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SYNTHESIS AND STUDY OF 1,2,4-TRIAZINE AND THIADIAZOLES BASED DERIVATIVES OF S-TRIAZINE AS ANTIMICROBIAL AGENTS

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Primary amine
Antimicrobial activity.

ABSTRACT

Some new substituted 1,3,5 triazine derivatives with 4-amino-6-(*tert*-butyl)-3-(methylthio)-1,2,4-triazin-5(*4H*)-one and 5-benzyl-1,3,4-thiadiazol-2-amine and primary amine were synthesized and evaluated for their *in vitro* antimicrobial activity against Gram positive and Gram negative strains using a micro dilution procedure. Synthesized compounds P1BF to P15BF prove to be effective with MIC (µg/mL), among them P2BF, P6BF, P15BF showed excellent activity against a panel of microorganisms. The newly synthesized compounds were characterized using IR, ^{1}H-NMR, ^{13}CNMR, MASS Analysis.

Contribution/ Originality: This study is one of very few studies which have investigated newly synthesized different types of derivatives. No one synthesized these types of compounds. This showed good antimicrobial activity so we can further modify with this compound to achieve excellent activity.

1. INTRODUCTION

In this context, s-triazine scaffold has attracted the attention of many researchers for its therapeutic potential [1] and ease of functionalization on it [2, 3]. For example, these compounds possess potent antiprotozoal [4] antimalarial [5, 6] antiviral [7-9] anticancer [10, 11] antimicrobial [12-14] anti-tuberculosis [15, 16]. Recently, the s-triazine derivatives were extensively investigated for anticancer activity with a particular target to mTOR/PI3K pathway [17, 18]. 1,2,4–Triazine derivatives are reported to possess a wide array of biological activities, including anti–inflammatory [19] analgesic [20] and anticancer activities [21]. The plethora of established biological activities associated with the 1,2,4–triazine nucleus ensures that the synthesis of novel chemical entities incorporating this important ring system remains a topic of current interest. The 1,2,4-triazine nucleus is considered an important chemical synthon exhibiting a broad range of therapeutic activities including COX-2 inhibition [22]. Thiadiazole has attracted a great deal of interest as a privileged scaffold due to its

significant therapeutic potential for central nervous system (CNS) disorders. 1,3,4-thiadiazole derivatives have been reported to exhibit a wide range of pharmacological effects including analgesic, antidepressant, anxiolytic and anticonvulsant activities. 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 [23-31]. 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 the previous work, we herein report newer s-triazine derivatives appended with 1,2,4-triazine and thiadiazole derivatives. Synthesized compounds were screened against antibacterial and anti fungal activity.

2. EXPERIMENTAL

2.1. 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-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.

2.2. Preparation of 4,6-dichloro-N-phenyl-1,3,5-triazin-2-amine: (P1)

To a stirred solution of cyanuric chloride (0.01 mol) in acetone (25 mL) at 0-5 ºC, the solution of primary amine 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.

2.3. Preparation of N^2-(5-benzyl-1,3,4-thiadiazol-2-yl)-6-chloro-N^4-phenyl-1,3,5-triazine-2,4-diamine: (P1B)

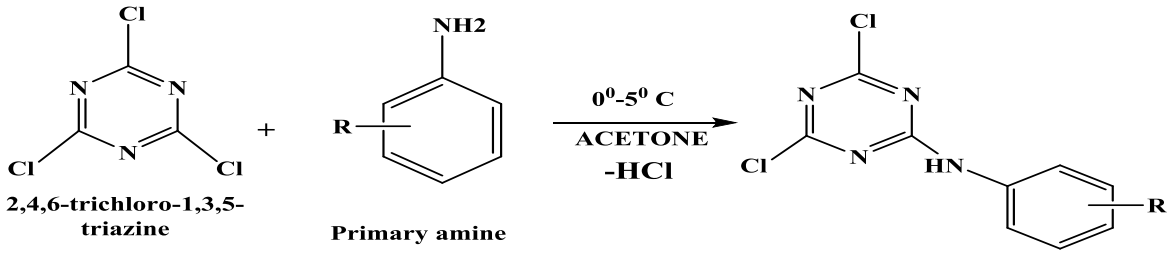
To a stirred solution of (P1) (0.01 mol) in DMF (25 mL) was added , the solution of 5-benzyl-1,3,4-thiadiazol-2-amine (0.01 mol) in DMF (15 mL) was added drop wise maintaining the temperature at 40 °C, the pH being maintained neutral by the addition of 10% sodium bi-carbonate solution from time to time 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.

2.4. Preparation of 4-((4-((5-benzyl-1,3,4-thiadiazol-2-yl)amino)-6-(phenyl amino) 1,3,5-triazin-2-yl)amino)-6-(tert-butyl)-3-(methylthio)-1,2,4-triazin-5(4H)-one : (P1BF)

A mixture of (P1B) (0.01 mol) and 4-amino-6-(*tert*-butyl)-3-(methylthio)-1,2,4-triazin-5(*4H*)-one (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.

3. REACTION SCHEME

3.1. Step-1:

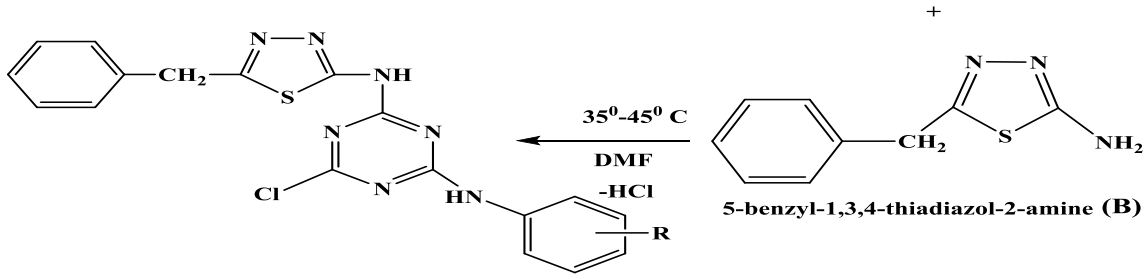


2,4,6-trichloro-1,3,5-triazine

Primary amine

4,6-dichloro-*N*-phenyl-1,3,5-triazin-2-amine

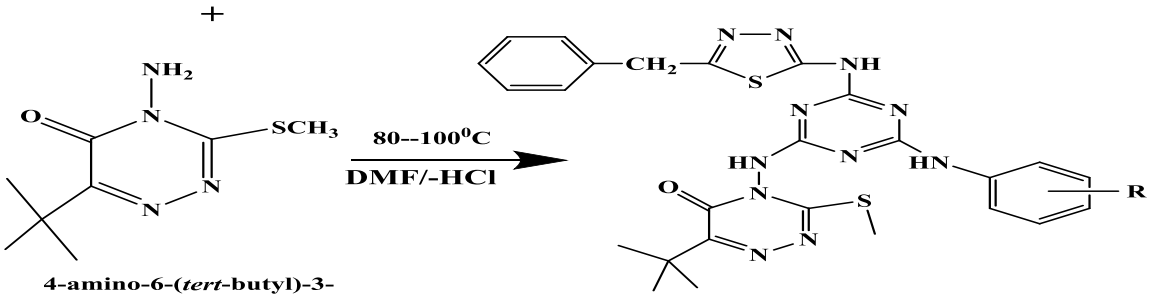
3.2 Step-II: (P1)



5-benzyl-1,3,4-thiadiazol-2-amine (B)

N^2-(5-benzyl-1,3,4-thiadiazol-2-yl)-6-chloro-N^4-phenyl-1,3,5-triazine-2,4-diamine

3.3 *Step-III:* (P1B)



4-amino-6-(*tert*-butyl)-3-(methylthio)-1,2,4-triazin-5(4*H*)-one

4-((4-((5-benzyl-1,3,4-thiadiazol-2-yl)amino)-6-(phenylamino)-1,3,5-triazin-2-yl)amino)-6-(*tert*-butyl)-3-(methylthio)-1,2,4-triazin-5(4*H*)-one

1.*Compound P1BF*: IR: -C-Cl str (738.1),-C=N str in s-triazine (789.1),-C-S-C str in thiazole (867.2), N-N-str in 5 member ring(1007.1), -C-CH_3 str (1314.1), =N- str in aromatic ring as -3^0 N(1350.1),-C-H bending in $-C(CH_3)_3$ (1382.1),-C-H bending in $-CH_2$(1448.1), C=C- str in aromatic ring(1492.3), -N-H deformation in-2^0 NH(1626.4), -C=O str in 1,2,4-triazine (1680.8), C-H str in as $-CH_2$ (2982.2),-C-H str in aromatic (3207.1), N-H str in -2^0 NH(3351.1). ^{1}H NMR (400.0MHz, DMSO-d_6, δ_H): 6.90–7.90 (m, 9H, Ar), 4.15-4.29 (s, 3H,-NH), 2.50-2.58 (s, 3H,-SCH_3), 1.30 (s, 9H, -C-CH_3), 3.46-3.70 (s, 2H, -CH_2). ^{13}C NMR (100 MHz, DMSO-d_6, δ_C ppm): 14.0,27.0(3C-trp),37.2,38.8,122.0(db),125.6,127.9,128.6(db),129.1(db),129.7(db),136.1,137.0,151.2,152.7,159.2,159.5,160.9,161.1,168.7, 179.6.MS (EI): m/z: 607.3 (M+), 609.2(M+2).

Table-1. Analytical and Physicochemical data of the synthesized compounds P1BF to P15BF:

Sr. No.	R	M.P. ^{O}C	Yield %	Mol. Formula	Calculated (Found) %		
					C	H	N
P1BF	4-Cl	225	60.50	$C_{26}H_{26}ClN_{11}OS_2$	51.35 (51.35	4.31 4.31	25.34 25.34)
P2BF	4-F	190	58.10	$C_{26}H_{26}FN_{11}OS_2$	52.78 (52.70	4.43 4.40	26.04 26.01)
P3BF	4-Br	149	60.40	$C_{26}H_{26}BrN_{11}OS_2$	47.85 (47.80	4.02 3.99	23.61 23.57)
P4BF	4-CH_3	140	59.30	$C_{27}H_{29}N_{11}OS_2$	55.18 (55.15	4.97 4.90	26.22 26.18)
P5BF	2-OCH_3	145	61.20	$C_{27}H_{29}N_{11}O_2S_2$	53.72 (53.70	4.84 4.79	25.52 25.48)
P6BF	2-CH_3	135	59.20	$C_{27}H_{29}N_{11}OS_2$	55.18 (55.11	4.97 4.91	26.22 26.18)
P7BF	H	180	60.25	$C_{26}H_{27}N_{11}OS_2$	54.43 (54.38	4.74 4.69	26.86 26.79)
P8BF	4-OCH_3	170	62.00	$C_{27}H_{29}N_{11}O_2S_2$	53.72 (53.70	4.84 4.80	25.52 25.46)
P9BF	4-$COCH_3$	190	70.00	$C_{28}H_{29}N_{11}O_2S_2$	54.62 (54.58	4.75 4.70	25.02 25.00)
P10BF	1-NH	210	68.34	$C_{26}H_{28}N_{12}OS_2$	53.05 (53.01	4.79 4.72	28.55 28.50)
P11BF	4-NO_2	225	72.12	$C_{26}H_{26}N_{12}O_3S_2$	50.47 (50.42	4.24 4.19	27.17 27.11)
P12BF	3-Cl	192	66.30	$C_{26}H_{26}ClN_{11}OS_2$	51.35 (51.29	4.31 4.26	25.34 25.30)
P13BF	-Phenyl	220	75.25	$C_{30}H_{29}N_{11}OS_2$	57.77 (57.69	4.69 4.61	24.70 24.64)
P14BF	2,5-Cl	180	55.25	$C_{26}H_{25}Cl_2N_{11}OS_2$	48.60 (48.52	3.92 3.88	23.98 23.93)
P15BF	4-Cl,2-NO_2	165	64.60	$C_{26}H_{25}ClN_{12}O_3S_2$	47.81 (47.75	3.86 3.80	25.73 25.71)

Source: SAIF, Panjab University, ,Chandigarh, India.

2.*Compound P2BF:* IR: -C=N str in s-triazine (782.1),-C-S-C str in thiazole (863.1), N-N-str in 5 member ring(1020.1), -C-F str (1095.5), -C-CH_3 str (1315.8), =N- str in aromatic ring as -3^0 N(1360.3),-C-H bending in –$C(CH_3)_3$ (1390.8),-C-H bending in –CH_2(1450.1), C=C- str in aromatic ring(1485.9), -N-H deformation in-2^0 NH(1642.8), -C=O str in 1,2,4-triazine (1702.3), C-H str in as –CH_2(2956.1),-C-H str in aromatic (3153.1), N-H str in -2^0 NH(3383.1).^{1}H NMR (400.0 MHz, DMSO-d_6, δ_H ppm): 7.01–7.75 (m, 9H, Ar), 3.93-4.09 (s, 3H,-NH), 2.32-2.71 (s, 3H,-SCH_3), 0.92-1.11 (s, 9H, -C-CH_3), 3.50-3.59 (s, 2H, -CH_2).

3.*Compound P3BF:*IR: -C=N str in s-triazine (782.1),-C-S-C str in thiazole (863.1), N-N-str in 5 member ring(1020.1), -C-F str (1095.5), -C-CH_3 str (1315.8), =N- str in aromatic ring as -3^0 N(1360.3),-C-H bending in –$C(CH_3)_3$ (1390.8),-C-H bending in –CH_2(1450.1), C=C- str in aromatic ring(1485.9), -N-H deformation in-2^0 NH(1642.8), -C=O str in 1,2,4-triazine (1702.3), C-H str in as –CH_2(2956.1),-C-H str in aromatic (3153.1), N-H str in -2^0 NH(3383.1).^{1}H NMR (400.0 MHz, DMSO-d_6, δ_H ppm): 7.01–7.75 (m, 9H, Ar), 3.93-4.09 (s, 3H,-NH), 2.32-2.71 (s, 3H,-SCH_3), 0.92-1.11 (s, 9H, -C-CH_3), 3.50-3.59 (s, 2H, -CH_2).

4.*Compound P4BF:*IR: -C=N str in s-triazine (782.1),-C-S-C str in thiazole (863.1), N-N-str in 5 member ring(1020.1), -C-F str (1095.5), -C-CH_3 str (1315.8), =N- str in aromatic ring as -3^0 N(1360.3),-C-H bending in –$C(CH_3)_3$ (1390.8),-C-H bending in –CH_2(1450.1), C=C- str in aromatic ring(1485.9), -N-H deformation in-2^0 NH(1642.8), -C=O str in 1,2,4-triazine (1702.3), C-H str in as –CH_2(2956.1),-C-H str in aromatic (3153.1), N-H str in -2^0 NH(3383.1).^{1}H NMR (400.0 MHz, DMSO-d_6, δ_H ppm): 7.01–7.75 (m, 9H, Ar), 3.93-4.09 (s, 3H,-NH), 2.32-2.71 (s, 3H,-SCH_3), 0.92-1.11 (s, 9H, -C-CH_3), 3.50-3.59 (s, 2H, -CH_2).

5.*Compound P5BF:*IR: -C=N str in s-triazine (782.1),-C-S-C str in thiazole (863.1), N-N-str in 5 member ring(1020.1), -C-F str (1095.5), -C-CH_3 str (1315.8), =N- str in aromatic ring as -3^0 N(1360.3),-C-H bending in –$C(CH_3)_3$ (1390.8),-C-H bending in –CH_2(1450.1), C=C- str in aromatic ring(1485.9), -N-H deformation in-2^0 NH(1642.8), -C=O str in 1,2,4-triazine (1702.3), C-H str in as –CH_2(2956.1),-C-H str in aromatic (3153.1), N-H str in -2^0 NH(3383.1).^{1}H NMR (400.0 MHz, DMSO-d_6, δ_H ppm): 7.01–7.75 (m, 9H, Ar), 3.93-4.09 (s, 3H,-NH), 2.32-2.71 (s, 3H,-SCH_3), 0.92-1.11 (s, 9H, -C-CH_3), 3.50-3.59 (s, 2H, -CH_2).

6.*Compound P6BF:*IR: -C=N str in s-triazine (782.1),-C-S-C str in thiazole (863.1), N-N-str in 5 member ring(1020.1), -C-F str (1095.5), -C-CH_3 str (1315.8), =N- str in aromatic ring as -3^0 N(1360.3),-C-H bending in –$C(CH_3)_3$ (1390.8),-C-H bending in –CH_2(1450.1), C=C- str in aromatic ring(1485.9), -N-H deformation in-2^0 NH(1642.8), -C=O str in 1,2,4-triazine (1702.3), C-H str in as –CH_2(2956.1),-C-H str in aromatic (3153.1), N-H str in -2^0 NH(3383.1).^{1}H NMR (400.0 MHz, DMSO-d_6, δ_H ppm): 7.01–7.75 (m, 9H, Ar), 3.93-4.09 (s, 3H,-NH), 2.32-2.71 (s, 3H,-SCH_3), 0.92-1.11(s, 9H, -C-CH_3),3.50-3.59 (s, 2H, -CH_2).

7.*Compound P7BF:*IR: -C=N str in s-triazine (782.1),-C-S-C str in thiazole (863.1), N-N-str in 5 member ring(1020.1), -C-F str (1095.5), -C-CH_3 str (1315.8), =N- str in aromatic ring as -3^0 N(1360.3),-C-H bending in –$C(CH_3)_3$ (1390.8),-C-H bending in –CH_2(1450.1), C=C- str in aromatic ring(1485.9), -N-H deformation in-2^0 NH(1642.8), -C=O str in 1,2,4-triazine (1702.3), C-H str in as –CH_2(2956.1),-C-H str in aromatic (3153.1), N-H str in -2^0 NH(3383.1).^{1}H NMR (400.0 MHz, DMSO-d_6, δ_H ppm): 7.01–7.75 (m, 9H, Ar), 3.93-4.09 (s, 3H,-NH), 2.32-2.71 (s, 3H,-SCH_3), 0.92-1.11 (s, 9H, -C-CH_3), 3.50-3.59 (s, 2H, -CH_2).

8.*Compound P8BF:*IR: -C=N str in s-triazine (782.1),-C-S-C str in thiazole (863.1), N-N-str in 5 member ring(1020.1), -C-F str (1095.5), -C-CH_3 str (1315.8), =N- str in aromatic ring as -3^0 N(1360.3),-C-H bending in –$C(CH_3)_3$ (1390.8),-C-H bending in –CH_2(1450.1), C=C- str in aromatic ring(1485.9), -N-H deformation in-2^0 NH(1642.8), -C=O str in 1,2,4-triazine (1702.3), C-H str in as –CH_2(2956.1),-C-H str in aromatic (3153.1), N-H str in -2^0 NH(3383.1).^{1}H NMR (400.0 MHz, DMSO-d_6, δ_H ppm): 7.01–7.75 (m, 9H, Ar), 3.93-4.09 (s, 3H,-NH), 2.32-2.71 (s, 3H,-SCH_3), 0.92-1.11 (s, 9H, -C-CH_3), 3.50-3.59 (s, 2H, -CH_2).

9.*Compound P9BF:*IR: -C=N str in s-triazine (782.1),-C-S-C str in thiazole (863.1), N-N-str in 5 member ring(1020.1), -C-F str (1095.5), -C-CH_3 str (1315.8), =N- str in aromatic ring as -3^0 N(1360.3),-C-H bending in –$C(CH_3)_3$ (1390.8),-C-H bending in –CH_2(1450.1), C=C- str in aromatic ring(1485.9), -N-H deformation in-2^0 NH(1642.8), -C=O str in 1,2,4-triazine (1702.3), C-H str in as –CH_2(2956.1),-C-H str in aromatic (3153.1), N-H str in -2^0 NH(3383.1).^{1}H NMR (400.0 MHz, DMSO-d_6, δ_H ppm): 7.01–7.75 (m, 9H, Ar), 3.93-4.09 (s, 3H,-NH), 2.32-2.71 (s, 3H,-SCH_3), 0.92-1.11 (s, 9H, -C-CH_3), 3.50-3.59 (s, 2H, -CH_2).

10.*Compound P10BF:*IR: -C=N str in s-triazine (782.1),-C-S-C str in thiazole (863.1), N-N-str in 5 member ring(1020.1), -C-F str (1095.5), -C-CH_3 str (1315.8), =N- str in aromatic ring as -3^0 N(1360.3),-C-H bending in –$C(CH_3)_3$ (1390.8),-C-H bending in –CH_2(1450.1), C=C- str in aromatic ring(1485.9), -N-H deformation in-2^0 NH(1642.8), -C=O str in 1,2,4-triazine (1702.3), C-H str in as –CH_2(2956.1),-C-H str in aromatic (3153.1), N-H str in -2^0 NH(3383.1).^{1}H NMR (400.0 MHz, DMSO-d_6, δ_H ppm): 7.01–7.75 (m, 9H, Ar), 3.93-4.09 (s, 3H,-NH), 2.32-2.71 (s, 3H,-SCH_3), 0.92-1.11 (s, 9H, -C-CH_3), 3.50-3.59 (s, 2H, -CH_2).

11.*Compound P11BF:*IR: -C=N str in s-triazine (782.1),-C-S-C str in thiazole (863.1), N-N-str in 5 member ring(1020.1), -C-F str (1095.5), -C-CH_3 str (1315.8), =N- str in aromatic ring as -3^0 N(1360.3),-C-H bending in –$C(CH_3)_3$ (1390.8),-C-H bending in –CH_2(1450.1), C=C- str in aromatic ring(1485.9), -N-H deformation in-2^0 NH(1642.8), -C=O str in 1,2,4-triazine (1702.3), C-H str in as –CH_2(2956.1),-C-H str in aromatic (3153.1), N-H str in -2^0 NH(3383.1).^{1}H NMR (400.0 MHz, DMSO-d_6, δ_H ppm): 7.01–7.75 (m, 9H, Ar), 3.93-4.09 (s, 3H,-NH), 2.32-2.71 (s, 3H,-SCH_3), 0.92-1.11 (s, 9H, -C-CH_3),3.50-3.5 (s, 2H, -CH_2).

12.*Compound P12BF:*IR: -C=N str in s-triazine (782.1),-C-S-C str in thiazole (863.1), N-N-str in 5 member ring(1020.1), -C-F str (1095.5), -C-CH_3 str (1315.8), =N- str in aromatic ring as -3^0 N(1360.3),-C-H bending in –$C(CH_3)_3$ (1390.8),-C-H bending in –CH_2(1450.1), C=C- str in aromatic ring(1485.9), -N-H deformation in-2^0

NH(1642.8), -C=O str in 1,2,4-triazine (1702.3), C-H str in as $-CH_2$(2956.1),-C-H str in aromatic (3153.1), N-H str in -2^0 NH(3383.1).^{1}H NMR (400.0 MHz, DMSO-d_6, δ_H ppm): 7.01–7.75 (m, 9H, Ar), 3.93-4.09 (s, 3H,-NH), 2.32-2.71 (s, 3H,-SCH_3), 0.92-1.11 (s, 9H, -C-CH_3), 3.50-3.59 (s, 2H, -CH_2).

13.*Compound P13BF*:IR: -C=N str in s-triazine (782.1),-C-S-C str in thiazole (863.1), N-N-str in 5 member ring(1020.1), -C-F str (1095.5), -C-CH_3 str (1315.8), =N- str in aromatic ring as -3^0 N(1360.3),-C-H bending in –$C(CH_3)_3$ (1390.8),-C-H bending in $-CH_2$(1450.1), C=C- str in aromatic ring(1485.9), -N-H deformation in-2^0 NH(1642.8), -C=O str in 1,2,4-triazine (1702.3), C-H str in as $-CH_2$(2956.1),-C-H str in aromatic (3153.1), N-H str in -2^0 NH(3383.1).^{1}H NMR (400.0 MHz, DMSO-d_6, δ_H ppm): 7.01–7.75 (m, 9H, Ar), 3.93-4.09 (s, 3H,-NH), 2.32-2.71 (s, 3H,-SCH_3), 0.92-1.11 (s, 9H, -C-CH_3), 3.50-3.59 (s, 2H, -CH_2).

14.*Compound P14BF*:IR: -C=N str in s-triazine (782.1),-C-S-C str in thiazole (863.1), N-N-str in 5 member ring(1020.1), -C-F str (1095.5), -C-CH_3 str (1315.8), =N- str in aromatic ring as -3^0 N(1360.3),-C-H bending in –$C(CH_3)_3$ (1390.8),-C-H bending in $-CH_2$(1450.1), C=C- str in aromatic ring(1485.9), -N-H deformation in-2^0 NH(1642.8), -C=O str in 1,2,4-triazine (1702.3), C-H str in as $-CH_2$(2956.1),-C-H str in aromatic (3153.1), N-H str in -2^0 NH(3383.1).^{1}H NMR (400.0 MHz, DMSO-d_6, δ_H ppm): 7.01–7.75 (m, 9H, Ar), 3.93-4.09 (s, 3H,-NH), 2.32-2.71 (s, 3H,-SCH_3), 0.92-1.11 (s, 9H, -C-CH_3), 3.50-3.59 (s, 2H, -CH_2).

15.*Compound P14BF*:IR: -C=N str in s-triazine (782.1),-C-S-C str in thiazole (863.1), N-N-str in 5 member ring(1020.1), -C-F str (1095.5), -C-CH_3 str (1315.8), =N- str in aromatic ring as -3^0 N(1360.3),-C-H bending in –$C(CH_3)_3$ (1390.8),-C-H bending in $-CH_2$(1450.1), C=C- str in aromatic ring(1485.9), -N-H deformation in-2^0 NH(1642.8), -C=O str in 1,2,4-triazine (1702.3), C-H str in as $-CH_2$(2956.1),-C-H str in aromatic (3153.1), N-H str in -2^0 NH(3383.1).^{1}H NMR (400.0 MHz, DMSO-d_6, δ_H ppm): 7.01–7.75 (m, 9H, Ar), 3.93-4.09 (s, 3H,-NH), 2.32-2.71 (s, 3H,-SCH_3), 0.92-1.11 (s, 9H, -C-CH_3), 3.50-3.59 (s, 2H, -CH_2).

Table-2. Antibacterial activity (MIC) of compound P1BF to P15BF:

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.	P1BF	4-Cl	>1000	**125**	**125**	250
2.	P2BF	4-F	500	500	**31.25**	**125**
3.	P3BF	4-Br	250	250	**125**	**62.5**
4.	P4BF	4-CH_3	**125**	1000	500	500
5.	P5BF	2-OCH_3	250	500	**62.5**	500
6.	P6BF	2-CH_3	**62.5**	**62.5**	500	250
7.	P7BF	H	>1000	500	1000	500
8.	P8BF	4-OCH_3	250	500	500	500
9.	P9BF	4-$COCH_3$	**125**	1000	**125**	1000
10.	P10BF	1-NH	250	500	**62.5**	1000
11.	P11BF	4-NO_2	**125**	250	**125**	500
12.	P12BF	3-Cl	250	250	250	>1000
13.	P13BF	-Phenyl	500	500	500	>1000
14.	P14BF	2,5-Cl	**125**	**125**	500	250
15.	P15BF	4-Cl,2-NO_2	**125**	**125**	500	**125**
16.	Ampicillin		100	100	100	250
17.	Chloramphenicol		50	50	50	50

Source: Central Kashiba Lab, Surat. Gujarat, India.

Table-3. Antifungal activity (MIC) of compound P1BF to P15BF:

NO	Compound	Functional group R=	FUNGAL SPECIES		
			C. albicans ATCC 10231	*A. niger* ATCC 2821	*A. clavatus* ATCC 1323
1.	P1BF	4-Cl	**250**	500	**250**
2.	P2BF	4-F	500	1000	500
3.	P3BF	4-Br	500	1000	1000
4.	P4BF	4-CH_3	**250**	500	>1000
5.	P5BF	2-OCH_3	**250**	500	500
6.	P6BF	2-CH_3	1000	**250**	**250**
7.	P7BF	H	1000	**125**	500
8.	P8BF	4-OCH_3	500	500	500
9.	P9BF	4-$COCH_3$	500	**250**	500
10.	P10BF	1-NH	**250**	**250**	1000
11.	P11BF	4-NO_2	**250**	500	1000
12.	P12BF	3-Cl	1000	1000	**250**
13.	P13BF	-Phenyl	500	>1000	500
14.	P14BF	2,5-Cl	500	>1000	500
15.	P15BF	4-Cl,2-NO_2	**250**	500	500
11.	Griseofulvin		500	100	100

Source: Central Kashiba Lab, Surat. Gujarat, India.

4. RESULT AND DISCUSSION

The entire synthesized compounds were prepared with good yield. Final compound P1BF-P15BF is synthesized as mention above method. The MICs of synthesized compounds were carried out by broth micro dilution method as described by Rattan [32]. All the compounds were tested for their in vitro antibacterial activity against Gram-positive (*Staphylococcus aureus* ATCC25922 and *Streptococcus pyogenes* ATCC 27853) and two gram negative (*Escherichia coli* ATCC25922 and *Pseudomonas aeruginosa* ATCC 27853 bacteria by using ampicillin as a standard antibacterial agent. Antifungal activity was screened against three fungal species(*Candida albicans* ATCC 10231, *Aspergillus niger* ATCC 2821 and *Aspergillus clavatus* ATCC 1323) and greseofulvin was used as a standard antifungal agent.

The results revealed that compound P2BF, P5BF, P10BF showed good activity (62.5µg/mL) as compared with ampicilin against *S. aureus*, while other compounds exhibited moderate activity (250µg/mL). Most of the compounds exhibited moderate activity against *S. pyogenus* except P3BF, which showed good activity (62.5µg/mL), P2BF and P15BF showed good activity (125µg/mL). Compounds P6BF possessed excellent activity (62.5µg/mL) while P4BF, P9BF, P11BF, P14BF, P15BF displayed good activity (125µg/mL) against *E. coli*. Compound P6BF showed good activity (62.5µg/mL) against *P. aeruginosawhile* other compounds P1BF, P14BF, P15BF exhibited good activity (125µg/mL) and others compounds exhibited moderate activity.

The results revealed that compounds P1BF, P4BF, P5BF, P10BF, P11BF, and P15BF possessed good activity (250µg/mL) as greseofulvin against *C. albicans*. Compound P7BF exhibited good activity against *A. niger* (125µg/mL) and P6BF, P9BF, P10BF exhibited good activity (250µg/mL). Compounds P1BF, P6BF, P12BF exhibited good activity (250µg/mL) against *A. clavatus* (62.5µg/mL) as compared with greseofluvin.

All remaining compounds exhibited weak activity against three fungal species *C. albicans*, *A. niger* and *A. clavatus*. Minimal inhibitory concentrations of tested compounds showed that 1,2,4-triazine and thiadiazole possessed weak to good activity but when they merged and produced a single moiety, the activity get increased or decreased depending upon the substituent's.

5. 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-florophenylamino)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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