Turk J. Pharm. Sci. 8 (3), 199-206, 2011

Original article

SYNTHESIS AND ANTIMICROBIAL ACTIVITY EVALUATION OF NEW HYDRAZIDE DERIVATIVES

Gülhan TURAN ZITOUNI[1]*, Ahmet ÖZDEMİR[1], Zafer Asım KAPLANCIKLI[1], Gilbert REVIAL[2], Fatih DEMİRCİ[3]

[1]Anadolu University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, 26470 Eskişehir, TURKEY

[2]Laboratoire de Transformations Chimiques et Pharmaceutiques, UMR-CNRS 7084, Cnam, 2 rue Conte´, 75003 Paris, FRANCE

[3]Anadolu University, Faculty of Pharmacy, Department of Pharmacognosy, 26470 Eskişehir, TURKEY

Abstract

The enhancement of bacterial resistance of pathogens to currently available antibiotics constitutes a serious public health threat. Therefore, intensive efforts are underway worldwide to develop new antimicrobial agents. To identify compounds with a potent antimicrobial profile, we designed and synthesized some hydrazide derivatives ***1a-e****. The chemical structures of the compounds were elucidated by elemental analyses, IR, ^{1}H-NMR, ^{13}C-NMR and FAB^{+}-MS spectral data. Their antimicrobial activities against to E. coli (NRRL B-3008), Staphylococcus aureus (ATCC 6538), Pseudomonas aeruginosa (ATCC 27853), Proteus vulgaris (NRRL B-123), Salmonella typhimurium (ATCC 13311), Methicillin-resistant Staphylococcus aureus (MRSA) (clinic isolate), Candida albicans (NRRL Y-12983) and Candida parapsilosis (NRRL Y-12696) were investigated. The results showed that all of the tested compounds were inactive against the test organism.*

Key words: *Hydrazide, 5,6,7,8-tetrahydro-2-naphthol, Aldehydes, Antimicrobial activity.*

Yeni Hidrazid Türevlerinin Sentezi ve Bunların Antimikrobiyal Aktivitelerinin Değerlendirilmesi

Mevcut antibiyotiklere patojenlerin bakteriyel direnç geliştirmesi ciddi bir halk sağlığı tehditi oluşturmaktadır. Dolayısıyla, yeni antibiyotiklerin geliştirilmesi için dünya çapında yoğun çabalar devam etmektedir. Güçlü antimikrobiyal profile sahip bileşikleri belirleyebilmek için bazı hidrazid türevleri ***1a-e*** *tasarlanmış ve sentezlenmiştir. Bileşiklerin kimyasal yapıları elemental analiz, IR, ^{1}H-NMR, ^{13}C-NMR ve FAB^{+}-MS spektral verileri ile aydınlatılmıştır. Bunların antimikrobiyal aktiviteleri Escherichia coli (NRRL B-3008), Staphylococcus aureus (ATCC 6538), Pseudomonas aeruginosa (ATCC 27853), Proteus vulgaris (NRRL B-123), Salmonella typhimurium (ATCC 13311), Methicillin-resistant Staphylococcus aureus (MRSA) (klinik izolat), Candida albicans (NRRL Y-12983) ve Candida parapsilosis (NRRL Y-12696) suşlarına karşı araştırılmıştır. Test edilen tüm bileşiklerin, test organizmalarına karşı inaktif olduğu sonuçlar gözlemlenmiştir.*

Anahtar kelimeler: *Hidrazid, 5,6,7,8-tetrahidro-2-naftol, Aldehidler, Antimikrobiyal aktivite.*

***Correspondence:** E-mail: gturan@anadolu.edu.tr
Telephone: +90 222 335 0580/3777; Fax : +90 222 3350750

INTRODUCTION

Infectious diseases are responsible for great number of deaths in the world. The reduction of sensibility to antimicrobial agents in actual use has been increasing for a great variety of pathogens and the resistance to multiple drugs is general for several microorganisms, particularly for Gram positive bacteria. Infections by methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant Enterococci (VRE) present an important problem for medicine (1). Furthermore, the treatment of infectious diseases is more complicated in immuno-suppressed patients, such as those infected with the HIV, undergoing cancer therapy or transplantations. Given the evidence for the fast world spread of resistant clinical isolates and the appearance of drug-resistant strains among community acquired infections, the need for discovery or optimization of antimicrobial agents active against these resistant strains is of paramount importance.

Lately, hydrazone derivatives have gained significance owing to their application in pharmaceutical chemistry. The biological activity associated with these compounds was attributed to the presence of the (-CONHN=CH-) moiety. Consequently, several hydrazide-hydrazone derivatives displayed broad spectrum of biological activities such as antimicrobial (2-7,12), antituberculosis (8-11), analgesic, and anti-inflammatory (12), anticonvulsant (13), antiproliferative (14) activities.

In our previous work, we synthesized some hydrazide-hydrazone derivatives which were shown to exhibit high antifungal activity (15). Some of these compounds showed interesting in vitro activity against *Candida* spp.; especially 5,6,7,8-tetrahydroimidazo(1,2-a)pyridine-2-carboxylic acid-(4-cyanobenzylidene)hydrazide, which showed the highest inhibitory (up to MIC 0.016 mg/mL) activity. The same compound showed no in vitro toxicity up to 25 mg/mL concentration suggesting that its antifungal activity (MICs 0.016-1 mg/mL) is selective.

Prompted by these observations and in continuation of our researchs on bioactive molecules, we designed the synthesis with a series of hydrazide derivatives with the aim of attaining more potent antimicrobial compounds to improve actual antimicrobial treatments.

EXPERIMENTAL

Chemistry

All chemicals were obtained from Aldrich Chemical Co. (Steinheim, Germany). All melting points (m.p.) were determined in open capillaries on a Gallenkamp apparatus (Weiss-Gallenkamp, Loughborough-United Kingdom) and are uncorrected. The purity of the compounds was checked by thin layer chromatography (TLC) using silica gel 60G (Merck, Darmstadt-Germany). Elemental analyses were performed on a Perkin Elmer EAL 240 elemental analyser. Spectroscopic data were recorded with the following instruments: IR; Shimadzu IR-435 spectrophotometer (Shimadzu, Tokyo, Japan); ^{1}H-NMR: Bruker 400 MHz spectrometer and ^{13}C-NMR Bruker 100 MHz spectrometer (Bruker, Billerica, Massachusetts, USA) in DMSO-d_6 using TMS as internal standard; and MS-FAB: VG Quattro Mass spectrometer (Agilent, Minnesota, USA).

General procedure for synthesis of the compounds:
Synthesis of (5,6,7,8-tetrahydronaphthalen-2-yl-oxy)acetylhydrazine

These compounds were prepared by reacting ethyl (5,6,7,8-tetrahydronaphthalen-2-yl-oxy)acetate with hydrazine hydrate according to the previously reported method (16,17).

(5,6,7,8-Tetrahydronaphthalen-2-yloxy)acetic acid (2-phenoxyethylidene) hydrazide derivatives (1a-e)

Equimolar quantities of (5,6,7,8-tetrahydronaphthalen-2-yl-oxy)acetylhydrazines (30 mmol) and appropriate aldehydes in 25 ml of absolute ethanol were refluxed for 10-12 h. The reaction mixture was then cooled and the solid precipitated was recrystallized from appropriate solvent. Some characteristics of the synthesized compounds are shown in Table 1.

Table 1. Some characteristics of the compounds.

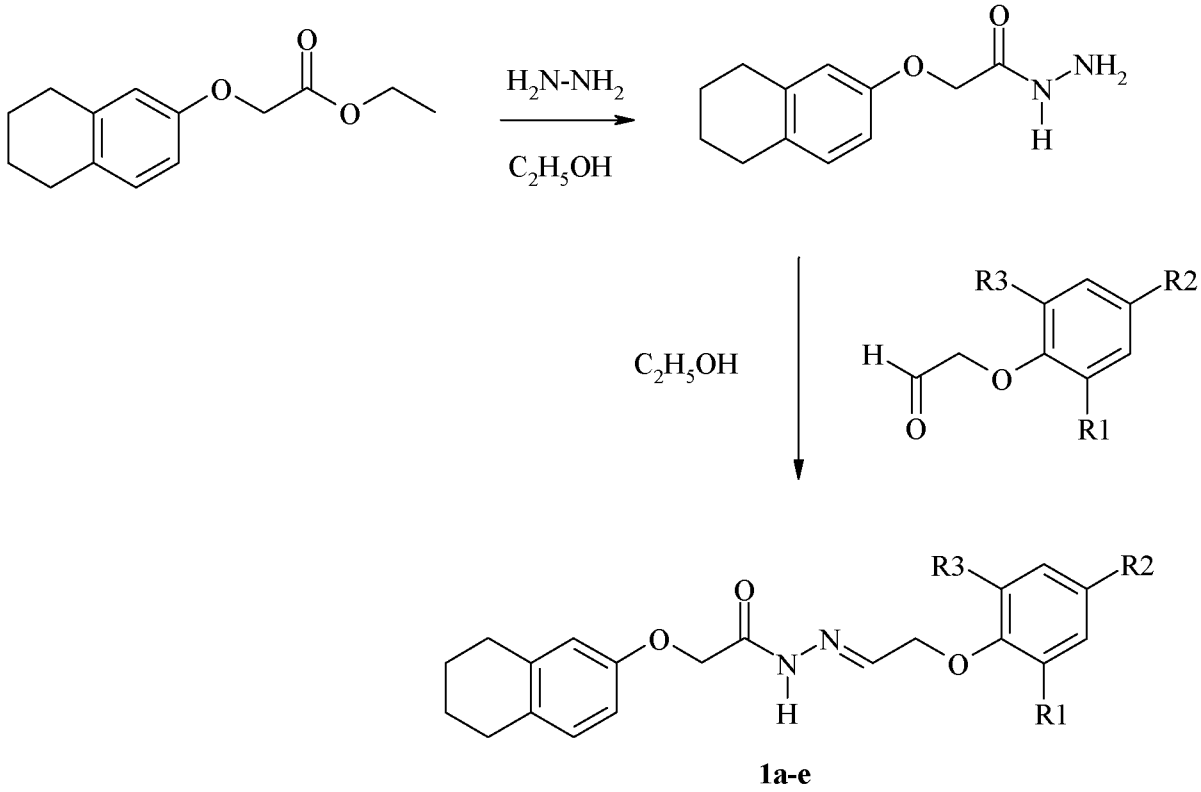
Comp.	R_1	R_2	R_3	Yield (%)	Empirical Formula	Mol. Weight	M.P. (°C)
1a	H	CH_3	H	75	$C_{21}H_{24}N_2O_3$	352.44	148-149
1b	H	$C(CH_3)_3$	H	76	$C_{24}H_{30}N_2O_3$	394.52	163-165
1c	H	OCH_3	H	72	$C_{21}H_{24}N_2O_4$	368.44	140-142
1d	CH_3	CH_3	H	69	$C_{22}H_{26}N_2O_3$	366.46	133-134
1e	CH_3	H	CH_3	78	$C_{22}H_{26}N_2O_3$	366.46	151-153

(5,6,7,8-Tetrahydronaphthalen-2-yloxy)acetic acid (2-(4-methylphenoxy)ethylidene) hydrazide (1a):

IR (ν, cm^{-1}, KBr): 3210, 1686, 1600, 1585, 1498. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 1.69-1.79 (4H, m), 2.23 (3H, s), 2.57-2.72 (4H, m), 4.55 and 4.89 (2H, s), 4.63-4.71 (2H, m), 6.54-6.66 (1H, d, J = 2.6 Hz), 6.60-6.71 (1H, dd, J = 8.4, 2.6 Hz), 6.85-6.99 (3H, m), 7.10 (2H, d, J = 8.2 Hz), 7.48-7.83 (1H, t, J = 5.0 Hz), 11.45-11.47 (1H, two bs). **^{13}C NMR** (100 MHz, DMSO-d_6): δ 20.01 (CH_3), 22.62 (CH_2), 22.89 (CH_2), 27.94 (CH_2), 29.03 (CH_2), 64.39 (CH_2), 66.67 (CH_2), 112.15 (CH), 114.08 (CH), 114.55 (2CH), 128.81 (C), 129.57 (CH), 129.76 (C), 129.82 (2CH), 137.45 (CH), 142.61 (CH), 155.48 (C), 155.77 (C), 164.57 (C). **MS-FAB$^+$**: m/z: 353 (M + 1). For $C_{21}H_{24}N_2O_3$ calculated: 71.57 % C, 6.86 % H, 7.95 % N; found: 71.78 % C, 6.91 % H, 7.93 % N.

(5,6,7,8-Tetrahydronaphthalen-2-yloxy)acetic acid (2-(4-tert-butylphenoxy) ethylidene) hydrazide (1b):

IR (ν, cm^{-1}, KBr): 3195, 1687, 1574, 1503, 1496. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 1.26 (9H, s), 1.70-1.80 (4H, m), 2.59-2.71 (4H, m), 4.55 and 4.90 (2H, s), 4.66-4.72 (2H, m), 6.56-6.67 (1H, d, J = 2.6 Hz), 6.61-6.72 (1H, dd, J = 8.4, 2.6 Hz), 6.88-6.99 (3H, m), 7.30 (2H, d, J = 8.2 Hz), 7.51-7.84 (1H, t, J = 5.0 Hz), 11.41-11.44 (1H, two bs). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 22.63 (CH_2), 22.89 (CH_2), 27.95 (CH_2), 29.04 (CH_2), 31.26 ($3CH_3$), 33.72 (C), 64.43 (CH_2), 66.66 (CH_2), 112.16 (CH), 114.10 (CH), 114.19 (2CH), 126.06 (2CH), 128.80 (C), 129.57 (CH), 137.43 (CH), 142.68 (CH), 143.21 (C), 155.48 (C), 155.64 (C), 164.56 (C). **MS-FAB$^+$**: m/z: 395 (M + 1). For $C_{24}H_{30}N_2O_3$ calculated: 73.07 % C, 7.66 % H, 7.10 % N; found: 73.03 % C, 7.65 % H, 7.13 % N.



Scheme 1.

(5,6,7,8-Tetrahydronaphthalen-2-yloxy)acetic acid (2-(4-methoxyphenoxy)ethylidene) hydrazide (*1c*)*:*

IR (ν, cm^{-1}, KBr): 3190, 1686, 1598, 1515, 1494. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 1.69-1.80 (4H, m), 2.59-2.70 (4H, m), 3.70 (3H, s), 4.55 and 4.89 (2H, s), 4.65-4.72 (2H, m), 6.54-6.66 (1H, d, J = 2.6 Hz), 6.60-6.71 (1H, dd, J = 8.4, 2.6 Hz), 6.84-6.99 (5H, m), 7.47-7.81 (1H, t, J = 5.0 Hz), 11.44-11.45 (1H, two bs). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 22.61 (CH_2), 22.88 (CH_2), 27.93 (CH_2), 29.02 (CH_2), 55.32 (CH_3), 64.38 (CH_2), 67.20 (CH_2), 112.15 (CH), 114.07 (CH), 114.61 (2CH), 115.71 (2CH), 128.81 (C), 129.58 (CH), 137.46 (CH), 142.77 (CH), 151.87 (C), 153.71 (C), 155.47 (C), 164.56 (C). **MS-FAB^{+}**: m/z: 369 (M + 1). For $C_{21}H_{24}N_2O_4$ calculated: 68.46 % C, 6.57 % H, 7.60 % N; found: 68.28 % C, 6.50 % H, 7.51 % N.

(5,6,7,8-Tetrahydronaphthalen-2-yloxy)acetic acid (2-(2,4-dimethylphenoxy) ethylidene) hydrazide (*1d*)*:*

IR (ν, cm^{-1}, KBr): 3190, 1686, 1585, 1535, 1495. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 1.68-1.78 (4H, m), 2.15 (3H, s), 2.20 (3H, s), 2.58-2.72 (4H, m), 4.55 and 4.88 (2H, s), 4.67-4.70 (2H, m), 6.55-6.67 (1H, d, J = 2.6 Hz), 6.60-6.71 (1H, dd, J = 8.4, 2.6 Hz), 6.85-6.99 (4H, m), 7.50-7.85 (1H, t, J = 5.0 Hz), 11.41-11.42 (1H, two bs). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 15.90 (CH_3), 20.02 (CH_3), 22.63 (CH_2), 22.90 (CH_2), 27.94 (CH_2), 29.03 (CH_2), 64.32 (CH_2), 66.87 (CH_2), 111.71 (CH), 112.13 (CH), 113.98 (CH), 125.60 (C), 127.02 (CH), 128.77 (C), 129.31 (C), 129.59 (CH), 131.24 (CH), 137.44 (CH), 142.76 (CH), 153.85 (C), 155.44 (C), 164.58 (C). **MS-FAB^{+}**: m/z: 367 (M + 1). For $C_{22}H_{26}N_2O_3$ calculated: 72.11 % C, 7.15 % H, 7.64 % N; found: 72.03 % C, 7.17 % H, 7.59 % N.

(5,6,7,8-Tetrahydronaphthalen-2-yloxy)acetic acid (2-(2,6-dimethylphenoxy) ethylidene) hydrazide (1e):

IR (ν, cm^{-1}, KBr): 3220, 1687, 1610, 1565, 1485. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 1.65-1.75 (4H, m), 2.25 (6H, s), 2.59-2.72 (4H, m), 4.55 and 4.87 (2H, s), 4.65-4.69 (2H, m), 6.55-6.68 (1H, d, J = 2.6 Hz), 6.60-6.72 (1H, dd, J = 8.4, 2.6 Hz), 6.89-7.00 (2H, m), 7.04 (2H, d, J = 8.2 Hz), 7.60-7.94 (1H, t, J = 5.0 Hz), 11.43-11.44 (1H, two bs). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 16.11 ($2CH_3$), 22.63 (CH_2), 22.90 (CH_2), 27.95 (CH_2), 29.04 (CH_2), 64.38 (CH_2), 71.05 (CH_2), 112.15 (CH), 114.09 (CH), 123.99 (CH), 128.75 (2CH), 128.82 (C), 129.56 (CH), 130.29 (2C), 137.44 (CH), 142.99 (CH), 155.30 (C), 155.49 (C), 164.64 (C). **MS-FAB$^+$**: m/z: 367 (M + 1). For $C_{22}H_{26}N_2O_3$ calculated: 72.11 % C, 7.15 % H, 7.64 % N; found: 72.29 % C, 7.07 % H, 7.59 % N.

Microbiology

Microdilution broth susceptibility assay was used for the antimicrobial evaluation of the compounds, whereas antifungal susceptibility of *Candida albicans* was examined according to NCCLS reference method for broth dilution antifungal susceptibility testing of yeasts (18,19). Chloramphenicol was used as standard antibacterial agent and ketoconazole was used as antifungal agent. Both are prepared as described in the related references.

Antimicrobial activity

Antimicrobial activities of compounds were tested using microbroth dilution method (18,19). Tested microorganism strains were; *Escherichia coli* (NRRL B-3008), *Staphylococcus aureus* (ATCC 6538), *Pseudomonas aeruginosa* (ATCC 27853), *Proteus vulgaris* (NRRL B-123), *Salmonella typhimurium* (ATCC 13311), Methicillin-resistant *Staphylococcus aureus* (MRSA) (clinic isolate), *Candida albicans* (NRRL Y-12983), *Candida parapsilosis* (NRRL Y-12696). The observed data on the antimicrobial activity of the compounds and control drugs are given in Table 2.

Table 2. Antimicrobial Activities of the Compounds 1a-e (mg/mL)

Comp.	A	B	C	D	E	F	G	H
1a	>1.25	>1.25	>1.25	1.25	1.25	1.25	1.25	>1.25
1b	>1.25	>1.25	>1.25	>1.25	>1.25	1.25	1.25	>1.25
1c	>1.25	>1.25	>1.25	1.25	>1.25	1.25	1.25	>1.25
1d	>1.25	>1.25	1.25	0.625	>1.25	1.25	1.25	>1.25
1e	>1.25	>1.25	>1.25	1.25	>1.25	1.25	1.25	>1.25
Chloramphenicol	0.0312	0.0312	0.5	0.0312	0.0156	0.0312	-	-
Ketoconazole	-	-	-	-	-	-	0.125	0.25

A: *Escherichia coli* (NRRL B-3008), **B:** *Staphylococcus aureus* (ATCC 6538), **C:** *Pseudomonas aeruginosa* (ATCC 27853), **D:** *Proteus vulgaris* (NRRL B-123), **E:** *Salmonella typhimurium* (ATCC 13311), **F:** Methicillin-resistant *Staphylococcus aureus* (MRSA) (clinic isolate) **G:** *Candida albicans* (NRRL Y-12983) **H:** *Candida parapsilosis* (NRRL Y-12696)

RESULTS AND DISCUSSION

Among several clear synthetic routes to derivatives **1a-e**, we decided to explore the acylhydrazine derivatives as a key intermediate in our synthetic approach. This compound could be transformed in **1a-e** using classical functional group interconversion, *i.e.* $CONHNH_2 \rightarrow CONHN=CH-CH_2-O-Ar$. Finally, the new target compounds **1a-e** were obtained, in good yields (69-78%), by condensing the acylhydrazine derivatives with the corresponding appropriate aldehydes in absolute ethanol, as illustrated in Table 1 and Scheme 1.

The purity of the synthesized compounds was checked by elemental analyses. The structures of the various synthesized compounds were determined on the basis of spectral data analysis; such as IR, ^{1}H-NMR, ^{13}C-NMR and FAB^+-MS.

IR data provided functional group evidence for the formation of the expected structures. In the IR spectra, some significant stretching bands due N-H, C=O, C=C and C=N were at 3220-3190 cm^{-1}, 1687-1686 cm^{-1}, and 1610-1485 cm^{-1}, respectively.

According to the literature, the hydrazones may exist as *E/Z* geometrical isomers about C=N double bonds and *cis/trans* amide conformers. Besides hydrazones derived from aldehydes and substituted hydrazides are present in solution in the *E* form. It has been reported that when hydrazones are dissolved in dimethylsulfoxide-d_6 solution, the *E* geometrical isomers of these compounds undergo a rapid *cis/trans* amide equilibrium, in which the *cis* conformer predominates (20,21).

In the ^{1}H-NMR spectra of the compounds, the C_6 and C_7 protons of 5,6,7,8-tetrahydronaphthalene were observed at 1.65-1.80 ppm as multiplets. The C_5 and C_8 protons of 5,6,7,8-tetrahydronaphthalene structure were observed at 2.57-2.72 ppm as multiplets. The -O-C*H*$_2$-CO protons were appeared as singlet at 4.55 and 4.90 ppm. The -O-C*H*$_2$-CH= protons were appeared as multiplets at 4.63-4.72 ppm. The -N=C*H*- proton was observed as triplet at 7.47-7.94 ppm. The -N*H*-N= proton was observed as two broad singlet at 11.41 and 11.47 ppm, respectively. All the other aliphatic and aromatic protons were observed at expected regions. The ^{1}H-NMR data were also consistent with the assigned structures. In ^{1}H-NMR spectrum of compounds; we observed paired peaks for each of the protons -O-C*H*$_2$-CH=, -N=C*H*-, and -N*H*-N= corresponding to (*E*)- and (*Z*)-forms of the compounds. For each compound, the intensities of these paired peaks differed from others, due to the variable amounts of *(E)* and *(Z)*, which are usually unequal.

Additional support for the structures of the synthesized compounds was provided by ^{13}C-NMR spectra. In the ^{13}C-NMR chemical shift values of the carbon atoms at around 164.56-164.64 ppm (hydrazide *C*=O), and about 142.61-142.99 ppm (imine N=*C*H) corroborate the hydrazide character deduced from the ^{1}H-NMR data. The mass spectra of compounds showed (M+1) peaks, in agreement with their molecular formula.

MIC's were recorded as the minimum concentration of compound, which inhibits the growth of tested microorganisms. The results indicated that all of the tested compounds were inactive against the test organism. The reason for this aspect may be the low solubility of such compounds in polar solvents.

CONCLUSION

The present study describes the synthesis of five (5,6,7,8-tetrahydronaphthalen-2-yloxy)acetic acid (2-phenoxyethylidene)hydrazide derivatives (Scheme 1;1a-e). Their antimicrobial activities have been evaluated. The results showed that all of the tested compounds were inactive against the test organism. Regarding the antimicrobial level of the tested substances when compared to previous studies (22-24) seem to be less active against the tested microorganism which does not mean they would be inactive against other pathogenic

microorganisms. So it is worthwhile to test these substances against other microorganism strains and isolates suggesting them rather for specific inhibitory activities rather than a wide antimicrobial spectrum in this case.

REFERENCES

1. Barret Bee KJ, Ryder NS, Biochemical aspects of ergosterol biosynthesis inhibition, Eds: Sutcliffe JM, Georgopapadakou NH, Emerging Targets in Antibacterial and Antifungal Chemoterapy, Chapman and Hall, New York, pp 410-436, 1992.
2. Vicini P, Zani F, Cozzini P, Doytchinova I, Hydrazones of 1,2-benzisothiazole hydrazides: synthesis, antimicrobial activity and QSAR investigations, Eur J Med Chem 37, 553-564, 2002.
3. Özdemir A, Turan Zitouni G, Kaplancıklı ZA, Tunalı Y, Synthesis and biological activities of new hydrazide derivatives, J Enzym Inhib Med Chem 24, 825-831, 2009.
4. Gürsoy A, Ünal B, Karalı N, Ötük G, Synthesis, characterization and primary antimicrobial activity evaluation of 3-phenyl-6-methyl-4(3H)-quinazolinone-2-yl-mercaptoacetic acid arylidenehydrazides, Turk J Chem 29, 233-245, 2005.
5. Kamel AM, Lobna MA, El-Sayed ML, Mohamed IH, Rania HB, Hydrazones of 2-aryl-quinoline-4-carboxylic acid hydrazides: Synthesis and preliminary evaluation as antimicrobial agents, Bioorg Med Chem 14, 8675-8682, 2006.
6. Gürsoy A, Terzioglu N, Ötük G, Synthesis of some new hydrazide-hydrazones, thiosemicarbazides and thiazolidinones as possible antimicrobials, Eur J Med Chem 32, 753-757, 1997.
7. Cukurovalı A, Yılmaz I, Gur S, Kazaz C, Synthesis, antibacterial and antifungal activity of some new thiazolylhydrazone derivatives containing 3-substituted cyclobutane ring, Eur J Med Chem, 41, 201-207, 2006.
8. Kaplancıklı ZA, Turan Zitouni G, Özdemir A, Teuladeb JC, Synthesis and antituberculosis activity of new hydrazide derivatives, Arch der Pharm, 341, 721-724, 2008.
9. Koçyiğit Kaymakçıoğlu B, Oruç E, Unsalan S, Kandemirli F, Shvets N, Rollas S, Anatholy D, Synthesis and characterization of novel hydrazide-hydrazones and the study of their structure-antituberculosis activity, Eur J Med Chem, 41, 1253-1261, 2006.
10. Daniela GR, Dayse NS, Leonardo S, Alberto M, Clarice QFL, Antonia TA, Elizabeth IF, Leoberto CT, Potential tuberculostatic agents. Topliss application on benzoic acid ((5-nitrothiophen-2-yl)-methylene)-hydrazide series, Bioorg Med Chem,10, 557-560, 2002.
11. Turan Zitouni G, Özdemir A, Kaplancıklı ZA, Benkli K, Chevallet P, Akalin G, Synthesis and Antituberculosis Activity of New Thiazolylhydrazone Derivatives, Eur J Med Chem, 43, 981-985, 2008.
12. Salgın Goksen U, Gokhan Kelekci N, Goktas O, Koysal Y, Kılıc E, Isik S, Aktay G, Ozalp M, 1-Acylthiosemicarbazides, 1,2,4-triazole-5(4H)-thiones, 1,3,4-thiadiazoles and hydrazones containing 5-methyl-2-benzoxazolinones: Synthesis, analgesic-anti-inflammatory and antimicrobial activities, Bioorg Med Chem, 15, 5738-5751, 2007.
13. Ragavendran J, Sriram D, Patel S, Reddy I, Bharathwajan N, Stables J. et al, Design and synthesis of anticonvulsants from a combined phthalimide-GABA-anilide and hydrazone pharmacophore, Eur J Med Chem, 42, 146-151, 2007.
14. Vicini P, Incerti M, Doytchinova IA, Colla PL, Busonera B, Loddo R, Synthesis and antiproliferative activity of benzo(d)isothiazole hydrazones, Eur J Med Chem, 41, 624-632, 2006.

15. Özdemir A, Turan Zitouni G, Kaplancıklı ZA, İşcan G, Khanc S, Demirci F, Synthesis and the selective antifungal activity of 5,6,7,8-tetrahydroimidazo(1,2-a)pyridine derivatives, Eur J Med Chem 45, 2080-2084, 2010.
16. Yale HL, Losee K, Martins J, Holsing M, Perry MF, Bernstein J, Chemotherapy of experimental tuberculosis. VIII. The synthesis of acid hydrazides, their derivatives and related compounds, J Am Chem Soc, 75, 1933-1942, 1953.
17. Turan Zitouni G, Kaplancikli ZA, Güven K, N-(chroman-4-ylidene) aryloxyacetohydrazones: Synthesis and antimicrobial activity, Farmaco 52, 631-633, 1997.
18. Koneman EW, Allen SD, Winn WC, Colour Atlas and Textbook of Diagnostic Microbiology Lippincott Raven Publishers, Philadelphia, USA, pp. 86-856, 1997.
19. NCCLS, Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts, Approved Standard-Second Edition, NCCLS document M27-A2, 2002, ISBN 1-56238-469-4.
20. Palla G, Predieri G, Domiano P, Conformational behaviour and E/Z isomerization of N-acyl and N-aroylhydrazones, Tetrahedron 42, 3649-3654, 1986.
21. Wyrzykiewicz E, Prukała D, New isomeric N-substituted hydrazones of 2-, 3-and 4-pyridinecarboxaldehydes, J Heterocyclic Chem, 35, 381-387, 1998.
22. Özdemir A, Turan Zitouni G, Kaplancikli ZA, Demirci F, Iscan G, Studies on hydrazone derivatives as antifungal agents, J Enzym Inhib Med Chem 23, 470-475, 2008.
23. Özdemir A, Turan Zitouni G, Kaplancikli ZA, Iscan G, Khan S, Demirci F, Synthesis and the selective antifungal activity of 5,6,7,8-tetrahydroimidazo(1,2-a)pyridine derivatives, Eur J Med Chem 45, 2080-2084, 2010.
24. Özdemir A, Kaplancıklı ZA, Turan Zitouni G, Revial G, Synthesis of some novel hydrazone derivatives and evaluation of their antituberculosis activity, Marmara Pharm J 14, 79-83, 2010.

Received:11.08.2010
Accepted:03.11.2010