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Synthesis and Biological Evaluation of some new Thiosemicarbazide , 4-Thiazolidinone, 1,3,4-Oxadiazole and 1,2,4-Triazole-3-thione Derivatives Bearing Imidazo[1,2-*a*]pyridine Moiety

İmidazo[1,2-*a*]piridin Artığı Taşıyan bazı yeni Tiyosemikarbazid, 4-Tiyazolidinon, 1,3,4-Oksadiazol ve 1,2,4-Triazol-3-tiyon Türevlerinin Sentezleri ve Biyolojik Etkilerinin İncelenmesi

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Abstract

In this study, twenty nine 1- [(2,7-dimethylimidazo [1,2-*a*] pyridine-3-yl) carbonyl] -4-alkyl/Arylthiosemicar-bazides 2- [(2,7-dimethylimidazo [1,2-*a*] pyridine-3-yl) carbonylhydrazono] -3-alkylthiazolidin-4-ones, 2-(2,7-di-methylimidazo [1,2-*a*]pyridine-3-yl)-5-arylamino-1,3,4-oxadiazoles and 4-alkyl/aryl-2,4-dihydro-5-(2,7-di-methylimidazo[1,2-*a*]pyridine-3-yl)-3*H*-1,2,4-triazole-3-thiones were synthesized. The structures of the compounds have been elucidated by IR, ^{1}H-NMR, EI mass spectra and elemental analysis. Antibacterial, antifungal and antimycobacterial activities of compounds were evaluated against various mićroorganisms and eighteen of them were found to be active in varying degrees against *Staphylococcus aureus*, *Staphylococcus epidermidis* or *Mycobacterium tuberculosis* $H_{37}R_v$.

Keywords: imidazo[1,2-*a*]pyridine, 4-thiazolidinone, 1,3,4-oxadiazole, 1,2,4-triazole-3-thione, antimicrobial activityIntroduction

Introduction

Imidazo[1,2-*a*]pyridines have been shown to possess diverse biological activities including analgesic, antipyretic (Abignente *et al.*,1986) ,antifungal (Cesur *et al.*,1994), anticonvulsant (Cesur and Cesur,1994),antituberculous (Cesur and Cesur,1998), antinociceptive (Figuerido *et al.*,2000) and antiviral (Mavel *et al.*,2001). Also many reports indicate that acylthiosemicarbazides and their corresponding cyclized derivatives, such as 4-thiazolidinones, 1,3,4-oxadiazoles and 1,2,4-triazole-3-thiones, possess anticonvulsant (Ergenç and Çapan,1994), antimicrobial (Ateş *et al.*,1997; Ulusoy *et al.*,1997; Doğan *et al.*,1997; Doğan *et al.*,1998; Shah *et al.*,1998), hypnotic (Ergenç *et al.*,1999) and antiinflammatory (Goel *et al.*,1999; Şahin *et al.*,2001) activities.

As a continuation of our programme on midazo[1,2-*a*]pyridine ring system (Cesur *et al.*,1989; Cesur *et al.*,1992; Cesur and Cesur,1994; Cesur *et al.*,1994; Cesur and Cesur,1998) we synthesized some new acylthiosemicarbazides, 4-thiazolidinones, 1,3,4-oxadiazoles and 1,2,4-triazole-3-thiones incorporating an imidazo[1,2-*a*]pyridine substituent to screen their antimicrobial activity.

Material and Methods

Melting points were determined on a Büchi 530 apparatus in open capillary tubes and are uncorrected. IR spectra were recorded on KBr discs, using a Perkin Elmer 1600 FT-IR spectrophotometer. ^{1}H-NMR spectra were obtained in DMSO-d_6 on a Bruker AC 200 (200 MHz) spectrophotometer using TMS as the internal standard. EIMS were performed on a VG Zab Spec(70 eV) instrument. Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer. The starting materials were either commercially available or synthesized according to the references cited.

1-[(2,7-Dimethylimidazo[1,2-a]pyridine-3-yl)carbonyl]-4-alkyl/arylthiosemicarbazides **(2a-j)**

0.01 mol of **1** , 0.01 mol of appropriate isothiocyanate and 15 ml absolute ethanol were refluxed for 3 h. The solid phase separated was filtered and recrystallized from ethanol (96 %).

2a : **IR** ν (cm^{-1}) :3520 (O-H), 3316, 3162 (N-H), 1626 (C=O), 1292 (C=S). **^{1}H-NMR** δ ppm: 9.49 (1H, s, N^1-H), 9.31 (1H, s, N^2-H), 8.90 (1H, d, J= 7.06 Hz ,C_5-H), 8.03 (1H, broad s, N^4-H), 7.37 (1H, s, C_8-H), 6.90 (1H, d, J= 6.14 Hz ,C_6-H), 2.90 (3H, d, N-CH_3), 2.60 (3H, s, C_7-CH_3), 2.38 (3H, s, C_2-CH_3). **EIMS** m/z (rel. abun.%): 277 (M^+, 28), 247 (3), 246 (10), 244 (30), 243 (100), 204 (17), 189 (4), 186 (48), 174 (20), 173 (94), 171 (31), 159 (11), 158 (56), 157 (19), 146 (10), 145 (14), 134 (1), 118 (17), 104 (10), 92 (14), 88 (2), 73 (12), 65 (13).

2b : **IR** ν (cm^{-1}) : 3326, 3175 (N-H), 1635 (C=O), 1291 (C=S). **^{1}H-NMR** δ ppm: 9.46 (1H, s, N^1-H), 9.19 (1H, s, N^2-H), 8.89 (1H, d, J= 7.06 Hz ,C_5-H), 8.00 (1H, broad s, N^4-H), 7.36 (1H, s, C_8-H), 6.90 (1H, d, J= 6.14 Hz ,C_6-H), 3.29-3.52 (2H, m, NCH_2), 2.61 (3H, s, C_7-CH_3), 2.38 (3H, s, C_2-CH_3), 1.09 (3H, t, ethyl CH_3).

2f : **IR** ν (cm^{-1}) : 3318,3164 (N-H), 1646 (C=O), 1229 (C=S).**^{1}H-NMR** δ ppm: 9.75 (1H, s, N^1-H), 9.68 (2H, s, N^2-H, N^4-H), 8.93 (1H, d, J= 7.05 Hz ,C_5-H), 7.11-7.52 (6H, m, C_6H_5 and C_8-H), 6.90 (1H, d, J= 7.24 Hz ,C_6-H), 2.64 (3H, s, C_7-CH_3), 2.38 (3H, s, C_2-CH_3). **EIMS** m/z (rel. abun.%): 339 (M^+, 5), 305 (32), 247 (2), 246 (4), 204 (28), 189 (3), 186 (11), 174 (20), 173 (100), 171 (25), 158 (12), 150(3),146 (5), 145 (13), 135 (62), 118 (9), 104 (13), 92 (11), 73 (13).

2g : **IR** ν (cm^{-1}) : 3181 (N-H), 1646 (C=O), 1258 (C=S). **^{1}H-NMR** δ ppm: 9.69 (3H, broad s, N^1-H, N^2-H, N^4-H), 8.92 (1H, d, J= 6.95 Hz ,C_5-H), 7.37 (1H, s, C_8-H), 7.35 (2H, d, J=8 Hz, phenyl C_3-H and C_5-H), 7.13 (2H, d, J= 7.13 Hz, phenyl C_2-H and C_6-H), 6.91 (1H, d, J= 6.87 Hz ,C_6-H), 2.63 (3H, s, C_7-CH_3), 2.38 (3H, s, C_2-CH_3), 2.28 (3H, s, phenyl C_4-CH_3). **EIMS** m/z (rel. abun.%): 237 (2), 205 (21), 204 (55), 189 (4), 173 (100), 164 (2), 149 (25), 147 (32), 146 (4), 145 (13), 118 (5), 91 (42), 65 (10).

2i : **IR** ν (cm^{-1}) : 3178 (N-H), 1646 (C=O), 1258 (C=S). **^{1}H-NMR** δ ppm: 9.75 (3H, broad s, N^1-H, N^2-H, N^4-H), 8.93 (1H, d, J= 6.98 Hz ,C_5-H), 7.55 (2H, d, J= 8.7 Hz, phenyl C_3-H and C_5-H), 7.39 (1H, s, C_8-H), 7.37 (2H, d, J= 6.42 Hz, phenyl C_2-H and C_6-H), 6.91 (1H, d, J=

6.93 Hz ,C_6-H), 2.64 (3H, s, C_7-CH_3), 2.39 (3H, s, C_2-CH_3). **EIMS** m/z (rel. abun.%): 373 (M^+, 33), 369 (3), 329 (55), 256 (2), 247 (3), 204 (55), 189 (2), 174 (33), 173 (100), 171 (50), 169 (85), 146 (3), 145 (16), 134 (10), 118 (10), 104 (16), 91 (5), 75 (26), 65 (14).

2-[(2,7-Dimethylimidazo[1,2-a]pyridine-3-yl)carbonylhydrazono]-3-alkylthiazolidin-4-one **(3a-e)**

0.01 mol of the appropriate thiosemicarbazide **(2a-e)** and 0.011 mol of ethyl bromoacetate were refluxed in 30 ml of absolute ethanol in the presence of 0.04 mol of anhydrous CH_3COONa for 2-4 h. The reaction mixture was cooled , diluted with water and allowed to stand overnight. The precipitate thus obtained was filtered, dried and recrystallized from ethanol (96 %).

3a : **IR** ν (cm^{-1}) : 3356 (N-H), 1712 (C=O,thiazolidinone), 1687 (C=O,hydrazide). **^{1}H-NMR** δ ppm: 10.19 (1H, s, CONH), 8.86 (1H, d, J= 7.12 Hz ,C_5-H), 7.37 (1H, s, C_8-H), 6.89 (1H, d, J= 6.89 Hz ,C_6-H), 4.05 (2H, s, S-CH_2), 3.17 (3H, s, N-CH_3), 2.59 (3H, s, C_7-CH_3), 2.38 (3H, s, C_2-CH_3). **EIMS** m/z (rel. abun.%): 317 (M^+, 18), 189 (3), 174 (9), 173 (100), 146 (30), 145 (1), 144(5), 117 (8), 77 (4), 65 (9).

3b : **IR** ν (cm^{-1}) : 3386 (N-H), 1720 (C=O, thiazolidinone), 1649 (C=O, hydrazide). **^{1}H-NMR** δ ppm: 10.28 (1H, s, CONH), 8.87 (1H, d, J= 7.04 Hz, C_5-H), 7.37 (1H, s, C_8-H), 6.90 (1H, d, J= 7.25 Hz, C_6-H), 4.06 (2H, s, S-CH_2), 3.75 (2H, q, N-CH_2), 2.59 (3H, s, C_7-CH_3), 2.37 (3H, s, C_2-CH_3), 1.18 (3H, t, ethyl CH_3). **EIMS** m/z (rel. abun.%): 331 (M^+, 1), 225 (3), 189 (1), 173 (3), 165 (2), 158 (2),145 (2), 144 (3), 143 (10), 116 (4), 91 (30), 43 (100).

2-(2,7-Dimethylimidazo[1,2-a]pyridine-3-yl)-5-arylamino-1,3,4-oxadiazole **(4a-e)**

4a-e were obtained from **2f-j** as described for **3a-e**.

4a : **IR** ν (cm^{-1}) : 3180 (N-H). **^{1}H-NMR** δ ppm: 10.46 (1H, s, NH), 8.96 (1H, d, J=6.00 Hz, C_5-H), 7.42-6.87 (6H, m, C_6H_5 and C_8-H), 6.73 (1H, d, J= 6.89 Hz, C_6-H), 2.52 (3H, s, C_7-

CH_3), 2.37 (3H, s, C_2-CH_3). **EIMS** m/z (rel. abun.%): 305 (M^+, 1), 246 (3), 204 (8), 187 (3), 186 (5), 174 (20), 173 (100), 158 (17), 146 (4), 145 (19), 135 (70), 132 (5),119 (10), 104 (17).

4b : **IR** ν (cm^{-1}) : 3450 (O-H), 3150 (N-H). **^{1}H-NMR** δ ppm: 10.47 (1H, s, NH), 9.08 (1H, d, J= 6.99 Hz, C_5-H), 7.51 (2H, d, J= 8.28 Hz, phenyl C_2-H and C_6-H), 7.46 (1H, s, C_8-H), 7.18 (2H, d, J= 8.40 Hz, phenyl C_3-H and C_5-H), 7.05 (1H, d, J= 6.83 Hz, C_6-H), 2.64 (3H, s, C_7-CH_3), 2.42 (3H, s, C_2-CH_3), 2.27 (3H, s, phenyl CH_3). **EIMS** m/z (rel. abun.%): 319 (M^+, 100), 262 (7), 213 (8), 204 (2), 187 (10), 186 (43), 173 (25), 171 (70), 158 (35), 149 (5), 147 (3),146 (4), 145 (3), 135 (10), 133 (3), 118(10).

4-Alkyl/aryl-2,4-dihydro-5-(2,7-dimethylimidazo[1,2-a]pyridine-3-yl)-3H-1,2,4-triazole-3-thiones **(5a-i)**

A mixture of the thiosemicarbazide (**2a-j**) (0.01 mol) and 2N NaOH (30 ml) was heated to reflux. After 3h the mixture was poored into crushed ice and acidified with dilute HCl to pH 6-8. The precipitate was filtered, washed with water and recrystallized from ethanol (96 %).

5a : **IR** ν (cm^{-1}) : 3520 (O-H),3150 (N-H), 1648 (C=N), 1278 (C=S). **^{1}H-NMR** δ ppm: 14.09 (1H, s, NH), 8.23 (1H, d, J= 6.96 Hz, C_5-H), 7.38 (1H, s, C_8-H), 6.83 (1H, d, J= 6.11 Hz, C_6-H), 3.25 (3H, s, N-CH_3), 2.38 (3H, s, C_7-CH_3), 2.32 (3H, s, C_2-CH_3). **EIMS** m/z (rel. abun.%): 259 (M^+, 56), 258 (63), 245(1), 244 (5), 204 (8), 200(5), 186 (18), 172 (11), 171 (100), 158 (17), 91 (15), 88 (2), 73 (2) , 59 (10).

5b : **IR** ν (cm^{-1}) : 3160 (N-H),1647 (C=N), 1275 (C=S). **^{1}H-NMR** δ ppm: 14.18 (1H, s, NH), 8.20 (1H, d, J= 6.91 Hz, C_5-H), 7.39 (1H, s, C_8-H), 6.81 (1H, d, J= 6.77 Hz, C_6-H), 3.75 (2H, q, N-CH_2), 2.37 (3H, s, C_7-CH_3), 2.28 (3H, s, C_2-CH_3), 0.98 (3H, t, ethyl CH_3).

5d : **IR** ν (cm^{-1}) : 3446 (O-H), 3190(N-H),1649 (C=N), 1277 (C=S). **^{1}H-NMR** δ ppm: 14.13 (1H, s, NH), 8.18 (1H, d, J= 6.87 Hz, C_5-H), 7.38 (1H, s, C_8-H), 6.82 (1H, d, J= 6.76 Hz, C_6-H), 3.73 (2H, t, N-CH_2), 2.38 (3H, s, C_7-CH_3), 2.29 (3H, s, C_2-CH_3), 1.37-1.55 (2H, m, CH_2**CH_2**CH_3), 0.59 (3H, t, Pr-CH_3). **EIMS** m/z (rel. abun.%): 287 (M^+, 38), 258 (3), 245

(100), 244 (1), 228 (1), 215 (4), 214 (1),186 (2), 172 (16), 171 (30), 169, (35), 116 (2), 73 (4), 59 (17).

5e : IR ν (cm^{-1}) : 3184 (N-H), 1646 (C=N), 1258 (C=S). **^{1}H-NMR** δ ppm: 14.27 (1H, s, NH), 8.30 (1H, d, J= 6.77 Hz, C_5-H), 7.34 (5H, s, C_6H_5), 7.24 (1H, s, C_8-H), 6.70 (1H, d, J=7.05 Hz, C_6-H), 2.31 (3H, s, C_7-CH_3), 1.96 (3H, s, C_2-CH_3). **EIMS** m/z (rel. abun.%): 321 (M^+, 100), 306 (4), 262 (4), 248 (17), 245 (1), 244 (4), 186 (4), 171 (25), 150 (4), 141 (1), 73 (2), 59 (5).

5g : IR ν (cm^{-1}) : 3160 (N-H), 1647 (C=N), 1234 (C=S). **^{1}H-NMR** δ ppm: 14.33 (1H, s, NH), 8.33 (1H, d, J= 7.02 Hz, C_5-H), 7.59 (2H, d, J= 8.31 Hz, phenyl C_3-H and C_5-H), 7.31 (2H, d, J= 8.62 Hz, phenyl C_2-H and C_6-H) 7.26 (1H, s, C_8-H), 6.73 (1H, d, J= 7.22 Hz , C_6-H), 2.33 (3H, s, C_7-CH_3), 1.97 (3H, s, C_2-CH_3). **EIMS** m/z (rel. abun.%): 400 (M^+, 1), 259 (41), 258 (53), 186 (4), 171 (55), 92 (22), 59 (100).

Microbiology

Antibacterial and antifungal activity

Disc diffusion method was used for antimicrobial activity. The cultures of bacteria and yeast strains were prepared in 4 ml of Mueller-Hinton Broth at 37°C . After 24 h of incubation, the turbidity of culture suspension was adjusted with sterile Mueller –Hinton broth in order to obtain a turbidity comparable to a No.1 Mc Farland turbidity standard. One milliliter of this suspension was pipetted into the Mueller –Hinton agar 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. Compound (200 µg) 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 (Barry and Thornsberry,1985).

The minimum inhibitory concentration (MIC) of the compounds were determined by the microbroth dilution technique using Muller-Hinton Broth. Serial two-fold dilutions ranged from 2500 to 2.4 µg /ml 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 105 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 (Jones *et al.*,1985).

Antimycobacterial activity

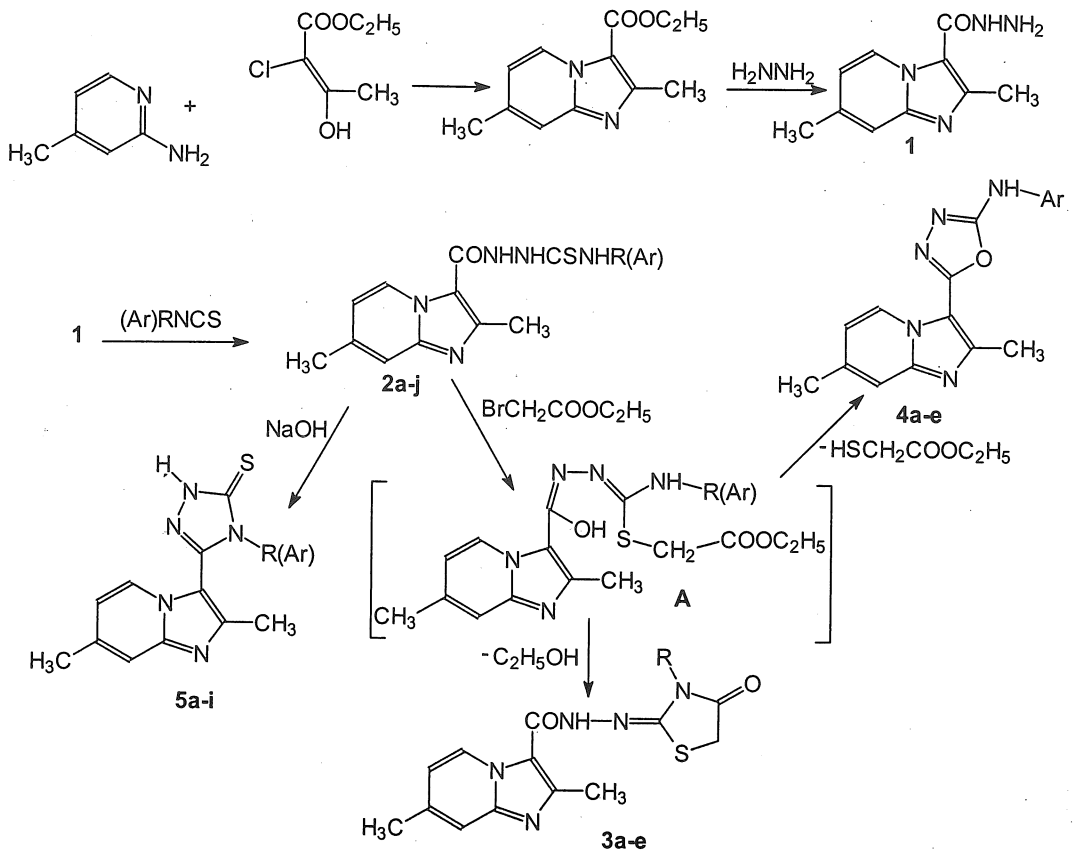
Primary screen was conducted at 12.5 μg/ml against *M.tuberculosis* $H_{37}R_v$ in BACTEC 12B medium using BACTEC 460 radiometric system. Compounds effecting <90 % inhibition in the primary screen (MIC >12.5 μg/ml) were not evaluated further (Inderleid,1991).

Results and discussion

2,7-Dimethylimidazo[1,2-*a*]pyridine-3-carbohydrazide (**1**) was prepared from 2-amino-4-methylpyridine by a two step synthesis as depicted in Scheme 1 (Oa *et al.*,1985).

1-[(2,7-Dimethylimidazo [1,2-*a*]pyridine-3-yl)carbonyl] -4 -alkyl/arylthiosemicarbazides **2a-j** were obtained from **1** and corresponding alkyl/arylisothiocyanates. On treatment with ethyl bromoacetate, **2a-e** yielded 4-thiazolidinones **3a-e**. In the case of arylthiosemicarbazides (**2f-j**) the same reaction resulted in 1,3,4-oxadiazole derivatives **4a-e** (Cesur *et al.*,1992). The thiosemicarbazides were cyclized to the corresponding 3*H*-1,2,4-triazole-3-thiones (**5a-i**) by sodium hydroxide (Scheme 1). Some physical data of the new thiosemicarbazides, 4-thiazolidinones, 1,3,4-oxadiazoles and 3*H*-1,2,4-triazole-3-thiones are given in Table 1.

The structures of the compounds were assigned by elemental analysis (CHN) and spectroscopic methods (IR, ^{1}H-NMR, EIMS). Spectral data of representative derivatives are given in the experimental . The IR spectra of **2a-j** showed the N-H and C=O bands at about 3326-3162 and 1646-1626 cm^{-1}, respectively. ^{1}H-NMR spectra displayed N^1-H , N^2-H and N^4-H



Scheme 1

resonances in the 9.46-9.75 , 9.19-9.75 and 8.00-9.75 ppm regions, respectively (Çapan et al.,1990-92). The C_5-H, C_8-H and C_6-H resonances of the imidazo [1,2-*a*] pyridine residue in all compounds appeared in the 8.89-8.93, 7.36-7.39 and 6.90-6.91 ppm regions, respectively .New C=O bands (1712-1720 cm^{-1}) in the IR spectra of 4-thiazolidinones (**3a-e**) were particularly diagnostic for thiazolidinone formation (Cesur *et al.*,1994; Ergenç and Çapan,1994;Ulusoy *et al.*,1997). Further support was obtained from the ^{1}H-NMR spectra of **3a-e** which showed signals due to the CH_2 protons at the 5 position of the 4-thiazolidinone ring at about 4.05-4.06 ppm. After cyclization, absence of resonances assigned to the N^2-H and N^4-H protons of the thiosemicarbazides **2a-e** provided confirmatory evidence of thiazolidinone formation.

Table 1. Physicochemical data of compounds **2**, **3**, **4** and **5**

Compound	R(Ar)	Formula (MW)	Mp (°C)	Yield (%)	Analysis (cal./found) C	H	N
2a	CH_3	$C_{12}H_{15}N_5OS$ .0.5H_2O	233-5	95	50.33	5.63	24.45
		(286.35)			50.76	5.68	25.18
2b	C_2H_5	$C_{13}H_{17}N_5OS$	214-6	91	53.59	5.88	24.04
		(291.37)			54.47	6.44	24.36
2c	CH_2=CH-CH_2	$C_{14}H_{17}N_5OS$	203-5	89	55.42	5.65	23.08
		(303.38)			55.75	5.34	22.73
2d	C_3H_7	$C_{14}H_{19}N_5OS$	212-3	86	55.06	6.27	22.93
		(305.4)			55.47	5.88	22.66
2e	C_4H_9	$C_{15}H_{21}N_5OS$	193-5	59	56.40	6.63	21.92
		(319.42)			55.75	6.92	21.65
2f	C_6H_5	$C_{17}H_{17}N_5OS$	240	93	60.16	5.05	20.63
		(339.41)			59.07	4.90	20.38
2g	$C_6H_4CH_3$(4-)	$C_{18}H_{19}N_5OS$	193-5	40	61.17	5.42	19.81
		(353.44)			60.84	5.75	20.06
2h	C_6H_4Br(4-)	$C_{17}H_{16}BrN_5OS$	220	93	48.81	3.86	16.74
		(418.31)			48.75	3.73	16.11
2i	C_6H_4Cl(4-)	$C_{17}H_{16}ClN_5OS$	218-20	93	54.61	4.31	18.73
		(373.86)			54.16	4.85	18.76
2j	C_6H_4F(4-)	$C_{17}H_{16}FN_5OS$	225-7	95	57.13	4.51	19.59
		(357.40)			57.67	4.32	19.32
3a	CH_3	$C_{14}H_{15}N_5O_2S$	248-50	82	52.98	4.76	22.07
		(317.36)			52.79	4.82	21.68
3b	C_2H_5	$C_{15}H_{17}N_5O_2S$	225-7	66	54.36	5.17	21.13
		(331.39)			54.68	4.76	20.93
3c	CH_2=CH-CH_2	$C_{16}H_{17}N_5O_2S$ .H_2O	185-9	84	53.16	5.29	19.37
		(361.42)			53.32	5.21	19.10
3d	C_3H_7	$C_{16}H_{19}N_5O_2S$ .H_2O	138-40	97	52.87	5.82	19.27

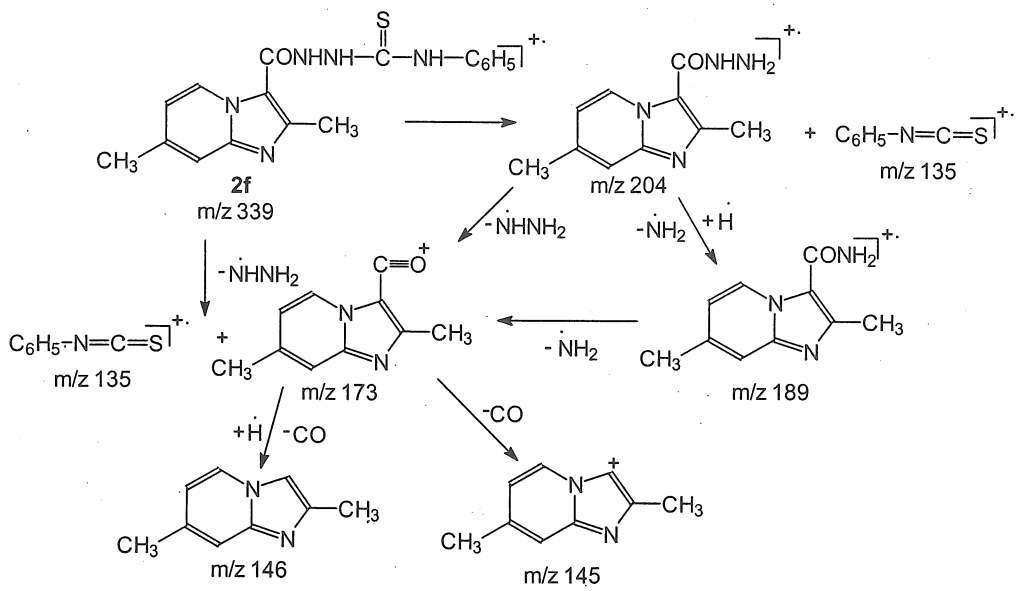
		(363.44)			52.16	5.88	18.54
3e	C_4H_9	$C_{17}H_{21}N_5O_2S$	189-90	86	56.80	5.89	19.48
		(359.44)			56.33	6.17	19.36
4a	C_6H_5	$C_{17}H_{15}N_5O$	266	68	66.87	4.95	22.94
		(305.33)			66.73	4.92	22.77
4b	$C_6H_4CH_3$(4-)	$C_{18}H_{17}N_5O.\ 1.5H_2O$	268-9	71	62.41	5.82	20.22
		(346.38)			63.28	6.07	19.46
4c	C_6H_4Br(4-)	$C_{17}H_{14}BrN_5O$	>270	95	53.14	3.67	18.23
		(384.23)			53.00	3.12	17.80
4d	C_6H_4Cl(4-)	$C_{17}H_{14}ClN_5O$	>270	97	60.09	4.15	20.61
		(339.77)			59.39	3.98	19.94
4e	C_6H_4F(4-)	$C_{17}H_{14}FN_5O\ .H_2O$	>270	97	59.81	4.72	20.51
		(341.34)			59.14	4.61	19.90
5a	CH_3	$C_{12}H_{13}N_5S\ .0.5H_2O$	>270	82	53.70	5.25	26.10
		(268.34)			54.37	5.05	26.05
5b	C_2H_5	$C_{13}H_{15}N_5S$	250	81	57.12	5.53	25.62
		(273.35)			57.50	5.08	25.36
5c	CH_2=CH-CH_2	$C_{14}H_{15}N_5S$	>270	71	58.92	5.30	24.54
		(285.36)			59.30	4.82	24.22
5d	C_3H_7	$C_{14}H_{17}N_5S\ .0.5H_2O$	>270	95	56.72	6.12	23.63
		(296.39)			57.05	6.27	24.27
5e	C_6H_5	$C_{17}H_{15}N_5S$	>270	57	63.53	4.70	21.79
		(321.40)			63.74	4.16	21.37
5f	$C_6H_4CH_3$(4-)	$C_{18}H_{17}N_5S$	>270	64	64.45	5.11	20.88
		(335.42)			64.68	4.66	20.61
5g	C_6H_4Br(4-)	$C_{17}H_{14}BrN_5S.\ 0.5H_2O$	>270	51	49.88	3.69	17.11
		(409.30)			50.28	3.56	16.75
5h	C_6H_4Cl(4-)	$C_{17}H_{14}ClN_5S$	>270	47	57.38	3.97	19.68
		(355.84)			57.69	3.23	19.28
5i	C_6H_4F(4-)	$C_{17}H_{14}FN_5S$	>270	85	60.16	4.16	20.64
		(339.39)			60.38	3.92	20.43

Cyclization of 1-[(2,7-dimethylimidazo[1,2-a]pyridine-3-yl)carbonyl]-4-arylthiosemicarbazides (**2f-j**) with ethyl bromoacetate to obtain desired 4-thiazolidinone derivatives, yielded unexpected products, which were identified as 2-(2,7-dimethylimidazo [1,2-*a*] pyridine-3-yl)-5-arylamino-1,3,4-oxadiazole **(4a-e)** , on the basis of analytical and spectral data. Cyclization to 4-thiazolidinones involves the formation of an isothiosemicarbazide intermediate (A) (Scheme 1) following ene-thiolization (Bulka *et al.*,1963 Ergenç and Çapan,1994). At this stage electronic effects (Cesur *et al.*,1992) or overall conformation of the isothiosemicarbazide intermediate can make the $SCH_2COOC_2H_5$ moiety a good leaving group and thus can lead to the formation of **4a-e**. **4a-e** are the amino tautomer (NH , 10.46-10.47 ppm). The absence of C=O bands in the IR spectra of **4a-e** also support the 1,3,4-oxadiazole structure.

In basic medium 1-acyl/aroyl-3-thiosemicarbazides are dehydrated by the condensation of the 4-amino group with the carbonyl function to give triazoline-3-thiones. The nucleophilicity of the terminal NH group of the thioamide determines whether it can go under a condensation reaction or not. In base, the sulfur function is ionized, and this increases the nucleophilicity of 4-NH group and promotes triazoline-3-thione formation (Çapan *et al.*,1990-1992).

Spectra of **5a-i** thus formed provide definitive evidence for ring closure. The C=O absorption f the thiosemicarbazides disappears as the group participates in ring formation and a new band in the 1649-1646 cm^{-1} region appears which may be assigned to the C=N group of the triazoline ring (Silverstein *et al.*,1981). ^{1}H-NMR spectra support ring closure as they show only one low field singlet in the 14.09-14.33 ppm region which is thus assignedto the N^2-H of the ring. 5-Substituted 2,4-dihydro-3*H*-1,2,4-triazole-3-thiones may exist in tautomeric forms. **5a-i** favors the thione form since no absorption indicative of a SH group (2500 cm^{-1}) is displayed in the solid state IR spectra (Çapan *et al.*,1990-1992). The low field N-H resonance in the ^{1}H-NMR spectra supports this form and the structure can be assigned to the thione form also in solution (Eweiss *et al.*,1986).

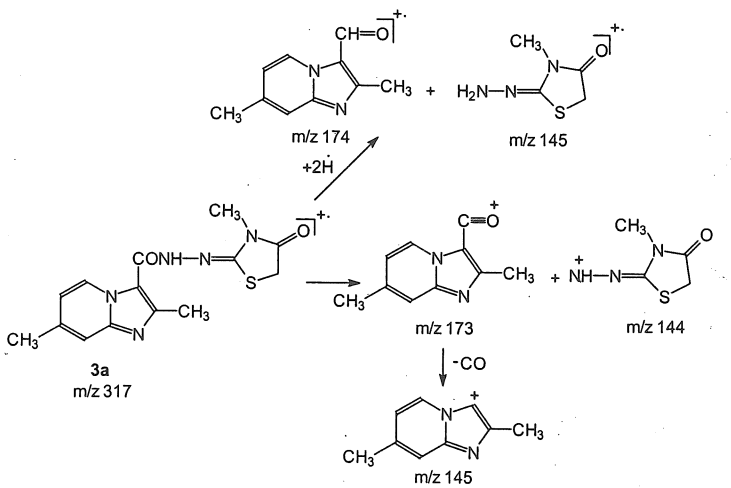
The EIMS of all representative examples showed moleculer ions of different intensity (except **2g**) .Thiosemicarbazides (**3a-e**) fragmented via two prominent pathways (Gürsoy *et al.*,1997) to afford the fragments at m/z 204 and m/z 173 (base peak in all compounds except **2a**) by NH-CS and CO-NH bonds cleavage. The fragmentation of **2f** is depicted in Scheme 2.



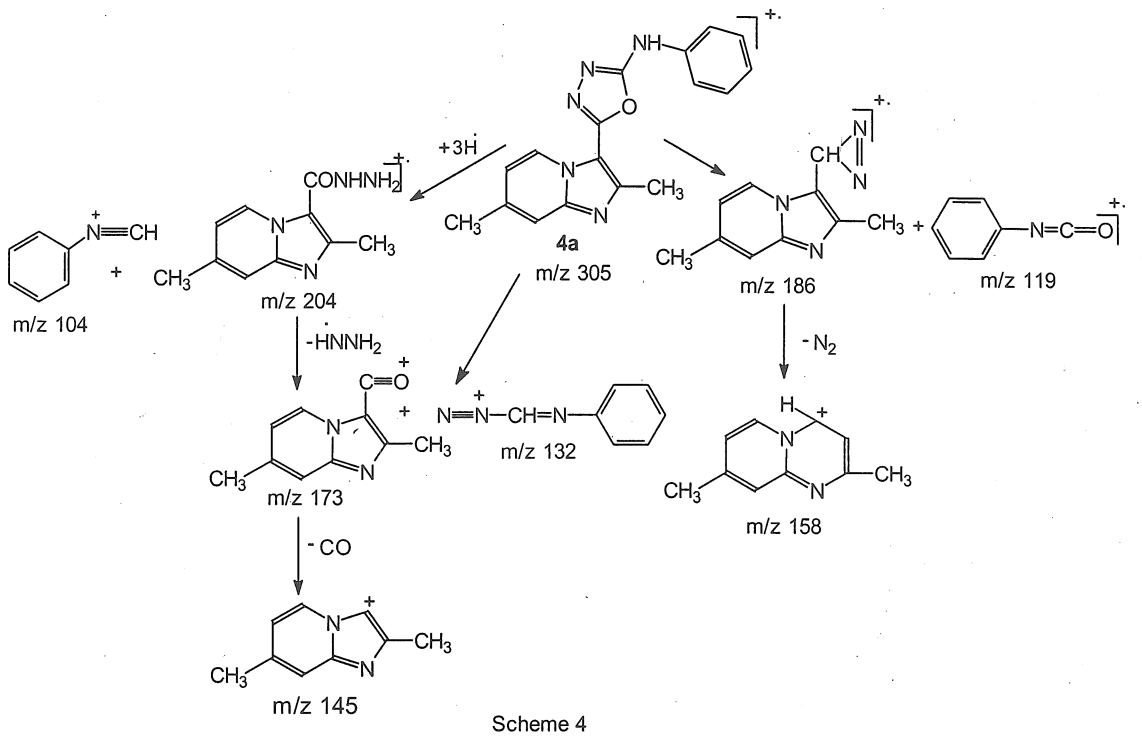
Scheme 2

In 4-thiazolidinones repture of the exocyclic CO-NH bond furnished common fragments m/z 174, m/z 173, m/z 146 and m/z 145 , respectively (Scheme 3).

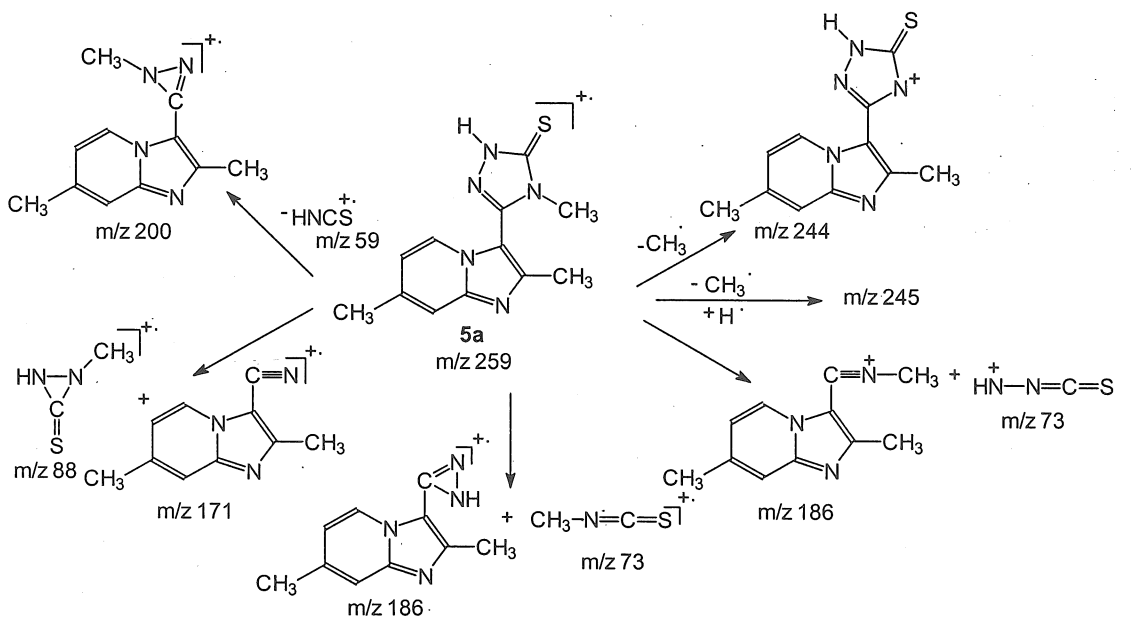
1,3,4-oxadiazole and 1,2,4-triazole-3-thione derivatives fragmented in accordance with the fragmentation routes given in literature (Bansal and Bhagchandani,1982; Cesur *et al.*,1994 ;Ateş *et al.*,1997). Proposed fragmentations of **4a** and **5a** are depicted in Scheme 4 and Scheme 5 respetively.



Scheme 3



Scheme 4



Scheme 5

Compounds **2-5** were evaluated for in vitro antibacterial activity against *Staphylococcus aureus* ATCC 6538, *Staphylococcus epidermidis* ATCC 12228, *Escherichia coli* ATCC 8739, *Klebsiella pneumoniae* ATCC 4352, *Pseudomonas aeruginosa* ATCC 1539, *Salmonella typhi*, *Shigella flexneri*, *Proteus mirabilis* ATCC 14153, *Candida albicans* ATCC 10231 using the disc diffusion method. Some of these compounds had appreciable activity for *S.epidermidis* and *S.aureus* (Table 2).

2 f-j were also evaluated for antimycobacterial activity against *Mycobacterium tuberculosis* $H_{37}R_v$. **2 f-j** exhibited varying degrees of inhibition in the *in vitro* primary screen conducted at 12.5 µg /ml (Table 3)

Table 2. MIC values of Compound **2-5**

Compound	MIC (µg/ml)		Compound	MIC(µg/ml)	
	S.epidermidis	*S.aureus*		*S.epidermidis*	*S.aureus*
2d	312	-	**3e**	312	-
2e	156	-	**4c**	78	-
2f	156	-	**4d**	19.5	-
2g	62.5	625	**4f**	78	-
2h	156	-	**5d**	312	-
2i	31.25	-	**5e**	78	-
2j	39	-	**5f**	312	-
3c	312	-	**5h**	312	-
3d	625	-	**5i**	312	-

Table 3. Primary antituberculosis screen results

Compound	MIC vs $H_{37}R_v$	Inhibition %
2g	>12.5	82
2f	>12.5	77
2j	>12.5	53
2i	>12.5	32
2h	>12.5	26

Özet

Bu çalışmada, 1-[(2,7-dimetilimidazo[1,2-*a*]piridin-3-il)karbonil] -4-alkil/ariltiyosemikar-bazid, 2- [(2,7-dimetilimidazo [1,2-*a*]piridin-3-il)karbonilhidrazono] -3-alkiltiyazolidin-4-on,2- (2,7-dimetilimidazo[1,2-*a*]piridin -3-il) -5-arilamino-1,3,4-oksadiazol ve 4-alkil/aril-2,4-dihidro-5- (2,7-dimetilimidazo [1,2-*a*]piridin-3-il) -3*H*-1,2,4-triazol-3-tiyon yapısında yirmidokuz yeni bileşik sentezlenmiş, yapıları IR, ^{1}H-NMR, EI kütle spektrumları ve elementel analizleri ile aydınlatılmıştır. Elde edilen bileşiklerin çeşitli mikroorganizmalara karşı antibakteriyel, antifungal ve antimikobakteriyel etkileri araştırılmış ve onsekiz madde, *Staphylococcus aureus*, *Staphylococcus epidermidis* ve *Mycobacterium tuberculosis* $H_{37}R_v$ e karşı değişen derecelerde etkili bulunmuştur.

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