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Synthesis, Characterization, Antimicrobial, Antifungal activity of some s-triazine Derivatives of Isoxazoline, Pyrazoline and PC model Computational Studies

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Abstract

Synthesis of N2-(4-(2-amino-3-(aryl substituted)2-substituted dinitro phenyl) pyrazolinphenyl)-N4,N6-bis(4-methoxyphenyl) -1,3,5-triazin-2,4,6-triamine1-(4-(4,6-Bis(4′-chlorophenylamino)-1,3,5-triazin-2-ylamino)-phenyl)-3-(aryl substituted) prop-2-en-1-one 3 has been used as precursor to synthesize some new pyrazoline, isoxazoline and derivatives. Several derivatives have been synthesized and evaluated for their antimicrobial efficacy against Bacillus subtilis, Escherichia coli, antifungal activity antifungal activity Penicillium citrinum, Aspergillus flavus, Aspergillus niger, PC-model computational studies.

Keywords: S-triazine. thiazoline, isoxazoline, PC-model, Heterocyclic.

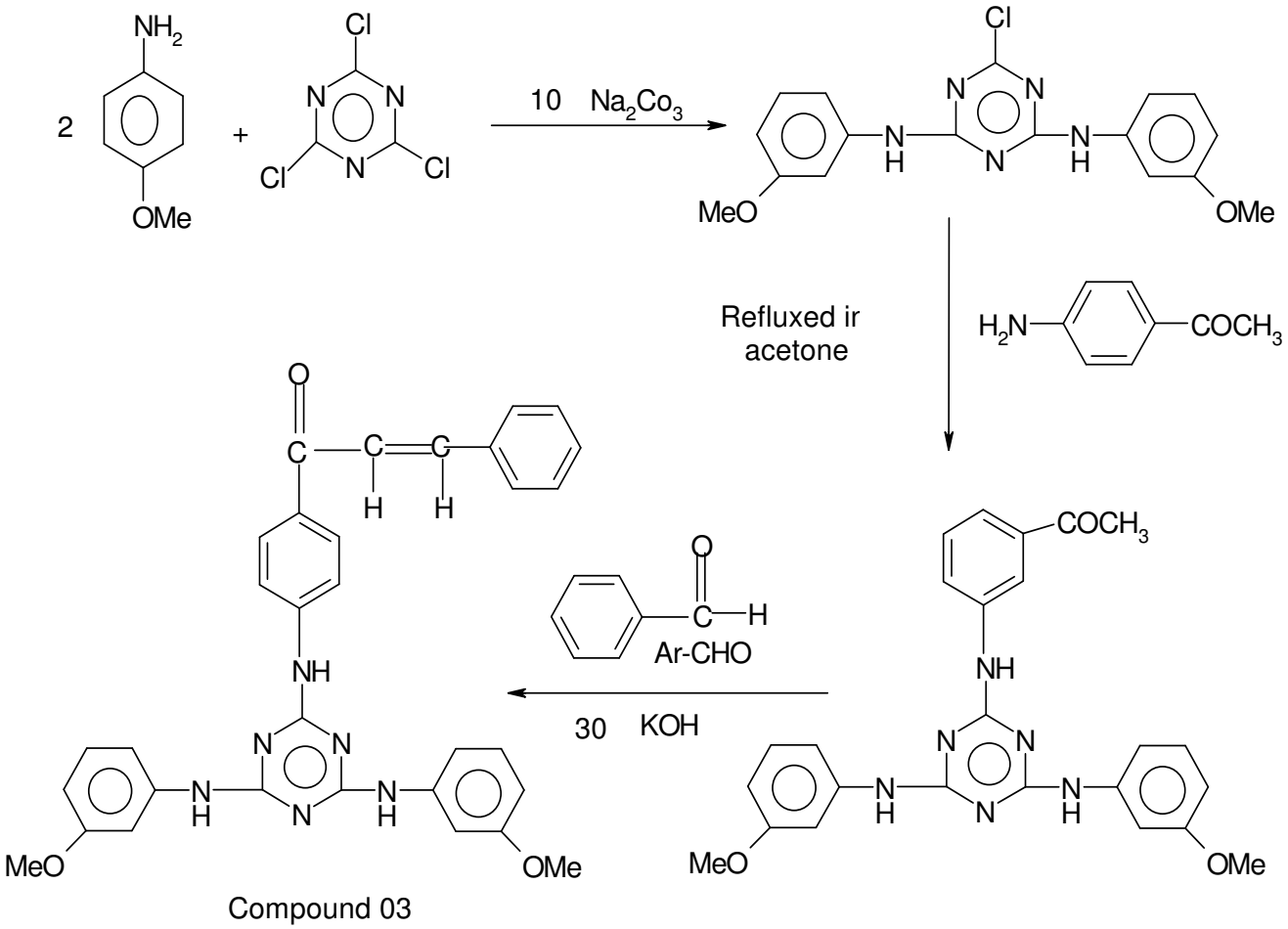
Introduction

Heterocyclic compounds play important roles in the drug discovery process[1-3] and analysis of drugs in late development or on the market shows that 68% of them are heterocycles. Therefore, it is not surprising that research on the synthesis of polyfunctionalized heterocyclic compounds has received special attention[4-6]. Of these heterocycles, pyridazine derivatives which are a rarity in nature have been reported to possess a wide range of biological activities[7-8]. These include antiviral and anticancer, antituberculosis, antihy-pertensive, anti-inflammatory, and antimicrobial, activities[9-11]. Pyridazine derivatives have also been the subject of extensive research in the agrochemical areas[12-14]. Moreover, pyridazines are useful intermediates in the construction of several other heterocycles and in physical organic chemistry and recently have been explored as new P-helix mimetics[15-16]. In this work is reported the synthesis and biologicalactivity of some isoxazoline and pyrazoline derivatives. Form a component in a number of useful drugs that are associated with many biological, pharmaceutical and therapeutical activities. Condensed derivatives of isoxazoline, have been reported as analgesics, antivirals, anti-inflammatory, antibacterial and antituberculosis agents. Diaryl pyrimidine (DAPY) appears to be the more effective against wild type andvarious mutant strains of HIV[17-18]. Pyrazolines are prominent nitrogen containing heterocycliccompounds and therefore, various procedures have been worked out for their synthesis. Pyrazolines andits derivatives have not been found in nature. The replacement of two methyne units in benzene by nitrogen atoms gives pyrimidines[19-21]. It has incidentalantiviral activity against herpes and vacciniainfections. Isoxazoline derivatives have played acruicial role in the theoretical development of heterocyclic chemistry and also find extensive application in organic synthesis[22]. The synthesis of isoxazoline derivatives remains the main focus of medicinal research. Because of the great synthetic potentiality, heterocyclic analogous of chalcones are among the most useful synthons. All these observations and the essential role of heterocyclic pyrimidine, isoxazoline, pyrazoline derivatives in certain biological reactions prompted the synthesis of all these derivatives, 1-Al, 13A-l and screening for their biological activity.

Material and Methods

Melting points were determined routinely in an open capillary tube and are uncorrected. Formation of synthesized heterocyclic derivatives was checked by TLC on silica gel-G plates of 0.5 mm thickness and the spots were located by exposure to iodine vapours. The 1H NMR spectra were recorded on a AVANCE II400 NMR spectrometer with CDCl3 as solvent and TMS as internal reference (chemical shift in δ□ ppm). The IR spectra were recorded in KBr pellets on a Shimadzu 8201 PC spectrophotometer (vmax in cm-1).Elemental analyses of the newly synthesized heterocyclics were carried out on a Calro Elba 1108 analyzer and the results were found within range of the theoretical value

Step 1.Synthesis of 2, 4-bis (4′-methoxy phenyl amino)-6-chloro-s-triazine, 1: S-Triazine (0.01 mol) was dissolved in acetone (25mL) and p-chloro aniline (0.02 mol) was added to it between 0-5ºC and stirred for 2 hr. This was followed by stirring at RT for 3 hr. Then 10% Na_2CO_3 was added and the reaction mixture was poured in to crushed ice. The solid separated out was filtered, washed with water and purified by recrystallization from ethanol and its homogeneity was checked by TLC to obtain compound 1.



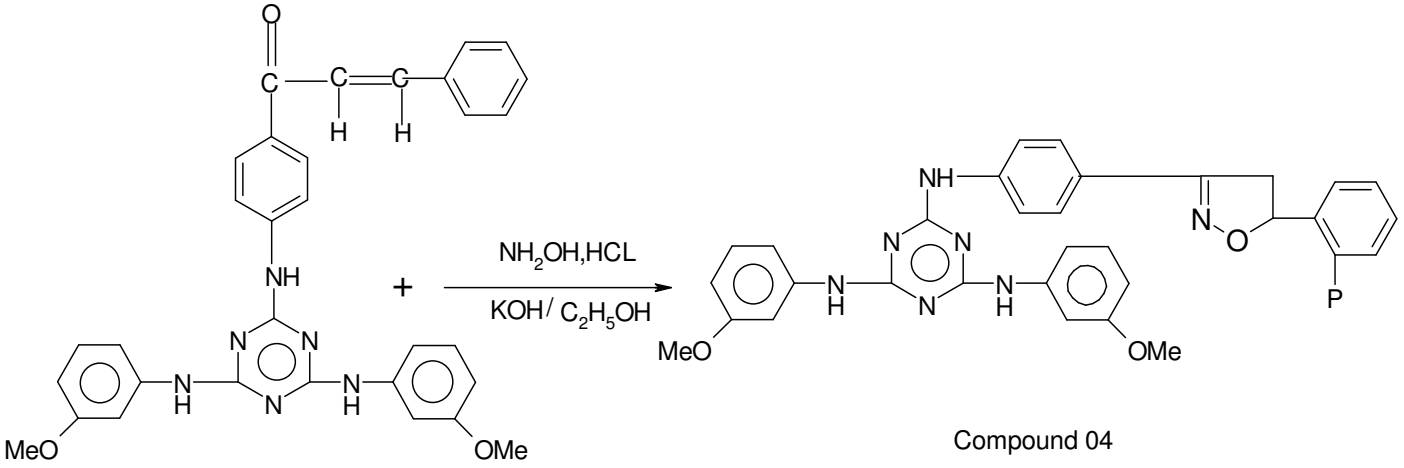
Scheme-I

Step 2 Synthesis of 2,4-bis (4′-methoxyphenyl amino)-6-(4′-acetyl phenyl amino)-s-triazine2: Compound 1 (0.01 mol) and p-amino acetophenone(0.01 mol) were dissolved in acetone (50 ml) and thereaction mixture was refluxed for 12 hr. Sodium carbonate (10% solution) was added to neutralize thereaction mixture and it was poured into crushed ice. The solid separated out was filtered, washed withwater and purified by recrystallization to obtain compound 2.

Step 3 Synthesis of 1-(4-(4,6-bis (4′-methoxy phenylamino)-1,3,5-triazin-2-ylamino)-phenyl)-3-(arylsubstituted) prop-2-en-1-one, 3: Compound 2 (0.01 mol) and substituted aromaticaldehyde (0.01 mol) was taken in 30 mL DMF. 40%KOH was added into the reaction mixture. Thereaction mixture was stirred for 2 hr and later overnight. The reaction mixture was then poured into ice water, neutralized with HCl, filtered, washed with water, and purified by recrystallization from ethanol to yield compound 3a-l. The homogeneity of compounds was checked by TLC

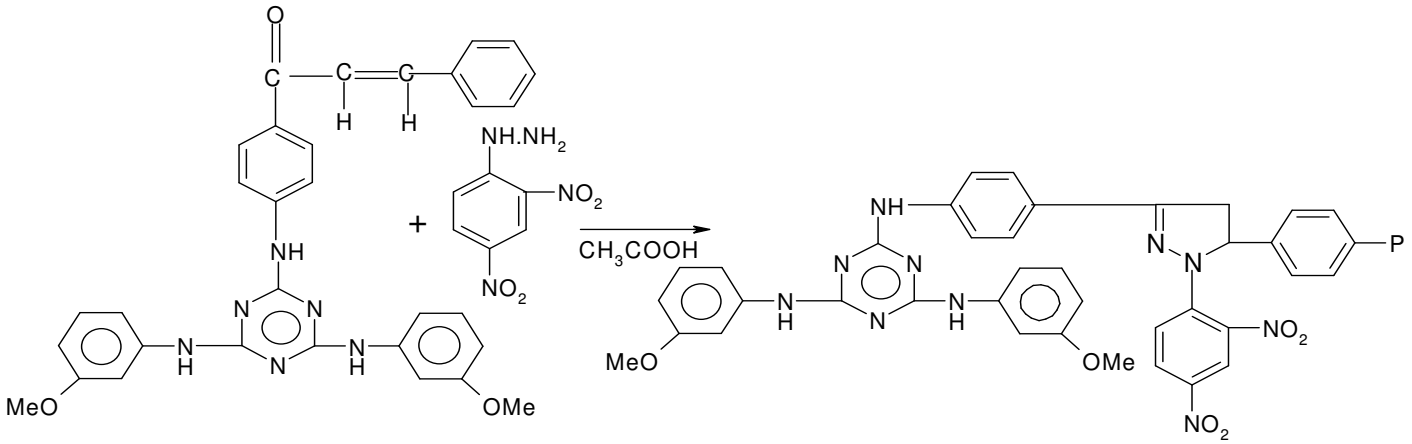
Step 4 Synthesis of N2-(4-(2-amino-6-(aryl substituted) isoxazolin phenyl)-N4, N6-bis (4- Methoxy phenyl)-1,3,5-triazin-2,4,6-triamine 4: A mixture of compound 3 (0.02 mol), hydroxyl amine hydrochloride (0.04 mol) and KOH (0.02 mol)was refluxed for 4 hr. The reaction mixture was cooled and acidified with glacial acetic acid. The resulting solid was washed with water and purified by recrystallization from rectified spirit. The homo-geneity of compounds has been checked by TLC. 5a. IR: 3355.76 (N-H), 3058.12 (Ar-H), 2955.14Ali(C-H), 1541.18 (C=C), 690.54 (Ar-Br), 833.28 (C-N), 1489.1 (C=N), 1368.64 (C-N), 1085.73 (N-O),1278.55(C-O-C), 669.32 cm-1 (C-H bending out ofplane); 1H NMR ($CDCl_3$): □ 7.581 (s, 3H, N-H), 6.456(Sym. multi, 8H, 2-OCH_3 subs. benzene rings), 6.262(Sym. multi, 4H, disubs. benzene rings), 3.425 (s,6H,2-OCH_3), 4.016 (d,2H,CH_2 of isoxaoline), 3.986(t,1H, CH of isoxazoline), 5.986(unsym. multi., 4H,subs. benzene ring). 5b. IR: 3308.13 (N-H), 3070.56 (Ar-H), 2908.23Ali(C-H), 1575.13 (C=C), 780.12 (Ar-Br), 830.21 (C-N), 1480.13 (C=N), 1360.29 (C-N), 1080.31 (N-O),1270.56(C-O-C), 1404.66 (C-H bending in plane),695.32 cm-1 (C-H bending out of plane); 1H NMR($CDCl_3$): 7.452 (s, 3H, N-H), 6.512 (sym. multi, 8H,2-OCH_3 subs. benzene rings), 6.132 (sym. multi, 4H,disubs. benzene rings), 3.321 (s, 6H,2-OCH_3), 4.002(d,2H,CH_2 of isoxaoline), 3.951 (t,1H, CH ofisoxazoline), 5.551 (unsym. multi., 4H, subs. benzenering).

Step 5 Synthesis of N2-(4-(2-amino-3-(aryl substituted)2-(substituted dinitro phenyl) pyrazolin phenyl)-N4,N6-bis(4-methoxyphenyl)-1,3,5-triazin-2,4,6-triamine: The compound 1-(4-(4,6-bis (4′-methoxy phenylamino)-1,3,5-triazin-2-ylamino)-phenyl)-3-(aryl substituted) prop-2-en-1-one 3 was taken in 30 mL acetic acid and 2,4-dinitrophenylhydrazine was addedover 10 hr. The contents were poured into ice, filtered and the products isolated and purified by recrystallization from ethanol to afford the required compound. The homogeneity of compounds has been checked by TLC (Scheme II).7a. IR: 3356 (N-H), 3081 (Ar-H), 2981Ali(C-H), 690.54 (Ar-Br), 833 (C-N), 1470.36(C=N), 1298(C-N), 1986 (N-O), 1281.36(C-O-C), 669 cm-1 (C-H bending out of plane); 1H NMR($CDCl_3$): 7.834 (s, 3H, N-H), 6.438 (sym. multi, 8H,2-OCH_3 subs. benzene rings), 6.234 (Sym. multi, 4H, disubs. benzene rings), 3.456 (s, 6H,2-OCH_3),4.012 (d,2H,CH_2 of isothiazoline), 3.156 (t,1H, CH of isothiazoline), 6.033 (unsym. multi., 4H, substitutedbenzene ring). 7b. IR: 3302.12 (N-H), 3103.38 (Ar-H), 2956.13Ali(C-H), 833.18 (C-N), 1502.13 (C=N), 1301.81(C-N), 1091.31 (N-O), 1289.31(C-O-C), (C-Cl) 754.32,1402.81 (C-H bending in plane), 692.33 cm-1 (C-H bending out of plane); 1H NMR (CDCl3): δ 7.535 (s,3H, N-H), 6.565 (sym. multi, 8 H,2-OCH_3 substituted benzene rings), 6.382 (sym. multi, 4H, disubstituted benzene rings), 3.813 (s,6H,2-OCH_3), 4.221(d,2H,CH2 of isothiazoline), 6.034 (unsym. multi.,4H, subs. benzene ring).rings), 3.565 (s, 6H,2-OCH_3), 4.034 (d,2H,CH_2 of isothiazoline), 3.156 (t,1H, CH of isothiazoline),6.001(unsym. multi., 4H, subs. benzene ring). 8b. IR: 3305.81 (N-H), 102.31(Ar-H), 2903.31Ali(C-H), 832.34 (C-N), 1304.61 (C=N), 1276.31 (N-O), 1281.36 (C-O-C), 753.25 (Ar-Cl), 1404.44 (C-H bending in plane), 701.61 cm-1 (C-H bending out of plane); 1H NMR ($CDCl_3$): δ 7.423 (s, 3H, N-H), 7.128 (s, 1H, N-H), 6.412(sym. multi., 4H, disubstituted benzene ring), 6.456 (sym. multi, 8 H,2-OCH_3substituted benzene ring), 6.412 (sym. multi, 4H,disubstituted benzene rings), 3.616 (s,6H,2-OCH_3),4.112 (d,2H,CH_2 of isothiazoline), 3.002 (t,1H, CH of isothiazoline), 5.998 (unsym. multi., 4H, subs.benzene ring).



Compound 04

Scheme-II



compound 05

Scheme-III

Table-1
Physical Characterization data pyrazoline S- traizine Compound

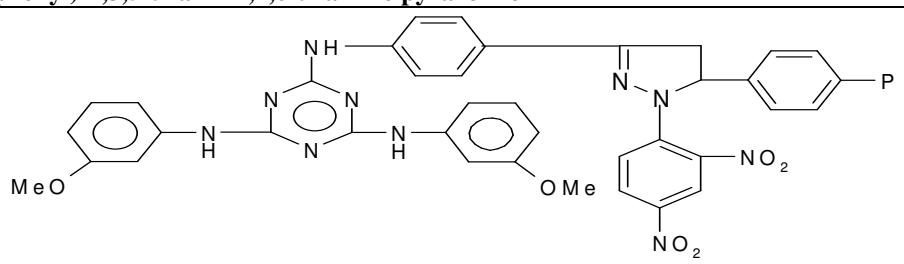
Name	**N4, N6-bis (4-methoxy phenyl)-1,3,5-triazin-2,4,6-triamine pyrazoline**					
Mol.Wt.	820.69					
M.P.°C	76					
Yield (%)	82%					
Mol.For.	C38N10O6H31Br					
		compound 05				
Elemental Analysis	**C %**		**H %**		**N %**	
	Found	**Calcu.**	**Found**	**Calcu.**	**Found**	**Calcu.**
	56.83	58.84	5.87	4.79	17.87	19.19

Table -2
Physical characterisation data of the synthesized isoxazoline,pyrazoline S-traizine derivatives

Compound		**Group P**	**Mol.For**	**Mol.wt.**	**M.P.**	**Yield (%)**	**C**	**H**	**N**
1	A	3-Br	C32N7O3H28Br	612. 64.	94	82	60.22	4.69	15.33
2	B	2-Cl	C32N7O3H28Cl	608.06	99	78	64.64	4.75	16.47
3	C	2-OH	C32N7O4H29	575.60	91	73	66.71	5.07	17.01
4	D	4-NO2	C32N8O5H28	620.59	94	75	61.90	4.54	18.01
5	E	3-OH,4-OCH3	C33N7O5H32	606.63	93	82	65.91	5.31	16.12
6	F	2-NO2	C32N8O5H28	620.59	91	81	62.98	4.54	18.01
7	G	4-OH	C32N7O4H29	575.60	98	79	61.92	5.07	17.00
8	H	4-N(CH3)2	C32N7O3H28	602.68	96	72	65.34	5.68	18.55
9	I	4-Cl	C32N7O3H28Cl	637.64	96	65	66.72	4.42	16.48
10	J	3-Cl	C32N7O3H28Cl	637.64	98	72	67.54	4.42	16.45
11	K	3-NO2	C32N8O5H28	620.59	93	73	67.73	5.07	18.03
12	L	4-OCH3	C33N7O4H31	689.63	95	69	64.92	5.29	16.60
13	A	3-Br	C38N10O6H31Br	820.69	76	82	56.83	3.87	17.41
14	B	2-Cl	C38N10O6H31Cl	753.15	77	78	60.58	4.11	19.02
15	C	2-OH	C38N10O7H32	740.65	75	73	61.61	4.32	18.09
16	D	4-NO2	C38N11O8H31	769.61	74	75	59.27	4.02	19.97
17	E	3-OH,4-OCH3	C39N10O8H35	771.72	74	82	60.63	4.53	18.14
18	F	2-NO2	C38N11O8H31	769.61	75	81	59.24	4.02	19.98
19	G	4-OH	C38N10O7H32	740.65	76	79	64.61	4.32	18.09
20	H	4-N(CH3)2	C40N11O6H37	793.70	74	72	60.51	4.68	19.38
21	I	4-Cl	C38N10O6H31Cl	753.15	75	65	65.56	4.12	19.03
22	J	3-Cl	C38N10O6H31Cl	753.15	74	72	67.57	4.12	18.02
23	K	3-NO2	C38N11O8H31	769.61	73	73	59.29	4.03	20.00
24	L	4-OCH3	C39N10O7H34	754.73	69	69	62.03	4.51	18.53

Table-3
Characterization of IR data pyrazoline S-traizine Compounds

Group type	Vibration mode	Frequency (cm^{-1})
Isoxazoline ring	-CH (str.) in–OCH_2	2913.44
	N-H (str.) in –NCH_2	3356.13
	-C-N (str.) in –NCH_2	3355.76
	N-O (Str.)	1276.31
	C-O-C in –OCH_2	1281.36
	Ali-C-H (bend.) in –NCH_2	2955.14
Aromatic ring	Ar-H (str.)	3081.72
	C=C (str.)	1541.18
	C=N (bend.)	1304.61
Ar-OCH_3	C-H(str.) in-OCH_3	2881.48
	C-O (str.) in Ar-OCH_3	1166.57
	Ar-Br	690.54

Table-4
Characterization of H^1 NMR data pyrazoline S-traizine Compounds

Signal No.	Chemical shift (in δ ppm)	Multiplicity	Relative no. of protons	Inference
1.	6.45	Multiplet	8	N-H of -OCH_3
2.	6.26	Multiplet	4	disub. of pyrazoline ring
3.	4.48	Singlet	2	C-N in CH_2 of pyrazoline ring
4.	5.98	Unsym.multiplet	4	Ar-OCH_3

Table-5
Antibacterial activityof S-triazine pyrazoline derivatives antibacterial activity zonesof inhibition (mm)

Compound code	*E. coli*		*Bacillus subtalis*		*Pseudomonas alcaligens*		*Salmonella* sp.	
	2%	4%	2%	4%	2%	4%	2%	4%
A1	11	15	16	11	14	21	22	28
B.2	13	17	12	15	15	19	12	21
C.3	10	15	20	24	14	25	15	18
D.4	13	16	15	18	13	18	15	19
E.5	17	24	10	12	10	14	15	19
F.6	13	20	23	24	21	24	28	30
G.7	14	21	23	24	30	24	29	30
H.8	12	16	16	19	10	13	13	11
I.9	12	16	16	19	10	13	13	11
J.10	12	16	16	19	10	13	13	11
K.11	12	16	16	19	10	13	13	11
L.12	12	16	16	19	10	13	13	11
Standard drug	18	24	26	29	24	26	24	27

Table-6
Antifungal activity S-triazine pyrazoline derivatives antifungal activity zonesof inhibition (mm)

Compound code	*Penicillium citrinum*		*Aspergillus flavus*		*Rhizoctonia bataticola*		*Aspergillus niger*	
	2%	4%	2%	4%	2%	4%	2%	4%
A.1	19	18	21	24	28	30	21	23
B.2	18	19	12	15	10	13	19	15
C.3	19	18	20	21	13	23	12	13
D.4	14	12	15	18	12	15	14	16
E.5	17	13	10	11	13	15	12	14
F.6	10	12	13	12	17	17	14	10
G.7	14	12	13	14	13	19	25	30
H.8	16	16	16	19	16	13	13	11
I.9	13	16	16	19	18	13	13	11
J.10	18	16	16	19	15	14	13	17
K.11	14	16	16	19	10	13	13	11
L.12	18	16	17	19	14	15	18	16
Standard drug	15	18	16	19	14	16	14	13

Table-7
Computer simulated PC Model data for marked bonds and their subsequent angles

Comcode	Substituent	B.L. C-N	B.A. N-C	Dihed. Ang. C-N-C	Mol. Vol.	VDW	Dip. Mom	MMX Energy
A-1	3-Br	1.564	120.67	162.37	276	18.03	4.197	36.398
B-2	2-Cl	1.474	121.02	165.39	276	12.11	2.18	31.364
C-3	2-OH	1.567	121.02	166.70	276	10.304	2.479	40.103
D-4	4-NO_2	1.534	120.13	178.47	286	15.44	2.312	74.366
E-5	3-OH,4-OCH_3	1.564	121.05	173.00	286	11.47	1.895	24.747
F-6	2-NO_2	1.573	120.85	165.95	286	29.96	1.736	22.452
G-7	4-OH	1.558	120.63	167.10	31	2.141	1.512	11.091
H-8	4-N(CH_3)2	1.561	121.16	167.76	323	10.74	1.089	29.206
I-9	4-Cl	1.560	121.02	173.00	286	11.47	1.895	24.747
J-10	3-Cl	1.564	120.13	165.95	286	29.96	1.736	22.452
K-11	3-NO_2	1.561	121.35	167.16	431	21.45	1.516	13.091
L-12	4-OCH_3	1.572	122.85	167.76	323	10.74	1.089	29.217
A-13	3-Br	1.562	120.67	162.37	276	18.03	4.197	36.398
B-14	2-Cl	1.473	121.02	165.39	276	12.11	2.18	31.364
C-15	2-OH	1.563	122.02	166.70	276	10.304	2.479	40.103
D-16	4-NO_2	1.532	121.13	178.47	286	15.44	2.312	74.366
E-17	3-OH,4-OCH_3	1.563	123.05	173.00	286	11.47	1.895	24.747
F-18	2-NO_2	1.573	122.85	166.95	286	29.96	1.736	22.452
G-19	4-OH	1.558	121.63	167.10	331	8.141	2.512	11.091
H-20	4-N(CH_3)2	1.561	123.16	167.76	323	10.74	1.89	29.206
I-21	4-Cl	1.560	124.02	173.00	286	17.47	1.895	24.747
J-22	3-Cl	1.564	121.13	165.95	286	29.96	1.736	28.452
K-23	3-NO_2	1.561	125.35	167.16	431	21.45	2.516	14.091
L-24	4-OCH_3	1.577	123.85	167.76	323	10.74	1.089	29.217

Results and Discussion

We reported 2,4-Bis(4′-methoxyphenylamino)-6-chloro-5-triazine1 has been prepared from 3-triazine in acetone and p-chloro aniline at 0ºC and constant stirring. In this step condensation reaction takes place. 2,4-Bis(4′-methoxy phenyl amino)-6-chloro 5-triazine 1reacts with p-amino acetophenone in acetone and gave 2,4-bis (4′-methoxy phenyl amino)-6-(4′-acetylphenyl amino) s-triazine 2. 10% sodium carbonate solution was added to keep the mixture alkaline. 2,4-Bis (4′-methoxy phenyl amino)-6-(4′-acetyl phenylamino-5-triazine reacted with various substituted aldehydes in DMF in the presence of 40% KOH and gave 1-(4-(4,6-bis (4′-methoxy phenyl amino)-1,3,5-triazin-2-yl amino)-phenyl)-3-(aryl substituted) prop-2-en-1-one 3a-l in quantitative yield. These synthesized derivatives 1-(4-(4,6-bis (4′-methoxyphenyl amino)-1,3,5-triazin-2-yl amino)-phenyl)-

3-(aryl substituted) prop-2-en-1-one compound 3 reacted with compound 3 refluxed with hydroxyl amine hydrochloride and KOH in ethanol gave N2-(4-(2-amino-6-(aryl substituted) isoxazoline phenyl)-N4, N6-bis (4-methoxy phenyl)-1,3,5-triazin-2,4,6-triamine 5. Compound 3 when refluxed with 2,4-dinitrophenylhydrazine in acetic acid gave N2-(4-(2-amino-3-(arylsubstituted)2-(substituted 4dinitro phenyl) pyrazoline phenyl)-N, N6-bis (4-methoxy phenyl)-1,3,5-triazine-2,4,6-triamine 7, isoxazoline, and pyrazoline derivatives 1A-l, , 13A-l have been screened for their antimicrobial, activities. The in vitro antimicrobial activity of the synthesized compounds have been investigated against several pathogenic bacteria Bacillus subtilis, Escherichia coli, and Staphyllo coccusaureus and fungi B. Aspergils niger Trichoderma viridae on going through the results of biological activity of synthesized , isoxazoline and pyrazoline derivatives 1A-l, 13A-l and it was shown that 4D,9I,10J,13A, 15C, 18F,10J, 11K, were highly active against both selected bacteria and fungi and the rest of the compounds have shown promising to moderate activity. comparison than that of standard drug and the rest of the compounds have shown promising to moderate activity. 1A, 6F, 10J, 12B, 13C, 18F, 10J, 11K, showed good antifungal activity and the rest of the compounds have shown promising to moderate activity. Thus it can be concluded that the synthesized pyrimidine,pyrazoline, isoxazoline, isothiazoline and pyrazoline derivatives 1A,13A and may function as good antimicrobial, and antifungal agents.

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