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

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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 acetoacetate, ethylcyanoacetate, 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)-5-(1-N-carboxyl-3-methyl-4,5-dihydro-*1H*-pyrazol-5-one)-thiazole **4,** 4-methyl-2-yl-amino-(1-N-carboxyl-3-amino-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-oxadiazolin-5-thione)-5yl-(1,3,4-oxadiazolin-5-thione-2yl)-thiazole **7** and 4-methyl-2-yl-amino-(5-substituted-1,3,4-oxadiazol-2yl)-5-(5-substituted-1,3,4-oxadiazol-2yl)-thiazole **8a-d,** respectively. All the synthesized compounds have been screened for their antimicrobial activity.

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

Heterocycles containing thiazole rings are associated with a wide range of biological properties such as antiprotozoal[1], anticonvulsant[2], depressant effect on the central nervous system[3], anti-helimintic[4], anti-diabetics[5], inhibitors of dihydrofolate[6], inflammation inhibitors[7,8], antitumor[9-11], herbicidal[12], antimicrobial[13-18], antiviral[19] and antianaphylactic[20] 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[21], antipyretic, analgesic and smooth muscle relaxant[22] activities. Many pyrazole derivatives are associated with antifungal, anti-diabetic[23] and bactericidal[24] 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[25] and anti-inflammatory[26] activities. Substituted 1,3,4-oxadiazole-2-thiones and their derivatives possess CNS depressant[27], pesticidal[28,29] and antitubercular[30] activities. In view of all these findings and in continuation of the research work on 4-substituted thiazole-2-semicarbazides and their derivatives[13,14], herein is reported the synthesis and antimicrobial activity of some 2 and 5-substituted 4-methylthiazolyl carbamates compounds (**Scheme I**).

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-methyl-thiazole-5-carboxylate **1** was prepared in the laboratory[31]. Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr discs (ν_{max} in cm^{-1}) on Perkin-Elmer FT-IR (Spectrum ONE) spectrometer and ^1H NMR spectra on a Bruker AMX (400 MHz) spectrometer using DMSO-d_6 as solvent unless otherwise stated,

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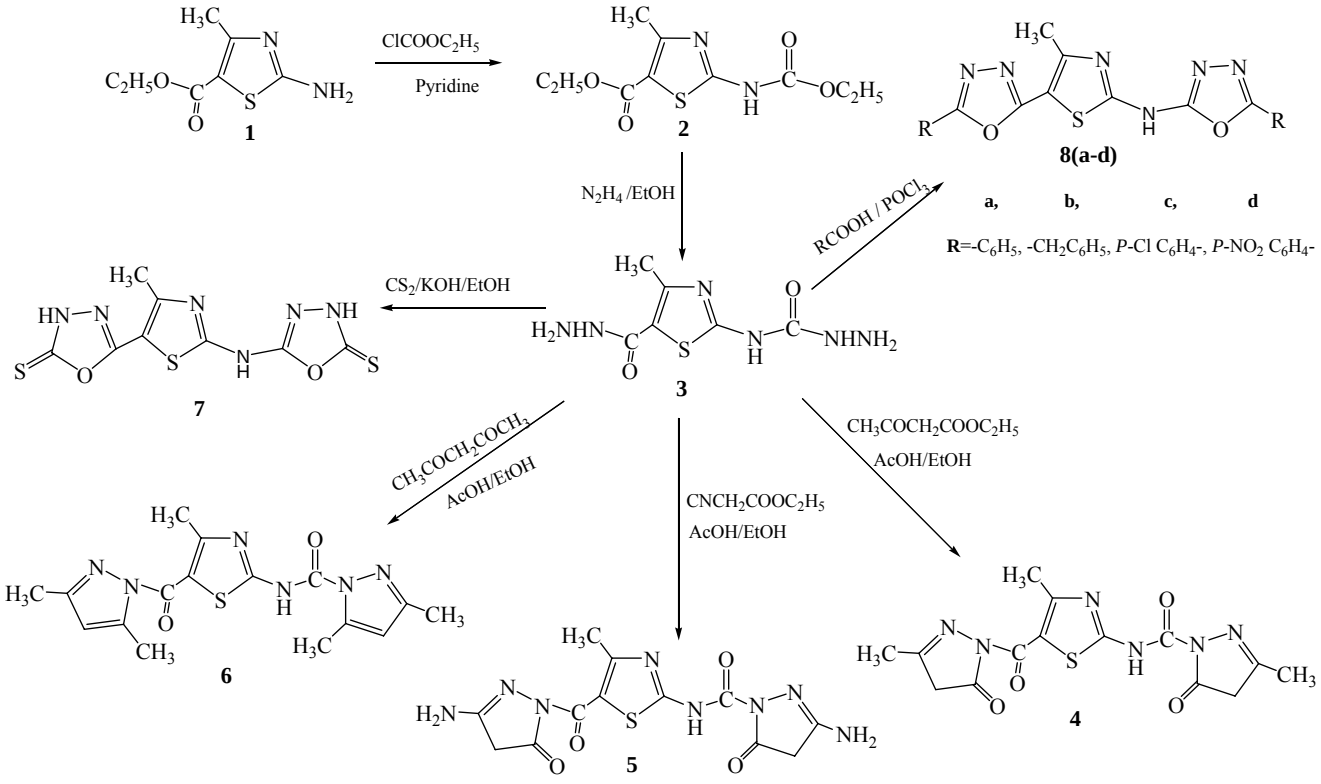

Scheme I

Table I — Antimicrobial activity of the synthesized compounds

Compd	Conc (μg/0.1mL) in DMF	Zone of inhibition in mm*				
		Antibacterial activity			Antifungal activity	
		S. aureus	*E. coli*	*B. subtilus*	*A. niger*	*C. albicans*
2	100	10	08	09	10	09
3	100	09	11	12	11	12
4	100	19	17	18	17	18
5	100	16	16	19	14	15
6	100	14	12	11	12	14
7	100	18	17	19	19	17
8a	100	14	13	16	16	17
8b	100	15	13	15	08	09
8c	100	18	19	18	18	17
8d	100	17	15	18	17	18
Gentamycin	100	22	20	21	-	-
Nystatin	100	-	-	-	22	21
Control (DMF)	-	-	-	-	-	-

*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 with stirring into ice-water and pyridine was removed by steam distillation. The obtained solid was filtered, dried and purified by recrystallization from absolute ethanol to yield colourless crystalline compound **2,** 71%, m.p.185°C. ^{1}H NMR ($CDCl_3$): δ 1.38 (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), 1706, 1720 (C=O), 3168 cm^{-1} (NH); MS: *m/z* (%) 259 (M+1, 100), 258 (20), 213 (10), 186 (9), 185 (4), 157 (8). Anal. Calcd for $C_{10}H_{14}N_2O_4S$: C, 46.51; H, 5.43; N, 10.85; S, 12.40. Found: C, 46.36; H, 5.40; N, 10.69; S, 12.28%.

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

A suspension of **2** (0.001 mole) in ethanol (10 mL) was refluxed with hydrazine 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 ethanol to get colourless crystalline **3,** 75%, m.p.169°C. ^{1}H NMR (DMSO-d_6): δ 2.58 (s, 3H, CH_3), 4.30 (s, 2H, NH_2), 4.75 (s, 2H, NH_2), 8.85 (s, 1H, NH), 9.15 (s, 1H, NH), 9.50 (s, 1H, NH); IR (KBr): 737 (C-S-C), 1551(C=N), 1651, 1673 (C=O), 3086, 3216, 3265 (NH), 3302, 3375 cm^{-1} (NH_2); MS: *m/z* (%) 230 (44), 229 (41), 187 (100), 159 (31), 141 (28). Anal. Calcd for $C_6H_{10}N_6O_2S$: C, 31.30; H, 4.35; N, 36.52; S, 13.91. Found: C, 31.22; H, 4.17; N, 36.29; S, 13.75%.

Synthesis of 4, 5 and 6

To a solution of **3** (0.001 mole) in ethanol (10 mL), appropriate diketone (ethylacetoacetate/ethylcynoacetate / acetylacetone, 0.002 mole) was added and the reaction-mixture was refluxed on a water-bath for 12 hr in presence of catalytic amount of glacial acetic acid (2-3 drops). The reaction contents were cooled to RT and the obtained product (**4**,**5**,**6**) was filtered, dried and purified by recrystallization from ethanol.

4: colourless crystals, 71%, m.p.155°C. ^{1}H 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 $C_{14}H_{14}N_6O_4S$: 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%.

5: colourless crystals, 74%, m.p.199°C. ^{1}H NMR (DMSO-d_6): δ 1.80 (s, 3H, CH_3), 3.70 (s, 2H, CH_2), 3.90 (s, 2H, CH_2), 4.56 (s, 2H, NH_2), 4.80 (s, 2H, NH_2), 10.20 (s, 1H, NH); IR (KBr): 736 (C-S-C), 1560, 1609, 1614 (C=N), 1671, 1682, 1718, 1721 (C=O), 3241 (NH), 3335, 3488 cm^{-1} (NH_2). Anal. Calcd for $C_{12}H_{12}N_8O_4S$: 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%.

6: colourless crystals, 68%, m.p.204°C. ^{1}H NMR ($CDCl_3$): δ 1.65 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 6.21 (s, 1H, CH), 6.48 (s, 1H, CH), 9.87 (s, 1H, NH); IR (KBr): 704 (C-S-C), 1567, 1599, 1622 (C=N), 1670, 1683 (C=O), 3285 cm^{-1}(NH). Anal. Calcd for $C_{16}H_{18}N_6O_2S$: C, 53.63; H, 5.03; N, 23.46; S, 8.94. Found: C, 53.55; H, 4.99; N, 23.31; S, 8.68%.

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

A mixture of **3** (0.001 mole), potassium hydroxide (0.005 mole) and carbon disulphide (0.005 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. ^{1}H 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. ^{1}H NMR ($CDCl_3$): δ 2.25 (s, 3H, CH_3), 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), 3264 cm^{-1}(NH); MS: *m/z* (%) 402 (100), 299 (41), 196 (48), 112 (46). Anal. Cacld. for $C_{20}H_{14}N_6O_2S$: C, 59.70; H, 3.48; N, 20.90; S, 7.96. Found: C, 59.52; H, 3.42; N, 20.67; S, 7.72%.

8b: colourless crystals, 75%, m.p.235°C. ^{1}H NMR ($CDCl_3$): δ 2.19 (s, 3H, CH_3), 4.10 (s, 2H, CH_2), 4.30 (s, 2H, CH_2), 7.10-7.89 (m, 10H, Ar-H), 9.68 (s, 1H, NH); IR (KBr): 701 (C-S-C), 1127, 1161 (C-O-C), 1539, 1548, 1601, 1635, 1651 (C=N), 3321 cm^{-1}(NH). Anal. Cacld. for $C_{22}H_{18}N_6O_2S$: C, 61.40; H, 4.19; N, 19.53; S, 7.44. Found: C, 61.29; H, 4.02; N, 19.26; S, 7.25%.

8c: colourless crystals, 74%, m.p.284°C. ^{1}H NMR ($CDCl_3$): δ 2.18 (s, 3H, CH_3), 7.18-8.19 (m, 8H, Ar-H), 9.60 (s, 1H, NH); IR (KBr): 699 (C-S-C), 1131, 1151 (C-O-C), 1539, 1548, 1601, 1635, 1642 (C=N), 3321 cm^{-1}(NH). Anal. Cacld. for $C_{20}H_{12}N_6O_2SCl_2$: C, 50.95; H, 2.54; N, 17.83; S, 6.79. Found: C, 50.79; H, 2.33; N, 17.81; S, 6.53%.

8d: brown crystals, 76%, m.p.222°C. ^{1}H NMR ($CDCl_3$): δ 1.92 (s, 3H, CH_3), 7.20-8.15 (m, 8H, Ar-H), 9.98 (s, 1H, NH); IR (KBr): 726 (C-S-C), 1106, 1156 (C-O-C), 1554, 1600, 1628, 1636 (C=N), 3180 cm^{-1}(NH). Anal. Cacld for $C_{20}H_{12}N_8O_6S$: C, 48.78; H, 2.44; N, 22.76; S, 6.50. Found: C, 48.56; H, 2.26; N, 22.50; S; 6.29%.

Antimicrobial activity

The *in-vitro* biological screening of the synthesized compounds was undertaken against the bacteria species, namely, *Staphylococcus aureus, Escherichia coli* and *Bacillus subtilus* and fungi species, namely, *Aspergillus niger* and *Candida albicans* by cup-plate method[13,14] using nutrient agar as medium. The holes of 6 mm diameter were punched carefully using a sterile cork borer and these were filled with test solutions (1000 µg/mL in DMF) and DMF was used as control. The plates were incubated at 37°C for 24 hr and 72 hr in case of antibacterial activity and antifungal activity, respectively. The diameter of 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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