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Synthesis and study of thiazoles and thiadiazoles based derivatives of s-triazine as antimicrobial agents

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ABSTRACT: Some new substituted 1,3,5 triazine derivatives with 4-phenylthiazol-2-amine and 5-methyl-1,3,4-thiadiazol-2-amine and substituted urea were synthesized and evaluated for their *in vitro* antimicrobial activity against Gram positive and Gram negative strains and antifungal activity using a micro dilution procedure. Synthesized compounds U1AC to U10AC prove to be effective with MIC (µg/mL), among them U2AC, U3AC, U7AC and U8AC showed excellent activity against a panel of microorganisms. The newly synthesized compounds were characterized using IR, ^{1}H-NMR, ^{13}CNMR, MASS Analysis.

KEYWORD: Cyanuric chloride, 4-phenylthiazol-2-amine, 5-methyl-1,3,4-thiadiazol-2-amine, substituted urea, antimicrobial activity.

I. INTRODUCTION

The treatment of infectious diseases still remains a challenging task because of combination of factors including increasing number of multidrug resistant, microbial pathogens and emerging newer infectious diseases **[1]**.The therapeutic problem is a crucial part of hospitalized patients, immune suppressed patients with AIDS and those undergoing anticancer therapy or organ transplants. In spite of a large number of antibiotics and chemotherapeutics available for medical use the emerging resistance to old and antibiotics has created a substantial need for novel classes of antimicrobial agents **[2]**. s-triazine is a potential core to develop less toxic bioactive compounds. Based on these criteria many scientists selected the s-triazine motif to develop potent drug-like molecules. In the design of new compounds development of hybrid molecules through the combination of different pharmacophores in one structure may lead to compounds with increased antimicrobial activity. Therefore, these observations prompted us to synthesize new s-triazine derivatives which were attached with different heterocyclic amine ring through **–NH** bridge**.** Thiazole derivatives are associated with a broad spectrum of biological properties including anticonvulsant, antimicrobial, antituberculous, bacteriostatic activities, antiviral, antimalarial, anticancer, hypertension, inflammation, schizophrenia, HIV infections, hypnotics and more recently for the treatment of pain, as fibrinogen receptor antagonists with antithrombotic activity as new inhibitors of bacterial DNA gyrase B **[3-7]**. Thiazole derivatives are also found in application in the drug development for the treatment of allergies **[8]**. The five-member heterocyclic compounds particularly nitrogen and sulphur heterocycles, thiadiazoles have been successfully tested against several diseases and therefore received special attention in pharmaceutical and medicinal chemistry due to their diverse potential applications. The sulfur atom of thiadiazole ring imparts improved liposolubility, important for the drugs active at CNS level. The mesoionic nature of 1,3,4-thiadiazoles allows these compounds to cross cellular membranes and interact with biological targets with distinct affinities **[9-17]**. Considering the potent bioactivities of compounds possessing an s-triazine core, we became interested to synthesize new s-triazine derivatives as antibacterial agents. In continuation to our previous work, we herein report newer s-triazine derivatives appended with thiazole and thiadiazole derivatives. Synthesized compounds were screened against antibacterial and anti fungal activity.

II. EXPERIMENTAL

A. Materials and physical measurements

All reactions except those in aqueous media were carried out by standard techniques for the exclusion of moisture. Melting points were determined on an electro thermal melting point apparatus and are reported uncorrected. TLC on silica gel plates were used for purity checking and reaction monitoring. Elemental analysis (% C, H, N) was carried out by a Perkin–Elmer 2400 CHN analyzer. IR spectra of all compounds were recorded on a Perkin–Elmer FT-

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IR spectrophotometer in KBr. ^{1}HNMR spectra were recorded on Bruker Avance II-400 MHz and ^{13}CNMR spectra on Bruker Avance II-400, 100 MHz in DMSO-d_6 as a solvent and tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on triple quadrapole LCMS-6410 from Agilent Technology.

B. Preparation of 1-(4,6-dichloro-1,3,5-triazin-2-yl)-3-phenylurea: (U1 to 10)

To a stirred solution of cyanuric chloride (0.01 mol) in acetone (25 mL) at 0-5 ºC, the solution of substituted urea compounds solution (0.01 mol) in acetone (15 mL) was added and pH being maintained neutral by the addition of 10% sodium bicarbonate solution from time to time as per requirement of reaction condition. The stirring was continued at 0-5 ºC for 2 hours. After the completion of reaction the stirring was stopped and the solution was treated with crushed ice. The solid product obtained was filtered and dried.

C. Preparation of 1-(4-chloro-6-((5-methyl-1,3,4-thiadiazol-2-yl)amino)-1,3,5-triazin-2-yl)-3-phenylurea: (U1 to 10A)

To a stirred solution of (A) (0.01 mol) in DMF (25 mL) was added, the solution of 5-methyl-1,3,4-thiadiazol-2-amine (0.01 mol) in DMF (15 mL) was added drop wise maintaining the temperature at 40 ºC, the pH being maintained neutral by the addition of 10% sodium bi-carbonate solution from time to time as per requirement of reaction condition. The temperature was gradually raised to 45 ºC during three hours. After the completion of reaction, the resultant content was poured into ice-cold water. The solid product obtained was filtered and dried. The crude product was purified by crystallization from absolute alcohol to get the title compound.

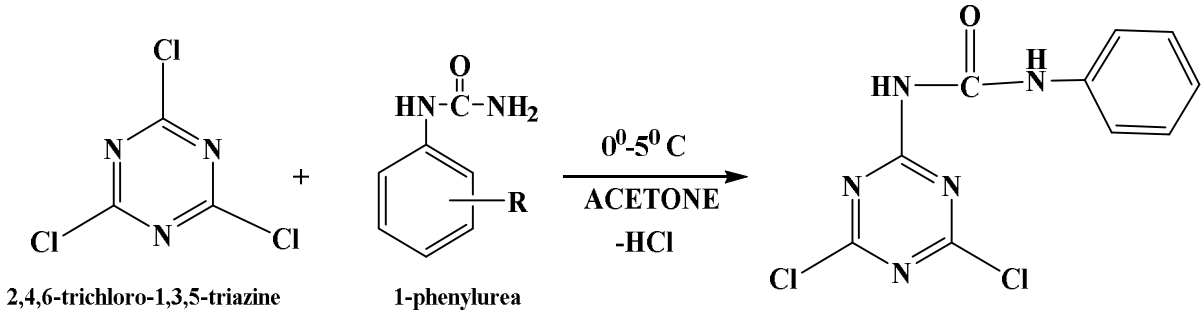
D. Preparation of 1-(4-((5-methyl-1,3,4-thiadiazol-2-yl-)amino)-6-((4-phenylthiazol-2-yl)amino-1,3,5-triazine-yl)-3-phenylurea: (U1 to 10AC)

A mixture of (U1 to 10A) (0.01 mol) and 4-phenylthiazol-2-amine (0.01 mol) in DMF (15mL) was refluxed in oil bath. The temperature was gradually raised to 80-100 ºC during four hours, the pH being maintained neutral by the addition of 10% sodium bi-carbonate solution from time to time as per requirement of reaction condition. After the completion of reaction add charcoal in R.B.F. and heat and filter into cold water. The solid product obtained was filtered and dried. The crude product was purified by recrystallization from absolute alcohol.

.

III. REACTION SCHEME

A. Step-1:



2,4,6-trichloro-1,3,5-triazine

1-phenylurea

1-(4,6-dichloro-1,3,5-triazin-2-yl)-3-phenylurea

(U1 to 10)

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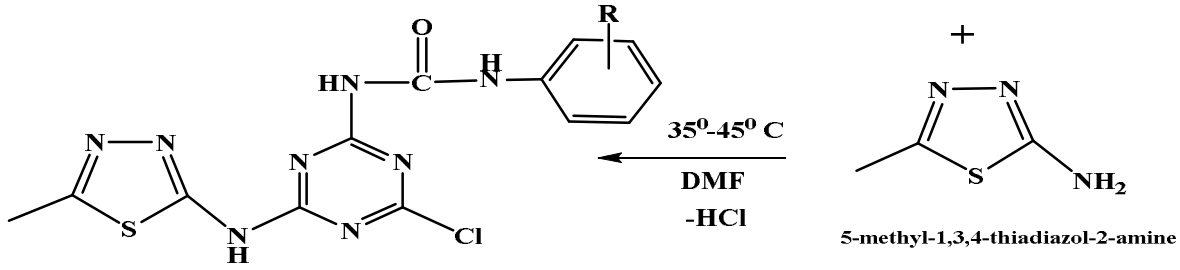
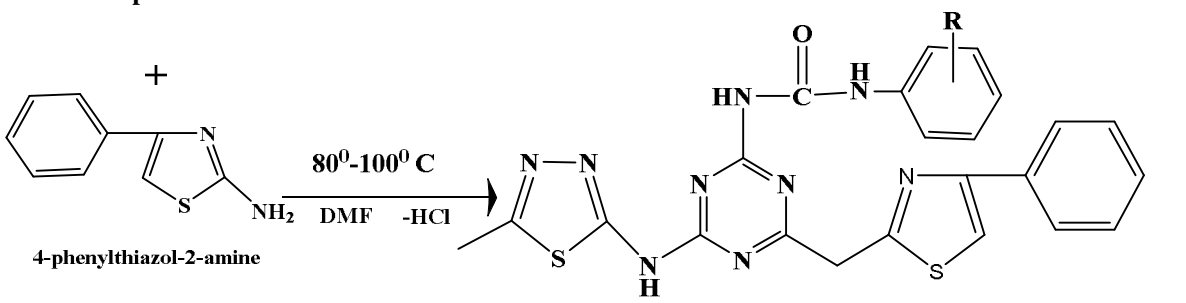
B. Step-2:



1-(4-chloro-6-((5-methyl-1,3,4-thiadiazol-2-yl)amino)-1,3,5-triazin-2-yl)-3-phenylurea

(U1 to 10A) **(A)**

C. Step-3:



1-(4-((5-methyl-1,3,4-thiadiazol-2-yl)amino)-6-((4-phenylthiazol-2-yl)methyl)-1,3,5-triazin-2-yl)-3-phenylurea

(C) **(U1 to 10AC)**

Where R= -H, 2-CH_3, 4-CH_3, 2-OCH_3, 4-Cl, 4-F, 4-Br, 2-NO_2, 2-Cl

Table 3.1: Analytical and Physicochemical data of the synthesized compounds U1AC to U10AC:

Sr. No.	R	M.P. ^{O}C	Yield %	Mol. Formula	Calculated (Found) %		
					C	H	N
U1AC	H	120	60	$C_{22}H_{18}N_{10}OS_2$	52.58 (52.50	3.61 3.54	27.87 27.79)
U2AC	2-CH_3	122	61	$C_{24}H_{22}N_{10}OS_2$	53.48 (53.45	3.90 3.81	27.11 27.09)
U3AC	4-CH_3	190	59	$C_{24}H_{22}N_{10}OS_2$	53.48 (53.43	3.90 3.85	27.11 27.05)
U4AC	2-OCH_3	220	74	$C_{23}H_{20}N_{10}O_2S_2$	51.87 (51.82	3.79 3.77	26.30 26.24)
U5AC	4-OCH_3	140	59	$C_{24}H_{22}N_{10}O_3S_2$	51.87 (51.80	3.79 3.73	26.30 26.27)
U6AC	4-Cl	140	58	$C_{22}H_{17}N_{10}OS_2Cl$	49.21 (49.11	3.19 3.14	26.08 26.02)
U7AC	4-F	135	62	$C_{22}H_{17}N_{10}OS_2F$	50.76 (50.70	3.29 3.24	26.91 26.85)
U8AC	4-Br	180	60	$C_{22}H_{17}N_{10}OS_2Br$	45.44 (45.37	2.95 2.87	24.09 24.01)
U9AC	2-NO_2	175	65	$C_{22}H_{17}N_{11}O_3S_2$	48.26 (48.19	3.13 3.07	28.14 28.09)
U10AC	2-Cl	195	69	$C_{22}H_{17}N_{10}OS_2Cl$	49.21 (49.15	3.19 3.16	26.08 26.06)

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1.*Compound U1AC*: IR: -C=N str in s-triazine(780.1), -C-S-C str in thiazole (825.3), -N-str in 5 member ring(1007), -C-CH_3 str in aromatic ring(1314), -C=C- str in aromatic ring(1485.1), -N-H deformation in-2^0 NH(1610), -C=O str in Urea(1700), -C-H str in aromatic (3170.1), N-H str in -2^0 NH(3394).^{1}H NMR (400.0MHz, DMSO-d_6, δ_H): 6.80-8.02 (m, 10H, Ar, 1H, thiazole ring), 3.92 (s, 2H,-NH), 8.90 (s, 2H,-CONH), 2.54-2.60(s, 3H, -CH_3).^{13}C NMR (100 MHz, DMSO-d_6,$\delta_C$ppm):19.2,100.2,109.5,121.3,121.9,124.5,127.1(db),127.9(db),128.0,128.2,135.5,145.4,149.0,150.9,153.6 ,153.9,161.0, 163.9,169.2,173.7.MS (EI): m/z: 501.0 (M+).

2. *Compound U2AC*: IR: -C=N str in s-triazine(782.1), -C-S-C str in thiazole (834.3), -N-str in 5 member ring(1011.1), -C-CH_3 str in aromatic ring(1308), -C=C- str in aromatic ring(1484.1), -N-H deformation in-2^0 NH(1611), -C=O str in Urea(1704), -C-H str in aromatic (3180.1), N-H str in -2^0 NH(3381).^{1}H NMR (400.0MHz, DMSO-d_6, δ_H): 7.01-8.22 (m, 9H, Ar, 1H, thiazole ring), 3.96-3.99 (s, 2H,-NH), 8.80-8.98 (s, 2H,-CONH), 2.55-2.64(s, 6H, -CH_3).^{13}C NMR (100 MHz,DMSO-d_6,$\delta_C$ppm):19.1(db),100.2,112.5,121.3,122.7,124.9,127.1(db),128.2(db),128.8,129.2,135.9,145.1,147.4, 150.5,151.6,152.1,160.9, 161.5,170.2,173.4.MS (EI): m/z: 515.6 (M+).

3. *Compound U3AC*: IR: -C=N str in s-triazine(786.1), -C-S-C str in thiazole (830.3), -N-str in 5 member ring(1001.1), -C-CH_3 str in aromatic ring(1311.5), -C=C- str in aromatic ring(1481.2), -N-H deformation in-2^0 NH(1620.2), -C=O str in Urea(1699.9),-C-H str in aromatic (3179.5.1), N-H str in -2^0 NH(3398.1).^{1}H NMR (400.0MHz, DMSO-d_6, δ_H): 6.99-8.09 (m, 9H, Ar, 1H, thiazole ring), 3.91-3.93 (s, 2H,-NH), 8.85-8.90 (s, 2H,-CONH), 2.50-2.60(s, 6H, -CH_3). ^{13}C NMR(100MHz,DMSO,d_6,$\delta_C$ppm):19.5(db),100.4,112.5,121.3,122.9,125.9,126.1(db),127.8(db),128.1,128.5,132.9, 146.5, 149.0,149.9,153.1,153.5,159.4, 164.7,169.7,170.7.MS (EI): m/z: 515.2 (M+).

4. *Compound U4AC*: IR: -C=N str in s-triazine(783.1), -C-S-C str in thiazole (831.3), -N-str in 5 member ring(1008), -C-CH_3 str in aromatic ring(1304), -C=C- str in aromatic ring(1487.1), -N-H deformation in-2^0 NH(1605), -C=O str in Urea(1698), -C-H str in -OCH_3 (2815), -C-H str in aromatic (3176.1), N-H str in -2^0 NH(3384).^{1}H NMR (400.0MHz, DMSO-d_6, δ_H): 6.83-8.15 (m, 9H, Ar, 1H, thiazole ring), 3.99 (s, 2H,-NH), 8.82 (s, 2H,-CONH), 3.57(s, 1H,-OCH_3), 2.51-2.54(s, 3H, -CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, δ_C ppm): 19.1,55.4,101.2,110.5,120.3,121.7,125.4, 126.9 (db),128.27(db),128.7,128.8,134.9,144.5,148.0,149.9,152.6,152.7,160.0, 162.9,168.2,171.7.MS (EI): m/z: 532.3 (M+).

5. *Compound U5AC*: IR: -C=N str in s-triazine(785.1), -C-S-C str in thiazole (833.3), -N-str in 5 member ring(1002.5), -C-CH_3 str in aromatic ring(1300), -C=C- str in aromatic ring(1481.1), -N-H deformation in-2^0 NH(1612.3), -C=O str in Urea(1705.5), -C-H str in -OCH_3 (2807.1), -C-H str in aromatic (3171.1), N-H str in -2^0 NH(3389.9).^{1}H NMR (400.0MHz, DMSO-d_6, δ_H):6.89-8.1 (m, 9H, Ar, 1H, thiazole ring),4.01(s, 2H,-NH),8.90-8.92(s, 2H,-CONH),3.54-3.61 (s,1H,-OCH_3),2.51-2.54(s,3H,-CH_3).^{13}CNMR(100MHz,DMSO,d_6,$\delta_C$ppm):19.3,55.1,102.2,109.5,119.1,122.5,124.9,126 (db),127.9(db),128.1,128.5,135.5,143.8,147.1,150.9,151.6,152.7,161.0,163.9,169.2,172.7.MS(EI):m/z:532.2 (M+).

6.*Compound U6AC*:-C-Cl str (754.5), -C=N str in s-triazine(789.7), -C-S-C str in thiazole (832.1), N-N-str in 5 member ring(1043),-C-CH_3 str in aromatic ring(1294.7), -C=C- str in aromatic ring (1478.5),-N-H deformation in-2^0 NH(1592),-C=O str in Urea(1721.1),-C-H str in aromatic (3200), N-H str in -2^0 NH(3300),^{1}H NMR (400.0 MHz, DMSO-d_6, δ_H ppm): 7.18-7.41 (m, 9H, Ar, 1H, thiazole ring), 4.05 (s, 2H,-NH), 9.02 (s, 2H,-CONH), 2.58-2.59(s, 3H, -CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, δ_C ppm):19.5,101.2,110.5,120.3,121.7,125.4, 126.9 (db),128.27(db), 128.7, 128.8, 134.9,144.5,148.0,149.9,152.6,152.7,160.0, 162.9,168.2,171.7.MS (EI): m/z: 535.8 (M+),538.9(M+2).

7.*Compound U7AC*: IR: -C=N str in s-triazine(780.1), -C-S-C str in thiazole (835.3), -N-str in 5 member ring(1012.5), -C-F str (1095.5), -C-CH_3 str in aromatic ring(1312.1), -C=C- str in aromatic ring(1491.1), -N-H deformation in-2^0 NH(1608.1), -C=O str in Urea(1702.1),-C-H str in aromatic(3171.1), N-H str in -2^0 NH(3399).^{1}H NMR (400.0MHz, DMSO-d_6, δ_H): 6.89-7.85 (m, 9H, Ar, 1H, thiazole ring),4.04 (s, 2H,-NH), 8.75-8.80 (s, 2H,-CONH), 2.53-2.62(s, 3H, -CH_3).^{13}CNMR(100MHz,DMSO-d_6,$\delta_C$ppm):20.1,101.2,110.5,120.3,121.7,125.4,126.9(db),128.27(db),128.7,128.8, 134.9,144.5,148.0, 149.9,152.6,152.7,160.0, 162.9,168.2,171.7.MS (EI): m/z: 519.3 (M+).

8. *Compound U8AC*: IR: -C-Br str (754.5), -C=N str in s-triazine(780.1), -C-S-C str in thiazole (828.3), -N-str in 5 member ring(1012.1), -C-CH_3 str in aromatic ring(1309), -C=C- str in aromatic ring(1481.1), -N-H deformation in-2^0 NH(1625.1), -C=O str in Urea(1701.1), -C-H str in aromatic (3179.1), N-H str in -2^0 NH(3391).^{1}H NMR (400.0MHz, DMSO-d_6, δ_H): 6.80-8.01 (m, 9H, Ar, 1H, thiazole ring), 3.97 (s, 2H,-NH), 8.78 (s, 2H,-CONH), 3.55-3.65(s, 1H,-OCH_3), 2.50-2.58(s, 3H, -CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, δ_C ppm):19.8,101.2,110.5,120.3,121.7,125.4, 126.9 (db),128.27(db),128.7,128.8,134.9,144.5,148.0,149.9,152.6,152.7,160.0, 162.9,168.2,171.7.MS (EI): m/z: 580.3 (M+).

9. *Compound U9AC*: IR: -C=N str in s-triazine(783.1), -C-S-C str in thiazole (832.3), -N-str in 5 member ring(1007.1), -C-CH_3 str in aromatic ring(1310.1), -C=C- str in aromatic ring(1481.1), -N-H deformation in-2^0 NH(1610.1), -C=O str in Urea(1702.2), -C-H str in aromatic (3170.1), N-H str in -2^0 NH(3380).^{1}H NMR (400.0MHz, DMSO-d_6, δ_H): 6.80-8.05 (m, 9H, Ar, 1H, thiazole ring), 3.99-4.02 (s, 2H,-NH), 8.72-8.80 (s, 2H,-CONH), 3.50-3.54(s, 1H,-OCH_3), 2.50-

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2.59(s,3H, -CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, δ_C ppm):19.4,101.2,110.5,120.3,121.7,125.4, 126.9 (db),128.27(db), 128.7, 128.8, 134.9,144.5,148.0,149.9,152.6,152.7,160.0, 162.9,168.2,171.7.MS (EI): m/z: 546.3 (M+).

10. *Compound U10AC*: IR: :-C-Cl str (751.5), -C=N str in s-triazine(781.7), -C-S-C str in thiazole (829.1), N-N-str in 5 member ring(1040),-C-CH_3 str in aromatic ring(1288.7), -C=C- str in aromatic ring (1488.5),-N-H deformation in-2^0 NH(1601),-C=O str in Urea(1711.1),-C-H str in aromatic (3205), N-H str in -2^0 NH(3350),^{1}H NMR (400.0 MHz, DMSO-d_6, δ_H ppm): 7.08-7.90 (m, 9H, Ar, 1H, thiazole ring), 3.98 (s, 2H,-NH), 9.11 (s, 2H,-CONH), 2.54-2.60(s, 3H, -CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, δ_C ppm): 19.6,101.1,109.5,121.3,121.7,124.4,127.9(db),128.5(db), 128.9, 128.1, 133.9,142.5,147.0,148.9,153.6,153.7,159.0, 161.9,167.2,173.7.MS (EI): m/z: 536.1 (M+), 538.1(M+2).

IV. ANTIMICROBIAL ACTIVITY

A. Table 4.1: Antibacterial activity (MIC) of compound U1AC to U10AC:

No	Compound	Functional Group R=	Minimum Inhibitory Concentration (µg/mL)			
			Gram Negative Bacteria		Gram Positive Bacteria	
			E .coli ATCC25922	*P. aeruginosa* ATCC 27853	*S. aureus* ATCC 25923	*S. pyogenes* ATCC 6633
1.	U1AC	H	500	500	1000	1000
2.	U2AC	2-CH_3	**125**	**125**	500	**62.5**
3.	U3AC	4-CH_3	250	**62.5**	500	**125**
4..	U4AC	2-OCH_3	500	**125**	250	500
5.	U5AC	4-OCH_3	500	250	250	500
6.	U6AC	4-Cl	250	250	**62.5**	**125**
7.	U7AC	4-F	**62.5**	**62.5**	250	500
8.	U8AC	4-Br	**62.5**	**62.5**	250	250
9.	U9AC	2-NO_2	**125**	500	**125**	1000
10.	U10AC	2-Cl	250	500	**125**	**62.5**
11.	Ampicillin		100	100	100	250
12.	Chloramphenicol		50	50	50	50

B. Table 4.2: Antifungal activity (MIC) of compound U1AC to U10AC:

No.	compound	Functional group R=	FUNGAL SPECIES		
			C. albicans ATCC 10231	*A. niger* ATCC 2821	*A. clavatus* ATCC 1323
1.	U1AC	H	**250**	>1000	500
2.	U2AC	2-CH_3	500	>1000	500
3.	U3AC	4-CH_3	1000	**250**	**250**
4.	U4AC	2-OCH_3	1000	**250**	500
5.	U5AC	4-OCH_3	500	**250**	500
6.	U6AC	4-Cl	**250**	500	500
7.	U7AC	4-F	**125**	**250**	1000
8.	U8AC	4-Br	**250**	**250**	1000
9.	U9AC	2-NO_2	1000	500	**250**
10.	U10AC	2-Cl	1000	500	500
11.	Griseofulvin		500	100	100

V. RESULT AND DISCUSSION

All ten compounds tested, exhibited considerable activities against four bacterial species, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococcus pyogenes*. Compounds U8AC (4-Br) and U7AC (4-F) exhibited excellent activity and U2AC (2-CH_3) and U9AC (2-NO_2) compound exhibited good activity against

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Escherichia coli as compared to Ampicillin (MIC= 100 µg/mL). Compounds U2AC (2-CH_3), U4AC (2-OCH_3) exhibited good activity at 100-125 µg/mL activity and U3AC (4-CH_3), U7AC (4-F), U8AC (4-Br) exhibited good activity at 62.5 µg/mL against *Pseudomonas aeruginosa* as compared to Ampicillin (MIC= 100 µg/mL). U9AC (2-NO_2), and U10AC (2-Cl) showed good activity at 100-125 µg/mL and compound U6AC (4-Cl) showed excellent activity at 62.5 µg/mL against *Staphylococcus aureus* as compared to Ampicillin (MIC= 250 µg/mL). Compounds U6AC (4-Cl), U3AC (4-CH_3) exhibited good activity at 100-125µg/mL and compound U10AC (2-Cl) and U2AC (2-CH_3) showed excellent activity at 62.5 µg/mL against *Streptococcus pyogenes* as compared to Ampicillin (MIC= 100 µg/mL).

The minimum inhibitory concentration (MIC) for antifungal activity of the tested compounds U1AC to U10AC is shown in **Table 4.2**. Most of the compounds showed very good antifungal activity against *Candida albicans*, their MIC values were in the range between (100-500 µg/mL). As far as the anti-fungal activity is concerned for substituted urea derivatives of s-triazine compounds U7AC (4-F) showed excellent activity at 125 µg/mL and compound U1AC (H), U6AC (4-Cl) and U8AC (4-Br) showed average activity at 250 µg/mL against *Candida albicans* as compared to Griseofulvin (MIC= 500 µg/mL). Whereas U4AC (2-OCH_3), U3AC (4-CH_3), U5AC (4-OCH_3), U7AC (4-F), U8AC (4-Br) compounds showed good activity against *Aspergillus niger* as compared to Griseofulvin (MIC= 100 µg/mL). All the screened compounds were less active against *Aspergillus clavatus* as compared to Griseofulvin (MIC= 100 µg/mL). The other compounds tested showed less activity against the fungal species.

VI. CONCLUSION

In this article we have report a series of 1,2,4-triazine and thiadiazole linked s-triazine i.e. 4-((4-((5-benzyl-1,3,4-thiadiazol-2-yl)amino)-6-(4-florophenyl amino) 1,3,5-triazin-2-yl)amino)-6-(tert-butyl)-3-(methylthio)-1,2,4-triazin-5(4H)-one showing better activity against gram positive bacteria, *S. aureus* and *S. pyogenes* with compare to standards and while P1BF showed better antifungal activity compared to standard. All the synthesized compounds have been established by elemental analysis, IR, ^{1}H NMR, ^{13}CNMR and mass spectral data. So, there is a future in doing more work on the synthesized compounds as some of them showed good activity against standard drugs.

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