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Synthesis, characterization and antimicrobial activity of novel 5-substituted aryl-2,7-diphenyl-1,3,4-thiadiazolo-[3,2-a]-1,3,5-triazine derivatives

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ABSTRACT

A new class of heterocyclic compounds 1,3,4-thiadiazolo[3,2-a]-s-triazine have been synthesized as schiff's base of 1,3,4- thiadiazole mix with ammonium acetate and various aromatic aldehyde treated in MW irradiation at 480 W. Reaction is based on microwave mediate multi-component reaction (MCRs). The structures of these compounds have been elucidated by spectral (IR, NMR & Mass) analysis. The title compounds were then evaluated for their in-vitro microbial activity against 2 gram –Ve bacteria (*E.coli, K. pneumoniae*), 2 gram +Ve bacteria (*S.aerues, B.subtilis*) and 1 fungal specie (*A.niger*). The some newly synthesized compounds have shown promising antimicrobial activity.

Keywords: 1,3,5-Triazine, 1,3,4-Thiadiazole, Thiosemicarbazone, Schiff's base, Antibacterial, Antifungal, Multi-component reaction (MCRs)

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INTRODUCTION

Due to the increasing number of multidrug resistant developed by the microbes, currently used antimicrobial agent are ineffective and antibacterial and antifungal diseases are very common, therefore, the design and synthesis of new antimicrobial molecules has been of enormous interest in recent year. The chemistry of heterocyclic compounds has been an interesting field of study for a long time. Nitrogen containing heterocyclics play important role in many biological interests. Among them 1,3,5-triazine represent a widely used lead structure with multitude of interesting application in numerous fields. Several derivatives of *s*-triazine show antimicrobial[1-3], anticancer[4-6], herbicidal activities[7], antimalarial[8-9], antiviral[10] and antitubercular[11].

1,3,4- thiadiazole ring is also associated with various biological activities. A number of condensed ring system incorporating 1,3,4- thiadiazole nucleus is reported as potential fungicides[12], bactericides[13] and anticancer activity. In continuous of our current works as synthesized fused heterocyclic compounds 1,3,4-thiadiazolo[3,2-a]-s-triazine derivatives and Both the nuclei i.e. 1,3,4- thiadiazole and 1,3,5-triazine might be show enhanced potency activity.

The present study report the synthesis of 5-substituted aryl-2,7-diphenyl-[1,3,4]-thiadiazolo-[3,2-a][1,3,5]-triazine (5a-5n).

Required thiosemicarbazone were prepared by using the reported method as a reaction between aldehyde and thiosemicarbazide (Vogel's,1996). Starting compound 2-amino-5-aryl-1,3,4-thiadiazole were synthesized by using thiosemicarbazone and sodium acetate were dissolved in glacial acetic acid taken in a round-bottomed flask equipped with a separating funnel for the addition of bromine. Bromine was added slowly to it, while stirring magnetically. The resulting solid was separated, dried and recrystallized from ethanol (Vogel's, 1996). Respective Schiff's base were synthesized reaction between 2-amino-5-aryl-1,3,4-thiadiazole and aromatic aldehyde[14].

A new class of heterocyclic compounds 5-substituted aryl-2,7-diphenyl-[1,3,4]-thiadiazolo-[3,2-a][1,3,5]-triazine have been synthesized as schiff's base of 1,3,4- thiadiazole mix with ammonium acetate and various aromatic aldehydes treated in MW irradiation at 480 W. Reaction is based on microwave mediate multi-component reaction (MCRs).[15]

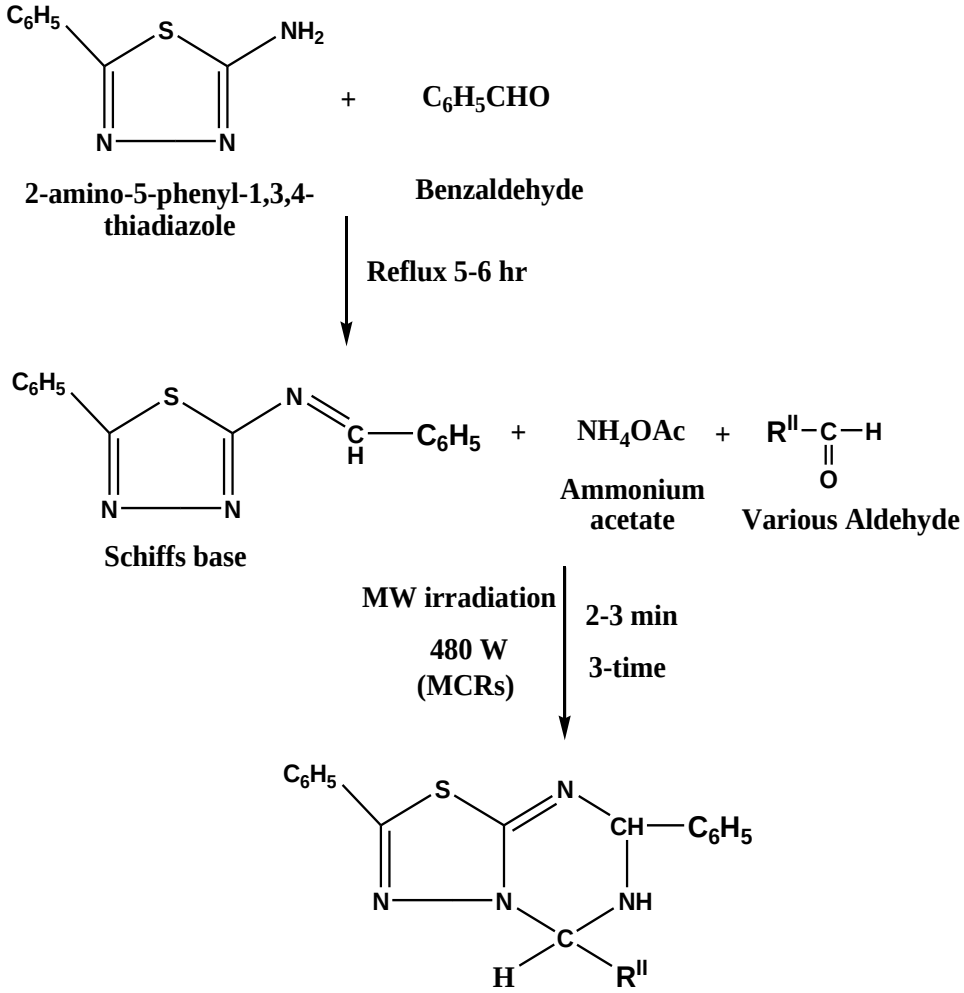
The structures of all the compounds were confirmed by spectral analysis (IR, ^{1}HNMR and Mass). The newly synthesized compounds were evaluated for antimicrobial activity against a

variety of bacterial strains and fungal strains and some of these compounds have shown significant antibacterial and antifungal activities.

Experimental Section

All the chemicals used are laboratory grade. Melting points were determined in open capillary tubes and were found uncorrected. The progress of reactions were monitored by TLC. All compounds were purified by recrystallization with suitable organic solvents. The Purity of all the compounds was checked on Precoated silica gel-G plates using iodine vapour as detecting agent. IR spectra were recorded on FT-IR Spectrometer using KBr disc method. ^{1}H-NMR spectra were recorded on *Bruker* Avance-*400 MHz NMR* spectrometer in DMSO, $CDCl_3$. Mass spectra were recorded on LC-MSD-Tranp-SL2010A Shimadzu.

Physical data of the compounds are recorded in table-01 and Antimicrobial activity of all synthesized compounds were reported in table-02 and table 03.



5-substituted aryl-2,7-diphenyl-[1,3,4]-thiadiazolo-[3,2-a][1,3,5]-triazine

Scheme 1: Scheme of work:

Chemistry

Synthesis of Schiff's base: A solution of 2-amino-5-aryl-1,3,4-thiadiazole (0.01 M) was prepared in 30 ml alcohol in a round-bottomed flask. Benzaldehyde (0.01 M) then added to it. The mixture was refluxed for 5–6 hr. The volume of alcohol was reduced to half by distillation under reduced pressure. The resulting solution was poured on crushed ice. The precipitate which got separated was dried and recrystallized from alcohol. (compound-1)

Synthesis of 5-substituted aryl-2,7-diphenyl-[1,3,4]-thiadiazolo-[3,2-a][1,3,5]-triazine(5a-5n) Schiff's base (compound-1) (0.01mol) was mix with ammonium acetate and various aromatic aldehydes treated in MW irradiation at 480 W for three times with minimum 2 min of intervals. Step-2 based on microwave mediate multi-component reaction (MCRs).

Antimicrobial activity

The compounds were tested against bacterial strains i.e. *Escherichia coli(Gram-ve), Klebsiella pneumoniae(Gram–ve), Staphylococcus aureus (Gram+ve), Bacillus subtilis (Gram+ve)* and fungal strains i.e. *Aspergillus niger* by using Cup-Plate method. Ciprofloxacin and Ketoconazole were used as standards for antibacterial and antifungal studies respectively. The stock solutions of the compounds were prepared in dimethyl sulfoxide (DMSO). The solutions of all the test compounds prepare at three different concentration 100µg/ml, 200µg/ml and 300µg/ml. Nutrient agar (beef extract 3 gm, Agar 15 g, Peptic Digest of Animal Tissue 5 g, sodium chloride 5 g and distilled water-q.s. to 1,000 ml) was employed as culture media for antimicrobial activity**.**

The sterilization of the nutrient broth, culture tubes, pipette and other glassware was done by autoclaving. For antibacterial studies, incubation was carried out at 37°C for 24 h and for antifungal studies, incubation was carried out at 25±2°c for 72 h. Diameters of zone of inhibition were measured for the plates in which the zones of inhibition in mm for each organism. The zone of inhibition were measured for all synthesized compounds.[16-17]

RESULTS AND DISCUSSION

The present study report the synthesis of 5-substituted aryl-2,7-diphenyl-1,3,4-thiadiazolo-[3,2-a]-1,3,5-triazine derivatives. The first step involve synthesized the Schiff's base as reaction between 2-amino-5-aryl-1,3,4-thiadiazole and aromatic aldehydes.

In Step-2 Schiff's base (compound-1) was mix with ammonium acetate and various aromatic aldehydes treated in MW irradiation at 480 W for three times with minimum 2 min of intervals.

The step-2 reaction based on microwave mediate multi-component reaction (MCRs). Series of compounds 5a-5n are synthesized by respected scheme.

The synthesized compounds were recrystallized and identified by TLC. The melting point were found uncorrected. The difference in the R_f value and melting point show the change in the structure between the molecules. All Physical data of the compounds are recorded in table-1.

Table 1: Physical Parameters

S. No.	Compound code	Molecular formula	Molecular weight	Melting point ^{0}C	R_f value	% yield	Appearance
1.	5a	$C_{22}H_{18}N_4S$	370.47	145^{o}C	0.70	77	Yellow
2.	5b	$C_{22}H_{18}N_4OS$	386.47	238^{o}C	0.67	60	Yellow
3.	5c	$C_{22}H_{18}N_4OS$	386.47	218^{o}C	0.78	68	Brown
4.	5d	$C_{22}H_{18}N_4OS$	386.47	220^{o}C	0.72	63	Yellow
5.	5e	$C_{22}H_{17}N_5O_2S$	415.47	216^{o}C	0.66	60	Light brown
6.	5f	$C_{22}H_{17}N_5O_2S$	415.47	224^{o}C	0.69	66	White
7.	5g	$C_{22}H_{17}N_5O_2S$	415.47	250^{o}C	0.75	71	Light Yellow
8.	5h	$C_{22}H_{17}ClN_4S$	404.92	223^{o}C	0.79	63	White
9.	5i	$C_{22}H_{17}ClN_4S$	404.92	186^{o}C	0.84	79	Light Yellow
10.	5j	$C_{24}H_{23}N_5S$	413.54	228^{o}C	0.77	73	White
11.	5k	$C_{25}H_{24}N_4O_3S$	460.55	240^{o}C	0.60	80	Yellow
12.	5l	$C_{23}H_{20}N_4OS$	400.50	195^{o}C	0.74	72	Dark brown
13.	5m	$C_{23}H_{20}N_4O_2S$	416.50	237^{o}C	0.82	66	Yellow
14.	5n	$C_{22}H_{16}C_{l2}N_4S$	439.36	233^{o}C	0.63	78	Light green

2,5,7-triphenyl-6,7-dihydro-5H-[1,3,4]thiadiazolo[3,2-a][1,3,5]triazine(5a):

M.P.-145^{o}C, IR(KBr): 3099.90 (N-H str.), 3042.74 (=C-H str.), 2930.71 (C-H str.), 1448.03 (C=C str.), 1662.47 (C=N str.), 770.68 (C-S-C str.), 1346.56 (N-N=C str.), ^{1}H-NMR(DMSO,δ ppm): 2.42 (s,1H, NH), 3.95 (s, 1H, CH), 5.23 (s, 1H, CH), 7.16–7.95 (m, 15H, Ar-H), MS: m/z-370.24

5-(2-hydroxyphenyl)-2,7-diphenyl-6,7-dihydro-5H-[1,3,4]thiadiazolo[3,2-a][1,3,5]triazine (5b): M.P.-238^{o}C, IR(KBr): 3403.96(O-H str.), 3136.32(=C- H str.), 2913.03(C-H str.), 1472.26 (C=C str.), 1606.37(C=N str.), 773.63(C-S-C str.), 1341.48(N-N=C str.), ^{1}H-NMR(DMSO,δ ppm): 2.14(s, 1H, NH), 3.90(s, 1H, CH), 5.27(s, 1H, OH), 5.61(s, 1H, CH), 6.63–7.70(m, 14H, Ar-H), MS: m/z-386.26

5-(3-hydroxyphenyl)-2,7-diphenyl-6,7-dihydro-5H-[1,3,4]thiadiazolo[3,2-[1,3,5]triazine(5c): M.P.-218^{o}C, IR(KBr): 3402.43(O-H str.), 3010.47(=C- H str.), 2945.79(C-H str.), 1438.22(C=C str.), 1640.50(C=N str.), 758.16(C-S-C str.), 1234.68(N-N=C str.), MS: m/z-386.15

5-(4-hydroxyphenyl)-2,7-diphenyl-6,7-dihydro-5H-[1,3,4]thiadiazolo[3,2][1,3,5]triazine(5d): M.P.-220^{o}C, IR(KBr): 3416.15(O-H str.), 3011.07(=C-H str.), 2879.25(C- H str.), 1446.94(C=C str.), 1663.68(C=N str.), 748.89(C-S-C str.), 1252.83(N-N=C str.), MS: m/z-386.11

5-(2-nitrophenyl)-2,7-diphenyl-6,7-dihydro-5H-[1,3,4]thiadiazolo[3,2-a][1,3,5]triazine(5e): M.P.-216^{o}C, IR(KBr): 3276.03(N-H str.), 2847.91(C- H str.), 1437.48(C=C str.), 1663.69(C=N str.), 759.61(C-S-C str.), 1254.81(N-N=C str.), 1589.30(C-NO_2 str.), ^{1}H-NMR (DMSO,δ ppm): 2.31 (s, 1H, NH), 4.25(s, 1H, CH), 5.38(s, 1H, CH), 7.03–8.07(m, 14H, Ar-H), MS: m/z-415.18

5-(3-nitrophenyl)-2,7-diphenyl-6,7-dihydro-5H-[1,3,4]thiadiazolo[3,2-a][1,3,5]triazine(5f): M.P.-224^{o}C, IR(KBr): 3323.22(N-H str.), 2964.37(=C- H str.), 2840.23(C- H str.), 1416.15(C=C str.), 1662.11(C=N str.), 770.22(C-S-C str.), 1250.50(N-N=C str.), 1560.04(C-NO_2 str.), MS: m/z-415.22

5-(4-nitrophenyl)-2,7-diphenyl-6,7-dihydro-5H-[1,3,4]thiadiazolo[3,2-a][1,3,5]triazine(5g): M.P.-250^{o}C, IR(KBr): 3314.4(N-H str.), 2851.4(C- H str.), 1434.2(C=C str.), 1671.1(C=N str.), 771.9(C-S-C str.), 1236.3(N-N=C str.), 1565.9(C-NO_2 str.), MS: m/z-415.66

5-(2-chlorophenyl)-2,7-diphenyl-6,7-dihydro-5H-[1,3,4]thiadiazolo[3,2-a][1,3,5]triazine(5h): M.P.-223^{o}C, IR(KBr): 3325.9(N-H str.), 3072.5(=C-H str.), 2839.1(C-H str.), 1448.3(C=C str.), 1672.7 (C=N str.), 711.3(C-S-C str.), 1250.5(N-N=C str.), 754.8(C-Cl str.),^{1}H-NMR (DMSO,δ ppm): 2.13(s, 1H, NH), 3.81(s, 1H, CH), 5.17(s, 1H, CH), 7.03-7.88(m, 14H, Ar-H), MS: m/z-404.10

5-(4-chlorophenyl)-2,7-diphenyl-6,7-dihydro-5H-[1,3,4]thiadiazolo[3,2-a][1,3,5]triazine(5i): M.P.-186^{o}C, IR(KBr): 3239.8(N-H str.), 3074.3(=C-H str.), 2853.1(C-H str.), 1445.0(C=C str.), 1677.4 (C=N str.), 710.7(C-S-C str.), 1298.9(N-N=C str.), 759.2(C-Cl str.), MS: m/z-404.12

5-(4-dimethylaminophenyl)-2,7-diphenyl-6,7-dihydro-5H-[1,3,4]thiadiazolo[3,2-a][1,3,5]triazine (5j): M.P.-228^{o}C, IR(KBr): 3263.4(N-H str.), 3035.2(=C-H str.), 2849.2(C-H str.), 1445.5(C=C str.), 1674.6(C=N str.), 698.4(C-S-C str.), 1238.6(N-N=C str.),^{1}H-NMR (DMSO,δ ppm): 2.01(s, 1H, NH), 2.87(s, 6H, CH_3), 3.86(s, 1H, CH), 5.05(s, 1H, CH), 6.44-7.44(m, 14H, Ar-H), MS: m/z-413.32

5-(3,4,5-trimethoxyphenyl)-2,7-diphenyl-6,7-dihydro-5H-[1,3,4]thiadiazolo[3,2-a][1,3,5]triazine (5k): M.P.-240^{o}C, IR(KBr): 3254.3(N-H str.), 2994.0(C-H str.), 1392.6(C=C str.), 1668.4(C=N str.), 674.8(C-S-C str.), 1234.1(N-N=C str.),MS: m/z-460.24

5-(4-methoxyphenyl)-2,7-diphenyl-6,7-dihydro-5H-[1,3,4]thiadiazolo[3,2-a][1,3,5]triazine (5l): M.P.-195^{o}C, (KBr): 3455.96(N-H str.), 3119.52(=C-H str.), 2841.86(C-H str.), 1447.16(C=C str.), 1634.75(C=N str.), 743.78(C-S-C str.), 1281.04(N-N=C str.), MS: m/z-400.14

5-(3-methoxy-4-hydroxyphenyl)-2,7-diphenyl-6,7-dihydro-5H-[1,3,4]thiadiazolo[3,2-a][1,3,5] triazine (5m): M.P.-237^{o}C, IR(KBr): 3444.25 (O-H str.), 3392.45(N-H str.),

3136.78(=C-H str.), 2924.68(C-H str.), 1472.31(C=C str.), 1671.03(C=N str.), 725.19(C-S-C str.), 1271.03(N-N=C str.), MS: m/z-416.17

5-(2,5-dichlorophenyl)-2,7-diphenyl-6,7-dihydro-5H-[1,3,4]thiadiazolo[3,2-a][1,3,5]triazine (5n): M.P.-233^{o}C, IR(KBr): 3398.38(N-H str.), 2956.81(=C-H str.), 2864.87(C-H str.), 1472.20 (C=C str.), 1622.46(C=N str.), 772.92(C-S-C str.), 1263.71(N-N=C str.), 721.90(C-Cl str.), MS: m/z-441.14

IR Spectra were recorded in KBr on FT-IR instrument. All the compounds show the presence of N-H stretching vibration in amine between 3323.2 to 3455.9 cm^{-1}, Aromatic C-H stretching between 3010.4-3136.7 cm^{-1}. Aliphatic C-H stretching between 2840.2 to 2930.7 cm^{-1}, C=N in ring between 1606.3-1677.4 cm^{-1} and C-S-C stretching between 710.7-773.6 cm^{-1} presence of cyclic ring system in [1,3,4] thiadiazoline. All the compounds show C=C stretching vibration at 1416.1-1472.2 cm^{-1}. Compound 5a, 5b, 5c, 5m show 0-H stretching vibration of 3402.4 to 3442.2

In compound 5j show C-H str. Due to CH_3 at 2849.2 cm^{-1}. Compounds 5e, 5f, 5g show characteristic C-NO_2 stretching vibration between 1560.0-1589.3 cm^{-1} may be due to nitro group in compounds. Compound 5h, 5i, 5n show C-Cl stretching vibration at 721.9-759.2 cm^{-1} presence of chlorine substitution in respective compounds .

^{1}NMR was recorded on *Bruker* Avance-*400 MHz NMR* spectrometer chemical shift was measured at part per million downfield from tetra methyl silane. All compounds show sharp singlet near δ 2.01 to 2.42 might be due to NH proton and sharp singlet near δ 3.81 to 3.95 might be due to CH proton in C-5 position in ring. Multiple between δ 6.63 to 7.795 showed the presence of aromatic proton (Ar-H). The singlet formed δ 5.27 might be due to presence of OH in compound. Compound 5j show sharp singlet at δ 2.87 due to presence of CH_3 in dimethylamine. All compounds show sharp singlet near δ 5.05 to 5.38 might be due to CH proton in C-7 position in ring.

Mass spectra were recorded on LC-MSD-Trap-SL which show characteristic molecular ion and base peak and further confirmed the compounds.

Antimicrobial activity of synthesized compounds was evaluated by cup-plate method. All the synthesized compounds show a moderate biological activity. The compound 5d, 5i and 5d, 5f show better significant antibacterial and antifungal activity respectively. Antimicrobial activity of synthesized compounds are recorded in table-2, table-3.

Table 2: Antimicrobial Activities of the Compounds

Compound Code	Diameter of Zone of Inhibition in mm											
	E. coli			*K. pneumonia*			*S. aureus*			*B. subtilis*		
	100 µg/ml	200 µg/ml	300 µg/ml	100 µg/ml	200 µg/ml	300 µg/ml	100 µg/ml	200 µg/ml	300 µg/ml	100 µg/ml	200 µg/ml	300 µg/ml
5a	13	15	17	14	15	17	13	14	15	12	13	15
5b	12	14	16	12	14	16	12	14	16	10	12	14
5c	13	14	15	11	13	15	11	13	15	11	13	15
5d	15	17	19	15	17	19	14	16	18	14	16	18
5e	12	14	16	12	13	15	11	13	15	12	14	16
5f	13	15	17	14	16	18	13	15	17	12	13	15
5g	11	13	15	11	12	14	12	14	16	11	13	15
5h	12	14	16	13	15	17	12	14	16	12	13	14
5i	14	16	19	15	17	20	15	17	19	14	16	18
5j	13	15	17	14	16	18	13	15	17	13	14	16
5k	12	14	16	12	14	16	12	14	16	13	14	15
5l	13	14	15	13	15	17	13	15	17	12	14	16
5m	11	13	15	12	14	16	13	15	17	11	13	15
5n	12	14	16	13	15	17	12	14	16	12	14	16
Std (10µg/ml)	22	22	22	23	23	23	21	21	21	20	20	20

Standard drug : Ciprofloxacin (10µg/ml)

Table 3: Antifungal Activity of the Compounds Against *Aspergillus niger*

Concentration µg/ml	Diameter of the Inhibition Zone (mm)														
	5a	5b	5c	5d	5e	5f	5g	5h	5i	5j	5k	5l	5m	5n	Std 10µg/ml
100	13	13	12	16	13	16	11	10	12	14	12	13	14	12	24
200	14	15	14	18	15	18	13	12	14	15	13	15	16	14	24
300	15	18	16	20	17	21	14	14	16	17	14	17	18	16	24

Antifungal Activity of 100µg/ml, 200µg/ml, 300µg/ml of test compounds against *Aspergillus niger* Ketoconazole 10µg/ml used as standard drug

Statistical Analysis

The results of the study were expressed as mean ± SEM. All the data is analyzed by one way Anova was used to analyze and compare the data, test for multiple comparisons. The value of probability less than 5% ($P < 0.05$) was considered statistically significant.

CONCLUSION

A series of novel heterocyclic compounds 1,3,4-thiadiazolo-[3,2-a]-1,3,5-triazine derivatives has been successfully synthesized. Compounds contain two bioactive heterocyclic rings 1,3,5-triazine and 1,3,4- thiadiazole. Synthesis reaction based on microwave mediate multi-component reaction (MCRs). Derivative of 1,3,4-thiadiazolo-[3,2-a]-1,3,5-triazine shown very good promising activity as compared to standard drug for all representative panel of bacterial and fungal strains and thus, there is enough scope for further study in developing such compounds as

a good lead moiety.

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