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Synthesis and Antimicrobial Activities of Some 2-[(Dialkylaminothiocarbonylthio)acetamido]-5-nitrothiazole Derivatives

Usama Abu Mohsen

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Al-Azhar – Gaza, Palestine

Abstract

In this study, some novel 2-[(dialkylaminothiocarbonylthio)acetamido]-5-nitrothiazole derivatives were synthesized by reacting 2-(chloroacetamido)-5-nitrothiazole and an appropriate potassium N,N-disubstituted dithiocarbamate. Their structures have been elucidated by IR, ^{1}H-NMR spectral data and elemental analyses. The antibacterial and antifungal activities of the obtained compounds were investigated in vitro and appreciable activities were obtained.

Key words : 5-Nitrothiazole, dithiocarbamate, antimicrobial activity

Introduction

Five membered heteroaromatic rings bearing nitro group on fifth position such as nitrofuran and nitroimidazoles are well known especially with their antimicrobial activity. 5-Nitrothiazole constitutes another well-studied bioisostere of this group (Ilvespaa, 1968; Bradford *et al.*, 1970; Werbel *et al.*, 1971; Tchelitcheff *et al.*, 1973; Islip *et al.*, 1974; Strehlke, 1974; Strehlke and Schröder, 1974; Demirayak *et al.*, 1989, Gellis *et al.*, 1997; Gellis *et al.*, 1997). Dithiocarbamate moiety is also of consideration with its potent antiviral (Field and Hanley, 1971), antifungal (Schade and Rieche, 1966; Ertan and Üreten, 1983; Cesur *et al.*, 1994; Günay *et al*, 1999) and antibacterial (Reuter *et al.*, 1971; Turan-Zitouni *et al.*, 1999; Ateş *et al.*, 2003) activities. In a similar rationale we planned to synthesize compounds bearing nitrothiazole and dithiocarbamate residues together in the same structure. To accomplish this, in this study we synthesized some new 2-[(dialkylaminothiocarbonylthio)acetamido]-5-nitrothiazole derivatives and elucidated their structure and tested their antimicrobial and antifungal activities on a number of bacteria and fungi.

Materials and Methods

Melting points were determined by using an Electrothermal 9100 digital melting point apparatus and were uncorrected. Spectroscopic data were recorded on the following instruments, FT-IR: Schimadzu 8400S spectrophotometer, ^{1}H-NMR: Bruker DPX 400 NMR spectrometer using TMS as internal standard. Analyses for C, H, N, S were within ± 0.4 % of the theoretical values. 2-(Chloroacetamido)-5-nitrothiazole was obtained by reacting 2-amino-5-nitrothiazole with chloroacetylchloride and triethylamine in THF in accordance with the procedure described previously (Usvi, 1968).

2-[(Dialkylaminothiocarbonylthio)acetamido]-5-nitrothiazoles: An appropriate secondary amine (10 mmol) was dissolved in 5 ml pyridine, %20 KOH (10 mmol) and then CS_2 (10 mmol) were

added dropwise while stirring in an ice bath. 30 Minutes later, a solution of 2-(chloroacetamido)-5-nitrothiazole (10 mmol) in 5 ml pyridine was added. The mixture was stirred for one hour. The resulting clear solution was poured into water. The precipitate formed was filtered and recrystallized from ethanol. Some characteristics of the synthesized compounds were given in Table 1.

1 IR ν (cm^{-1}) : 3143 (N-H), 1681 (C=O), 1558,1346 (N=O), 1515-1429 (C=N, C=C). ^{1}H-NMR δ ppm: 3.42 (3H, s, N-CH_3), 3.44 (3H, s, N-CH_3), 4.41 (2H, s, S-CH_2CO), 8.64 (^{1}H, s, thiazole-4-H), 13.42 (1H, bs, NH).

2 IR ν (cm^{-1}) : 3152 (N-H), 1689 (C=O), 1555,1337 (N=O), 1520-1415 (C=N, C=C). ^{1}H-NMR δ ppm: 1.25 (6H, t, J: 6.2 Hz, two -CH_3), 3.66 (2H, q, J: 6.1 Hz, N-CH_2), 4.25 (2H, q, J: 6.1 Hz, N-CH_2), 4.42 (2H, s, S-CH_2CO), 8.64 (1H, s, thiazole-4-H), 13.42 (1H, s, NH).

5 IR ν (cm^{-1}) : 3099 (N-H), 1708 (C=O), 1539,1352 (N=O), 1492-1423 (C=N, C=C). ^{1}H-NMR δ ppm: 1.59-1.65 (6H, m, -$(CH_2)_3$-), 3.93 (2H, t, J: 6.0 Hz, N-CH_2), 4.18 (2H, t, J: 6.0 Hz, N-CH_2), 4.42 (2H, s, S-CH_2CO), 8.64 (1H, s, thiazole-4-H), 13.42 (1H, s, NH).

6 IR ν (cm^{-1}) : 3132(N-H), 1700 (C=O), 1531,1348 (N=O), 1507-1423 (C=N, C=C). ^{1}H-NMR δ ppm: 3.67-3.72 (4H, m, -CH_2OCH_2)-), 3.96 (2H, bs, N-CH_2-), 4.18 (2H, bs, N-CH_2-), 4.46 (2H, s, S-CH_2CO), 8.64 (1H, s, thiazole-4-H), 13.44 (1H, bs, NH).

8 IR ν (cm^{-1}) : 3083 (N-H), 1691 (C=O), 1525,1346 (N=O), 1498-1427 (C=N, C=C). ^{1}H-NMR δ ppm: 3.25-3.48 (4H, m, two Ph-N-$\underline{CH_2}$-), 4.11 (2H, bs, N-CH_2-), 4.33 (2H, bs, N-CH_2-), 4.47 (2H, s, S-CH_2CO), 6.81-6.84 (1H, m, Ar-H), 6.95-6.97 (2H, m, Ar-H), 7.23-7.27 (2H, m,Ar-H), 8.64 (1H, s, thiazole-4-H), 13.45 (1H,bs,NH).

9 IR ν (cm^{-1}) : 3151 (N-H), 1693 (C=O), 1535,1338 (N=O), 1510-1417 (C=N, C=C). ^{1}H-NMR δ ppm: 1.45-1.57 (4H, m, -$\underline{CH_2)_2}$-), 1.73-1.77 (2H, m, -CH_2-), 1.81-1.85 (2H, m, -CH_2-), 3.94 (2H, t, J:6.0 Hz,N-CH_2-), 4.10 (2H, t, J:6.0 Hz,N-CH_2-), 4.42 (2H, s, S-CH_2CO), 8.64 (1H, s, thiazole-4-H), 13.42 (1H,bs,NH).

Microbiology: The antibacterial and antifungal activities of the compounds were determined in vitro by using the tube dilution technique (Finegold *et al.*, 1978; Mc Ginnis *et al.*, 1991). The MIC values were given in μg/mL. The stock solutions of the compounds were prepared in DMSO. Chloramphenicol and ketoconazole were used as control antibacterial and antifungal agents, respectively. The standard bacteria and fungi strains used were: Escherichia coli ATCC 25922, Proteus vulgaris NRRL B-123, Pseudomonas aeruginosa ATCC 27853, Staphylococcus aureus NRRL B-767, Candida albicans* (*: University of Osmangazi, Eskişehir, TÜRKİYE).

Results and Discussion

2-(Chloroacetamido)-5-nitrothiazole (I) was prepared from 2-amino-5-nitrothiazole and chloroacetyl chloride by a single step synthesis as depicted in Scheme 1 (Usvi, 1968). 2-[(Dialkylaminothiocarbonyl thio)acetamido]-5-nitrothiazoles were obtained from the reaction of I and corresponding dialkylaminothiocarbonylthio potassium salt. Some physical data of the new 2-[(dialkylaminothiocarbonylthio)acetamido]-5-nitrothiazoles are given in Table 1.The structures of the compounds were assigned by elemental analysis (C, H, N, S) and spectroscopic methods (IR, ^{1}H-NMR). Spectral data of representative derivatives are given in the experimental. In the IR spectra; N-H, C=O, C=C, C=N and N=O stretching bands were observed at expected frequencies. ^{1}H-NMR spectra, N-H protons, thiazole-4-H protons and methylene protons of acetyl residues which are common in all compounds were obtained at about 13.4, 8.64 and 4.4 ppm respectively. The neighbouring methyl or methylene protons to nitrogen atom in secondary amine side of the molecule were observed as two different chemical shift values. Although these two methyl or methylene groups were seemed as equivalent, it should be noted that this anomaly might arise from magnetic anisotropy and conformational differences due to tautomerizm in dithiocarbamate structure.

In the introductory part it was denoted that, nitrothiazoles are well known antibacterials and dithiocarbamate residue plays an essential role for antifungal activity. Therefore, when the MIC values of the compounds in table 2 are taken into consideration, in regard to the effects of the control antibacterial chloramphenicole and control antifungal ketoconazole, it is seen that, the compounds showed antibacterial and antifungal activity as expected. Also we may conclude that, antifungal activity of the compounds' is more appreciable than their antibacterial activity. However, it is not possible to classify the results according to neither compound groups nor substituents.

Table 1. Some characteristics of the synthesized compounds

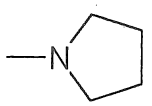
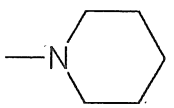
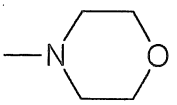
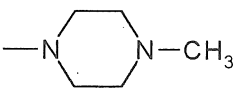
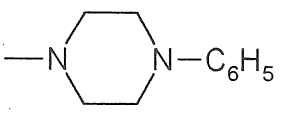
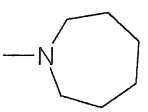
Comp.	R	Yield (%)	M.p (°C)	Formula M.W.	Analyses C	H	N	S
1	$-N(CH_3)_2$	92	177	$C_8H_{10}N_4O_3S_3$	31.36	3.29	18.29	31.39
				(306.39)	31.54	3.34	18.11	31.51
2	$-N(C_2H_5)_2$	78	184	$C_{10}H_{14}N_4O_3S_3$	35.91	4.22	16.75	28.76
				(334.44)	36.12	4.27	16.90	29.11
3	$-N(C_3H_7)_2$	82	128	$C_{12}H_{18}N_4O_3S_3$	39.76	5.01	15.46	26.53
				(362.49)	39.44	4.82	15.40	26.41
4		77	181	$C_{10}H_{12}N_4O_3S_3$	36.13	3.64	16.85	28.93
				(332.42)	35.85	3.24	17.10	29.27
5		84	196	$C_{11}H_{14}N_4O_3S_3$	38.14	4.07	16.17	27.76
				(346.45)	38.70	4.29	15.86	28.04
6		65	206	$C_{10}H_{12}N_4O_4S_3$	34.47	3.47	16.08	27.60
				(348.42)	34.20	3.02	15.91	27.76
7		70	233	$C_{11}H_{15}N_5O_3S_3$	36.55	4.18	19.37	26.61
				(361.47)	36.91	3.90	18.93	26.94
8		68	193	$C_{16}H_{17}N_5O_3S_3$	45.37	4.05	16.54	22.71
				(423.54)	45.23	4.19	16.05	22.66
9		67	175	$C_{12}H_{16}N_4O_3S_3$	39.98	4.47	15.54	26.68
				(360.48)	40.22	4.67	15.75	27.02

Table 2. Antimicrobial activity of the compounds.

	MIC values (µg / mL)				
Compounds	A	B	C	D	E
1	50	50	50	50	50
2	50	25	50	25	50
3	50	25	50	50	50
4	50	50	50	50	50
5	50	25	50	25	50
6	50	50	50	50	50
7	50	50	50	50	25
8	50	25	50	25	50
9	25	50	25	50	25
Chloramphenicol	25	12.5	12.5	25	-
Ketoconazole	-	-	-	-	75

A: *P. aeruginosa*, B: *S. aureus*, C: *E.coli*, D: *P.vulgaris*, E: *Candida albicans*

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