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Synthesis of Some New Bridgehead Thiadiazolo [3,2-a] Pyrimidine Derivatives Under Microwave Irradiations And Their Antimicrobial Evaluation

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ABSTRACT

In this report, we describe an efficient one pot cyclocondensation of 2-amino-5-phenyl-1,3,4-thiadiazole (1), various substituted aromatic aldehydes and ethylacetoacetate to yield 5H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-6-carboxylate (2a-2h) under microwave irradiation. The structures of the synthesized compounds were characterized by analytical and spectroscopic methods (IR, ^{1}H-NMR, MS). The antimicrobial screening of the compounds (2a-2h) was also evaluated. In the antifungal screening, compound 2c showed promising activity comparable to the standard Fluconazole against the tested fungal strain Neurospora crassa.

Keywords: Thiadiazolo [3,2-a]pyrimidines, Microwave, One pot synthesis, Antimicrobial activity.

INTRODUCTION

Recently, the chemistry of 1,3,4-thiadiazole derivatives is highlighted due to their wide spectrum of biological activities including antimicrobial [1-3], anti-inflammatory[4,5], antioxidant[6,7], anti-tumour [8], anti-cancer[9] and have other pharmacological activities[10,11]. Moreover, this ring system is valuable building block for the synthesis of other fused heterocyclic systems. One such system is thiadiazolo [3,2-a]pyrimidine derivatives resulting from the annulations of a pyrimidine ring on thiadiazole as potential bioactive molecules. These fused heterocyclic derivatives have generated great interest in recent years due to their wide range of biological and pharmacological activities including antibacterial[12], antitumor[13,14], fungicidal[15], neuraminidase inhibitors[16] etc.

In view of all these observations and in continuation of our effort in search of potent heterocyclic systems possessing biological activities, we have undertaken the synthesis of some new derivatives of thiadiazolo [3,2-a]pyrimidine derivatives. The existing synthetic methodologies to synthesize these compounds are associated with many drawbacks like multiple steps, longer reaction time with drastic conditions, low yield and not satisfactory with regard to the isolation of the product[17,18]. In these environmentally conscious days, research and development are directed towards devising cleaner processes. Therefore, it is quite significant to develop an efficient and green method to synthesize this potential bioactive molecule. The

main objective of this study was therefore to synthesize new targets by one-pot multicomponent reaction under microwave irradiation and evaluated their antimicrobial activities.

MATERIALS AND METHODS

Experimental: Melting points were taken in open end capillaries and were uncorrected. The purity of the synthesized compounds was checked by thin layer chromatography on silica gel G (Merck) plates and spots were located by iodine vapours. ^{1}H NMR spectra were recorded on BRUKER AVANCE II 400 NMR Spectrometer with auto sampler in $CDCl_3$ using tetramethylsilane (TMS) as internal standard. All chemical shifts were reported as delta (ppm) value. The IR spectra were recorded on Perkin-Elmer spectrum RX IFT-IR System using KBr pellets. The elemental analyses were recorded on VARIO MICRO CHNS ANALYZER. All the compounds gave satisfactory results within $\pm$ 0.4% of theoretical values. The mass spectra were recorded by GC-MS with model GC-MS-QP2010 Plus (Shimadzu Corporation, Kyoto, Japan). All the biological activities were performed at Biogenic Research and Training Centre in Biotechnology, Hubli, Karnatka. For all the reactions, chemicals of SD fine standards were used. All solvents were distilled before use.

General procedure for the synthesis of 2-amino-5-phenyl-1,3,4-thiadiazole [19](1): 10mmol (1.2g) of benzoic acid, 10mmol(0.91g) thiosemicarbazide and 5mL phosphorous oxychloride was gently refluxed for 3hrs on heating mantle. To the cooled reaction mixture, 25mL water was added slowly and the reaction mixture was refluxed for 3 hrs on heating mantle. The reaction mixture was filtered. Residue was discarded and the filtrate was neutralized with concentrated solution of potassium hydroxide (5g of KOH dissolved in 15 mL of H_2O) and the precipitate was filtered and recrystalized from ethanol as light brown solid, m.p. 218-220^{0}C, and experimental yield-69%.

General procedure for the synthesis of ethyl-7-methyl-2-phenyl-5-(substituted phenyl)-8,8a-dihydro-5*H*-[1,3,4]thiadiazolo[3,2-a]pyrimidine-6-carboxylate (2a-2h): The desired compounds (2a-2h) were synthesized by irradiating a mixture of 0.01mol of ethylacetoacetate, 0.01mol of appropriate aromatic aldehyde and 0.01mol of 5-phenyl-1,3,4-thiadiazole-2-amine (1), in unmodified domestic microwave oven at 320W using absolute ethanol as an energy transfer medium and 3-4 drops of concentrated HCl as a catalyst. The progress of the reaction was monitored by thin layer chromatography using silica gel G plates. Appropriate mixture of benzene and ethyl acetate used as eluting solvent. After drying the plates, spots were visualized by iodine vapours. The reaction mixture was allowed to cool, treated with ethanol and the crystals were filtered off. The crude product was recrystalized with methanol. All the compounds were obtained in good yield (37 % - 58 %).

Ethyl-7-methyl-2,5-diphenyl-8,8a-dihydro-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-6-arboxylate (2a): Yield 37 % (methanol);m.p. 108-110^0 C; IR ν_{max} (KBr,cm^{-1})**:** 3105.9 (Aromatic C-H), 2924.9 (Aliphatic C-H str.), 1630.4 (C=O), 1610.1(C=C), 1590.1, 1568.3, 1533.8 (C=C Aromatic skeleton vib.), 1331.9 (C-N str.); ^{1}H NMR: (400 MHz, $CDCl_3$), δ (ppm): 7.78-7.61 (5H, m, H-2$'$, 3$'$, 4$'$, 5$'$, 6$'$), 7.45-7.18 (5H, m, H-2$''$, 3$''$, 4$''$, 5$''$, 6$''$), 5.72 (1H, s, H-5), 3.53(2H, q, O-$\underline{CH_2}$-CH_3), 2.12(3H, s,7-CH_3), 1.14(3H, t, O-CH_2-$\underline{CH_3}$), GC-MS (m/z): 377, 348, 304, 300(100), 272, 161,121, 103, 77, 51; Anal. Calc. For $C_{21}H_{19}O_2N_3S$: C, 66.84; H, 5.03; N, 11.14; Found C, 66.72; H, 4.94; N, 11.07.

Ethyl-5-(2,4-dichlorophenyl)-7-methyl-2-phenyl-8,8a-dihydro-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-6-carboxylate (2b): Yield–58% (methanol);m.p. 162-164^0 C ; IR ν_{max}(KBr,cm^{-1})**:** 3060.6 (Ar- H str.), 2987.6 (C-H str.), 1701.2 (C=O), 1587.3, 1501.1, 1483.1(C=C Aromatic skeleton vib.), 1372.3 (C-N str.); ^{1}H NMR: (400 MHz, $CDCl_3$), δ (ppm): 7.63(1H, d, J_m= 1.1, H-3$''$), 7.61(1H, d, J_o=7.8, H-5$''$), 7.45-7.37(5H, m, H-2$'$, 3$'$, 4$'$, 5$'$, 6$'$), 7.20(1H, d, J_o=7.2, H-6$''$), 6.91(1H, s, H-5), 4.08(2H, q, O-$\underline{CH_2}$-CH_3), 2.5(3H, s,7-CH_3), 1.25(3H, t, O-CH_2-$\underline{CH_3}$); GC-MS (m/z): 445, 416, 372, 307, 300(100), 272, 161,103, 77, 51; Anal. Calc. for $C_{21}H_{17}O_2N_3SCl_2$: C, 56.62; H, 3.82; N, 9.43; Found C, 56.49; H, 3.73; N, 9.35.

Ethyl-5-(3-nitrophenyl)-7-methyl-2-phenyl-8,8a-dihydro-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-6-carboxylate (2c): Yield - 46 %(methanol);m.p. 225-226^0 C ; IR ν_{max} (KBr,cm^{-1})**:** 3084.6 (Ar- H str.), 2976.4 (C-H str.), 1702.5 (C=O), 1586.2, 1526.3, 1486.5 (C=C Aromatic skeleton vib.), 1348.7 (C-N str.) ^{1}H NMR: (400 MHz, $CDCl_3$), δ (ppm): 8.32(1H, t, J_m-1.8, H-2''), 8.21(1H, d, J_o-8.2, H-4''), 7.69-7.67(2H, d, J_o=7.8, H-5'', 6''), 7.61-7.34(5H, m, H-2', 3', 4', 5', 6'), 6.65(1H, s, H-5), 4.16(2H, q, O-$\underline{CH_2}$-CH_3), 2.62(3H, s,7-CH_3),1.20(3H, t, O-CH_2-$\underline{CH_3}$). ; Anal. Calc. For $C_{21}H_{18}O_4N_4S$: C, 59.71; H, 4.26; N, 13.27; Found C, 59.82; H, 4.35; N, 13.36.

Ethyl-5-(4-hydroxyphenyl)-7-methyl-2-phenyl-8,8a-dihydro-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-6-carboxylate (2d): Yield - 52 % ($CHCl_3$: MeOH 1:1) ;m.p. 244-246^0 C ; IR ν_{max} (KBr,cm^{-1})**:** 3366.4 (O-H str.), 3061.6 (Ar-H str.), 1627.5 (C=O), 1513.3 (C=C Aromatic skeleton vib.). ^{1}H NMR: (400 MHz, $CDCl_3$) δ (ppm): 9.55(1H, s, 4''-OH), 7.16-7.09(9H, m, H-2', 3', 4', 5',6', 2'', 3'', 5'', 6''), 5.59(1H, s, H-5), 3.50(2H, q, O-$\underline{CH_2}$-CH_3), 2.62(3H, s,7-CH_3), 1.08(3H, t, O-CH_2-CH_3).; Anal. Calc. for $C_{21}H_{19}O_3N_3S$: C, 64.12; H, 4.83; N, 10.68; Found C, 64.03; H, 4.75; N, 10.52.

Ethyl-5-(4-hydroxy-3-methoxyphenyl)-7-methyl-2-phenyl-8,8a-dihyro-5*H*-[1,3,4]thiadiazolo[3,2-*a*] pyrimidine-6-carboxylate (2e): Yield - 48 % ($CHCl_3$: MeOH 1:1) ;m.p. 118-119^0 C ; IR ν_{max} (KBr,cm^{-1})**:** 3060.4 (Ar-H str.), 2940.7 (C-H str.), 1635.8 (C=O), 1620 (C=C Aromatic skeleton vib.) , ^{1}H NMR: (400 MHz, $CDCl_3$), δ(PPM): 9.35(1H, s, 4''-OH), 7.45-7.38(5H, m, H-2', 3', 4', 5', 6'), 6.94(1H, d, J_o=8.3, H-5''), 6.85 (1H, s, H-2''), 6.69(1H, d, J_o=8.3, H-6''), 6.45(1H, s, H-5), 3.75(3H, s, 3''-OCH_3), 3.57(2H, q, O-$\underline{CH_2}$-CH_3), 2.62(3H, s,7-CH_3), 1.18(3H, t, O-CH_2-$\underline{CH_3}$); GC-MS (m/z): 423, 394, 350, 320, 300(100), 272, 161, 121, 103, 77, 51. Anal. Calc. For $C_{22}H_{21}O_4N_3S$: C, 62.41; H, 4.96; N, 9.92; Found C, 62.52; H, 5.07; N, 10.01.

Ethyl-5-(4-methoxyphenyl)-7-methyl-2-phenyl-8,8a-dihydro-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-6-carboxylate (2f): Yield - 42 % (methanol) ;m.p. 265-267^0 C ; IR ν_{max} (KBr,cm^{-1})**:** 3060.4 (Ar-H str.), 2931.6 (C-H str.), 1637.5 (C=O), 1623.3 (C=C), 1570.6 (C=C Aromatic skeleton vib.), 1250 (C-O-C str.), ^{1}H NMR: (400 MHz, $CDCl_3$), δ (ppm): 7.38(5H, m, H-2', 3', 4', 5', 6'), 7.23(2H, d, J_o=8.3, H-2'',6''), 7.05(2H, d, J_o=7.72, H-3'', 5''), 6.48(H, s, H-5), 3.81(3H, s, 4''-OCH_3), 3.58(2H, q, O-$\underline{CH_2}$-CH_3), 2.21(3H, s,7-CH_3), 1.13(3H, t,O-CH_2-$\underline{CH_3}$).; GC-MS (m/z): 407, 378, 334, 300(100), 272, 121, 103, 77, 51.Anal. Calc. For $C_{22}H_{21}O_3N_3S$: C, 64.86; H, 5.15; N, 10.31; Found C, 64.73; H, 5.03; N, 10.22.

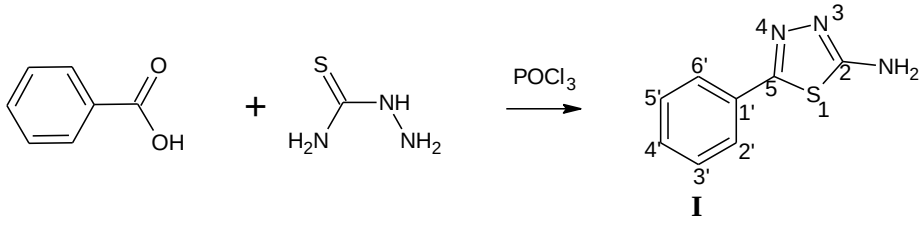
Ethyl-5-(2,3-methylenedioxyphenyl)-7-methyl-2-phenyl-8,8a-dihyro-5*H*-[1,3,4]thiadiazolo[3,2-*a*] pyrimidine-6-carboxylate (2g): Yield - 50 % (methanol) ;m.p. 167-168^0 C ; IR ν_{max} (KBr,cm^{-1})**:** 3080.4 (Ar-H str.), 2920.7 (C-H str.), 1630.8 (C=O), 1520, 1500.2, 1485.5 (C=C Aromatic skeleton vib.), 1234.5 (C-O-C str.). . ^{1}H NMR: (400 MHz, $CDCl_3$), δ(ppm): 7.85-7.78(5H, m, H-2', 3', 4', 5', 6'), 6.79-6.73(3H, m, H-4'', 5'', 6''), 6.08(2H, s, 2'', 3''-OCH_2-O), 5.66(1H, s, H-5), 3.61(2H, q, O-$\underline{CH_2}$-CH_3), 2.16(3H, s,7-CH_3), 1.26(3H, t, O-CH_2-$\underline{CH_3}$); Anal. Calc. For $C_{22}H_{19}O_4N_3S$: C, 62.70; H, 4.51; N, 9.97; Found C, 62.59; H, 4.44; N, 10.06.

Ethyl-5-(4-nitrophenyl)-7-methyl-2-phenyl-8,8a-dihyro-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-6-carboxylate (2h): Yield - 49 % ($CHCl_3$: MeOH 1:1) ; m.p. 188-200^0 C ; IR ν_{max} (KBr,cm^{-1})**:** 3084.4 (Ar-H str.), 2960.7 (C-H str.), 1705.8 (C= O), 1620 (C=C), 1560.8 (C=C Aromatic skeleton vib.).^{1}H NMR: (400 MHz, $CDCl_3$), δ(ppm): 8.23(2H, d, J_o=8.6, H-3'', 5''), 7.53(2H, d, J_o=8.2, H-2'', 6''), 7.45-7.38(5H, m, H-2', 3', 4', 5',6'), 3.53(2H, q, O-$\underline{CH_2}$-CH_3), 2.29(3H, s, 7-CH_3), 1.18(3H, t, O-CH_2-$\underline{CH_3}$); Anal. Calc. for $C_{21}H_{18}O_4N_4S$: C, 59.71; H, 4.26; N, 13.27; Found C, 59.58; H, 4.15; N, 13.15.

RESULTS AND DISCUSSION

Chemistry: The starting material 2-amino-5-phenyl-1,3,4-thiadiazole required for the synthesis of the compounds II(a-h) was synthesized by reacting benzoic acid and thiosemicarbazide in the presence of

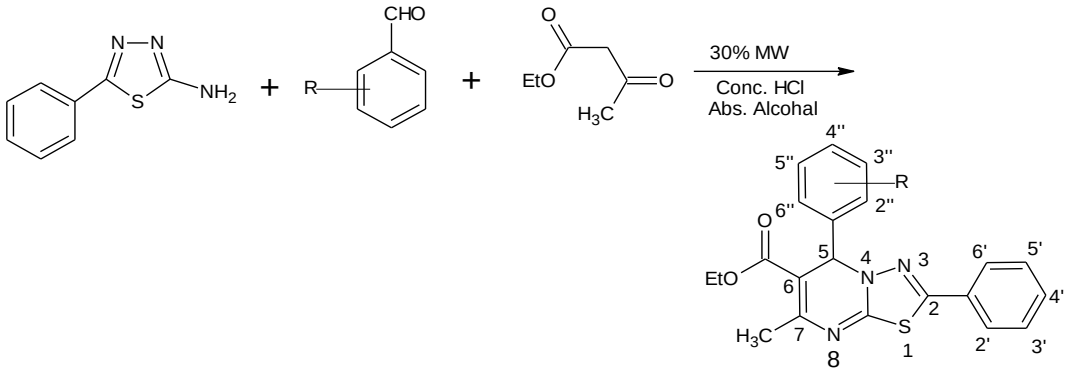
$POCl_3$. The synthetic detail about this method is given under experimental section and chemical reaction is presented in **scheme-1**.



I

Scheme-1

The synthesis of thiadiazole [3,2-a] pyrimidines 2(a-h) was carried out through one pot multicomponent condensation reaction of equimolar mixture of thiadiazole, ethyl acetoacetate and substituted aromatic aldehydes using 3-4 drops of conc. HCl and absolute alcohol as energy transfer solvent under microwave irradiation for few minutes. The details about this method are given under experimental section and synthetic part of this work is presented in **scheme-2**. The optimum reaction conditions determined for the synthesis are summarized in Table-1. Formation of thiadiazolo [3, 2-a] pyrimidine compounds 2a-2h were determined from the rigorous analysis of their spectral data (IR, ^{1}H NMR and Mass spectra). The physical data is given in table 2.



I II(a-h)

Scheme-2

R(a-h): a=H, b=2,4-Cl, c=3-NO_2, d=4-OH, e=3-OCH_3, 4-OH, f=4-OCH_3, g=2,3-[O-CH_2-O], h=4-NO_2

Table1. Physical Data of products (2a-2h)

Product	R	Reaction Time (MW)	Product m.p (^{0}C)	Yield (%)	Molecular formula
2a	H	8	108-110	$C_{21}H_{19}O_2N_3S$	37
2b	2,4-Cl	11	162-164	$C_{21}H_{17}O_2N_3SCl_2$	58
2c	3-NO_2	7	225-226	$C_{21}H_{18}O_4N_4S$	46
2d	4-OH	9	244-246	$C_{21}H_{19}O_3N_3S$	52
2e	3-OCH_3, 4-OH	10	118-119	$C_{22}H_{21}O_4N_3S$	48
2f	4-OCH_3	8	265-266	$C_{22}H_{21}O_3N_3S$	42
2g	2,3-[O-CH_2-O]	12	167-168	$C_{22}H_{19}O_4N_3S$	50
2h	4-NO_2	7	188-200	$C_{21}H_{18}O_4N_4S$	49

The IR spectra of compound 2(b) exhibit absorption band at 3060.6 cm^{-1} for aromatic C-H stretching and an aliphatic C-H stretching vibration at 2987.6 cm^{-1}. The ester carbonyl stretching frequency was observed at 1701.2 cm^{-1}. The skeletal vibration of phenyl ring was observed at 1587.3 cm^{-1}, 1501.1 cm^{-1}, 1483.1cm^{-1} and the band due to C-N stretching vibration was observed at 1372.3 cm^{-1}.

The ^{1}H NMR spectrum of the compound 2(b) showed a characteristic doublet at δ 7.63 ppm with a J_m value of 1.1 Hz due to H-3" proton. This is due to the coupling between H-3"and H-6". Another doublet at δ 7.61 ppm with J_0 = 7.8 Hz was due to H-5" proton which show coupling between H-5" & H-6". The aromatic protons of 2 - phenyl ring i.e. H-2', 3', 4', 5', 6' appeared as multiplet at δ7.45 – δ7.37 ppm. One another doublet appeared at δ7.20 ppm was assigned to H-6" proton with J_0 = 7.2 Hz, which again show ortho coupling between H-6" & H-5". Moreover it's ^{1}H NMR spectrum revealed characteristic singlet signal at δ6.95 ppm due to proton at C-5 of pyrimidine moiety which confirmed the formation of thiadiazolo pyrimidine compound. A three proton singlet signal appeared at δ2.50 which confirmed the presence of 7-CH_3 protons. A two protons quartet at δ4.08 ppm was assigned to O-$\underline{CH_2}$-CH_3 and three proton triplet was observed at δ1.25 ppm for O-CH_2-$\underline{CH_3}$. Mass spectra showed M^+ peak at 445 and base peak at 300 and other peaks at 416, 372, 307, 272, 161,103, 77, 51.The elemental analysis of compound was found to be in agreement with the calculated values (± 0.4%).

APPLICATIONS

Antimicrobial Studies: Some of the newly synthesized compounds 2b-2h were screened for antimicrobial activity by "Agar diffusion method" [20]. The bacterial strains used in the present study were *Staphylococcus aureus* (MTCC 3160), *Staphylococcus aureus* (MRSA) (MTCC 9542) and *Streptococcus pyogenes* (MTCC 1927) (all are Gram-positive). The fungal strains used are *Aspergillus Niger* (MTCC 1881) and *Neurospora crassa* (MTCC 1855). M.I.C. was determined by choosing lowest concentration in which no growth occurs (Table-2).

Initially, the stock cultures of microorganism were revived by inoculating in agar media(for bacteria) and Potato Dextrose Agar medium (for fungi) These cultures were grown at 37^{0}C for 18 h (for bacteria) and at 27^{0}C for 48 h (for fungi). The agar plates of the above media were prepared and wells (5 mm) were made in the plate. Each plate was inoculated with 18 hours old cultures (100 µL, 10^{-4} cfu) (for bacteria) and 48 h old cultures (100 µL, 10^{-4} cfu) (for fungi) and spread evenly on the plate. After 20 min, the wells were filled with compounds and antibiotic at different concentrations. The final concentration of the solutions was 25, 50, 100, 250, 500 and 1000 µg mL^{-1}. All the plates were incubated at 37^{0}C for 24 h (for bacteria) and at 27^{0}C for 96 h (for fungi). After Incubation, the antimicrobial activities of compounds were evaluated by measuring the zones of growth inhibition around each well. The diameters of zone of inhibition produced by the agent were compared with those produced by the commercial control antibiotic. This procedure was performed in three replicate plates for each organism to minimize the error. The results of antimicrobial screening of all tested compounds against different strains in terms of diameter of inhibition in mm and MIC in µg are summarised in table-2.

Table 2: Antimicrobial screening of different compounds against different strains

Tested Samples	*S. Aureus*		MRSA		*S. Pyogens*		*A. Niger*		*N. Crassa*	
	A	MIC (µg)	A	MIC (µg)	A	MIC (µg)	A	MIC (µg)	A	MIC (µg)
2b	2	1000	0	NF	0	NF	0	NF	0	NF
2c	5	1000	5	500	0	NF	6	1000	14	500
2d	2	1000	0	NF	0	NF	0	NF	0	NF
2e	0	NF	0	NF	0	NF	0	NF	0	NF

2f	2	1000	2	1000	0	NF	0	NF	0	NF
2g	0	NF	2	1000	0	NF	0	NF	0	NF
2h	5	1000	7	1000	8	1000	0	NF	3	1000
Ciprofloxacin	*	*	41	25	36	25	--	--	--	--
Fluconazole	--	--	--	--	--	--	16	1000	14	1000

A= Zone of inhibition in mm. at a concentration of 800 µg mL^{-1}, * = Inhibition zone were too big to measure

Some of the newly synthesized compounds 2b-2h was tested for their anti-microbial activities by the "Agar diffusion method" and the M.I.C. (Minimum Inhibitory Concentration) was determined in µg/mL. Standard antibacterial Ciprofloxacin and fungicide Fluconazole were also screened to evaluate the potency of the tested compounds under the similar conditions. The results showed that by replacing the substituent R in the 5-aryl group at position 3" of the thiadiazolo [3-2,a] pyrimidine with electron withdrawing group e.g., R= NO_2 as in 2c leads to a increase in the antifungal activity with lower M.I.C. than the stranded drug used i.e. Fluconazole against the fungal strain *N. Crassa*. On the other hand, compound 2h has high potency towards bacterial strains than fungal in comparison to compound 2c. The activity of compounds 2c,h can be attributed to the structure activity relationship in these two compounds , as with the change in position of the same substituent i.e. NO_2 from 3" to 4" effect the potency towards bacterial as well as fungal strains. In addition, compounds 2b, 2d and 2g have low activity against any one bacterial strain, compound 2f show some activity against two bacterial strains and all remain inactive against the fungal strains. While compound 2e has no activity against any of the tested microbial strain so compound 2b – 2n with various substituatants in the 5-aryl group will be useful in understanding the influence of steric and electronic effects on the biological studies.

CONCLUSIONS

In conclusion, a series of 5*H*-[1,3,4]thiadiazolo[3, 2-a] pyrimidine-6-carboxylate derivatives were successfully synthesized through one pot multicomponent cyclocondensation of various aromatic aldehydes, 2-amino thiadiazole and ethylacetoacetate under microwave irradiation. These were characterized by IR, NMR, mass and elemental analysis. Some of the prepared compounds 2b-2h are also evaluated for their antimicrobial activity by "Agar diffusion method" and the M.I.C. (Minimum Inhibitory Concentration) was determined in µg mL^{-1}. The obtained results revealed that the nitro-substituted compound (2c) have low M.I.C. than the stranded drug used i.e. Fluconazole against the fungal strain *N. Crassa* and showed same zone of inhibition(14mm) at conc.1000 µg. So, this compound is more potent at low concentration as compared to the stranded drug.

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