Synthesis and antimicrobial activity of novel ethyl-5-(ethoxycarbonyl)-4-methylthiazol-2-yl-carbamate compounds†

B H M Mruthyunjayswamy* & S M Basavarajaiah
Department of Studies and Research in Chemistry, Gulbarga University, Gulbarga 585 106, India
E-mail: bhmmswamy53@rediffmail.com

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Ethyl-2-amino-4-methylthiazol-5-carboxylate 1 on treatment with ethylchloroformate followed by reaction with hydrazine hydrate gave ethyl-5-(ethoxycarbonyl)-4-methylthiazol-2-yl-carbamate 2 and 4-methylthiazol-2-yl-semicarbazido-5-carboxyhydrazide 3 respectively. Compound 3 on further reaction with ethyl acetooacetate, ethylecyanoacetate, acetylacetone, carbondisulphide-potassium hydroxide and different substituted aromatic acids yielded the corresponding 4-methyl-2-yl-amino-(1-N-carboxyl-3-methyl-4,5-dihydro-1H-pyrazol-5-one)thiazole 4, 4-methyl-2-yl-amino-(1-N-carboxyl-3-methyl-4,5-dihydro-1H-pyrazol-5-one)5-(1-N-carboxyl-3-amino-4,5-dihydro-1H-pyrazol-5-one)-thiazole 5, 4-methyl-2-yl-amino-(1-N-carboxyl-3,5-dimethyl-1H-pyrazol)-5-(1-N-carboxyl-3,5-dimethyl-1H-pyrazol)-thiazole 6, 4-methyl-2-yl-amino-(1,3,4-oxadiazo-5-thione)-5yl-(1,3,4-oxadiazo-5-thione-2yl)-thiazole 7 and 4-methyl-2-yl-amino-(5-substituted-1,3,4-oxadiazo-2yl)-5-(5-substituted-1,3,4-oxadiazo-2yl)-thiazole 8a-d, respectively. All the synthesized compounds have been screened for their antimicrobial activity.

Keywords: Thiazole, pyrrole, oxadiazole-2-thione, substituted oxadiazole, antimicrobial activity

Heterocycles containing thiazole rings are associated with a wide range of biological properties such as antiprototool, anticonvulsant, depressant effect on the central nervous system, anti-diabetics inhibitors of dihydrofolate, inflammation inhibitors, antitumor, herbicidal, antimiicrobial, antiviral and antianaphylactic activities due to toxophoric -N=C-S- group. Pyrazoles represent one of the most active classes of compounds possessing a wide spectrum of biological activities, such as anti-inflammatory, antipyretic, analgesic and smooth muscle relaxant activities. Many pyrazole derivatives are associated with antifungal, antidiabetic and bactericidal activities. Large number of oxadiazole derivatives reported in the literature possesses a broad spectrum of pharmacological activities such as antimicrobial, antimalarial, anticonvulsant, anticancer, cyclooxygenase, anti-HIV property and anti-inflammatory activities. Substituted 1,3,4-oxadiazole-2-thiones and their derivatives possess CNS depressant, pesticidal and antitubercular activities. In view of all these findings and in continuation of the research work on 4-substituted thiazole-2-semicarbazides and their derivatives herein is reported the synthesis and antimicrobial activity of some 2 and 5-substituted 4-methylthiazolyl carbamates compounds (Scheme 1).

Results and Discussion

The synthesized compounds were evaluated for their antibacterial as well as antifungal activities, in comparison with the standards, namely, Gentamycin and Nystatin, respectively. In the overall bioassay (Table I) in general, the compounds 4, 7, 8c and 8d exhibited good antimicrobial potency against both types of test species.

Experimental Section

The starting material, ethyl 2-amino-4-methylthiazol-5-carboxylate 1 was prepared in the laboratory. Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr discs (νmax in cm⁻¹) on Perkin-Elmer FT-IR (Spectrum ONE) spectrometer and 1H NMR spectra on a Bruker AMX (400 MHz) spectrometer using DMSO-d6 as solvent unless otherwise stated.
Scheme I

Table I — Antimicrobial activity of the synthesized compounds

<table>
<thead>
<tr>
<th>Compd</th>
<th>Conc (μg/0.1mL) in DMF</th>
<th>Zone of inhibition in mm*</th>
<th>Antibacterial activity</th>
<th>Antifungal activity</th>
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<td>S. aureus</td>
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<tr>
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<td>Control (DMF)</td>
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</table>

* Diameter of well (bore size) - 6 mm
using TMS as an internal standard (chemical shifts in δ, ppm) and mass spectra on a Jeol SX-102 (FAB) mass spectrometer.

**Synthesis of ethyl-5-(ethoxycarbonyl)-4-methylthiazol-2-yl-carbamate, 2**

Compound 1 (0.001 mole) was dissolved in minimum amount of pyridine (2 mL) and cooled to 0°C under anhydrous conditions. Ethyl chloroformate (0.001 mole) was added to it dropwise at 0-2°C with stirring under anhydrous conditions and stirring was continued at same temperature for 1 hr, further 0.5 hr at RT and then the reaction-mixture was heated for 12 hr on a water-bath. The contents were poured into ice-water and pyridine was removed by steam distillation. The obtained solid was filtered, dried and purified by recrystallization from water, dried and purified by recrystallization from absolute ethanol to furnish colourless crystalline compound 2, 71%, m.p.185°C. 1H NMR (CDCl 3): δ 1.38 (t, 3H, CH 3), 2.15 (q, 2H, OCH 2), 4.45 (q, 2H, OCH 2), 9.23 (s, 1H, NH); IR (KBr): 704 (C-S-C), 1148, 1169 (C-O-CH 3), 1560, 1609, 1636 (C=N), 1671, 1682, 1718, 1721 (C=O), 3241 (NH), 3335, 3488 cm -1 (NH 2). Anal. Calcd for C 12H12N8O4S: C, 39.56; H, 3.30; N, 30.77; S, 8.79. Found: C, 39.28; H, 3.14; N, 30.59; S, 8.56%.

**Synthesis of 4-methylthiazole-2-yl-semicarbazido-5-carboxyhydrazide, 3**

A suspension of 2 (0.001 mole) in ethanol (10 mL) was refluxed with hydradine hydrate (2 mL, 99%) on a water-bath for 9 hr. The reaction-mixture was cooled to RT to offer a white solid, which was filtered, dried and purified by recrystallization from absolute ethanol to yield colourless crystalline compound 3, 75%, m.p.169°C. 1H NMR (DMSO-d 6): δ 1.40 (s, 3H, CH 3), 1.65 (s, 3H, CH 3), 2.05 (s, 3H, CH 3), 4.55 (s, 2H, CH 2), 4.81 (s, 2H, CH 2), 9.89 (s, 1H, NH); IR (KBr): 735 (C=S-C), 1563, 1601, 1610 (C=N), 1667, 1699, 1713, 1745 (C=O), 3332 cm -1 (NH); MS: m/z (%) 362 (18), 307 (48), 265 (10), 237 (42), 168 (100). Anal. Calcd for C 14H14N6O4S: C, 46.41; H, 3.87; N, 23.20; S, 8.84. Found: C, 46.25; H, 3.60; N, 23.12; S, 8.69%. 4: colourless crystals, 74%, m.p.199°C. 1H NMR (DMSO-d 6): δ 1.35 (t, 3H, CH 3), 1.51 (t, 3H, CH 3), 2.31 (s, 3H, CH 3), 4.45 (q, 2H, OCH 2), 4.68 (q, 2H, OCH 2), 9.81 (s, 1H, NH); IR (KBr): 711 (C-S-C), 1578 (C=N), 1601, 1610 (C=O), 3285 cm-1 (NH). Anal. Calcd for C 16H18N6O2S: C, 53.63; H, 5.03; N, 23.46; S, 8.94. Found: C, 53.57; H, 4.99; N, 23.31; S, 8.86%.

**Synthesis of 4-methyl-2-yl-amino-(1, 3, 4-oxadiazolin-5-thion)-2-yl)-5-thion-2-yl)-1, 3, 4-oxadiazolin-5-thion, 7**

A mixture of 3 (0.001 mole), potassium hydroxide (0.005 mole) and carbon disulphide (0.001 mole) in methanol (20 mL) was heated on a steam-bath until the evolution of hydrogen sulphide ceases (42 hr). After evaporation of solvent the residue was dissolved in ice-cold water. The resulting solution (filtered if necessary) was acidified with dilute hydrochloric acid. The obtained solid was filtered, washed with water, dried and purified by recrystallization from dioxane to furnish pale yellow crystals of compound 7, 72%, m.p.265°C. 1H NMR (DMSO-d 6): δ 1.90 (s, 3H, CH 3), 9.10 (s, 1H, NH) 9.28 (s, 1H, NH), 9.80 (s, 1H, NH); IR (KBr): 726 (C-S-C), 1148, 1169 (C-O-C), 1275, 1298 (C=S), 1584, 1598, 1636 (C=N), 3181, 3237, 3285 cm -1 (NH); MS: m/z (%) 314 (48), 241 (33), 169 (100), 141 (32). Anal. Calcd for C 8H 6N 6O 2S 3: C, 30.57; H, 1.91; N, 26.75; S, 50.30. Found: C, 30.50; H, 1.65; N, 26.50; S, 30.37%.
Synthesis of 4-methyl-2-yl-amino-(5-substituted-1, 3, 4-oxadiazol-2-yl)-5-(5-substituted-1, 3, 4-oxadiazol-2-yl)-thiazole, 8a-d

A mixture of 3 (0.001 mole), substituted aromatic acid(s) (0.002 mole) and phosphorous oxychloride (15 mL) was refluxed on the oil-bath at 100-110°C for 6 hr. The excess of phosphorous oxychloride was distilled off and cooled residue was poured into ice-cold water. The contents were neutralized with ammonia to offered crude product(s) 8a-d, which were filtered, dried and purified by recrystallization from 1, 4-dioxane.

8a: colourless crystals, 69%, m.p.241°C. 1H NMR (CDCl3): δ 2.25 (s, 3H, CH3), 7.20-8.09 (m, 10H, Ar-H), 9.55 (s, 1H, NH); IR (KBr): 703 (C-S-C), 1122, 1155 (C-O-C), 1523, 1565, 1598, 1623, 1641 (C=N), 3321 cm−1(NH). Anal. Cacld. for C20H14N6O2S: C, 48.78; H, 11.26; N, 22.76; S, 6.50. Found: C, 48.56; H, 2.26; N, 22.50; S, 6.79. The zone of inhibition for all the test compounds was measured and the results were compared with the standard drug gentamycin for antibacterial activity and Nystatin for antifungal activity (Table I).

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References