activity at **50µg/mL, VJT_2** (R_1 = -Br and R_3 = -Cl), **VJT_3** (R_1 = -Br and R_4 = -Cl), **VJT_9** (R_1 = $-NO_2$ and R_4 = -Cl), **VJT_{11}** (R_1 = $-OCH_3$ and R_3 = -Cl) and **VJT_{13}** (R_2 = -OH and R_3 = -Cl) exhibited good activity at **100µg/mL** against *S. Aureus* as compared to Ampicillin (MIC=250µg/mL) and equal as Chloramphenicol (MIC=50µg/mL). Antibacterial activity triazine-pyrimidine derivatives such as, **VJT_1** (R_1 = -Br and R_3 = $-OCH_3$), **VJT_2** (R_1 = -Br and R_3 = -Cl), **VJT_6** (R_1 = -Cl and R_3 = $(CH_3)_2N$-), **VJT_9** (R_1 = $-NO_2$ and R_4 = -Cl), **VJT_{11}** (R_1 = $-OCH_3$ and R_3 = -Cl), **VJT_{12}** (R_2 = $-NO_2$ and R_3 = -Cl) and **VJT_{13}** (R_2 = -OH and R_3 = -Cl) exhibited good activity at **100µg/mL** *S. Pyogenes* as compared to Ampicillin (MIC=100µg/mL).

Antifungal activity

The minimum inhibition concentration of the triazine-pyrimidine derivatives **(VJT_1 to VJT_{14})** is shown in **Table-5.4** (Graph-5.2). Most of the compounds tested, exhibited considerable activities against *C. Albicans, A. Niger* and *A. Clavatus*. According to data of antifungal activity triazine-pyrimidine derivative such as **VJT_6** (R_1 = -Cl and R_3 = $-N(CH_3)_2$) exhibited the best activity at **50µg/mL, VJT_2** (R_1 = -Br and R_3 = -Cl) exhibited the best activity at **62.5µg/mL, VJT_5** (R_1 = -Cl and R_4 = -Cl) and **VJT_7** (R_1 = $-CH_3$ and R_3 = -Cl) exhibited very good activity at **100µg/mL** against *C. Albicans* as compared Nystatin (MIC=100µg/mL) and Griseofulvin (MIC=500µg/mL). Triazine-pyrimidine derivatives such as, VJT_6 (R_1 = -Cl and R_3 = $-N(CH_3)_2$) exhibited the best activity at **50µg/mL** and **VJT_2** (R_1 = -Br and R_3 = -Cl) exhibited very good activity at **100µg/mL** against *A. Niger* as compared Nystatin (MIC=100µg/mL) and Griseofulvin (MIC=500µg/mL) Triazine-pyrimidine derivatives such as, **VJT_2** (R_1 = -Br and R_3 = -Cl) and **VJT_6** (R_1 = -Cl and R_3 = $-N(CH_3)_2$) exhibited the best activity at **100µg/mL** against *A. Niger* as compared Nystatin (MIC=100µg/mL) and Griseofulvin (MIC=500µg/mL).

Antitubercular activity

The encouraging results of antibacterial activity study of triazine-pyrimidine derivatives **(VJT_1 to VJT_{14})** impelled to carry out further preliminary screening against *M. tuberculosis*. The results of antitubercular activity of triazine-pyrimidine derivatives are shown in **Table-5.4** (Graph-5.3). In the screening tests of these compounds 1000, 500 and 250µg/mL concentration were taken. Among these compounds the compounds which showed activity in the screening were further used for the testing for secondary screening against *M. tuberculosis* $H_{37}RV$ in the L. J. Medium (conventional method). The data of the antitubercular activity was compared with Rifampicin at 40µg/mL concentration. Triazine-pyrimidine derivatives such as **VJT_1**, **VJT_5, VJT_6, VJT_7** and **VJT_{11}** containing chloro, dimethylamine and chloro substituted showed *M. tuberculosis* MIC values in the range between **100µg/mL** which indicated 95-99% better results. While remaining derivatives showed moderate to weak activity against *M. tuberculosis* $H_{37}RV$.

Antimalarial activity

Antimalarial activity of triazine-pyrimidine derivatives **(VJT_1 to VJT_{14})** shown in **Table-5.5.** Antimalarial activity compared with standard drug such as Chloroquine and Quinine. The minimum inhibition concentration is 0.020µg/mL and 0.268µg/mL respectively. Triazine-pyrimidine derivatives such as, **VJT_1, VJT_7, VJT_8, VJT_9, VJT_{10}, VJT_{13}** and **VJT_{14}** exhibited very good activity at **0.29µg/mL, 0.74µg/mL, 0.72µg/mL**, **0.89µg/mL, 0.28µg/mL, 0.39µg/mL** and **0.26µg/mL**, respectively as antimalarial compared to Quinine (MIC=0.268 µg/mL).

Conclusion

Synthesized triazine-pyrimidine derivatives (**VJT_1 to VJT_{14}**) possessed excellent antibacterial activity. Triazine-pyrimidine derivatives, **VJT_3** and **VJT_9** exhibited the best activity at 50µg/mL. Triazine-pyrimidine derivatives, **VJT_9** exhibited the best activity at 50µg/mL exhibited the best activity at 50µg/mL against *P. Aeruginosa.* Triazine-pyrimidine derivative, **VJT_6** exhibited the best activity at 50µg/mL exhibited the best activity at 50µg/mL against *S. Aureus.* Triazine-pyrimidine derivatives, **VJT_1, VJT_2, VJT_6, VJT_9 VJT_{11}, VJT_{12}** exhibited the best activity at 100µg/mL against *S. Pyogenes.* Synthesized triazine-pyrimidine derivatives (**VJT_1 to VJT_{14}**) possessed excellent antifungal and antitubercular activity. Triazine-pyrimidine derivative, **VJT_6** exhibited the best activity at 50µg/mL exhibited the best activity at 50µg/mL against *C. Albicans.* Triazine-pyrimidine derivative, **VJT_6** exhibited the best activity at 62.5µg/mL exhibited the best activity at 50µg/mL against *A. Niger.* Triazine-pyrimidine derivatives, **VJT_2,** and **VJT_6** exhibited the best activity at 100µg/mL exhibited the best activity at 62.5µg/mL against *A. Clavatus.* Triazine-pyrimidine derivatives, **VJT_1, VJT_5, VJT_6, VJT_7** and **VJT_{11}** exhibited the best activity at 100µg/mL exhibited the best activity at 100µg/mL against *$H_{37}RV$.* Synthesized triazine-pyrimidine derivatives (**VJT_1 to VJT_{14}**) possessed good antimalarial activity. Triazine-pyrimidine derivative, **VJT_1, VJT_{10}** and **VJT_{14}** exhibited the best activity at 0.29µg/mL, 0.28µg/mL and 0.26µg/mL exhibited the best activity at 0.36µg/mL.

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References

1) Khalil AEGM, Berghot M. A., Gouda M. A., "Design, synthesis and antibacterial activity of new phthalazinedione derivatives", *Journal of the Serbian Chemical Society*, 76, 329-39, **2011.**
2) Patel R. B., Chikhalia K. H., "Synthesis of novel PETT analogues, 3,4-dimethoxy phenyl ethyl 1,3,5-triazinyl thiourea derivatives and their antibacterial and anti-HIV studies", *Journal of the Brazilian Chemical Society,* 18, 312-21, **2007.**
3) Elgazwy ASH, Zaky H. T., "2(3*H*)-Furanones as synthons for polyamides of 1,3-diazines and 1,3,5-triazines", *ARKIVOC*, 10, 162-72, **2006.**
4) Dawane B. S., Kadam S. N., Shaikh B. M., "An efficient synthesis of 1,2,4-triazine derivatives and their in vitro antimicrobial activity", *Der Pharmacia Letters,* 2, 126- 31, **2010.**
5) Stevens MFG, Ellis G. P., West G. B., Progress in Medicinal Chemistry, North Holland, *Amsterdam*, pp. 205-69, **1976.**
6) Butler R. N., Fahy A. M., "New reactive fluorophores in the 1,2,3-triazine series", *Tetrahedron Letters*, 47, 1721-4, **2006.**
7) Vora J. J., Vasava S. B., "Synthesis, characterization and antibacterial activity of a new series of s-triazines derived with quinolines", *E-Journal of Chemistry*, 6, 201-6, **2009.**
8) Dawane B. S., Kadam S. N., Shaikh B. M., "An efficient synthesis of 1,2,4-triazine derivatives and their in vitro antimicrobial activity", *Der Pharmacia Lettre*, 2, 126- 31, **2010.**
9) Pal R. R., Lee D. S., "Synthesis and pH-dependent micellization of a novel block copolymer containing striazine linkage, Macromolecular Research", 13, 373- 84, **2005.**
10) Vora J. J., Vasava S. B., "Synthesis, characterization and antibacterial activity of a new series of s-triazines derived with quinolines", *E-Journal of Chemistry*, 6, 201-6, **2009.**
11) Afonso C. A. M., Lourenco N. M. T., "Synthesis of 2,4,6-trisubstituted-1,3,5-triazines", Molecules, 11, 81-102, **2006.**