Synthesis of Some New 6-Methylimidazo[2,1-b]thiazole-5-carbohydrazide Derivatives and their Antimicrobial Activities

Füsun Ur[a], Nesrin Cesur[a], Seher Birteksöz[b], and Gülten Ötük[b]

Department of Pharmaceutical Chemistry[a] and Department of Pharmaceutical Microbiology[b], Faculty of Pharmacy, Istanbul University, Istanbul (Turkey)

Summary

In this study, 14 new compounds having 6-methyl-N^2-(alkylidene/cycloalkylidene)imidazo[2,1-b]thiazole-5-carbohydrazide (3a-g), 3-[[(6-methylimidazo[2,1-b]thiazole-5-yl)carbonyl]amino]-4-thiazolidinone (4a-d) and 4-[[(6methylimidazo[2,1-b]thiazole-5-yl)carbonyl]amino]-1-thia-4-azaspiro[4.4]nonan/[4.5]decan-3-one (4e–g) structures were synthesized. The structures of the compounds were elucidated by UV, IR, ^{1}H-NMR, ^{13}C-NMR, ^{1}H-^{13}C-COSY, mass spectra and elemental analysis. All compounds synthesized were tested for antimicrobial activity against *Staphylococcus aureus* ATCC 6538, *Staphylococcus epidermidis* ATCC 12228, *Escherichia coli* ATCC 8739, *Klebsiella pneumoniae* ATCC 4352, *Pseudomonas aeruginosa* ATCC 1539, *Salmonella thypi*, *Shigella flexneri*, *Proteus mirabilis* ATCC 14153, *Candida albicans* ATCC 10231 and *Mycobacterium tuberculosis* H_{37}Rv. Only *4d* and *4f* demonstrated antimicrobial activity against *S. epidermidis* ATCC 12228 (MIC: 19.5 µg/ml and 39 µg/ml, respectively).

Zusammenfassung

Synthese neuer 6-Methylimidazo[2,1-b]thiazol-5-carbohydrazid-Derivate und Bewertung ihrer mikrobiologischen Wirkung

In dieser Arbeit wurden 14 neue Verbindungen mit den Grundstrukturen 6-Methyl-N_2-(alkyliden/cycloalkyliden)imidazo[2,1-b]thiazol-5-carbohydrazid (3a-g), 3-[[(6–Methylimidazo[2,1-b]thiazol-5-yl)carbonyl]amino]4-thiazolidinon (4a-d) und 4-[[(6–Methylimidazo[2,1-b]thiazol-5-yl)carbonyl]amino]-1-thia-4-azaspiro[4.4]nonan/[4.5]decan-3-on (4e-g) dargestellt. Alle Strukturen wurden mittels UV, IR, ^{1}H-NMR, ^{13}C-NMR, ^{1}H-^{13}C-COSY, Massenspektroskopie und Elementaranalyse aufgeklärt. Alle Verbindungen wurden gegen *Staphylococcus aureus* ATCC 6538, *Staphylococcus epidermidis* ATCC 12228, *Escherichia coli* ATCC 8739, *Klebsiella pneumoniae* ATCC 4352, *Pseudomonas aeruginosa* ATCC 1539, *Salmonella thypi*, *Shigella flexneri*, *Proteus mirabilis* ATCC 14153, *Candida albicans* ATCC 10231 und *Mycobacterium tuberculosis* H_{37}Rv mikrobiologisch getestet. Nur *4d* und *4f* erwiesen sich gegen *S. epidermidis* ATCC 12228 als aktiv (MIC: 19.5 µg/ml und 39 µg/ml).

Key words

- Hydrazide-hydrazones
- Imidazo[2,1-b]thiazoles, antimicrobial activity, synthesis
- 1-Thia-4-azaspiro[4.4]nonan-3-one, antimicrobial activity, synthesis
- 1-Thia-4-azaspiro[4.5]decan-3-ones, antimicrobial activity, synthesis
- 4-Thiazolidinones, antimicrobial activity, synthesis

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1. Introduction

4-Thiazolidinones have been synthesized for a wide range of pharmaceutical and biological purposes, including antibacterial [1], antifungal [2], anticonvulsant [3], antituberculous [4], antiinflammatory [5], antihistaminic [6] and antidepressant [7] properties. The discovery of antihelmintic properties of levamisole ((–)-2,3,5,6 - tetrahydro - 6 - phenylimidazo [2,1 - b] thiazole) provoked a great deal of research on imidazo[2,1-b]thiazole derivatives [8].

Furthermore, recently researchers have revealed that imidazo[2,1-b]thiazoles of different pharmacodynamic moieties possess potent biological activities viz. antimicrobial [9, 10], antitumor [11], antiinflammatory [12], herbicidal [13], immunomodulatory [14] and antiulcer [15].

These observations prompted us to synthesize new imidazo[2,1-b]thiazole derivatives to investigate their possible antimicrobial activities.

2. Materials and methods

2.1. Chemistry

All chemicals were obtained from Merck-Schuchardt (Munich, Germany). Melting points were determined on a Büchi 530 capillary melting point apparatus (Flawil, Switzerland) in open capillaries and are uncorrected. The purities of the compounds were controlled by TLC on silica gel $HF_{254+366}$ (E. Merck, Darmstadt, Germany). UV spectra were determined using Shimadzu 1601 UV spectrophotometer (Kyoto, Japan). IR spectra were recorded on a Perkin-Elmer 1600 FT (Fourier transform) infrared spectrophotometer in potassium bromide pellets (ν in cm^{-1}) (Norwalk, CT, USA). ^1H and ^{13}C-NMR spectra and 2D-NMR experiments [^1H-^{13}C-COSY (^1H-^{13}C correlated spectroscopy)] were recorded on a Bruker AC-L 200 and 300 MHz spectrophotometer using tetramethylsilane as internal standard (Rheinstetten, Germany). All chemical shifts were reported as δ (ppm) values and spin-spin couplings J were exposed in Hz. EI/MS were determined on a VG Zab Spec (70 eV) (Manchester, England). Elementary analyses were performed on a Carlo Erba 1106 elemental analyzer (Milan, Italy) at the Scientific and Technical Research Council of Turkey.

2.1.1. 6-Methyl-N^2-(alkylidene/cycloalkylidene) imidazo[2,1-b]thiazole-5-carbohydrazides (3a-g)

A mixture of 0.005 mol 6-methylimidazo[2,1-b]thiazole-5-carbohydrazide **2** [16], 0.01 mol appropriate ketone, a drop of conc. H_2SO_4 and 10 ml of C_2H_5OH (96 %) was refluxed for 6 h. The crude product which precipitated on cooling was filtered and crystallized from C_2H_5OH-H_2O mixture.

Spectral data of **3a**: UV (λ_{max} EtOH, log ε, nm): 208.5 (4.23); 244.5 (3.95); 286.5 (4.30). IR (KBr, cm^{-1}): 3273, 3143 (NH); 1659 (C=O).^{1}H-NMR ($CDCl_3$): 1.97 (3H, s, CH_3); 2.15 (3H, s, CH_3); 2.64 (3H, s, 6- CH_3); 6.89 (1H, d, J = 4.4 Hz, C_2-H); 8.24 (1H, d, J = 4.4 Hz, C_3-H); 8.34 (1H, s, CONH). ^{13}C-NMR ($CDCl_3$): 16.62 (6-CH_3); 16.83, 25.40 (=C-CH_3); 112.64 (C_2); 117.50 (C_5); 121.58 (C_3). EIMS (70 eV) m/z (%): 236 (M^+, 74), 181 (2), 165 (100), 137 (22), 71 (3), 57 (12).

Spectral data of **3e**: UV (λ_{max} EtOH, log ε, nm): 208.5 (4.32); 245.5 (4.00); 286.5 (4.32). IR (KBr, cm^{-1}): 3323, 3143 (NH); 1625 (C=O). ^{1}H-NMR ($CDCl_3$): 1.65–1.75 (6H, m, cyclohex.); 2.33 (2H, t, J = 7.5 Hz, cyclohex. C_2-H/C_6-H); 2.45 (2H, t, J = 7.5 Hz; cyclohex. C_2-H/C_6-H); 2.61 (3H, s, 6-CH_3); 6.86 (1H, d, J = 4.4 Hz, C_2-H); 8.19 (1H, d, J = 4.4 Hz, C_3-H); 8.56 (1H, s, CONH). ^{13}C-NMR ($CDCl_3$): 16.79 (6-CH_3), 25.40 (cyclohex. C_4); 25.78, 27.00 (cyclohex. C_3/C_5); 26.71, 35.33 (cyclohex. C_2/C_6); 112.53 (C_2); 117.65 (C_5); 121.48 (C_3); 145.99 (C_6); 151.62 (C_{7a}); 158.00 (C=N); 161.03 (CONH). EIMS (70 eV) m/z (%): 276 (M^+, 23), 181 (14), 165 (100), 137 (7), 111 (5), 97 (10).

2.1.2. 3-[(6–Methylimidazo[2,1-b]thiazole-5-yl) carbonyl]amino]-4-thiazolidinones and 4-[[(6-methylimidazo[2,1-b]thiazole-5-yl)carbonyl]amino]-1-thia-4-azaspiro[4.4]nonan/[4.5]decan-3-ones (4a-g)

Method A

A mixture of **3** (0.005 mol) and $HSCH_2COOH$ (0.15 mol) was refluxed in dry benzene (30 ml) using a Dean-Stark trap for 6 h. Excess benzene was evaporated *in vacuo*. The residue was triturated with saturated $NaHCO_3$ until CO_2 evaluation ceased and allowed to stand overnight.

The solid thus obtained was filtered, washed with H_2O and crystallized from C_2H_5OH-H_2O mixture.

Method B

To a solution of **2** (0.005 mol) in dry benzene (30 ml) was added appropriate ketone (0.01 mol) and the mixture was refluxed for 1.5 h. using a Dean-Stark trap. After cooling the room temperature, $HSCH_2COOH$ (0.15 mol) was added dropwise to the solution and the resulting mixture was refluxed for 6 h. The compounds were purified using the procedure as described in method A.

Spectral data of **4d**: UV (λ_{max} EtOH, log ε, nm): 207.0 (4.26); 248.0 (3.89); 279.0 (4.24). IR (KBr, cm^{-1}): 3300, 3192 (NH); 1708, 1661 (C=O). ^{1}H-NMR ($CDCl_3$): 0.88 (3H, t, J = 6.67 Hz, CH_2CH_3); 1.03 (3H, t, J = 7.27 Hz $(CH_2)_4CH_3$); 1.20–1.50 (4H, m, $2CH_2$); 1.75–1.89 (6H, m, $3CH_2$); 2.62 (3H, s, 6-CH_3); 3.56 (2H, s, thia. CH_2); 6.89 (1H, d, J = 4.40 Hz, C_2-H); 7.76 (1H, s, CONH); 8.10 (1H, d, J = 4.59 Hz, C_3-H). ^{13}C-NMR ($CDCl_3$): 8.58 (CH_2CH_3); 14.02 (pentyl. CH_3); 16.77 (6-CH_3); 22.51, 23.90 (CH_2); 29.48 (thia. C_5); 31.82, 32.79, 39.58 (CH_2); 113.07 (C_2); 116.51 (C_5); 121.34 (C_3); 148.28 (C_6); 152.00 (C_{7a}); 160.30 (CONH/thia. C=O); 169.62 (thia. C=O/CONH). EIMS (70 eV) m/z (%): 380 (M^+, 39), 238 (21), 200 (1), 181 (14), 165 (100), 141 (3), 137 (6), 127 (1).

Spectral data of **4f**: UV (λ_{max} EtOH, log ε, nm): 201.5 (4.34); 245.5 (3.84); 278.0 (4.19). IR (KBr, cm^{-1}): 3143 (NH); 1707, 1671 (C=O). ^{1}H-NMR (DMSO-d_6): 0.99–1.24 (1H, m, cyclohex.); 1.35–1.60 (3H, m, cyclohex.); 1.72–1.86 (6H, m, cyclohex); 2.56 (3H, s, 6-CH_3); 3.61 (2H, s, thia. CH_2); 7.37 (1H, d, J = 4.42 Hz, C_2-H); 7.99 (1H, d, J = 4.41Hz C_3-H); 9.82 (1H, s, CONH). EIMS (70 eV) m/z (%): 350 (M^+, 31), 238 (12), 181 (9),170 (1), 165 (100), 137 (4), 111 (2), 97 (1).

2.2. Antimicrobial activity

Disc diffusion method was used for antimicrobial activity [17]. The cultures of bacteria were prepared in 4 ml Mueller-Hinton Broth (Difco) at 37 °C. After 24 h incubation, the turbidity of culture suspension was adjusted with sterile Mueller-Hinton Broth in order to obtain a turbitidy comparable to a No. 1 McFarland turbidity standard. One milliliter of this suspension was pipetted onto the Mueller-Hinton agar (Difco Laboratories,

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Detroit, MI, USA) plate and distributed evenly over the surface of the medium by gently rocking the plate. Excess suspension was pipetted off. The surface of the medium was allowed to dry for 15 min at room temperature. The 200 µg compound impregnated discs were applied to the surface of inoculated plates. The petri plates were placed in an incubator at 37 °C. After 18–24 h of incubation, the petri plates were examined and the diameter of the inhibition zone was measured. The actual minimum inhibitory concentrations (MIC) (µg/ml) of active compounds were determined using microdilution method [18] using Mueller-Hinton broth · Serial two-fold dilutions ranged from 2500 to 2.4 mg/l for compounds. The inoculum was prepared in broth which had been kept overnight at 37 °C and which had been diluted with Mueller-Hinton broth to give a final concentration of 10^5 cfu/ml in the test tray. The trays were covered and placed in plastic bags to prevent drying. After incubation at 37 °C for 18–20 h, the MIC was defined as the lowest concentration of compound giving complete inhibition of visible growth.

Primary screen for antituberculous activity was conducted at 6 µg/ml against *Mycobacterium tuberculosis* $H_{37}Rv$ in BACTEC 12 B 19 medium using BACTEC 460 radiometric system [19]. Compounds affecting < % 90 inhibition in the primary screen (MIC > 6 µg/ml) were not evaluated further.

3. Results

The key intermediate 6-methylimidazo[2,1-b]thiazole-5-carbohydrazide **2** [16] was prepared by the reaction of hydrazine hydrate with ethyl 6-methylimidazo[2,1-b]thiazole-5-carboxylate **1** [20]. The reaction of **2** with different (alkyl/cycloalkyl)ketones furnished the corresponding 6-methyl-N^2-(alkylidene/cycloalkylidene)imidazo[2,1-b]thiazole-5-carbohydrazides (**3a–g**).

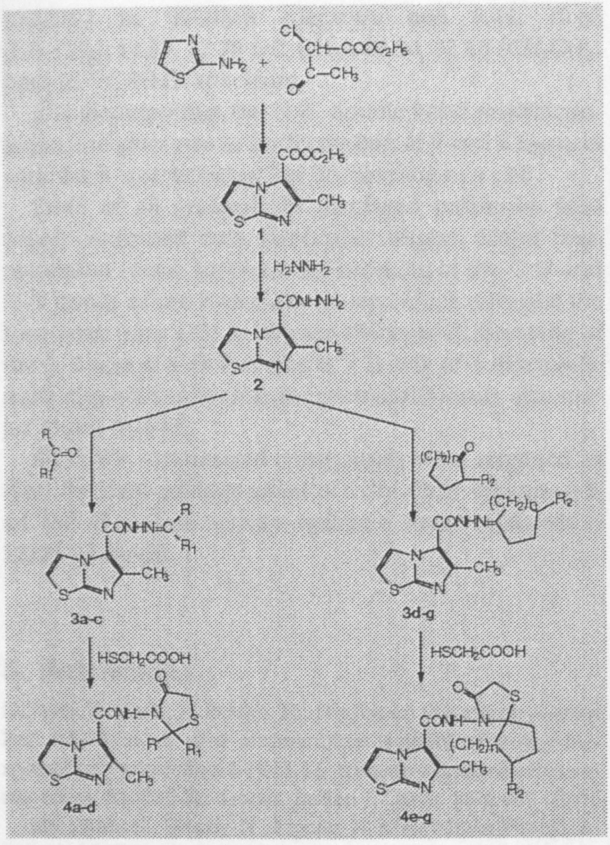
The hydrazide hydrazones **3a–g** on cyclocondensation with thiogylcolic acid led to formation of 3-[[(6-methylimidazo[2,1-b] thiazole-5-yl) carbonyl] amino]- 4-thiazolidinones (**4a–d**) and 4-[[(6–methyl-imidazo[2,1-b] thiazole-5-yl) carbonyl] amino]- 1- thia- 4- azaspiro [4.4]nonan/[4.5]decan-3-ones (**4e–g**) (Method A).

On the other hand heating a mixture of **2**, $HSCH_2COOH$ and the appropriate ketone together also produced the target compounds (**4a–g**) (Method B). As a one pot reaction method B resulted in higher yields than those of Method A (Scheme 1). Melting points, % yields and formulae of the compounds are given in Table 1. The structures were confirmed by spectral methods (UV, FTIR, ^{1}H-NMR, ^{13}C-NMR, ^{1}H-^{13}C-COSY, EI-MS [electron impact mass spectrometry]) and elemental analysis. Spectral data of representative derivatives are given in the Materials and methods section.

All the compounds were tested for antimicrobial activity against *S. aureus* ATCC 6538, *S. epidermidis* ATCC 12228, *E. coli* ATCC 8739, *K. pneumoniae* ATCC 4352, *P. aeruginosa* ATCC 1539, *S. typhi*, *S. flexneri*, *P. mirabilis* ATCC 14153 and *C. albicans* ATCC 10231. **4d** and **4f** demonstrated varying degrees of antimicrobial activity against *S. epidermidis* ATCC 12228 (Table 2).

Table 1: Some physical and analytical data of compounds.

Comp.	R	R_1	R_2	n	M.p. (°C)	Yield (%)	Formula (Mol. weight)	Analysis (%) Calc./found		
								C	H	N
3a	CH_3	CH_3	–	–	127–31	91	$C_{10}H_{12}N_4OS.H_2O$ (254.31)	47.22 47.57	5.54 5.97	22.03 21.22
3b	CH_3	C_2H_5	–	–	128–30	87	$C_{11}H_{14}N_4OS$ (250.31)	52.77 52.37	5.63 5.97	22.38 22.03
3c	C_2H_5	C_2H_5	–	–	154– 6	84	$C_{12}H_{16}N_4OS$ (264.34)	54.52 54.11	6.10 6.54	21.19 21.75
3d	–	–	H	1	192– 4	96	$C_{12}H_{14}N_4OS$ (260.31)	54.94 54.75	5.38 5.07	21.36 21.10
3e	–	–	H	2	103– 5	93	$C_{13}H_{16}N_4OS.H_2O$ (294.37)	53.03 53.38	6.16 5.79	19.03 19.57
3f	–	–	CH_3	2	165– 8	94	$C_{14}H_{18}N_4OS.H_2O$ (308.39)	54.52 54.61	6.53 5.83	18.16 18.06
3g	–	–	C_2H_5	2	190– 2	91	$C_{15}H_{20}N_4OS$ (304.40)	59.18 59.20	6.62 6.93	18.41 17.91
4a	CH_3	CH_3	–	–	130– 2	41	$C_{12}H_{14}N_4O_2S_2.H_2O$ (328.40)	43.88 44.15	4.91 5.20	17.06 17.00
4b	CH_3	C_2H_5	–	–	115– 8	69	$C_{13}H_{16}N_4O_2S_2.H_2O$ (342.43)	45.59 45.60	5.29 5.49	16.36 16.86
4c	C_2H_5	C_2H_5	–	–	116– 9	53	$C_{14}H_{18}N_4O_2S_2.H_2O$ (338.43)	47.17 47.41	5.65 5.95	15.71 15.42
4d	C_2H_5	C_5H_{11}	–	–	145– 9	57	$C_{17}H_{24}N_4O_2S_2$ (380.51)	53.66 53.73	6.36 6.83	14.72 15.02
4e	–	–	H	1	126– 8	42	$C_{14}H_{16}N_4O_2S_2.H_2O$ (354.44)	47.43 47.80	5.11 5.28	15.80 15.46
4f	–	–	H	2	245– 8	63	$C_{15}H_{18}N_4O_2S_2$ (350.44)	51.41 52.18	5.18 5.23	15.99 15.91
4g	–	–	C_2H_5	2	145– 8	80	$C_{17}H_{22}N_4O_2S_2$ (378.50)	53.95 53.16	5.86 5.74	14.80 14.31



Scheme 1

The compounds were also evaluated for antituberculous activity against *M. tuberculosis* $H_{37}Rv$ but no significant activity was observed at the tested concentration (6 µg/ml).

4. Discussion

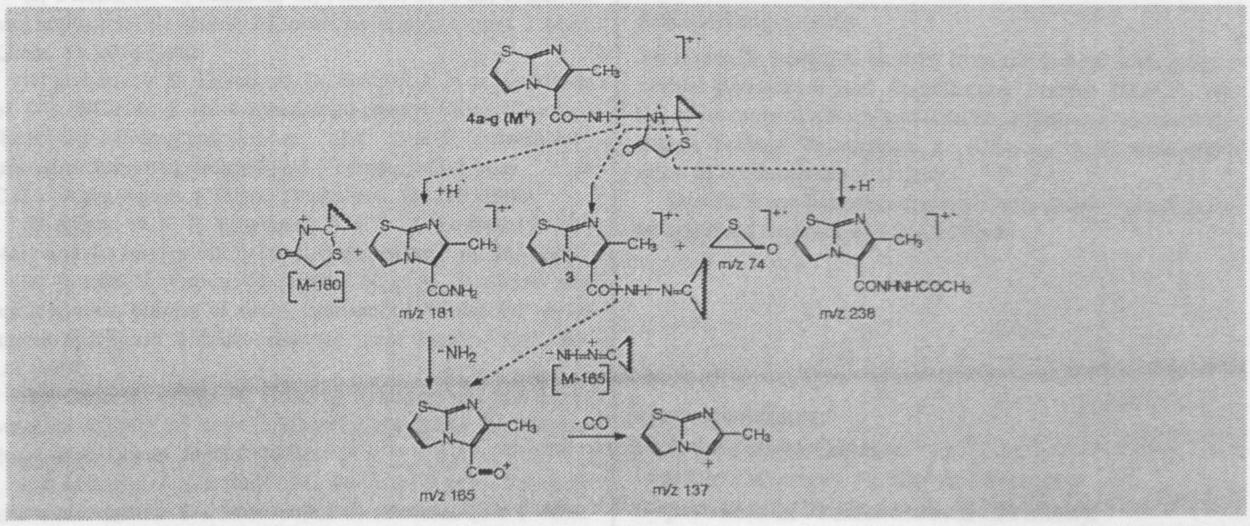
The IR spectra exhibited N-H and C=O bands in the 3375–3125 cm^{-1} and 1671–1618 cm^{-1} regions attributed to the common CONH functions of **3** and **4**. A new C=O band at 1708–1681 cm^{-1} in the spectra of **4** provided evidence for the 4-thiazolidinone structure [2, 20, 21]. In the ^{1}H-NMR spectra **3** and **4** the CONH protons were observed at 7.70–9.83 ppm as a singlet. Further support was obtained from ^{1}H-NMR spectra of **4** which showed the resonance of the CH_2 protons at position **2** of the 4-thiazolidinone ring, at 3.56–3.68 ppm. The ^{13}C-NMR spectra of **3** displayed resonances assigned to the C=N carbon at about 157.28–158.00 ppm. The ^{13}C-NMR spectra of **4** did not show C=N carbon, whereas they displayed the thiazolidinone C_5 carbon (δ: 28.66–29.45 ppm); thiazolidinone C_2 carbon (δ: 71.91–77.61 ppm); and thiazolidinone C=O carbon (δ: 160.11/169.78 ppm) peaks, which verified the proposed thiazolidinone/spirothiazolidinone structures [22, 23].

Table 2: Antimicrobial activity of 4d and 4f (MIC µg/ml).

Compound	*S.epidermidis* ATCC 12228
4d	19.5
4f	39

The upfield shift resonance observed of the thiazolidinone C_2 carbon is consistent with the change in the hybridization state of the involved carbon atom, brought about by the addition of the SH function to the N=CH bond of **3**.

The ^{1}H-^{13}C-COSY experiments were successfully performed to establish the interfragment relationship and assign the proton and carbon signals of compounds **3d**, **4b** and **4e**. Especially with those experiments it was possible to differentiate the resonance of thiazolidinone C_5 carbon atom from the other signals of methylene carbon atoms. The ^{1}H-NMR and ^{13}C-NMR spectra of **3b** revealed the presence of two isomers in a ratio of 1:4 in $CDCl_3$ as concluded from the CH_3 and CH_2CH_3 protons and carbons resonating as double signals at about 1.13–1.24 (m, CH_2CH_3); 1.95, 2.12 (2s, C-CH_3); 2.32, 2.44 (2q,



Scheme 2

CH_2CH_3) in ^{1}H-NMR spectrum and 9.44, 10.85 (CH_2CH_3); 14.99, 22.70 (=C-CH_3); 23.50, 32.20 (CH_2CH_3) ppm in ^{13}C-NMR spectrum.

It is assumed that the N=C double bond restricts rotation and gives rise to the formation of E and Z isomers with the E isomer being the dominating one [24].

EIMS of all compounds displayed molecular ions which confirmed their molecular weights. Major fragmentation routes involved the breaking of the C-N and N-N bonds of the hydrazide moiety which afforded the base peak (m/z 165) in all case (Scheme 2). Breaking of the 1, 2 and 3, 4 or 2, 3 and 5, 1 bonds of 4-thiazolidinone ring with concominant protonation were also major routes in **4** [3].

All of the synthesized compounds were screened *in vitro* for their antimicrobial activity. Only compounds **4d** and **4f** showed activity against *S. epidermidis* ATCC 12228 (Table 2).

5. References

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Acknowledgements

We thank Dr. Joseph A. Maddry from the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF), National Institute of Allergy and Infectious Diseases Southern Research Institute, Birmingham, AL (USA) for the in vitro evaluation of antituberculous activity.

This work was partially supported by Istanbul University Research Fund Project No. T-744/251099.

Correspondence:
Prof. Dr. Nesrin Cesur,
Istanbul University, Faculty of Pharmacy,
Department of Pharmaceutical Chemistry,
Beyazıt 34452, Istanbul (Turkey)

Editors: Prof. Dr. Hans-Georg Classen, Viktor Schramm. Secretary's Office: Christine Schäffer. Publisher: ECV · Editio Cantor Verlag für Medizin und Naturwissenschaften GmbH, P.O.B. 12 55, 88322 Aulendorf (Germany), Phone +49 (0) 7525-9400, Fax +49 (0) 7525-940 180; e-mail: redaktion@ecv.de; http://www.ecv.de. Printed by VeBu Druck + Medien GmbH, Am Reutele 18, 88427 Bad Schussenried (Germany).

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