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### A Facile Synthesis of Novel 9-Methyl[1, 2, 3]Selenadiazoles[4, 5-b]Quinoline and 9-Methyl[1, 2, 3]Thiadiazole[4, 5-b]Quinoline as a New Class of Antimicrobial Agents

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Published online: 01 Feb 2007.

To cite this article: Halehatty S. Bhojya Naik, Machenahalli S. Ramesha, Boovanahalli V. Swetha & Thopenahalli R. Roopa (2006) A Facile Synthesis of Novel 9-Methyl[1, 2, 3]Selenadiazoles[4, 5-b]Quinoline and 9-Methyl[1, 2, 3]Thiadiazole[4, 5-b]Quinoline as a New Class of Antimicrobial Agents, *Phosphorus, Sulfur, and Silicon and the Related Elements*, 181:3, 533-541, DOI: [10.1080/10426500500267590](https://doi.org/10.1080/10426500500267590)

To link to this article: <http://dx.doi.org/10.1080/10426500500267590>

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## A Facile Synthesis of Novel 9-Methyl[1,2,3]Selenadiazoles[4,5-*b*]Quinoline and 9-Methyl[1,2,3]Thiadiazole[4,5-*b*]Quinoline as a New Class of Antimicrobial Agents

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*2-chloro-4-methyl quinoline 2 on condensation with semicarbazide hydrochloride gave its semicarbazone. This on reaction with SeO<sub>2</sub> and SOCl<sub>2</sub> yielded a new class of novel selenadiazoles 4 and thiadiazoles 5, respectively. The structure of all the compounds were elucidated on the basis of elemental analysis, IR, <sup>1</sup>H NMR, and the mass spectral data. Some derivatives of 9-methyl[1,2,3]selenadiazole[4,5-*b*] quinoline and 9-methyl[1,2,3]thiadiazole [4,5-*b*]quinoline have been screened for antimicrobial activities.*

**Keywords** 2-Chloro-4-methyl quinoline; microbial activities; semicarbazones; selenadiazoles; thiadiazoles

## INTRODUCTION

The quinoline ring has been the subject of continued interest as several derivatives of this exhibited a wide range of biological activities including antitumour,<sup>1</sup> hypoglycemic properties,<sup>2</sup> antihistamine,<sup>3</sup> and anticarcinogenic,<sup>4</sup> activities etc. They have been used to synthesize various fused heterocyclic ring systems and they show a wide range of pharmacological activities.<sup>5–8</sup> Further, it is well known that a number of heterocyclic compounds containing N and S exhibit a wide variety

Received April 14, 2005; accepted May 16, 2005.

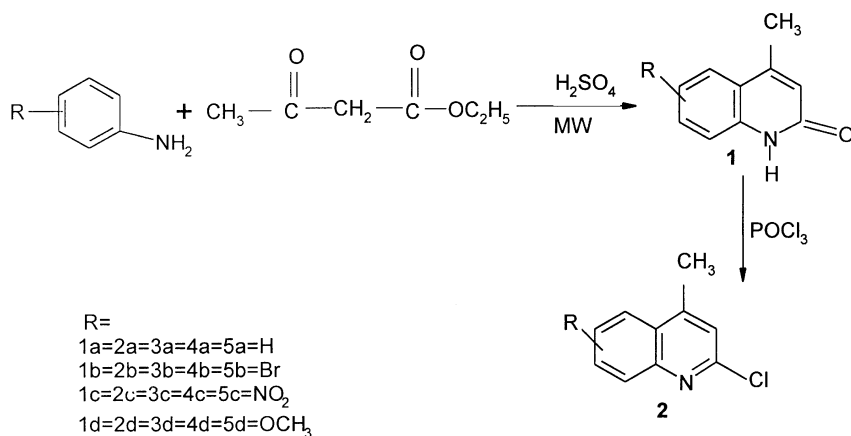
One of the authors, M. S. Ramesha, thanks Kuvempu University for providing a research fellowship.

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of biological activities.<sup>9–12</sup> Even though sulphur and selenium are considered to be isosteric as defined by Langmiur<sup>13</sup> and Erlenmeyer,<sup>14</sup> the reports about selenium-containing heterocyclics are relatively few.<sup>5–17</sup> However, the medicinal application of isosterism has been reviewed by Klayman and Gunther.<sup>18</sup> Recently, the synthesis of some fused selenadiazoles and thiodiazoles has been reported.<sup>19–25</sup> Therefore, in continuation of our work on the synthesis of quinoline derivatives<sup>23,24</sup> and in view of the biological importance of selenium and sulphur, here we wish to report a facile synthesis of quinoline derivatives of [1,2,3]selenadiazoles and [1,2,3]thiadiazoles.

## RESULTS AND DISCUSSION

2-hydroxy-4-methyl quinolines **1a–d** was prepared by using microwave irradiation.<sup>24</sup> It reacts with phosphorus oxychloride and affords the corresponding 2-chloro-4-methyl quinoline **2a–d** (Scheme 1). The spectral data of the compounds **1a–d** and **2a–d** are in agreement with the theoretical data. The IR (cm<sup>-1</sup>) spectrum of all the compounds exhibited absorption bands in the region of 1432–1440, 1320–1325, and 2010–2015 for (N=C), (C=C), and (C–H), respectively.



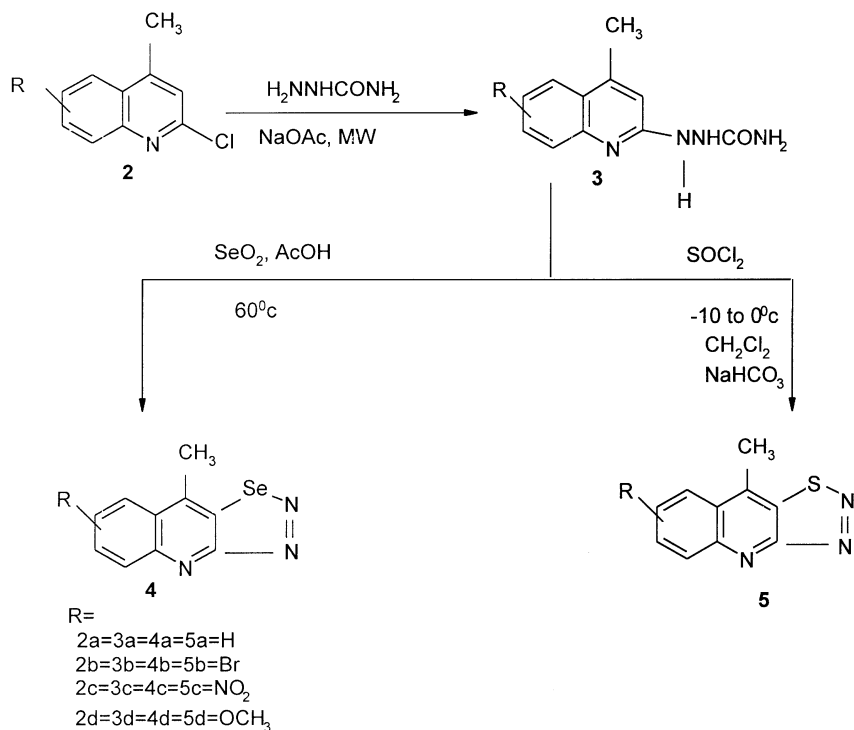
**SCHEME 1**

The microwave irradiation of compound **2a–d** with semicarbazide hydrochloride in sodium ethoxide leads to the formation of substituted semicarbazone **3a–d**. The absence of chlorine was confirmed by Beilstein's test. The IR (cm<sup>-1</sup>) spectrum of **3a** shows the bands for (C=N) at 1432, (NHCO, CONH<sub>2</sub>) at 34460, 3246, (N=N) at 1585, and (CONH<sub>2</sub>) at 1721. Some important spectral data are presented in Table I.

**TABLE I** Some Important Spectral Data of Synthesized Compounds

| Compound no. | IR (cm <sup>-1</sup> )   | <sup>1</sup> H NMR (δ ppm)                                    |
|--------------|--|---|
| <b>2a-d</b>  | 1432–1440 (C=N, 3449 (N–H)   | 8.4 (s, 9H), 2.31 (3H, CH <sub>3</sub> )                      |
| <b>3a</b>    | 1432 (C=N), 3446–3246 (NHCO–CONH <sub>2</sub> ), 1585 (N=N), 1721 (CONH <sub>2</sub> ) | 2.31(s, 3H), 9.2 (s, 9H), (N=CH), 2.31 (3H, CH <sub>3</sub> ) |
| <b>4a</b>    | 685 (C–Se–N), 1487 (N=N), 1430 (C=N)   | 7.4 (s, 7H), 2.5 (s, 3H, CH <sub>3</sub> )                    |
| <b>5a</b>    | 700 (C–S–N), 1485 (N=N), 1434 (C=N)  | 7.2 (m, 7H), 2.6 (s, 3H, CH <sub>3</sub> )                    |

The formation of 9-methyl[1,2,3] selenadiazole[4,5-b] quinoline **4a-d** was assumed to proceed via the addition of selenium dioxide, followed by the intermolecular cyclization (Scheme 2). Elemental analyses and spectral data confirmed the structures of **4a-d**. The IR (cm<sup>-1</sup>) spectra

**SCHEME 2**

of the molecule **4a** shows absorption bands at 685, 1487, and 1430, which are assigned for (C–Se–N), (N=N), and (C=N), respectively. The <sup>1</sup>HNMR spectra of the molecule **4a** showed signals at  $\delta = 7.4$  (s, 7H) and  $\delta = 2.5$  (s, 3H, CH<sub>3</sub>). The mass spectrum of the compound **4a** was found to be 248 (M<sup>+</sup>).

On the other hand, **3a–d** on treatment with thionylchloride at  $-10-0^{\circ}\text{C}$  yielded 9-methyl[1,2,3]thiadiazole[4,5-b]quinoline **5a–d** (Scheme 2). The analytical and spectral data were consistent with the assigned structure of the compounds **5a–d**. The IR (cm<sup>-1</sup>) spectra of **5b** revealed absorption bands at 700, 1485, and 1434 for (C–S–N), (N=N), and (C=N), respectively. The <sup>1</sup>HNMR spectrum in DMSO-d<sub>6</sub> showed signals at  $\delta = 7.9$  (m, 7H) and  $\delta = 2.6$  (s, 3H, CH<sub>3</sub>). The mass spectra of the compound **5a** were found to be 201 (M<sup>+</sup>).

## EXPERIMENTAL

Melting points were determined in open capillaries and were uncorrected. The IR spectra were measured in KBr pellets on Shimadzu FT-IR 200-spectrophotometer. <sup>1</sup>H NMR spectra were recorded in DMSO-d<sub>6</sub> on 200 MHz on a Perkin Elmer instrument and chemical shifts are expressed in  $\delta$  units using TMS as an internal reference. Mass spectra were recorded on a Jeol JMS-D 300 instrument at 70 eV. Elemental analyses were carried out at the Department of Chemistry, University of Mysore, Mysore, India. The characteristic data of synthesised compounds are given in Table II some and important spectral data are presented in Table I

### Synthesis of 2-Hydroxyl-4-Methyl Quinoline 1(a–d)

A mixture of distilled aniline (Ig, 0.01 mol) and ethylacetoacetate (1.3 g, 0.013 mol) was irradiated in microwave oven for 4 min, and 2 to 4 drops of H<sub>2</sub>SO<sub>4</sub> were added and again irradiated for 5 min. The solid product obtained was filtered and recrystallized from ethanol to give **1a**. The same procedure was adopted for the synthesis of **1b–d**.

### General Procedure for the Synthesis of 2-Chloro-4-Methyl Quinoline 2(a–d)

A mixture of **1a–d** (1.6 g, 0.01 mol) and POCl<sub>3</sub> was mixed and refluxed separately for 10 h on a water bath. The product that produced **2a–d** was isolated, filtered, and recrystallized from a suitable solvent (Tables I and II).

TABLE II Analytical Data of the Synthesized Compounds

| Compound no. | Yield<br>(%)<br>colour | M.P<br>[°C] | Molecular<br>formula<br>[mol. wt.]                                      | Elemental analysis<br>calcd./found [%] |              |                |
|--------------|------------------------|-------------|---|--|--------------|----------------|
|              |                        |             |   | C%                                     | H%           | N%             |
| <b>2a</b>    | 82                     | 220         | C <sub>10</sub> H <sub>8</sub> NCl<br>177.5                             | 67.58<br>67.48                         | 4.51<br>4.49 | 7.79<br>7.75   |
| <b>3a</b>    | 66<br>Pale yellow      | 208         | C <sub>11</sub> H <sub>12</sub> N <sub>4</sub> O<br>215                 | 61.37<br>61.30                         | 5.48<br>5.46 | 26.04<br>26.00 |
| <b>4a</b>    | 88<br>Brown            | 177         | C <sub>10</sub> H <sub>7</sub> N <sub>3</sub> Se<br>310                 | 68.70<br>68.54                         | 2.15<br>2.08 | 13.36<br>13.01 |
| <b>4b</b>    | 86<br>Deep brown       | 168         | C <sub>10</sub> H <sub>6</sub> N <sub>3</sub> SeBr<br>388.9             | 30.65<br>30.58                         | 1.50<br>1.41 | 10.67<br>10.28 |
| <b>4c</b>    | 82<br>Yellow           | 170         | C <sub>10</sub> H <sub>4</sub> NO <sub>2</sub> Se<br>277.9              | 43.00<br>42.93                         | 2.01<br>2.00 | 20.10<br>20.00 |
| <b>4d</b>    | 85<br>Pale yellow      | 173         | C <sub>11</sub> H <sub>9</sub> N <sub>3</sub> OSe<br>278.9              | 47.32<br>46.91                         | 3.23<br>3.20 | 15.06<br>15.05 |
| <b>5a</b>    | 73<br>Dark brown       | 210         | C <sub>10</sub> H <sub>7</sub> N <sub>3</sub> S<br>204.5                | 58.44<br>58.40                         | 3.03<br>3.00 | 20.5<br>20.00  |
| <b>5b</b>    | 70<br>Yellow           | 195         | C <sub>10</sub> H <sub>6</sub> N <sub>3</sub> SBr<br>283.4              | 42.28<br>42.01                         | 2.01<br>1.94 | 14.68<br>14.41 |
| <b>5c</b>    | 76<br>Yellow           | 198         | C <sub>10</sub> H <sub>6</sub> N <sub>4</sub> SO <sub>2</sub><br>246.06 | 48.66<br>48.49                         | 2.36<br>2.33 | 22.68<br>22.42 |
| <b>5d</b>    | 74<br>Black            | 203         | C <sub>11</sub> H <sub>10</sub> N <sub>3</sub> OS<br>235.5              | 56.05<br>55.02                         | 4.25<br>4.23 | 17.83<br>16.92 |

### General Synthesis of 2-Chloro-4-Methyl Quinoline 3(a–d)

A mixture of **2a–d** (0.18 g, 0.001 mol) and semicarbazide hydrochloride (0.11 g, 0.001 mol) in sodium ethoxide was irradiated in microwave oven for about 30 min. The obtained solid product was isolated, filtered, and recrystallized from a suitable solvent to give **3a**. The same procedure was used for the preparation of **3b–d**. The elemental analysis and spectral data are presented in Tables I and II.

### Synthesis of 9-Methyl[1,2,3]Selenadiazoles (4a)

The compound **3a** (1.075 g, 0.005 mol) was dissolved in 15–20 mL of acetic acid and kept in an oil bath at 60°C with constant mechanical stirring. Then SeO<sub>2</sub> (0.05 g, 0.005 mol) was added portionwise with stirring, maintaining the temperature 60°C until the entire SeO<sub>2</sub> got transferred. Then the reaction mixture was stirred for about 1 h, maintaining the same temperature. After, the mixture was cooled to f. t. and poured on crushed ice. The precipitate **4a** thus obtained was filtered, dried, and recrystallized (Tables I and II).

### Synthesis of 11-Bromo-9-Methyl[1,2,3]Selenadiazoles (4b)

A solution of **3b** (1.470 g, 0.005 mol) and selenium dioxide (0.5 g, 0.005 mol) was added portionwise to an acetic acid medium with constant stirring, maintaining the temperature at 60°C. It was refluxed for 10 h until a clear solution was obtained. The completion of the reaction was monitored by TLC. The solution mixture was cooled and poured into crushed ice with stirring. The bromo compound **4b** thus formed was collected and crystallized from chloroform.

### Synthesis of 11-Nitro 4-Methyl [1,2,3]Selenadiazoles Quinoline (4c)

A mixture of compound **3c** (1.470 g, 0.005 mol) and selenium dioxide (0.5 g, 0.005 mol) was added portionwise to an acetic acid medium with stirring and refluxed for 9 h. Again the reaction mixture was placed on a water bath for 5 min, cooled, and poured into crashed ice with stirring. **4c** was collected and recrystallized from ethanol.

### Synthesis of 11-Methoxy 9-Methyl [1,2,3]Selenadiazoles Quinoline (4d)

Compound **3d** (1.225 g, 0.005 mol) and selenium dioxide (0.5 g, 0.005 mol) were added to a round-bottom flask in an acetic acid medium. The reaction mixture was refluxed for 7 h, and the mixture was kept on a water bath for 5 min and poured into crushed ice. The completion of the reaction was confirmed by TLC. The resulting solid **4d** was collected, washed, and recrystallized from ethanol.

### Synthesis of 9-Methyl[1,2,3]Thiadiazole Quinoline (5a)

Redistilled thionylchloride (4 mL, 0.05 mol) was added to a clean dry 250-mL round-bottom flask kept in a salt ice bath and the temperature was allowed to drop to -10°C. The compound **3a** (1.075 g 0.005 mol) was added to it with constant magnetic stirring, maintaining the temperature below 0°C. After the complete addition, the temperature was allowed to rise to r.t. and 30 mL of dichloromethane was added. The mixture was stirred for a further 2 h. Excess thionylchloride was removed using a saturated NaHCO<sub>3</sub> solution. The product **5a** was isolated using an extractive isolation technique, then recrystallized (Tables as I and II).



### Synthesis of 11-Bromo-9-Methyl[1,2,3]Thiadiazole Quinoline (5b)

The compound **5b** was synthesized by using the same procedure as described for **5a**. The isolated compound **5b** was washed and recrystallized in ethanol.

### Synthesis of 11-Nitro-9-Methyl[1,2,3]Thiadiazole Quinoline (5c)

The compound **5c** was synthesized by varying the reaction temperature using the procedure used for the preparation of **5a**. The compound **5c** was isolated, washed, and recrystallized in ethanol.

### Synthesis of 11-Methoxy-9-Methyl[1,2,3]Thiadiazole Quinoline (5d)

The compound **5d** was synthesized by using the same procedure as described for **5a**. The solid compound **5d** was isolated by using extractive isolation technique and was washed and recrystallized in ethanol.

## BIOLOGICAL SCREENING

The antimicrobial activity of the newly synthesized compounds was screened with *in vitro* for Euro strains of bacteria *Staphylococcus aureus* and *Escherichia coli* using the cup plate method. The antimicrobial activity was carried out against 24-hour-old cultures of two bacteria. The compounds were tested at a concentration (0.001 mol/mL) in dimethylformamide against both organisms. Ciprofloxacin (0.001 mol/mL) was used as a standard for comparison of antimicrobial activities. The plates were inoculated with a 24-hour-old culture of bacteria. The zone of inhibition was compared with the standard drug after 24 hours of inoculation at 37°C for antimicrobial activity. The results are presented in Table III. The results reveal that the compound **4b** shows higher activity with respect to *Staphylococcus aureus* and *Escherichia coli* compared to other compounds. This may be due to the compound having a bromo group besides a selenium atom in its structure. Compounds **5b** and **5c** exhibited the same activities with respect to *Escherichia coli* and *Staphylococcus aureus*. Most of the synthesised compounds showed moderate microbial activity against the tested organisms.

**TABLE III Antibacterial Activity of the Synthesized Compounds. +: (0.2–0.5 cm) less active; ++: (0.6–1.4 cm) moderately active; +++: (1.5–3 cm) highly active. Standard: Ciprofloxacin (25  $\mu\text{g mL}^{-1}$ )**

| Compound no. | <i>Staphylococcus aureus</i> | <i>Escherichia coli</i> |
|--------------|------------------------------|-------------------------|
| <b>4a</b>    | +                            | ++                      |
| <b>4b</b>    | +++                          | +++                     |
| <b>4c</b>    | ++                           | ++                      |
| <b>4d</b>    | ++                           | ++                      |
| <b>5a</b>    | ++                           | ++                      |
| <b>5b</b>    | ++                           | +++                     |
| <b>5c</b>    | +++                          | +                       |
| <b>5d</b>    | ++                           | +                       |

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