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Microwave Assisted Synthesis and Bioactivity of s-Triazolo[3,4-b][1,3,4] Thiadiazoles, s-Triazolo [3,4-b][1,3,4] Thiadiazines and s-Triazolo [3′,4′: 2,3]-Thiadiazino[5,6-b] Quinoxaline

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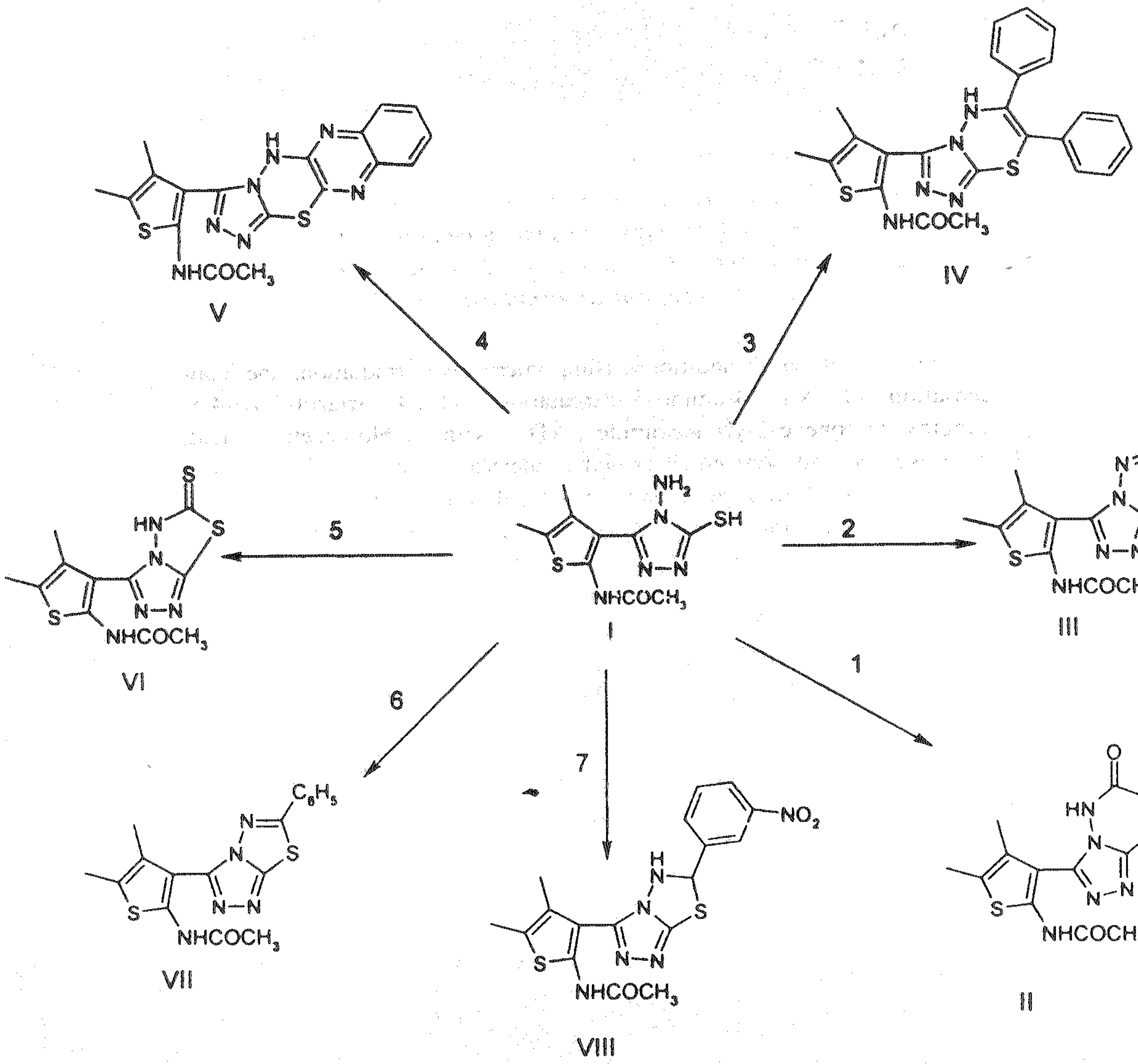
The solvent free conditions using microwave irradiation, the condensation of *N*-[3-(4-amino-5-mercapto-4*H* [1,2,4] triazol-3-yl)-4,5-dimethyl-thiophene-2-yl]-acetamide (I) with chloroacetic acid, α-haloketone and benzoin furnished condensed products [1,2,4] triazolo [3,4-b] [1,3,4] thiadiazine derivative, *viz*., **II, III, IV** respectively. Similarly, the condensation with 2,3-dichloro quinoxaline, carbon disulphide, aromatic carboxylic acid and aromatic carboxaldehydes furnished the cyclic products [1,24] triazolo [3,4-b] [1,3,4] thiadiazole derivatives, *viz*., **V, VI, VII, VIII** respectively. The compounds have been charactetrized on the basis of elemental analysis and spectral data. The antibacterial, antifungal and antitubercular activities of the compounds have also been evaluated.

Key Words: **Synthesis, Microwave irradiation, Thiadiazoles, Thiadiazines and Quinoxaline derivatives.**

INTRODUCTION

1,2,3-triazolo[3,4-b][1,3,4]thiadiazine and 1,2,3-triazolo[3,4-b][1,3,4]thiadiazole have been reported to have important biological activities[1, 2], *viz*., antibacterial, antifungal, analgesic and antiinflammatory. Microwave assisted reactions[3] using dry media[4] have attracted much interest because of the simplicity in operation, greater selectivity and rapid synthesis of a variety of heterocyclic compounds[5]. Keeping this in mind, it was worthwhile to develop rapid syntheses of title compounds under solvent free conditions using microwave irradiation. Earlier thiadiazoles and thiadiazines were synthesized in 6–7 h[6], while on solid support under microwave, the reaction was completed within 40–80 seconds with improved yield. The reaction of (I) with chloroacetic acid, α-haloketone, benzoin and 2,3-dichloroquinoxaline yield **(II), (III), (IV),** (V) respectively in good yield. The reaction of **I** with carbon disulphide in the presence of alcoholic KOH, aromatic carboxylic acid in the presence of $POCl_3$ and aromatic carboxaldehyde in the presence of *p*-toluene sulphonic acid yields the expected products **(VI), (VII), (VIII)** respectively **(Scheme-1)**. The structures **II–VIII** have been established on the basis of their ^{1}H NMR and IR data.



(1) $ClCH_2COOH$,NaOAc (2) CH_3COCH_2Br, K_2CO_3 (3) $C_6H_5CHOHCOC_6H_5$, KOH
(4) 2,3-Dichloroquinoxaline, NaOAc (5) CS_2, KOH (6) C_6H_5COOH, $POCl_3$ (7) $C_6H_4NO_2$

Scheme-1

EXPERIMENTAL

The melting points were recorded on electrothermal apparatus and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer-983 and PMR spectrum on Bruker Avance 300 MHz instrument using $CDCl_3$ as solvent (chemical shifts in δ ppm), using TMS as internal standard. Mass spectra were charted on Finning LCQ mass spectrometer. Microwave irradiations were carried out in Padmini Essentia oven, model Brownie, at 2450 MHz. Elemental analyses were performed on a Heracus CHN rapid analyzer.

***N*-[3-Amino-5-mercapto-4*H*-[1,2,4]triazol-3-yl]-4,5-dimethyl thiophene-2-yl]-acetamide (I):** This compounds was synthesized by the reported method[7, 8]. IR (KBr, cm^{-1}): 1525 ν(C—N str.), 1620 ν(C═N), 2645 ν(S—H str.), 3145, 3330 ν(N—H str.). ^1H NMR ν($CDCl_3$): δ 2.0 ν(s, 2H, NH_2), δ 2.02 ν(s, 3H, CH_3), δ 2.21 ν(s, 3H, CH_3), δ 2.41 ν(s, 3H, CH_3), δ 3.0 ν(s, 1H, aromatic SH), δ 8.0 ν(s, 1H, NH).

***N*-[4,5-Dimethyl-3-(6-oxo-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)-thiophene-2-yl]-acetamide (II):** A solution of (I) (0.01 mol), chloroacetic acid (0.01 mol) and freshly prepared fused sodium acetate (0.01 mol) was prepared. Acidic alumina[9] was added to the above solution at room temperature. The reaction mixture was mixed, adsorbed, dried and kept inside the alumina bath[10] and irradiated for 40–80 s. The mixture was cooled and then the product was extracted with dry methanol and poured on to crushed ice. The solid thus separated was filtered, washed thoroughly with water and recrystallized from aqueous ethanol. IR (KBr, cm^{-1}): 1530 ν(C—N str.), 1635 ν(C═N), 1675 ν(C═O). ^1H NMR ($CDCl_3$): δ 2.02 (s, 3H, CH_3), δ 2.21 (s, 3H, CH_3), δ 2.41 (s, 3H, CH_3), δ 3.8 (s, 2H, CH_2 group in thiadiazine), δ 8.0 (s, 2H, NH).

***N*-[4,5-Dimethyl-3-(6-methyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl) thiophene-2-yl]-acetamide (III):** Solution of (I) (0.01 mol) and *p*-bromophenacyl bromide (0.01 mol) was added to acidic alumina at room temperature. The reaction mixture was mixed, adsorbed, dried and kept inside the alumina bath and irradiated for 40–80 s. The mixture was cooled and then the product was extracted with dry methanol and neutralized with aqueous potassium carbonate. The solid thus separated was filtered, washed thorouhly with water and recrystallized from ethanol. IR (KBr, cm^{-1}): 830 ν(1,4-disubstituted benzene ring), 1535 ν(C—N str.), 1625 ν(C═N), 3035 ν(aromatic C—H str.). ^1H NMR ($CDCl_3$): δ 0.9 (s, 3H, CH_3), δ 2.02 (s, 3H, CH_3), δ 2.21 (s, 3H, CH_3), δ 2.41 (s, 3H, CH_3), δ 3.0 (s, 2H, CH_2 group in thiadiazole), δ 8.0 (s, 1H, NH).

***N*-[3-(6,7-Diphenyl-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)-4,5-dimethyl-thiophen-2-yl]-acetamide (IV):** A solution of (I) (0.01 mol), benzoin (0.01 mol) and 2 N KOH solution was prepared. Acidic alumina was added to the above solution at room temperature. The reaction mixture was mixed, adsorbed, dried and kept inside the alumina bath and irradiated for 40–80 s. The mixture was cooled and then the product was extracted with acetone and was evaporated to dryness. The solid thus separated was washed thoroughly with water and recrystallized from ethanol. IR (KBr, cm^{-1}): 715, 755 ν(monosubstituted benzene ring), 1600, 1620 ν(C═C), 1665 ν(C═N), 3035 ν(aromatic C—H str.), 3420 ν(N—H str.). ^1H NMR ($CDCl_3$): δ 2.0 (s, 1H, NH in thiadiazole), δ 2.02 (s, 3H, CH_3), δ 2.21 (s, 3H, CH_3), δ 2.41 (s, 3H, CH_3), δ 7.1–7.4 (m, 5H, ArH), δ 8.0 (s, 1H, NH).

***N*-[4,5-Dimethyl-3-(4*H*-11-thia-1,2,3a,4,5,10-hexaaza-cyclopenta[*b*]anthracen-3-yl)-thiophen-2-yl]-acetamide (V):** Solution of (I) (0.01 mol), 2,3-dichloroquinoxaline (0.01 mol) and fused sodium acetate (0.02 mol) was added to acidic alumina at room temperature. The reaction mixture was mixed, adsorbed, dried and kept inside the alumina bath and irradiated for 40–80 s. The mixture was cooled and then the product was extracted with dry methanol, concentrated and cooled. The solid thus separated was filtered, washed thoroughly with water and recrystallized from ethanol. IR (KBr, cm^{-1}): 745 ν(1,4-disubstituted benzene ring), 1510 ν(C—N str.), 1620 ν(C═C), 1655 ν(C═N), 3040 ν(aromatic C—H str.). ^1H NMR ($CDCl_3$): δ 2.02 (s, 3H, CH_3), δ 2.21 (s, 3H, CH_3), δ 2.41 (s, 3H, CH_3), δ 4.0 (s, 1H, NH group in thiadiazine), δ 7.7–8.1 (m, 5H, ArH), δ 8.0 (s, 1H, NH).

***N*-[4,5-Dimethyl-3-[6-thioxo-5,6-dihydro-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)-thiophen-2-yl]-acetamide (VI):** Carbon disulphide (0.015 mol) was added dropwise with constant stirring to the solution of (**I**) (0.01 mol) in methanolic KOH solution. Acidic alumina was added to the above solution at room temperature. The reaction mixture was mixed, adsorbed, dried and kept inside the alumina bath and irradiated for 40–80 sw. The mixture was cooled and then the product was extracted with dry methanol, which was then poured on to ice and acidified with dilute HCl. The solid thus separated was filtered, washed thoroughly with water and recrystallized from aq. ethanol. IR (KBr, cm^{-1}): 1120 ν(CS), 1510 ν(C—N str.), 1610 ν(C═C), 1655 ν(C═N), 3055 ν(aromatic C—H str.). ^1H NMR ($CDCl_3$): δ 2.0 (s, 1H, NH in thiadiazole), δ 2.02 (s, 3H, CH_3), δ 2.21 (s, 3H, CH_3), δ 2.41 (s, 3H, CH_3), δ 8.0 (s, 1H, NH).

***N*-[4,5-Dimethyl-3-[6-phenyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)-thiophen-2-yl]-acetamide (VII):** A solution of (**I**) (0.01 mol) and *p*-toluic acid (0.01 mol) in $POCl_3$ (5 mL) was prepared. Acidic alumina was added to the above solution at room temperature. The reaction mixture was mixed, adsorbed, dried and kept inside the alumina bath and irradiated for 40–80 s. The mixture was cooled and then poured on to ice and neutralized with aqueous potassium carbonate solution. The solid thus separated was filtered, washed thoroughly with water and recrystallized from hexane. IR (KBr, cm^{-1}): 835 ν(1,4-disubstituted benzene ring), 1530 ν(C—N str.), 1610 ν(C═C), 1625 ν(C═N), 3065 ν(aromatic C—H str.). ^1H NMR ($CDCl_3$): δ 2.02 (s, 3H, CH_3), δ 2.21 (s, 3H, CH_3), δ 2.41 (s, 3H, CH_3), δ 7.2–7.4 (m, 5H, ArH), δ 8.0 (s, 1H, NH).

***N*-[4,5-Dimethyl-3-[6-(3-nitro-phenyl)-5,6-dihydro-[1,2,4]triazolo[3,4-*b*]-[1,3,4] thiadiazol-3-yl)-thiophen-2-yl]-acetamide (VIII):** A solution of (**I**) (0.01 mol) and *m*-nitrobenzaldehyde (0.01 mol) was prepared. Acidic alumina was added to the above solution at room temperature. The reaction mixture was mixed, adsorbed, dried and kept inside the alumina bath and irradiated for 40–80 s. The mixture was cooled and then the product was extracted with dry toluene, concentrated and cooled. The solid thus separated was filtered, washed thoroughly with water and recrystallized from ethanol. IR (KBr, cm^{-1}): 1355, 1545 ν(NO_2), 1510 ν(C—N str), 1610 ν(C═C), 1615 ν(C═N), 3065 ν(aromatic C—H str.). ^1H NMR ($CDCl_3$): δ 2.0 (s, 1H, NH in thiadiazole), δ 2.02 (s, 3H, CH_3), δ 2.21 (s, 3H, CH_3), δ 2.41 (s, 3H, CH_3), δ 4.95 (s, 1H, CH group in thiadiazole), δ 7.4–8.0 (m, 5H, ArH), δ 8.0 (s, 1H, NH).

Antimicrobial activity

All the compounds were screened for antibacterial activity against *S. aureus* and *E. coli* by paper disc technique[11]. The concentration of the test compound used was 100 μg. Gentamycin was used as standard. The antifungal activity of all the compounds was evaluated against *C. albicans* using the same technique. Nystatin was used as standard.

Antitubercular activity

The title compounds were tested *in vitro* for their antitubercular activity against *M. tuberculosis* $H_{37}Rv$. The antitubercular evaluation of compounds was carried out at "Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF)' USA. Primary screening of the compounds for antitubercular activity was conducted using the CABTEC 460 radiometric system. Compounds demonstrating at least > 90% inhibition in the primary screening were retested at lower concentration against *M. tuberculosis* $H_{37}Rv$ to determine the actual minimum inhibitory concentration (MIC) in CABTEC 460. The data were compared with the standard drug Rifampin at 0.03 μg/mL concentration, which showed 97% inhibition.

TABLE-1

Compd.	m.f.	m.p. (°C)	M.W.	Yield (%)	Nitrogen (%)		Carbon (%)	
					Calcd.	Found	Calcd.	Found
1.	$C_{10}H_{13}N_4OS_2$	199	269	89	44.60	44.45	20.81	20.68
2.	$C_{11}H_{13}N_5O_2S_2$	217	311	80	42.44	42.63	22.50	22.63
3.	$C_{12}H_{15}N_5OS_2$	222	309	84	46.60	46.52	22.65	22.47
4.	$C_{24}H_{21}N_5OS_2$	235	459	86	62.74	62.57	15.25	15.21
5.	$C_{18}H_{15}N_7OS_2$	241	409	75	52.81	52.72	23.96	23.77
6.	$C_{11}H_{11}N_5OS_3$	265	325	71	40.61	40.50	21.53	21.48
7.	$C_{17}H_{15}N_5OS_2$	231	369	86	55.28	55.20	18.97	18.91
8.	$C_{16}H_{16}N_6O_3S_2$	252	404	85	47.52	47.45	20.79	20.72

RESULTS AND DISCUSSION

Compounds (**II**), (**VI**) and (**VIII**) displayed maximum activity against *S. aureus* and *E. coli*. Compound (**IV**) and (**VII**) showed moderate activity against *S. aureus* but inactive against *E. coli*. All the other compounds were inactive against both the organisms. Compounds (**II**), (**VI**) and (**VIII**) showed highest activity against *C. albicans*, compounds (**IV**) and (**VII**) showed moderate activity while others were inactive against the test organism. Compounds (**II**), (**VI**) and (**VIII**) were most active against *M. tuberculosis* $H_{37}Rv$ (> 90% inhibition) that will be retested at lower concentration to determine the actual minimum inhibitory concentration (MIC). Other compounds, *viz*., (**IV**) and (**VII**) were moderately active against *M. tuberculosis* $H_{37}Rv$ strain (> 50% inhibition).

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