



## GREEN SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF SOME TRIAZOLE AND THIADIAZOLE

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### ABSTRACT

A series of fluorine-containing triazoles **3** and thiadiazoles **4** were synthesized from thiosemicarbazides **2**. These reactions were carried out by green synthesis method such as ultrasonication and microwave technique. All products have been characterized by IR, <sup>1</sup>H NMR, and Mass spectral study. All the compounds were screened for their antimicrobial activity using *Bacillus cereus* and *Klebsiella pneumoniae* bacteria.

**Key words:** Ultrasound irradiation, Microwave-assisted synthesis, Triazole, Thiadiazole.

### INTRODUCTION

It is known that introduction of fluorine atom in molecule may lead to significant influence on the biological and physical properties of compounds due to increase of membrane permeability, hydrophobic bonding, stability against metabolic oxidation<sup>1</sup>. Since fluorine containing compound is of promising pharmacological activities which are originated from their unique high thermal stabilities and lipophilicity<sup>2</sup>. Therefore, the development of synthetic methods for fluorine-containing compounds has been an important field in both organofluorine chemistry synthesis. Triazoles and their derivatives have enhanced considerable attention for the past few decades due to their chemotherapeutical value<sup>3</sup>. In particular fluorinated triazoles are of significant interested because they possess antitubercular<sup>4</sup> and anticancer<sup>5</sup> activity. Literature survey indicates that thiosemicarbazides are found to associate with antibacterial<sup>6</sup>, antifungal<sup>7</sup> activities. Compounds containing 1,3,4-thiadiazole nucleus has been reported to be a variety of biological activities like fungitoxic<sup>8</sup>, CNS stimulant<sup>9</sup>, anticholinergic<sup>10</sup> and anticonvulsant<sup>11</sup>.

The advantageous use of ultrasound irradiation technique for activating various reactions are found in the literature such as synthesis of azoles and diazenes<sup>12</sup>, reformatsky reaction<sup>13</sup>, oxidation of substrates like hydroquinones<sup>14</sup>, pinacol coupling<sup>15</sup>, suzuki cross-coupling<sup>16</sup>. Commercial microwave-assisted organic reactions occurs more rapidly, safely and with higher chemicals yields<sup>17-19</sup>, render the microwave method superior to conventional method. The growing number of publication in microwave-assisted synthesis includes virtually all types of synthesis like knoevenagel condensation<sup>20</sup>.

In the present investigation, we synthesize some triazole and thiadiazole derivatives by conventional and ultrasonication as well as microwave irradiation methods and their comparison have been made between three methods. The structures of synthesized compounds were confirmed on the basis of spectral data. The compounds were also tested for their antimicrobial activities by standard methods.

## EXPERIMENTAL

All melting points were determined in open capillary tubes and are uncorrected. The purity of the compounds was determined by thinlayer chromatography on silica gel-G plate. IR spectra were recorded on Perkin-Elmer FTIR spectrophotometer in KBr disc. The  $^1\text{H}$  NMR spectra of some of the compounds of this series were scanned on 400 MHz spectrophotometer respectively using DMSO- $d_6$  as a solvent and TMS as an internal standard. Peak values are shown in  $\delta$  ppm. Mass spectra were obtained by Finnigan mass spectrometer. Experiment under ultrasound irradiation was carried out in ultrasonic cleaner model EN-20U-S manufactured by EnerTech Electronics PVT. LTD, Mumbai, India having maximum power output of 100W and 33 KHz operating frequency. All experiments under microwave irradiation were carried out in unmodified domestic microwave oven model MC-7148MS manufactured by LG Electronics India Pvt. Ltd, Noida, India having maximum power output of 800W and 2450 MHz frequency.

### Synthesis of 1-(2-(6-methyl-2-p-tolyl-1H-imidazo[1,2-a]pyridin-3-yl)-acetyl-4-phenyl thiosemicarbazides (2a-2e)

Acid hydrazide (0.01 mol) (**1**) and aryl isothiocyanates (0.01 mol) were taken in 15 mL of ethanol and the reaction mixture was heated under reflux for 60 min. After completions of the reaction (monitored by TLC) contents were cooled to room temperature, the white product obtained was separated by filtration. The formation of the compounds (**2**) was confirmed by m.p., mixed m.p. and spectral data. Their characterization data is given in the Table 1.

#### Spectral interpretation

**(2a)** IR (KBr)  $\nu/\text{cm}^{-1}$ : 3334 (-NH), 1669 (-C=O), 1582 (-C=N), 1506 (-C=S), 1102 (-C-F);  $^1\text{H-NMR}$  (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 2.36 (s, 3H), 2.56 (s, 3H), 4.03(s, 2H), 6.74 to 7.72 (m, 11H), 9.45 (s, 2H), 10.54 (s, 1H); MS (m/z): 448 (M+1).

**(2b)** IR (KBr)  $\nu/\text{cm}^{-1}$ : 3329 (-NH), 1670 (-C=O), 1589 (-C=N), 1509 (-C=S), 1101 (-C-F);  $^1\text{H-NMR}$  (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 2.35 (s, 3H), 2.57 (s, 3H), 4.01 (s, 2H), 6.78 to 7.74 (m, 10H), 9.46 (s, 2H), 10.56 (s, 1H); MS (m/z): 466 (M+1).

**(2c)** IR (KBr)  $\nu/\text{cm}^{-1}$ : 3330 (-NH), 1668 (-C=O), 1615 (-C=N), 1519 (-C=S), 1110 (-C-F);  $^1\text{H-NMR}$  (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 2.33 (s, 3H), 2.38 (s, 3H), 4.08 (s, 2H), 7.06 to 8.19 (m, 10H), 9.63 (s, 2H), 10.6 (s, 1H); MS (m/z): 566 (M+1).

**(2d)** IR (KBr)  $\nu/\text{cm}^{-1}$ : 3336 (-NH), 1672 (-C=O), 1609 (-C=N), 1409 (-C=S), 1101 (-C-F);  $^1\text{H-NMR}$  (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 2.32 (s, 3H), 2.34(s, 3H), 4.08 (s, 2H), 7.02 to 8.18 (m, 10H), 9.59 (s, 2H), 10.53 (s, 1H); MS (m/z): 566 (M+1).

**(2e)** IR (KBr)  $\nu/\text{cm}^{-1}$ : 3332 (-NH), 1671 (-C=O), 1608 (-C=N), 1408 (-C=S), 1103 (-C-F);  $^1\text{H-NMR}$  (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 2.33 (s, 3H), 2.39 (s, 3H), 4.09 (s, 2H), 7.03 to 8.19 (m, 11H), 9.60 (s, 2H), 10.54 (s, 1H); MS (m/z): 498 (M+1).

### Synthesis of 5-((6-methyl-2-p-toly-1H-imidazo[1,2-a]pyridine-3-yl)methyl-4-phenyl 4H-1,2,4-triazole-3-thiols (3a-3e)

**By conventional method:** Thiosemicarbazide (**2**) (0.005 mol) and 10 mL of 2 N sodium hydroxide solution were taken in 100 mL RBF and the reaction mixture was heated under mild reflux for 90 min. Progress of the reaction was monitored by TLC. The reaction mixture was cooled and poured over ice water and acidified with dilute hydrochloric acid. Product was separated by filtration and crystallized with

DMF/water to afford the title compounds (**3**). The formation of the compounds (**3**) was confirmed by m.p., mixed m.p., and spectral data. Their characterization data is given in Table 1.

**Table 1: Characterization data of synthesized compounds 2, 3 and 4**

Compd.	Fluorinated group	M.P. (°C)	Conventional method		Ultrasound method		Microwave method	
			Time (min.)	Yield (%)	Time (min.)	Yield (%)	Time (min.)	Yield (%)
<b>2a</b>	(3-F)	218	60	78	-	-	-	-
<b>2b</b>	(2,5-F)	208	60	84	-	-	-	-
<b>2c</b>	(3,5-CF <sub>3</sub> )	223	60	72	-	-	-	-
<b>2d</b>	(3,4-CF <sub>3</sub> )	226	60	77	-	-	-	-
<b>2e</b>	(4-CF <sub>3</sub> )	214	60	69	-	-	-	-
<b>3a</b>	(3-F)	257	90	54	27	82	3.2	75
<b>3b</b>	(2,5-F)	268	90	57	30	81	3.0	72
<b>3c</b>	(3,5-CF <sub>3</sub> )	274	90	62	33	86	2.8	78
<b>3d</b>	(3,4-CF <sub>3</sub> )	286	90	55	30	76	2.5	71
<b>3e</b>	(4-CF <sub>3</sub> )	281	90	56	32	83	3.2	79
<b>4a</b>	(3-F)	240	120	63	30	89	3.0	78
<b>4b</b>	(2,5-F)	238	120	61	35	83	3.2	76
<b>4c</b>	(3,5-CF <sub>3</sub> )	255	120	65	32	86	3.4	72
<b>4d</b>	(3,4-CF <sub>3</sub> )	246	120	58	32	81	3.2	75
<b>4e</b>	(4-CF <sub>3</sub> )	251	120	64	35	88	3.5	81

Abbreviations used: MP = melting point, min = minute

**By ultrasonic irradiation:** Thiosemicarbazide (**2**) (0.005 mol) and 10 mL of 2 N sodium hydroxide solution was taken in a beaker (50 mL) and the reaction mixture was subjected to ultrasonic irradiated for 30–35 min at room temperature. Progress of the reaction was monitored by TLC. The reaction mixture was then poured into ice water and acidified with dilute hydrochloric acid. Product was separated by filtration and crystallized with DMF/water to afford the title compounds (**3**). The formation of the compounds (**3**) confirmed by m.p., mixed m.p., and spectral data. Their characterization data is given in Table 1.

**By microwave method:** Thiosemicarbazide (**2**) (0.005 mol) was taken in 50 mL borosilicate glass beaker with 10 mL of 2 N sodium hydroxide solution. The reaction mixture was irradiated inside a microwave oven for 1 min to 2.5 min at an output of 300W power, with short interruption of 15 s. TLC monitored progress of reaction. The reaction mixture was cooled and poured into crushed ice. Product was separated by filtration and crystallized with DMF/water to afford the titled the compounds. Their characterization data is given in Table 1.

### Spectral interpretation

**(3a) IR (KBr)  $\nu/\text{cm}^{-1}$ :** 3425 (-NH), 3031 (=C-H), 1675 (-C=N), 1583 & 1513 (aromatic), 1372 (C=S), 1021 (-C-F);  **$^1\text{H NMR}$  (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm):** 2.34 (s, 3H), 2.56 (s, 3H), 4.07 (s, 2H), 7.29 to 7.89 (m, 11H), 10.72 (s, 1H, -NH); **MS (m/z):** 430 (M+1).

**(3b) IR (KBr)  $\nu/\text{cm}^{-1}$ :** 3411 (-NH), 3032 (=C-H), 1675 (-C=N), 1585 & 1507 (aromatic); 1372 (C=S), 1024 (-C-F);  **$^1\text{H NMR}$  (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm):** 2.37 (s, 3H), 2.58 (s, 3H), 4.09 (s, 2H), 7.13 to 7.91 (m, 10H), 10.67 (s, 1H, -NH); **MS (m/z):** 448 (M+1).

**(3c) IR (KBr)  $\nu/\text{cm}^{-1}$ :** 3382 (-NH), 2974 (=C-H), 1677 (-C=N), 1611 & 1515 (aromatic); 1365 (C=S), 1112 (-C-F);  **$^1\text{H NMR}$  (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm):** 2.38 (s, 3H), 2.56 (s, 3H), 4.16 (s, 2H), 7.10 to 8.12 (m, 10H), 10.78 (s, 1H, -NH); **MS (m/z):** 548 (M+1).

**(3d) IR (KBr)  $\nu/\text{cm}^{-1}$ :** 3419 (-NH), 3034 (=C-H), 1647 (-C=N), 1578 & 1505 (aromatic), 1394 (C=S), 1092 (-C-F);  **$^1\text{H NMR}$  (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm):** 2.36 (s, 3H), 2.52 (s, 3H), 4.1 (s, 2H), 7.12 to 7.95 (m, 10H), 10.23 (s, 1H, -NH); **MS (m/z):** 548 (M+1).

**(3e) IR (KBr)  $\nu/\text{cm}^{-1}$ :** 3432 (-NH), 3031 (=C-H), 1656 (-C=N), 1581 & 1512 (aromatic), 1392 (C=S), 1094 (-C-F);  **$^1\text{H NMR}$  (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm):** 2.33 (s, 3H), 2.49 (s, 3H), 4.22 (s, 2H), 7.14 to 7.98 (m, 11H), 10.3 (s, 1H, -NH); **MS (m/z):** 480 (M+1).

### Synthesis of 5-(6-methyl-2-p-tolyl-1H-imidazo[1,2-a]pyridine-3-yl)methyl-N-phenyl-1,3,4-thiadiazol-2-amine (4a-4e)

**By conventional method:** Thiosemicarbazide (**2**) (0.005 mol) and concentrated sulphuric acid (5 mL) were taken in a beaker (50 mL) and the reaction mixture was kept at room temperature for 2 h. The reaction mixture was then poured over ice water. Product was separated by filtration and crystallized with DMF to afford the title compounds **4**. The formation of compounds **4** was confirmed by m.p., mixed m.p., and spectral data. Their characterization data is given in Table 1.

**By ultrasonic irradiation:** Thiosemicarbazide (**2**) (0.005 mol) and concentrated sulphuric acid (5 mL) were taken in beaker (50 mL) and the reaction mixture was subjected to ultrasonic irradiated for 30–35 min at room temperature. Progress of reaction was monitored by TLC. The reaction mixture was then poured over ice water. Product was separated by filtration and crystallized with DMF to afford the title compounds (**4**). The formation of the compounds (**4**) was confirmed by m.p., mixed m.p., and spectral data. Their characterization data is given in Table 1.

**By microwave method:** Thiosemicarbazide (**2**) (0.005 mol) was taken in 50 mL borosilicate glass beaker with 15 mL concentrated sulphuric acid. Reaction mixture was irradiated inside a microwave oven for 1–2.5 min at an output of 300W power, with short interruption of 15 s. Progress of the reaction was monitored by TLC. The reaction mixture was cooled and poured into crushed ice. Product was separated by filtration and crystallized with DMF/water to afford the titled the compounds. Their characterization data is given in Table 1.

**(4a) IR (KBr)  $\nu/\text{cm}^{-1}$ :** 3466 (-NH), 2911 (=C-H), 1618 (-C=N), 1545 & 1525 (aromatic), 1031 (-C-F), 745 (-C-S);  **$^1\text{H-NMR}$  (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm):** 2.34 (s, 3H), 2.43 (s, 3H), 4.74 (s, 2H), 6.95 to 8.52 (m, 11H), 9.98 (s, 1H, -NH); **MS (m/z):** 430 (M+1).

**(4b) IR (KBr)  $\nu/\text{cm}^{-1}$ :** 3372 (-NH), 2921 (=C-H), 1622 (-C=N), 1551 & 1524 (aromatic), 1031 (-C-F), 750(-C-S);  **$^1\text{H-NMR}$  (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm):** 2.31 (s, 3H), 2.42 (s, 3H), 4.72 (s, 2H), 7.12 to 8.53 (m, 10H), 9.91 (s, 1H, -NH); **MS (m/z):** 448 (M+1).

**(4c) IR (KBr)  $\nu/\text{cm}^{-1}$ :** 3413 (-NH), 3052 (=C-H), 1621(-C=N), 1571 & 1518 (aromatic), 1041 (-C-F), 772 (-C-S);  **$^1\text{H-NMR}$  (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm):** 2.34 (s, 3H), 2.44 (s, 3H), 4.68 (s, 2H), 7.02 to 8.43 (m, 10H), 9.64 (s, 1H, -NH); **MS (m/z):** 548 (M+1).

**(4d) IR (KBr)  $\nu/\text{cm}^{-1}$ :** 3422 (-NH), 2951 (=C-H), 1655 (-C=N), 1564 & 1509 (aromatic), 1012 (-C-F), 751 (-C-S);  **$^1\text{H-NMR}$  (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm):** 2.39 (s, 3H), 2.48 (s, 3H), 4.75 (s, 2H), 6.95 to 8.13 (m, 10H), 9.94 (s, 1H, -NH); **MS (m/z):** 548 (M+1).

**(4e) IR (KBr)  $\nu/\text{cm}^{-1}$ :** 3424 (-NH), 2955 (=C-H), 1658 (-C=N), 1541 & 1519 (aromatic), 1018(-C-F), 753(-C-S);  **$^1\text{H-NMR}$  (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm):** 2.41 (s, 3H), 2.56 (s, 3H), 4.68 (s, 2H), 7.08 to 8.29 (m, 11H), 10.05 (s, 1H, -NH); **MS (m/z):** 480 (M+1).

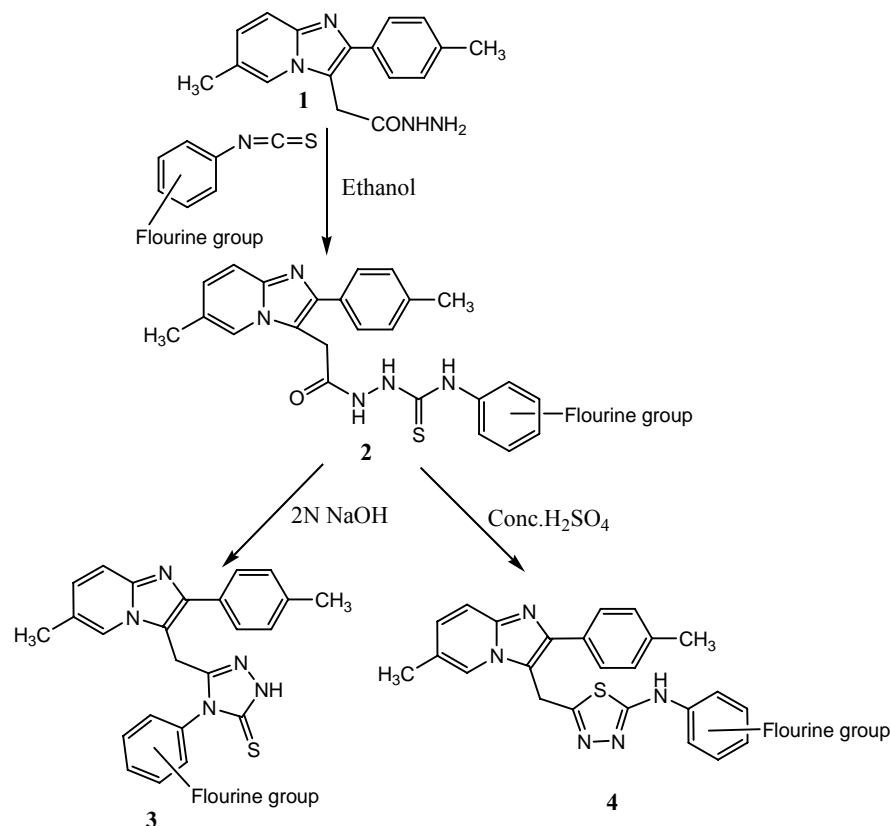
### Antibacterial activity

Antibacterial activities were determined by filter paper disc method against *Bacillus cereus* and *Klebsiella pneumoniae* bacteria. The antibiotic tetracycline (40  $\mu\text{gms}$ ) was used as control. The samples (40  $\mu\text{gms}$ ) were dissolved in dimethyl formamide (DMF) and used for the antibacterial activity. The bacterial cultures of known inoculum size (0.2 CFU/mL) of test microorganism were spread on nutrient agar plates. The Whatman filter paper discs of 5 mm were placed on the plate and the sample of appropriate concentration was added to the filter disc. The plates were further incubated for 18-24 hrs at 37 °C. The investigation of antibacterial screening data revealed that all the tested compounds 2, 3 and 4 showed moderate to excellent antibacterial activities against *Bacillus cereus* and *Klebsiella pneumoniae*.

The **2a-c**, **3a-c** and **4a-c** are active against *Bacillus cereus* and *Klebsiella pneumoniae*. Among these compounds, **4e** and **3a** exhibited less active than the Gatifloxacin against *Bacillus cereus* and *Klebsiella pneumoniae* bacterial strain respectively. The most active compounds **2a**, **3b** and **4a** are passive for both gram-ve *Bacillus cereus* and gram+ve *Klebsiella pneumoniae*. **2b**, **2c**, **3c** and **4b** compound also shows excellent activity against both bacterial strains. Their Antibacterial activity data is given in Table 2.

**Table 2: Antibacterial activity of synthesized compounds 2, 3 and 4**

Compound No.	Fluorinated group	Zone of inhibition	
		<i>Bacillus cereus</i> (gram -ve)	<i>Klebsiella pneumoniae</i> (gram +ve)
<b>2a</b>	(3-F)	14.8	13.7
<b>2b</b>	(2,5-F)	14.1	13.1
<b>2c</b>	(3,5-CF <sub>3</sub> )	13.2	11.3
<b>2d</b>	(3,4-CF <sub>3</sub> )	8.7	7.1
<b>2e</b>	(4-CF <sub>3</sub> )	8.2	6.9
<b>3a</b>	(3-F)	7.8	7.1
<b>3b</b>	(2,5-F)	13.9	13.5
<b>3c</b>	(3,5-CF <sub>3</sub> )	12.7	12.1
<b>3d</b>	(3,4-CF <sub>3</sub> )	8.2	7.9
<b>3e</b>	(4-CF <sub>3</sub> )	7.9	7.3
<b>4a</b>	(3-F)	12.4	6.9
<b>4b</b>	(2,5-F)	7.2	11.7
<b>4c</b>	(3,5-CF <sub>3</sub> )	7.8	6.2
<b>4d</b>	(3,4-CF <sub>3</sub> )	7.7	6.8
<b>4e</b>	(4-CF <sub>3</sub> )	7.1	6.1
<b>Gatifloxacin</b>	-	18.3	15.4



**Scheme 1: Synthesis of thiosemicarbazides 2, triazoles 3, thiadiazoles 4.**

## RESULTS AND DISCUSSION

This study reports the successful synthesis of the fluorinated azoles using green technique with 72–88% yield. These green techniques required less time for the completion of the reaction as compared to conventional method. The newly synthesized heterocycles exhibited moderate to promising antimicrobial activity against moderate range of bacterial stains. These results make them interesting lead molecules for further synthetic and biological evaluation. It can be concluded that ultrasonicated synthesis is very clean, while microwave method required shorter time for completion and azoles certainly hold great promise towards the pursuit of discovering novel classes of antimicrobial agents.

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## REFERENCES

1. L. Kuznetsova, M. I. Ungureanu and A. Pepe, *J. Fluorine Chem.*, **125**, 415 (2004).
2. T. Haga, K. Fujikawa, T. Koyanag, T. Nakajima and K. Hayashi, *Heterocycles*, **22**, 117 (1984).
3. Y. S. Sanghvi, B. K. Bhattacharya, G. D. Kini, S. S. Matsumoto, S. B. Larson, W. B. Jolley, R. K. Robins and G. R. Revankar, *J. Med. Chem.*, **33**, 336 (1990).
4. C. H. Gill, G. Jadhav, M. Shaikh, R. Kale, A. Ghawalkar, D. Nagargoje and M. S. Shiradkar, *Bioorg. Med. Chem. Lett.*, **18**, 6244 (2008).

5. R. Lin, P. J. Connolly, S. Huang, S. K. Wetter, Y. Lu, W. V. Murray, S. L. Emanuel, R. H. Gruninger, A. R. Fuentes, C. A. Rugg, S. A. Middleton and L. K. Jolliffe, *J. Med. Chem.*, **48**, 4208 (2005).
6. R. P. Bhamaria, R. A. Bellare and C. V. Deliwala, *Indian J. Exp. Biol.*, **6**, 62 (1968).
7. G. J. M. Vander Kerk, *Proc. Br. Insectic Fungic Conf. IV*, **2**, 562 (1967).
8. S. Giri and H. Singh, *J. Indian Chem. Soc.*, **49**, 175 (1972).
9. V. K. Pandey, H. C. Lohani and A. K. Agarwal, *Indian J. Pharm. Sci.*, **44**, 155 (1982).
10. Z. Muhi-eldeen, F. Al-Jawed, S. Eldin, S. Abdul-Kadir and M. Carabet, *Eur. J. Med. Chem.*, **17**, 479 (1982).
11. C. B. Chapleo, M. Myers and P. L. Meyers, *J. Med. Chem.*, **29**, 2273 (1986).
12. M. Kidwai, R. Venkataramanan and B. Dave, *J. Heterocycl. Chem.*, **39**, 1045 (2002).
13. N. A. Ross and R. A. Bartsch, *J. Heterocycl. Chem.*, **38**, 1255 (2001).
14. V. Singh, V. Sapehiya and G. L. Kad, *Synthesis*, **2**, 198 (2003).
15. M. Robin, V. Pique, R. Faure and J. Glay, *J. Heterocycl. Chem.*, **39**, 1083 (2002).
16. R. Rajagopal, D. V. Jarikote and K. V. Srinivasan, *Chem. Commun.*, **61**, 616 (2002).
17. T. V. Maruthikumar, V. P. Reddy and P. H. Rao, *Indian J. Chem. Sect. B*, **44**, 1931 (2005).
18. T. Yakaiah, G. V. Reddy, B. P. V. Lingaiah, P. S. Rao and B. Narsaiah, *Indian J. Chem. Sect. B*, **44**, 1301 (2005).
19. V. O. Chornous, M. K. Bratenko and M. V. Vovk, *Synth. Commun.*, **34**, 79 (2004).
20. G. Wang and B. Cheng, *ARKIVOC*, **IX**, 4 (2004).