*Asian Journal of Chemistry* Vol. 19, No. 4 (2007), 2603-2608

# 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: Part-III

MAHENDRA SHIRADKAR*, B.P. BHASKARA†, RANJIT KAUR‡, RAJENDRA DIGHE, PRASHANT BURANGE and RACHIT SHAH
*AISSMS College of Pharmacy, Kennedy Road, Near RTO, Pune-411 001, India*
*Tel: (91)(20)25204012, (91)(0)9860087611; E-mail: rrshiradkar@rediffmail.com*

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

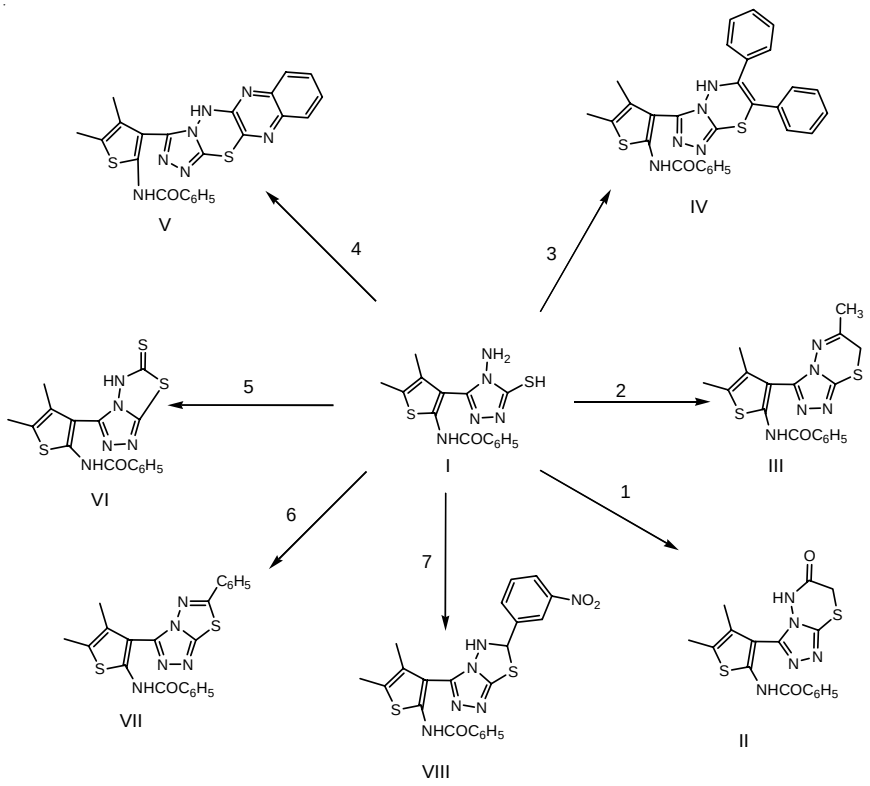
**Key Words: Thiadiazines, Thiadiazoles, Quinoxaline, Microwave synthesis, Bioactivity.**

## 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 variety of heterocyclic compounds[5]. Keeping this in mind, it is worthwhile to develop rapid syntheses of title compounds under solvent free conditions using MWI. Earlier thiadiazoles and thiadiazines were synthesized in 6-7 h[6], while on solid support under microwave reaction was completed within 40-80 s 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

†KLE's College of Pharmacy, Bangalore
‡St. Johns College of Pharmacy, Vijayanagar, Bangalore-40

alc. 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-I**). The structures of **II-VIII** have been established on the basis of their $^1H$ 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-I**

## 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.

### *N*-[3-(4-Amino-5-mercapto-4*H*-[1,2,4]triazol-3-yl)-4,5-dimethyl-thiophene-2-yl]benzamide (I)

The compound was synthesized by reported method[7,8].

### *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]benzamide (II)

A solution of **I** (0.01mol), 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 product was extracted with dry methanol and poured onto crushed ice. The solid thus separated was filtered, washed thoroughly with water and recrystallized from aqueous ethanol.

### *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]benzamide (III)

Solution of **I** (0.01mol) 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 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.

### *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]benzamide (IV)

A solution of **I** (0.01mol), benzoin (0.01 mol) and 2N 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 the product was extracted with acetone. The solid thus separated was washed thoroughly with water and recrystallized from ethanol.

### *N*-[4,5-Dimethyl-3-(4*H*-11-thia-1,2,3a,4,5,10-hexaaza-cyclopenta[*b*]-anthracen-3-yl)thiophen-2-yl]benzamide (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 product was extracted with dry methanol, concentrated and cooled. The solid thus separated was filtered, washed thoroughly with water and recrystallized from ethanol.

**_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]benzamide (VI)**

Carbon disulphide (0.015 mol) was added drop wise with constant stirring to the solution of **I** (0.01mol) 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 s. The mixture was cooled and then product was extracted with dry methanol, which was then poured onto ice and acidified with dilute HCl. The solid thus separated was filtered, washed thoroughly with water and recrystallized from aqueous ethanol.

**_N_-[4,5-Dimethyl-3-[6-phenyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)thiophen-2-yl]benzamide (VII)**

A solution of **I** (0.01mol) 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 onto ice and neutralized with aqueous solution of potassium carbonate. The solid thus separated was filtered, washed thoroughly with water and recrystallized from hexane.

**_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]benzamide (VIII)**

A solution of **I** (0.01mol) 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 product was extracted with dry toluene, concentrated and cooled. The solid thus separated was filtered, washed thoroughly with water and recrystallized from ethanol.

**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 has been conducted using the BACTET 460 radiometric system. Compounds demonstrating at least > 90 % inhibition in the primary screening. These compound have

been retested at lower concentration against *M. tuberculosis* $H_{37}Rv$ to determine the actual minimum inhibitory concentration (MIC) in BACTET 460. The data were compared with the standard drug rifampin at 0.03 µg/mL concentration, which showed 97 % inhibition.

## RESULTS AND DISCUSSION

The physical data of the synthesized compounds (**I-VIII**) are given in Table-1. All the synthesized compounds are characterized by their spectral data.

**Spectral Data:**

**I:** IR (KBr, $cm^{-1}$): 1522 ν(C-N), 1624 ν(C=N), 2648 ν(S-H), 3152, 3347 ν(N-H). $^1$H NMR ($CDCl_3$): δ 2.0 (s, 2H, $NH_2$), δ 2.21 (s, 3H, $CH_3$), δ 2.41 (s, 3H, $CH_3$), δ 3.0 (s, 1H, aromatic sh), δ 7.2-7.8 (m, 5H, ArH), δ 8.0 (s, 1H, NH).

**II:** IR (KBr, $cm^{-1}$): 1542 ν(C-N), 1641 ν(C=N), 1661 ν(C=O). $^1$H NMR ($CDCl_3$): 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 7.2-7.8 (m, 5H, ArH), δ 8.0 (s, 2H, NH).

**III:** IR (KBr, $cm^{-1}$): 847 ν(1,4-Disubstituted benzene ring), 1546 ν(C-N), 1640 ν(C=N), 3051 ν(aromatic C-H). $^1$H NMR ($CDCl_3$): δ 0.9 (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 7.2-7.8 (m, 5H, ArH), δ 8.0 (s, 1H, NH).

**IV:** IR (KBr, $cm^{-1}$): 726, 732 ν(monosubstituted benzene ring), 1623, 1640 ν(C=C), 1678 ν(C=N), 3021 ν(aromatic C-H), 3431 ν(N-H). $^1$H NMR ($CDCl_3$): δ 2.0 (s, 1H, NH in thiadiazole), δ 2.21 (s, 3H, $CH_3$), δ 2.41 (s, 3H, $CH_3$), δ 7.1-7.4 (m, 5H, ArH), δ 7.2-7.8 (m, 5H, ArH), δ 8.0 (s, 1H, NH).

**V:** IR (KBr, $cm^{-1}$): 732 ν(1,4-Disubstituted benzene ring), 1524 ν(C-N), 1632 ν(C=C), 1667 ν(C=N), 3051 ν(aromatic C-H). $^1$H NMR ($CDCl_3$): δ 2.21 (s, 3H, $CH_3$), δ 2.41 (s, 3H, $CH_3$), δ 4.0 (s, 1H, NH group in thiadiazine), δ 7.3-7.8 (m, 9H, ArH), δ 8.0 (s, 1H, NH).

**VI:** IR (KBr, $cm^{-1}$): 1135 ν(CS), 1531 ν(C-N), 1615 ν(C=C), 1662 ν(C=N), 3061 ν(aromatic C-H). $^1$H NMR ($CDCl_3$): δ 2.0 (s, 1H, NH in thiadiazole), δ 2.21 (s, 3H, $CH_3$), δ 2.41 (s, 3H, $CH_3$), δ 7.2-7.8 (m, 5H, ArH), δ 8.0 (s, 1H, NH).

**VII:** IR (KBr, $cm^{-1}$): 838 ν(1,4-Disubstituted benzene ring), 1543 ν(C-N), 1614 ν(C=C), 1631 ν(C=N), 3070 ν(aromatic C-H). $^1$H NMR ($CDCl_3$): δ 2.21 (s, 3H, $CH_3$), δ 2.41 (s, 3H, $CH_3$), δ 7.2-7.9 (m, 10H, ArH), δ 8.0 (s, 1H, NH).

**VIII:** IR (KBr, $cm^{-1}$): 1349, 1550 ν($NO_2$), 1517 ν(C-N), 1615 ν(C=C), 1621 ν(C=N), 3071 ν(aromatic C-H). $^1$H NMR ($CDCl_3$): δ 2.0 (s, 1H, NH in thiadiazole), 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, 10H, ArH), δ 8.2 (s, 1H, NH).

TABLE-1
PHYSICAL DATA OF SYNTHESIZED COMPOUNDS (**I-VIII**)

| Comp. | m.f. | m.p. (ºC) | m.w. | Yield (%) |
|---|---|---|---|---|
| **I** | $C_{15}H_{15}N_4OS_2$ | 261 | 269 | 89 |
| **II** | $C_{16}H_{15}N_5O_2S_2$ | 279 | 311 | 80 |
| **III** | $C_{17}H_{17}N_5OS_2$ | 284 | 309 | 84 |
| **IV** | $C_{29}H_{23}N_5OS_2$ | 297 | 459 | 86 |
| **V** | $C_{23}H_{17}N_7OS_2$ | 303 | 409 | 75 |
| **VI** | $C_{16}H_{13}N_5OS_3$ | 327 | 325 | 71 |
| **VII** | $C_{22}H_{17}N_5OS_2$ | 293 | 369 | 86 |
| **VIII** | $C_{21}H_{18}N_6O_3S_2$ | 354 | 404 | 85 |

Compounds **II**, **VI** and **VIII** displayed maximum activity against *S. aureus* and *E. coli*. Compounds **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. Other compounds *viz.*, **IV** and **VII** were moderately active against *M. tuberculosis* $H_{37}Rv$ strain (> 50 % inhibition).

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(*Received*: 23 January 2006; *Accepted*: 27 December 2006) AJC-5293