Microwave-Assisted Synthesis, Antioxidant, and Antimicrobial Evaluation of Piperazine-Azole-Fluoroquinolone Based 1,2,4-Triazole Derivatives

Serap Basoglu Ozdemir,[a] Neslihan Demirbas,[a]* Ahmet Demirbas,[a] Faik Ahmet Ayaz,[b] and Nesrin Çolak[b]

[a]Department of Chemistry, Faculty of Science, Karadeniz Technical University, Trabzon, Turkey
[b]Department of Biology, Faculty of Science, Karadeniz Technical University, Trabzon, Turkey
*E-mail: neslihan@ktu.edu.tr

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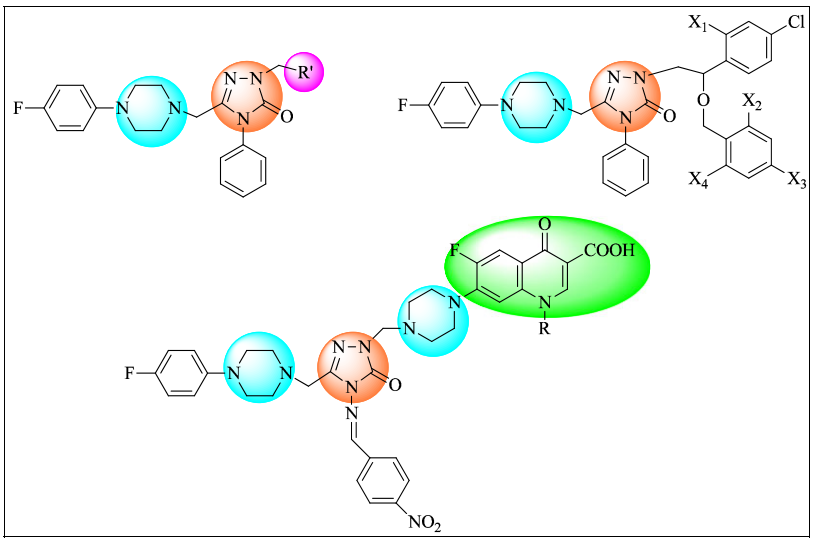

Azole derivatives (**10a**–**f**) obtained starting from 1-(4-fluorohenyl)piperazine were converted to the corresponding Mannich bases (**7a**–**d**, **12a**,**b**, and **16a**,**b**) containing β-lactame or flouroquinolone core via a one-pot three-component reaction. The synthesis of conazole analogues was carried out starting from triazole by three steps. Reactions were carried out under conventional-mediated and microwave-mediated conditions. All the newly synthesized compounds were screened for their antimicrobial, antioxidant activity, and most of them displayed good–moderate activity.

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INTRODUCTION

The increasing incidence of bacterial and fungal resistance to a large number of antimicrobial agents in both community and hospital acquired infections has been a serious and global health problem with nearly 15 million deaths every year, because currently available drugs will be no longer effective on resistant infections, as a result of pathogenic microorganisms adopt diverse strategies to enhanced ability to survive in the presence of antibiotics [1–5]. This unwanted event has prompted medicinal chemists to study on the development of new antimicrobial compounds with fewer tendencies to drug resistance. For the rational design of new biologically active compounds, the molecular manipulation or conjugation of promising lead compounds with recognized pharmacophoric units derived from known bioactive molecules has become a major strategy of approach [6–10]. Due to the excellent selectivity with versatile biological activities and low toxicity, the chemistry of nitrogen containing heterocyclic compounds has been a most referenced building blocks in the pharmaceutical research areas [11].

As one of the five-membered nitrogen-containing heterocycles, 1,2,4-triazole derivatives exhibit a wide-range spectrum of biological activities including antibacterial [12–14], anti-inflammatory [15], anticancer [16–18], antifungal [19], antioxidant [20], enzyme inhibition [21,22], insecticidal [23], and plant growth regulating activities [24]. Beside this, piperazine ring constitutes another important heterocyclic unit that has preferred properties including a wide-range biological activity and low toxicity [25–27]. Piperazine ring forms multiple hydrogen bonds or ionic bonds easily. Moreover, it has functional effect that modulating drug lipid water partition coefficient and acid–base equilibrium constant [19]. In biologically active products, piperazine is often present as a fused or oxidized form or is substituted with an azole (1,2,4-triazole and/or imidazole) [28]. Highly substituted piperazines can be expected to increase antimicrobial activity probably by enhancing lipophilicity of molecule [29]. Mainly, piperazine nucleus

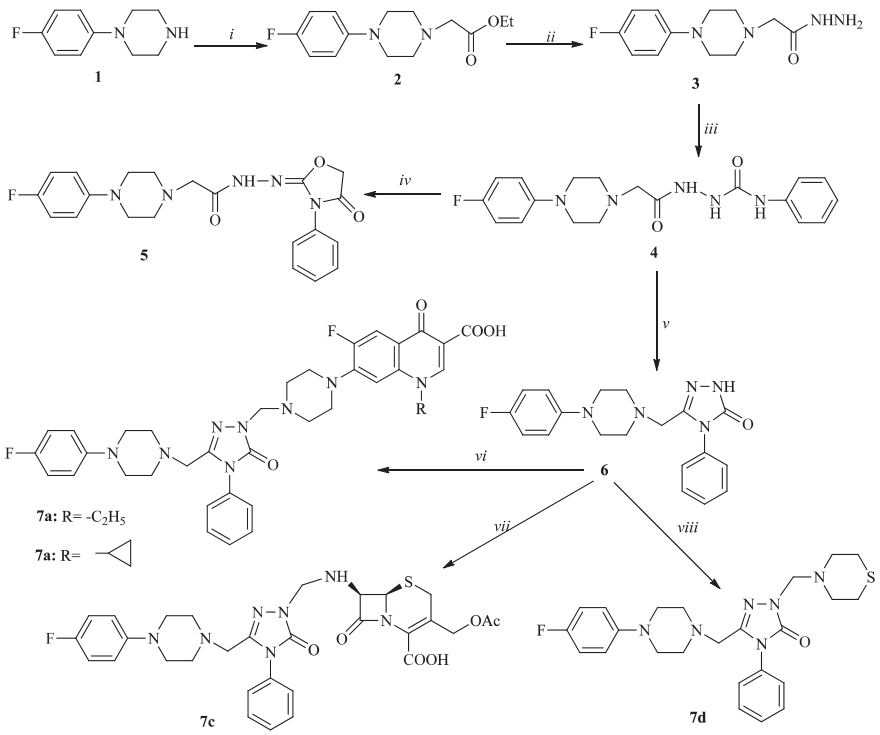
constitutes an active part of fluoroquinolone class antibacterial drugs such as ciprofloxacin, enoxacine, pefloxacine, fleroxacine, ofloxacine, and grepafloxacine [30–34]. In some of our previous studies, some 1,2,4-triazole-*N*-substituted piperazine conjugates have been obtained as antibacterial and/or antifungal agents [35–37].

However, the increase of opportunistic fungal infections and the emergence of azole resistance strains have led the medicinal and organic chemists to design and synthesize of new compounds with new mechanism of action [38–41]. 1,3,4-Oxadiazole ring has been extensively used as another pharmacophore, because some superior properties of it, such as being a good bioisostere of amides and esters, which can contribute significant pharmacokinetic properties by increasing the lipophilicity and the ability of drugs to reach their targets by transmembrane diffusion [42]. The application of microwave techniques for organic synthesis has attracted considerable interest in recent years. Microwave-assisted organic synthesis has proven to be a valuable technique for reducing reaction times, giving cleaner reactions, improving yields, simplifying work-up, and designing energy-saving protocols [43]. Moreover, with the development of "green chemistry," the focus has now shifted to less cumbersome solvent-free methods, undergoing facile reactions to provide high yields of pure products, thus eliminating or minimizing the use of organic solvents [44–46]. In light of these considerations, as the continuation of our ongoing efforts endowed with the discovery of new compounds with biological activity, we reported here the microwave irradiated and conventional synthesis and antimicrobial activity screening studies of new azole class antifungals. Moreover, the synthesis of piperazine-azole-fluoroquinolone hybrids were intended as well, based on molecular conjugation. Piperazine scaffold was selected as the key prototype structural unit and the integration of piperazine skeleton, azole, and fluoroquinolone pharmacophores with different mode of action in the one molecular frame was performed with the aim to prepare new antibacterial agents with preferably therapeutic profile having fewer tendencies to antibacterial resistance.

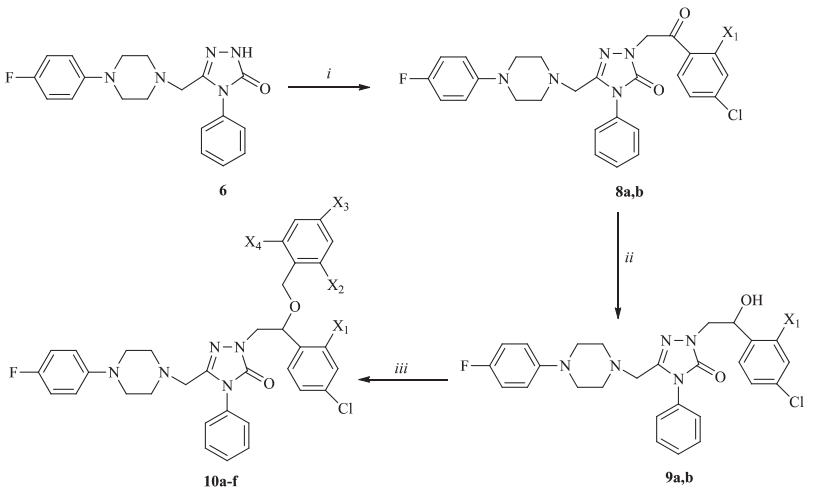
RESULT AND DISCUSSION

In the present study, microwave-assisted green synthesis, antimicrobial, enzyme inhibition, and antioxidant activity screening studies of novel heterocyclic molecules were intended. Microwave irradiation was applied in addition to traditional methods to find more efficient synthetic conditions for these reactions. The synthetic strategies adopted to obtain the target compounds are depicted in Schemes 1–3.

Scheme 1. Synthetic route of compounds **2**–**7**. Reagent and conditions. (i): $BrCH_2COOEt$, Et_3N, THF, rt of Mw; (ii): H_2NNH_2, EtOH reflux or Mw; (iii): C_6H_5NCO,DCM, rt or Mw; (iv): NaOAc, $BrCH_2COOEt$, EtOH, reflux or Mw; (v): NaOH, reflux or Mw; (vi–viii): suitable amine, HCHO, DMF, rt or MW; Mw conditions were given in Table 1.

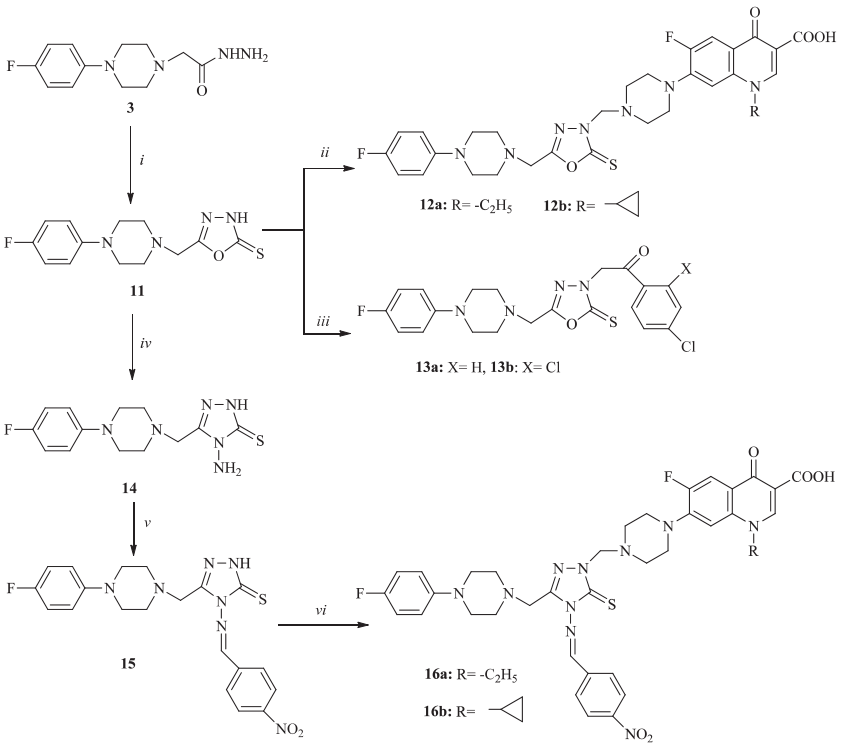


Scheme 2. Synthetic route of compounds **8**–**10**. Reagent and conditions: (i): NaOEt, 2-bromo-1-(4-chlorophenyl)ethanone (for **8a**) and 2,2,4-trichloroacetophenone (for **8b**) reflux or Mw; (ii): $NaBH_4$, reflux or Mw; (iii): NaH, suitable benzyl chloride, THF, reflux or Mw; Mw conditions were given in Table 1.



8a, **9a**, **10a-c**: X_1= H; **8b**, **9b**, **10d-f**: X_1= Cl; **10a**, **10d**: X_2, X_4=H, X_3= Cl; **10b**, **10e**: X_3, X_4= Cl, X_2=H; **10c**, **10f**: X_2, X_4= Cl, X_3=H

Scheme 3. Reagents and Conditions: (i): CS_2, KOH, EtOH, reflux or Mw; (ii): HCHO, DMF, suitable amine, rt or Mw; (iii): NaOEt, 2-bromo-1-(4-chlorophenyl)ethanone (for **13a**) and 2,2,4-trichloroacetophenone (for **13b**) reflux or Mw; (iv): $H_2NNH_2.H_2O$, EtOH, reflux or Mw; (v): 4-nitrobenzaldehyde, EtOH, reflux or Mw; (vi): HCHO, DMF, suitable amine, rt or Mw; Mw conditions were given in Table 1.



The treatment of compound **2** with hydrazine hydrate by conventional and microwave-assisted techniques afforded the corresponding hydrazide **3**. The reaction was investigated in ethanol under reflux conditions as well as under microwave irradiation conditions with a view to maximizing the yield of the product and minimizing the reaction time. Thus, the yield of the reaction was improved to good level (91%); however, more

significantly, the reaction time for complete consumption of starting materials was lowered from 27 h with conventional heating to a remarkable 30 min using MW irradiation. The optimal MW power in terms of yields and product stability was assessed at 125 W and 125°C in the closed vessel that afforded 96% yield (Table 1).

The hydrazide **3** was characterized by the presence of three strong bands at 3166 (NH), 3295, and 3255 cm^{-1} (NH_2) in the FT IR spectrum. This group was recorded at 4.28 (NH_2) and 8.94 (NH) ppm in the ^1H NMR spectrum as D_2O exchangeable singlets. This compound gave mass fragmentation and elemental analysis results consistent with the assigned structure.

The nucleophilic addition of compound **3** with phenyl isocyanate yielded the corresponding hydrazinecarboxamide (**4**), which are considered as useful intermediates for further cyclization reactions (Scheme 1). The synthesis of compound **4** was examined after microwave irradiation at 150 W for 7 min. Compared with conventional thermal heating, microwave irradiation decreased the reaction time from 24 h to 7 min. FT IR spectra of compound **4** revealed the presence of —C═O group 1703 cm^{-1}. Another evidence for the formation of carboxamide was the presence of three —NH signals at 8.04–9.59 ppm in the ^1H NMR spectra as D_2O exchangeable singlet. In the ^{13}C NMR spectra of these compounds, C═O function resonated at 169.51 ppm. The structures of this compound was also elucidated by the appearance of [M + 1] ion peak at the corresponding *m/z* values confirming their molecular masses and also have given elemental analysis results consistent with the proposed structure.

Table 1

Time, power, and yield data for compounds **3**–**16**.

	Microwave irradiation method			Conventional method	
Comp. No	Time (min)	Power (W)	Yield (%)	Time (h)	Yield (%)
3	30	125	96	27	91
4	7	150	87	24	50
5	30	150	77	17	65
6	15	150	90	5	83
7a	6	100	80	24	65
7b	15	150	84	24	72
7c	6	100	49	24	25
7d	15	150	70	24	54
8a	40	125	89	14	75
8b	40	125	84	14	76
9a	12	100	72	15	60
9b	12	100	75	15	60
10a	25	120	45	8	24
10b	25	120	50	10	32
10c	25	120	40	10	15
10d	25	120	60	12	42
10e	25	120	55	12	47
10f	25	120	61	12	43
11	20	125	78	10	53
12a	8	100	55	24	25
12b	8	100	85	24	78
13a	40	125	87	14	70
13b	40	125	70	14	50
14	20	125	77	16	54
15	10	150	94	3	75
16a	8	100	58	24	45
16b	8	100	55	24	32

The cyclocondensation of compound **4** with ethyl bromoacetate produced the corresponding hybrid compound incorporating 1,3-oxazole nucleus linked to the 1-(4-fluorophenylpiperazine) skeleton via an acetohydrazide linkage. Compared with a conventional heating, MW irradiation decreased the reaction time from 17 h to 30 min and increased the yields from 65% to 77%. The best yields were obtained at 150 W maximum powers. Compound **5** was characterized by the presence of additional strong band at 1712 cm^{-1} in the FT IR spectrum corresponding to second carbonyl function that arose from ring closure. This was considered as a confirmation of oxazolidin nucleus formation.

Another piece of evidence for cyclocondensation is the appearance of a singlet signal at 3.39 ppm in the ^1H NMR spectrum integrating for two protons, which apparently are the C5 protons of oxazolidin nucleus. This carbon has resonated at 60.54 ppm in the ^{13}C NMR spectrum. Moreover, the elemental analyses and mass spectral data of were compatible with the suggested structure.

The synthesis of compound **6** was performed by the intramolecular cyclization of compound **4** in basic media with conventional and also MW-mediated methods with the aim to introduce the 1,2,4-triazole nucleus into piperazine skeleton, because it is well known that more efficacious bioactive compounds can be designed by joining two or more biologically active heterocyclic systems together in a single molecular framework [7,36,37]. Moreover, it is well known that the presence of fluorinated units in organic compounds may dramatically modify the physicochemical profile of organic molecules. Thus, the heterocyclic compounds containing fluorine atom have been attracting much interest due to their potent biological activities and their role in the development of new drug candidates [29]. In addition, type of compound **6** can be considered as useful tolls having active NH group for further one-pot three-component amino alkylation reactions leading to the formation of new bioactive compounds (Scheme 1). Compared with conventional thermal heating, microwave irradiation decreased the reaction time from 5 h to 15 min and increased the yields from 83% to 90% (Table 1).

The synthesis of compounds **7a**–**d** and **16a**,**b** was carried out by the treatment of compounds **6** and **15** with several amines, namely, norfloxacin, ciprofloxacin, 7-

aminocephalosporanic acid, and thiomorpholine, in the presence of formaldehyde. This idea originated from the intend to introduce a fluoroquinolone, cephalosporin, which are the known antibiotics or thiomorpholine core to the azole skeleton. Two methods were applied for this treatment including conventional-assisted and microwave-assisted techniques. In comparison with the long refluxing time, microwave irradiation provided more efficient and green way for one-pot Mannich type condensation with higher product yield. For MW-mediated reactions leading to the formation of these Mannich bases (**7a–d** and **16a**,**b**), the production of compound **7a** was selected as model and the effects of various reaction parameters, including temperature, time, and MW power, were examined on the model reaction, and the results are summarized in Table 1.

The treatment of **6** and **11** with 2-bromo-1-(4-chlorophenyl)ethanone and 2,2,4-trichloroacetophenone produced the corresponding ethenone derivatives (**8a**,**b** and **13a**,**b**). Compared with a conventional heating, MW irradiation decreased the reaction time from 14 h to 40 min and increased the yields from 50–76% to 70–89% (Table 1). In the ^{1}H NMR and ^{13}C NMR spectra, additional signals corresponding to the substituted phenylethanone moiety were recorded at the related chemical shift values, while the spectra of these compounds (**8a**,**b** and **13a**,**b**) showed the disappearance of the characteristic bands of triazole or oxadiazole–NH (Scheme 2).

The reduction of carbonyl group of compounds **8a**,**b** to alcohol afforded compounds **9a**,**b** that, again, was achieved using both classical heating and MW irradiation. These compounds gave ^{1}H NMR, ^{13}C NMR, FT IR, and mass spectroscopic data and elemental analysis results compatible with the proposed structures. The synthesis of compounds **10a–f** that can be considered as new analogues of azole class antifungals was achieved by treatment of compounds **9a**,**b** with substituted benzyl chlorides in the presence of NaH. Two methods were applied for this treatment including conventional-assisted and microwave-assisted techniques. In comparison with the long refluxing time, microwave irradiation provided more efficient and green way for one-pot Mannich type condensation with higher product yield. The most important evidence in the FT-IR and ^{1}H NMR spectra of compounds **10a–f** are the disappearance of the signal originated from hydroxyl group. The appearance of additional signals belonging to (di)chlorobenzyl group supported the formation of new conazole derivatives. Furthermore, the mass spectral data and elemental analysis results are in accordance with their structures.

The cyclization of hydrazide (**3**) with carbon disulfide in basic media produced the corresponding 1,3,4-oxadiazole derivative (**11**), then this compound was converted to 4-{[(4-nitrophenyl)methylene]amino}-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (**15**) derivative via the treatment of **11** with hydrazine hydrate and 4-nitrophenylbenzaldehyde, respectively, in the conventional-mediated and also microwave-mediated conditions. The structure of **15** was elucidated on the basis of spectroscopic data and elemental analysis results (Scheme 3).

Biological activity. ***Antimicrobial activity.*** All the newly synthesized compounds were screened for their antimicrobial activity, and the results obtained were presented in Table 2. Among these, compounds **7a**,**b**, **12a**,**b**, and **16a**,**b** that contain a fluoroquinolone nucleus linked to the 1,2,4-triazole or 1,3,4-oxadiazole core exhibited excellent antibacterial and antimycobacterial (on *Micobacterium Smegmatis*) activity with the minimal inhibition concentration values varying between 0.24 and 3.9 μg/mL. It can be suggested that excellent activity of these compounds is due to the presence of a fluoroquinolone core in their structures. Compounds **10a–d** exhibited Gram (+) bacteria, *Staphylococcus aureus* (Sa), *Enterococcus faecalis* (Ef), *Bacillus cereus* (Bc), and micobacteria *Micobacterium smegmatis* (Ms). In fact, the activity of compounds **10a–d** on Sa was better than standard drug ampicillin. On the other hand, although these compounds (**10a–d**) were designed as new analogues of azole class antifungals, they did not show activity on *Saccharomyces cerevisiae* (Sc) and *Candida albicans* (Ca), yeast like fungy. The remaining compounds displayed slight activities on some of the test microorganisms.

Antioxidant activity. ***Principal component analysis.*** The three sets of antioxidant capacity (AC) values representing 40 measurements were modeled on a principal component (PC) analysis to visualize possible variation and correlation patterns of the AC values of the synthesized compounds (Fig. 1). The AC values compared in Table 3 have revealed two PCs accounted totally 97.26% (PC1; 67.31% and PC2; 29.95%). Data exhibited strong positive loadings at the right upper and lower quadrants on PC1 with the five compounds (**5**, **12b**, **12a**, **4**, and **11**), respectively. They all were associated, but only the AC values obtained from the compounds **11** and **5** are unique and significantly strong correlated (r = 0.887, $P < 0.05$). The remaining 10 compounds shared more or less the same AC values, closing to the center on the PC that negatively located at the upper and lower quadrant on PC2 with variation 29.95%. They all were closely associated and insignificantly low correlated (r = 0.144, 0.372, $P < 0.05$) with the three AC assays (Fig. 1).

Compounds given in Table 3 exhibited different AC values using the three different assays (2,2-Diphenyl-1-picrylhydrazyl [DPPH], ferric reducing ability of plasma

Table 2

Screening for the activity of compounds **4**–**16**.

No	Microorganisms and minimal inhibition concentration								
	Ec	Yp	Pa	Sa	Ef	Bc	Ms	Ca	Sc
4	125	–	–	–	–	–	–	125	125
5	–	–	–	–	–	–	125	–	500
6	125	–	–	–	–	–	62.5	–	125
7a	<0.24	<0.24	<0.24	<0.24	<0.24	<0.24	<0.24	125	–
7b	<0.24	<0.24	<0.24	<0.24	<0.24	<0.24	<0.24	125	
7c	125	125	250	125	–	250	–	125	
7d	–	–	–	–	–	–	–	–	
8a	–	–	500	–	–	–	62.5	250	
8b	–	–	–	250	–	–	–	–	–
9a	–	–	–	–	–	–	–	250	–
9b	–	–	–	–	–	–	–	250	–
10a	–	–	–	31.25	31.25	31.25	125	–	–
10b	625	–	–	31.25	31.25	31.25	125	–	–
10c	–	–	–	31.25	31.25	125	125	–	–
10d	–	–	–	31.25	31.25	31.25	125	–	–
11	125	–	–	–	–	–	125	125	62.5
12a	<0.24	<0.24	<0.24	<0.24	<0.24	<0.24	<0.24	<0.24	–
12b	<0.24	<0.24	<0.24	<0.24	<0.24	<0.24	<0.24	<0.24	–
13a	–	–	–	–	62.5	–	62.5	500	–
13b	125	–	–	125	500	–	62.5	125	–
14	–	–	125	–	–	–	–	–	–
15	–	–	–	250	–	–	–	–	–
16a	<1	<1	<1	1.9	–	1.9	<1	–	62.5
16b	<1	3.9	3.9	3.9	–	1.9	1.9	–	–
DMSO	125	125	125	–	–	500	125	500	–
Amp.	10	18	>128	35	10	15			
Strep.							4		
Flu								<8	<8

Amp., Ampicillin; Bc, *Bacillus cereus* 702 Roma; Ca, *Candida albicans* ATCC 60193; Ec, *Escherichia coli* ATCC 25922; Ef, *Enterococcus faecalis* ATCC 29212; Ms, *Micobacterium smegmatis* ATCC607; Pa, *Pseudomonas aeruginosa* ATCC 43288; Sa, *Staphylococcus aureus* ATCC 25923; Sc, *Saccharomyces cerevisiae* RSKK 251; Strep., streptomycin; Yp, *Yersinia pseudotuberculosis* ATCC 911; –, no activity.

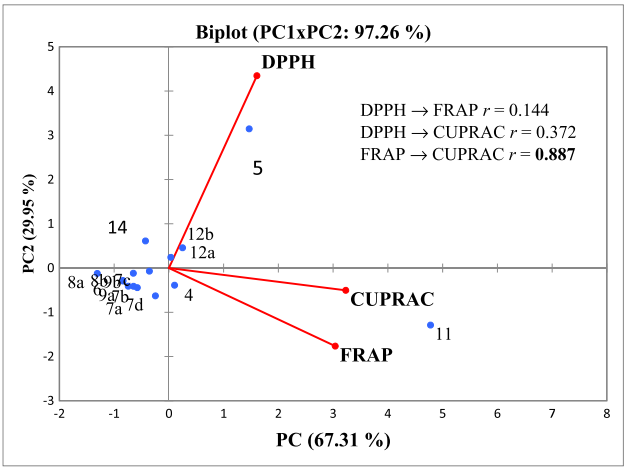


Figure 1. Principal component (PC) analysis applied to the antioxidant capacity (AC) values of the synthesized 15 novel compounds listed in Table 3. [Color figure can be viewed at wileyonlinelibrary.com]

[FRAP], and cupric ion reducing antioxidant capacity [CUPRAC]). Among the 15 novel synthesized compounds, only the compounds **8a**, **9a**, **7a**, **7b**, and **7d**

Table 3

Antioxidant capacity (*μmol TE/g, AC) values of synthesized 15 novel compounds.

No	DPPH*	FRAP*	CUPRAC*
4	20.64 ± 1.09^{b}	1698.33 ± 35.51^{k}	1607.33 ± 54.23^{v}
5	629.54 ± 17.08^{v}	2049.26 ± 4.18^{o}	1497.06 ± 81.16^{u}
6	8.13 ± 0.06^{a}	$1415.15 \pm 13.42^{g\text{-}j}$	263.46 ± 7.59^{c}
7a	n.d.	1795.63 ± 82.70^{L}	421.72 ± 10.82^{fg}
7b	n.d.	1952.46 ± 146.90^{n}	456.69 ± 10.74^{gh}
7c	63.78 ± 2.25^{f}	1870.72 ± 56.75^{Lm}	629.35 ± 16.51^{kL}
7d	n.d.	2982.27 ± 56.66^{p}	483.92 ± 6.52^{gh}
8a	n.d.	338.45 ± 10.67^{a}	67.95 ± 0.84^{a}
8b	3.76 ± 0.11^{a}	1293.84 ± 32.56^{ef}	343.52 ± 23.15^{de}
9a	n.d.	1896.68 ± 42.91^{mn}	216.29 ± 10.21^{BC}
9b	43.52 ± 4.40^{c}	1618.45 ± 53.94^{k}	249.51 ± 13.08^{de}
11	161.61 ± 0.12^{s}	9826.25 ± 44.42^{r}	4673.21 ± 95.69^{x}
12a	119.96 ± 0.09^{op}	1682.58 ± 81.90^{k}	1156.58 ± 9.28^{p}
12b	$154.75 \pm 0,05^{r}$	$1434.53 \pm 128.19g^{h\text{–}j}$	1501.14 ± 23.02^{u}
14	151.49 ± 5.24^{r}	894.88 ± 93.53^{b}	684.42 ± 32.28^{Lm}

Values represent the mean ± SD of three determinations. An analysis of variance (SPSS version 11.5. one-way analysis of variance) was used for comparisons among the means. The values with the same letter at superscripts within a column are not significantly different at $P < 0.05$, n.d., not detected. CUPRAC, cupric ion reducing antioxidant capacity; DPPH, 2,2-diphenyl-1-picrylhydrazyl; FRAP, ferric reducing ability of plasma.

did not show any AC values in the DPPH assay, while the other had. Compounds **5** (629.54 ± 17.08) and **8b** (8.13 ± 0.06) in DPPH, **11** (9826.25 ± 44.4) and **8a** (338.45 ± 10.67) in FRAP and **11** (4673.21 ± 95.69) and **8a** (67.95 ± 0.84) in CUPRAC had the highest and the lowest AC values, respectively (Table 3).

MATERIAL AND METHODS

All the chemicals were purchased from Fluka Chemie AG Buchs (Switzerland) and used without further purification. Melting points were determined in open capillaries on a Büchi B-540 melting point apparatus and are uncorrected. Reactions were monitored by thin-layer chromatography 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 FT IR 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). Microwave-assisted syntheses were carried out using monomode CEM-Discover microwave apparatus. The chemical shifts are given in ppm relative to Me4Si 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. Compound **2** was prepared by the way reported earlier [47].

EXPERIMENTAL

Ethyl[4-(4-fluorophenyl)piperazin-1-yl]acetate (2). Method 1: Ethyl bromoacetate (10 mmol) was added to the solution of 1-(4-fluorophenyl)piperazine (10 mmol) in tetrahydrofuran (THF) drop wise, and the mixture was stirred at room temperature in the presence of triethylamine (15 mmol) for 24 h. The solid formed was removed by filtration, and the solvent was evaporated under reduced pressure. The oily crude product was recrystallized from ethanol to afford the desired compound.

Method 2: The mixture of ethyl bromoacetate (1.5 mmol), 1-(4-fluorophenyl)piperazine (1.0 mmol) and trimethylamine (3.0 mmol) in THF was stirred at room temperature for 5 min and then irradiated in closed vessels with the pressure control at 110°C for 15 min (hold time) at 150 W maximum power. The precipitate was removed by filtration, and the resulting solution was evaporated under reduced pressure to dryness. The oily crude recrystallized from ethanol. Yield: 75% (method 1), 90% (method 2); mp 54–55°C. FT IR (ν_{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 (CH_3), 49.38 ($2CH_2$), 52.38 ($2CH_2$), 58.78 (CH_2), 60.33 (CH_2), arC: [115.57 and 115.79 (d, 2CH, J = 22.0 Hz), 117.59 and 117.67 (d, 2CH, J = 8.0 Hz), 148.34 and 148.35 (d, C, J = 1.0 Hz), 155.30 and 157.64 (d, C, $J_{C\text{-}F}$ = 234.0 Hz)], 170.29 (C═O). EI MS *m/z* (%): 267.23 ([M + 1]$^+$, 100), 193.14 (39), 188.18 (39), 160.19 (34). Elemental analysis for $C_{14}H_{19}FN_2O_2$, calculated (%): C, 63.14; H, 7.19; N, 10.52. Found: C, 63.47; H, 7.29; N, 10.55.

2-[4-(4-Fluorophenyl)piperazin-1-yl]acetohydrazide (3). Method 1: Hydrazine hydrate (30 mmol) was added to the solution of compound **2** (10 mmol) in absolute ethanol, and the mixture was refluxed for 27 h. Then, the solvent was removed under reduced pressure and the obtained oily mass was recrystallized from ethyl acetate:diethyl ether (1:3) to give the target compound. [48]. Yield 91%, mp 155–156°C.

Method 2: The mixture of hydrazine hydrate (2.5 mmol) and compound **2** (1 mmol) was irradiated in closed vessels with the pressure control at 125°C, 125 W for 30 min. The product obtained was recrystallized from ethyl acetate: diethyl ether (1:3) to give the pure compound. Yield 96%. FT IR (ν_{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 ($2CH_2$), 53.20 ($2CH_2$), 60.26 (CH_2), arC: [115.57 and 115.79 (d, 2CH, J = 22.0 Hz), 117.49 and 117.57 (d, 2CH, J = 8.0 Hz), 148.36 (C), 155.44 and 157.58 (d, C, $J_{C\text{-}F}$ = 214.0 Hz)], 168.57 (C═O). EI MS *m/z* (%): 293.30 (43), 193.18 (100), 178.16 (20), 150.13 (62), 138.11 (37).

2-{[4-(4-Fluorophenyl)piperazin-1-yl]acetyl}-*N*-phenylhydrazinecarboxamide (4). Method 1: Phenyl isocyanate (20 mmol) was added to the solution of compound **3** (10 mmol) in dichloromethane, and the mixture was stirred at room temperature for 24 h. After evaporating the solvent, a solid appeared. This solid was recrystallized from acetone:diethyl ether (1:2).

Method 2: The solution of the corresponding aryl isothiocyanate (2 mmol) in dichloromethane (DCM) was added to the solution of compound **3** (1 mmol). Then, the reaction mixture was irradiated in microwave reactor in closed vessels with the pressure control at 100°C, for 7 min at 150 W. After evaporating the solvent under reduced pressure, a solid appeared. This was

recrystallized from acetone:diethyl ether (1:2) to give the desired product. Yield 50% (method 1), 87% (method 2); mp 151–152°C. FT IR (ν_{max}, cm^{-1}): 3379 (NH), 3307 (2NH), 3091 (Aromatic CH), 2882, (Aliphatic CH), 1713 (C=O), 1662 (C=O). ^{1}H NMR (DMSO-d_6, δ ppm): 2.66 (s, 4H, $2CH_2$), 3.11 (s, 4H, $2CH_2$), 3.38 (s, 2H, CH_2), 6.93–6.96 (m, 3H, ArH), 7.02–7.06 (m, 2H, ArH), 7.25 (t, 2H, ArH, J = 8.0 Hz), 7.45 (d, 2H, ArH, J = 8.0 Hz), 8.04 (s, 1H, NH), 8.79 (s, 1H, NH), 9.59 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, δ ppm): 49.24 ($2CH_2$), 53.12 ($2CH_2$), 60.12 (CH_2), arC: [115.58 and 115.80 (d, 2CH, J = 22.0 Hz), 117.50 and 117.58 (d, 2CH, J = 8.0 Hz), 124.62 (CH), 129.12 (2CH), 129.27 (2CH), 140.08 (C), 148.34 (C), 155.26 and 157.60 (d, C, $J_{C\text{-}F}$ = 234.0 Hz)], 155.69 (C=O), 169.51 (C=O). EI MS m/z (%): 372.36 ($[M + 1]^+$, 100), 253.29 (77), 193.23 (48). Elemental analysis for $C_{19}H_{22}FN_5O_2$, calculated (%): C, 61.44; H, 5.97; N, 18.86. Found: C, 61.87; H, 6.09; N, 18.55.

2-[4-(4-Fluorophenyl)piperazin-1-yl]-*N*′-[(2Z)-4-oxo-3-phenyl-1,3-oxazolidin-2-ylidene]acetohydrazide (5). Method 1: Ethyl bromo acetate (10 mmol) was added to the solution of compound **4** (10 mmol) in ethanol. The mixture was refluxed for 17 h in the presence of dry sodium acetate (50 mmol). After evaporating the solvent under reduced pressure, a solid was occurred and washed with water. This crude product crystallized from ethanol:water (1:3).

Method 2: The mixture of compound **4** (1 mmol) and ethyl bromoacetate (1 mmol) and sodium acetate (5 mmol) in ethanol was irradiated in microwave reactor in closed vessels with the pressure control at 150°C, 150 W for 30 min. After evaporating the solvent under reduced pressure, a solid was occurred and washed with water. This crude product crystallized from ethanol:water (1:3). Yield 65% (method 1), 77% (method 2); mp 135–137°C. FT IR (ν_{max}, cm^{-1}): 3306 (NH), 3038 (Aromatic CH), 2919 (Aliphatic CH), 1712 (C=O), 1662 (C=O), 1509 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 2.64 (s, 4H, $2CH_2$), 3.08 (s, 4H, $2CH_2$), 3.39 (s, 4H, $2CH_2$), 6.94–6.96 (m, 3H, ArH), 7.01–7.06 (m, 2H, ArH), 7.23 (t, 2H, ArH, J = 8.4 Hz), 7.46 (d, 2H, ArH, J = 6.8 Hz), 9.63 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, δ ppm): 49.28 ($2CH_2$), 53.13 ($2CH_2$), 60.22 (CH_2), 60.54 (CH_2), arC: [115.57 and 115.79 (d, 2CH, J = 22.0 Hz), 117.49 and 117.56 (d, 2CH, J = 7.0 Hz), 122.73 (CH), 129.03 (2CH), 129.15 (2CH), 140.49 (2C), 155.24 and 157.58 (d, C, $J_{C\text{-}F}$ = 234.0 Hz)], 148.39 (C=N), 169.46, (C=O), 175.81 (C=O). EI MS m/z (%): 411.36 ($[M^+]$, 25), 394.33 (68), 193.04 (100). Elemental analysis for $C_{21}H_{22}FN_5O_3$, calculated (%): C, 61.30; H, 5.39; N, 17.02. Found: C, 61.37; H, 5.09; N, 17.15.

5-{[4-(4-Fluorophenyl)piperazin-1-yl]methyl}-4-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (6). Method 1: A solution of the corresponding compound **4** (10 mmol) in refluxed in the presence 2% NaOH solution for 5 h. Then, solution was cooled to room temperature and acidified to pH 5 with 37% HCl. The precipitate formed was filtered and washed with water. This compound recrystallized from ethyl acetate.

Method 2: The mixture of compound **4** (1 mmol) and 2 mol/L NaOH (2 mmol) in water (10 mL) was irradiated in monomode microwave reactor in closed vessel with the pressure control at 120°C for 15 min at 150 W. Then, the resulting solution was cooled to room temperature and acidified to pH 5 with 37% HCl. The precipitate formed was filtered off, wash with water, and recrystallized from ethanol. Yield: 83% (method 1), 90% (method 2); mp 200–201°C. FT IR (ν_{max}, cm^{-1}): 3175 (NH), 3067 (Aromatic CH), 2940 (Aliphatic CH), 1694 (C=O). ^{1}H NMR (DMSO-d_6, δ ppm): 2.42 (s, 4H, $2CH_2$), 2.90 (s, 4H, $2CH_2$), 3.34 (s, 2H, CH_2), 6.85–6.89 (m, 2H, ArH), 7.00 (t, 2H, ArH, J = 8.0 Hz), 7.48 (s, 5H, ArH), 11.78 (brs, 1H, NH). ^{13}C NMR (DMSO-d_6, δ ppm): 49.34 ($2CH_2$), 52.35 ($2CH_2$), 52.86 (CH_2), arC: [115.55 and 115.77 (d, 2CH, J = 22.0 Hz), 117.52 and 117.60 (d, 2CH, J = 8.0 Hz), 127.56 (CH), 128.59 (2CH), 129.34 (2CH), 133.93 (C), 144.44 (C), 155.27 and 157.61 (d, C, $J_{C\text{-}F}$ = 234.0 Hz)], 148.24 (triazole C-3), 154.88 (triazole C-5). EI MS m/z (%): 377.37 ($[M + 1 + Na]^+$, 21), 376.36 ($[M + Na]^+$, 100). Elemental analysis for $C_{19}H_{20}FN_5O$, calculated (%): C, 64.57; H, 5.70; N, 19.82. Found: C, 64.87; H, 5.55; N, 19.59.

General procedure for the synthesis of compounds 7a–d, 12a,b, and 16a,b. Method 1: To a solution of corresponding compounds **6**, **11**, and **15** (10 mmol) in dimethylformamide (DMF) containing suitable primary or secondary amine (10 mmol) was added, and the mixture was stirred at room temperature in the presence of formaldehyde (50 mmol) for 24 h. The solid precipitated was filtered off and recrystallized from dimethyl sulfoxide:water (1:1) for compounds (**7a**,**b**, **12a**,**b**, and **16a**,**b**) and ethyl acetate for compounds (**7c**,**d**).

Method 2: The mixture of compounds **6**, **11**, and **15** (1 mmol), suitable amine (1 mmol), HCl (5 mmol), and formaldehyde (5 mmol) in DMF was irradiated in the microwave reactor in the closed vessel with pressure control (physical parameters were given Table 1). The solid formed after the mixture was poured to ice-water was filtered off and purified by recrystallization from dimethyl sulfoxide:water (1:3).

1-Ethyl-6-fluoro-7-{4-[(3-{[4-(4-fluorophenyl)piperazin-1-yl]methyl}-5-oxo-4-phenyl-4,5-dihydro-1H-1,2,4-triazol-1-yl)methyl]piperazin-1-yl}-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (7a). Yield: 65% (method 1), 80% (method 2); mp >260°C. FT IR (ν_{max}, cm^{-1}): 3067 (Aromatic CH), 2920 (Aliphatic CH), 1708 (C=O), 1627 (2C=O). ^{1}H NMR (DMSO-d_6, δ ppm): 1.41 (s, 3H, CH_3), 2.41 (s, 4H, $2CH_2$), 2.73 (s, 4H, $2CH_2$), 2.89 (s, 4H, $2CH_2$), 3.38 (s, 6H, $3CH_2$), 4.57 (s, 2H, CH_2), 4.72 (s, 2H, CH_2), 6.82 (brs, 2H, ArH), 6.98 (brs, 2H, ArH),

7.15 (brs, 1H, ArH), 7.52 (s, 4H, ArH), 7.85 (s, 1H, ArH), 7.95 (s, 1H, ArH), 8.91 (s, 1H, quinolone CH), 15.32 (s, 1H, OH). ^{13}C NMR (DMSO-d_6, δ ppm): 14.79 (CH_3), 49.28 (CH_2), 49.49 ($2CH_2$), 49.75 (CH_2), 49.89 (CH_2), 51.06 (CH_2), 52.36 ($2CH_2$), 52.64 (CH_2), 66.15 (CH_2), 79.95 (CH_2), 107.51 (C), arC: [106.18 (CH), 111.46 and 111.69 (d, CH, J = 23.2 Hz), 115.51 and 115.73 (2CH), 117.44 and 117.52 (2CH), 119.52 and 119.59 (d, C, J = 7.0 Hz), 127.55 (CH), 128.86 (2CH), 129.41 (2CH), 133.87 (C), 137.58 (C), 143.30 (C), 145.71 and 145.81 (d, C, J = 10.0 Hz), 148.13 and 151.98 (d, C, $J_{C\text{-}F}$ = 385.0 Hz), 154.10 and 157.60 (d, C, $J_{C\text{-}F}$ = 350.0 Hz)], 148.78 (CH), 154.46 (triazole C-3), 162.77 (triazole C-5), 166.54 (C═O), 176.53 (C═O). EI MS *m/z* (%): 723.04 ([M + K]$^+$, 29), 708.16 ([M + 1 + Na]$^+$, 43), 707.28 ([M + Na]$^+$, 100), 685.31 ([M + 1]$^+$, 32). Elemental analysis for $C_{36}H_{38}F_2N_8O_4$, calculated (%): C, 63.15; H, 5.59; N, 16.36. Found: C, 63.17; H, 5.51; N, 16.56.

1-Cyclopropyl-6-fluoro-7-{4-[(3-{[4-(4-fluorophenyl) piperazin-1-yl]methyl}-5-oxo-4-phenyl-4,5-dihydro-1H-1,2,4-triazol-1-yl)methyl]piperazin-1-yl}-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (7b). Yield: 72% (method 1), 84% (method 2); mp >280°C. FT IR (ν_{max}, cm^{-1}): 3065 (Aromatic CH), 2950 (Aliphatic CH), 1711 (C═O), 1626 (2C═O). ^{1}H NMR (DMSO-d_6, δ ppm): 1.18 (s, 2H, CH_2), 1.32 (s, 2H, CH_2), 2.42 (s, 2H, CH_2), 2.50 (s, 2H, CH_2), 2.73 (s, 2H, CH_2), 2.89 (s, 4H, $2CH_2$), 3.34 (s, 8H, $4CH_2$), 3.82 (s, 1H, CH), 4.72 (s, 2H, CH_2), 6.83–6.86 (m, 2H, ArH), 6.99 (t, 2H, ArH, J = 8.8 Hz), 7.49–7.57 (m, 5H, ArH), 7.87 (d, 1H, ArH, J = 13.2 Hz), 7.95 (s, 1H, ArH), 8.65 (d, 1H, quinolone CH, J = 4.8 Hz), 15.19 (s, 1H, OH). ^{13}C NMR (DMSO-d_6, δ ppm): 8.02 ($2CH_2$), 36.29 (CH), 48.38 (CH_2), 49.30 (CH_2), 49.73 (CH_2), 49.85 (CH_2), 51.08 ($2CH_2$), 52.37 ($2CH_2$), 52.65 (CH_2), 66.17 (CH_2), 107.21 (C), arC: [106.87 (CH),111.26 and 111.51 (d, CH, J = 25.0 Hz), 115.51 and 115.54 (d, 2CH, J = 3.0 Hz), 117.48 and 117.56 (d, 2CH, J = 8.0 Hz), 118.97 and 119.05 (d, C, J = 7.5 Hz), 127.58 (CH), 128.88 (2CH), 129.35 (2CH), 133.88 (2C), 139.60 and 139.64 (d, C, J = 4.1 Hz), 145.49 (C), 145.59 and 148.16 (d, C, $J_{C\text{-}F}$ = 257.0 Hz), 152.18 and 154.10 (d, C, $J_{C\text{-}F}$ = 192.0 Hz)], 143.33 (triazole C-3), 148.37 (CH), 155.27 (triazole C-5), 166.36 (C═O), 176.78 (C═O). EI MS *m/z* (%): 720.21 ([M + 1 + Na]$^+$, 48), 719.21 ([M + Na]$^+$, 100), 697.18 ([M + 1]$^+$, 59), 398.24 (34), 376.21 (37). Elemental analysis for $C_{37}H_{38}F_2N_8O_4$, calculated (%): C, 63.78; H, 5.50; N, 16.08. Found: C, 63.67; H, 5.41; N, 16.06.

(6R,7R)-3-[(Acetyloxy)methyl]-7-{[(3-{[4-(4-fluorophenyl) piperazin-1-yl]methyl}-5-oxo-4-phenyl-4,5-dihydro-1H-1,2,4-triazol-1-yl)methyl]amino}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (7c). Yield: 25% (method 1), 49% (method 2); mp 208–211°C. FT IR (ν_{max}, cm^{-1}): 3400 (OH), 3045 (Aromatic CH), 2933 (Aliphatic CH), 1766 (C═O), 1713 (2C═O), 1647 (C═O). ^{1}H NMR (DMSO-d_6, δ ppm): 2.02 (s, 3H, CH_3), 2.43 (s, 4H, $2CH_2$), 2.73 (s, 4H, $2CH_2$), 2.89 (s, 4H, $2CH_2$), 4.65 (d, 1H, CH, J = 10.4 Hz), 4.79 (d, 1H, CH, J = 11.6 Hz), 4.89–5.07 (m, 4H, $2CH_2$), 6.88 (s, 2H, ArH), 7.01 (s, 2H, ArH), 7.46 (s, 5H, ArH). ^{13}C NMR (DMSO-d_6, δ ppm): 25.89 (CH_3), 49.32 ($2CH_2$), 52.35 (CH_2), 52.68 (CH_2), 52.85 (CH_2), 59.21 (CH), 59.28 (CH_2), 63.20 (CH_2), 67.66 (CH_2), 68.90 (CH), arC: [115.55 and 115.77 (d, 2CH, J = 22.0 Hz), 117.52 and 117.60 (d, 2CH, J = 8.0 Hz), 127.56 (CH), 128.61 (2CH), 129.35 (2CH), 143.43 and 143.56 (d, C, $J_{C\text{-}F}$ = 13.0 Hz), 144.47 (C), 153.29 and 155.28 (d, C, $J_{C\text{-}F}$ = 199.0 Hz)], 133.80 (C), 134.01 (C), 148.22 (triazole C-3), 157.62 (triazole C-5), 170.66 (3C═O). EI MS *m/z* (%): 660.48 ([M + Na]$^+$, 24), 638.40 ([M + 1]$^+$, 100). Elemental analysis for $C_{30}H_{32}FN_7O_6S$, calculated (%): C, 56.50; H, 5.06; N, 15.38. Found: C, 56.17; H, 5.01; N, 15.66.

***5-{[4-(4-Fluorophenyl)piperazin-1-yl]methyl}-4-phenyl-2-(thiomorpholin-4-ylmethyl)-2,4-dihydro-3*H-1,2,4-triazol-3-one (7d).** Yield: 54% (method 1), 70% (method 2); mp. 151–153°C. FT IR (ν_{max}, cm^{-1}): 3063 (Aromatic CH), 1706 (C═O), 1507 (C═N). ^{1}H NMR (DMSO-d_6 δ ppm): 2.42 (s, 6H, $3CH_2$), 2.61 (s, 4H, $2CH_2$), 2.89 (s, 4H, $2CH_2$), 3.38 (s, 4H, $2CH_2$), 4.61 (s, 2H, CH_2), 6.88 (s, 2H, ArH), 7.00 (s, 2H, ArH), 7.51 (s, 5H, ArH). ^{13}C NMR (DMSO-d_6, δ ppm): 27.65 (CH_2), 49.32 ($2CH_2$), 52.37 ($2CH_2$), 52.47 ($2CH_2$), 52.66 ($2CH_2$), 67.76 (CH_2), arC: [115.55 and 115.77 (d, 2CH, J = 22.0 Hz), 117.53 and 117.61 (d, 2CH, J = 8.0 Hz), 127.55 (2CH), 129.41 (CH), 129.47 (2CH), 133.90 (C), 148.18 and 148.20 (d, C, J = 2.0 Hz), 154.04 and 157.63 (d, C, $J_{C\text{-}F}$ = 359.0 Hz)], 143.19 (triazole C-3), 155.29 (triazole C-5). EI MS *m/z* (%): 470.48 ([M + 2]$^+$, 24), 325.01 (100). Elemental analysis for $C_{24}H_{29}FN_6OS$, calculated (%): C, 61.52; H, 6.24; N, 17.93. Found: C, 61.77; H, 6.56; N, 17.56.

General procedure for the synthesis of compounds 8a,b and 13a,b. Method 1: The solution of the corresponding compound **6** or **11** (10 mmol) in ethanol was refluxed in the presence of sodium ethoxide (10 mmol) for 2 h. Then, 2-bromo-1-(4-chlorophenyl)ethanone (for **8a**, **13a**) and 2,2,4-trichloroacetophenone (for **8b**, **13b**) (10 mmol) was added into it, and the mixture was refluxed for additional 12 h. After evaporating the solvent, a solid appeared. This crude product was recrystallized from acetone:water (1:3) to give the target compound.

Method 2: The solution of the corresponding compound **6** or **11** (1 mmol) in ethanol was irradiated in microwave reactor in the closed vessel with pressure control at 125°C, 120 W for 10 min in the presence of metallic sodium (1 mmol). Then, 2-bromo-1-(4-chlorophenyl) ethanone (1 mmol) was added into it and the reaction mixture was irradiated at 125°C, 120 W for 30 min.

After evaporating the solvent under reduced pressure, a solid appeared. This was washed with water and recrystallized from acetone to afford the desired compound.

2-[2-(4-Chlorophenyl)-2-oxoethyl]-5-{[4-(4-fluorophenyl) piperazin-1-yl]methyl}-4-phenyl-2,4-dihydro-3H-1,2,4-triazol-3-one (8a). Yield: 75% (method 1), 89% (method 2); mp 156–158°C. FT IR (ν_{max}, cm^{-1}): 3071 (Aromatic CH), 2964 (Aliphatic CH), 1716 (C═O), 1693 (C═O), 1509 (C═N). ^{1}H NMR (DMSO-d_6, δ ppm): 2.41 (s, 2H, CH_2), 2.90 (s, 4H, $2CH_2$), 3.35 (s, 4H, $2CH_2$), 5.45 (s, 2H, CH_2), 6.89 (brs, 2H, ArH), 7.02 (brs, 2H, ArH), 7.34–7.53 (m, 5H, ArH), 7.67 (d, 2H, ArH, J = 7.2 Hz), 8.07 (d, 2H, ArH, J = 7.2 Hz). ^{13}C NMR (DMSO-d_6, δ ppm): 49.32 (CH_2), 52.79 ($2CH_2$), 52.61 (CH_2), 56.35 (CH_2), 64.36 (CH_2), arC: [115.56 and 115.77 (d, 2CH, J = 21.0 Hz), 117.54 and 117.61 (d, 2CH, J = 7.0 Hz), 127.40 (CH), 128.01 (2CH), 128.91 (2CH), 129.52 (2CH), 130.53 (2CH), 133.49 (C), 133.84 (C), 139.43 (C), 153.96 and 157.64 (d, C, $J_{C\text{-}F}$ = 368.0 Hz)], 148.21 (triazole C-3), 155.30 (triazole C-5), 192.98 (C═O). EI MS m/z (%): 528.16 ([M + Na]$^+$, 45), 506.33 ([M + 1]$^+$, 9), 448.52 (29), 447.58 (100). Elemental analysis for $C_{27}H_{25}ClFN_5O_2$, calculated (%): C, 64.09; H, 4.98; N, 13.84. Found: C, 64.17; H, 4.56; N, 13.56.

2-[2-(2,4-Dichlorophenyl)-2-oxoethyl]-5-{[4-(4-fluorophenyl) piperazin-1-yl]methyl}-4-phenyl-2,4-dihydro-3H-1,2,4-triazol-3-one (8b). Yield: 76% (method 1), 84% (method 2); mp 165–166°C. FT IR (ν_{max}, cm^{-1}): 3088 (Aromatic CH), 2921 (Aliphatic CH), 1698 (2C═O), 1508 (C═N). ^{1}H NMR (DMSO-d_6, δ ppm): 2.41 (s, 2H, CH_2), 2.89 (s, 4H, $2CH_2$), 3.34 (s, 6H, $3CH_2$), 6.88 (s, 2H, ArH), 7.01 (s, 2H, ArH), 7.43 (s, 8H, ArH). ^{13}C NMR (DMSO-d_6, δ ppm): 48.06 (CH_2), 49.34 (CH_2), 52.17 ($2CH_2$), 52.35 (CH_2), 52.85 (CH_2), arC: [115.56 and 115.77 (d, 2CH, J = 21.0 Hz), 117.52 and 117.60 (d, 2CH, J = 8.0 Hz), 127.56 (2CH), 128.61 (CH), 129.35 (2CH), 130.59 (2CH), 133.90 (CH), 144.47 (2C), 148.22 (2C), 154.89 (2C)], 155.27 (triazole C-3), 157.62 (triazole C-5), 195.37 (C═O). EI MS m/z (%): 564.21 ([M + 1 + Na]$^+$, 76), 562.21 (100). Elemental analysis for $C_{27}H_{24}Cl_2FN_5O_2$, calculated (%): C, 60.01; H, 4.48; N, 12.96. Found: C, 60.10; H, 4.51; N, 12.86.

General procedure for the synthesis of compounds 9a,b. Method 1: A solution of the corresponding compound **8** (10 mmol) in ethanol was refluxed in the presence of $NaBH_4$ (30 mmol) for 15 h. After evaporating the solvent, an oily mass appeared. This crude product was recrystallized from acetone:water (1:3) to afford the desired product.

Method 2: The mixture of compound **8** (1 mmol) and $NaBH_4$ (3 mmol) in ethanol (10 mL) was irradiated in monomode microwave reactor in closed vessel with the pressure control at 100°C for 12 min at 100 W. After evaporating the solvent, a solid appeared. This crude product was washed with water and recrystallized from acetone:water (1:3) to yield the target product.

2-[2-(4-Chlorophenyl)-2-hydroxyethyl]-5-{[4-(4-fluorophenyl)piperazin-1-yl]methyl}-4-phenyl-2,4-dihydro-3H-1,2,4-triazol-3-one (9a). Yield: 60% (method 1), 72% (method 2); mp141–142°C. FT IR (ν_{max}, cm^{-1}): 3428 (OH), 3050 (Aromatic CH), 2958 (Aliphatic CH), 1679 (C═O), 1512 (C═N). ^{1}H NMR (DMSO-d_6, δ ppm): 2.35 (s, 4H, $2CH_2$), 2.89 (s, 4H, $2CH_2$), 3.34 (s, 2H, CH_2), 3.77–4.97 (m, 2H, CH_2), 4.98 (t, 1H, CH, J = 8.0 Hz), 5.78 (brs, 1H, OH), 6.89–6.91 (m, 2H, ArH), 7.00–7.02 (m, 2H, ArH), 7.38–7.49 (m, 9H, ArH). ^{13}C NMR (DMSO-d_6, δ ppm): 49.33 (CH_2), 52.26 ($2CH_2$), 52.36 (CH_2), 52.52 (CH_2), 56.34 (CH_2), 70.07 (CH), arC: [115.58 and 115.80 (d, 2CH, J = 22.0 Hz), 117.51 and 117.59 (d, 2CH, J = 8.0 Hz), 127.42 (CH), 128.52 (2CH), 128.62 (2CH), 128.80 (2CH), 129.42 (2CH), 132.33 (C), 133.89 (C), 142.01 (C), 142.90 (C), 153.31 and 155.29 (d, C, $J_{C\text{-}F}$ = 198.0 Hz)], 148.23 (triazole C-3), 157.64 (triazole C-5). EI MS m/z (%): 532.17 (36), 530.17 ([M + Na]$^+$, 100), 376.25 (31). Elemental analysis for $C_{27}H_{27}ClFN_5O_2$, calculated (%): C, 63.84; H, 5.36; N, 13.79. Found: C, 63.99; H, 5.51; N, 13.86.

2-[2-(2,4-Dichlorophenyl)-2-hydroxyethyl]-5-{[4-(4-fluorophenyl)piperazin-1-yl]methyl}-4-phenyl-2,4-dihydro-3H-1,2,4-triazol-3-one (9b). Yield: 60% (method 1), 75% (method 2); mp 98–100°C. FT IR (ν_{max}, cm^{-1}): 3255 (OH), 3009 (Aromatic CH), 2987 (Aliphatic CH), 1680 (C═O), 1512 (C═N). ^{1}H NMR (DMSO-d_6, δ ppm): 2.41 (s, 4H, $2CH_2$), 2.90 (s, 4H, $2CH_2$), 3.33 (s, 5H, CH + $2CH_2$), 6.88 (brs, 2H, ArH), 7.01 (brs, 2H, ArH), 7.49 (brs, 8H, ArH). ^{13}C NMR (DMSO-d_6, δ ppm): 49.31 (CH_2), 52.20 ($2CH_2$), 52.66 (CH_2), 52.92 (CH_2), 56.90 (CH_2), 70.08 (CH), arC: [115.68 and 115.90 (d, 2CH, J = 22.0 Hz), 117.51 and 117.58 (d, 2CH, J = 7.0 Hz), 127.42 (2CH), 128.62 (2CH), 128.69 (CH), 128.84 (2CH), 129.40 (2CH), 132.30 (C), 133.79 (C), 142.03 (C), 142.99 (C), 153.33 and 155.31 (d, C, $J_{C\text{-}F}$ = 198.0 Hz)], 150.34 (triazole C-3), 157.68 (triazole C-5). EI MS m/z (%): 542.46 ([M]$^+$, 70), 451.09 (100), 176.15 (31). Elemental analysis for $C_{27}H_{26}Cl_2FN_5O_2$, calculated (%): C, 59.78; H, 4.83; N, 12.91. Found: C, 59.98; H, 4.54; N, 12.86.

General procedure for the synthesis of compounds 10a–f. Method 1: NaH (10 mmol) was added to the solution of the corresponding compound **9** (10 mmol) in THF, and the mixture was refluxed for 2 h. Then, the suitable benzyl chloride (30 mmol) was added and the mixture was refluxed for an additional 8–12 h. After evaporating the solvent, an oily mass formed. This was extracted with 15 mL of ethyl acetate for three times in the presence of K_2CO_3, and the organic layer was dried on Na_2SO_4. After the removal of solvents at a reduced

pressure, a solid or an oily product was obtained, which was recrystallized from acetone (for **10a**, **10c**) or purified by column chromatography (ethyl acetate/n-hexane) (3/7) for (**10b**, **10d**–**f**).

Method 2: The mixture of NaH (1 mmol) and the corresponding compound **9** (1 mmol) in the THF were irradiated in microwave reactor in the closed vessel with pressure control at 70°C, 100 W for 5 min. Then, suitable benzylchloride (3 mmol) was added and the irradiation was continued for 20 min at 100°C, 120 W. After evaporating the solvent under reduced pressure, an oily mass formed. This was extracted with 15 mL of ethyl acetate for three times in the presence of K_2CO_3, and the organic layer was dried on Na_2SO_4. After the removal of solvents at a reduced pressure, a solid or an oily product was obtained, which was recrystallized from acetone (for **10a**, **10c**) or purified by column chromatography (ethyl acetate/n-hexane) (3/7) for (**10b**, **10d**–**f**).

2-[2-[(4-Chlorobenzyl)oxy]-2-(4-chlorophenyl)ethyl]-5-{[4-(4-fluorophenyl)piperazin-1-yl]methyl}-4-phenyl-2,4-dihydro-3H-1,2,4-triazol-3-one (10a). Yield: 24% (method 1), 45% (method 2); mp 120–122°C. FT IR (ν_{max}, cm^{-1}): 3054 (Aromatic CH), 2956 (Aliphatic CH), 1706 (C═O), 1508 (C═N). ^{1}H NMR (DMSO-d_6, δ ppm): 2.32 (s, 4H, $2CH_2$), 2.82 (s, 4H, $2CH_2$), 3.33 (s, 6H, $3CH_2$), 3.90 (brs, 1H, CH), 6.87 (d, 2H, ArH, J = 3.2 Hz), 7.02 (s, 2H, ArH), 7.29 (s, 2H, ArH), 7.39–7.49 (m, 11H, ArH).^{13}C NMR (DMSO-d_6, δ ppm): 45.63 (CH_2), 49.26 ($2CH_2$), 50.47 ($2CH_2$), 52.22 (CH_2), 69.67 (CH_2), 78.21 (CH), arC: [115.59 and 115.80 (d, 2CH, J = 21.0 Hz), 117.49 and 117.56 (d, 2CH, J = 7.0 Hz), 127.35 (2CH), 128.66 (2CH), 129.06 (2CH), 129.37 (2CH), 129.42 (2CH), 129.48 (2CH), 132.44 (CH), 133.28 (C), 133.79 (C), 137.61 (C), 138.18 (C), 142.00 (C), 143.09 (C), 153.34 and 155.29 (d, C, $J_{C\text{-}F}$ = 195.0 Hz)], 148.17 (triazole C-3), 157.63 (triazole C-5). EI MS m/z (%): 632.27 ($[M]^+$, 68), 178.28 (100). Elemental analysis for $C_{34}H_{32}Cl_2FN_5O_2$, calculated (%): C, 64.56; H, 5.10; N, 11.07 Found: C, 64.66; H, 5.11; N, 11.16.

2-{2-(4-Chlorophenyl)-2-[(2,4-dichlorobenzyl)oxy]ethyl}-5-{[4-(4-fluorophenyl)piperazin-1-yl]methyl}-4-phenyl-2,4-dihydro-3H-1,2,4-triazol-3-one (10b). Yield: 32% (method 1), 50% (method 2); brown oil. FT IR (ν_{max}, cm^{-1}): 3002 (Aromatic CH), 2958 (Aliphatic CH), 1712 (C═O), 1473 (C═N).^{1}H NMR (DMSO-d_6, δ ppm): 2.39 (s, 2H, CH_2), 2.89 (s, 2H, CH_2), 3.31 (s, 2H, CH_2), 3.44 (s, 2H, CH_2), 3.62 (s, 1H, CH),4.78 (s, 6H, $3CH_2$), 6.85 (brs, 2H, ArH), 6.99 (d, 2H, ArH, J = 8.0 Hz), 7.38–7.41 (m, 5H, ArH), 7.56–7.61 (m, 7H, ArH). ^{13}C NMR (DMSO-d_6, δ ppm): 43.28 (CH_2), 52.22 (CH_2), 56.34 (CH_2), 56.56 (CH_2), 60.26 (CH_2), 64.43 (CH_2), 65.89 (CH_2), 70.11 (CH), arC: [115.55 and 115.77 (d, 2CH, J = 22.0 Hz), 117.61 (2CH), 127.95 (CH), 128.20 (2CH), 128.48 (CH), 128.55 (2CH), 129.05 (2CH), 129.57 (CH), 129.91 (CH), 133.17 (2CH), 134.55 (C), 134.72 (C), 134.85 (C), 137.83 (C), 140.33 (C), 141.62 and 141.96 (d, C, J = 34.0 Hz), 153.27 (C), 155.99 and 157.78 (d, C, $J_{C\text{-}F}$ = 179.0 Hz)], 152.90 (triazole C-3), 155.42 (triazole C-5). EI MS m/z (%): 668.09 ($[M + 1]^+$, 100), 143.87 (51). Elemental analysis for $C_{34}H_{31}Cl_3FN_5O_2$, calculated (%): C, 61.22; H, 4.68; N, 10.50. Found: C, 61.29; H, 4.53; N, 10.86.

2-{2-(4-Chlorophenyl)-2-[(2,6-dichlorobenzyl)oxy]ethyl}-5-{[4-(4-fluorophenyl)piperazin-1-yl]methyl}-4-phenyl-2,4-dihydro-3H-1,2,4-triazol-3-one (10c). Yield: 15% (method 1), 40% (method 2); mp 163–165°C. FT IR (ν_{max}, cm^{-1}): 3063 (Aromatic CH), 2975 (Aliphatic CH), 1681 (C═O), 1510 (C═N). ^{1}H NMR (DMSO-d_6, δ ppm): 2.35 (s, 4H, $2CH_2$), 2.89 (s, 4H, $2CH_2$), 3.34 (s, 6H, $3CH_2$), 3.77–3.81 (m, 1H, CH), 6.87–6.91 (m, 3H, ArH), 7.00–7.05 (m, 3H, ArH), 7.36–7.48 (m, 7H, ArH), 7.49 (s, 3H, ArH). ^{13}C NMR (DMSO-d_6, δ ppm): 49.33 ($2CH_2$), 52.26 ($2CH_2$), 52.36 (CH_2), 52.52 (CH_2), 65.37 (CH_2), 70.07 (CH), arC: [115.59 and 115.81 (d, 2CH, J = 22.0 Hz), 117.51 and 117.59 (d, 2CH, J = 8.0 Hz), 127.43 (3CH), 128.53 (3CH), 128.63 (2CH), 128.80 (2CH), 129.42 (2CH), 132.33 (C), 133.90 (2C), 142.01 (C), 142.91 (2C), 148.22 and 148.24 (d, C, J = 22.0 Hz), 153.32 (C)], 155.30 (triazole C-3), 157.64 (triazole C-5). EI MS m/z (%): 667.09 ($[M]^+$, 56), 400.54 (100), 341.09 (75). Elemental analysis for $C_{34}H_{31}Cl_3FN_5O_2$, calculated (%): C, 61.22; H, 4.68; N, 10.50. Found: C, 61.28; H, 4.43; N, 10.78.

2-[2-[(4-Chlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-5-{[4-(4-fluorophenyl)piperazin-1-yl]methyl}-4-phenyl-2,4-dihydro-3H-1,2,4-triazol-3-one (10d). Yield: 42% (method 1), 60% (method 2); brown oil. FT IR (ν_{max}, cm^{-1}): 3014 (Aromatic CH), 2956 (Aliphatic CH), 1709 (C═O), 1491 (C═N). ^{1}H NMR (DMSO-d_6, δ ppm): 2.88 (s, 2H, CH_2), 3.36 (s, 8H $4CH_2$), 4.76 (s, 2H, CH_2), 4.96 (brs, 1H, CH), 6.88 (d, 2H, ArH, J = 4.4 Hz), 7.00 (d, 2H, ArH, J = 8.4 Hz), 7.43–7.48 (m, 12H, ArH). ^{13}C NMR (DMSO-d_6, δ ppm): 40.22 (CH_2), 40.39 (CH_2), 40.42 (CH_2), 40.60 (CH_2), 45.63 (CH_2), 49.31 (CH_2), 52.34 (CH_2), 70.15 (CH), arC:[115.57 (2CH), 117.62 (2CH), 127.58 (2CH), 129.11 (3CH), 129.38 (3CH), 130.02 (2CH), 131.18 (2CH), 133.42 (3C), 134.87 (2C), 137.19 (3C)], 155.57 (triazole C-3), 158.64 (triazole C-5). EI MS m/z (%): 668.11 ($[M + 1]^+$, 100), 524.75 (56). Elemental analysis for $C_{34}H_{31}Cl_3FN_5O_2$, calculated (%): C, 61.22; H, 4.68; N, 10.50. Found: C, 61.48; H, 4.73; N, 10.88.

2-[2-[(2,4-Dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-5-{[4-(4-fluorophenyl)piperazin-1-yl]methyl}-4-phenyl-2,4-dihydro-3H-1,2,4-triazol-3-one (10e). Yield: 47% (method 1), 55 (method 2); brown oil. FT IR (ν_{max}, cm^{-1}): 3063 (Aromatic CH), 2956 (Aliphatic CH), 1712 (C═O), 1508 (C═N). ^{1}H NMR (DMSO-d_6, δ ppm): 2.41 (brs, 4H, $2CH_2$), 2.88 (brs, 4H, $2CH_2$), 3.00–3.44 (m, 2H, CH_2),

4.77 (s, 4H, $2CH_2$), 5.04 (s, 1H, CH), 6.82–6.96 (m, 2H, ArH), 6.98–7.00 (m,2H, ArH), 7.38 (s, 4H, ArH), 7.38–7.48 (m, 2H, ArH), 7.50–7.61 (m, 5H, ArH). ^{13}C NMR (DMSO-d_6, δ ppm): 43.29 (CH_2), 46.05 (CH_2), 49.31 (CH_2), 52.26 (CH_2), 52.32 (CH_2), 60.29 (CH_2), 60.50 (CH_2), 78.28 (CH), arC:[115.51 and 115.73 (d, 2CH, J = 22.0 Hz), 117.50 and 117.57 (d, 2CH, J = 7.0 Hz), 127.39 (CH), 127.50 (2CH), 127.95 (CH), 128.21 (2CH), 129.03 (CH), 129.33 (CH), 129.41 (2CH), 129.59 (CH), 133.49 (C), 133.66 (C), 133.70 (C), 134.56 (2C), 134.73 (C), 134.86 (C), 153.27 and 155.36 (d, C, $J_{C\text{-}F}$ = 209.0 Hz), 148.08 (C)], 153.36 (triazole C-3), 157.70 (triazole C-5). EI MS m/z (%): 701.67 ([M]$^+$, 45), 500.50 (100). Elemental analysis for $C_{34}H_{30}Cl_4FN_5O_2$, calculated (%): C, 58.22; H, 4.31; N, 9.98. Found: C, 58.48; H, 4.55; N, 9.88.

2-[2-[(2,6-Dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-5-{[4-(4-fluorophenyl)piperazin-1-yl]methyl}-4-phenyl-2,4-dihydro-3H-1,2,4-triazol-3-one (10f). Yield: 43% (method 1), 61% (method 2); orange oil. FT IR (ν_{max}, cm^{-1}): 3073 (Aromatic CH), 2925 (Aliphatic CH), 1713 (C═O), 1508 (C═N). ^{1}H NMR (DMSO-d_6, δ ppm): 2.32 (s, 2H, CH_2), 2.82 (s, 2H, CH_2), 3.29 (s, 2H, CH_2), 3.38 (s, 2H, CH_2), 4.88 (s, 6H, $3CH_2$), 5.17 (s, 1H, CH), 6.81–6.90 (m, 2H, ArH), 6.98–7.00 (m, 2H, ArH), 7.40–7.42 (m, 5H, ArH), 7.51 (d, 6H, ArH, J = 7.6 Hz).^{13}C NMR (DMSO-d_6, δ ppm): 41.48 (CH_2), 44.29 (CH_2), 49.24 ($2CH_2$), 52.16 ($2CH_2$), 52.34 (CH_2), 75.39 (CH), arC: [115.51 and 115.56 (d, 2CH, J = 5.0 Hz), 117.55 (2CH), 127.33 (2CH), 127.46 (2CH), 127.97 (CH), 128.83 (CH), 129.00 (CH), 129.14 (CH), 129.30 (2CH), 129.43 (CH), 130.28 (C), 131.20 (C), 131.85 (C), 133.29 (C), 133.87 (C), 135.61 (C), 136.32 (C), 136.53 (C), 152.98 and 155.33 (d, C, J = 235.0 Hz)], 148.14 (triazole C-3), 157.64 (triazole C-5). EI MS m/z (%): 702.07 ([M + 1]$^+$, 10), 514.25 (67), 512.24 (100), 332.20 (27), 159.07 (43). Elemental analysis for $C_{34}H_{30}Cl_4FN_5O_2$, calculated (%): C, 58.22; H, 4.31; N, 9.98. Found: C, 58.42; H, 4.33; N, 10.09.

5-{[4-(4-Fluorophenyl)piperazin-1-yl]methyl}-1,3,4-oxadiazole-2(3*H*)-thione (11). Method 1: The solution of KOH (10 mmol) in water was added to the solution of compound **3** in ethanol, and the mixture was refluxed in the presence of CS_2 (20 mmol) for 10 h. Then, ethanol was evaporated and the aqueous solution acidified to pH 4 with acetic acid. On cooling the mixture in cold overnight, a solid obtained. The crude product was filtered off and recrystallized from ethyl acetate to yield to pure compound.

Method 2: The solution of KOH (1 mmol) in water was added to the solution of compound **3** in ethanol, and the mixture was irradiated in closed vessels with the pressure control 125°C, 125 W for 20 min. Then, ethanol was evaporated and the aqueous solution acidified to pH 4 with acetic acid. On cooling the mixture in cold overnight, a solid obtained. The crude product was filtered off and recrystallized from ethyl acetate to yield to pure compound. Yield: 53% (method 1), 78% (method 2); mp 190–192°C.FT IR (ν_{max}, cm^{-1}): 3079 (NH), 3019 (Aromatic CH), 2988 (Aliphatic CH), 1509 (C═N), 1226 (C═S). ^{1}H NMR (DMSO-d_6, δ ppm): 2.62 (d, 4H, $2CH_2$, J = 4.0 Hz), 3.07 (d, 4H, $2CH_2$, J = 4.4 Hz), 3.71 (s, 2H, CH_2), 6.91–6.95 (m, 2H, ArH), 7.01–7.05 (m, 2H, ArH). ^{13}C NMR (DMSO-d_6, δ ppm): 49.38 ($2CH_2$), 51.65 (CH_2), 52.44 (CH_2), arC: [115.59 and 115.81 (d, 2CH, J = 21.0 Hz), 117.72 and 117.79 (d, 2CH, J = 7.0 Hz), 148.27 (C), 155.36 and 157.70 (d, C, $J_{C\text{-}F}$ = 234.0 Hz)], 161.12 (triazole C-3), 178.65 (triazole C-5). EI MS m/z (%): 294.34 ([M]$^+$,12), 293.40 (71), 193.14 (100). Elemental analysis for $C_{13}H_{15}FN_4OS$, calculated (%): C, 53.05; H, 5.14; N, 19.03. Found: C, 53.40; H, 5.50; N, 19.18.

1-Ethyl-6-fluoro-7-(4-{[5-{[4-(4-fluorophenyl)piperazin-1-yl]methyl}-2-thioxo-1,3,4-oxadiazol-3(2H)-yl]methyl}piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylicacid (12a). Yield: 25% (method 1), 55% (method 2); mp 210–211°C. FT IR (ν_{max}, cm^{-1}): 3075 (Aromatic CH), 2945 (Aliphatic CH), 1725 (C═O), 1625 (C═O), 1505 (C═N), 1217 (C═S). ^{1}H NMR (DMSO-d_6, δ ppm): 1.40 (t, 3H, CH_3, J = 6.8 Hz), 2.65 (s, 4H, $2CH_2$), 2.93 (s, 4H, $2CH_2$), 3.06 (d, 4H, $2CH_2$), 3.33 (s, 4H, $2CH_2$), 3.77 (s, 2H, CH_2), 4.56 (d, 2H, CH_2, J = 6.8 Hz), 5.05 (s, 2H, CH_2), 6.88–6.91 (m, 2H, ArH), 6.98–7.03 (m, 2H, ArH), 7.13 (d, 1H, ArH, J = 7.2 Hz), 7.85 (d, 1H, ArH, J = 13.2 Hz), 8.91 (s, 1H, quinolone CH), 15.30 (s, 1H, OH). ^{13}C NMR (DMSO-d_6, δ ppm): 14.78 (CH_3), 49.38 ($2CH_2$), 49.50 ($2CH_2$), 49.81 (CH_2), 51.05 (CH_2), 51.62 (CH_2), 52.43 ($2CH_2$), 68.93 ($2CH_2$), 107.54 (C), arC: [106.33 (CH), 111.50 and 111.73 (d, CH, J = 23.2 Hz), 115.56 and 115.78 (d, 2CH, J = 22.0 Hz), 117.67 and 117.75 (d, 2CH, J = 8.0 Hz), 119.64 and 119.72 (d, C, J = 7.7 Hz), 137.58 (C), 145.64 and 145.74 (d, C, J = 10.0 Hz), 151.99 and 154.47 (d, C, $J_{C\text{-}F}$ = 248.0 Hz), 157.69 and 159.44 (d, C, $J_{C\text{-}F}$ = 175.0 Hz), 155.35 (C)], 148.19 (oxadiazole C-2), 148.84 (CH), 166.52 (C═O), 176.56 (C═O), 178.49 (C═S). EI MS m/z (%): 625.36 ([M]$^+$, 16), 302.24 (33), 276.19 (56), 256.31 (23), 233.15 (100). Elemental analysis for $C_{30}H_{33}F_2N_7O_4S$, calculated (%): C, 57.59; H, 5.32; N, 15.67. Found: C, 57.40; H, 5.51; N, 15.88.

1-Cyclopropyl-6-fluoro-7-(4-{[5-{[4-(4-fluorophenyl)piperazin-1-yl]methyl}-2-thioxo-1,3,4-oxadiazol-3(2H)-yl]methyl}piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (12b). Yield: 78% (method 1), 85% (method 2); mp 185–186°C. FT IR (ν_{max}, cm^{-1}): 3661 (OH), 3020 (Aromatic CH), 2970 (Aliphatic CH), 1726 (C═O), 1675 (C═O), 1449 (C═N), 1252 (C═S).^{1}H NMR (DMSO-d_6, δ ppm): 1.16 (s, 2H, CH_2), 1.31 (d, 2H, CH_2,

J = 6.4 Hz), 2.65 (s, 4H, $2CH_2$), 2.73 (s, 2H, CH_2), 2.89 (s, 2H, CH_2), 2.95 (s, 4H, $2CH_2$), 3.06 (s, 4H, $2CH_2$), 3.77 (s, 3H, CH_2 + CH), 5.06 (s, 2H, CH_2), 6.89–6.92 (m, 2H, ArH), 6.99–7.04 (m, 2H, ArH), 7.53 (d, 1H, ArH, J = 8.8 Hz), 7.85 (d, 1H, ArH, J = 13.2 Hz), 8.62 (s, 1H, quinolone CH), 15.17 (s, 1H, OH). ^{13}C NMR (DMSO-d_6, δ ppm): 8.03 ($2CH_2$), 36.28 (CH), 49.38 ($2CH_2$), 49.74 ($2CH_2$), 51.61 ($2CH_2$), 52.43 ($2CH_2$), 69.91 ($2CH_2$), 107.21 (C), arC: [106.96 (CH), 111.28 and 111.51 (d, CH, J = 23.0 Hz), 115.57 and 115.79 (d, 2CH, J = 22.0 Hz), 117.68 and 117.76 (d, 2CH, J = 8.0 Hz), 119.02 and 119.09 (d, C, J = 7.0 Hz), 139.56 (C), 145.36 and 145.46 (d, C, J = 10.0 Hz), 148.20 and 152.15 (d, C, $J_{C\text{-}F}$ = 363.0 Hz), 154.63 (C), 155.36 and 159.45 (d, C, $J_{C\text{-}F}$ = 385.0 Hz)], 148.36 (CH), 162.76 (C), 166.33 (C═O), 176.77 (C═O), 178.49 (C═S). EI MS m/z (%): MA = 637.70 ([M]$^+$ 12), 632.61 (14), 332.32 (100). Elemental analysis for $C_{31}H_{33}F_2N_7O_4S$, calculated (%): C, 58.39; H, 5.22; N, 15.38. Found: C, 58.40; H, 5.21; N, 15.78.

1-(4-Chlorophenyl)-2-[5-{[4-(4-fluorophenyl)piperazin-1-yl]methyl}-2-thioxo-1,3,4-oxadiazol-3(2H)-yl]ethanone (13a). Yield: 70% (method 1), 87% (method 2); mp 108–110°C. FT IR (ν_{max}, cm^{-1}): 3089 (Aromatic CH), 2921 (Aliphatic CH), 1682 (C═O), 1488 (C═N), 1218 (C═S). ^{1}H NMR (DMSO-d_6, δ ppm): 2.58 (s, 4H, $2CH_2$), 3.04 (t, 4H, $2CH_2$, J = 4.0 Hz), 3.84 (s, 2H, CH_2), 5.07 (d, 2H, CH_2, J = 13.6 Hz), 6.89–6.93 (m, 2H, ArH), 7.00–7.05 (m, 2H, ArH), 7.63 (d, 2H, ArH, J = 8.4 Hz), 8.06 (d, 2H, ArH, J = 8.4 Hz). ^{13}C NMR (DMSO-d_6, δ ppm): 49.36 ($2CH_2$), 51.29 (CH_2), 51.87 (CH_2), 52.38 (CH_2), 52.51 (CH_2), arC: [115.58 and 115.79 (d, 2CH, J = 21.0 Hz), 117.67 and 117.75 (d, 2CH, J = 8.0 Hz), 129.56 (2CH), 130.82 (2CH), 134.20 (C), 139.39 (C), 148.22 and 148.24 (d, C, J = 2.0 Hz), 155.35 and 157.70 (d, C, J = 235.0 Hz)], 163.97 (oxadiazole C-2), 165.12 (oxadiazole C-5), 192.04 (C═O). EI MS m/z (%): 294.34 ([M]$^+$, 12), 293.40 (71), 193.14 (100). Elemental analysis for $C_{21}H_{20}ClFN_4O_2S$, calculated (%): C, 56.44; H, 4.51; N, 12.54. Found: C, 56.60; H, 4.71; N, 12.48.

1-(2,4-Dichlorophenyl)-2-[5-{[4-(4-fluorophenyl)piperazin-1-yl]methyl}-2-thioxo-1,3,4-oxadiazol-3(2H)-yl] ethanone (13b). Yield: 50% (method 1), 70% (method 2); mp 165–166°C. FT IR (ν_{max}, cm^{-1}): 3077 (Aromatic CH), 2988 (Aliphatic CH), 1687 (C═O), 1508 (C═N), 1226 (C═S). ^{1}H NMR (DMSO-d_6, δ ppm): 2.63 (s, 4H, $2CH_2$), 3.07 (s, 4H, $2CH_2$), 3.73 (s, 2H, CH_2), 3.85 (s, 2H, CH_2), 6.94 (d, 2H, ArH, J = 3.6 Hz), 7.03 (t, 2H, ArH, J = 8.0 Hz), 7.61 (d, 1H, ArH, J = 8.4 Hz), 7.78 (s, 1H, ArH), 7.90 (d, 1H, ArH, J = 8.4 Hz). ^{13}C NMR (DMSO-d_6, δ ppm): 42.70 (CH_2), 49.35 (CH_2), 51.27 (CH_2), 51.56 (CH_2), 52.41 ($2CH_2$), arC: [115.59 and 115.81 (d, 2CH, J = 22.0 Hz), 117.73 and 117.81 (d, 2CH, J = 8.0 Hz), 128.12 (CH), 130.75 (CH), 131.96 (CH), 132.24 (C), 135.29 (C), 137.57 (C), 148.22 (C), 155.37 and 157.72 (d, C, J = 235.0 Hz)], 165.14 (oxadiazole C-2), 178.52 (oxadiazole C-5), 193.88 (C═O). EI MS m/z (%): 481.18 ([M]$^+$, 22), 193.17 (100), 181.15 (23). Elemental analysis for $C_{21}H_{19}Cl_2FN_4O_2S$, calculated (%): C, 52.40; H, 3.98; N, 11.64. Found: C, 52.60; H, 3.71; N, 11.48.

4-Amino-5-{[4-(4-fluorophenyl)piperazin-1-yl]methyl}-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (14). Method 1: The solution of compound **11** (10 mmol) in ethanol was added to hydrazine hydrate and the mixture was refluxed for 16 h. After evaporating the solvent, a solid appeared. This crude product was recrystallized from ethyl acetate to yield the target product.

Method 2: The solution of compound **11** (mmol) in ethanol was added to hydrazine hydrate and the mixture was irradiated in closed vessels with the pressure control 125°C, 125 W for 20 min. After evaporating the solvent, a solid appeared. This crude product was recrystallized from ethyl acetate to yield the target product. Yield: 54% (method 1), 77% (method 2); mp 167–169°C. FT IR (ν_{max}, cm^{-1}): 3312 and 3215 (NH_2), 3109 (NH), 3061 (Aromatic CH), 1254 (C═S).^{1}H NMR (DMSO-d_6, δ ppm): 2.60 (s, 4H, $2CH_2$), 3.06 (s, 4H, $2CH_2$), 3.65 (s, 2H, CH_2), 5.57 (s, 2H, NH_2), 6.94 (d, 2H, ArH, J = 4.4 Hz), 7.02 (d, 2H, ArH, J = 8.8 Hz), 7.13 (s, 1H, NH).^{13}C NMR (DMSO-d_6, δ ppm): 49.34 (CH_2), 49.37 (CH_2), 50.76 (CH_2), 50.88 (CH_2), 52.66 (CH_2), arC: [115.58 and 115.80 (d, 2CH, J = 22.0 Hz), 117.55 and 117.68 (d, 2CH, J = 13.0 Hz), 148.33 and 148.92 (d, C, J = 59.0 Hz), 155.27 and 157.61 (d, C, $J_{C\text{-}F}$ = 234.0 Hz)], 162.36 (triazole C-3), 166.19 (triazole C-5). EI MS m/z (%): 309.65 ([M]$^+$, 43), 181.15 (100), 171.20 (78). Elemental analysis for $C_{13}H_{17}FN_6S$, calculated (%): C, 50.63; H, 5.56; N, 27.25. Found: C, 50.60; H, 5.71; N, 27.40.

5-{[4-(4-fluorophenyl)piperazin-1-yl]methyl}-4-{[(4-nitrophenyl)methylene]amino}-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (15). Method 1: The solution of compound **14** (10 mmol) in absolute ethanol was refluxed with 4-nitrobenzaldehyde (10 mmol) for 3 h. On cooling the reaction content to room temperature, a solid appeared. This crude product was filtered off and recrystallized from ethanol.

Method 2: 4-nitrobenzaldehyde (1 mmol) was added to the solution of compound **14** (1 mmol) in absolute ethanol, and the reaction mixture was irradiated by microwave at 150 W and 110°C for 10 min. After removing in the solvent under reduced pressure, a solid product obtained. This crude product was recrystallized from ethanol. Yield 75% (method 1), 94% (method 2); mp148–150°C. FT IR (ν_{max}, cm^{-1}): 3365 (NH), 3085 (Aromatic CH), 2989 (aliphatic CH), 1543 (C═N), 1510 and 1340 (NO_2). ^{1}H NMR (DMSO-d_6, δ ppm):

3.42–3.47 (m, 6H, $3CH_2$), 3.71–3.76 (m, 2H, CH_2), 4.65 (s, 2H, CH_2), 7.03 (t, 2H, ArH, J = 4.8 Hz), 7.11 (t, 2H, ArH, J = 4.8 Hz), 8.03 (d, 2H, ArH, J = 7.2 Hz), 8.28 (d, 2H, ArH, J = 8.8 Hz), 11.20 (s, 1H, N=CH). ^{13}C NMR (DMSO-d_6, δ ppm): 47.83 (CH_2), 51.90 (CH_2), 52.05 (CH_2), 56.48 (CH_2), 61.68 (CH_2), arC: [115.88 and 116.10 (d, 2CH, J = 32.0 Hz), 118.32 and 118.40 (d, 2CH, J = 8.0 Hz), 124.41 (CH), 124.59 (CH), 128.18 (2CH), 130.05 (CH), 141.39 (C), 146.79 (C), 147.96 (C), 152.14 and 155.94 (d, C, $J_{C\text{-}F}$ = 380.0 Hz)], 148.62 (triazole C-3), 158.29 (triazole C-5). EI MS m/z (%): 442.65 ([M + 1]$^+$, 67), 320.76 (100). Elemental analysis for $C_{20}H_{20}FN_7O_2S$, calculated (%): C, 54.41; H, 4.57; N, 22.21. Found: C, 54.60; H, 4.71; N, 22.49.

1-Ethyl-5-fluoro-6-{4-[(3-{[4-(4-fluorophenyl)piperazin-1-yl]methyl}-4-{[(4-nitrophenyl)methylene]amino}-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)methyl]piperazin-1-yl}-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (16a). Yield: 45% (method 1), 58% (method 2); mp 184–186°C. FT IR (ν_{max}, cm^{-1}): 3365 (OH), 3085 (Aromatic CH), 2989 (Aliphatic CH), 1705 (2C=O), 1510 (C=N), 1209 (C=S). ^{1}H NMR (DMSO-d_6, δ ppm): 1.40 (s, 3H, CH_3), 2.09 (s, 2H, CH_2), 2.50 (s, 4H, $2CH_2$), 2.73 (s, 6H, $3CH_2$), 3.35 (s, 8H, $4CH_2$), 4.58 (s, 2H, CH_2), 7.00 (brs, 1H, ArH), 8.02 (brs, 4H, ArH), 8.30 (brs, 5H, ArH), 8.95 (s, 1H, quinolone CH), 11.21 (s, 1H, N=CH), 15.38 (s, 1H, OH). ^{13}C NMR (DMSO-d_6, δ ppm): 14.87 (CH_3), 46.65 ($2CH_2$), 48.90 ($2CH_2$), 50.01 ($2CH_2$), 51.25 ($2CH_2$), 56.65 ($2CH_2$), 65.24 (CH_2), 106.67 (C), arC: [107.21 (CH), 112.14 and 112.34 (d, 2CH, J = 20.0 Hz), 114.25 and 114.46 (d, 2CH, J = 21.0 Hz), 118.45 (CH), 120.12 and 120.20 (d, C, J = 8.0 Hz), 124.26 and 124.36 (d, C, J = 10.0 Hz), 127.65 (2CH), 129.50 (2CH), 131.24 (C), 134.45 (C), 137.65 (2C), 141.54 and 141.64 (d, C, J = 10.0 Hz), 152.14 and 155.94 (d, C, $J_{C\text{-}F}$ = 380.0 Hz)], 148.31 (CH), 152.23 (N=CH), 149.54 (triazole C-3), 158.76 (triazole C-5), 165.25 (C=O), 172.34 (C=O). EI MS m/z (%): 772.65 ([M]$^+$, 54), 300.15 (100). Elemental analysis for $C_{37}H_{38}F_2N_{10}O_5S$, calculated (%): C, 57.50; H, 4.96; N, 18.12. Found: C, 57.68; H, 4.77; N, 18.19.

1-cyclopropyl-5-fluoro-7-{4-[(3-{[4-(4-fluorophenyl)piperazin-1-yl]methyl}-4-{[(4-nitrophenyl)methylene]amino}-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)methyl]piperazin-1-yl}-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (16b). Yield: 32% (method 1), 55% (method 2); mp 175–178°C. FT IR (ν_{max}, cm^{-1}): 3226 (OH), 3078 (Aromatic CH), 2929 (Aliphatic CH), 1698 (C=O), 1661 (C=O), 1586 (C=N), 1508 and 1340 (NO_2). ^{1}H NMR (DMSO-d_6, δ ppm): 1.17 (brs, 2H, CH_2), 1.30 (brs, 2H, CH_2), 2.72 (s, 4H, $2CH_2$), 2.88 (s, 4H, $2CH_2$), 3.34 (s, 12H, $6CH_2$), 3.79 (s, 1H, CH), 7.00 (brs, 1H, ArH), 7.57 (s, 1H, ArH), 8.03 (brs, 4H, ArH), 8.29 (brs, 4H, ArH), 8.65 (s, 1H, quinolone CH), 11.20 (s, 1H, N=CH), 15.21 (brs, 1H, OH). ^{13}C NMR (DMSO-d_6, δ ppm): 8.08 ($2CH_2$), 36.23 (CH), 46.63 ($2CH_2$), 48.99 ($2CH_2$), 50.09 ($2CH_2$), 51.85 (CH_2), 56.85 ($2CH_2$), 66.24 (CH_2), 106.07 (C), arC: [107.31 (CH), 112.18 and 112.38 (d, 2CH, J = 20.0 Hz), 114.20 and 114.36 (d, 2CH, J = 16.0 Hz), 118.05 (CH), 120.02 and 120.20 (d, C, J = 18.0 Hz), 124.16 and 124.26 (d, C, J = 10.0 Hz), 126.05 (CH), 127.50 (2CH), 128.90 (CH), 133.45 (C), 135.65 (C), 141.38 (C), 142.63 (C), 147.95 (C), 152.14 and 155.94 (d, C, $J_{C\text{-}F}$ = 380.0 Hz)], 148.47 (CH), 152.13 (N=CH), 148.54 (triazole C-3), 160.64 (triazole C-5), 166.38 (C=O), 173.34 (C=O). EI MS m/z (%): 785.65 ([M + 1]$^+$, 34), 300.19 (100). Elemental analysis for $C_{38}H_{38}F_2N_{10}O_5S$, calculated (%): C, 58.15; H, 4.88; N, 17.85 Found: C, 58.18; H, 4.70; N, 17.99.

Biological activities. ***Antimicrobial activity.*** The test microorganisms were obtained 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. aerugi-nosa*) 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 *Saccharo-myces cerevisiae* (*S. cerevisia*) RSKK 251. All the newly synthesized compounds were weighed and dissolved in dimethyl sulfoxide to prepare extract stock solution of 20.000 microgram/milliliter (mg/mL). The antimicrobial effects of the substances were tested quantitatively in respective broth media by using double micro-dilution and the minimal inhibition concentration values (mg/mL) were determined. The antibacterial and antifungal assays were performed in Mueller–Hinton broth (Difco, Detroit, MI, USA) 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 (Difco, Detriot, MI) was used for *M. smegmatis* and incubated for 48–72 h at 35°C [49]. Ampicillin (10 mg) and fluconazole (5 mg) were used as standard antibacterial and antifungal drugs, respectively. Dimethyl sulfoxide with dilution of 1:10 was used as solvent control. Only positive results were presented in Table 2.

Antioxidant activity. ***2,2-Diphenyl-1-picrylhydrazyl radical scavenging activity.*** The scavenging activity of the synthesized novel compounds was determined using the free radical DPPH according to method of with slight modifications. Blois [50]. In brief, a 100-μL compound solution was mixed with 1 mL of freshly prepared methanolic DPPH solution. The reaction mixture was incubated for 30 min at room temperature in the dark and then measured at 520 nm using a UV–VIS spectrophotometer (Thermo, Evolution 100, and England). The results were expressed as μmol Trolox equivalent.

The ferric reducing ability of plasma. The method of Benzie and Strain [51] with slight modifications was applied to measure FRAP of the synthesized compounds. Accordingly, to 100 μL of each sample was added 2900 μL of freshly prepared FRAP reagent [300 mM of acetate buffer, pH 3.6, 10 mM of 2,4,6-tripyridyle-s-triazine and 20 mM of $FeCl3.6H_2O$ in proportions of 10:1:1 (*v*/v)]. The reaction mixture was incubated for 30 min at 37°C and measured at 593 nm using a UV–VIS spectrophotometer (Thermo, Evolution 100, and England). The results were expressed as μmol of Trolox/g.

Cupric ion reducing antioxidant capacity. The CUPRAC method measured for the compounds was followed according to the procedure described by Apak et al. [52] with slight modifications. In brief, 100 μL of solution each compound was mixed with 900 μL of bidistilled water, 1 mL of acetate buffer solution (1 mM, pH 7.0), 1 mL of $CuCl_2$ (10 mM), and 1 mL of 7.5-mM neocuproine to a final volume of 4 mL. After incubating the reaction mixture 30 min at room temperature, the absorbance was measured at 450 nm against a water blank using a UV–VIS spectrophotometer (Thermo, Evolution 100, and England). Trolox was used as the standard calibration curves, and the results were expressed as μmol Trolox equivalent/g.

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SUPPORTING INFORMATION

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