Istanbul J Pharm 50 (1): 49-53
DOI: 10.26650/IstanbulJPharm.2019.0027
Original Article

Synthesis and antimicrobial activity evaluation of new hydrazide-hydrazones derived from 1,2,4-triazole

Nuray Ulusoy Güzeldemirci[1], Dilek Şatana[2], Ömer Küçükbasmacı[3]

[1]Istanbul University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Istanbul, Turkey
[2]Istanbul University, Istanbul Faculty of Medicine, Department of Microbiology, Istanbul, Turkey
[3]Istanbul University Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Microbiology, Istanbul, Turkey

ORCID IDs of the authors: N.U.G. 0000-0002-4495-4282; D.Ş. 0000-0002-8827-1504; Ö.K. 0000-0002-8678-4218;

Cite this article as: Ulusoy Guzeldemirci, N., Satana, D., & Kucukbasmaci, O. (2020). Synthesis and antimicrobial activity evaluation of new hydrazide-hydrazones derived from 1,2,4-triazole. *İstanbul Journal of Pharmacy, 50* (1), 49–53.

ABSTRACT

Background and Aims: The aim in this study was to synthesize new 2-[[4-(4-chlorophenyl)-5-(furan-2-yl)-4*H*-1,2,4-triazol-3-yl]sulfanyl]-*N'*-[(substituted phenyl/furanyl)methylidene]acetohydrazides and screen for their *in vitro* antimicrobial activity.
Methods: Novel compounds (**6a-g**) were synthesized starting with furan-2-carbohydrazide (**1**) using five step reactions. The structures of the the resulting compounds were characterized by IR, ^{1}H-NMR and elemental analysis. All compounds were evaluated for antibacterial and antifungal activities against *Staphylococcus aureus* ATCC 29213, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Candida albicans* ATCC 10231, *Candida krusei* ATCC 6258, *Candida parapsilosis* ATCC 22019, *Microsporum gypseum* NCPF 580, *Trichophyton mentagrophytes* var. *erinacei* NCPF 375 and *Trichophyton tonsurans* NCPF 245 using a microbroth dilution method.
Results: The biological assay results showed that all of the compounds displayed varying degrees of antimicrobial activity in this series.
Conclusion: The preliminary results revealed that some of the new synthesized derivatives exhibited promising antimicrobial activities. Further investigation may be completed on similar molecules in the future.

Keywords: Synthesis, hydrazide-hydrazone, antibacterial activity, antifungal activity

INTRODUCTION

1,2,4-Triazole derivatives have a high potency for different biological activities, such as anticancer (Boraei et al., 2019; El-Sherief et al., 2018), antiproliferative and anti-tubulin (Mustafa et al., 2019; Mustafa et al., 2017), antibacterial (Özkırımlı et al., 2009; Turan-Zitouni et al., 2005; Sztanke et al., 2008; Demirbaş et al., 2004; Ulusoy et al., 2001*a*), analgesic (Turan-Zitouni, Kaplancıklı, Erol, & Kılıç, 1999), anti-inflammatory (Tozkoparan, Gökhan, Aktay, Yeşilada, & Ertan, 2000) and antitumour (Demirbaş et al., 2004; Al-Soud et al., 2004; Holla et al., 2003) properties. Moreover, hydrazide-hydrazone derivatives have been reported to posses antimicrobial (Rollas, Güleman, & Erdeniz, 2002), antituberculosis (Koçyiğit-Kaymakçıoğlu et al., 2006; Imramovsky et al., 2007), herbicidal (Weng, Huang, Zeng, Deng, & Hu, 2012), antiviral (Završnik et al., 2011), analgesic-anti-inflammatory (Salgın-Gökşen et al., 2007), anticonvulsant (Dimmock, Vashishtha, & Stables, 2000) and anticancer (Savini et al., 2004) activities.

In continuation with our previous work in the antimicrobial activity research area, in the present study we have demonstrated the structural diversity of 1,2,4-triazoles as potent antimicrobial agents (Ergenç et al., 1996; İlhan et al., 1996; Günay et al., 1999;

Address for Correspondence:
Nuray ULUSOY GÜZELDEMİRCİ, e-mail: nulusoy@istanbul.edu.tr

Submitted: 03.07.2019
Revision Requested: 22.10.2019
Last Revision Received: 03.11.2019
Accepted: 05.12.2019

Ulusoy et al., 2001*a*; 2001*b*; 2003; Ulusoy Güzeldemirci et al., 2010; 2013), we report here the synthesis and investigation of antimicrobial activity of new 1,2,4-triazole compounds.

MATERIALS AND METHODS

Chemistry

All reagents for synthesis were commercially available. The melting points were determined on a Büchi 530 melting point apparatus (Flawil, Switzerland) in open capillary method and are uncorrected. Elemental analyses were analysed on a Carlo Erba 1106 elemental analyzer (Milano, Italy). IR spectra were obtained on KBr discs, using a Perkin Elmer 1600 FT-IR spectrophotometer (Waltham, MA, USA). ^{1}H NMR (DMSO-d_6/TMS) spectra were measured on VarianUNITY INOVA (500 MHz) spectrophotometer.

General procedure for the preparation of 2-[[4-(4-chlorophenyl)-5-(furan-2-yl)-4H-1,2,4-triazol-3-yl] sulfanyl]acetohydrazide (5)

Compound **5** was *prepared from* furan-2-carbohydrazide (**1**) using four step reactions *according to literature* procedures (Çapan et al., 1990-92; Çapan et. al., 1993; Ulusoy et al., 2001*b*).

General procedure for the preparation of 2-[[4-(4-chlorophenyl)-5-(furan-2-yl)-4H-1,2,4-triazol-3-yl] sulfanyl]-N'-[(substituted phenyl/furanyl)methylidene]acetohydrazides (6a-g)

A solution of **5** (0.005 mol) and the appropriate aromatic aldehyde (0.005 mol) in ethanol (30 mL) was heated under reflux for 3h. The precipitate thus obtained was filtered and purified either by washing with hot ethanol or recrystallization from ethanol.

2-[[4-(4-chlorophenyl)-5-(furan-2-yl)-4H-1,2,4-triazol-3-yl] sulfanyl]-N'-[(3-methoxyphenyl)methylidene]acetohydrazide (6a)

Yield 70%; mp 108-109°C; IR(KBr) υ cm^{-1}: 3440 (NH), 1676 (C=O), 1576, 1494, 1431 (C=N/C=C); ^{1}HNMR (DMSO-*d6*) δ (ppm): 11.72; 11.64 (2s, 1H, CONH), 8.15; 7.96 (2s, 1H, N=CH), 7.75 (d, *J*=1.95 Hz, 1H, furan C_5-H), 7.69-7.65 (m, 2H, ClPh$C_{2,6}$-H), 7.58-7.54 (m, 2H, ClPh$C_{3,5}$-H), 7.35-7.20 (m, 3H, arylidene $C_{2,5,6}$-H), 7.00-6.96 (m, 1H, arylidene C_4-H), 6.52 (dd, *J*=3.42; 1.95 Hz, 1H, furan C_4-H), 6.29 (d, *J*=3.42 Hz, 1H, furan C_3-H), 4.45; 4.05 (2s, 2H, SCH_2), 3.77 (s, 3H, OCH_3). Anal. Calcd. for $C_{22}H_{18}ClN_5O_3S.1.5\ H_2O$: C, 53.38; H, 4.27; N, 14.15; Found: C, 53.47; H, 4.07; N, 14.27%.

2-[[4-(4-chlorophenyl)-5-(furan-2-yl)-4H-1,2,4-triazol-3-yl] sulfanyl]-N'-[(4-chlorophenyl)methylidene]acetohydrazide (6b)

Yield 59%; mp 119-120°C; IR(KBr) υ cm^{-1}: 3446 (NH), 1675 (C=O), 1610, 1559, 1514 (C=N/C=C); ^{1}HNMR (DMSO-*d6*) δ (ppm): 11.77; 11.68 (2s, 1H, CONH), 8.69; 8.18 (2s, 1H, N=CH), 7.88 (d, *J*=1.96 Hz, 1H, furan C_5-H), 7.75-7.46 (m, 8H, ClPh), 6.53 (dd, *J*=3.42; 1.95 Hz, 1H, furan C_4-H), 6.29 (d, *J*=3.42 Hz, 1H, furan C_3-H), 4.44; 4.05 (2s, 2H, SCH_2). Anal. Calcd. for $C_{21}H_{15}Cl_2N_5O_2S.H_2O$: C, 51.43; H, 3.49; N, 14.28; Found: C, 51.22; H, 3.27; N, 13.66%.

2-[[4-(4-chlorophenyl)-5-(furan-2-yl)-4H-1,2,4-triazol-3-yl] sulfanyl]-N'-[(4-bromophenyl)methylidene]acetohydrazide (6c)

Yield 79%; mp 124-125°C; IR(KBr) υ cm^{-1}: 3440 (NH), 1676 (C=O), 1621, 1582, 1479 (C=N/C=C); ^{1}HNMR (DMSO-*d6*) δ (ppm): 11.78 (s, 1H, CONH), 8.68; 8.16 (2s, 1H, N=CH), 7.80 (s, 1H, furan C_5-H), 7.75-7.53 (m, 8H, ClPh, BrPh), 6.52 (dd, *J*=3.41; 1.47 Hz, 1H, furan C_4-H), 6.29 (d, *J*=3.41 Hz, 1H, furan C_3-H), 4.44; 4.05 (2s, 2H, SCH_2). Anal. Calcd. for $C_{21}H_{15}BrClN_5O_2S.H_2O$: C, 47.15; H, 3.20; N, 13.09; Found: C, 47.22; H, 2.64; N, 12.72%.

2-[[4-(4-chlorophenyl)-5-(furan-2-yl)-4H-1,2,4-triazol-3-yl] sulfanyl]-N'-[(4-carboxyphenyl)methylidene]acetohydrazide (6d)

Yield 74%; mp 265-266°C; IR(KBr) υ cm^{-1}: 3487, 3189 (OH/NH), 1671 (C=O), 1603, 1567, 1494 (C=N/C=C); ^{1}HNMR (DMSO-*d6*) δ (ppm): 11.86; 11.77 (2s, 1H, CONH), 8.23; 8.05 (2s, 1H, N=CH), 7.99-7.96 (m, 2H, arylidene $C_{3,5}$-H), 7.81-7.74 (m, 3H, arylidene $C_{2,6}$-H, furan C_5-H), 7.69-7.66 (m, 2H, ClPh$C_{2,6}$-H), 7.58-7.54 (m, 2H, ClPh$C_{3,5}$-H), 6.52 (dd, *J*=3.42; 1.95 Hz, 1H, furan C_4-H), 6.29 (d, *J*=3.42 Hz, 1H, furan C_3-H), 4.47; 4.07 (2s, 2H, SCH_2). Anal. Calcd. for $C_{22}H_{16}ClN_5O_4S.1.5\ H_2O$: C, 51.91; H, 3.76; N, 13.76; Found: C, 51.52; H, 3.59; N, 13.88%.

2-[[4-(4-chlorophenyl)-5-(furan-2-yl)-4H-1,2,4-triazol-3-yl]sulfanyl]-N'-[(2,6-dichlorophenyl)methylidene]acetohydrazide (6e)

Yield 75%; mp 228-229°C; IR(KBr) υ cm^{-1}: 3400 (NH), 1684 (C=O), 1610, 1579, 1494 (C=N/C=C); ^{1}HNMR (DMSO-*d6*) δ (ppm): 12.01; 11.87 (2s, 1H, CONH), 8.38; 8.24 (2s, 1H, N=CH), 7.74 (d, *J*=0.98 Hz, 1H, furan C_5-H), 7.71-7.65 (m, 2H, ClPh$C_{2,6}$-H), 7.57-7.53 (m, 3H, ClPh$C_{3,5}$-H, arylidene C_4-H), 7.46-7.39 (m, 2H, arylidene $C_{3,5}$-H), 6.52 (dd, *J*=3.42; 1.95 Hz, 1H, furan C_4-H), 6.28 (d, *J*=3.42 Hz, 1H, furan C_3-H), 4.38; 4.08 (2s, 2H, SCH_2). Anal. Calcd. for $C_{21}H_{14}Cl_3N_5O_2S.H_2O$: C, 48.05; H, 3.07; N, 13.34; Found: C, 48.69; H, 2.71; N, 13.66%.

2-[[4-(4-chlorophenyl)-5-(furan-2-yl)-4H-1,2,4-triazol-3-yl] sulfanyl]-N'-[(3,4-dichlorophenyl)methylidene]acetohydrazide (6f)

Yield 63%; mp 158-159°C; IR(KBr) υ cm^{-1}: 3400 (NH), 1676 (C=O), 1494, 1473 (C=N/C=C); ^{1}HNMR (DMSO-*d6*) δ (ppm): 11.88; 11.77 (2s, 1H, CONH), 8.67; 8.15 (2s, 1H, N=CH), 7.95-7.54 (m, 8H, ClPh, arylidene $C_{2,5,6}$-H, furan C_5-H), 6.51 (dd, *J*=3.41; 1.47 Hz, 1H, furan C_4-H), 6.27 (d, *J*=3.42 Hz, 1H, furan C_3-H), 4.44; 4.05 (2s, 2H, SCH_2). Anal. Calcd. for $C_{21}H_{14}Cl_3N_5O_2S.H_2O$: C, 48.05; H, 3.07; N, 13.34; Found: C, 47.98; H, 2.82; N, 12.74.

2-[[4-(4-chlorophenyl)-5-(furan-2-yl)-4H-1,2,4-triazol-3-yl] sulfanyl]-N'-[(5-nitrofuran-2-yl)methylidene]acetohydrazide (6g)

Yield 51%; mp 190-191°C; IR(KBr) υ cm^{-1}: 3096 (NH), 1683 (C=O), 1610, 1563, 1472 (C=N/C=C); ^{1}HNMR (DMSO-*d6*) δ (ppm): 12.11; 11.99 (2s, 1H, CONH), 8.70; 8.16 (2s, 1H, N=CH), 7.81-7.44 (m, 6H, ClPh, furfurylidene C_4-H, furan C_5-H), 7.22, 7.20 (2d, 1H, *J*=3.90; 3.91 Hz furfurylidene C_3-H), 6.52; 6.48 (2dd, 1H, *J*=3.41; 1.95, 3.42; 1.47 Hz furan C_4-H), 6.30; 6.22 (2d, *J*=2.93; 3.41 Hz, 1H, furan C_3-H), 4.31; 4.08 (2s, 2H, SCH_2). Anal. Calcd. for $C_{19}H_{13}ClN_6O_5S.1/2H_2O$: C, 47.35; H, 2.92; N, 17.44; Found: C, 46.91; H, 2.47; N, 17.91%.

Microbiology

The tested compounds were dissolved in DMSO at a stock concentration of 3200 µg.cm^{-3}. The final required concentrations were prepared with RPMI 1640 medium for *Candida* species

and dermatophytes and with Mueller-Hinton broth of bacteria. The last DMSO concentration was reduced to 1%.

Antibacterial activity

This was performed according to the literature method (Wayne, 2005).

Antifungal activity

Antifungal activity for Candida species

This was applied according to the literature (Wayne, 2002*a*).

Antifungal activity for dermatophytes

The microdilution method was used according to the literature (Wayne, 2002*b*; Fernández-Torres, 2002).

RESULTS AND DISCUSSION

4-(4-Chlorophenyl)-2,4-dihydro-5-(2-furyl)-3*H*-1,2,4-triazole-3-thione (**3**) was prepared from furan-2-carbohydrazide (**1**) with two-step synthesis (Çapan, Ergenç, & Ötük, 1990-92). Treatment of compound (**3**) with ethyl bromoacetate gave an ester derivative (**4**), which yielded a hydrazide compound (**5)** on reaction with hydrazinium hydroxide. Condensation of **5** with substituted aromatic aldehydes gave **6a**–**g**. *The synthesis of* the title compounds is shown in Figure 1. IR and ^{1}H NMR data confirmed the proposed structures. IR spectra showed the NH bands of **6a**–**g** in the 3487–3096 cm^{-1} regions. The CO groups of **6a**-**g** absorbed in the 1684–1671 cm^{-1} regions, respectively. The other bands which appeared in the spectra of **6a**–**g** in the 1621–1431 cm^{-1} region were attributed to the exocyclic C=N group. The ^{1}H NMR spectra of **6a**–**g** revealed the presence of two isomers in DMSO-*d6* as supported by the NH, N=CH, and SCH_2 protons resonating as double singlets at about 12.11-11.64, 8.70–7.96 and 4.47–4.05 ppm. It is supposed that the N=CH double bond limits rotation and causes the formation of *E* and *Z* isomers with the *E* isomer dominating (Çapan, Ulusoy, Ergenç, & Kiraz, 1999).

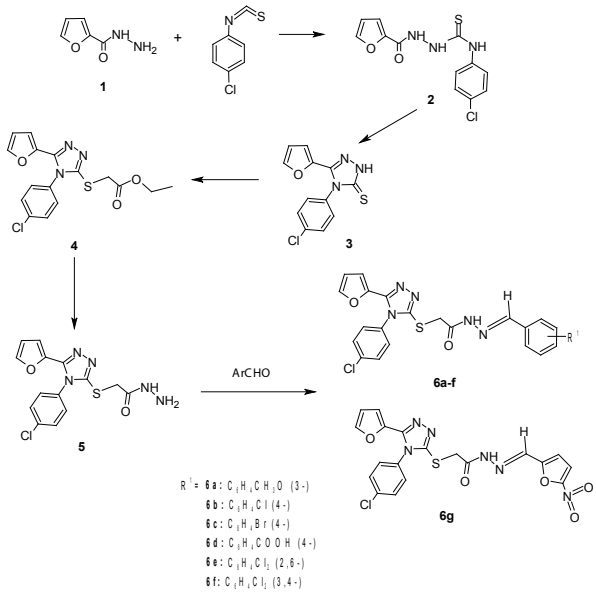

Figure 1. Synthetic route of compounds **6a-g**.

The newly synthesized compounds **6a**-**g** were evaluated for *in vitro* antibacterial activity against *Staphylococcus aureus* ATCC 29213, *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853, and for antifungal activity against *Candida albicans* ATCC 10231, *C. krusei* ATCC 6258, *C. parapsilosis* ATCC 22019, *Microsporum gypseum* NCPF 580 *T. var. erinacei* NCPF 375 and, *T. tonsurans* NCPF 245 using the microbroth dilution method (Wayne, 2005) (Tables 1 and 2).

Table 1. Antibacterial activity of compounds 6a-g (MIC ug/mL)

Comp.	Microorganisms*		
	A	B	C
6a	64	64	>64
6b	>64	>64	>64
6c	64	64	>64
6d	64	64	64
6e	64	>64	>64
6f	>64	>64	>64
6g	32	64	>64
Levofloxacin	0.12	0.5	0.015

***A=** *S. aureus* ATCC 29213, **B=** *E. coli* ATCC 25922, **C=** *P. aeruginosa* ATCC 27853

Table 2. Antifungal activity of compounds 6a-g (MIC ug/mL)

Comp.	Microorganisms*					
	A	B	C	D	E	F
6a	32	32	32	32	16	16
6b	64	64	>64	16	16	8
6c	64	64	64	16	16	16
6d	32	64	32	16	16	8
6e	>64	>64	>64	16	16	8
6f	64	64	64	64	32	32
6g	64	32	32	16	16	16
Itraconazole	0.12	0.06	0.12	n.t.	n.t.	n.t.
Amphotericin B	n.t.	n.t.	n.t.	0.5	0.5	0.25

***A=** *C. albicans* ATCC 10231, **B=** *C. krusei* ATCC 6258, **C=** *C. parapsilosis* ATCC 22019, **D=** *M. gypseum* NCPF 580, **E=** *T. mentagrophytes var. erinacei* NCPF 375, **F=** *T. tonsurans* NCPF 245

5-Nitrofuryl substituted compound **6g**, showed the highest antibacterial activity against *S. aureus* ATCC 29213 (MIC=32 μg/cm^{-3}) (Table 1). Additionally, derivatives **6b** (R^1=4-ClPh), **6d** (R^1=4-COOHPh) and **6e** (R^1=2,6-$(Cl)_2$Ph), were most active against *T. tonsurans* NCPF 245 (MIC=8 μg/cm^{-3}) (Table 2). Compounds **6b**, **6c** (R^1= 4-BrPh), **6d**, **6e** and **6g** showed the highest effect against *M. gypseum* NCPF 580 (MIC=16 μg/cm^{-3}). Compounds **6a** (R^1=3-CH_3OPh), **6b**, **6c**, **6d**, **6e** and **6g** also showed the highest activity against *T. mentagrophytes var. erinacei* NCPF 375 (*MIC*=16 μg/cm^{-3}).

CONCLUSION

A new series of hydrazide-hydrazone compounds derived from 1,2,4-triazole (**6a**-**g**) were obtained from furan-2-carbohydrazide. The activity results indicated that some of the title compounds showed promising antimicrobial activity.

Peer-review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- N.U.G.; Data Acquisition- N.U.G., D.Ş., Ö.K.; Data Analysis/Interpretation- N.U.G., D.Ş., Ö.K.; Drafting Manuscript- N.U.G., D.Ş., Ö.K.; Critical Revision of Manuscript- N.U.G.; Final Approval and Accountability- N.U.G., D.Ş., Ö.K.; Technical or Material Support- N.U.G., D.Ş., Ö.K.; Supervision- N.U.G., D.Ş., Ö.K.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: This study was funded by Scientific Research Projects Coordination Unit of Istanbul University. Project number: 52074 and TSA-2017-26543.

REFERENCES

- Al-Soud, Y. A., Al-Dweri, M. N., & Al-Masoudi, N. A. (2004). Synthesis, antitumor and antiviral properties of some 1,2,4-triazole derivatives. *Farmaco, 59*(10), 775–783.
- Boraei, A. T. A., Singh, P. K., Sechi, M., & Satta, S. (2019). Discovery of novel functionalized 1,2,4-triazoles as PARP-1 inhibitors in breast cancer: Design, synthesis and antitumor activity evaluation. *European Journal of Medicinal Chemistry, 182,* 111621.
- Çapan, G., Ergenç, N., & Ötük, G. (1990-92). Synthesis and biological evaluation of 4-alkyl/aryl-1-(2-furoyl)-3-thiosemicarbazides and 4-alkyl/aryl-2,4-dihydro-5-(2-furyl)-3*H*-1,2,4-triazole-3-thiones. *Journal of Faculty of Pharmacy of Istanbul, 26-28,* 23–30.
- Çapan, G., Ergenç, N., & Ötük, G. (1993). Synthesis, characterization and biological evaluation of 1,2,4-triazole-3-mercaptoacetic acid derivatives. *Acta Pharmaceutica Turcica, 35*, 51–58.
- Çapan, G., Ulusoy, N., Ergenç, N., & Kiraz, M. (1999). New 6-phenylimidazo[2,1-b]thiazole derivatives: Synthesis and antifungal activity. *Monatshefte fur Chemie, 130*(11), 1399–1407.
- Demirbaş, N., Karaoğlu, S. A., Demirbaş, A., & Sancak, K. (2004). Synthesis and antimicrobial activities of some new 1-(5-phenylamino-[1,3,4] thiadiazol-2-yl)methyl-5-oxo-[1,2,4]triazole and 1-(4-phenyl-5-thioxo-[1,2,4] triazol-3-yl)methyl-5-oxo-[1,2,4]triazole derivatives. *European Journal of Medicinal Chemistry, 39*(9), 793-804.
- Dimmock, J. R., Vashishtha, S. C., & Stables, J. P. (2000). Anticonvulsant properties of various acetylhydrazones, oxamoylhydrazones and semicarbazones derived from aromatic and unsaturated carbonyl compounds. *European Journal of Medicinal Chemistry, 35*(2), 241–248.
- El-Sherief, H. A. M., Youssif, B. G. M., Abbas Bukhari, S. N., Abdelazeem, A. H., Abdel-Aziz, M., & Abdel-Rahman, H. M. (2018). Synthesis, anticancer activity and molecular modeling studies of 1,2,4-triazole derivatives as EGFR inhibitors. *European Journal of Medicinal Chemistry, 156*, 774–789.
- Ergenç, N., Ulusoy, N., Çapan, G., Sanis, G. Ö., & Kiraz, M. (1996). Synthesis and antimicrobial properties of new 4-(alkylidene/arylidene)-amino-5-(2-furanyl)-2,4-dihydro-3H-1,2,4-triazole-3-thiones and 6-aryl-3-(2-furanyl)-7H-1,2,4-triazolo[3,4-b][1,3,4] thiadiazines. *Archiv der Pharmazie, 329*(8–9), 427–430.
- Fernández-Torres, B., Cabañes, F. J., Carrillo-Muñoz, A. J., Esteban, A., Inza, I., Abarca, L., & Guarro, J. (2002). Collaborative evaluation of optimal antifungal susceptibility testing conditions for dermatophytes. *Journal of Clinical Microbiology, 40*(11), 3999–4003.
- Günay, N. S., Çapan, G., Ulusoy, N., Ergenç, N., Ötük, G., & Kaya, D. (1999). 5-Nitroimidazole derivatives as possible antibacterial and antifungal agents. *Farmaco, 54*(11-12), 826–831.
- Holla, S., B., Veerendra, B., Shivananda, M. K., & Poojary, B. (2003). Synthesis characterization and anticancer activity studies on some Mannich bases derived from 1,2,4-triazoles. *European Journal of Medicinal Chemistry, 38*(7-8), 759–767.
- İlhan, E. Ergenç, N., Ulusoy, N., & Ötük Sanış, G., (1996). Synthese und antimikrobielle Untersuchung einiger 4-Arylidenamino-3-(α,α-diphenyl-α-hydroxymethyl)-1,4-dihydro-5*H*-1,2,4-Triazol-5-thione und 6-Aryl-3-(α,α-diphenyl-α-hydroxymethyl)-7*H*-s-Triazolo[3,4-*b*][1,3,4]thiadiazine. *Die Pharmazie, 51*(2), 123–124.
- Imramovský, A., Polanc, S., Vinšová, J., Kočevar, M., Jampílek, J., Rečková, Z., & Kaustová, J. (2007). A new modification of antitubercular active molecules. *Bioorganic and Medicinal Chemistry, 15*(7), 2551–2559.
- Koçyiğit Kaymakçıoğlu, B., Oruç, E., Ünsalan, S., Kandemirli, F., Shvets, N., Rollas, S., & Dimoglo, A. (2006). Synthesis and characterization of novel hydrazide-hydrazones and the study of their structure-antituberculosis activity. *European Journal of Medicinal Chemistry, 41*(11), 1253–1261.
- Mustafa, M., Abdelhamid, D., Abdelhafez, E. S. M. N., Ibrahim, M. A. A., Gamal-Eldeen, A. M., & Aly, O. M. (2017). Synthesis, antiproliferative, anti-tubulin activity, and docking study of new 1,2,4-triazoles as potential combretastatin analogues. *European Journal of Medicinal Chemistry, 141*, 293–305.
- Mustafa, M., Anwar, S., Elgamal, F., Ahmed, E. R., & Aly, O. M. (2019). Potent combretastatin A-4 analogs containing 1,2,4-triazole: Synthesis, antiproliferative, anti-tubulin activity, and docking study. *European Journal of Medicinal Chemistry, 183*, 111697.
- Özkırımlı, S., Kazan, F., & Tunalı, Y. (2009). Synthesis, antibacterial and antifungal activities of 3-(1,2,4-triazol-3- yl)-4-thiazolidinones. *Journal of Enzyme Inhibition and Medicinal Chemistry, 24*(2), 447–452.
- Rollas, S., Gülerman, N., & Erdeniz, H. (2002). Synthesis and antimicrobial activity of some new hydrazones of 4-fluorobenzoic acid hydrazide and 3-acetyl-2,5-disubstituted-1,3,4-oxadiazolines. *Farmaco, 57*(2), 171–174.
- Salgın-Gökşen, U., Gökhan-Kelekçi, N., Göktaş, Ö., Köysal, Y., Kılıç, E., Işık, Ş., Aktay, G. & Özalp, M. (2007). 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. *Bioorganic and Medicinal Chemistry, 15*(17), 5738–5751.
- Savini, L., Chiasserini, L., Travagli, V., Pellerano, C., Novellino, E., Cosentino, S., & Pisano, M. B. (2004). New α-(N)-heterocyclichydrazones: Evaluation of anticancer, anti-HIV and antimicrobial activity. *European Journal of Medicinal Chemistry, 39*(2), 113–122.
- Sztanke, K., Tuzimski, T., Rzymowska, J., Pasternak, K., & Kandefer-Szerszeń, M. (2008). Synthesis, determination of the lipophilicity, anticancer and antimicrobial properties of some fused 1,2,4-triazole derivatives. *European Journal of Medicinal Chemistry, 43*(2), 404–419.
- Tozkoparan, B., Gökhan, N., Aktay, G., Yeşilada, E., & Ertan, M. (2000). 6-Benzylidenethiazolo[3,2-*b*]-1,2,4-triazole-5(6*H*)-ones substituted with ibuprofen: Synthesis, characterization and evaluation of anti-inflammatory activity. *European Journal of Medicinal Chemistry, 35*(7), 743–750.
- Turan-Zitouni, G., Kaplancıklı, Z. A., Erol, K., & Kılıç, F. S. (1999). Synthesis and analgesic activity of some triazoles and triazolothiadiazines. *Farmaco, 54*(4), 218–223.
- Turan-Zitouni, G., Kaplancıklı, Z. A., Yıldız, M. T., Chevallet, P., & Kaya, D. (2005). Synthesis and antimicrobial activity of 4-phenyl/cyclohexyl-5-(1-phenoxyethyl)-3-[N-(2-thiazolyl)acetamido]thio-4H-1,2,4-triazole derivatives. *European Journal of Medicinal Chemistry, 40*(6), 607–613.

- Ulusoy Güzeldemirci, N., & Küçükbasmacı, Ö. (2010). Synthesis and antimicrobial activity evaluation of new 1,2,4-triazoles and 1,3,4-thiadiazoles bearing imidazo[2,1-*b*]thiazole moiety. *European Journal of Medicinal Chemistry, 45*(1), 63–68.
- Ulusoy Güzeldemirci, N., Şatana, D., & Küçükbasmacı, Ö. (2013). Synthesis, characterization, and antimicrobial evaluation of some new hydrazinecarbothioamide, 1,2,4-triazole and 1,3,4-thiadiazole derivatives. *Journal of Enzyme Inhibition and Medicinal Chemistry, 28*(5), 968–973.
- Ulusoy, N., Ateş, Ö., Küçükbasmacı, Ö., Kiraz, M., & Yemenoğlu, Y. (2003). Synthesis, Characterization, and Evaluation of Antimicrobial Activity of Some 1,2,4-Triazole Derivatives Bearing an Antipyryl Moiety. *Monatshefte für Chemie, 134*(3), 465–474.
- Ulusoy, N., Ergenç, N., Ötük, G., & Kiraz, M. (2001*a*). Synthesis of some 4-(alkylidene/arylidene)amino-2,4-dihydro-5-(2-thienyl)-3*H*-1,2,4-triazole-3-thiones tested for antimicrobial activity. *Bollettino Chimico Farmaceutico, 140*(6), 417–421.
- Ulusoy, N., Gürsoy, A., & Ötük, G. (2001*b*). Synthesis and antimicrobial activity of some 1,2,4-triazole-3-mercaptoacetic acid derivatives. *Farmaco, 56*(12), 947–952.
- Wayne, P. A. (2005). Clinical and Laboratory Standards Institute. Performance standards for antimicrobial testing, 15th informational supplement. M100-S15. Clinical and Laboratory Standards Institute.
- Wayne, P. A. (2002*a*). National Committee for Clinical Laboratory Standards. Reference method for broth dilution antifungal susceptibility testing of yeasts; Approved standard-2nd Edition. M27-A2. Clinical and Laboratory Standards Institute.
- Wayne, P. A. (2002*b*). National Committee for Clinical Laboratory Standards. Reference method for broth dilution an antifungal susceptibility testing filamentous fungi; Approved standard M38-A2. Clinical and Laboratory Standards Institute.
- Weng, Q., Huang, J., Zeng, Y., Deng, Y., & Hu, M. (2012). Synthesis and herbicidal activity evaluation of novel β-carboline derivatives. *Molecules, 17*(4), 3969–3980.
- Završnik, D., Muratović, S., Makuc, D., Plavec, J., Cetina, M., Nagl, A., Clercq, E. D., Balzarini, J., & Mintas, M. (2011). Benzylidene-bis-(4-hydroxycoumarin) and benzopyrano-coumarin derivatives: Synthesis, 1H/13C-NMR conformational and X-ray crystal structure studies and in vitro antiviral activity evaluations. *Molecules, 16*(7), 6023–6040.