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Microwave Assisted Synthesis and Bioactivity of Condensed Bridgehead Nitrogen Heterocyclic Systems

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A successful application of microwave irradiation has been studied in which a series of different triazolyl thiophenes were synthesized under solventless conditions and evaluated for antimycobacterial and antibacterial activities. Many of these compounds have shown better antimycobacterial and antibacterial activities while others were inactive.

Key Words: Microwave irradiation, Bioactivity, Heterocyclic compounds.

INTRODUCTION

In the last 10 years though significant progress has been made in the treatment and control strategies of tuberculosis by introducing new diagnostic and monitoring tools and combination therapy, it still continues to be a very severe problem. The synergy of this disease with AIDS and resistance to almost every drug in clinics has further worsened the problem[1]. Microwave assisted reactions[2] using dry media[3] have attracted much interest because of the simplicity in operation, greater selectivity and rapid synthesis of a variety of heterocyclic compounds[4]. 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[5, 6], *viz.*, antibacterial, antifungal, analgesic and antiinflammatory. Thus with the aim of developing novel molecules with improved potential for treating tuberculosis and with decreased probability of developing drug resistance, here the synthesis of triazolyl thiophene derivatives and results of investigations of their antimycobacterial and antibacterial activities have been discussed. A general synthetic route for synthesis of title compounds is described in **Scheme-1.** The structures **II-VIII** have been established on the basis of their ^{1}H NMR, elemental analysis and IR data.

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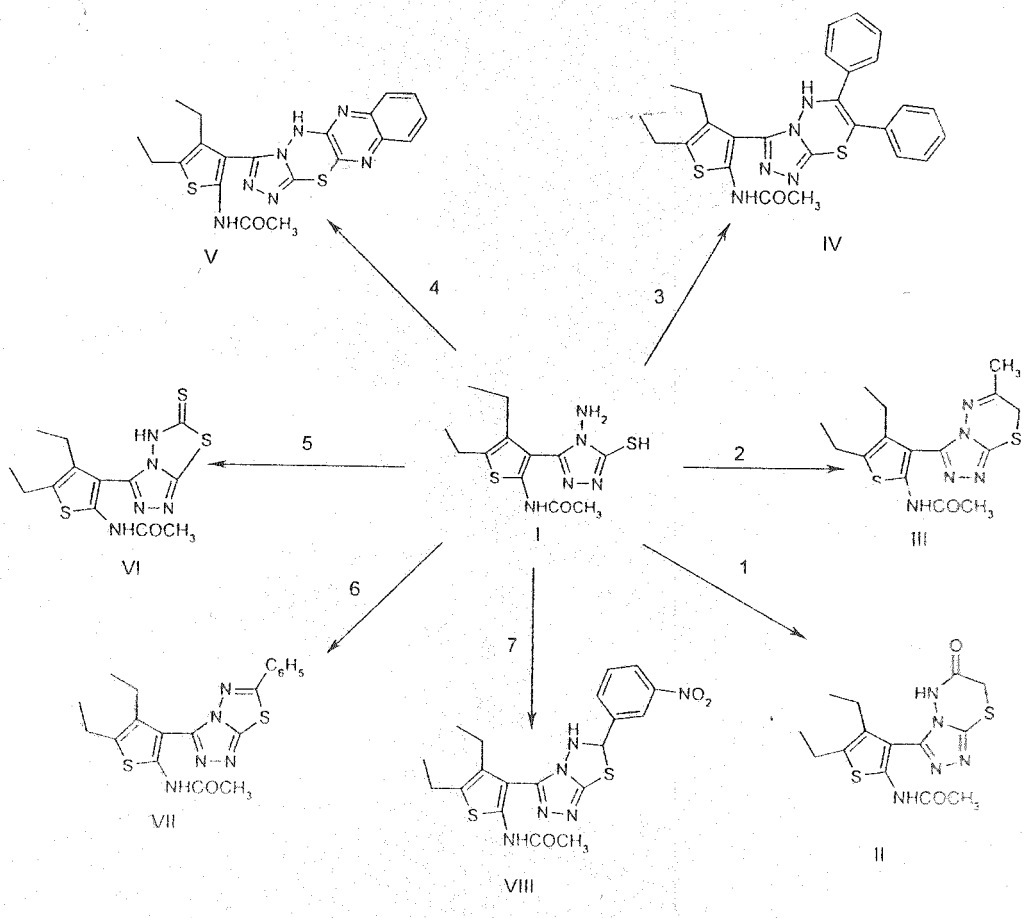

(1) $ClCH_2COOH$,NaOAc (2) CH_3COCH_2Br, K_2CO_3(3) $C_6H_5CHOHCOC_6H_5$, KOH
(4) 2,3-Dichloroquinoxaline, NaOAc (5) CS_2, KOH(6) C_6H_5COOH, $POCl_3$(7) $C_6H_4NO_2$

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. 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 irradiation were carried out in Padmini Essentia oven, Model Brownie at 2450 MHz. Elemental analysis were performed on a Heracus CHN-rapid analyzer.

N-[3-(4-Amino-5-mercapto-4H-[1,2,4]triazol-3-yl)-4,5-diethyl-thiophene-2-yl]-acetamide (1): This compound was synthesized by the reported method[7,8]. IR (KBr, cm^{-1}): 1532 ν(C—N), 1624 ν(C=N), 2664 ν(S—H), 3123, 3335 ν(N—H); ^1H NMR ($CDCl_3$): δ 0.9 (t J = 7.2 Mz, 3H, CH_3), 1.2 (t J = 7.2 Mz, 3H, CH_3), 1.7 (s, 2H, NH_2), 2.0 (s, 3H, CH_3), 2.5 (q J = 7.2 Mz, 2H, CH_2), 3.0 (s, 1H, aromatic SH), 3.7 (q J = 7.2 Mz, 2H, CH_2), 7.7 (m, 4H, Ar), 9.7 (s, 1H, NH).

N-[4,5-Diethyl-3-(6-oxo-6,7-dihydro-5H-[1,2,4]triazolo[3,4b][1,3,4]thiadiazin-3-yl)-thiophene-2-yl]acetamide (2): A solution of **1** (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 an 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}): 1522 ν(C—N stretching), 1627 ν(C=N), 1669 ν(C=O); ^1H NMR ($CDCl_3$): δ 0.92 (t J = 7.2 Mz, 3H, CH_3), 1.3 (t J = 7.2 Mz, 3H, CH_3), 2.1 (s, 3H, CH_3), 2.5 (q J = 7.2 Mz, 2H, CH_2), 3.7 (q J = 7.2 Mz, 2H, CH_2), 4.1 (s, 2H, CH_2 group in thiadiazine), 9.7 (s, 1H, NH).

N-[4,5-Diethyl-3-(6-methyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl)-thiophene-2-yl]acetamide (3): Solution of **1** (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 an 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 thoroughly with water and recrystallized from ethanol-water. IR (KBr, cm^{-1}): 827 ν(1,4-Disubstituted benzene ring), 1530 ν(C—N stretching), 1625 ν(C=N), 3031 ν(aromatic C—H stretching); ^1H NMR ($CDCl_3$): δ 0.7 (s, 3H, CH_3), 0.92 (t J = 7.2 Mz, 3H, CH_3), 1.22 (t J = 7.2 Mz, 3H, CH_3), 2.13 (s, 3H, CH_3), 2.47 (q J = 7.2 Mz, 2H, CH_2), 3.0 (s, 2H, CH_2 of Thiadiazine), 3.5 (q J = 7.2 Mz, 2H, CH_2), 9.7 (s, 1H, NH).

N-[3-(6,7-Diphenyl-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl)-4,5-diethylthiophen-2-yl]acetamide (4): A solution of **1** (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 an 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-water. IR (KBr, cm^{-1}): 722, 753 ν(monosubstituted benzene ring), 1612, 1629 ν(C=C), 1656 ν(C=N), 3024 ν(aromatic C—H stretching), 3427 ν(N—H stretching); ^1H NMR ($CDCl_3$): δ 0.9 (t J = 7.2 Mz, 3H, CH_3), 1.2 (t J = 7.2 Mz, 3H, CH_3), 2.1 (s, 3H, CH_3), 2.4 (q J = 7.2 Mz, 2H, CH_2), 3.7 (q J = 7.2 Mz, 2H, CH_2), 7.1–7.6 (m, 10H, Ar), 9.6 (s, 2H, NH).

N-[4,5-Diethyl-3-(4H-11-thia-1,2,3a,4,5,10-hexaaza-cyclopenta[b]anthracen-3-yl)-thiophen-2-yl]acetamide (5): Solution of **1** (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 an 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}): 735 ν(1,4-Disubstituted benzene ring), 1521 ν(C—N stretching), 1614 ν(C=C), 1662 ν(C=N), 3047 ν(aromatic C—H stretching); ^1H NMR ($CDCl_3$): δ 0.9 (t J = 7.2 Mz, 3H, CH_3), 1.2 (t J = 7.2

Mz, 3H, CH_3), 2.0 (s, 3H, CH_3), 2.5 (q J = 7.2 Mz, 2H, CH_2), 3.7 (q J = 7.2 Mz, 2H, CH_2), 7.7–8.1 (m, 4H, Ar), 9.65 (s, 2H, 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 (6): Carbon disulphide (0.015 mol) was added dropwise with constant stirring to the solution of **1** (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 an alumina bath and irradiated for 40–80 s. 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 aqueous ethanol-water. IR (KBr, cm^{-1}): 1117 ν(CS), 1514 ν(C—N stretching), 1623 ν(C=C), 1645 ν(C=N), 3064 ν(aromatic C—H stretching); ^{1}H NMR ($CDCl_3$): δ 0.9 (t J = 7.2 Mz, 3H, CH_3), 1.2 (t J = 7.2 Mz, 3H, CH_3), 2.0 (s, 3H, CH_3), 2.5 (q J = 7.2 Mz, 2H, CH_2), 3.7 (q J = 7.2 Mz, 2H, CH_2), 9.65 (s, 2H, NH).

N-[4,5-Diethyl-3-[6-phenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl)-thiophen-2-yl]acetamide (7): A solution of **1** (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 an 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 isopropyl alcohol. IR (KBr, cm^{-1}): 822 ν(1,4-Disubstituted benzene ring), 1535 ν(C—N stretching), 1626 ν(C=C), 1614 ν(C=N), 3058 ν(aromatic C—H stretching); ^{1}H NMR ($CDCl_3$): δ 0.9 (t J = 7.2 Mz, 3H, CH_3), 1.2 (t J = 7.2 Mz, 3H, CH_3), 2.0 (s, 3H, CH_3), 2.5 (q J = 7.2 Mz, 2H, CH_2), 3.7 (q J = 7.2 Mz, 2H, CH_2), 7.2–7.5 (m, 5H, Ar), 9.6 (s, 1H, NH).

N-[4,5-Diethyl-3-[6-(3-nitrophenyl)-5,6-dihydro-[1,2,4]triazolo[3,4-b][1,3,4]-thiadiazol-3-yl)-thiophen-2-yl]acetamide (8): A solution of **1** (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 an 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 ethyl acetate. IR (KBr, cm^{-1}): 1348, 1552 ν(NO_2), 1519 ν(C—N stretching), 1623 ν(C=C), 1627 ν(C=N), 3056 ν(aromatic C—H stretching); ^{1}H NMR ($CDCl_3$): δ 0.9 (t J = 7.2 Mz, 3H, CH_3), 1.2 (t J = 7.2 Mz, 3H, CH_3), 2.0 (s, 3H, CH_3), 2.5 (q J = 7.2 Mz, 2H, CH_2), 3.7 (q J = 7.2 Mz, 2H, CH_2), 4.9 (s, 1H, CH of thiadiazolyl), 7.4–7.9 (m, 4H, Ar), 9.7 (s, 2H, NH).

The physical data of the synthesized compounds are given in Table-1.

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 BACTEC 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
PHYSICAL DATA OF COMPOUNDS (I)–(VIII)

Compds.	m.p. (°C)	m.w.	Yield (%)	% Found (Calcd.)	
				C	N
1	191–97	287	85	46.21 (45.99)	19.46 (19.51)
2	205–09	329	81	43.92 (43.76)	21.45 (21.27)
3	203–09	327	82	47.52 (47.70)	21.52 (21.40)
4	169–73	477	79	62.77 (62.89)	14.78 (14.67)
5	251–55	427	90	53.23 (53.39)	23.14 (22.95)
6	211–13	343	86	42.17 (41.98)	20.63 (20.40)
7	223–27	387	85	55.98 (55.81)	18.26 (18.08)
8	221–26	422	87	48.51 (48.34)	19.74 (19.90)

RESULTS AND DISCUSSION

Compounds **III, VI** and **VIII** displayed maximum activity against *S.aureus* and *E. coli*. Compounds **III** and **VIII** showed moderate activity against *S. aureus* but inactive against *E. coli*. All the other compounds were inactive against both the organisms. Compounds **III, V** and **VII** showed highest activity against *C. albicans*, compounds **IV** and **VII** showed moderate activity while others were inactive against the test organism. Compounds **III, V** and **VII** 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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