

Vilsmeier Haack reaction of substituted 2-acetamidothiazole derivatives and their antimicrobial activity

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Vilsmeier Haack (VMH) reaction of 2-acetamidothiazole having carbethoxy group at C-4 affords the unexpected N-formylated product, which is followed by deacetylation. The same reaction with substituents other than carbethoxy group at C-4 position (*viz* CH₃, CH₂COOC₂H₅, coumarinyl, phenyl, *etc.*) gives the expected C-5 formylated products. The structures of all the newly prepared compounds have been established on the basis of their analytical and spectral data. All the synthesized compounds have been screened for their antimicrobial activity against two strains of bacteria and fungi.

Keywords: 2-Acetamidothiazole, Vilsmeier Haack reaction, N-formylation, deacetylation, antimicrobial activity

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In view of the sustained interest in preparing the thiazole fused diazepinones of pharmacological interest by employing intramolecular transamidation, it was desired to introduce the amine moiety in the ethoxycarbonyl 2-acetamidothiazole derivatives by carrying out Vilsmeier Haack reaction (VMH) followed by condensation with hydrazine hydrate. During the course of this investigation, some interesting results were observed, which enabled the study of the behavior of differently 4-substituted 2-acetamidothiazole derivatives towards the Vilsmeier Haack reaction. Also, in view of the pharmacological significance of the amino thiazole derivatives it was thought worthwhile to synthesize different 4-substituted 2-acetamidothiazole derivatives and study their behavior under Vilsmeier Haack conditions.

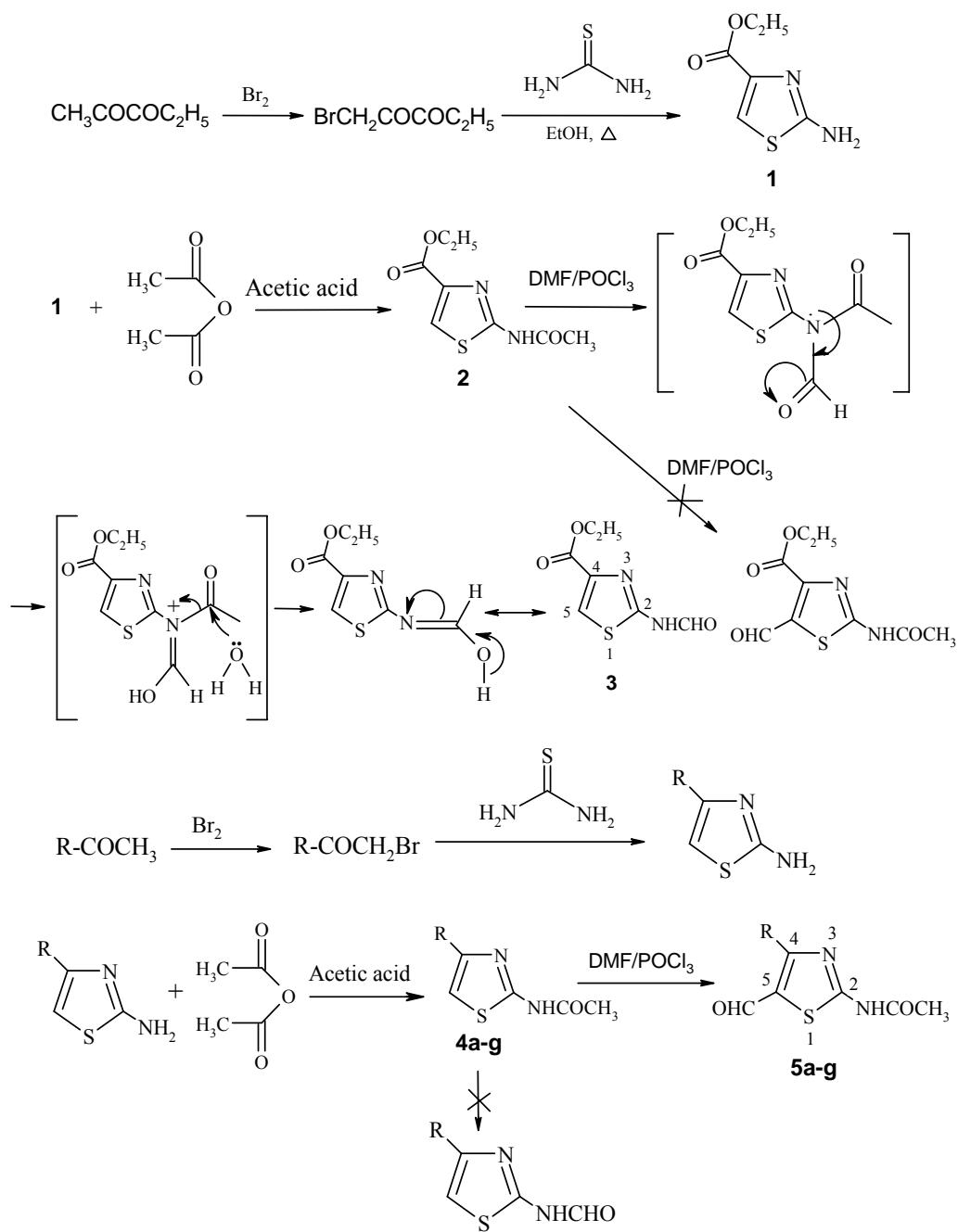
Results and Discussion

A suitable substituted thiazole was required for the synthesis of thiazole fused diazepinones. Thiazole derivatives with a carbonyl residue at C-4 (COOC₂H₅, CH₂COOC₂H₅, coumarinyl, *etc.*) and an amine (NHNH₂) residue at C-5 are of particular interest as they are the precursors for carrying out the intramolecular amidation¹ resulting in the formation of thiazolodiazepinones. In order to introduce an amine input at C-5 the ethyl 2-acetamidothiazole-4-carboxylate had to be formylated by Vilsmeier Haack reaction, which can be further reacted with hydrazine hydrate to have an amine residue to carry out the

intramolecular amidation. But when ethyl 2-acetamido thiazole-4-carboxylate was subjected to Vilsmeier Haack reaction (**Scheme I**), it was found that the product obtained was not 5-formyl derivative but instead deacetylated N-formyl product as established by its analytical and spectral data. The IR spectrum of the product showed bands at 1728 (v_{C=O} of ester) and 1687 cm⁻¹ (v_{C=O} of aldehyde) whereas the v_{C=O} of amide (-NHCOCH₃) was absent. The ¹H NMR spectrum of the said compound showed the peaks at δ 12.59 (br s, 1H, NH), 8.55 (s, 1H, CHO), 8.08 (s, 1H, 5H), 4.28 (q, 2H, CH₂ of ester), 1.29 (t, 3H, CH₃ of ester). There was no peak due to methyl group of acetamido group (-NHCOCH₃). The appearance of C-5 proton indicates that formylation has not taken place at C-5 position whereas the aldehydic proton position in the ¹H NMR was a characteristic of N-formylated product which was confirmed by ¹³C NMR, which showed two carbonyl carbons at 161.73 (C=O of ester) and 161.03 ppm (C=O of aldehyde). The acetamido carbonyl carbon was once again not observed. Finally, the mass spectra confirmed the N-formylation. There are reports in the literature² where N-formylation has taken place with Vilsmeier Haack reagent.

The formation of N-formylated product followed by deacetylation is explained on the basis of the mechanism given in **Scheme II**.

These results led to a detailed study of Vilsmeier Haack reaction of different 2-acetamido-4-substituted thiazoles (**Scheme I**). It was observed that when the



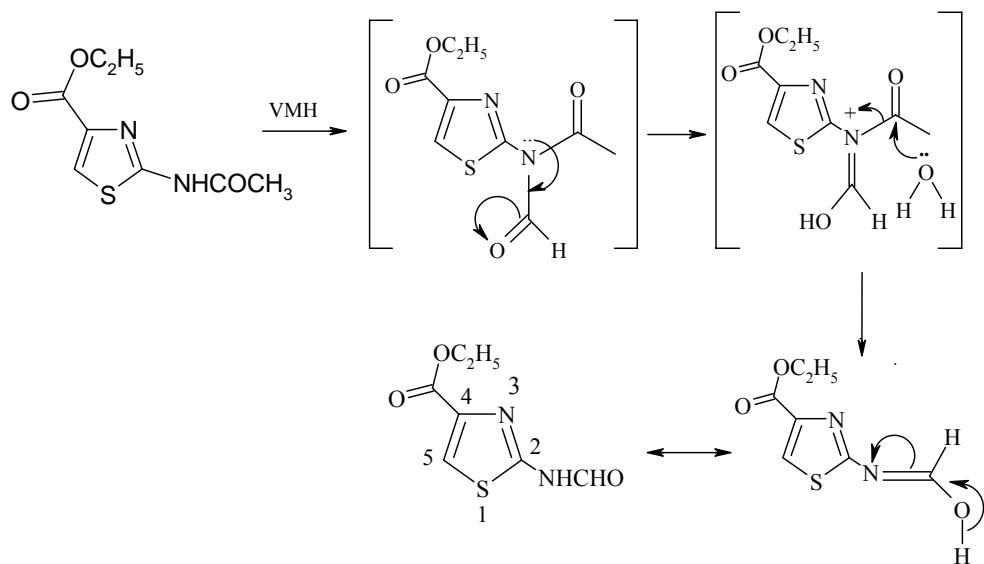
Scheme I

thiazole contains 4-substituent other than ethoxycarbonyl group (*viz.* CH₃, CH₂COOEt, Coumarinyl, Ph, *etc.*) formylation conveniently takes place at C-5. However, in case of 4-ethoxycarbonyl-2-acetamidothiazole, N-formylation appears to have occurred. The structures of various formyl derivatives

prepared during the present investigation were established from their analytical and spectral data.

Antimicrobial activity³

All compounds were screened at 100 µg/mL concentration in DMF. Antimicrobial activity was



Scheme II

evaluated against gram-negative bacterium *Escherichia coli*, gram-positive bacterium *Staphylococcus aureus* and fungi—*Aspergillus niger* and *Candida albicans*. Except for the 3-coumarinyl derivative (**5g**), all other compounds exhibited poor antimicrobial activity when compared to standard Norfloxacin and Griseofulvin (**Table I**).

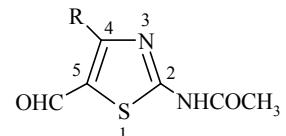
Experimental Section

All melting points were determined in open capillaries and are uncorrected. Various 2-bromoketones⁴⁻¹³, ethyl 2-aminothiazole-4-carboxylate¹⁴ and ethyl-[2-(acetylamino)-1,3-thiazol-4-yl] acetate¹⁵ were prepared according to reported methods. The IR spectra (KBr pellet) were recorded on Nicolet FT-IR 410 spectrometer and the values are expressed in cm^{-1} . The ^1H and ^{13}C NMR spectra (CDCl_3) were recorded on Bruker AC-300F 300 MHz spectrometer using TMS as internal reference compound. The chemical shifts are expressed in δ (ppm). These data were obtained from University Scientific Instruments Centre, Karnatak University, Dharwad. EI-MS were recorded on JEOL MS-DX 303 spectrometer (NCL, Pune) at 70 eV and 150-200°C source temperature. The observed elemental analysis (Heraus CHN rapid analyzer) results are within 0.4% of the theoretical values.

Ethyl 2-(formylamino)-1,3-thiazole-4-carboxylate, **3**

Vilsmeier Haack reagent was prepared by adding phosphorous oxychloride (2.5 mL) in DMF (7.5 mL)

Table I—Antimicrobial activity of N-[5-formyl-4-alkyl/aryl-1,3-thiazol-2-yl] acetamides



| R | Antibacterial activity | | Antifungal activity | |
|--------------------------------------|------------------------|--------------------------|----------------------------|-------------------------|
| | <i>E. coli</i> (mm) | <i>S. aureus</i> (mm) | <i>C. albicans</i> (mm) | <i>A. niger</i> (mm) |
| $\text{CH}_2\text{COOC}_2\text{H}_5$ | 13 | 12 | 11 | 12 |
| Phenyl | 13 | 11 | 12 | 10 |
| 2-Thienyl | 11 | 12 | 14 | 11 |
| 5-Nitrothienyl | 13 | 11 | 13 | 11 |
| 4-Nitrophenyl | 12 | 10 | 12 | 10 |
| Methyl | 11 | 11 | 11 | 12 |
| 3-Coumarinyl | 16 | 15 | 15 | 14 |
| Norfloxacin | 23 | 22 | - | - |
| Griseofulvin | - | - | 22 | 21 |

at 0°C. Then, ethyl-[2-(acetylamino)-1,3-thiazol-4-yl] acetate (2.14 g, 0.01 mole) was added to the reagent at 0°C. The reaction mixture was stirred at RT for 2 hr and further at 60°C for 2 hr. The reaction mixture was then poured into cold aq. sodium carbonate solution (10%) and stirred at 90°C for 2 hr. After cooling down to RT, the solution was extracted with chloroform. The chloroform layer was washed repeatedly with water and dried over anhydrous sodium sulfate. The combined extracts were evaporated to dryness and purified by recrystallization from rectified spirit, yield 50%, m.p. 232°C; IR

(KBr): 3134-2924 (CH stretching bands), 1728 (C=O of ester) and 1687 cm^{-1} (C=O of aldehyde); ^1H NMR (CDCl_3): δ 12.59 (br s, NH), 8.55 (s, 1H, CHO), 8.08 (s, 1H, C5-H), 4.28 (q, 2H, CH_2 of ester), 1.29 (t, 3H, CH_3 of ester); ^{13}C NMR (CDCl_3): δ 161.73 (C=O of ester), 161.03 (C=O of CHO), 157.30 (C-2), 141.89 (C-4), 123.94 (C-5), 61.48 (OCH_2), 14.98 (CH_3); MS: m/z 200 (M^+). Anal. Calcd for $\text{C}_7\text{H}_8\text{N}_2\text{O}_3\text{S}$: C, 41.75; H, 3.85; N, 13.80. Found: C, 41.96; H, 4.01; N, 13.99%.

General procedure for the preparation of N-[(4-alkyl/aryl)-1,3-thiazol-2-yl]acetamides, 4a-g

To a mixture of 4-alkyl/aryl-2-aminothiazole (0.1 mole) in acetic acid (50 mL) was added acetic anhydride (10.2 g, 0.1 mole) and pyridine (0.5 mL) slowly with stirring and heated to reflux for 4h. The reaction mixture was cooled and poured into crushed ice (300 g). The crude acetamido derivative that separated was filtered, washed with ice cold water and dried. The compound was purified by recrystallization from aqueous ethanol. The physicochemical and spectral data of various 4a-g are described below.

N-[(4-carbacetoxy)-1,3-thiazol-2-yl]acetamide, 4a: yield 60%, m.p. 200°C; IR (KBr): 3173 (NH), 1731 (C=O of ester) and 1659 cm^{-1} (C=O of amide); ^1H NMR (CDCl_3): δ 8.80 (s, 1H, NH), 7.70 (s, 1H, C5-H), 4.21 (q, 2H, CH_2 of ester), 3.70 (s, 2H, CH_2 of CH_2COOEt), 2.18 (s, 3H, COCH_3), 0.93 (t, 3H, CH_3 of acetate). Anal. Calcd for $\text{C}_9\text{H}_{12}\text{N}_2\text{O}_3\text{S}$: C, 47.36; H, 5.26; N, 12.28. Found: C, 47.05; H, 4.95; N, 12.51%.

N-[(4-phenyl)-1,3-thiazol-2-yl]acetamide, 4b¹⁶: yield 62%, m.p. 212-13°C.

N-[(4-thienyl)-1,3-thiazol-2-yl]acetamide, 4c: yield 50%, m.p. 196°C; IR (KBr): 3160 (NH), 1687 cm^{-1} (C=O of amide); ^1H NMR (CDCl_3): δ 8.50 (s, 1H, NH), 7.70 (s, 1H, C5-H of thiazole), 7.50-7.13 (m, 3H, ArH), 3.16 (s, 3H, COCH_3). Anal. Calcd for $\text{C}_9\text{H}_8\text{N}_2\text{O}_3\text{S}_2$: C, 48.21; H, 3.57; N, 12.50. Found: C, 47.90; H, 3.45; N, 12.15%.

N-[(4-nitrothienyl)-1,3-thiazol-2-yl]acetamide, 4d: yield 60%, m.p. 188°C; IR (KBr): 3385 (NH), 1619 cm^{-1} (C=O of amide); ^1H NMR (CDCl_3): δ 8.42 (s, 1H, NH), 7.85 (s, 1H, C5-H of thiazole), 7.60-7.10 (m, 2H, ArH), 3.18 (s, 3H, COCH_3). Anal. Calcd for $\text{C}_9\text{H}_7\text{N}_3\text{O}_3\text{S}_2$: C, 40.14; H, 2.60; N, 15.61. Found: C, 39.75; H, 2.49; N, 15.30%.

N-[(4-nitrophenyl)-1,3-thiazol-2-yl]acetamide, 4e: yield 61%, m.p. 216°C; IR (KBr): 3174 (NH), 1644 cm^{-1} (C=O of amide); ^1H NMR (CDCl_3): δ 8.60 (s, 1H, NH), 7.90 (s, 1H, C5-H of thiazole), 7.70 (d,

J =8.6 Hz, 2H, ArH), 7.49 (d, 2H, J =8.6 Hz, ArH) 3.16 (s, 3H, COCH_3). Anal. Calcd for $\text{C}_{11}\text{H}_9\text{N}_3\text{O}_3\text{S}$: C, 41.82; H, 3.42; N, 15.96. Found: C, 41.65; H, 3.28; N, 15.68%.

N-[(4-methyl)-1,3-thiazol-2-yl]acetamide, 4f¹⁷: yield 56%, m.p. 132-33°C.

N-[4-(3-coumarinyl)-1,3-thiazol-2-yl]acetamide, 4g: yield 55%, m.p. 192°C; IR (KBr): 3154 (NH), 1738 (C=O of lactone) and 1715 cm^{-1} (C=O of amide); ^1H NMR (CDCl_3): δ 8.85 (s, 1H, NH), 8.57 (s, 1H, coumarinyl C4-H), 7.98 (s, 1H, C5-H of thiazole), 7.85-7.37 (m, 4H, ArH), 3.18 (s, 3H, COCH_3). Anal. Calcd for $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_3\text{S}$: C, 58.74; H, 3.49; N, 9.79. Found: C, 58.42; H, 3.35; N, 9.36%.

General procedure for the preparation of N-[(5-formyl-4-alkyl/aryl)-1,3-thiazol-2-yl]acetamides, 5a-g.

Vilsmeier Haack reagent was prepared by adding phosphorous oxychloride (2.5 mL) in DMF (7.5 mL) at 0°C. Then, N-(4-alkyl/aryl-1,3-thiazol-2-yl) acetamide (4, 0.01 mole) was added to the reagent at 0°C. The reaction mass was stirred at RT for 2 hr and further at 60°C for 2 hr. The reaction mixture was then poured into cold aq. sodium carbonate solution (20 mL, 10%) and stirred at 90°C for 2 hr. After cooling, the solution was extracted with chloroform, washed repeatedly with water and dried over anhydrous sodium sulfate. The combined extracts were evaporated to dryness and purified by recrystallization from rectified spirit. The physicochemical and spectral characterization data are described below.

N-[(5-formyl-4-carbacetoxy)-1,3-thiazol-2-yl]acetamide, 5a: yield 55%, m.p. 230°C; IR (KBr): 3173 (NH), 1735 (C=O of ester), 1642 (C=O of aldehyde) and 1622 cm^{-1} (C=O of amide); ^1H NMR (CDCl_3): δ 9.60 (s, 1H, CHO), 8.18 (s, 1H, NH), 4.23 (q, 2H, CH_2 of ester), 3.72 (s, 2H, CH_2 of acetate), 3.18 (s, 3H, COCH_3), 0.94 (t, 3H, CH_3 of ester). Anal. Calcd for $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_4\text{S}$: C, 46.87; H, 4.68; N, 10.93. Found: C, 46.54; H, 4.49; N, 10.62%.

N-[(5-formyl-4-phenyl)-1,3-thiazol-2-yl]acetamide, 5b: yield 52%, m.p. 220°C; IR (KBr): 3169 (NH), 1644 cm^{-1} (C=O of amide); ^1H NMR (CDCl_3): δ 9.82 (s, 1H, CHO), 8.44 (s, 1H, NH), 7.88-7.47 (m, 5H, ArH), 3.17 (s, 3H, COCH_3); ^{13}C NMR (CDCl_3): 183.9 (C=O of CHO), 179.8 (C=O of amide), 163.4 (C-2), 157.3 (C-4), 134.1 (C-1'), 130.1 (C-3' & C-5'), 128.9 (C-4'), 128.2 (C-2' & C-6'), 106.5 (C-5), 35.77 (CH_3). Anal. Calcd for $\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}_2\text{S}$: C, 58.53; H, 4.06; N, 11.38. Found: C, 58.10; H, 3.98; N, 11.04%.

N-[5-formyl-4-thienyl]-1,3-thiazol-2-yl]acetamide, 5c: yield 55%, m.p. 204°C; IR (KBr): 3160 (NH), 1687 (C=O of aldehyde) and 1621 cm^{-1} (C=O of amide); ^1H NMR (CDCl_3): δ 10.11 (s, 1H, CHO), 8.41 (s, 1H, NH), 7.53-7.13 (m, 3H, thienyl H), 2.97 (s, 3H, COCH_3). Anal. Calcd for $\text{C}_{10}\text{H}_8\text{N}_2\text{O}_2\text{S}_2$: C, 47.61; H, 3.17; N, 11.11. Found: C, 47.20; H, 3.05; N, 10.95%.

N-[5-formyl-4-(5-nitrothienyl)-1,3-thiazol-2-yl]acetamide, 5d: yield 50%, m.p. 214°C; IR (KBr): 3385 (NH), 1619 (C=O of aldehyde) and 1610 cm^{-1} (C=O of amide); ^1H NMR (CDCl_3): δ 10.10 (s, 1H, CHO), 8.42 (s, 1H, NH), 8.37-7.85 (m, 2H, ArH), 3.18 (s, 3H, COCH_3). Anal. Calcd for $\text{C}_{10}\text{H}_7\text{N}_3\text{O}_4\text{S}_2$: C, 40.40; H, 2.35; N, 14.14. Found: C, 40.05; H, 2.24; N, 14.50%.

N-[5-formyl-4-(4-nitrophenyl)-1,3-thiazol-2-yl]acetamide, 5e: yield 58%, m.p. 222°C; IR (KBr): 3174 (NH), 1644 (C=O of aldehyde) and 1611 cm^{-1} (C=O of amide); ^1H NMR (CDCl_3): δ 9.80 (s, 1H, CHO), 8.39 (s, 1H, NH), 8.12 (d, $J=8.5$ Hz, 2H, ArH), 7.88 (d, $J=8.5$ Hz, 2H, ArH), 3.21 (s, 3H, COCH_3). Anal. Calcd for $\text{C}_{12}\text{H}_9\text{N}_3\text{O}_4\text{S}$: C, 49.48; H, 3.09; N, 14.43. Found: C, 49.10; H, 3.14; N, 14.20%.

N-[5-formyl-(4-methyl)-1,3-thiazol-2-yl]acetamide, 5f: yield 56%, m.p. 232°C; IR (KBr): 3160 (NH), 1665 (C=O of aldehyde) and 1610 cm^{-1} (C=O of amide); ^1H NMR (CDCl_3): δ 10.00 (s, 1H, CHO), 8.60 (s, 1H, NH), 3.35 (s, 3H, COCH_3), 2.25 (s, 3H, CH_3). Anal. Calcd for $\text{C}_7\text{H}_8\text{N}_2\text{O}_2\text{S}$: C, 45.65; H, 4.34; N, 15.21. Found: C, 45.25; H, 4.16; N, 14.92%.

N-[5-formyl-4-(3-coumarinyl)-1,3-thiazol-2-yl]acetamide, 5g: yield 52%, m.p. 210°C; IR (KBr): 3098 (NH), 1731 (C=O of lactone), 1657 (C=O of aldehyde) and 1628 cm^{-1} (C=O of amide); ^1H NMR (CDCl_3): δ 9.77 (s, 1H, CHO), 8.51 (s, 1H, NH), 8.48 (s, 1H, coumarinyl $\text{C}_4\text{-H}$), 7.85-7.39 (m, 4H, ArH), 3.20 (s, 3H, COCH_3); ^{13}C NMR (CDCl_3): δ 197.5 (C=O of CHO), 171.9 (C=O of amide), 163.8 (C=O of coumarin), 162.6 (C-2), 155.5 (C-4), 149.4 (C-10'), 38.1(C-4'), 130.1 (C-8'), 128.0(C-5'), 127.6 (C-6'), 127.1(C-3'), 126.5 (C-7'), 124.1(C-5), 120.8 (C-9'), 20.1 (CH_3). Anal. Calcd for $\text{C}_{15}\text{H}_{10}\text{N}_2\text{O}_4\text{S}$: C, 57.32; H, 3.18; N, 8.91. Found: C, 56.98; H, 3.30; N, 8.72%.

Procedure of antimicrobial tests

A solution of the tested compounds (0.01 mole) [prepared by dissolving 100 $\mu\text{g}/\text{mL}$ (w/v) in sterile DMF] was poured aseptically in a well of 6 mm diameter made by a borer in the seeded agar medium. After transferring *via* pipette the same volume in wells of all tested microorganisms, bacterial test plates were incubated at 37°C for 24 hr and fungal test plates were incubated at 25°C for 48 hr. The activities were expressed as inhibition zones (mm, diameter, as clear areas). Norfloxacin and Grieseofulvin were used as standard.

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References

- 1 Vasudevan A, Villamil C I & Djuric S W, *Org Lett*, 6(19), 2004, 3361.
- 2 Bruche L, Garanti L & Zecchi G, *J Chem Research (S)*, 1994, 318.
- 3 Seely H W & Van Demark D J, *Microbes in action-A laboratory Manual of Microbiology*, (D B Taraporvala and Sons Pvt. Ltd., Bombay) 1975, 73.
- 4 Cowper R M & Davidson L H, *Organic Synthesis Coll. Vol. II*, p. 480.
- 5 Judefind W L & Reid E M, *J Am Chem Soc*, 63, 1941, 2490.
- 6 Naidir F B, *Khim-Farm Zh*, 10, 1976, 117; *Dictionary of Organic Compounds*, 5th edition (Chapman and Hall), 1982, 847.
- 7 Knoevenagel E, *Chem Ber*, 31, 1898, 730.
- 8 Koelsch C F, *J Am Chem Soc*, 72, 1950, 2993.
- 9 Archer S & Pratt M G, *J Am Chem Soc*, 66, 1944, 1657.
- 10 Berger A & Ullerot G, *J Org Chem*, 12, 1947, 346.
- 11 Schevchuk M I & Dombrovskii A V, *Zh Obshch Khim*, 34, 1964, 916; *Chem Abstr*, 60, 1964, 15810h.
- 12 Fournari P R & Chane J, *Bull Soc Chim France*, 1963, 479; *Chem Abstr*, 59, 1963, 1570.
- 13 Arya V P, Fernandes F & Sudarsanam V, *Indian J Chem*, 10, 1972, 598.
- 14 Sprague I M, Lincoln R M & Ziegler C, *J Am Chem Soc*, 68, 1946, 266.
- 15 Backer H J & Buisman J A K, *Rec Trav Chim*, 63, 1944, 226.
- 16 Selim M, Tetu O, Martin G & Rumpf P, *Bull Soc Chim France*, 5, 1968, 2117.
- 17 Coburn R A & Glennon R A, *J Pharm Sci*, 62, 1973, 1785.