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Synthesis and Antimicrobial activities of New 1,2,4- Triazoles, Mannich Bases, Conazoles, and Fluoroquinolones

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Abstract: Triazoles are heterocyclic compounds which have been of interest in the development of novel compounds with antidepressant, anti-inflammatory, analgesic, antibacterial, antimycobacterial, antifungal, antiviral, anticancer, and other activities. In this article, a series of fluorine- and piperazine-containing some novel biologically active 1,2,4-triazole-3-one derivatives were synthesized by the Mannich reaction of triazole intermediates. The structures for novel synthesized compounds were elucidated using elemental analysis and FT IR, ^{13}C NMR, ^{1}H NMR, EI MS techniques. These compounds were investigated *in vitro* for their antimicrobial properties and several compounds have fungicidal activity against *Candida albicans* and *Saccharomyces cerevisiae*. And also some of the compounds exhibited excellent activity on *Mycobacterium smegmatis*, a nonpigmented fast-rising mycobacterium, at the concentration of <1 μg/mL is better than standard drug streptomycin.

Keywords: 1,2,4-triazole, piperazine, conazole, mannich base, biological activity.
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INTRODUCTION

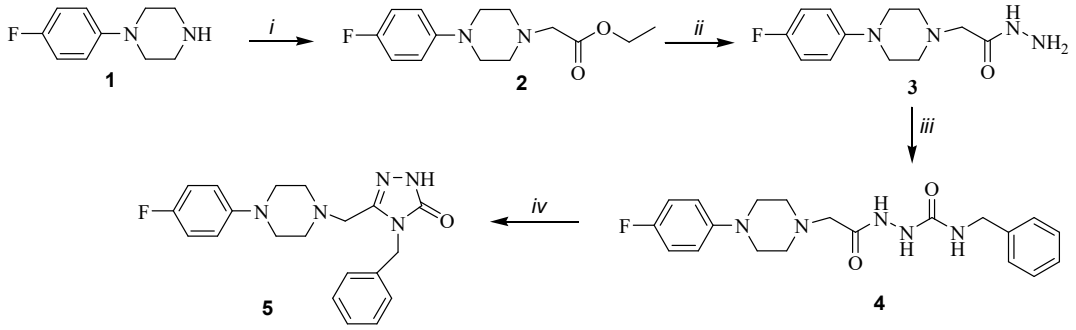
On account of growing number of multidrug resistant microbial pathogens, rising infectious infirmity and the cure of infectious illness still remain serious and challenging problem. For this reason, novel species of antimicrobial compounds are vitally important in fight with multidrug-resistant microbial diseases [1-5]. The most important and challenge of pharmaceutical chemistry is to design and synthesis of novel combinational chemotherapeutics constitute for coping with the antimicrobial resistance. There are two approaches for overcome multidrug-resistant bacteria. One of them is the synthesis of entirely novel compounds having unlike chemical structures than available ones, the other method is to unite two or more active groups into one compound. Thus, a single compound possessing more than one active group, each with varied form of activity, might be advantageous for the cure of bacterial diseases [6, 7]. Heterocycle- and fluorine-containing compounds play a crucial role both in the research field of organic chemistry and in a variety of practical chemistry fields, such as, material science, medicinal chemistry, and pesticide chemistry [8–12]. 1,2,4-triazole is a five-membered heterocycle, and has a broad spectrum of biological properties containing anticancer [13, 14], insecticidal [15], antifungal [16], anti-inflammatory [17], and plant growth regulating activities [18]. Moreover, one of the significant heterocycles is piperazine. Piperazine ring has different features, for example, simple building multiple ionic or hydrogen bonds appear low toxicity and functional influence. Thus it is frequently placed into various main compounds for increasing the antimicrobial activities along the applied medicine. It is mentioned that *N*-substituted piperazine structures possess a broad range of biological properties, like anticancer [20], antimicrobial [19], herbicidal activities [21], especially that compounds were frequently used as antibacterial material. Mannich bases of 1,2,4-triazole derivatives having a piperazine moiety have been determined to possess antifungicidal activity [22, 23], and some Mannich bases containing piperazine-4,5-disubstituted-1,2,4-triazole were reported to have tuberculostatic property [24]. However, there are relatively not many researches concerning the piperazine-possesing compounds about the design and enhance of pesticides. In view of these facts and as a piece of our continuing study on the synthesis of active hybrid compounds, we expected to get novel 1,2,4-triazole compounds having azole moieties and their Mannich bases as potential biodynamic agents.

RESULTS AND DISCUSSION

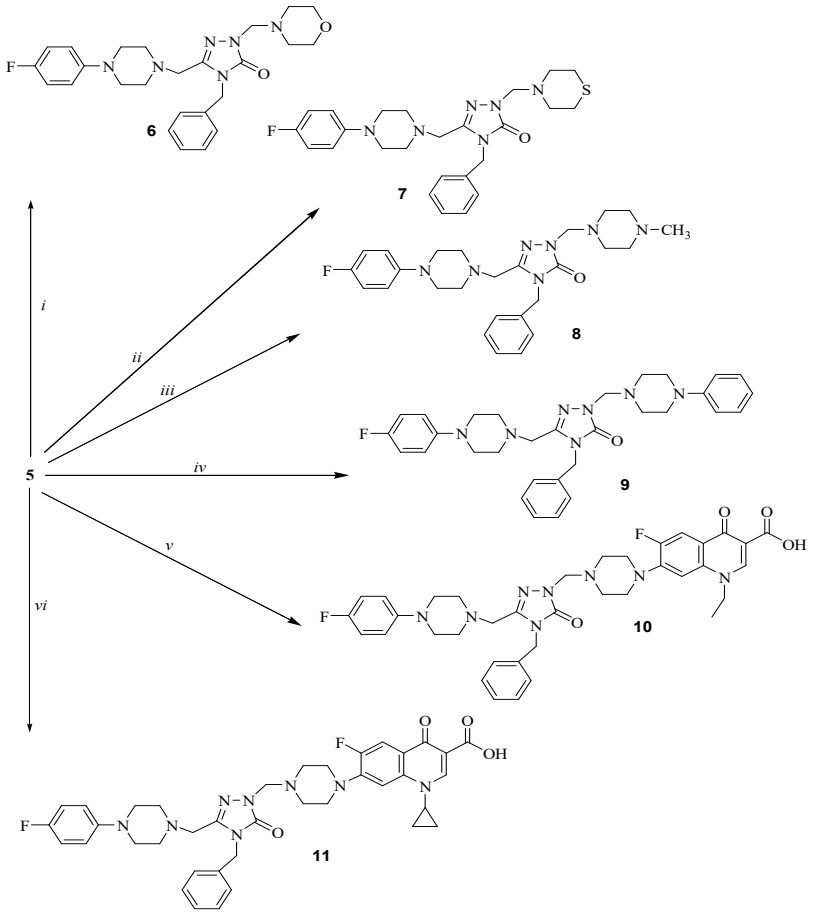
Chemistry

The basic purpose of this research is to synthesize and examine the antimicrobial properties of some novel hybrid compounds containing different heterocyclic moieties,

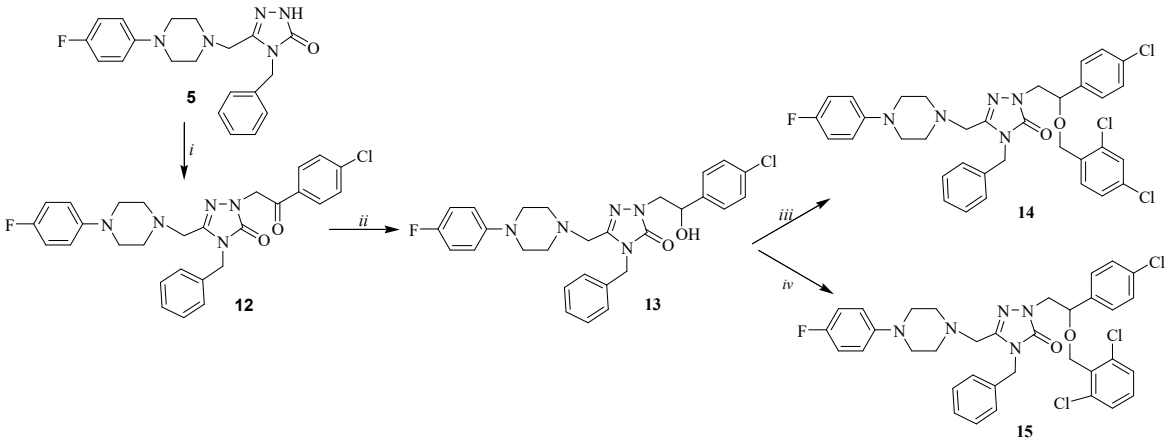
the pharmacological importance of which is well documented. The synthetic methods accepted to acquire the aimed molecules are showed in Schemes 1, 2, and 3. The structures for novel synthesized molecules were explained using physicochemical, elemental analysis, and spectral methods (FT IR, ^{1}H NMR, ^{13}C NMR and EI-MS).



Scheme 1. Reactions and conditions. *i*: triethylamine, $BrCH_2COOC_2H_5$, THF, 24 h rt; *ii*: EtOH, H_2NNH_2, reflux, 27 h; *iii*: CH_2Cl_2, $PhCH_2NCO$, 24 h rt; *iv*: 2 N NaOH in EtOH/H_2O, reflux, 5 h.



Scheme 2. Reactions and conditions. *i*: morpholine, HCHO in DMSO, 24 h rt; *ii*: thiomorpholine, HCHO in DMSO, 24 h rt; *iii*: methylpiperazine, HCHO in DMSO, 24 h rt; *iv*: 1-phenylpiperazine, HCHO in DMSO, 24 h rt; *v*: norfloxacin, HCHO in DMSO, 24 h rt; *vi*:ciprofloxacin, HCHO in DMSO, 24 h rt.



Scheme 3. Reactions and conditions. *i*: EtOH, Na, $ClC_6H_4COCH_2Br$, reflux, 17 h; *ii*: EtOH, $NaBH_4$, reflux, 15 h; *iii*: THF, NaH, 2-4-dichlorobenzyl chloride, reflux, 15 h; *iv*: THF, NaH, 2-6-dichlorobenzyl chloride reflux, 15 h.

The esterification of 1-(4-fluorophenyl)piperazine (**1**) by tetrahydrofuran and ethyl bromoacetate in the presence of triethylamine generated the corresponding ester (**2**). Then, the ester **2** was changed to the corresponding hydrazide (**3**) by the reaction with hydrazine hydrate. The ^{1}H NMR and FT-IR spectra for compound **3** showed signals pointing the presence of hydrazide group, while the signals because of the ester function were not seen in the NMR spectrum.

Compound **3** was changed to the corresponding carboxamide by the reaction with benzyl isocyanate. Compounds (**4**) was evaluated by the existence of absorption bands at 1655 cm^{-1} due to -C=O stretching in the FT-IR spectra. In the ^{13}C NMR spectra of this compound (**4**), -C=O function resonated at 158.59 ppm. The other proof for the appearance of carboxamides was the presence of three NH signals at 7.86-9.45 ppm in the ^{1}H NMR spectra as D_2O-exchangeable singlets. Moreover, the signals refer to alkyl or aryl function of isothiocyanate ring were observed at the appropriate chemical shift range.

The synthesis of the triazole (**5**) was carried out by the intramolecular cyclization of compound **4** by treatment with base; we aimed to bind the 1,2,4-triazole ring to fluorophenylpiperazine nucleus, it is stated that more efficient antimicrobial molecules may be planned by combined two or more biologically active heterocyclic groups together in a single molecular structure [25-27]. In the ^{1}H NMR spectra of compound **5** the signal obtained at 9.25 ppm was described to –NH proton. The signal owing to this function was observed at 3167 cm^{-1} in the FT-IR spectra. In addition, compound **5** showed stable

$[M+1]^+$ and $[M+Na]^+$, signals in the mass spectra and also the elemental analysis data are coherent with the appointed molecules. Because of their basic purpose depicting the compound solvable in aqueous solvents when it is converted into aminium salt, Mannich bases are physiologically reactive and they have been noticed as possible biological materials [28]. Moreover, it is stated that the function connected to parent amine by Mannich reaction rises the lipophilicity of compound [29]. In view of these facts, we treated compounds **5** with several amines, namely morpholine, thiomorpholine, methylpiperazine, 1-phenylpiperazine, norfloxacine, and ciprofloxacine due to their therapeutic effect [30-32]. The successful synthesis of the alkylaminomethylation was provided by the disappearance of peak for the proton at the *N*-1 nitrogen (**5**) of the 1,2,4-triazole derivative. In addition, in the ^{1}H and ^{13}C NMR spectra of compounds **6-11** displayed additional peaks resulting from alkylaminomethyl group at the connected chemical shift ranges.

Treatment of compound **5** with 4-chlorophenacyl bromide gave compound **12** which was converted into compound **13** by reduction of the ketone functionality using sodium borohydride. The treatment of compound **13** with 2-4-dichlorobenzyl chloride or 2-6-dichlorobenzyl chloride generated the corresponding conazole derivatives **14** and **15** respectively. The structures of molecules **12-15** were confirmed using spectroscopic techniques such as FT-IR, EI-MS, ^{1}H NMR, ^{13}C NMR, and elemental analysis.

BIOLOGICAL ACTIVITY

Antimicrobial activity

All the novel synthesized molecules were investigated for their antibacterial activities but only the values of the compounds which have activities were shown in Table 1. Among the novel synthesized molecules, compounds **4, 6, 7, 10, 11, 14,** and **15** displayed moderate-slight activities against to the tested microorganisms with the mic values between <1-125 µg/mL.

Moderate activities were observed for compound **4**, a carboxamide derivative, on Gram-positive bacteria, *Mycobacterium smegmatis* (Ms), and yeast like fungi, *Candida albicans* (Ca), and *Saccharomyces cerevisiae* (Sc).

The conversion of compounds **5** to their Mannich bases resulted in an increase in the antimicrobial activity. Mannich base derivatives **6, 7, 10** and **11** were obtained to have good activity against on some of the test microorganisms. Among these, compound **6** and **7** namely a 1,2,4-triazole compound containing a thiomorpholine or a morpholine moiety have moderate antibacterial activity only against Ms, Ca and Sc with the MIC

values between of 15.6-125 mg/mL. However, Mannich compounds **10** and **11,** containing a norfloxacin or ciprofloxacin nucleus attached to 1,2,4-tirazole nucleus showed perfect antimicrobial activities on Gram-negative and Gram-positive bacteria, except Ca and Sc. Especially, 7-{4-[(4-benzyl-3-{[4-(4-fluorophenyl)piperazin-1-yl]methyl}-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)methyl]piperazin-1-yl}-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid compound (**11**) exhibited good activity on Ms, a nonpigmented fast-rising mycobacterium, with the mic value <1 µg/mL is better than standard drug streptomycin or *Escherichia coli* (Ec), a Gram-negative, facultative anaerobic bacterium, with the mic value <1 µg/mL is better than standard drug ampicillin. Conazole derivative, **14** and **15**, were found to have a slight activity only against Ms with the mic values 125 µg/mL. Nevertheless, none of the compounds **2-15** exhibited activity on *Enterococcus faecalis* (Ef).

Table 1. Antimicrobial activity of the compounds (µg/mL)

Comp.No	Minimal Inhibition Concentration Values (µg/mL)								
	Ec	Yp	Pa	Sa	Ef	Bc	Ms	Ca	Sc
4	-	-	-	-	-	-	62.5	125	125
6	-	-	-	-	-	-	62.5	15.6	31.2
7	-	-	-	-	-	-	125	15.6	31.2
10	<1	<1	3.9	<1	-	<1	3.9	-	-
11	<1	<1	<1	<1	-	<1	<1	-	-
14	-	-	-	-	-	-	125	-	-
15	-	-	-	-	-	-	125	-	-
Amp.	10	32	>128	35	10	15			
Strep.							4		
Flu.								<8	<8

Ec: *E. coli* ATCC 35218, Yp: *Y. pseudotuberculosis* ATCC 911, Pa: *P. aeruginosa* ATCC 10145, Ef: *E. faecalis* ATCC 29212, Bc: *B. cereus* 709 Roma, Ms: *M. smegmatis* ATCC607, Ca: *C. albicans* ATCC 60193, *S. cerevisiae* RSKK 251, Amp.: Ampicillin, Strep.: Streptomycin, Flu.: Fluconazole, (—): no activity of test concentrations

CONCLUSIONS

This research reports the successful synthesis of some new hybrid compounds starting from 1-(4-fluorophenyl)piperazine. The antimicrobial activity investigation studies were also performed in this study. The antimicrobial investigation provides that the molecules containing norfloxacine, ciprofloxacine acid nucleus displayed excellent antibacterial activity. In addition, some of them showed inhibition properties on *Escherichia coli* (Ec) and *Mycobacterium smegmatis* (Ms) better to ampicillin or streptomycin.

EXPERIMENTAL

General

All the chemicals were bought from Fluka Chemie AG Buchs (Switzerland) and used without further purification. Melting points of the synthesized compounds were determined in open capillaries on a Büchi B-540 melting point apparatus and are uncorrected. Reactions were monitored by thin-layer chromatography (TLC) on silica gel 60 F254 aluminum sheets. The mobile phase was ethyl acetate:diethyl ether (1:1), and detection was made using UV light. FT-IR spectra were recorded using a *Perkin Elmer* 1600 series FTIR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were registered in DMSO-d_6 on a *BRUKER AVENE II* 400 MHz NMR Spectrometer (400.13 MHz for ^{1}H and 100.62 MHz for ^{13}C). The chemical shifts are given in ppm relative to Me_4Si as an internal reference, *J* values are given in Hz. The elemental analysis was performed on *a Costech Elemental Combustion System* CHNS-O elemental analyzer. All the compounds gave C, H and N analysis within ±0.4% of the theoretical values. The Mass spectra were obtained on a *Quattro GC-MS* (70 eV) Instrument. Nalidixic acid (**1**) was provided commercially from Sigma-Aldrich.

Ethyl [4-(4- fluorophenyl)piperazine-1-yl]acetate (2)

1-(4-fluorophenyl)piperazine **1** (1.80 g, 10 mmol) in tetrahydrofuran, triethylamine (2.10 mL, 15 mmol) and ethyl bromoacetate (1.13 mL, 10 mmol) were added and the mixture was stirred at room temperature for 24 hours. After evaporating the solvent under reduced pressure, a solid appeared. The crude product was recrystallized from chloroform–petroleum ether (1:3) to yield the target compounds. Yield 90%, mp: 54-55°C. FT-IR (υ_{max}, cm^{-1}): 3015 (aromatic CH), 2986 (aliphatic CH), 1736 (C=O); ^{1}H NMR (DMSO-d_6, δ ppm): 1.19 (t, 3H, CH_3, *J*= 6.8 Hz), 2.65 (t, 4H, $2CH_2$, *J*= 4.8 Hz), 3.06 (d, 4H, $2CH_2$, *J*= 5.2 Hz), 3.27 (s, 2H, CH_2), 4.09 (q, 2H, CH_2, *J*= 7.2 Hz), 6.91-6.95 (m, 2H, arH), 7.00-7.05 (m, 2H, arH); ^{13}C NMR (DMSO-d_6, δ ppm): 14.58, 49.38, 52.38, 58.78, 60.33, 115.54 and 115.79, 117.59 and 117.67, 148.34 and 148.35, 155.30 and 157.64, 170.29; EI-MS *m/z* (%): 267.23 ([M+1]$^{+}$, 100), 193.14 (39), 188.18 (39), 160.19 (34).

Anal. Calcd. for $C_{14}H_{19}FN_2O_2$: C, 63.14; H, 7.19; N, 10.52%. Found: C, 63.30; H, 7.48; N, 10.21%

2-(4-(4-fluorophenyl)piperazine-1-yl)acetohydrazide (3)

A solution of compound **2** (2.66 g, 10 mmol) in ethanol was refluxed with hydrazine hydrate (1.21 mL, 25 mmol) for 27 h (controlled with TLC). After cooling the reaction mixture to room temperature, the mixture was kept overnight in cold. The resulting solid was collected by filtration and recrystallized from ethyl acetate–diethyl ether (1:3) to afford the desired product **3**. Yield 91%, mp: 155-156 °C.

FT-IR (υ_{max}, cm^{-1}): 3295 and 3255 (NH_2), 3166 (NH), 3051 (aromatic CH), 2962 (aliphatic CH), 1666 (C=O); ^{1}H NMR (DMSO-d_6, δ ppm): 2.56 (t, 4H, $2CH_2$, *J*= 4.8 Hz), 2.96 (s, 2H, CH_2), 3.08 (t, 4H, $2CH_2$, *J*= 4.4 Hz), 4.28 (brs, 2H, NH_2), 6.91-6.95 (m, 2H, ArH), 7.00-7.05 (m, 2H, ArH), 8.94 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, δ ppm): 49.31, 53.20, 60.26, 115.57 and 115.79, 117.49 and 117.57, 148.36, 155.44 and 157.58, 168.57; EI-MS *m/z* (%):293.30 (43), 193.18 (100), 178.16 (20), 150.13 (62), 138.11 (37); Anal. Calcd. for $C_{12}H_{17}FN_4O$: C, 57.13; H, 6.79; N, 22.21%. Found: C, 57.32; H, 6.59; N, 22.57%.

N-benzyl-2-{[4-(4-fluorophenyl)piperazin-1-yl]acetyl}hydrazinecarboxamide (4)

To a solution of corresponding compound **3** (2.52 g, 10 mmol) in dichloromethane, benzyl isocyanate (2.57 mL, 20 mmol) was added and the mixture was stirred at room temperature for 24 hours. After evaporating the solvent under reduced pressure, a solid appeared. The crude product was recrystallized from acetone–diethyl ether (1:3) to yield the target compounds. Yield 91%, mp: 195-196 °C.

FT-IR (υ_{max}, cm^{-1}): 3249 (2NH), 3219 (NH), 3090 (aromatic CH), 2958 (aliphatic CH), 1655 (2C=O); ^{1}H NMR (DMSO-d_6, δ ppm): 2.63 (s, 4H, $2CH_2$), 3.07 (s, 4H, $2CH_2$), 3.34 (s, 2H, CH_2), 4.24 (d, 2H, CH_2, *J*= 8.0 Hz), 6.87 (s, 1H, NH), 6.92-6.95 (m, 2H, ArH), 7.04 (t, 2H, ArH, *J*= 8.0 Hz), 7.22-7.32 (m, 5H, ArH), 7.86 (s, 1H, NH), 8.97 (s, 1H, NH), 9.45 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, δ ppm): 43.11, 49.22, 53.13, 60.08, 115.59 and 115.80, 117.50 and 117.57, 127.00, 127.39, 128.58, 140.95, 148.33, 155.25 and 157.59, 158.59, 169.46; EI-MS *m/z* (%): 430.33 (10), 408.13 ($[M+Na]^+$, 47), 386.22 ($[M+1]^+$, 62), 273.16 (15); Anal. Calcd. for $C_{20}H_{24}FN_5O_2$: C, 62.32; H, 6.28; N, 18.17%. Found: C, 62.11; H, 6.57; N, 18.56%.

5-{[4-(4-fluorophenyl)piperazin-1-yl]methyl}-4-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (5)

A solution of carbothioamide **4** (3.85 g, 10 mmol) in ethanol/water (1:1) was refluxed in the presence of 2 N NaOH for 5 h (the progress of the reaction was monitored by TLC). Then, the resulting solution was cooled to room temperature and acidified to pH 7 with 37% HCl. The precipitate formed was filtered off, washed with water, and recrystallized from ethyl acetate to give the target compound **5**. Yield 70%, mp: 185-186 °C.

FT-IR (υ_{max}, cm^{-1}): 3167 (NH), 3035 (aromatic CH), 2919 (aliphatic CH), 1696 (C=O), 1511 (C=N); ^{1}H NMR (DMSO-d_6, δ ppm): 2.43 (s, 2H, CH_2), 2.89 (s, 2H, CH_2), 3.30 (s, 2H, CH_2), 3.34 (s, 4H, $2CH_2$), 4.88 (s, 2H, CH_2), 6.87-6.89 (m, 2H, ArH), 7.02 (t, 2H, ArH, *J*= 7.2 Hz), 7.04-7.25 (m, 3H, ArH), 7.32 (t, 2H, ArH, *J*= 4.4 Hz), 9.25 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, δ ppm): 44.20, 49.11, 52.65, 53.43, 115.59 and 115.80, 117.57 and 117.80, 127.53, 127.71, 128.87, 137.67, 144.75, 148.27 and 155.29, 155.97, 157.63; EI-MS *m/z* (%): 459.33 (25), 407.39 ($[M+1+K]^+$, 47), 390.25 ($[M+Na]^+$, 62), 367.10 ($[M]^+$, 70), 261.11 (10); Anal. Calcd. for $C_{20}H_{22}FN_5O$: C, 65.38; H, 6.04; N, 19.06%. Found: C, 65.11; H, 6.32; N, 19.33%.

General Synthetic Method of Compounds 6-11

To a solution of compound **5** (3.67 g, 10 mmol) in dimethyl sulfoxide (10 mL), morpholine (for **6**) (0.87 mL, 10 mmol) or thiomorpholine (for **7**) (0.94 mL, 10 mmol) or methyl piperazine (for **8**) (1.11 mL, 10 mmol) or 1-phenylpiperazine (for **9**) (1.52 mL, 10 mmol), or norfloxacin (for **10**) (3.19 g, 10 mmol) or ciprofloxacin (for **11**) (3.31 g, 10 mmol) was added in the presence of formaldehyde (37%, 3.72 mL, 50 mmol) and the mixture was stirred at room temperature for 24 hours. The resulting solution was poured into ice-cold water and a solid appeared. The crude product was recrystallized from ethanol–water (1:3) (for **6** and **7**), from ethyl acetate (for **8** and **9**), from dimethyl sulfoxide–water (1:3) (for **10** and **11**) to yield the target compounds.

4-Benzyl-5-{[4-(4-fluorophenyl)piperazin-1-yl]methyl}-2-(morpholin-4-ylmethyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (6)

Yield 87%, mp: 102-103 °C; FT-IR (υ_{max}, cm^{-1}): 3053 (aromatic CH), 2938 (aliphatic CH), 1701 (C=O), 1508 (C=N); ^{1}H NMR (DMSO-d_6, δ ppm): 2.08 (s, 2H, CH_2), 2.43 (s, 4H, $2CH_2$), 2.89 (s, 4H, $2CH_2$), 3.34 (s, 10H, $5CH_2$), 4.88 (s, 2H, CH_2), 6.86-6.89 (m, 2H, ArH), 7.02 (t, 2H, ArH, *J*= 8.8 Hz), 7.25 (d, 3H, ArH, *J*= 6.4 Hz), 7.31 (d, 2H, ArH, *J*= 6.8 Hz); ^{13}C NMR (DMSO-d_6, δ ppm): 40.60, 44.20, 49.11, 52.65, 53.43, 115.59 and 115.80, 117.58 and 117.65, 127.52, 127.71, 128.87, 137.64, 140.23, 144.77 and 148.25, 148.05, 155.98; EI-MS *m/z* (%): 490.39 ($[M+1+Na]^+$, 70), 467.61 ($[M+1]^+$,

100), 390.20 (24), 292.21(16); Anal. Calcd. for $C_{25}H_{31}FN_6O_2$: C, 64.36; H, 6.70; N, 18.01%. Found: C, 64.13; H, 6.92; N, 18.30%.

4-Benzyl-5-{[4-(4-fluorophenyl)piperazin-1-yl]methyl}-2-(thiomorpholin-4-ylmethyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (7)

Yield 91%, mp: 118-120 °C; FT-IR (υ_{max}, cm^{-1}): 3052 (aromatic CH), 2820 (aliphatic CH), 1695 (C=O), 1509 (C=N); ^{1}H NMR (DMSO-d_6, δ ppm): 2.45 (s, 6H, $3CH_2$), 2.89 (s, 6H, $3CH_2$), 3.35 (s, 6H, $3CH_2$), 4.92 (s, 2H, CH_2), 5.03 (d, 2H, CH_2, *J*= 7.2 Hz), 6.86-6.89 (m, 2H, ArH), 7.02 (t, 2H, ArH, J= 12.0 Hz), 7.25- 7.34 (m, 5H, ArH); ^{13}C NMR (DMSO-d_6, δ ppm): 27.59, 43.87, 44.78, 49.09, 49.60, 52.68, 53.23, 67.50, 115.59 and 115.80, 117.59 and 117.67, 127.57, 127.80, 128.56, 137.33, 143.90 and 148.23, 155.30, 154.04, 157.64; EI-MS *m/z* (%): 482.71 ($[M]^+$, 90); Anal. Calcd. for $C_{25}H_{31}FN_6OS$: C, 62.22; H, 6.47; N, 17.41%. Found: C, 62.02; H, 6.62; N, 17.29%.

4-Benzyl-5-{[4-(4-fluorophenyl)piperazin-1-yl]methyl}-2-[(4-methylpiperazin-1-yl)methyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (8)

Yield 85%, mp: 127-128 °C; FT-IR (υ_{max}, cm^{-1}): 3061 (aromatic CH), 2939 (aliphatic CH), 1701 (C=O), 1508 (C=N); ^{1}H NMR (DMSO-d_6, δ ppm): 2.44 (s, 3H, CH_3), 2.49 (s, 4H, $2CH_2$), 2.89 (s, 4H, $2CH_2$), 3.34 (s, 10H, $5CH_2$), 4.92 (s, 2H, CH_2), 5.02 (d, 2H, CH_2, *J*= 7.6 Hz), 6.86-7.00 (m, 2H, ArH), 7.00-7.05 (m, 2H, ArH), 7.23-7.27 (m, 3H, ArH), 7.32 (d, 2H, ArH, *J*= 7.2 Hz); ^{13}C NMR (DMSO-d_6, δ ppm): 43.87, 44.78, 46.20, 49.09, 49.89, 52.68, 53.23, 54.99, 66.03, 67.49, 115.59 and 115.80, 117.59 and 117.66, 127.58, 128.80, 128.92, 137.34 and 137.49, 143.89, 148.25, 154.03, 157.75; EI-MS *m/z* (%):589.26 (41), 519.60 ($[M+1+K]^+$, 25), 502.81 ($[M+Na]^+$, 16), 479.71 ($[M]^+$, 90), 376.57 (38); Anal. Calcd. for $C_{26}H_{34}FN_7O$: C, 65.11; H, 7.15; N, 20.44%. Found: C, 65.33; H, 7.01; N, 20.18%.

4-Benzyl-5-{[4-(4-fluorophenyl)piperazin-1-yl]methyl}-2-[(4-phenylpiperazin-1-yl)methyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (9)

Yield 88%, mp: 140-141 °C; FT-IR (υ_{max}, cm^{-1}): 3063 (aromatic CH), 2917 (aliphatic CH), 1698 (C=O), 1512 (C=N); ^{1}H NMR (DMSO-d_6, δ ppm): 2.43 (s, 2H, CH_2), 2.72 (s, 4H, $2CH_2$), 2.86 (s, 4H, $2CH_2$), 3.13 (s, 4H, $2CH_2$), 3.35 (s, 4H, $2CH_2$), 4.65 (s, 2H, CH_2), 4.93 (s, 2H, CH_2), 6.76 (t, 1H, ArH, *J*= 8.0 Hz), 6.84-6.92 (m, 4H, ArH), 7.01 (t, 2H, ArH, *J*= 12.0 Hz), 7.18-7.25 (m, 5H, ArH), 7.30-7.33 (m, 2H, ArH); ^{13}C NMR (DMSO-d_6, δ ppm): 43.88, 44.82, 48.60, 49.05, 49.60, 49.97, 52.64, 53.20, 66.04, 115.57 and 115.79 , 117.54 and 117.62, 119.28, 127.39, 127.76, 128.92, 129.36, 137.46, 143.54, 148.22, 151.36 and 155.16, 155.28, 157.42; EI-MS *m/z* (%): 579.60 ($[M-1+K]^+$, 19), 564.54 ($[M+Na]^+$, 40), 560.39 ($[M+1+H_2O]^+$, 42), 542.77 ($[M+1]^+$, 70), 531.37 (100);

Anal. Calcd. for $C_{31}H_{36}FN_7O$: C, 68.74; H, 6.70; N, 18.10%. Found: C, 68.38; H, 6.60; N, 18.18%.

7-{4-[(4-Benzyl-3-{[4-(4-fluorophenyl)piperazin-1-yl]methyl}-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)methyl]piperazin-1-yl}-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (10)

Yield 84%, mp: 205-206 °C; FT-IR (υ_{max}, cm^{-1}): 3391 (OH), 3090 (aromatic CH), 2946 (aliphatic CH), 1702 (2C=O), 1623 (C=O), 1508 (C=N); ^{1}H NMR (DMSO-d_6, δ ppm): 1.39 (t, 3H, CH_3, *J*= 7.2 Hz), 2.49 (s, 4H, $2CH_2$), 2.80 (s, 2H, CH_2), 2.85 (s, 4H, $2CH_2$), 3.34 (s, 8H, $4CH_2$), 4.59 (d, 2H, CH_2, *J*= 6.8 Hz), 4.67 (s, 2H, CH_2), 4.93 (s, 2H, CH_2), 6.82-6.86 (m, 2H, ArH), 7.01 (t, 2H, ArH, *J*= 8.8 Hz), 7.18-7.30 (m, 6H, ArH), 7.92 (d, 1H, ArH, *J*= 13.2 Hz), 8.95 (s, 1H, quinolone CH), 15.36 (s, 1H, OH); ^{13}C NMR (DMSO-d_6, δ ppm): 14.79, 44.84, 49.06, 49.51, 49.77, 49.86, 52.65, 53.19, 66.01, 107.53,106.41, 111.56 and 111.79, 115.36 and 115.58, 117.54 and 117.62, 119.62 and 119.69, 127.46, 127.79, 128.90, 137.43 and 137.64, 143.65, 145.74 and 145.85, 148.19, 152.04 and 154.52, 155.29 and 157.63, 148.99, 155.19, 166.57, 176.38; EI-MS *m/z* (%):738.73 (50), 700.73 (47), 699.98 ($[M+1]^+$, 94), 698.81 ($[M]^+$,100), 675.23 ($[M-Na]^+$, 38), 589.59 (41); Anal. Calcd. for $C_{37}H_{40}F_2N_8O_4$: C, 63.60; H, 5.77; N, 16.04%. Found: C, 63.38; H, 5.81; N, 16.17%.

7-{4-[(4-Benzyl-3-{[4-(4-fluorophenyl)piperazin-1-yl]methyl}-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)methyl]piperazin-1-yl}-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (11)

Yield 88%, mp: 258-260 °C; FT-IR (υ_{max}, cm^{-1}): 3400 (OH), 3090 (aromatic CH), 2937 (aliphatic CH), 1702 (2C=O), 1627 (C=O), 1509 (C=N); ^{1}H NMR (DMSO-d_6, δ ppm): 1.13 (s, 2H, CH_2), 1.32 (s, 2H, CH_2), 2.44 (s, 2H, CH_2), 2.85 (s, 10H, $5CH_2$), 3.35 (s, 6H, $3CH_2$), 3.79 (s, 1H, CH), 4.68 (s, 2H, CH_2), 4.94 (s, 2H, CH_2), 6.84 (d, 2H, ArH, *J*= 4.0 Hz), 6.99 (t, 2H, ArH, *J*= 8.4 Hz), 7.24-7.30 (m, 5H, ArH), 7.52 (d, 1H, ArH, J= 6.0 Hz), 7.83 (d, 1H, ArH, J= 13.2 Hz), 8.61 (s, 1H, quinolone CH), 15.17 (s, 1H, OH); ^{13}C NMR (DMSO-d_6, δ ppm): 8.02, 36.26, 40.59, 44.85, 49.07, 49.75, 52.66, 53.21, 66.03, 107.17, 106.81, 111.24 and 111.47, 115.56 and 115.78, 117.53 and 117.60, 118.90 and 118.98, 127.47, 127.78, 128.98, 137.41, 139.54, 143.66, 145.43 and 145.53, 152.14 and 154.62, 155.20 and 157.62, 148.30, 155.28, 166.35, 176.73; EI-MS *m/z* (%): 765.22 (88), 711.36 ($[M+1]^+$, 67), 522.29 (47), 332.27 (76), 205.15 (82), 195.92 (100); Anal. Calcd. for $C_{38}H_{40}F_2N_8O_4$: C, 64.21; H, 5.67; N, 15.77%. Found: C, 64.38; H, 5.82; N, 15.51%.

4-Benzyl-2-[2-(4-chlorophenyl)-2-oxoethyl]-5-{[4-(4-fluorophenyl)piperazin-1-yl]methyl}-2,4-dihydro-3*H*-1,2,4-triazol-3-one (12)

Compound **3** (2.52 g, 10 mmol) was added to a solution of Na (0.23 g, 10 mmol) in ethanol. The reaction mixture was refluxed for 2 h. Then, the resulting solution was cooled to room temperature and 4-chlorophenacyl bromide (2.33 g, 10 mmol) was added to the reaction mixture. After that the mixture was refluxed for 15 h, cooled to room temperature, and after evaporating the solvent under reduced pressure, a solid appeared. The formed solid was filtered, washed with water and recrystallized from acetone–water (1:3) to afford the pure compound **12**. Yield 65%, mp: 152-153°C. FT-IR (υ_{max}, cm^{-1}): 3037 (aromatic CH), 2920 (aliphatic CH), 1699 (2C=O), 1509 (C=N); ^{1}H NMR (DMSO-d_6, δ ppm): 2.43 (s, 4H, $2CH_2$), 2.88 (s, 4H, $2CH_2$), 3.35 (s, 4H, $2CH_2$), 4.88 (s, 2H, CH_2), 6.88 (s, 2H, ArH), 7.00 (s, 2H, ArH), 7.26 (s, 5H, ArH), 7.65 (d, 2H, ArH, *J*= 8.0 Hz), 8.03 (d, 2H, ArH, *J*=4.0 Hz); ^{13}C NMR (DMSO-d_6, δ ppm): 44.19, 44.88, 49.03, 52.27, 52.54,115.60 and 115.82, 117.61 and 117.68, 127.33, 127.52, 127.77, 128.90, 130.51, 133.50, 137.33, 139.37, 148.18, 155.06 and 157.67, 155.33, 155.92, 193.16; EI-MS *m/z* (%): 543.03 ($[M+Na]^+$, 69), 521.08 ($[M+1]^+$, 100), 520.19 ($[M]^+$, 70), 503.27 (44), 490.85 (50); Anal. Calcd. for $C_{28}H_{27}ClFN_5O_2$: C, 64.67; H, 5.23; N, 13.47%. Found: C, 64.28; H, 5.32; N, 13.60%.

4-benzyl-2-[2-(4-chlorophenyl)-2-hydroxyethyl]-5-{[4-(4 fluorophenyl)piperazin-1-yl]methyl}-2,4-dihydro-3*H*-1,2,4-triazol-3-one (13)

To a solution of corresponding compound **10** (5.20 g, 10 mmol) in ethanol, sodium borohydride (1.11 g, 30 mmol) was added and the mixture was refluxed for 15 h. After evaporating the solvent under reduced pressure, a solid appeared. The crude product was recrystallized from acetone–water (1:3) to yield the target compounds. Yield 78%, mp: 100-101 °C. FT-IR (υ_{max}, cm^{-1}): 3376 (OH), 2956 (aliphatic CH), 1692 (C=O); ^{1}H NMR (DMSO-d_6, δ ppm): 2.43 (s, 4H, $2CH_2$), 2.88 (s, 4H, $2CH_2$), 3.35 (s, 4H, $2CH_2$), 4.88 (s, 2H, CH_2), 6.88 (s, 2H, ArH), 7.00 (s, 2H, ArH), 7.26 (s, 5H, ArH), 7.65 (d, 2H, ArH, *J*= 8.0 Hz), 8.03 (d, 2H, ArH, *J*=4.0 Hz), 10.03 (s, 1H, OH); ^{13}C NMR (DMSO-d_6, δ ppm): 44.20, 44.67, 49.03, 49.12, 52.52, 52.65, 79.21, 115.59 and 115.81, 117.55 and 117.61, 127.28, 127.53, 127.63, 128.48, 128.72, 128.75, 128.87, 132.30, 137.39 and 137.67, 141.97, 143.34, 148.25 and 154.28, 155.29, 157.73; EI-MS *m/z* (%): 523.03 ($[M+1]^+$, 100), 483.27 (34), 460.85 (16); Anal. Calcd. for $C_{28}H_{29}ClFN_5O_2$: C, 64.42; H, 5.60; N, 13.42%. Found: C, 64.18; H, 5.48; N, 13.75%.

General Synthetic Method of Compounds 14 and 15

To a solution of corresponding compound **13** (5.22 g, 10 mmol) in tetrahydrofuran, sodium hydride (0.24 g, 10 mmol) was added and the reaction mixture was refluxed for

7 h. Then, the resulting solution was cooled to room temperature and 2,4-dichlorobenzyl chloride (4.17 mL, 30 mmol) (for **14**) or 2,6-dichlorobenzyl chloride (4.17 mL, 30 mmol) (for **15**) was added in the presence of reaction mixture. After that the mixture was refluxed for 8 h, the mixture was cooled to room temperature. After evaporating the solvent under reduced pressure, an oily product appeared. Oily product was extracted with ethyl acetate and potassium carbonate. Then organic phase was dried and the solvent was evaporated under reduced pressure. The formed oily product recrystallized from acetone to afford the desired compounds **14** and **15**.

4-Benzyl-2-{2-(4-chlorophenyl)-2-[(2,4-dichlorobenzyl)oxy]ethyl}-5-{[4-(4-fluorophenyl) piperazin-1-yl]methyl}-2,4-dihydro-3*H*-1,2,4-triazol-3-one (14)

Yield 51%, mp: 70-71 °C; FT-IR (υ_{max}, cm^{-1}): 3085 (aromatic CH), 2927 (aliphatic CH), 1698 (C=O), 1509 (C=N), 1138 (C-O); ^{1}H NMR (DMSO-d_6, δ ppm): 2.08 (s, 4H, $2CH_2$), 2.36 (s, 2H, CH_2), 2.88 (s, 2H, CH_2), 3.36 (s, 5H, $2CH_2$+CH), 4.81 (s, 2H, CH_2), 5.00 (s, 2H, CH_2), 6.85-7.00 (m, 2H, ArH), 7.00-7.23 (m, 2H, ArH), 7.25-7.43 (m, 8H, ArH), 7.44-7.64 (m, 3H, ArH), 7.66-7.69 (m, 1H, ArH); ^{13}C NMR (DMSO-d_6, δ ppm): 43.35, 43.89, 44.68, 45.01, 45.96, 49.07, 49.61, 51.87, 70.21, 115.58 and 115.80, 117.58 and 117.65, 127.28, 127.37, 127.82, 128.06, 128.47, 128.75, 129.43, 130.86, 132.30, 133.34 and 133.67, 134.70, 137.29, 137.84, 141.97, 154.30 and 155.51, 148.21, 157.75; EI-MS *m/z* (%): 704.26 ($[M+Na]^+$, 10), 703.19 ($[M-1+Na]^+$, 12), 683.48 ($[M+2]^+$, 16), 681.47 ($[M]^+$,20), 674.44 (40), 673.37 (100); Anal. Calcd. for $C_{35}H_{33}Cl_3FN_5O_2$: C, 61.73; H, 4.88; N, 10.28%. Found: C, 61.58; H, 4.82; N, 10.41%.

4-Benzyl-2-{2-(4-chlorophenyl)-2-[(2,6-dichlorobenzyl)oxy]ethyl}-5-{[4-(4-fluorophenyl) piperazin-1-yl]methyl}-2,4-dihydro-3*H*-1,2,4-triazol-3-one (15)

Yield 45%, mp: 65-66 °C; FT-IR (υ_{max}, cm^{-1}): 3095 (aromatic CH), 2937 (aliphatic CH), 1701 (C=O), 1510 (C=N), 1125 (C-O); ^{1}H NMR (DMSO-d_6, δ ppm): 2.08 (s, 6H, $3CH_2$), 2.36 (s, 2H, CH_2), 2.84 (s, 2H, CH_2), 3.24 (s, 1H, CH), 3.37 (s, 2H, CH_2), 4.89 (s, 4H, $2CH_2$), 6.84-6.88 (m, 2H, ArH), 6.98-7.04 (m, 2H, ArH), 7.25-7.45 (m, 8H, ArH), 7.52-7.57 (m, 4H, ArH); ^{13}C NMR (DMSO-d_6, δ ppm): 40.61, 41.64, 49.27, 52.87, 70.11, 110.93, 111.91, 115.57 and 115.80, 117.25 and 117.32, 118.46, 118.92, 121.52 , 123.68, 127.50, 129.12, 130.05, 131.20, 136.64, 155.25 and 157.85, 152.26, 165.28; EI-MS *m/z* (%): 720.26 ($[M+K]^+$, 16), 705.19 ($[M+1+Na]^+$, 32), 681.47 ($[M]^+$,70), 670.37 (100); Anal. Calcd. for $C_{35}H_{33}Cl_3FN_5O_2$: C, 61.73; H, 4.88; N, 10.28%. Found: C, 61.95; H, 5.02; N, 10.13%.

BIOLOGICAL ACTIVITY

Antimicrobial activity

The test microorganisms were acquired from the Hifzissihha Institute of Refik Saydam (Ankara, Turkey) and were as follows: *Escherichia coli* (*E. coli*) ATCC35218, *Yersinia pseudotuberculosis (Y. pseudotuberculosis*) ATCC911, *Pseudomonas aeruginosa* (*P. aeruginosa*) ATCC43288, *Enterococcus faecalis* (*E. faecalis*) ATCC29212, *Staphylococcus aureus* (*S. aureus*) ATCC25923, *Bacillus cereus* (*B. cereus)* 709 Roma, *Mycobacterium smegmatis* (*M. smegmatis*) ATCC607, *Candida albicans* (*C. albicans*) ATCC60193 and *Saccharomyces cerevisiae* (*S. cerevisia*) RSKK 251 which are laboratory strains. All the novel synthesized molecules were weighed and dissolved in hexane to prepare extract stock solution of 20.000 microgram/milliliter (µg/mL). The antimicrobial effects of the compounds were tested quantitatively in respective broth media by using double microdilution and the minimal inhibition concentration (MIC) values (µg/mL) were determined. The antibacterial and antifungal assays were performed in Mueller-Hinton broth (MH) (Difco, Detroit, MI) at pH.7.3 and buffered Yeast Nitrogen Base (Difco, Detroit, MI) at pH 7.0, respectively. The micro dilution test plates were incubated for 18-24 h at 35 °C. Brain Heart Infusion broth (BHI) (Difco, Detriot, MI) was used for *M. smegmatis,* and incubated for 48-72 h at 35 °C [33]. Ampicillin (10 µg) and fluconazole (5 µg) were used as standard antibacterial and antifungal drugs, respectively. Dimethyl sulfoxide with dilution of 1:10 was used as solvent control.

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Türkçe Öz ve Anahtar Kelimeler

Yeni 1,2,4-Triazoller, Mannich Bazları, Konazoller ve Florokinolinlerin Sentezi ve Antimikrobiyal Aktivitesi

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Öz: Triazoller antidepresan, antienflamatuar, analjezik, antibakteriyel, antimikobakteriyel, antifungal, antiviral, antikanser ve diğer aktivitelere sahpi olan yeni bileşiklerin geliştirilmesinde ilgi çeken heterosiklik bileşiklerdir. Bu makalede, bir seri florlu ve piperazinli yeni biyolojik aktif 1,2,4-triazol-3-on türevleri triazol öncül maddelerinin Mannich reaksiyonuyla sentez edilmiştir. Sentezlenmiş yeni bileşiklerin yapıları elementel analiz, FT-IR, ^{13}C NMR, ^{1}H NMR ve EI MS teknikleriyle aydınlatılmıştır. Bu bileşikler *in vitro*'da antimikrobiyal özellikleri açısından incelenmiştir ve pek çok bileşiğin *Candida albicans* ve *Saccharomyces cerevisiae*'ye karşı fungusidal aktivitesi olduğu bulunmuştur. Bazı bileşikler ise *Mycobacterium smegmatis* (pigmentsiz, hızlı yükselen bir mikobakteri) üzerinde mükemmel bir aktivite göstermişlerdir, uygulama konsantrasyonu <1 µg/mL olup standart ilaç olan streptomisin'den daha iyidir.

Anahtar kelimeler: 1,2,4-triazol, piperazin, konazol, mannich bazı, biyolojik aktivite.

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