Hydrazones of [(2-Benzothiazolylthio)acetyl]hydrazine: Synthesis and Antimicrobial Activity

Hydrazone des [(2-Benzothiazolylthio)acetyl]hydrazins: Synthese und antimikrobielle Aktivität

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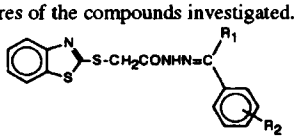
2-Mercaptobenzothiazole derivatives show antibacterial and antifungal activity [1–3]. *Labouta et al.* synthesized some hydrazones of (2-benzimidazolyl)acetohydrazide and reported the antimicrobial activity of the compounds against some Gram(+) and Gram(–) bacteria and against *Candida albicans* [4]. *Gürsoy et al.* synthesized some hydrazones of 2-thiadiazolylthioacetohydrazide and 2-triazolylthioacetohydrazide and reported antifungal activity [5]. In addition to these findings, it is well known that hydrazide hydrazones have antimicrobial activity in general [6–8].

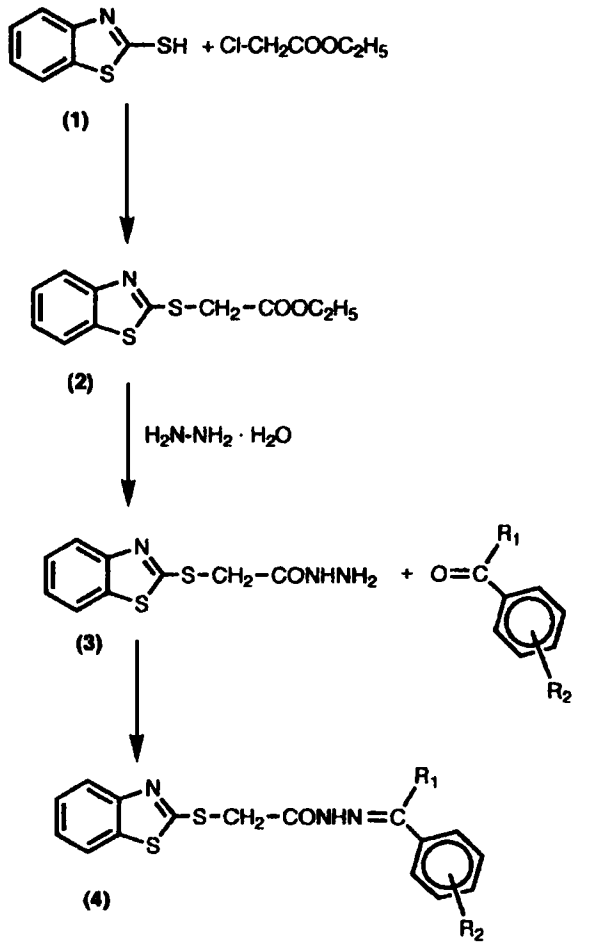
On the basis of these data, we have synthesized some hydrazones of acetyl hydrazide bearing a benzothiazolylthio residue on the acetyl increment (Table 1).

Ethyl (2-benzothiazolylthio)acetate **2** was prepared by reaction of 2-mercaptobenzothiazole **1** and ethyl chloroacetate. [(2-Benzothiazolylthio)acetyl]hydrazide **3** was obtained from **2** and hydrazine hydrate. Condensation of **3** with appropriate aromatic aldehydes and acetophenone derivatives gave the title compounds **4** (Scheme 1).

Table 1: The structures of the compounds investigated.



Compound	R_1	R_2	m.p.	Yield (%)
4a	CH_3	H	179	88
4b	CH_3	4-Cl	198	85
4c	CH_3	4-CH_3	164	92
4d	CH_3	4-NH_2	184	80
4e	CH_3	4-NO_2	214	93
4f	CH_3	4-OH	140	91
4g	CH_3	2-OH	209	84
4h	CH_3	4-OCH_3	154	95
4i	CH_3	2-OCH_3	209	94
4j	H	H	109	95
4k	H	4-Cl	122	98
4l	H	2-Cl	177	97
4m	H	4-OH	78	85
4n	H	2-OH	181	88
4o	H	4-OCH_3	153	95
4p	H	2-OCH_3	160	93
4r	H	4-OC_2H_5	152	90
4s	H	2-OC_2H_5	155	92
4t	H	4-NO_2	205	88
4u	H	2-NO_2	164	91
4v	H	4-$N(CH_3)_2$	158	94
4x	H	4-$NHCOCH_3$	212	96



Scheme 1

Yields and melting points of the compounds are also shown in Table 1. Table 2 lists the minimum inhibitory concentrations (MIC) of the title compounds **4**. Seven of the title compounds, **4a**, **4f**, **4j**, **4k**, **4l**, **4n**, and **4v** have been reported before [9–11].

In the ^1H NMR spectra of compounds **4**, there are two singlets at about 4.30 and 4.70 ppm (2H) of the CH_2- groups of the thioacetyl moiety. This phenomenon may be attributed to the folding of the side chain on to the sulfur bridge in solution: in other words these two singlets might represent two rotamers. In accordance with our suggestion, N-H signals also appear as two singlets at *ca* δ = 12.00 ppm. The same feature of similar compounds has been reported by *Gürsoy* and *Dimmrock* [5,12].

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Table 2: Antimicrobial activity (MIC [a], μg ml^{-1}) of compounds **4a–x**.

Compound	Organism [b]							
	A	B	C	D	E	F	G	H
4a	50	50	50	50	25	25	25	25
4b	50	50	50	50	25	25	25	25
4c	50	50	50	50	25	25	25	25
4d	50	50	50	50	25	25	25	25
4e	50	50	50	50	25	25	25	25
4f	50	50	50	50	25	25	25	25
4g	50	25	50	50	25	25	25	12.5
4h	50	50	50	50	25	25	25	12.5
4i	50	50	50	50	25	25	25	25
4j	50	50	50	50	25	25	25	25
4k	50	50	50	50	12.5	25	25	25
4l	50	50	50	50	25	25	25	25
4m	50	50	50	50	25	25	25	25
4n	50	50	50	50	25	25	25	25
4o	50	50	50	50	25	25	25	25
4p	50	50	50	50	12.5	25	25	25
4r	50	50	50	50	12.5	25	25	25
4s	50	50	50	50	12.5	25	25	25
4t	50	50	50	50	12.5	25	25	25
4u	50	50	50	50	12.5	25	12.5	25
4v	50	50	50	50	12.5	25	12.5	25
4x	50	50	50	50	12.5	25	12.5	25
Ampicillin sodium	6.25	6.25	6.25	6.25				
Clotrimazole					3.15	3.15	3.15	3.15

[a] Minimal inhibitory concentration

[b] A, *Escherichia coli*; B, *Pseudomonas aeruginosa*; C, *Streptococcus faecalis*; D, *Staphylococcus aureus*, E, *Candida albicans*; F, *Candida pseudotropicalis*; G, *Candida parapsilosis*; H, *Candida stellatoidea*

Complete ^{1}H NMR and IR data have only been given in the Experimental Part for compound **4a**. Complete data can be obtained from the authors on request.

Elemental analysis of the compounds were within the range ± 0.4 % (Table 3).

Table 3: Results from elemental analysis.

Cmpd	Calculated (%)			Found (%)		
	C	H	N	C	H	N
4a	59.82	4.39	12.31	60.21	4.39	11.92
4b	54.32	3.72	11.18	54.38	4.08	11.21
4c	60.68	4.78	11.83	61.05	4.83	11.59
4d	57.30	4.49	15.73	57.64	4.85	15.35
4e	52.84	3.62	14.50	53.17	3.94	14.28
4f	57.14	4.20	11.76	57.51	4.53	11.45
4g	54.14	4.20	11.76	54.06	4.38	11.55
4h	58.22	4.58	11.32	58.61	4.86	10.90
4i	58.22	4.58	11.32	58.68	4.73	10.92
4j	58.71	3.37	12.84	58.46	3.73	13.06
4k	53.11	3.31	11.61	53.01	3.45	11.33
4l	53.11	3.31	11.61	53.45	3.49	11.98
4m	55.97	3.79	12.24	55.76	4.20	11.97
4n	55.97	3.79	12.24	56.35	4.39	11.86
4o	57.14	4.20	11.76	56.88	4.54	12.03
4p	57.14	4.20	11.76	57.55	4.22	11.39
4r	58.06	4.83	11.29	58.09	5.27	11.03
4s	58.06	4.83	11.29	57.95	4.92	11.24
4t	51.47	3.48	15.01	51.82	3.69	14.68
4u	51.47	3.48	15.01	51.09	3.74	14.82
4v	58.22	5.12	15.09	58.09	5.32	14.71
4x	56.10	4.41	14.54	56.41	4.42	14.69

All the compounds are highly potent against the yeast-like fungi and bacteria tested, **4g** and **4h** being more potent than the others against *Candida stellatoidea*. One can say that **4k** and **4p–4x** are equally potent against *Candida albicans* whereas **4u–4x** are also equally potent against *Candida parapsilosis*. None of the compounds have higher activity than ampicillin sodium against both Gram(–) and Gram(+) bacteria.

Experimental Part

Melting points: Electrothermal melting point apparatus, uncorrected.– IR spectra: (KBr, $\tilde{\nu}$ cm^{-1}) Perkin Elmer 1330 spectrometer.– ^{1}H NMR: ([D6]DMSO, TMS as internal standard, chemical shifts, δ, in ppm), Bruker 200 FT-NMR spectrometer.– Elemental analyses: Hewlett-Packard 185 C, H, N, analyzer, Chemistry Department, Middle East Technical University, Ankara, Turkey.

2-Mercaptobenzothiazole **1** [13], *ethyl (2-benzothiazolylthio)acetate* **2** [14,15], *2-(2-benzothiazolylthio)acetohydrazide* **3** [10], *and hydrazone of 2-(2-benzothiazolylthio)acetohydrazide* **4**

0.003 Mole of **3** was dissolved in 10 mL of EtOH and 0.003 mole of the corresponding carbonyl compounds (benzaldehydes or acetophenones) were added. The mixture was refluxed for 8 h, then left overnight at room temp. The solid material which precipitated was crystallized from EtOH The % yield and m.p. are given in Table 1.

4a IR: $\tilde{\nu}$ (*cm*$^{-1}$) = 3500–2800 (N-H), 3100 (C-H aromatic), 2980, 2910 (C-H aliphatic), 1670 (C=O), 1620, 1580, 1450 (C=N and C=C), 750, 740 (C-H out of plane bending).– ^{1}H NMR: 2.25 (s, 3H, CH_3), 4.20 and 4.60 (2s, 2H, CH_2), 7.05–8.10 (m, 9H, aromatic), 10.7 and 10.9 (2s, 1H, NH)

Microbiology

The microdilution susceptibility test in Müller-Hinton Broth (Oxoid) and Sabouraud Liquid Medium (Oxoid) was used for the determination of antibacterial and antifungal activity [16,17]. Test organisms: *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 as Gram(–) bacteria, *Streptococcus faecalis* ATCC 19433 and *Staphylococcus aureus* ATCC 25923 as Gram(+) bacteria, and *Candida albicans*, *Candida parapsilosis*, *Candida pseudotropicalis*, and *Candida stellatoidea* as yeast-like fungi.

The compounds ampicillin sodium and clotrimazole as references were dissolved in DMSO at 800 μg ml^{-1}. Two-fold dilutions of the compounds and references were prepared (800, 400, 200, ... 6.25 μg ml^{-1}). Microorganism suspensions at 10^6 cfu (colony forming units) ml^{-1} were inoculated to the wells. The plates were incubated at 36 °C for 24–48 h. The incubation chamber was kept sufficiently humid. The minimal inhibitory concentrations (MIC) were determined at the end of the incubation period.

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