Synthesis and antimicrobial activity of some new oxazolone derivatives of 4,5-disubstituted-2-aminothiazoles

Smitha Nair, S. P. Garg and Pramilla Sah*

Department of Chemistry, J. N. V. University, Jodhpur-342 005, Rajasthan, India

Manuscript received 30 December 2004, revised 26 July 2005, accepted 31 October 2005

Abstract: Some new 4-arylidene-2-(4'-4'·,5'-disubstituted-2'-thiazylylamino)-3-nitrophenyl)-4,5-dihydro-oxazole-5-ones have been synthesized and screened for their antimicrobial activity.

Keybords: Oxazolone derivatives, synthesis, antimicrobial activity.

The biological activity of thiazoles has been studied extensively and they have been reported to exhibit antibacterial, antifungal, anti-inflammatory, antiviral and anticancer activities. Oxazoles and oxadiazoles are other classes of compounds reported to possess immense pharmaceutical potential. In continuation with our work on these azoles we report here the synthesis of the compounds incorporating these systems with a view to obtain pharmacologically more potential heterocyclic systems.

Results and discussion

3-Nitro-4-(4'-phenylthiazol-2-yl-amino)benzoic acid (3a) was converted to the acid chloride by reacting with thionyl chloride and further with glycine in methanolic solution of KOH forming N-(4-(4'-phenylthiazol-2-yl)amino-3-nitrobenzoyl)glycine (5a). Infrared spectrum of 3a showed characteristic vibrations at 1680 cm⁻¹ for the carbonyl group of the carboxylic group, at 3310 cm⁻¹ for the -NH bond and at a higher frequency, 3400 cm⁻¹ for the non H-bonded -OH group. In another derivative (3c) where a carbethoxy group was present at 5-position of the thiazole nucleus, another band at 1720 cm⁻¹ for the carbonyl group of the ester was observed. The PMR spectrum of 3a showed a singlet at ~7.63 for 5-H of the thiazole ring, singlet at ~9.55 for the -NH and another singlet downfield at ~10.22 for the single proton of the hydroxyl group which confirmed the formation of this derivative.

In compound 5a, the infrared spectrum showed vibrations at 1670 cm⁻¹ which indicated the presence of an amido group while an absorption band at 1685 cm⁻¹ was observed due to the carbonyl group vibration of the carboxyl group. The PMR spectrum showed a triplet at ~8.23 for one proton and a doublet at ~4.24 integrating for two protons. This confirmed the presence of -NHCH₂ moiety being introduced on reaction with glycine. In the next step conversion to the oxazolone derivatives took place by reacting with benzaldehyde in presence of sodium acetate and acetic anhydride. In IR spectrum of 4-arylidene-2-(4'-4'-methyl-2'-thiazolylylamino)-3-nitrophenyl)-4,5-dihydrooxazol-5-one (6d) a stretching vibration at 1800 cm⁻¹ indicated the presence of a cyclic keto group and at 1640 cm⁻¹ for an olefinic bond C=C. In the PMR spectrum signal at ~5.82 as a singlet was visible for a single proton i.e. C=CH, which supported the formation of the oxazolone derivative.

The antibacterial activity was done by the disc diffusion technique at 250 and 500 μg/disc with Ampicillin and Streptomycin as the standard drugs. The gram negative strains of bacteria taken were E. coli, Klebsiella species, S. typhi, the gram positive S. aureus and S. albus. The antimicrobial activity was conducted against a single strain of fungi A. flavus and yeast C. albicans with Griesofulvin as the reference drug.

Compounds 5a, 5b, 5d, 5e, 5f, 5g (E. coli), 5a and 5e (S. aureus) and 5b and 5e (S. typhi) gave zone of inhibition comparable to the standard drugs. One derivative 5g (S. albus) gave zone of inhibition comparable to the standard drugs. One derivative 5g (S. albus), while two other compounds 5d and 5e against S. typhi and also against Klebsiella species displayed a lesser zone of inhibition.

Against Aspergillus flavus, 5a, 5e, 5g and 5h were very active while 5e and 5f also inhibited the growth of Candida albicans comparable to the standard drug Griesofulvin.

Experimental

The IR spectra were recorded on Shimadzu B101A...
4,5-Disubstituted-2-aminothiazoles (1) were synthesized by the method of Dodson and King:3

3-Nitro-4-(4'-phenylthiazol-2-ylamino)benzoic acid (3a):

Equimolar quantities of 2-amino-4-phenylthiazole and 4-chloro-3-nitrobenzoic acid were refluxed for 4 h in presence of anhydrous potassium carbonate (1 mmol) and dry acetone (15 mL). Excess solvent was distilled off and the solid obtained was washed with water and recrystallised from acetone. yield 65%. m.p. 195°C. Molecular Formula C_{16}H_{11}N_{3}SO_{4}. % Found (Calcd.): C, 56.36 (56.30); H, 3.20 (3.22); N, 12.30 (12.32); IR : 1455 cm^{-1} (N=C=S); 1680 cm^{-1} (>C=O); 1500 cm^{-1} (-NO_{2}); 3400 cm^{-1} (-OH). PMR: δ 7.63 (1H, s, H-5 thiazole); 9.55 (1H, s, NH), 10.22 (1H, s, OH); 7.88–8.01 (8H, m, ArH).

Other derivatives were synthesized in similar manner.

3b: R_{1} = CH_{3}, R_{2} = H, yield 60%, m.p. 180 °C. Molecular Formula C_{15}H_{12}N_{3}SO_{4}. % Found (Calcd.): C, 47.30 (47.31); H, 3.25 (3.22); N, 15.10 (15.05).

3c: R_{1} = CH_{3}, R_{2} = COOC_{2}H_{5}, Yield 65%, m.p. 188 °C. Molecular Formula C_{14}H_{13}N_{3}SO_{6}. % Found (Calcd.) C, 47.89 (47.86); H, 3.67 (3.70).

Other derivatives were synthesized in similar manner. 3d: R_{1} = CH_{3}, R_{2} = H, yield 70%, m.p. 175 °C. Molecular Formula C_{16}H_{16}N_{4}SO_{7}. % Found (Calcd.) C, 47.11 (47.06); H, 3.95 (3.92).

N-(4-(4'-phenylthiazol-2-yl)amino-3-nitrobenzoylglycine (5a):

3-Nitro-4-(4'-phenylthiazol-2-ylamino)benzoic acid (0.01 mol) and thionyl chloride (0.02 mol) were refluxed under anhydrous conditions for 1 h. Excess thionyl chloride was distilled off under reduced pressure and the acid chloride (4a) so formed was subsequently treated with a solution of glycine (0.01 mol) in methanol (25 mL) and potassium hydroxide (0.05 mol). The reaction mixture was stirred for 12 h at room temperature and then poured into ice cold water. Acidification with dil. HCl gave a precipitate which was filtered, dried and recrystallised from methanol. Yield 75%, m.p. 160 °C. Molecular Formula C_{18}H_{14}N_{4}SO_{5}. % Found (Calcd.) C, 54.31 (54.27); H, 3.48 (3.52); N, 14.00 (14.07). IR: 1260 cm^{-1} (N-N =C); 1670 (-CONH); 1685 (>C=O); 3300 (-NH); 1520 cm^{-1} (-N02). PMR: δ 8.23 (1H, t, NHCH_{2}); 4.24 (2H, d, CH_{2}CO); 7.88 (1H, s, H-5 thiazole); 9.02 (1H, s, NH); 10.05 (1H, s, OH); 7.95–8.13 (8H, m, ArH).

Other derivatives were synthesized following the same procedure. 5b: R_{1} = CH_{3}, R_{2} = H, yield 70%, m.p. 166 °C. Molecular Formula C_{19}H_{12}N_{4}SO_{5}. % Found (Calcd.) : C, 46.42 (46.43); H, 3.51 (3.57); N, 16.66 (16.67). 5c: R_{1} = CH_{3}, R_{2} = COOC_{2}H_{5}, yield 70%, m.p. 175 °C. Molecular Formula C_{16}H_{16}N_{4}SO_{7}. % Found (Calcd.) : C, 47.11 (47.06); H, 3.95 (3.92); N, 13.69 (13.73).

4-Arylidene-2-(4'-(4'-methyl-2'-thiazolylamino)-3-nitrophenyl)-4,5-dihydrooxazol-5-one (6d):

N-(4-(4'-Phenythiazol-2-yl)amino-3-nitrobenzoylglycine (0.01 mol), benzaldehyde (0.01 mol) and (0.02 mol) of anhydrous sodium acetate in acetic anhydride (5 mL) were fused together on an electric hot plate. When the contents liquified, further heating was done on a water bath for 2–3 h. After cooling, the contents were diluted with ethanol and left in a freezer overnight. The solid so obtained was filtered, washed with hot water,
Note

dried, and recrystallised from methanol. Yield 55%, m.p. 195 °C. Molecular Formula C_{20}H_{14}N_{4}SO_{4}. % Found (Calcd.) : C, 59.17 (59.11); H, 3.38 (3.47); N, 13.76 (13.79). IR : 1800 (>C=O, cyclic), 1640 (C=CH), 1525 and 3320 for the cyclic –N=C=S of the thiazole ring, the nitro group and the -NH bond. PMR : δ 2.56 (3H, s, CH_{3}); 5.82 (1H, s, C=CH), 7.88 (1H, s, 5-H thiazole); 9.34 (1H, s, NH); 7.42-7.71 (8H, m, ArH): 6e : R_{1} = CH_{3}, R_{2} = H, R_{3} = 3-OH, 4-OCH_{3}, yield 60%. m.p. 210 °C. Molecular Formula C_{21}H_{16}N_{4}SO_{6}. % Found (Calcd.): C, 55.63 (55.75); H, 3.65 (3.54); N, 12.36 (12.39); IR : 1790 (>C=O, cyclic), 1640 (-C=CH), 3310 cm^{-1} (-NH). PMR: δ 2.32 (3H, s, CH_{3}); 3.97 (3H, s, OCH_{3}); 5.96 (1H, s, C=CH); 7.86 (1H, s, 5-H thiazole); 9.32 (1H, s, NH); 10.01 (1H, s, OH); 7.33-7.80 (6H, m, ArH).

6h : R_{1} = CH_{3}, R_{2} = COOC_{2}H_{5}, R_{3} = 3-OH, 4-OCH_{3}, yield 70%, m.p. 212 °C. Molecular Formula C_{24}H_{20}N_{4}SO_{8}. % Found (Calcd.) : C, 54.90 (54.96); H, 3.90 (3.81); N, 10.67 (10.69); IR : 1720 (>C=O ester); 1800 (>C=O cyclic); 1630 (C=CH); 3320 (NH). PMR : δ 2.45 (3H, s, CH_{3}); 4.01 (3H, s, OCH_{3}); 5.82 (1H, s, C=CH); 3.80 (2H, q, CH_{2}CH_{3}); 1.75 (3H, t, CH_{2}CH_{3}); 9.05 (1H, s, NH); 10.15 (1H, s, OH); 7.20-7.90 (6H, m, ArH).

6a (65%), m.p. 190 °C (Found : C, 63.99; H, 3.36; N, 11.89. C_{25}H_{16}N_{4}SO_{4} calcd. for : C, 64.10; H, 3.46; N, 11.97%). b (65%), m.p. 208 °C (Found : C, 60.68; H, 3.58; N, 10.77. C_{26}H_{18}N_{4}SO_{6} calcd. for : C, 60.70; H, 3.61; N, 10.89%). c (65%), m.p. 185 °C (Found : C, 61.85; H, 3.40; N, 11.55. C_{25}H_{16}N_{4}SO_{5} calcd. for : C, 61.98; H, 3.30; N, 11.57%). f (55%), m.p. 180 °C (Found : C, 56.74; H, 3.25; N, 13.24. C_{20}H_{14}N_{4}SO_{5} calcd. for : C, 56.89; H, 3.32; N, 13.27%). g (70%), m.p. 185 °C (Found : C, 57.68; H, 3.87; N, 11.69. C_{23}H_{18}N_{4}SO_{6} calcd. for : C, 57.74; H, 3.76; N, 11.72%).

Acknowledgement

The authors express their thanks to the Directors of CDRI, Lucknow, DRDO and AFRI, Jodhpur for the elemental and spectral analysis. Thanks are also due to the Head, Microbiology Division, S. N. Medical College, Jodhpur for the antimicrobial activity and Head, Department of Chemistry, J. N. Vyas University, Jodhpur, for providing the necessary facilities.

References

1. P. Sah, S. P. Garg and S. R. Nautiyal, Indian J. Heterocycl. Chem., 1997, 6, 229; B. K. Kalluraya and S. N. Shetty, Oriental J. Chem., 1996, 12, 141; S. K. Vingar, A. S. Bobade and B. G. Khadse, Indian J. Heterocycl. Chem., 2001, 11, 35; S. Nair, P. Sah and S. P. Garg, Oriental J. Chem., 2003, 19, 373.

2. S. K. Srivastava, S. Srivastava and S. D. Srivastava, Indian J. Chem., 1999, 38, 183; M. G. H. Zaidi, Chem. Env. Res., 1998, 7, 141; M. Kidwai, Y. Goel and P. Kumar, Indian J. Pharm. Sci., 1998, 60, 396; V. N. Sonar, S. K. Yazadan and N. Sreenivasulu, Indian J. Heterocycl. Chem., 2001, 10, 299; V. Rastogi, S. P. Garg and P. Sah, Indian J. Heterocycl. Chem., 2003, 12, 301.

3. R. M. Dodson and L. C. King, J. Am. Chem. Soc., 1945, 67, 2242.

4. A. L. Barry, L. J. Joyce, A. P. Adams and E. J. Benner, Am. J. Clin. Pathol., 1973, 59, 693.